

Exhaustion disorder

- identification, characterisation and course of illness

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logga

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*To my parents
Hezel and Åke Jönsson*

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- identification, characterisation and course of illness

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ABSTRACT

Aim. The overall aim of the thesis was to study exhaustion disorder (ED) with respect to identification, characterisation and course of illness, as well as some properties of an instrument of self-rated ED (s-ED).

Method. The first two studies were based on longitudinal register data of patients referred to a specialist clinic and fulfilling the criteria for ED diagnosis. The burden of mental and somatic symptoms including course of illness were studied, inclusive possible influence of sex and age. The third study was a cross-sectional primary care study of patients seeking for any reason, and completing a stress item and mental health questionnaires including s-ED. Those that indicated mental health problems were invited for clinical examination and assessment for ED. The fourth study was based on data from a longitudinal cohort with the primary aim to investigate how self-rated ED relates to other self-rating scales of mental health and work-ability, and to follow up the predictive validity of s-ED regarding sickness absence.

Results. The main finding of the first study was the long duration of mental illness seen in ED patients. Further important findings were the high burden of co-morbid conditions such as depression and anxiety. There were no sex or age group differences. Self-reported symptom duration before seeking care was the only significant predictor of recovery. In the second study the main finding was multiple somatic symptoms reported by patients with ED, without sex or age group differences. The number of somatic symptoms was significantly related to the severity of mental health problems. Nearly half of both female and male patients reported six symptoms or more during the first visit at the clinic and one-fifth of the total at 18-month follow-up. Pain in arms, legs and joints was the only single symptom that persisted at a constant level. The main finding in the third study was that approximately one-third of those invited for clinical examination fulfilled the diagnostic criteria for ED. This corresponded to

9 % of the total primary care study population. Furthermore, co-morbid depression and anxiety were common in ED patients, and the burden of somatic symptoms was high. Those not fulfilling ED (non-ED) showed a similar burden of somatic symptoms, but less mental health symptoms compared to ED patients. In non-ED patients with pronounced s-ED mental health symptoms were similar to ED, except for anxiety being more prevalent in ED. The main finding from the fourth study of a working population was that s-ED corresponded well to other mental health measurements. With increasing severity of s-ED, symptoms of depression, anxiety and burnout rose, and furthermore the rate of poor work-ability and the risk of future sick leave increased. Further results were that one out of six reported self-reported exhaustion.

Conclusions. Patients with ED presented long-lasting course of mental health problems. There was extensive comorbidity including depression, anxiety and multiple somatic symptoms. Similar pattern with regard to both burden of symptoms and course of symptom are seen for all patients irrespective of sex or age. Among patients seeking primary care and reporting elevated stress and mental health problems, one-third was found to fulfil the diagnostic criteria for ED, which is nearly one out of ten of the total group. Patients that did not completely fulfil the criteria but reported pronounced s-ED showed similar burden of mental and somatic health problems. This implies that self-reporting s-ED irrespective of ED diagnosis should be considered an important health problem. The s-ED instrument was found to correlate well with other mental health measures, and the predictive value with regard to future sick leave indicated that this instrument could be considered as a potential tool for early identification of patients risking high burden of stress-related health problems and long sick-leaves.

Key words: Exhaustion, anxiety, depression, burnout, multiple somatic symptoms, symptom duration, stress related mental health problems, sex, age, early detection.

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Svensk sammanfattning

Syfte Det övergripande syftet med avhandlingen var att studera diagnosen utmattningssyndrom (UMS) avseende identifikation, karakteristika och sjukdomsförlopp samt att studera några egenskaper hos instrumentet för självskattat UMS (s-UMS).

Metod De två första studierna baserades på data från ett longitudinellt register över patienter som remitterats till en specialistklinik, och som uppfyllde kriterierna för UMS. Den tredje var en tvärsnittsstudie i primärvården av patienter som oavsett sökorsak besvarade en stressfråga och frågeformulär om psykisk ohälsa inkluderande s-UMS. De som indikerade mental ohälsa inbjöds till klinisk undersökning och test av UMS. Den fjärde var baserad på data från en longitudinell kohort av anställda arbetstagare med primära syftet att undersöka hur s-UMS relaterar till andra självskattningsskalor för psykisk hälsa och arbetsförmåga samt hur instrumentet predikterar sjukskrivning.

Resultat Det viktigaste fyndet i den första studien var det långdragna sjukdomsförloppet avseende psykiska symptom hos UMS patienter. Andra viktiga fynd var den omfattande samsjukligheten med depression och ångest. Det fanns inga köns eller ålderskillnader. Självrapporterad symptomduration före konsultation var den enda variabel som signifikant predikterade sjukdomsförloppet. Det viktigaste fyndet i den andra studien var multipla somatiska symptom utan köns- eller ålderskillnader. Antalet symptom var associerade med allvarlighetsgraden av de psykiska symptomen. Vid den första undersökningen rapporterade knappt hälften av patienterna sex symptom eller mer, och en femtedel vid 18 månader. Smärtor i armar, ben och leder var det enda symptom som låg kvar på samma nivå över tid. Det viktigaste fyndet i den tredje studien var att cirka en tredjedel av dem som inviterats till klinisk undersökning, uppfyllde de diagnostiska kriterierna för UMS. Detta motsvarar 9% av den totala populationen i primärvårdsstudien. Ytterligare fynd var att samsjuklighet med depression och ångest var vanlig bland UMS patienterna, och sjukdomsbördan avseende somatiska symptom var hög. De som inte uppfyllde kriterierna för UMS hade lika stor sjukdomsbörda avseende somatiska symptom men mindre psykiska symptom. Patienter som inte uppfyllde kriterierna för UMS men som självskattade uttalat s-UMS, hade lika stor sjukdomsbörda avseende somatiska och psykiska symptom som UMS patienterna, förutom ångest som var vanligare vid UMS. Huvudresultatet i den fjärde studien, var att s-UMS var hade god samstämmighet med andra instrument för psykisk ohälsa. Med stigande allvarlighetsgrad av s-UMS sågs ett samband med ökade depressions- och ångestsymptom och självskattad låg arbetsförmåga samt en ökad risk för framtida sjukskrivning. Andra fynd var att en av sex arbetstagare rapporterade självskattad utmattning.

Sammanfattning Patienter med UMS hade ett långt sjukdomsförlopp avseende mentala symptom och en omfattande samsjuklighet med depression, ångest och multipla somatiska symptom. Oavsett kön eller ålder var symptombördan och sjukdomsförloppet lika. Bland primärvårdspatienter som angav ökad stress och psykiska symptom, uppfyllde en tredjedel de diagnostiska kriterierna för UMS, vilka utgjorde nästan en tiondel av totala studiegruppen. Patienter som inte helt uppfyllde UMS kriterierna, men som skattade ett uttalat utmattningssyndrom med s-UMS, hade liknande sjukdomsbörda avseende somatiska och psykiska symptom som vid UMS, men ångest var vanligare bland UMS patienter. Självrapporterad utmattning med s-UMS, oavsett UMS diagnos, tycks indikera ett allvarligt hälsoproblem. S-UMS hade god samstämmighet med andra instrument för psykisk ohälsa och predikterade framtida sjukskrivning. Detta gör instrumentet till ett värdefullt redskap för tidig upptäckt av individer med hög stressbelastning och risk för stressrelaterade hälsoproblem samt lång sjukskrivning.

List of original papers

This thesis is based on the following papers, referenced in the text by their Roman numerals I-IV.

I. **Glise K**, Ahlborg G Jr, Jonsdottir IH. Course of mental symptoms in patients with stress-related exhaustion: does sex or age make a difference? *BMC Psychiatry* 2012 12:18.

II. **Glise K**, Ahlborg G Jr, Jonsdottir IH. Prevalence and course of somatic symptoms in patients with stress related exhaustion: Does sex or age matter? Accepted for publication in *BMC Psychiatry*.

III. **Glise K**, Wiegner L, Ahlborg G Jr, Jonsdottir IH. Exhaustion Disorder in Primary care Patients 18 to 65 years of age. Manuscript.

IV. **Glise K**, Hadzibajramovic E, Jonsdottir IH, Ahlborg G Jr. Self reported exhaustion: a possible indicator of reduced work ability and increased risk of sickness absence among human service workers. *Int Arch Occup Environ Health*. 2010 Jun;83(5):511-20.

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LIST OF ABBREVIATIONS

ASD	Acute stress disorder
CBT	Cognitive behaviour therapy
CFS	Chronic fatigue syndrome
CI	Confidence intervals
DSM IV	Diagnostic and statistical manual of mental disorders, fourth edition
DSM-5	Diagnostic and statistical manual of mental disorders, fifth edition
ED	Exhaustion disorder
GAD	General anxiety disorder
GP	General practitioner
HAD	Hospital anxiety and depression scale
ICD-10	International classification of diseases
ISM	Institute of Stress Medicin
KEDS	Karolinska exhaustion disorder scale
MBI	Maslach burnout inventory
MMT	Multimodal treatment
Non-ED	Patient that not fulfil the diagnostic criteria of exhaustion disorder
PHQ-15	Patient health questionnaire
PR	Prevalence ratios
PRIME MD	Primary care evaluation of mental disorders
PTSD	Post-traumatic stress disorder
QPSNordic	Nordic questionnaire for psychological and social factors at work
RR	Relative risk
SA 14	14 days of ongoing sick leave or sickness benefit
SA 60	60 days of sick leave during the last 12 months
SBU	The Swedish council on health and technology assessment
SD	Standard deviation
SF-36	Short-Form health survey
SMBQ	Shirom Melamed burnout questionnaire
S-ED	Self-reported exhaustion disorder
VGR	Region Västra Götaland
WAI	Work ability index
WHO	World Health Organisation

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PREFACE

At an occupational health care centre in Western Sweden where I worked, there was an increase in the number of patients seeking for severe mental health problems from 1992 and onwards. At that time the Swedish economy deteriorated and there was an extensive reorganisation of the public sector. The main symptoms of the patients were exhaustion, cognitive dysfunction, sleep problems, reduced tolerance to further stress, and somatic symptoms. Symptoms of depression and anxiety were common. From the official reports of 1997 and onwards there was increasing rates of sick leave due to common mental health problems. A few years thereafter the Swedish National Board of Health and Welfare responded by calling an expert group to analyse the problem. The Institute of Stress Medicine (ISM) was established in 2002 by Region Västra Götaland (VGR), initially as a co-operation between VGR and the Swedish Social Insurance Agency operating in the region. The Government provided initial funding for ISM and its research. The task of the Institute was to study different aspects of mental health problems related to long-lasting stress exposure, and the aim was to gain a better knowledge of stress-related mental health problems. In 2004 when the patient clinic at ISM started, the idea of the present thesis emerged. At that time it was obvious that stress related exhaustion should be considered as a significant medical problem affecting people exposed to high levels of stress over a long period of time, without successful recovery/coping. A combination of personal suffering for the patients and the relatives and high costs for the society made this complex problem necessary to further explore.

1. INTRODUCTION

1.1. Background

In the early years of the new millennium there was much concern about the rising rates of mental health problems (1). This was shown to be a substantial problem in many countries, and a major cause of the increase was generally believed to be related to psychosocial stress (2). Psychosocial factors in working-life including heavy demands, high workloads, organisational changes and psychological harassment, were believed to be important contributors to the problems (3, 4). Increased knowledge including clinical studies was needed in order to explore this extensive problem and the characteristics of patients seeking help for stress-related mental health problems.

1.2. Stress and health

The word stress has several connotations and is used in different ways. Here stress is defined as the biological and psychological reaction to different challenges, i.e. the mobilisation of resources to cope with demands, referred to as stress exposure. The reaction includes the psychological experience of the exposure, as well as emotional and physiological responses. Both acute and chronic stress exposure that exceeds the capacity for adequate mobilisation of resources can, if not sufficiently dealt with, result in negative behavioural consequences and in some cases cause somatic and/or mental health problems.

Research in both animals and humans has shown that long-lasting stress exposure, or a traumatic event, can have an impact on health (5). In humans a long-lasting high level of stress could initially be associated with minor problems such as various somatic and/or mental symptoms (6), but as the stress process proceeds more severe problems including both somatic and/or mental disorders may in some cases occur. Thus it has clearly been shown that prolonged psychosocial stress is an independent predictor of cardiovascular diseases (7-9), and metabolic disturbances (10). Prolonged stress exposure without sufficient recovery has also been clearly shown to be related to various mental health problems such as depression, adjustment disorders, and burnout, often leading to long sick leave (11-14). The most extreme cases of stress-related problems are individuals that after exposure to a severe traumatic event develop acute stress disorder or post-traumatic stress disorders (PTSD) (15). It is also known

from several studies that psychosocial stress can aggravate symptoms in patients with several different diseases, two examples being gastroesophageal reflux and Menière's disease (16-18). In recent decades work-related stress in Europe has increased as a result of changes in the content and organisation of work (19). Intensification of work, which is one consequence, is commonly regarded as a major cause of stress-related problems. This is the case with both quantitative but more especially qualitative demands. Occupational stressors have been shown to be significantly related to physical symptoms such as gastrointestinal symptoms, headaches, dizziness, backache and other musculoskeletal pain, sleep disturbances and fatigue (6). There is also robust evidence that work-related factors such as high demands, low decision latitude, high efforts and low rewards are prospective risk factors for common mental disorders (20). Bullying is another work-related stressor that has been shown to be associated with mental disorders (21, 22). It has becoming clearer in the area of stress research that stress outside work is of equal importance, affecting health in similar manner as work-related stress. Thus, both types of stress has been shown to be related to somatic as well as mental health related problems, such as cardiovascular disease and depression (7, 23). Patients with exhaustion disorder were recently shown to report work-related and non-work related stressors as being the main cause for the exhaustion (24). Conclusively, it seems obvious that psychosocial stress can have impact on health in different ways and that work related and private stressors are of equal importance.

1.3. Exhaustion disorder

1.3.1. Background

The growing mental health problems in Sweden included patients that often complained of long periods of stress during which the symptoms developed and there was lack of consensus about how to examine, diagnose and treat these patients (25). The expert panel that was initiated by the National Board of Health and Well Fare suggested a new criterion-based diagnosis exhaustion disorder (ED). ED could be used in clinical practice to better define patients with stress-related mental health problems, see table 1. ED was established in 2005 to improve diagnostics in cases of stress-related exhaustion (26), and was assigned the code F43.8 of ICD-10 (27).

Table 1. Diagnostic criteria for stress-related exhaustion disorder as proposed by the Swedish National Board of Health and Welfare

A	Physical and mental symptoms of exhaustion of at least two weeks' duration. The symptoms have developed in response to one or more identifiable stressors, which have been present for at least six months
B	Markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance, or increase in time needed for recovery after mental effort
C	At least four of the following symptoms have been present most of the day, nearly every day, during the same 2-week period: <i>1 Persistent complaints of impaired memory</i> <i>2 Markedly reduced capacity to tolerate demands or to work under time pressure</i> <i>3 Emotional instability or irritability</i> <i>4 Insomnia or hypersomnia</i> <i>5 Persistent complaints of physical weakness or fatigue</i> <i>6 Physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds</i>
D	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
E	The symptoms are not due to the direct physiological effects of a substance (such as drug abuse or medication) or a general medical condition (such as hypothyroidism, diabetes and infectious disease)
F	If criteria for major depressive disorder, dysthymic disorder or generalized anxiety disorder are met, exhaustion disorder is considered a co-morbid condition

1.3.2. The diagnostic criteria of exhaustion disorder

The diagnostic criteria include the main symptoms presented by patients seeking health care for mental health problems due to stress: exhaustion, cognitive dysfunction, sleep problems, reduced tolerance to further stress, and somatic symptoms. Lack of energy is a major criterion, and this pronounced energy depletion and the cognitive problems often become long-lasting (28, 29). The criteria include one item about previous stress exposure of at least six months, which the patients consider to be the cause of the illness. The stress question is unspecific regarding sources of stress, and this should be assessed separately in a clinical interview.

1.3.3. Treatment of exhaustion disorder

There was clinical consensus with regard to which treatments could be used in this group

of patients, as suggested by the expert group, and in the present thesis called multimodal treatment (MMT) (27). At the specialist clinic where this thesis was conducted one form of MMT treatment was developed, and all patients treated at the clinic were offered individualized such treatment. This treatment included regular visits to the physician at intervals of four to six weeks. In addition to current symptoms, physical activity and other lifestyle topics were discussed. A stress reduction program in a group and a lecture about stress-related mental health problems were offered. The employer and relatives were offered a lecture on stress-related mental health problems. Cognitive behavioural group therapy (CBT) or individual psychotherapies, aerobic exercise group and strength training were other treatment methods. Antidepressant medication was offered when needed. Finally, communication with the Social Insurance Office and the employer was facilitated. Since the study was designed, several randomised trial studies have been conducted, all of which have compared one particular treatment component such as CBT, qi gong or others. A randomized control trial of burnout cases, which offered qi gong intervention in addition to care as usual, showed no further effect of intervention compared to treatment as usual (30). Further randomized trials have evaluated interventions directed at the individual, including principles of CBT, with marginal effect on psychological variables (31, 32), return to work and sick leave (33). Interventions at the workplace were shown to have a favourable effect on return to work (32, 34).

1.4. Mental health problems related to exhaustion disorder

1.4.1. Background

A term often used in the literature is common mental disorder and is mainly composed of symptoms of depression and anxiety (35). It is often measured with simple self-report questionnaires and could be defined differently. In a review of the general and working populations, common mental disorders comprised simple phobias, depression, anxiety including general anxiety disorder (GAD), panic disorders, PTSD and dysthymia (36). The World Health Organisation (WHO) reported a wide variation between different countries in the prevalence of individuals experiencing one or several mental disorders such as anxiety and depression during their lives (37). In several European countries common mental disorders was reported by one quarter to one-third, anxiety and depressive disorders being most prevalent (37). In a Finnish study of the working population aged 45-60 years, the overall prevalence of common mental disorders was 26% of women and 23% of men (38). Among common mental disorders, many co-occur with each other (39). Co-morbidity was related to

symptom severity, degree of impairment, course and outcome (40). Among the general population aged 14-24 years, a considerable increase in depression among those with anxiety was reported, indicating that over time more pronounced co-morbid conditions could be expected (39, 41). A large Spanish primary care study showed that more than half of the patients had mental disorders, and a third reported more than one disorder (42). Several mental health problems other than depression and anxiety are related to common mental disorders, including burnout, adjustment disorders, acute stress disorder and PTSD. These mental health problems also share similar symptoms with ED, and thus they are of interest to introduce in this thesis.

1.4.2. Burnout

Burnout has been defined in several ways and consequently there are different self-report instruments constructed for its assessment (11, 43). Burnout was first described by Freudenberger in 1974 (44). He stated that burnout was accompanied by a feeling of exhaustion and fatigue in combination with different physical symptoms. Early research also showed that depression seems to be a co-morbid condition in individuals who report burnout (44). Maslach's original work on burnout was published in 1976 (45), and defined burnout as emotional exhaustion, cynicism and depersonalisation which are the dimensions that are included in the widely used Maslach burnout inventory (MBI) (46, 47). Another conceptual frame for burnout was suggested by Shirom and Melamed, who stated that the core element of burnout is chronic depletion of an individual's energetic resources, emotional exhaustion, physical tiredness and mental weariness following prolonged stress exposure, not only focused on work (48). Burnout was originally considered to be work-related but later research has shown that burnout can be developed as a consequence of different kind of stressors, including private life stressors, depending on the questionnaire used (46, 49). It is difficult to estimate prevalence of burnout in different populations. Depending on the questionnaire used prevalence can vary. In a Swedish working population using SMBQ, the total group reported a prevalence of 13%, ranging between 5% and 22% depending on age and sex (50). This was different from Maslach's finding that gender is a weak predictor of burnout (11). There are other Swedish working population studies showing prevalence between 6% and 18% (51, 52). Burnout can be seen as a chronic stress syndrome that develops gradually, a process that includes different reactions to problems, and is not necessary an illness or disorder but could grow into symptoms that resembles those that are seen in patients with ED (53). Attempts have been made to formulate burnout as a clinical diagnosis. Thus, in the Netherlands the

diagnostic criteria of neurasthenia according to the ICD-10 criteria has been adapted by adding that the problem should be work-related, and reformulating this condition as “clinical burnout” (54). In Sweden, a decision was made to form diagnostic criteria including the core symptoms of burnout, namely exhaustion, resulting in the main object of this thesis, the ED diagnosis. Thus, exhaustion is also included as a core symptom in ED (55), but cynicism does not seem to be prominent in ED.

1.4.3. Depression

The diagnosis of depression includes a distinct lowering of mood, with sadness and irritability, and such symptoms as disturbed sleep, loss of ability to feel pleasure, slowing of speed and action, cognitive disturbances, somatic symptoms, suicidal thoughts of at least two weeks’ duration, and interference with daily activities (56). Depression is related to normal emotions of sadness and bereavement (57). The symptoms do not remit when the external cause of these emotions disappears and it is disproportionate to their cause (57). There have been discussions about the definition and classification of depression, and it includes a variety of disorders (57-59). The course can be episodic, remitting, or chronic. In patients with different chronic somatic disorders, depressive symptoms are not uncommon (60). The prevalence of depression in the general population in Sweden was estimated at approximately five per cent (61). In primary care every third patient was shown to suffer from depression, anxiety, or alcohol problems (62). Considering sex differences and depression, irrespective of clinical diagnosis or questionnaires, in the majority of cases women are overrepresented (61, 63), although there are population studies reporting minimal sex differences (64). Women were also shown to be more susceptible to stress-induced depression (65). There is some inconsistency concerning age and depression. A study of patients from 29 different countries, showed a lower prevalence of depression in both younger and older age groups compared to middle-aged (66). Similarly in a large population study in US the lifetime prevalence of depression increased with age among those aged 45 or younger, and decreased among over 45s (67). However, a Norwegian population study showed that the prevalence of depressive disorders increased from ages 20 to 89 years (64).

There has long been considerable debate about the similarities between depression and burnout. Glass and McKnight concluded in a review 1996, that burnout and depression were related but different concepts (68). Shaufeli and Enzmann in 1998 reported similarly that depression and burnout especially in the emotional exhaustion component are related but not

identical concepts (55). Depression and ED have also been discussed as two different concepts suggested by Asberg et al, see table 2. This could be helpful for clinicians to know in order to distinguish between depression and ED. As shown in table 2, the long duration of symptoms before ED occurs, the acute debut and the slow recovery with exhaustion and cognitive problems are considered to be the main difference between ED and depression. In a study exploring the relationship between self-rated symptoms of exhaustion disorder, depression and anxiety was shown that they reflect three different underlying dimensions (69).

Table 2. Exhaustion disorder in comparison with depression. Adapted from Asberg et al 2010 (53)

	Exhaustion disorder	Depression
Course of illness	Long lasting, fluctuating prodromal symptoms Often acute debut with panic attack or other dramatic event Recovery phase with cognitive failures, fatigue and extreme sensitivity to stress over-load remaining for years ED does not resolve when depressive symptoms disappear	Episodic disorder After some months remission in most cases High risk of recurrence
Biological characteristics	Decreased sensitivity in the stress-hormone-axis Different activation of the brain and different sleep disturbances compared to depression	Increased sensitivity in the stress hormone axis
Characteristics	Exhaustion Cognitive failures Sleep disturbances Somatic symptoms	Depressed mood Anhedonia Sleep disturbances Cognitive failures Somatic symptoms
Treatment	Insufficient evidence of adequate treatment. Antidepressants doubtfully effective Work-related rehabilitation has been shown effective* Physical activity has been shown effective**	Antidepressant Cognitive psychotherapy Physical activity

*Karlson et al. 2010 (34)

**Gerber et al. 2013 (70)

1.4.4. Anxiety

Anxiety disorders defined by WHO include panic disorder, agoraphobia, phobias, GAD, PTSD, and separation anxiety disorders (71). The definition of GAD in the Diagnostic and statistical manual of mental disorders (DSM IV), and ICD-10, requires at least six months of uncontrollable and diffuse anxiety or worry, and several related symptoms (56, 72). Patients with panic disorder suffer from brief periods of intense fear, hypervigilance, and distress, including autonomic symptoms (73). Panic attacks could be the initial symptom of ED, sometimes leading to visits to the health service. Recently it was shown that women possess a vulnerability factor that entails inflexibility of response to stimuli, and then an anxiety

disorder may be more likely to develop (74). Co-morbidity with depression is common, a community study of anxiety disorder showed that the rates of co-morbid depression increased substantially over time (39). The prevalence in a Swedish population was 15% for anxiety disorders and 9% for GAD; women had higher rates (61). In primary care a 30-day prevalence of 11% for GAD was reported (75). The 12-month prevalence of panic disorders was shown to be 3%, and women had higher rates (76).

1.4.5. Adjustment disorders

The main features in adjustment disorders are that the symptoms arise in response to a stressful event within three months, according to the DSM IV (56), or within one month according to the ICD-10 (72). The symptoms must be clinically significant and resolve within six months once the stressor is removed. Clinical assessment is central for diagnosis, and the presence of an external stressor of sufficient severity to justify clinical attention is obligatory (77, 78). Adjustment disorder describes widespread psychological reactions and current dysfunction, and the diagnosis does not contain subsequent impairment (77). A limitation of the diagnosis is that it is diverse and poorly defined. It can start with a panic attack or suicidal thoughts. The diagnosis maladaptive stress reaction can also be used (72). Adjustment disorders can be characterized by mild to moderate symptoms for a prolonged period, or severe symptoms for a short period, and the distinction from depressive disorder is unclear (79). Adjustment disorders were suggested as a diagnosis based on the longitudinal course of symptoms in the context of a stressor, while a diagnosis of major depression is cross-sectional, based on numbers and severity of symptoms (13). There are no differences between depressive disorder and adjustment disorders when symptom severity or social functioning is measured (79). Of patients in the working population on sick leave due to adjustment disorders, the majority return to work after only three months of treatment (31). The prevalence of adjustment disorders and depression was studied in a community sample and an overall prevalence of 9% was reported for the two diagnoses (80). Adjustment disorders are common in primary care with rates ranging from 1% to 18% in patients seeking for mental health problems (81, 82). Adjustment disorders and ED can be considered similar conditions, but ED demands a longer exposure to a stressor, six compared to three months. However, in more long-lasting cases, a new category has recently been added in DSM IV called “chronic adjustment disorders” (56).

1.4.6. Acute stress disorder

Acute stress disorder (ASD) describes acute stress reactions that occur from 48 hours to less than a month after exposure to a traumatic event, and is used before it is possible to diagnose PTSD (83). ASD is limited to severe acute stress reactions that are not necessarily precursors of PTSD. The primary difference between ASD and PTSD is the duration of symptoms, and the ASD focus on dissociative reactions to the trauma. ASD includes symptoms during the period from two days to four weeks post-trauma, but PTSD can only be diagnosed after four weeks. The diagnostic criteria of ASD require an exposure to a catastrophic stressor, and an intense emotional reaction. The traumatic event is persistently re-experienced and there is avoidance of stimuli that can revive the trauma. Furthermore there are marked symptoms of anxiety or increased arousal, and the disturbance causes significant distress or impairment. ASD focuses on anxiety responses and neglects other distressing emotional reactions which can lead to misdiagnosis, such as adjustment disorders. ASD is different from adjustment disorders where the stressful events may not necessarily be traumatic, and the diagnosis can be made immediately after the trauma (83).

1.4.7. Post-traumatic stress disorder

In the mid-twentieth century a clinical description began to appear, as physicians described a syndrome among combat veterans and civilians including many of the current PTSD symptoms (15). The PTSD criteria include re-experiencing, avoidance/numbing and hyperarousal (84). It also includes the possibility that exposure to overwhelming stress may precede the onset of clinically significant and persistent alterations in cognitions, feelings, and behaviour. Epidemiological studies have confirmed that exposure to extreme stress may be followed by long-lasting psychopathology (85). The criterion of extreme stress exposure in the PTSD diagnosis remains in DSM-5, although debated (84). The lifetime prevalence of exposure to traumatic events was 21%; women had a lower risk but a significant higher risk of meeting the lifetime criteria of PTSD (86). Traumatic events and PTSD were strongly associated with other mental disorders. PTSD patients were shown to have cognitive impairment such as executive function deficits, similar to ED (87, 88). PTSD, ASD and ED include a criterion of identifiable external stressors, private or at work. ED is a result of a continuing period of high stress level in contrast to PTSD and ASD, which are caused by a stressful event (83, 89).

1.5. Other related symptoms and disorders

1.5.1. Fatigue and sleepiness

Fatigue is reported by one-fifth of primary care patients (90); it includes lack of energy, mental exhaustion, poor muscle endurance, delayed recovery after physical exertion, and non-restorative sleep. Fatigue can be classified as secondary to an underlying medical condition, and may last between one and six months. Physiological fatigue is defined as an imbalance in the routines of exercise, sleep, diet or other activity not caused by a medical condition and can usually be relieved with rest. Patients with fatigue report that they are unable to complete specific activities because of lack of energy or stamina. Fatigue in depression is a more global problem, being unable to do anything. Sleepiness is the impairment of the normal arousal mechanism, and is characterized by a tendency to fall asleep (90).

1.5.2. Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is characterised by unexplained severe, disabling physical and mental fatigue, and accompanied by other symptoms such as musculoskeletal pain, sleep problems, impaired concentration and headaches, similarly to ED (91). The fatigue is a profound feeling of lack of energy which becomes exacerbated by exertion. Lack of energy should be distinguished from sleepiness that instead could indicate a major sleep disorder, or lack of interest and pleasure that could indicate depressive syndrome (92). Frequent somatic symptoms in chronic fatigue syndrome can be swollen or tender lymph nodes, sore throat different from ED, but arthralgias and especially headaches are similar to ED. CFS requires a duration longer than six months and is not relieved with rest (90). The onset is often sudden and could be related to viral infections or injury, or a period of high stress level, differences from diagnostic criteria for ED and other mental health problems have to be considered.

1.5.3. Fibromyalgia

Fibromyalgia is a condition of chronic widespread pain and tenderness to palpation (93). Pain symptoms include generalised aching and stiffness of the trunk, hip and shoulder, or generalised aching and muscle weakness. Several characteristic symptoms are associated with fibromyalgia, such as fatigue, sleep disturbances, mood disturbances (93), and these symptoms are similar to ED. The fatigue is similar to that experienced in CFS. Depressive symptoms and symptoms of anxiety are frequent (93).

1.6. The rationales of the studies

Considering the rise in sick leave rates due to mental health problems, further clinical research with regard to different aspects of stress-related mental health problems was needed. The

patients with those mental health problems were seeking for help, and the problems were shown to be serious, with long-lasting consequences for the individuals and for society. When the ED diagnosis was introduced into clinical practice very little knowledge existed with regard to the clinical characteristics of the patient that fulfilled the ED criteria. Knowledge of other conditions such as burnout, depression and adjustment disorder could initially be applied, but the need for increasing knowledge of this clinical condition was obvious. Questions with regard to symptoms, course of illness, co-morbidity and early detection became relevant. There was also a desire to find tools for early detection. The clinical work and the large patient registry that was initiated at ISM, made it possible to study the clinical characteristics of patients with ED. A separate study with the aim of studying stress level in primary care patients was also initiated, which made it possible to study primary-care patients with ED. Furthermore, a longitudinal study of the working population was performed, to screen for stress and mental health problems in employees at work, and a self-rating instrument for ED (s-ED), developed at ISM was tested.

2. AIM of the THESIS

The overall aim of the thesis was to study patients fulfilling the criteria for ED with respect to identification, characterisation and course of illness and some properties of an instrument for self-reported exhaustion disorder (s-ED).

The specific aims of Papers I-IV were:

Paper I. To explore the course of mental symptoms related to sex and age in patients who fulfil the ED diagnosis and to study predictors of recovery.

Paper II. To study the prevalence and course of somatic symptoms related to sex and age in patients with ED and to study predictors of recovery.

Paper III. To clinically assess the prevalence of ED among primary care patients with self-reported exhaustion and/or burnout, and to compare patients that meet the ED criteria with those who do not, with respect to mental and somatic symptoms.

Paper IV. To investigate how s-ED relates to other self-rating scales of mental health and work ability and to study the predictive validity of s-ED regarding sick leave.

3. METHODS

3.1. Study design and subjects

The participants included in this thesis are recruited from three different sources. The patients studied in Papers I and II are outpatients in VGR that have been referred to a specialist clinic for exhaustion disorder. Register data from these patients are included in two of the studies (Papers I and II). The other two studies consist of primary care population (Paper III), and working population, mainly health care workers (Paper IV). For more detailed information on respective study population and study design, see table 3.

Table 3. Study design and subjects included in Paper I-IV

	Study design	Inclusion criteria	Exclusion criteria	Subjects
Paper I Course of mental symptoms in patients with stress-related exhaustion: does sex or age make a difference?	Longitudinal explorative study	Stress-related exhaustion with no apparent somatic disorder or abuse that could explain the exhaustion, and a maximum duration of current sick leave of six months. Only patients who fulfilled the diagnostic criteria for ED (table 1), were included	Somatic diseases, generalised pain, thyroid disease, vitamin B-12 deficiency or obesity that could explain the exhaustion and alcohol abuse or serious psychiatric diagnoses other than depression and anxiety. Patients who fulfil the criteria for chronic fatigue syndrome , and fibromyalgia were not included	232 patients, 158 women and 74 men
Paper II Prevalence and course of somatic symptoms in patients with stress-related exhaustion. Does sex or age matter?	Same as Paper I	Same as Paper I	Same as Paper I	228 patients, 156 women and 72 men
Paper III Exhaustion disorder in Primary care patients 18 to 65 years of age.	Cross-sectional study	Primary care patients aged 18-65 regardless of reason for appointment	Problem to understand the Swedish language and/or an acute severe disorder	587 patients, 377 women and 210 men
Paper IV Self-reported exhaustion: a possible indicator of reduced work ability and increased risk of sickness absence among human service workers.	Longitudinal cohort study	Employed > 50%, one year or more, 3717 subjects (62%) participated at baseline, and were the target population for the follow-up two years later, response rate of 85% (n= 2683)	Participants on sick leave or parental leave at baseline were excluded	2683 employees, 2286 women and 397 men

The participants included in Papers I and II, derived from the same patient registry from the specialist clinic. This register includes data of 1225 patients that were the basis for the patients included in Paper I, and of 1678 patients in Paper II. The reason for this difference in number of patients was that selection of patients for Paper II was performed approximately 1½ year later, and more patients were thus available to be included from the patient registry. Of these around 900 in Paper I and 1200 in Paper II respectively, were offered consultation. The major reason for not offering the patient consultation at the clinic was mainly somatic or other mental disorders than ED, or longer duration of sick leave than six months. Patients

accepted for consultation were asked about participation in the register and in different studies (figure 2).

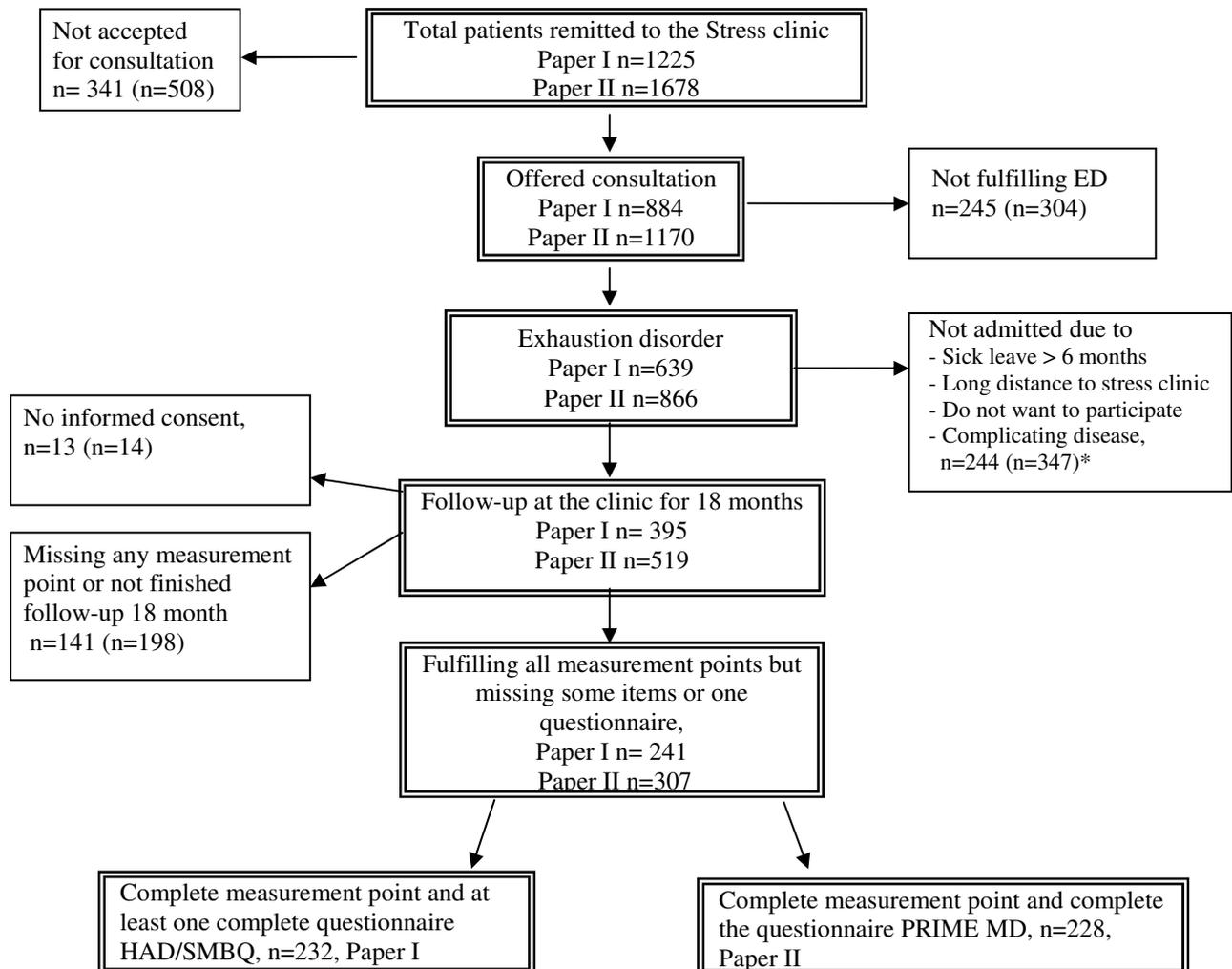


Figure 2. Flow chart of the influx of patients to the specialist clinic that forms the base for the patient population included in Paper I and II. Inclusion of patients is based on available data on the questionnaires used in the studies. When appropriated information related to Paper I is written first, followed by information related to Paper II in bracket signs. Thus, patients that had completed either of the Hospital anxiety and depression scale (HAD) subscales or SMBQ, were included in Paper I, and those that had completed Primary care evaluation of mental disorder (PRIME MD), were included in Paper II.

Notably 174 patients were included in both Paper I and II. For complete baseline data, see Paper I, table 2, and Paper II, table 1. In Paper I there were no sex differences with regard to baseline characteristic, but in Paper II a higher proportion of women reported high education 76% compared to 62% of men ($p=0.039$), and 89% of men compared to 78% of women

reported co-morbid anxiety ($p=0.042$). In Papers I and II use of antidepressants was reported in 29%, and 28% respectively.

The participants included in Paper III are a sub-population of a large cross-sectional study with the overall aim of studying stress load and exhaustion in primary care patients. In short; five geographically spread primary care health centres in the VGR were recruited by advertisement for participation in a study of stress in primary care patients. The initial study population included primary care patients seeking for any reason during 2-5 consecutive days in the spring, and in the autumn 2009, women 64% $n=377$, and men 36% $n=210$, aged 18 to 65, mean age 42 years. The majority, 67% were married, and 69% had employment (figure 3). For further characteristics, see table 1. In Wiegner L, Hange D, Björkelund C, Ahlborg G.jr. Unpublished data 2014.

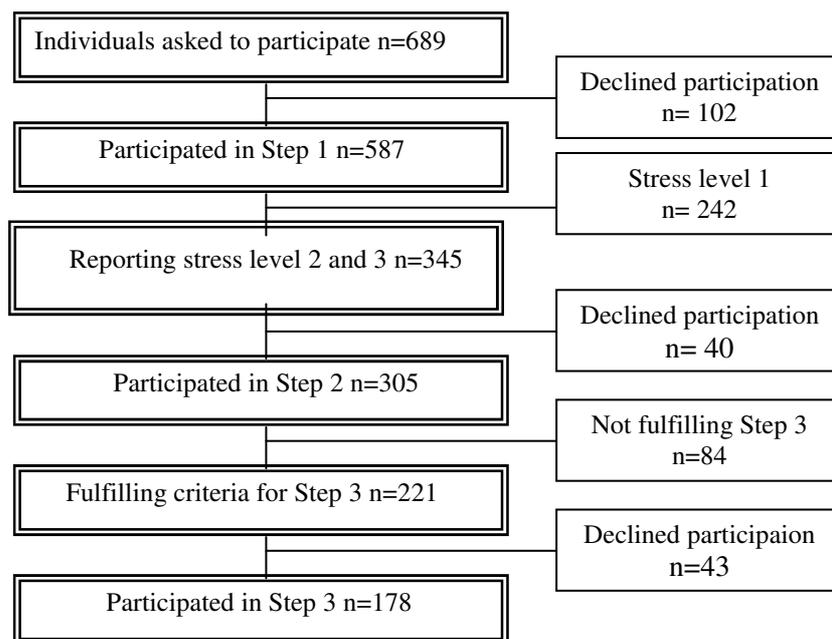


Figure 3. Flow chart of the primary care study, Paper III includes step 3. In the first step, step 1, the patients were screened for stress by a single stress item, and those who scored positive were defined as stress level 2 or 3, depending on positive items answered. Patients with stress level 2 or 3 were measured by SMBQ, s-ED and HAD in step 2. In step 3, clinical examination and test of ED diagnosis were offered those who scored positive on SMBQ, or s-ED

Among those participating in step 3, 78% were females, and the total group reported in mean 14.1 (SD 3.0) years of education, and 65% were employed. For complete demographics, see Paper III, table 2.

The study population in Paper IV consisted of 6000 employees at work, randomly selected from lists of employees working at least 50% of full time, and employed for at least one year in the VGR. Of those invited 3717 (62%) answered the questionnaire at baseline, and they were the target population for follow-up two years later. The final study population, after exclusion of those on sick leave or parental leave at baseline, comprised 2683 occupationally active persons, and 85% were females. The mean age for the total population was 47.2 years (SD 9.8); there was no significant sex difference. For baseline characteristics see Paper IV, table 3.

3.2. Study procedures

Paper I and II includes data from patients with ED that during the years from 2004 to 2010, were referred from primary health care centres or occupational health service centres in VGR, to a specialist clinic exclusively treating patients with exhaustion disorder. All patients that were offered treatment fulfilled the ED criteria. The treatment at the clinic was followed up for a maximum of 18 months during which different measures were conducted forming the base for the patient registry that was used in Papers I and II in this thesis. The reason for not admitting a patient at the clinic could be sick leave longer than six months, too long distance to travel to the specialist clinic with respect to the illness, did not want to continue for other reasons, or complicating diseases. After one consultation these patients were re-referred with advice on further treatment and rehabilitation. The final study population of patients fulfilling the diagnostic criteria for ED in the respective study was dependent on the completeness of data of the required measures to be used in the study (different questionnaires) (figure 2). Before the first consultation, and then during 3, 6, 12 and 18 month follow-ups, the patients filled in several questionnaires described in detail in table 4. The physician carried out a diagnostic procedure at the first appointment, and the PRIME MD patient questionnaire was used as a support to identify depressive and/or anxiety disorders. Different anxiety disorders were set when present, but in Papers I-III general anxiety, unspecific anxiety and panic disorders were combined and referred to as “any anxiety”. Different treatments had been initiated by the general practitioner (GP) before the consultation at the specialist clinic, but complete information on this is not available. The patients were offered individualised MMT custom-made for mental health problems as was described earlier, see Paper I.

The study in Paper III was conducted in three different steps. In the first step a screening form was distributed to all patients that had a booked appointment for any reason with a physician

at any of the five centres invited. The screening form included a single-item question measuring symptoms of stress with five possible answers, see table 4. Patients who reported elevated levels of stress were asked to participate in step 2, and fill in three self-report mental health scales s-ED, SMBQ, and Hospital anxiety and depression scale (HAD). Those with affirmative answers indicating self-rated exhaustion on s-ED and/or high levels of burnout according to SMBQ were asked to participate in step 3, and were invited to a clinical examination and diagnosis, performed by one of two senior physicians from ISM. The results from step 3 are reported in Paper III in this thesis. Results from steps 1 and 2 will be described elsewhere (Wiegner L, Hange D, Björkelund C, Ahlborg G.jr. Unpublished data 2014).

In Paper IV data were collected by a mailed questionnaire to participants at baseline in 2004, with a follow-up two years later.

Table 4. Measurements included in Paper I-IV

Measurements	Included in	Description of the questionnaire
The self-rated exhaustion disorder (s-ED)	Paper III and IV	A self-rating scale of four items based on the diagnostic criteria for ED (see table 1, and 2). The response alternatives “Yes, a little” and “Yes, pronounced” to the fourth item were used to discriminate between “light/moderate” and “pronounced” s-ED
The Shirom Melamed burnout questionnaire (SMBQ) (49)	Paper I and II, baseline and follow-up, Paper III and IV, single measure	Includes 22 items and four subscales: “burnout”, “tension”, “listlessness” and “cognitive weariness”. The mean score 4.0 or more was used as cut off for burnout in Paper I and II, and 3.75 or more in Paper II and IV*
The hospital anxiety and depression scale (HAD) (94)	Paper I and II, baseline and follow-up, Paper III and IV, single measure	Includes 14 items, seven items in two subscales. The sum score of each subscale is used to classify “non-cases” (0–6), “possible cases” (7–10), and “cases” (>10). In Paper I and II, a sum score of 11 or more was used as cut off for probable depression and in Paper III and IV, a sum score of 8 or more was used for possible cases
The primary care evaluation of mental disorder (PRIME MD) (95)	Paper I and II, baseline and follow-up, Paper III	A self-rated patient questionnaire of 28 items, Yes or No, including modules of somatisation, depression and anxiety**. Affirmative responses were followed-up according to (DSM IV) (56), for depression and anxiety disorders
The single stress item from Nordic questionnaire for psychological and social factors at work (QPSNordic) (96)	Paper III and IV	The participants are asked to rate stress levels according to following statement: “Stress means a situation in which a person feels tense, restless, nervous or anxious or is unable to sleep at night because his/her mind is troubled all the time. Do you feel this kind of stress these days.” Five possible answers were given: “not at all”, “just a little”, “to some extent”, “pretty much” and “very much”. Paper III included 3 levels: the 2 items of low stress= level 1, the middle item = level 2, the 2 items of high stress= level 3. Paper IV included 2 levels: “pretty much” and “very much” indicating a high level, and the remaining indicating a low level of perceived stress
The short-form health survey (SF-36), single item (97)	Paper IV	A measure of self-rated general health with a single item: “In general, how would you describe your health?” From the five response alternatives, three categories were formed: very good (excellent/very good), good (good) or not good (fair/poor)
Work ability index (WAI) (98)	Paper IV	WAI includes seven items: current work ability compared to lifetime best, work ability in relation to job demands, currently diagnosed diseases, estimated work impairment due to diseases, number of days absent due to own illness over the past 12 months, personal prognosis of work ability 2 years from now, and mental ability related to daily work tasks. The maximum score is 49, and a score of 44–49 indicate excellent work ability, 37–43 good, 28–36 moderate and 7–27 poor (99). Work ability was dichotomized into “excellent/good” and “moderate/poor” categories
Sickness absence (SA14) and (SA60)	Paper IV	1. More than 14 days of ongoing full, or part-time sick-leave or sickness benefit (SA14), 2. a period of continuous sickness absence >60 days during the last 12 months (SA60)

* In Paper IV, additionally the SMBQ subscale burnout with cut off 4.0 or more was used

** The somatisation module included 12 items, mean values, grouping in four; 0, 1-2, 3-5 and 6 symptoms or more as dichotomy variable was used describing and following the population over time and for comparison

3.3 Measurements

3.3.1. Characteristics of participants

Information regarding characteristics in Papers I and II was collected by a postal questionnaire including baseline data as sex, age, and marital status, use of antidepressants, symptom duration and level of education, in Paper III by the questionnaire filled in before appointment with GP, and in Paper IV it was embedded in the postal questionnaire.

3.3.2. Self-reported exhaustion disorder

The self-reporting instrument for ED, s-ED, was developed at ISM and is based on the ED criteria. The purpose of the instrument is to capture stress-related problems early (table 5). The questions were formulated to promote sensitivity rather than specificity in relation to the clinical diagnosis. The classification of s-ED is in accordance with the classification used for diagnostic criteria for items A through D, but does not include criteria E and F (table 1), as these two items need to be assessed by a physician. To be classified as having self-rated exhaustion, a participant had to provide affirmative answers to the first, second and fourth items and meet four of the six conditions specified in the third item (table 5). The response alternatives “Yes, a little” and “Yes, pronounced” to the fourth item were used to discriminate between “light/moderate” and “pronounced” s-ED. This is another deviation from the diagnostic criteria, which give no option of grading the ED severity.

Table 5. The self-reported exhaustion disorder (s-ED) instrument which is based on the clinical diagnostic criteria for exhaustion disorder

1. Do you currently feel, and have you felt for more than two weeks, physically and/or mentally exhausted?

Answer: Yes or No

2. Do you consider this exhaustion to be caused by long-term stress exposure (that you have been exposed to great strain or experienced pressure for six months or more)?

Answer: Yes or No

3. During the last two weeks, have you experienced (*Answers: Yes or No*):

a) Concentration or memory problems?

b) Markedly reduced capacity to tolerate demands or to work under time pressure?

c) Emotional instability or irritability?

d) Sleep problems?

e) Physical weakness or being more easily fatigued?

f) Physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds?

4. Have the complaints above (questions 1–3) markedly decreased your well-being and/or your functional capacity (work ability, family life, leisure activities or in other important ways)?

Answer: Yes, to a great extent

Yes, somewhat

No, not at all

3.3.3. Other measurements

Other measurement used in this thesis are the SMBQ, HAD, PRIME MD, QPSNordic single stress item, SF-36 single item and WAI, detailed information on these self-rated measures is shown in table 4.

4. STATISTICAL METHODS

Several different statistical analyses were used in the different papers. The level of significance was set at $p < 0.05$ in all four papers. For detailed information see table 6.

Table 6. Statistical analyses included in Paper I-IV

Statistical analyses	Paper I	Paper II	Paper III	Paper IV
Descriptive statistics	- Count and percentages for categorical data - Mean (SD) for continuous data	- Count and percentages, mean (SD)	- Count and percentages, mean (SD)	- Count and percentages, mean (SD)
Testing differences between groups	- Independent samples t-test for continuous data - Pearson's chi square test non-parametric, for categorical data. - Mann Whitney U-test, non-parametric for continuous data	- Independent samples t-test - Pearson's chi square test non-parametric. - Mann Whitney U-test, non-parametric	- Independent samples t-test - Pearson's chi square test	- Independent samples t-test - Pearson's chi square test
Testing change over time	- Mc Nemar non-parametric test for two paired proportions - Cochran Q non-parametric test for several paired proportions	- Mc Nemar - Cochran Q - Wilcoxon's signed rank test, non-parametric paired-samples t-test, two repeated measures in one group, continuous data		
Associations between independent and dependent variables	- Cox regression with constant time at risk, bivariate and multivariate analyses	- Cox regression with constant time at risk, bivariate analyses		- Cox regression with constant time at risk, bivariate and multivariate analyses

5. ETHICS

All studies included in this thesis were approved by the Regional Ethical Review Board in Gothenburg, Sweden, and conducted according to the 1964 Declaration of Helsinki. Only patients who gave written informed consent to the use of their data for research purposes were included. Paper I-II: approval number 243-05, 2005, Paper III approval number 093-09, 2009 and Paper IV approval number 099-04, 2004 and 259-06, 2006. For an overview of the Papers included in the thesis see table 7.

6. RESULTS

6.1. Paper I

The main finding of this study was the long duration of mental illness. Over time the proportion of patients with high burnout scores significantly decreased, but after 18 months one-third of the patients still reported high levels of burnout. Symptoms indicating probable depression or anxiety (HAD subscore 11 or more), were initially reported by 34% and 65% of the patients respectively. These symptoms declined rapidly within three months and were present in only one out of 10 after 18 months, see Figure 4 a-c. The course of illness was not related to sex or age.

Figure 4a

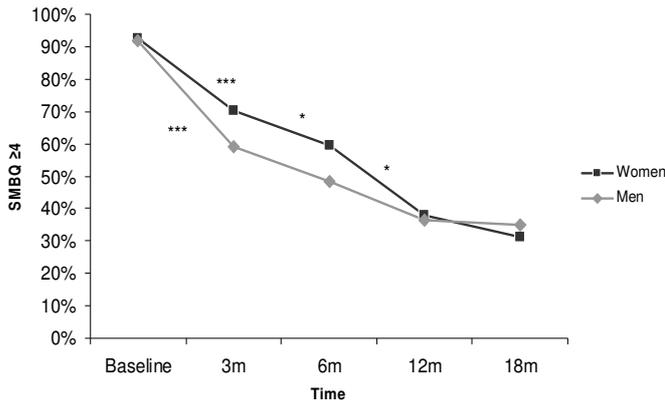


Figure 4b

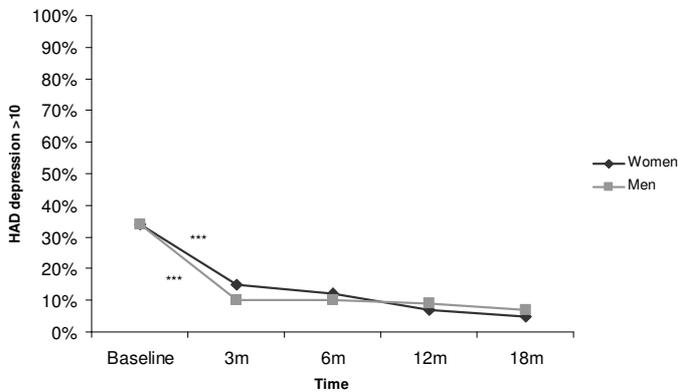


Figure 4c

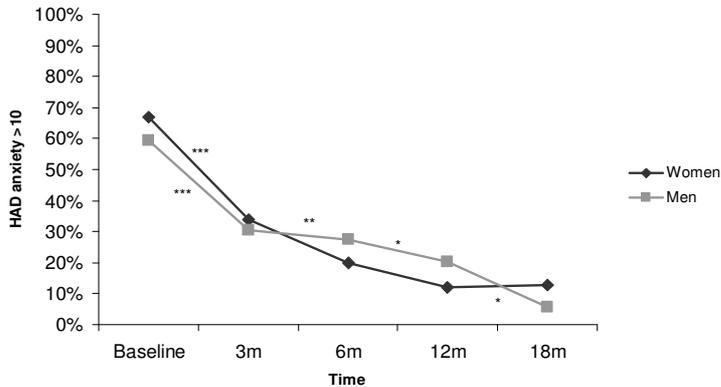


Figure 4a-c. a. Proportion (%) of male and female patients with exhaustion disorder scoring 4.0 or more on the Shirom-Melamed burnout questionnaire (SMBQ). Pairwise comparisons indicate that the difference between two adjacent time points are statistically significant (* $p < 0.05$ ** $p < 0.005$ *** $p < 0.0005$), separately for women (black) and men (grey). b. Proportion female and male patients with exhaustion disorder scoring 11 or more on the depression subscale of the Hospital depression and anxiety (HAD) scale. c. Proportion of female and male patients with exhaustion disorder scoring 11 or more on the anxiety subscale of the HAD scale

Further results from this study were that patients with ED showed a high burden of mental illness, measured both as co-morbidity and self-reported symptoms of burnout, depression or

anxiety. An important finding was that women and men did not differ in this respect and no differences were seen between younger (22-39 years), and older patients (40-64 years). In the total group clinical diagnosis depression was found at the first follow-up in four out of five, (any) anxiety in more than three out of four, and both depression and anxiety in two-thirds as co-morbid conditions. Prevalence of co-morbid conditions divided by sex is shown in figure 5.

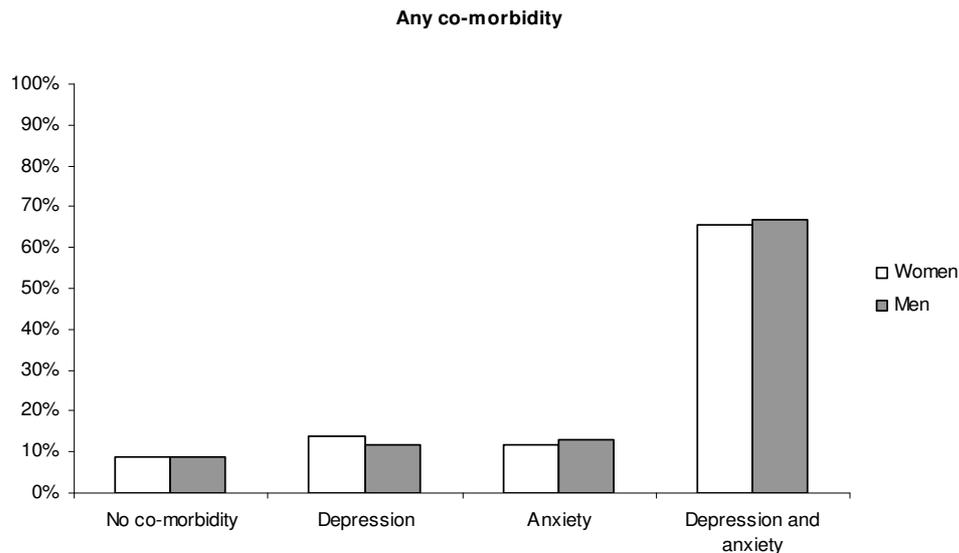


Figure 5. Proportion (%) of ED patients included in Paper I (N=232), that reported no co-morbid condition, co- morbid depression, or (any) anxiety only, or combined depression and anxiety at baseline

Several different factors were analysed as possible predictors of recovery from mental symptoms. It was shown that the only significant predictor was duration of self-reported symptom before seeking medical care. Thus, experiencing stress-related symptoms for a year or longer before seeking care predicted prolonged recovery, and there was no sex difference. A total of 129/224 or 58% of the patients reported that they had experienced symptoms for more than a year prior to seeking care (figure 6). Other plausible predictors such as antidepressant use or level of education did not predict recovery.

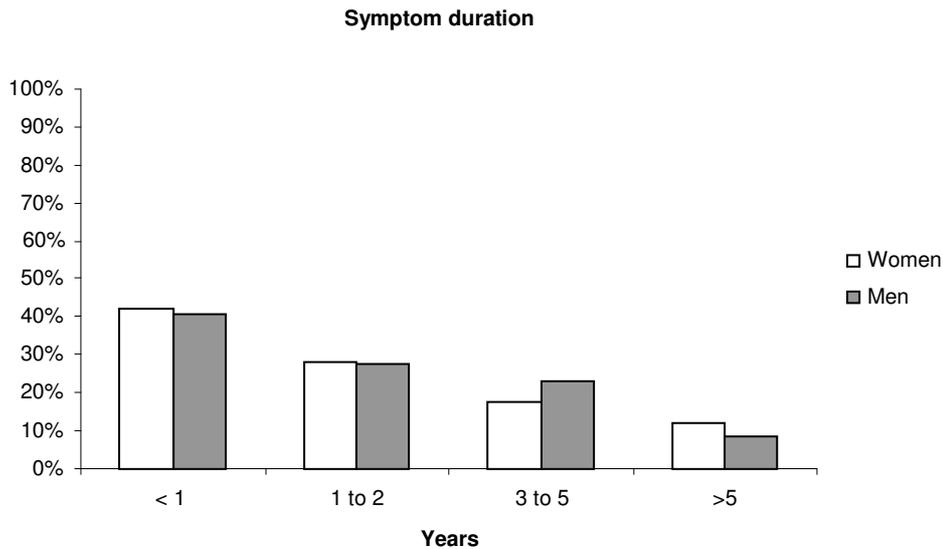


Figure 6. Proportion (%) of patients included in Paper I (N=224), that reported different duration of experiencing symptoms before seeking medical care; The four different groups are; less than one year, 1 to 2 years, 3 to 5 years, and more than five years

6.2 Paper II

The main finding was that the ED-patients reported multiple somatic symptoms, more than half reporting six such symptoms or more. Almost all patients reported at least one somatic symptom in addition to the core symptoms tiredness and low energy. Nausea, gas or indigestion were the most common symptoms reported by two thirds, a similar proportion reported headache and slightly more than half reported dizziness. The number of symptoms reported was significantly related to the severity of the mental health problems. Women and men reported similar burden of somatic symptoms and the only clear difference was seen at the 18-months follow-up when women reported more symptoms than men. There was a decline in the proportion scoring multiple symptoms to one-fifth at the last follow-up, and there were no significant differences between the sexes (see table 8, and figure 7). Neither did the different age groups among the patients differ in this respect (data not shown).

Table 8. Prevalence of self-reported somatic symptoms in patients with ED, using the 12 symptoms PRIME MD patient questionnaire. Four groups are formed depending on how many symptoms the patient has reported, from none (0) to the range of 1-2 symptoms, 3-5 symptoms or 6 symptoms or more at baseline and 18-months follow-up. Differences between sexes were tested by Pearson Chi-Square at baseline and 18-month follow-up showing no significant differences between the groups

No. of somatic symptoms	At baseline			At 18-month follow-up								
	Women n=156		Men n=72		Total N=228		Women n=156		Men n=72		Total N=228	
	%	n	%	n	%	n	%	n	%	n	%	n
0	1	2	3	2	2	4	16	25	21	15	18	40
1-2	12	19	10	7	11	26	26	41	39	28	30	69
3-5	40	63	46	33	42	96	35	55	26	19	33	74
6 or more	46	72	42	30	45	102	22	35	14	10	20	45

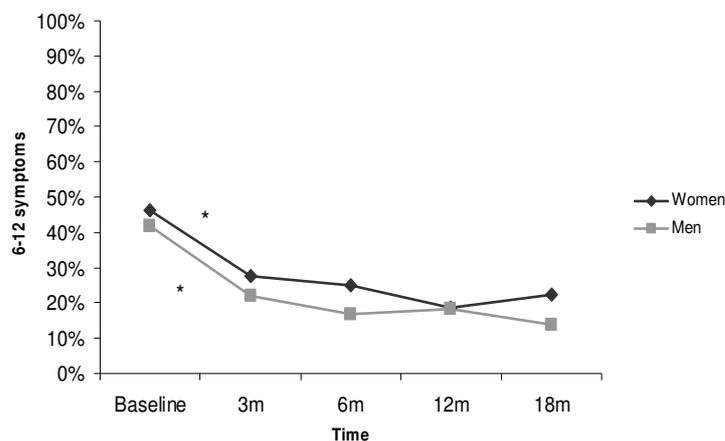


Figure 7. Proportion (%) of women and men with ED that reported six somatic symptoms or more at baseline and at follow-up after 3, 6, 12, and 18 months

*= significant decrease between two adjacent measurement points

The only differences with regard to single somatic symptoms at baseline were that men more often reported chest pain and problems during sexual intercourse and at 18 months women more frequently reported stomach pain. Pain in arms, legs and joints persisted at a relatively constant level in the group as a whole, at baseline 49% reported such pain compared to 43% at 18 months, which was not a statistically significant difference. However, symptoms of pain fluctuated on the individual level. Some patients or 13% (n=29) did not report pain problems at baseline, but did report these problems at the 18-month follow-up. Of those reporting symptoms at baseline, 39% had recovered and 61% still reported pain problems at 18-month follow-up. At 18 months with higher severity on HAD depression, the proportion that

reported pain in arms legs and joints rose. Older patients compared to younger reported significantly more pain in arms, legs or joints at all measurement points, no other significant age group differences was found. Lastly, among the plausible predictors available (sex, age, education, symptom duration, co-morbid depression), none was found to significantly predict recovery from multiple somatic symptoms. However, when applying a cut-off of three instead of six for multiple somatic symptoms; female sex was shown to be associated with longer recovery.

6.3. Paper III

The main findings of this study were that 29% of the patients invited to clinical examination were shown to fulfil the diagnostic criteria for ED. This corresponds to 9% of the total primary care study group. The ED criteria were strictly applied in the clinical assessment, and many patients did not fulfil the criteria due to other mental or somatic disorders. Further results were firstly that co-morbid depression and anxiety were common among the ED patients, and secondly that the burden of somatic symptoms was high. Thirdly, the clinical picture was similar among male and female patients. The only sex difference found was that the single symptom dizziness was more frequent among women. Fourthly, patients not fulfilling criteria for ED (non-ED) showed a similar burden of somatic symptoms, but fewer mental symptoms. However, half of them reported pronounced exhaustion on s-ED, and this group showed similar levels of somatic and mental symptoms to those of the ED patients, except for less co-morbid anxiety. Finally, there were a higher proportion of smokers among ED patients compared to non-ED.

6.4. Paper IV

The main finding was that s-ED corresponded well to other measures of mental health. With increased severity of s-ED the scores of symptoms of depression, anxiety and burnout rose (table 9).

Table 9. The relation between increasing severity of self-rated exhaustion disorder (s-ED) and increased likelihood of reporting self-rated depression, anxiety and burnout expressed as prevalence ratios (PR) with 95% confidence intervals (CI)

	Depression ¹ N=2571		Anxiety ² N=2559		Burnout ³ N=2453	
	%	PR (95% CI)	%	PR (95% CI)	%	PR (95% CI)
No s-ED	7	1	23	1	14	1
Light/moderate s-ED	39	5.9 (4.7-7.4)	76	3.4 (3.0-3.8)	78	5.5 (4.8-6.2)
Pronounced s-ED	70	10.7 (8.9-12.9)	87	3.8 (3.5-4.2)	88	6.2 (5.5-6.9)

¹A score of ≥ 7 on the depression subscale of the Hospital anxiety and depression scale

² A score of ≥ 7 on the anxiety subscale of the Hospital anxiety and depression scale

³ A score of >3.75 on the global Shirom-Melamed burnout scale

Furthermore, the s-ED scale predicted sick leave two years later with the highest risk estimate for the more severe condition (i.e. pronounced s-ED), confirming the predictive properties of the scale, see table 10. For comparison, pronounced ED showed a stronger prospective relation to sick leave than the subscale burnout on SMBQ (data not shown). Women and men reported similar rates of 14 days of ongoing sick leave or sickness benefit (SA14), but women reported more 60 days of sick leave during the last 12 months (SA60). A history of long-term sick leave at baseline did not change the estimates notably. In men the two s-ED categories combined resulted in approximately six times the risk of reporting current sick leave, and the corresponding estimates for women were nearly twice the risk of SA14.

Table 10. Self-rated ED at baseline and adjusted relative risk (RR) with 95% confidence interval (CI), for sickness absence (SA14^a or SA60^b), at follow-up

Self-rated ED 2004	SA14 ^a		SA60 ^b	
	RR ^c	(CI)	RR ^d	(CI)
No s-ED	1		1	
Light/moderate s-ED	1.6	(1.0–2.5)	1.6	(1.0–2.7)
Pronounced s-ED	2.7	(1.8–4.0)	3.4	(2.3–5.2)

^a Participants reporting more than 14 days of ongoing full- or part-time sick leave or sickness benefit at follow-up

^b Participants reporting a period of more than 60 days of sickness absence during the last 12 months at follow-up

^c Adjusted for age (>54 years), marital status (single), length of education (short), and physical activity (sedentary lifestyle or light physical activity)

^d Adjusted for physical activity (sedentary lifestyle or light physical activity)

Further findings were that sixteen percent reported self-rated exhaustion according to their answers to the s-ED questions. The responses to the fourth s-ED item showed that 10% of the women and 7% of the men were classified as having light/moderate, and 7% of women and

6% of men were classified as having pronounced s-ED. There were no statistically significant differences between the sexes. Fourteen percent reported symptoms of depressed mood, higher among men (18%). Symptoms of anxiety were found in one-third, similar for women and men. With increasing severity of s-ED, the likelihood of reporting symptoms of depression, anxiety and burnout (table 8), and poor work ability increased. This pattern was similar for women and men, except that men with light/moderate s-ED were more likely than women in this category to report a depressed mood, approximately two-thirds compared to one-third, which was statistically significant. Lastly, fourteen percent of the total group reported that they had visited and been treated by a physician or psychologist due to mental health problems at follow-up. This proportion increased with higher severity of s-ED reported at baseline. Those who had sought and received treatment were more likely to report sickness absence at follow-up with no sex difference. For those not being treated during the last two years, the results were similar as for the total population.

7. DISCUSSION

The main findings of the thesis

The long-lasting course of mental symptoms in ED patients and the extensive co-morbidity with depression and anxiety were important findings of this thesis. Another striking finding was the heavy burden of somatic symptoms associated with ED, and that pain in arms, legs and joints, in contrast to the other symptoms assessed, seemed to persist in most cases over the follow-up period of 18 months. Surprisingly few differences were found between women and men in this respect or between younger and older patients. Symptom duration was the only predictor of recovery from mental symptoms, but no factor was found to significantly predict recovery from somatic symptoms among those evaluated. In primary care patients that reported moderate or high stress level and self-reported exhaustion or burnout, approximately one third fulfilled the diagnosis of ED. A similar burden of mental and somatic symptoms was seen in these patients as was reported in the patients referred to specialist care at ISM. Even in non-ED patients that self-reported pronounced exhaustion a high burden of mental and somatic symptoms was present. In the study of a working population, more than one of six employees met the criteria for self-reported exhaustion. The s-ED instrument used to capture feelings of exhaustion corresponded well to established measures of mental health and work ability, and was shown to have good predictive validity for sick leave two years later.

7.1 Exhaustion disorder, characteristics

The most typical ED patient seen both in the study from specialist care and the study of primary care was a woman slightly over forty years of age and with high education. The majority of the patients in specialist care were married or co-habiting, more often so compared to the primary care patients. In all studies most patients reported a high level of education, indicating socioeconomic resources above average. In such a population one would expect a lower than average risk of mental health problems and disability (100). This means that the present findings could be less generalizable in populations with lower socioeconomic resources, which is a limitation.

Co-morbidity seems to be common in individuals with mental health problems. Thus, the majority of ED patients in both specialist care and primary care reported extensive co-morbidity of depression and anxiety. Patients that did not fully fulfil the ED diagnosis but reported pronounced s-ED showed similar high prevalence of co-morbid depression however, anxiety was more prevalent in ED patients. It is noteworthy and seems to be a general characteristic of this type of severe stress-related mental condition that the exhaustion is often accompanied by symptoms of depression and anxiety. It could illustrate that the feelings of loss of control and energy, along with cognitive failure as a result of prolonged exposure to stress, could give increasing problems of anxiety and depression. This issue has been touched upon in previous research on burnout, a related condition, where a considerable overlap with depressive symptoms is also seen (68). This finding could probably also be applicable to ED. There was a similar picture of increasing symptoms of depression and anxiety with increasing severity of self-reported ED in working population. Furthermore it is not uncommon in other populations as general population and in primary care (39, 41, 42).

Both specialist care patients with ED, and primary care patients that self-reported ED showed similar high burden of somatic symptoms, and the number of symptoms rose with increased mental health problems. Headaches and chest pain were more prominent in specialist care patients that perhaps could indicate that they represented the most severe cases. There are several studies showing association between mental health problems and somatic symptoms (101-104). In the Whitehall II study of civil servants in London a linear association between emotional distress and number of somatic symptoms was shown (101). In a global study of more than 25 000 consecutive primary care patients by WHO, increasing somatic symptoms were followed by a higher level of mental health problems (102). Kroenke and co-workers

reported that primary care patients seeking for somatic symptoms and indicating depression and/or anxiety, reported a mean of more than six somatic symptoms, and without mental problems three symptoms on average (103). The level of symptoms found among those with mental health problem was similar to the present findings in specialist care. An explanation for the finding that ED patients report all types of somatic symptoms could be that ED could lead to a general increase in the tendency to experience and report symptoms of minor physical health problems. It could also be that ED is secondary, and that multiple somatic symptoms appear as primary symptoms in distressed patients. Furthermore a cross sectional primary care study from the Netherlands showed that patients with distress reported different types of somatic symptoms more often than patients without distress (104). It seems clear that mental health problems and somatic symptoms have to be considered simultaneously in ED patients to get a holistic view of the total burden of illness.

7.2. Course of illness in exhaustion disorder

There was a pronounced decline of mental symptoms during the first three months in specialist care patients, and the decline continued but to a lesser degree thereafter. The same pattern was described in a study from the Netherlands where patients on sick leave with work-related stress improved considerably with respect to symptom and sick leave during the first months of treatment, thereafter complaints remained approximately stable although sick leave was further reduced (33). In the present study symptoms of depression and anxiety resolved within 12 to 18 months, but burnout persisted in one-third of the cases. One important factor for this initial decline of symptoms could be that the patient value that they were taken care of by a specialist clinic, now given the opportunity to better focus on recovery and the treatment offered. Another important factor could be the part of the MMT treatment that is related to teaching the patients to structure their life in decreasing the stress exposure and increasing resources such as improved sleep and daily physical activity. The long-lasting duration of burnout seen in this patient group needs to be highlighted. Shirom and co-workers reported that burnout could be long-lasting regardless of sample, cultural context or length of follow up (48). A study of middle-aged women at work aiming at identifying developmental patterns of burnout, and to determine if work-related and individual factors were associated with concurrent changes in burnout, showed four different patterns during a 9-year period (105). Thus, the pattern of symptom of burnout can differ considerably from high levels followed by recovery, increasing levels, increasing and diminishing levels, or stable high or low levels during several years. Less than half of the study group had recovered after nine years. The

reason for the long period of illness was shown to be associated with stressors still being present, or that new stressors have arisen leading to persistent burnout symptoms, an explanation that also could be suggested in specialist care (105).

The underlying mechanism for ED and the persistence in symptoms is still poorly understood. It has been shown that personality traits such as neuroticism are associated with burnout and this could probably also contribute to persistence in some cases (11). Another suggestion is that prolonged stress exposure has negatively affected brain function (106). Impaired cognitive function on neuropsychological testing has been seen in patients with exhaustion (28, 107), and a recent follow-up study showed persistence of lower cognitive performance than expected after two years (29). A fairly recent study also showed that patients on long-term sick leave due to work-related stress showed different brain activation pattern, with a slowed response and reduced frontal activity during cognitive demand task that differed from both patients with depression and from healthy controls (108). This supports the theory that there might be some pathological processes going on in the brain in patients with ED that could explain the long recovery time. Further studies are needed to explore this plausible underlying mechanism. Questions could be raised if the patients were burnout cases even a long time before the actual stressors appeared. From the patient history (clinical observation) we have no reason to believe that this was the case; however we have not specifically addressed this question in our studies.

Symptom duration was the only predictor of recovery from mental symptoms in specialist care. Fifty-eight percent of the patients reported that for a year or more they had felt similar symptoms as those they were seeking for. We have reason to believe that a considerable proportion of these patients have sought for help, once or frequently before the first appointment explored in this study. The reason for the late detection of the health problem could be questioned. Perhaps the patients were not aware of their situation. It could also be that those that sought for help, the symptoms were not fully understood by the health care provider.

The multiple somatic symptoms were resolved with MMT designed for mental health problems. In the general population the majority of somatic symptoms resolve within a few weeks but in a quarter of the cases there is persistence for years (109). Musculoskeletal complaints are more persistent than other somatic symptoms (110). The persistence could be

due to lack of adequate treatment, a specific stressor still being present, or the appearance of new stressors maintaining pain. Exposure to stressors was shown to be related to increased pain intensity, the body's pain threshold decreased and the pain signalling pathways became increasingly sensitive (6). Co-morbid depression could lead to more resistant symptoms of pain (111), which was also shown in the present study.

No predictor tested, such as sex, age or co-morbid depression, was found to predict recovery from somatic symptoms. This could be due to the multiple symptoms being too heavy to be influenced by the mild depressive symptoms or by the other predictors. It could also be due to the endpoints chosen. When using cut-off three instead of six that was cut-off level used for multiple somatic symptoms, female sex was shown to predict persistence.

Depression has, in previous research, been shown to be an important factor for recovery. Thus, co-morbid depression was associated with disability pension in a Norwegian population study, and if combined with anxiety the estimates became higher (112). In primary care patients that were treated for depression, a lower severity or complexity of the symptoms predicted recovery (113). Different from this, among ED patients in specialist care co-morbid depression did not predict recovery of neither mental nor somatic symptoms. Perhaps the heavy symptoms of ED were not possible for the mild or moderate depressive symptoms to influence. Antidepressants did influence on the course of mental symptoms. One reason could be that the long-lasting pronounced symptoms of burnout including fatigue and cognitive problems were not within the reach of antidepressants.

In working population individuals that self-reported ED, one-third had sought for help and been treated during the last two years. These individuals showed higher risk of sick leave. One could suspect that the severity of symptoms was not fully understood by the health care provider or that they had been offered inadequate treatment.

Thus, ED was shown to have a long-lasting course of illness with extensive co-morbidity with depression and anxiety, and no sex or age group differences. This implies that ED must be considered a severe health problem that has to be dealt with in time to avoid worsening problems and long lasting sick leave. Symptom duration was the only predictor of recovery from mental symptoms and efforts has to be done for early detection. Self-reporting ED was

also shown to be a severe health problem with increased risk of future sickness absence in working population.

7.3. Sex and exhaustion disorder

Women were overrepresented among both the specialist care- and primary health care patients diagnosed with ED, but we found marginal sex differences when looking at the clinical picture and course of illness. It seems that when the problem has once developed, sex has no bearing on the course of the illness. Epidemiological surveys have documented higher rates of depression and anxiety in women (114, 115). A cross-national study of gender and lifetime risk of mental disorders by WHO, showed an overrepresentation of women (116). However, sex differences with regard to prevalence of depression were shown to have diminished in some countries. This was explained by increased female participation in society in later years, measured as higher education levels and higher employment rate that promote improvements in mental health. This change in gender roles could perhaps be part of the explanation of the absence of sex differences in mental health problems in the present studies including patients with high education. However, there were more females that were remitted for consultation. Furthermore, Maslach and co-worker reported that sex had little impact on burnout in a working population, and that the only consistent difference was that men score higher on cynicism (11). In line with this, no sex difference of self-reported exhaustion and burnout was seen in the working population included in this thesis, although data is insecure due to low number of men. Thus, sex might not be of such a large importance when it comes to prevalence of burnout and related mental health problems. With regard to symptoms and course of illness studied in specialist care and primary care populations we found no sex differences. One could suspect that in severe cases as the present patients, potential sex differences could diminish. Socioeconomic factors could also be important in this respect, and since the majority of the patients were highly educated this, together with other socioeconomic similarities, could lead to smaller differences.

In the specialist care sample there were no sex differences in reporting multiple somatic symptoms, and in both specialist care and primary care populations there were only a few differences regarding single somatic symptoms. The same reason for this observation could apply as for the mental health symptoms, that in clinical practice it can be expected that the burden of somatic symptoms is similar in men and women seeking for stress-related exhaustion. In line with the present findings a Norwegian population study showed that the

association between somatic symptoms and symptoms of depression and anxiety was similar in both sexes (117). Similar to this, a primary care study from the Netherlands showed that the level of mental distress rather than gender accounted for many somatic symptoms (104). There are different findings pointing in a direction that was expected; Women reported a higher number of somatic symptoms than men in a study of general primary care patients seeking for any reason in the US (118). In this study sexual problems only were more commonly reported by men (118). This was in line with the present study where a higher proportion of men reported sexual problems, however also showing an extensive co-morbidity with depression. At 18-months follow-up the sexual problems approximated to that level of what is reported by the female patients. This improvement was different from a study including patients with major depression that were on antidepressants, at follow-up after one month symptoms of depression was significantly improved, but little improvement was observed for the sexual symptoms (119). Perhaps improvement in the present study could be due to MMT designed for mental health problems was effective, or the longer follow-up time. Furthermore, men reported a higher prevalence of chest pain. In line with this, Stansfeld and co-workers reported in the Whitehall II study that chest pain was associated with psychiatric disorders in men but not in women (101). This indicates that chest problems in men should be considered a symptom not only of a somatic disorder but also of mental health problems. When signs of disorders have been removed underlying mental health problems have to be highlighted.

There was no sex differences in recovery from mental or somatic symptoms among patients with ED referred to specialist care. There have been some inconsistent findings in literature if recovery of mental health problems differs between men and women. In line with the present findings a review of prognostic factors for recovery in mental disorders including participants fully or partly disabled aged 18-64 years, showed that sex had no important effect on symptom recovery (120). Contradictory findings were shown in a population study of depression, where longer episodes were shown in women (121). From earlier studies and the present findings it can be concluded that sex seem to play different roles in various populations.

In the working population most of the results were similar for men and women indicating sufficient validity for both sexes. The observation that men in the non-ED and light/moderate ED categories reported more symptoms of depression compared to the corresponding women

was somewhat unexpected. There are indications from the literature that men tend to negate symptoms for a longer time before seeking for help (122, 123). However, we have no support for this assumption, and there was no sex difference in those reporting that they had sought for help during the last two years at follow-up. An unexpected finding was the high risk estimate for SA14 in men with s-ED compared to women, although no further conclusion could be drawn as data is unsecure.

7.4. Age and exhaustion disorder

Age does not seem to be of major importance when considering burden of mental or somatic symptoms or course of illness in patients with ED. Thus, both young and old patients in specialist care reported similar patterns in this respect. Age has been shown to be important in some, but not all, previous studies. In working-populations there was an increase with age in self-reported stress and exhaustion (96). However, similar to the present findings, a primary care study exploring major symptoms reported by the patients, showed no association between number of symptoms and age (124). Another primary care study of psychological disorders in patients 65 years or more, showed that older compared to younger (average age 40 years) patients were less likely to have a psychological disorder, and they reported significantly less severe psychological symptoms (125). This was different from the present study that included patients with a much narrower age range, which makes age comparisons difficult. Also differing from the present findings, a study of depression showed that patients aged 50 years or more reported a longer duration of illness (126). A review of prognostic factors of long-term disability due to mental disorder found in line with the previous study, strong evidence that 50 years or more was associated with continuing disability (120). Pain in arms, legs and joints was more prevalent among older patients in specialist care. Although there was a higher persistence rate in musculoskeletal complaints compared to other somatic symptoms, there is not complete consistency about influence of age on the prevalence of pain. Pointing in the same direction as the present finding, a general population study in Sweden showed an increase in chronic regional pain with age (127). Differently, a population study from Norway reported a lower prevalence of headaches and neck pain in the age group 50 years or more (128). To sum up, there are inconsistent results about the impact of age on burden of mental or somatic symptoms or course of illness. The present findings could be a result of a special group studied with high education and narrow age range.

7.5. Early identification of exhaustion disorder

ED patients in specialist care were severely ill and showed a long-lasting course of illness. Obviously it would have been an advantage of recovery if they had been detected earlier. The fact that the only predictor of recovery from mental illness, of the factors evaluated, was symptom duration before seeking medical care underscores the importance of early detection in preventing worse problems. The present primary care study showed that symptoms of burnout and exhaustion were quite common among patients of working age with a doctor's appointment for any health complaint. A Swiss study showed that patients seeking for somatic symptoms in primary care and who reported one or more psychosocial stressors that caused them considerable bother, had a 2.5 times higher risk of suffering from mental disorders after one year (14). It was clear that screening focusing on stress-related mental health problems including stressors, at least in selected groups of patients, should be considered in primary care.

A further step in attempting to identify this type of problems early would be to screen working populations exposed to potential stressors in the work environment. Occupational health services often use questionnaires designed for such purposes and the s-ED instrument was developed with such an aim, and proved to be useful in identifying health care workers at increased risk of sickness absence. S-ED has an advantage in grading the severity of the self-reported condition, but it was not designed to follow course of illness. The pronounced cases showed similar burden of somatic and mental symptoms to ED patients. This means that self-reported ED is an important finding that will have consequences for health, irrespective of ED diagnosis. The result is easy to interpret since the questions are based on the clinical criteria of ED, and not on scores as for example SMBQ. Compared to the single stress item used for primary screening in the large primary care study, s-ED captures broader information about the current symptoms, and about the patient's opinion that symptoms have developed in response to identifiable stressors. The latter could be used to initiate discussions about problem solving strategies. Moreover, s-ED was found to be easy to administer and for the patients to answer. Recently a more comprehensive instrument for detection and follow-up of ED was developed, Karolinska exhaustion disorder scale (KEDS), so far mostly used in clinical settings (69).

8. METHODOLOGICAL CONSIDERATIONS

The strength of this thesis is that ED was explored from different perspectives including burden of mental and somatic symptoms, and course of illness during treatment and follow-up for 18 months. Furthermore prevalence in primary care was studied and the self-reporting instrument for exhaustion, s-ED, was tested in primary care and working population. The ED diagnosis is fairly new and it was important to explore the usability in different clinical settings, although no validation study yet has been performed. ED seems to be a usable complementary diagnosis for severely ill patients with exhaustion caused by long-term stress exposure in specialist care. ED has advantages in a clearly clinical definition and also that it includes the stressors. The item about stress exposure is unspecific and gives an opportunity to focus on important problems in life and discuss problem-solving. However, it is evident that one diagnosis is not enough to describe all symptoms in ED. Depression and anxiety seem to be closely connected to ED, and could be an intrinsic part of the disorder, at least in the most severe cases.

ED was also found to be a useful diagnosis in primary care patients with exhaustion caused by long-term stress exposure. However, there are considerations; in the present primary care study a strict testing procedure for ED was used. The main reason for non-ED diagnosis was other mental or somatic disorders that could cause similar symptoms. Thus, a considerable proportion of those classified as non-ED among those clinically tested reported multiple somatic symptoms and mental health problems similar to the ED patients. In primary care there seems to be an important proportion of patients that suffer from high levels of stress that could have an impact on health irrespective of ED diagnosis. Consequently, the present non-ED patients deserve special attention as they should have a similar advantage of stress relief in addition to ordinary treatment.

Psychiatric diagnoses, unlike most somatic diagnoses, are based on different subjective symptoms (129). The cause of illness is often not fully understood and thus difficult to define. Mental diagnoses overlap, as can often be seen for depression and anxiety (39, 41). Jablensky and co-workers in 2002 wrote: "There is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders" (129). When describing mental health problems in specific patients, more than one diagnosis may be needed to thoroughly describe the symptoms of today's mental health problems. It has been suggested that using two different diagnostic systems could be more appropriate than today's system for describing mental health problems; one including

symptoms and the other the context or exposure affecting or causing the disorder (129). Diagnoses are made for the purpose of identifying and classifying different disorders or entities improving communication among physicians and ensuring comparability of research findings (129). Today's psychiatric diagnoses are gradually progressing and new diagnoses are emerging as knowledge increases.

8.1. Study design, population and procedure

In the two studies of the patients with ED at the Stress clinic (Papers I and II), data from the patient's registry was used. The registry was specially designed to follow the course of illness during a plausible long enough period of time to be able to explore the recovery from mental and somatic symptoms. Five measurement time-points were considered suitable for exploring changes in scores for burnout, depression and anxiety from baseline to the last follow-up at 18 months. The remission criteria to the clinic gave an opportunity to follow the course of ED in relatively pure cases i.e. there were no cases with very long sick leave or other complicating diseases when entering the study. Even though 18 months may seem like a rather long follow-up time, it is our experience that some patients need treatment even longer in order to recover fully. A longer follow-up would make it possible also to assess the stability of the mental health status after recovery from ED. However, to our knowledge there are no previous studies showing the course of illness in ED patients for such a long follow-up period as in these two studies.

The patients were recruited from those consecutively referred to the Stress clinic by other physicians. The majority reported high education. This was unexpected as individuals with high education have consistently been shown to have a lower risk of having to take sick leave (130). There are, however, some indications that mental health problems may not follow the well-known socioeconomic gradient (131). Individuals with high education are more likely to have jobs with higher responsibilities and stress exposure, which could increase the risk of developing mental health problems (11). Furthermore, it has been shown that individuals with high education were at higher risk of developing burnout (55, 132). One could expect that those individuals also have a high personal ambition level that could further worsen the symptoms. Even so, recruiting patients referred to specialist care could introduce a selection bias in relation to the general population of patients with ED seen in primary care, since persons with high education probably are more aware of available specialist care and more likely to ask for referral when becoming ill. Thus, the course of illness described in these

two studies may not necessarily be representative of all ED patients.

The collection of data for the two studies of ED patients in specialist care was ongoing for as long as six years. Thus, only a small number of patients could be accepted to the clinic each year. During this time there were changes in the sickness benefit regulations which caused problems for some patients in qualifying for sickness compensation. This could have caused a prolonged recovery time in a few cases, but we have no reason to believe that this influenced the overall results.

Another methodological issue that should be raised is the diagnostic procedure, particularly since the diagnostic criteria for ED were fairly new to the clinicians. A Scandinavian study reported that physicians use several different diagnoses for the same subjective symptoms (133). This seems to be a common problem and illustrates difficulties in how to classify symptoms, and problems in finding adequate diagnoses in cases with subjective symptoms. In the present study three physicians at the Stress clinic diagnosed and treated the patients, and efforts were made to diagnose and treat all the patients according to agreed criteria. There was an ongoing dialogue between the three physicians in order to maintain this throughout the period that data was collected. We believe that this served to minimise differences in the clinical handling of the patients. The treatment initiated by the physician who referred the patient to the specialist clinic may have varied but those who remitted to the specialist clinic were all still severely ill and thus in similar need of treatment.

The cross-sectional study of primary care patients (Paper III) was designed to estimate the prevalence of ED among patients of working age in primary care. For practical reasons primary care centres in the greater Gothenburg area were selected, which implies that the results may not be generalized to primary care populations in e.g. rural areas, or other sparsely populated areas. It may be seen as a strength that the clinically assessed study population was selected from among nearly 600 patients of working age, seeking for any reason, and representing a variation mainly between urban/suburban populations. Although it was not intended, the selected centres were shown to include patients with fairly high socio-economic status, as the majority was married, reported high education and held employment. However, some were unemployed or on long-term sick leave or had a disability pension, which is a difference compared with the studies of patients at the specialist clinic. Patients with problems in understanding Swedish were not included, which is a limitation as the generalizability of

the study decrease. In 2013 15% of the general population in Sweden was born outside Sweden (134), and in some parts of the Gothenburg area these account for a considerable part of the population, Statistics Sweden [http://www.scb.se/sv/_Hitta-statistik/Artiklar/Fortsatt-okning-av-utrikes-fodda-i-Sverige/.] On the other hand one could argue that the homogeneity of the group could be a strength in the sense that cultural differences that could make it more difficult to interpret answers to the questionnaires used were not prominent in the studied groups. A further strength of the study was that the clinical assessment was performed by two senior physicians only, both experienced in the field and from the same specialist clinic, using the same strict diagnostic procedures.

Another consideration regarding the study design is that the patients were selected based on answers to the first and second steps of the original study screening for stress in primary care. The first step of that study included a validated single-item screening question about current stress. Only those that indicated an elevated stress level were offered to fill out the more extensive mental health questionnaires. Similar numbers of men and women declined to participate in the second step, and there were no significant differences in demographics compared to participants. There is the possibility that some patients scoring negative on the initial stress item would have scored positive on s-ED or SMBQ, if they had had the opportunity. However, we consider it highly unlikely, except perhaps in a very few cases, and we have no reason to believe that this would have influenced results. Of the patients eligible for the clinical assessment according to responses to s-ED and/or SMBQ, a smaller group declined further participation. They shared similar characteristics to the participants, but reported fewer symptoms of anxiety, depression and burnout. Probably the proportion that would have received an ED diagnosis after clinical assessment would have been smaller in this group compared to the group that participated.

The working population study (Paper IV), was performed as a part of a longitudinal cohort study designed to examine relations between psychosocial factors, stress experience and mental health in a sample of employees in public health care and Social insurance offices. Data were collected by postal questionnaire starting in 2004 (135). Non-participation analyses at baseline and the first follow-up, used in the present study, indicated an underrepresentation of men and a possible healthy worker effect. This means that outcomes related to mental health at follow-up could be underestimated, and that results regarding men, based on a much smaller sample compared to women, should be interpreted with caution.

8.2. Measurements

There were several methodological considerations concerning the questionnaires used in this thesis. S-ED was constructed from the criteria-based diagnosis ED, so consideration of scale properties of the instrument is not relevant. The s-ED instrument was tested in a clinical setting in the study reported in Paper III, and in a working population in Paper IV. It was found easy to distribute and to use. In order to validate the s-ED instrument in Paper IV, measures of related mental conditions used were selected from clinical experience. This scale has however not yet been validated against clinical diagnosis. However it is plausible to believe that there is good agreement between clinical diagnosis and s-ED, as it is developed from the clinical diagnosis. In specialist care patients at ISM, a pilot study of validation of s-ED against clinical diagnosis was performed and showed good agreement, and a pilot study has been performed of test/re-test reliability, showing satisfactory percentage agreement (data not shown).

The SMBQ scale was used to assess symptoms of burnout both in clinical populations not currently working, and in workers. SMBQ is viewing burnout as a multidimensional construct not only focused on work (48). The most commonly used self-report instruments for burnout MBI, was designed for use in working populations only, and included other dimensions not suitable for clinical purposes (72). However, the overall SMBQ score correlates highly with the emotional exhaustion subscale in the MBI (136). Furthermore, the Shirom Melamed burnout measure (SMBM), view burnout as an outcome of chronic exposure to work-related stress, why it was not used for the studies (137). A total mean score of 4.0 or more on SMBQ was used as the cut-off level for burnout in specialist care. In studies of working populations this cut-off has been used to indicate significant burnout symptoms (50, 138). A total mean score of 4.4 or more was suggested in a recent study to be a more proper cut-off level to distinguish burnout levels found in patients with stress-related exhaustion from levels in persons at work (139). Around ninety percent of ED patients in specialist care scored above this cut-off, indicating that ED and burnout levels above this cut-off still show a good deal of overlap. In the primary care study and in the study of the working population the reason for using a lower total SMBQ score (≥ 3.75) was to avoid missing any individual with possible ED, and for early detection of increased symptoms of burnout, respectively. Of course, other cut-offs for burnout could have been selected but we consider that the ones we used were sufficiently motivated.

The HAD scale was used in all four studies of the thesis to follow symptoms of depression or anxiety, as it is an easily self-reported instrument and highly used in clinical settings, and in several related studies (94, 140). There are several other validated self-rating scales designed to assess symptoms of depression and/or anxiety in clinical settings, as diagnostic tools or to follow-up effects of treatment, for example Montgomery Asberg depression rating scale (MADRS), or Beck depression or anxiety inventory (BDI, BAI) (141-143). However, we found HAD to be most suitable for our purpose as it was well known to the authors, simple and used in related studies.

The PRIME MD patient questionnaire and the evaluation guide according to DSM IV (144), were well known to the physicians at ISM, who found it easy to use in clinical settings. PRIME MD gives a quick broad view of symptoms that had often occurred during the past month and includes modules of somatic symptoms, and depression and anxiety disorders. It was found to be more useful than the Patient health questionnaire 15 (PHQ-15), derived from PRIME MD, but including only the somatic symptom module and a severity scale (145). There are other symptom check lists, such as the Hopkins symptom check list (HSCL), but PRIME MD was well known and therefore used. At the first consultation in specialist clinic (Papers I and II), and before clinical examination in primary care (Paper III), PRIME MD was filled in by the patient. The somatic symptom module includes 90% of symptoms reported in outpatient clinics, but no respiratory symptoms. This was not a problem for the monitoring and follow-ups of multiple somatic symptoms in Paper II, or the monitoring of symptoms in Paper III, as the most frequent symptoms reported by the patients were included. PRIME MD was found to have very good sensitivity for any psychiatric diagnosis (95). The sensitivity for anxiety was good but for depressive disorders somewhat lower. The Swedish council on health and technology assessment (SBU) published in 2012: “Case finding, diagnosis and follow-up of patients with affective disorders” [<http://www.sbu.se/sv/Publicerat/Gul/Diagnostik-och-uppfoljning-av-forstamningssyndrom/>], and concluded that PRIME MD was not sensitive enough for diagnostics in cases of depression. In the present studies, depression and anxiety were assessed by clinical interview in combination with PRIME MD, leading to a minor risk of missing depressive disorders. Patients with PRIME MD mental disorders have been shown to have significantly impaired functioning, greater health care consumption and higher self-reported symptom severity (95), which makes the instrument even more useful.

8.3. Other methodological considerations

All the patients in specialist care (Papers I and II) were offered individualised MMT during follow-up. There seems to have been little variation in the different treatments offered. All patients underwent a stress reduction programme in a group, and a majority was offered individualised psychotherapy. Lifestyle topics were regularly discussed at the appointments focusing on graded physical activity and other issues when needed. Antidepressants were used in cases with more severe symptoms of depression and anxiety. We have no reason to believe that differences in treatment could have importantly influenced results.

9. ETHICAL CONSIDERATIONS

In specialist care, data were collected to ensure correct diagnosis, treatment and rehabilitation similar to usual care. No important risk or complication was expected as no further information was collected for the study, but there were several questionnaires to fill in which could cause fatigue and make the patient focus unnecessarily on mental health problems. It could be difficult for the patients not to agree to participation in the studies, as they were dependent and severely ill. Patients remitted to ISM and not admitted to follow-up underwent assessment, and the ordinary GPs were advised on further rehabilitation. For ethical reasons we could not use a waiting list to get a control group since the patients were severely ill and in need of immediate treatment. In the primary care study no severe risk or complication was expected, but the questionnaires on mental health problems could lead to sensitive patients focusing unnecessarily on health problems. For those invited to clinical examination blood-testing for differential diagnosis could cause a short feeling of pain, but the procedure is similar to an ordinary appointment with a physician. Patients with serious mental health problems received advice from the physician from ISM, or were asked if contact could be taken with the regular GP to inform about the problems and make a new appointment. In the working population study no severe risk or complication was expected, but the questionnaire on mental health problems could lead a sensitive individual to focus unnecessarily on health problems. Individuals that contacted ISM about health questions after filling in the questionnaire got an answer, or were advised to contact the occupational health care service. No other individual feedback was offered.

10. CLINICAL IMPLICATIONS

Important findings for clinical practice

- Early detection is urgent and implies that the long course of mental and somatic illness could be shortened. Symptom duration before seeking care was the only predictor of recovery from mental illness in ED. We have reason to believe that patients are seeking for help during the symptom period, and it is thus plausible to detect this serious problem earlier. The s-ED instrument was shown to be helpful for this purpose and it was a quick and simple tool for screening for stress-related health symptoms in clinical settings, and as a screening instrument for occupational health care to find individuals at risk of worsening problems, or for prevention.

- The long course of mental illness without sex or age group differences is a valuable knowledge for practitioners in primary care and occupational health care, when making a prognosis for patients with stress-related exhaustion. Rehabilitation time could be extended for several years in severe cases, and a similar prognosis of recovery should be considered irrespective of sex or age.

- The extensive co-morbidity with anxiety and depression is important to consider as there are treatments available. Panic attacks could be an initial problem leading to repeated consultations and acute visits to health care. Furthermore, it is important that patients seeking emergency departments with panic attacks are followed up in primary care within a short time for penetration of underlying stress-related problems.

- The multiple somatic symptoms in patients seeking for mental health problems were striking and there has to be enough consultation time for these patients to give an overview of the total burden of illness. At the first consultation differential diagnostic considerations of the somatic symptoms should be raised. If no somatic disorders can be identified, the symptoms should be followed carefully and further examination is only needed in cases without improvement. With individualised MMT designed for mental health problems, the symptoms seem to decline. However, pain in arms, legs and joints persists, and supplementary treatment should be considered, especially in older patients.

11. FUTURE NEEDS

- The underlying mechanisms for the long duration of mental symptoms need to be explored. Of particular interest is the possible effect on brain function that has been suggested. Patients with prolonged symptoms beyond 18 months have to be further explored and cognitive problem should be one of the main focuses in these studies.

- There is a need for validation of s-ED against clinical diagnosis.

- There is a need for further training in health care to detect early signs of high stress level in patients seeking for different reasons. There is a need for further studies on how, and when, to screen for high level of stress at workplaces and in primary care focusing on both private and work related stress, and s-ED could be a useful tool. There is a need for further training in psychiatric diagnostics for physicians in order to better detect mental disorders possible to treat.

- There have to be further studies of how to use the ED diagnosis concomitantly with other somatic or mental disorders. One suggestion could be to use “primary ED” for patients without complicating disorders, and “secondary ED” in cases of stress-related exhaustion in combination with mental or somatic disorders that could cause similar symptoms to those of ED.

- There is a need for further studies of stress-related mental health problems in other populations: in adolescents, the unemployed, living in different cultural environments and individuals born in other countries. These characteristics could be associated with an elevated risk of mental health problems and they were not covered in the present studies.

12. CONCLUSIONS

The most important findings of the thesis were the long duration of mental symptoms without sex or age group differences. Other important findings were the extensive co-morbidity with depression and anxiety, and the heavy burden of somatic symptoms with persistence of pain after 18 months. Symptom duration was the only predictor of recovery from mental symptoms, while none of the variables analysed was found to significantly predict recovery of somatic symptoms.

Of primary care patients that self-reported exhaustion or burnout, approximately one-third fulfilled the diagnosis of ED. In non-ED patients, especially those that self-reported pronounced exhaustion, there was a similar high burden of mental and somatic symptoms compared to ED, except for anxiety being more prevalent in ED.

The instrument s-ED for self-reported exhaustion, was explored in a working population. It was easy to use and corresponded well to established measures of mental health and work ability, and was shown to have good predictive validity for sick leave two years later. More than one out of six employees at work rated exhaustion by using s-ED.

The present findings should be an important contribution to the knowledge of stress-related exhaustion that constituted the major reason for the rise in sick leave from the end of the 1990s and onwards in Sweden. Prevention and early detection seems urgent for the individuals, for the workplaces and for society.

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