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COGNITIVE BEHAVIORAL THERAPY FOR STRESS-RELATED DISORDERS

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Cognitive Behavioral Therapy for Stress-Related Disorders

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To Julia, Majken, and Lovis

ABSTRACT

Background: Stress-related disorders in the form of adjustment disorder (AD) and exhaustion disorder (ED) are prevalent and associated with significant suffering, functional impairment and high societal costs. Cognitive behavioral therapy (CBT) may be effective in reducing stress, but studies using clinical samples diagnosed with stress-related disorders are few, and evidence is lacking to support treatment guidelines. Because accessibility to CBT is limited, it is important to investigate treatment delivery formats that enable high scalability. Health economic evaluations of treatments are needed to guide decision makers in how to use limited healthcare resources efficiently. Further, the study of potential mediators of treatment effect is important to inform treatment development for patients diagnosed with AD or ED.

Aims: The overall aim of Study I was to evaluate the effect of CBT, a return-to-work intervention (RTW-I), and a combination of the two (COMBO) for patients on sick leave due to a common mental disorder (CMD; AD, ED, anxiety disorders, depression, and insomnia). Of particular interest to the present thesis was to evaluate the effect of a new CBT protocol used to treat patients with stress-related disorders in Study I. In Study II, the aim was to evaluate the efficacy of that same CBT protocol when delivered as a therapist-guided internet-based treatment (ICBT) for individuals with AD or ED. In Study III, we aimed to investigate cost-effectiveness of the ICBT. In Study IV, we aimed to investigate sleep impairment as a putative mediator of the effect of ICBT on symptoms of stress and exhaustion.

Methods: In Study I, consecutively recruited primary care patients (N = 211) who were on sick leave due to a CMD were randomized to disorder specific CBT, a RTW-I, or to COMBO. Main outcomes were symptom severity and net days on sick leave. Of the total sample, a majority (72%) of patients met diagnostic criteria for AD or ED and were treated with the new CBT protocol for stress-related disorders. In Study II, nationally recruited participants (N = 100) diagnosed with AD or ED were randomized to ICBT for stress-related disorders or to a waitlist control condition (WLC). Level of perceived stress was the main outcome. Studies III and IV were based on data collected in Study II. In Study III, cost-effectiveness and cost-utility of the ICBT were evaluated from a societal and a healthcare perspective, using remission rates and health-related quality of life to calculate incremental cost-effectiveness and cost-utility ratios respectively. In Study IV, weekly measurements of sleep impairment (the putative mediator) and outcomes (perceived stress and exhaustion) throughout the course of ICBT were analyzed using latent growth models within a structural equation framework.

Results: Results of Studies I and II indicated that the CBT for stress-related disorders was effective in reducing symptoms compared with the RTW-I and the WLC respectively. Subgroup analyses of AD and ED in Study II indicated that the treatment was equally effective for both diagnostic groups. Treatment effect on sick leave (Study I) and work ability (Study II) was, however, small and non-significant compared with control conditions. Results from Study III suggested that, compared with the WLC, ICBT was a cost effective treatment,

yielding large effects at no or minimal societal net costs in only 12 weeks. In Study IV, reduced sleep impairment was found to statistically mediate the effect of ICBT on symptoms of perceived stress and exhaustion.

Conclusions: A relatively short CBT protocol designed to meet the presumed needs of patients diagnosed with AD or ED was indicated to be effective in reducing symptoms both when delivered as a face-to-face treatment and when delivered via the internet. If implemented in routine care, ICBT has the potential to increase access to efficacious treatment for many suffering individuals at no additional societal net costs. Reduced sleep impairment may be of importance to achieve successful treatment outcomes. The results motivate further investigation of the treatment using different control groups, longer follow-up periods, and more fine-grained evaluations of treatment mechanisms. Further investigation into interventions that may have an effect on work-related outcomes is warranted.

LIST OF SCIENTIFIC PAPERS

I. Salomonsson, S., Santoft, F., Lindsäter, E., Ejeby, K., Ljótsson, B., Öst, L-G., Ingvar, M., Lekander, M., Hedman-Lagerlöf, E. (2017). Cognitive-behavioural therapy and return-to-work intervention for patients on sick leave due to common mental disorders: a randomised controlled trial. *Occupational and Environmental Medicine, 74*(12), 905-912. Doi: 10.1136/oemed-2017-104342

II. Lindsäter, E., Axelsson, E., Salomonsson, S., Santoft, F., Ejeby, K., Ljótsson, B., Åkerstedt, T., Lekander, M., Hedman-Lagerlöf, E. (2018). Internet-based Cognitive Behavioral Therapy for Chronic Stress: A Randomized Controlled Trial. *Psychotherapy and Psychosomatics, 87*(5), 296-305. Doi: 10.1159/000490742

III. Lindsäter, E., Axelsson, E., Salomonsson, S., Santoft, F., Ljótsson, B., Åkerstedt, T., Lekander, M., Hedman-Lagerlöf, E. (2019). Cost-Effectiveness of Therapist-Guided Internet-Based Cognitive Behavioral Therapy for Stress-Related Disorders: Secondary Analysis of a Randomized Controlled Trial. *Journal of Medical Internet Research, 21(8),* e14675. Doi: 10.2196/14675

IV. Lindsäter, E., Axelsson, E., Salomonsson, S., Santoft, F., Ljótsson, B., Åkerstedt, T., Lekander, M., Hedman-Lagerlöf, E. (Manuscript). The Mediating Role of Sleep in Internet-Based Cognitive Behavioral Therapy for Chronic Stress: Results from a Randomized Controlled Trial.

CONTENTS

LIST OF ABBREVIATIONS

AD	Adjustment disorder
CBT	Cognitive behavioral therapy
CMD	Common mental disorder
COMBO	Combined CBT and RTW-I
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Exhaustion disorder
ICBT	Internet-based cognitive behavioral therapy
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
ISI	Insomnia Severity Index
MMR	Multimodal rehabilitation
PSS	Perceived Stress Scale
RCT	Randomized controlled trial
RTW-I	Return-to-work Intervention
SMBQ	Shirom-Melamed Burnout Questionnaire
TAU	Treatment-as-usual
WLC	Waitlist control condition
WTP	Willingness to pay

1 INTRODUCTION

Studying "stress" can be quite a stressful task if one wishes to grasp the full meaning of the concept. Where to begin? Stress is a commonly used word in our day-to-day language; one could ask any parent, teacher, nurse or neighbor and get a personal account, or just read about the deleterious consequences of stress in the daily newspaper. If a more scientific perspective is sought, there is an abundance of reading to do. Stress has been studied from many angles in the past century, across a wide range of fields. Definitions and theories vary, as do populations studied, terminology used, and outcomes measured. Models have placed varying emphasis on stress as "input" (i.e., what external events may act as generic stressors), "output" (i.e., the stress response, ranging from microbiological substrates of stress to its overt cognitive, emotional and behavioral expressions), and potential factors that interact with the experience of a stressful life event on the individual stress reaction (e.g., coping strategies, social support, self-esteem, or mastery). Clearly, there is a lot to learn and many who want to have a say in the matter.

Working as a clinical psychologist in a primary care setting for over 10 years, I have been struck by the fact that there is so much knowledge about stress as a phenomenon, yet relatively limited research regarding how to best help individuals who suffer from prolonged or repeated exposure to stress. In stark contrast to what we know of treatment for many common mental disorders (e.g., depression, anxiety disorders, and insomnia), randomized controlled trials of interventions targeting stress-related disorders are few, and treatment guidelines rely largely on clinical experience and on findings from non-clinical populations. It seems the plethora of stress research, with different sample characteristics, methods and paradigms studied, has focused our attention on how to integrate findings and understand the wide array of terminology used, rather than develop efficacious treatments. Seeing the large proportion of patients who seek help in primary care for stress-related symptoms and disorders, the lack of evidence-based treatments has contributed to continued frustration for me and my colleagues (not to mention for the patients). We find that it is time for a shift of attention.

In the present thesis, I will not attempt to give a comprehensive review of the different perspectives on stress and related research. Rather, I want to narrow the perspective to the field of clinical psychology and particularly to that of treatment. With the four papers presented in this thesis, I hope to provide a building block on which we can systematically accumulate evidence of interventions to alleviate suffering and increase functioning for the many individuals who are in need of treatment. My driving force is the provision of even-handed, gender equal, easily accessible and cost effective care for patients with stress-related disorders, as for all patients suffering from common mental disorders.

Stockholm, December 2019

2 BACKGROUND

2.1 STRESS AND STRESS-RELATED DISORDERS

2.1.1 Definition of stress

Today, most researchers within the field of psychological stress recognize that how individuals respond to life events and commonly identified stressors is the result of a complex interaction of individual traits (e.g., genetics, early childhood experiences, and personality), perceptions, lifestyle factors and the context in which the stressors occur [1]. In line with a transactional model of stress [2] and the allostatic load model [3], the work in this thesis is based on the conceptualization of stress as a continuous interaction between the individual and his or her environment. In short, "stress" is defined as the psychophysiological process that initiates when an individual perceives external demands to tax or exceed his or her resources at a specific time.

Importantly, stress is not something negative by default. On the contrary, it is crucial to our survival and functioning in every day life. Our brains react to challenges ("stressors") by activation of the autonomic nervous system, the hypothalamic-pituitary-adrenal axis, as well as the metabolic, immune- and cardiovascular systems. By the immediate release of chemical mediators by the brain (e.g., adrenaline and noradrenaline), the sympathetic nervous system contributes to increased blood pressure, heart rate, availability of energy to the muscles, and mental activity to help us effectively deal with the challenges (whether they be threats to our survival or running to catch a bus) [3]. This reaction in response to perceived stressors is often referred to as "acute stress" and is generally short-lived (minutes to hours). After the stressful situation, the parasympathetic nervous system restores the organism to a relaxed state by, for example, slowing the heart rate and decreasing muscle tension. The adaptive interplay between biological systems (such as the sympathetic and the parasympathetic nervous systems) that serves to maintain homeostasis in a changing external and internal environment, has been termed "allostasis" [4]. Figure 1 illustrates the many interacting components of stress, where allostatis and adaptation are central for our health.

If allostasis is activated repeatedly or for long periods (in response to, for example, low-grade every-day stressors related to home and work life), the allostatic response may be insufficiently shut off between challenges. This can result in an overexposure to stress hormones (e.g., contributing to chronically elevated heart rate and blood pressure) and, over time, a dysregulation of the allostatic system [5]. The term "chronic stress" is often used to infer prolonged stress-reactions that last for several hours per day for weeks or months [6]. McEwen and collegues use the term "allostatic load" (see Figure 1) to mark the cumulative wear and tear that can result from chronically increased allostatis [3]. Allostatic load (or, chronic stress) can contribute to a range of pathophysiologic states, such as psychiatric, endocrine, and inflammatory disorders [7, 8].

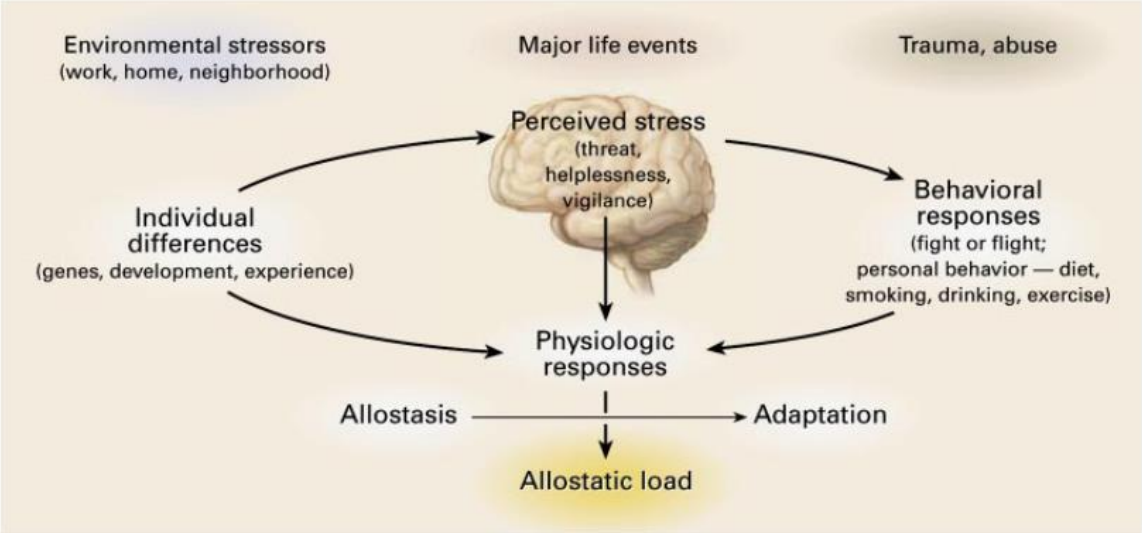

Figure 1. A model of stress with the different interacting factors that may lead to chronic stress, or allostatic load. Reproduced (with permission from the author) from McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338:171-179. Copyright © Massachusetts Medical Society 1998.

In plain language, "adaptation" can be equated with recovery. Recovery refers to psychophysiological unwinding and stabilization after effortful expenditure, and incomplete recovery has been suggested to be an explanatory mechanism underlying the relationship between stress and chronic health impairment [9]. Our behavioral responses to perceived stressors can trigger a negative cycle of chronic stress in such a way that recovery, or adaptation, is aggravated. For example, many low-grade, chronically operating stressors may cause us to neglect seeing friends and minimize leisure time and physical activity. Further, we may decrease time for sleep, and increase intake of fatty foods, alcohol and nicotine. These behaviors, in turn, may affect our perceptions of threats and demands, and impede our ability to adapt to challenges in a resilient way.

In summary, stress is natural and necessary as it allows for the accumulation of resources to meet, and adapt to, perceived challenges. Prolonged or repeated allostatic activation without adequate recovery, however, leads to a wear and tear of our biological systems and may conduce to changes in our perceptions, behaviors, and coping abilities that can ultimately lead to health impairment.

In the following, I will use the term *chronic stress* when generally referring to the negative health consequences presumed to result from prolonged or repeated stress. Specific diagnostic terms for chronic stress such as adjustment disorder and exhaustion disorder (on which the studies in this thesis are based), are discussed below and will henceforth collectively be referred to as *stress-related disorders.*

2.1.2 Stress-related disorders

Chronic stress can lead to a range of clinical outcomes that cut across traditional boundaries of medical disciplines [7, 10, 11]. It can be difficult to demarcate stress-related disorders from other health conditions, not least to define them with clear-cut, specific criteria [12-15]. Nevertheless, our major diagnostic systems DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) and ICD-10 (International Statistical Classification of Diseases and Related Health Problems, 10th edition) include sections dedicated to describing stress-related disorders: *Trauma and Stressor Related Disorders* (DSM-5) and *Reaction to Severe Stress, and Adjustment disorders* (ICD-10). These sections include acute and prolonged reactions to traumatic stressors (acute stress reaction and post-traumatic stress disorder, PTSD), as well as reactions to non-traumatic stressors (adjustment disorders and, in the Swedish version of the ICD-10, exhaustion disorder – see below). Unspecific diagnostic terms are also included, such as "other specified trauma/stressor-related disorders" in the DSM-5 and "other reactions to severe stress" in the ICD-10. A common denominator of all stress-related disorders is that they should be directly related to a traumatic or stressful event (or a series of events) in such a way that it can be assumed that the disorder would not have occurred without experiencing the stressor. Also, it is the nature, pattern and duration of the symptoms, together with the associated dysfunction, that distinguishes the disorders [16, 17].

Acute stress reaction and PTSD (i.e., reactions related to life-threatening or traumatic events) are beyond the scope of the present thesis, which rather focuses on reactions to the most common stressors. These are, at least in the western world, chronically operating, non-traumatic stressors such as difficulties at work, interpersonal conflict, and family or economic problems [18]. In my clinical experience from working in primary care, the majority of patients who seek help for symptom of stress, fatigue, anxiety, low mood, and/or disturbed sleep, struggle with this kind of stressors. Many do not meet criteria for a specific psychiatric or somatic disorder, and yet they experience a high level of distress and functional disability to a varying extent. For these patients, the diagnoses adjustment disorder (AD) or exhaustion disorder (ED) may be applicable. Table 1 gives an overview of the main diagnostic features of these disorders. In the following sections, I will describe the disorders further.

Table 1. *Overview of the main diagnostic features of adjustment disorder and exhaustion disorder*

	Adjustment disorder, F43.2	**Exhaustion disorder, F43.8A**
Trigger	One or many identifiable stressors	One or many identifiable stressors
Symptoms	Emotional symptoms (anxiety, depressed mood) or behavioral changes	Physical and psychological fatigue and: • Impaired concentration/memory • Intolerance to stress/time pressure • Emotional lability and irritability • Sleep disturbance • Bodily weakness • Physical symptoms
Impairment	Significant distress or functional impairment in occupational, social, or other important areas of functioning	Significant distress or functional impairment in occupational, social, or other important areas of functioning
Time	Symptoms within 3 months* after onset of stressor/s. Do not persist more than 6 months after termination of the stressor or its consequences	Stressors present for at least 6 months. At least 4 symptoms almost every day for at least 2 weeks

Note: Symptoms are not due to direct physiological effects of drug abuse or medication. If diagnostic criteria for other psychiatric or somatic disorders better explain symptoms, these diagnoses should primarily be used.
*according to the DSM-5. 1 month according to the ICD-10.

2.1.2.1 Adjustment disorder – diagnostic features

The diagnosis AD can be used when an individual responds to stressful events with clinically significant disturbance in mood or behavior (e.g., anxiety, depressed mood, and/or impulse control problems) [16]. Stressors typically comprise non-traumatic events such as interpersonal conflict, work stress, divorce, illness, and socioeconomic difficulties. However, with an increasing number of refugees in the world, stressors related to forced migration, acculturation to a new culture, and economic hardship are also common [19]. The onset of the symptoms is within three months of exposure to the stressor(s) (one month according to the ICD-10), and tend to resolve within six months of termination of the stressor or its consequences [16]. If stressors are persistent or recurring (e.g., chronic disease or marital conflicts), AD may become chronic [16, 20]. Symptoms are clinically significant in that they are distressing and in excess of what could be expected of exposure to the stressor (taking into account contextual and cultural factors), OR in that there is significant impairment in social or occupational functioning. The DSM-5 specifies six subtypes of AD, each signifying the presence of specific symptoms: (a) depressed mood, (b) anxiety, (c) mixed anxiety and depressed mood, (d) disturbance of conduct, (e) mixed disturbance of emotions and conduct, and (f) unspecified [16]. The symptoms do not represent bereavement and are not of sufficient specificity or severity to justify another psychiatric diagnosis [16]. Following is a case vignette of a primary care patient diagnosed with AD.

Linda is 36 years old. She is a generally healty woman, but the past few years have been rather taxing for her due to having three small children, working full time, and spending quite some time commuting to work. Four months ago, Linda's oldest son was diagnosed with dyslexia. Since then, she describes feeling constantly anxious and tense. She has had a hard time relaxing and focusing on tasks at home and at work, struggeling with recurrent thoughts about how her son's life will turn out, if he will get sufficient support at school… She has had frequent angry outbursts at her husband, which has led to many conflicts. Linda cries on a daily basis. She has difficulties falling asleep, and often drinks whine in the evenings to help calm herself.

Over the years, the AD diagnosis has received a lot of critique pointing to (amongst other things) difficulties in differentiating the disorder from adaptive reactions to stress and from other mental health disorders [13, 19-22]. AD is sometimes referred to as a residual ("waste-basket") category for patients who do not meet diagnostic criteria for other psychiatric disorders [e.g., 13, 23, 24]. It is beyond the scope of this thesis to give an account of the debates surrounding AD. Importantantly, however, efforts have been made to improve the clinical utility of the condition. In the 11th version of the ICD (ICD-11), positive symptom criteria for AD have been established for the first time, relating to excessive preoccupation about the stressor or its consequences (for example, excessive worry, recurrent and distressing thoughs, or constant rumination about the consequences of the stressor). Further, AD subtypes have been removed in an attempt to build a more unifaceted diagnostic concept [e.g., 25].

It should be noted that, although quite a few studies of AD based on the ICD-11 criteria have already been published, AD in the current thesis was defined based on criteria in DSM-4 (Study I) and DSM-5 (Study II, III and IV). Diagnostic criteria for AD in these two versions of the DSM are essentially the same, even though the DSM-5 reclassified AD to belong to the section *Trauma- and stressor-related disorders*.

2.1.2.2 Exhaustion disorder – diagnostic features

Because ED is a diagnosis unique to the Swedish ICD-10, a brief background to the diagnostic terminology related to chronic stress will be given before the disorder is described more specifically.

As mentioned, in AD, symptoms usually subside within six months after the termination of the stressor(s). However, many times stressors are recurring or chronic in nature in such a way that symptoms may develop and exacerbate over the course of years (which is not unusual when it comes to, for example, relational conflicts or disease in the family). In cases where a person experiences chronic stress, symptoms of increasing fatigue, cognitive deficits, disturbed sleep,

and a range of somatic symptoms (e.g., pain, palpitations) are common [7, 10, 11]. When these symptoms do not clearly map onto established psychiatric or somatic disorders, however, there are large international inconsistencies regarding how they should be understood and categorized.

If stressors are predominantly work-related, the term "burnout" is often used in the international literature [14, 26]. Burnout is thought to emerge as a prolonged response to chronic work-related stressors [27], characterized by constant feelings of helplessness and exhaustion that are believed to represent the last stage of an adaptive breakdown [28]. Burnout has been defined in slightly different ways by different research groups over the years [29]. However, emotional exhaustion has remained a common core factor for the condition, indicated to be the most predictive of stress-related health outcomes such as headaches, chronic fatigue, gastrointestinal disorders, muscle tension, and sleep disorders [29]. Despite severe clinical implications, burnout is not a medical diagnosis in any diagnostic system and lacks diagnostic criteria.

Another approach to define chronic stress-related conditions has been made by proposing criteria for allostatic overload [15]. These criteria postulate similar symptom development in response to chronic or recurring stressors as burnout (albeit not limiting stressors to the work context). Because the diagnosis is not included in the major diagnostic systems ICD or DSM, however, like burnout it holds limited clinical value to healthcare staff.

The ICD includes the diagnostic term "reaction to severe stress" (F43.8), which is defined by symptoms of emotional stress, muscle tension, mixed disturbance of emotion and conduct, and psychomotor agitation [17]. Because the criteria are vague and lack, for example, any reference to time perspective regarding symptom development or functional impairment, the Swedish National Board of Health and Welfare suggested the term exhaustion disorder (ED) in 2003, in order to operationalize the clinical diagnosis and facilitate rehabilitation of the severe stress-related condition commonly seen in clinical practice [30]. ED was accepted as a formal diagnosis in the Swedish version of the 10th revision of the ICD, accredited with the diagnostic code F43.8A.

ED is characterized by symptoms of mental and physical fatigue (present for a minimum of two weeks) that are assumed to result from exposure to psychosocial stressors that have been present for at least six months before diagnosis. Core symptoms include markedly reduced mental energy, which is manifested by reduced initiative, lack of endurance, or an increase in time needed for recovery after mental effort. At least four of the ED symptoms specified in Table 1 must be present nearly every day for at least two weeks, and lead to clinically significant distress or impairment [30]. Compared with AD, ED is by definition a more chronic and debilitating condition. However, as seen in Table 1, the diagnoses have important commonalities.

2.1.2.3 Natural course

In a German population sample, Maercker et al. [31] found that, in 72% of people meeting criteria for AD, symptoms had developed in 6 to 24 months prior to assessment. There is empirical evidence to suggest that AD is a transient disorder from which most people remit spontaneously [32, 33]. However, studies indicate that there are subpopulations of AD in which symptoms increase over time and mark a trajectory toward a more severe disorder [34, 35]. Five year follow-ups show that about 20% of patients with AD develop a psychiatric disorder, most commonly depression and alcoholism [36]. Both the DSM and the ICD recognize that AD can become chronic given persistent stressors, with symptoms present for up to two years [31].

When it comes to ED, empirical evidence of disorder development and natural course is scarce. It seems, however, that ED entails a gradual increase in symptoms (e.g., infection, anxiety/depression, pain, fatigue) for which individuals repeatedly seek help in primary care years before a diagnosis of ED is set [37]. Based on clinical observations, the natural course of the disorder is often described as moving through different phases [30]: First, a "risk phase", or a prodromal phase, may be observed, during which symptoms gradually accumulate in response to stressors and insufficient recovery. Second, an "acute phase" may accrue that often implies drastic cognitive difficulties, affective reactions and functional impairment, as well as anxiety related to ones own reactions. When the acute phase diminishes (usually after a few weeks), the third "recovery phase" begins. During this phase, depressive symptoms and anxiety tend to subside as daily activities and routines are resumed [38]. Some afflicted individuals may experience a heightened stress sensitivity and cognitive deficiencies that remain for years [39, 40]. The clinically observed longitudinal course of ED and the severity of symptoms have amounted to sick leave recommendations of 6 to 12 months [41], which far exceed sick leave recommendations for other common mental disorders.

2.1.2.4 Differentiatial diagnostics

Because AD, according to the DSM-5, is in part defined by symptoms of depression and anxiety, it is sometimes difficult to distinguish this stress-related disorder from depressive disorders and anxiety disorders (specifically the unspecified forms, e.g., depressive disorder, not otherwise specificed). This is particularly the case when a depressive or anxiety disorder is precipitated by a stressful life event. As mentioned, according to the DSM-5, AD should be diagnosed only when symptoms are not sufficiently specific to justify another disorder, and when symptoms do not represent a deterioration of a previously existing mental disorder. For example, in the aftermath of a stressful life event, a patient may suffer from intense anxiety, recurrent worry, and bodily tension leading to functional disability. If symptoms are not specific enough to meet criteria for, for example, generalized anxiety disorder, AD can be diagnosed.

Differentiating AD from depression can be particularly challenging [42]. If all diagnostic criteria for a depressive disorder are fulfilled and there is a known history of previous

depressive episodes, a diagnosis of depressive disorder should be set rather than AD, independent of whether the depressive symptoms were triggered by a stressful life event or not.

Symptoms of anxiety and depression are also very common in patients with ED. In fact, in a study of 232 clinically referred patients with ED, 67% were assessed to also meet criteria for both depression and an anxiety disorder, 13% were diagnosed with depression only alongside ED, and 11% with a comorbid anxiety disorder [38]. With this large symptomatic overlap, determining which disorder should be the primary target of intervention can be difficult. Diagnostic guidelines state that ED should be set as a secondary diagnosis in cases when a patient also meets diagnostic criteria for depression or generalized anxiety disorder [30]. However, clinical observations suggest that, while depression is common during some phase of an ED, core symptoms indicative of ED (mental and physical fatigue, disturbed sleep, and cognitive deficiencies) often remain when the depression subsides [43]. Depression has been suggested to many times develop as a consequence or a complicating factor of ED, rather than vice versa [44].

In my clinical experience, patients with ED often formally meet criteria for depression (for which the threshold is quite low), but differ somewhat in their clinical presentation with regard to symptoms. For instance, patients with ED may attest to depressed mood and diminished interest or pleasure sustained for two weeks (core criteria for depression) [16]. However, they commonly specify that the low mood is *due to fatigue* and that, even though the general interest in activities may remain intact, pleasure in these activities is diminished due to fatigue or cognitive difficulties. When assessing generalized anxiety disorder, patients with ED may, again, formally meet criteria. However, the content of the worry may differ from what is commonly seen in patients with generalized anxiety disorder. For example, patients with ED tend to worry about whether or not they will regain their previous capacity, or about the real life challenges with which they are faced (e.g., psychosocial difficulties, disease in the family, difficult work situations). The content of the worry is often understandable and rarely excessive. In contrast, worry content of patients with generalized anxiety disorder tends to be more miscellaneous and particularly characterized by minor, routine issues [45].

What about differentiating between AD and ED? These diagnoses share the presumed aetiology of identifiable life stressors as prerequisite for symptom development, and they share a putative longitudinal course of symptoms. Both AD and ED have large overlaps with depressive- and anxiety disorders [16, 30]. Although not empirically investigated, to my knowledge, it is plausible that AD and ED represent different clinical severity levels of stress, or allostatic load, on a continuum that ranges from adaptive, subclinical stress to chronic load reactions with severe functional disability. In this line of reasoning, it is conceivable that AD, in cases where stressors are chronic and symptoms enduring, may constitute a precursor to ED. In my clinical experience, patients with AD many times present with a clinical picture that suits well with the "risk phase" described in the presumed developmental course of ED (see section 2.1.2.3). Whereas diagnostic criteria for AD are quite broad and suggest a reaction within three months

of a life event, diagnostic criteria for ED are more specific and require stressors to have been present for at least six months.

2.1.2.5 Prevalence

Due to vague diagnostic criteria, differences in sampling, and lack of common diagnostic tools to assess AD, prevalence estimates of AD vary markedly between studies. Population based studies, using new diagnostic tools to assess ICD-11 AD, indicate a prevalence of around 1-2% in the general population [31, 46]. In clinical settings worldwide, however, AD is one of the most commonly used psychiatric diagnosis [47, 48]. Of studies conducted in the 1980s, a prevalence range of 11-18% was found in primary care settings, and 10-35% in consultation liaison psychiatry [49]. Similar estimates have been found in more recent studies, as indicated by a prevalence rate of 11.5% in outpatient psychiatric clinics in Kurdistan [50], and 9.2% in Swedish primary care [51]. Some studies indicate lower extimates, such as 2.9% of primary care patients in Catalonia [52].

Because ED is a Swedish diagnosis, no large-scale epidemiological studies have been conducted and the prevalence of ED is largely unknown. Studies have found high levels of emotional exhaustion (assessed by self-report forms) in approximately 13-18% in the general Swedish population [53-55]. One study that investigated self-rated ED in a large sample of healthcare workers and social insurance officers found a prevalence of 16% [56]. Of patients in primary care, 30% reported symptoms that indicated ED (also by self-report questionnaire) [57]. Of note, self-rated symptoms of ED are not equivalent to the actual disorder, and hence the above mentioned estimates should be interpreted with causion. Symptoms of ED, such as lack of energy, disturbed sleep, difficulties remembering things or focusing attention, may be common to many somatic and psychiatric conditions, and careful clinical assessment regarding exposure to stressors, course of symptoms, and other potential psychiatric and somatic disorders are needed to set the diagnosis. A more representative prevalence estimate of ED amongst patients in primary care might be 9%, which was found in a study in which clinical assessment was conducted according to diagnostic criteria [58].

2.1.2.6 Gender differences

With few exceptions, the prevalence, incidence and morbidity rates of mental health disorders are higher in women than in men [59, 60]. There are indications that this pattern may hold true also for stress-related disorders. Statistics from the Swedish Social Insurance Agency indicate that, between the years 2010 and 2015, the increase in sick leave due to psychiatric disorders (predominantly stress-related disorders) was approximately four times higher for women than for men [61]. In some countries, women in the general population are diagnosed with AD over six times more often than men [62], and women are overrepresented amongst patients diagnosed with AD at psychiatric emergency care clinics [63]. In clinical trials of chronic stress, the proportion of female participants often exceeds 80% [64]. This being said, once a person has been diagnosed with a stress-related disorder, there seems to be no differences between the sexes when it comes to symptom severity or course of symptoms [38].

There are likely many explanations for the gender differences seen, such as differences between sexes when it comes to responsibility for home and family [65], and differences in help-seeking behavior. A recent report by the Swedish National Audit Office (2019:19) [66] indicated that general practitioners may play a role in the scewed sick leave pattern between men and women. According to the report, women with mild to moderate mental disorders receive sick leave 30% more often than do men, even though they are assessed to have the same limitations in activity and functional ability. Possible explanations proposed by the report include that women may have a more open attitude toward sick leave than do men, and that general practitioners may be influenced by certain gender norms. Also, the report suggests that general practitioners may overestimate work ability in men compared with women, and fail to recognize signals of mental ill health in men [66].

A further elaboration on the topic of gender differences in stress-related disorders is beyond the scope of this thesis. The interested reader can get a short review of some theories put forth, for example the Rumination theory or the Gender role theory, as summarized in the article by Almeida et al. [67], the Biopsychosocial theory of stress presented by Frankenhaeuser [68], or a neurochemical explanation given by McEwen [69].

2.1.3 Clinical correlates

Chronic stress is associated with a range of adverse physiological and psychological outcomes. In the following, I will give an overview of some of the established clinical correlates.

2.1.3.1 Mortality

Chronic stress, specified as work-related exhaustion, has been found to predict all-cause mortality among industrial employees [70]. A Swedish study found that long-term sick leave due to a psychiatric disorder is associated with increased risk of mortality due to all causes (cardiovascular disease, cancer, suicide) [71]. This finding may be particularly pertinent to individuals with stress-related disorders seeing that they account for the longest sick leave periods in Sweden [72]. AD is associated with high suicidal ideation [73] and has been found to lead to higher rates of psychiatric morbidity, for example by suicide [74].

2.1.3.2 Cardiovascular disease

There is a comprehensive body of research linking acute and chronic stress to cardiovascular disease [75, 76]. In a recent review, Kivimäki et al. [77] concluded that adults in the general population who experience stress in work or in private life have a 1.1 to 1.6-fold increased risk of stroke and incident coronary heart disease. A prospective cohort study found that the *perception* that stress affects ones health negatively can further increase the risk of coronary death or incident coronary heart disease, compared with those who experience stress but do not perceive the stress to be negative for their health [78].

2.1.3.3 Disorders of the immune system

Whereas short-term, acute stress can enhance the immune system [79], chronic stress has been associated with immune dysregulation [80]. This is indicated by, for example, increased susceptibility to infectious diseases and chronic low-grade inflammation [81]. Further, chronic stress might influence immune function indirectly by modulating the adoption of health-related behaviors [81]. Stress-related disorders (including PTSD and acute stress reaction) have been shown to be associated with an increased risk of autoimmune disease [82] and subsequent life-threatening infection [83]. This being said, research on specific biomarkers in samples with burnout or ED compared with healthy controls have generated conflicting results [84-87].

2.1.3.4 Cognitive impairments

Associations between chronic stress and cognitive deficits have long been observed clinically. In particular, the prefrontal cortex (involved in, for example, controlling high-level executive functions such as working memory, novelty seeking and decision-making) and the hippocampus (involved in, for example, memory formation, learning, and spacial cognition) seem to be affected by chronic exposure to stress hormones, potentially resulting in dysfunction within these areas [88-92]. A systematic review of burnout and cognitive functioning concluded that executive functions, attention, and memory are the cognitive functions that are particularly affected by chronic stress [93]. Significant differences in scoring on neuropsychological tests have been found between patients with ED compared with healty controls [94, 95], and long term follow-ups indicate that cognitive impairments in these patients may be long-lasting [39]. Importantly, however, findings from cross-sectional studies using neuropsychological tests to compare clinical and non-clinical stress samples do not always yield consistent results [96], and no conclusions can be drawn with regard to causality.

2.1.3.5 Psychiatric correlates

Individuals suffering from chronic stress often struggle with depression [97, 98], anxiety [99, 100], and insomnia [101, 102]. Whether or not any causal relationships exist between chronic stress and other psychiatric disorders is largely unknown. Some researchers suggest that there may be a progressive and dynamic relationship between stress and depression over time. For example, chronic stress might make a person more vulnerable to develop a major depression. When depressed, the person might, in turn, behave in ways that creates a greater vulnerability to exposure to further stressors, thus predicting recurrences of depression in a self-perpetuating cycle of depression and stress [97, 99]. Similar reciprocal relationships have been suggested between stress and anxiety disorders [99] and stress and insomnia [103, 104].

2.1.4 Socioeconomic implications

Chronic stress is associated with substantial individual suffering, and stress-related disorders are often related to frequent and long term sick leave [47, 72]. The high incidence of sickness absence for individuals with chronic stress, coupled with factors such as increased staff-

turnover and extended usage of healthcare, implies high costs for employers and for society as a whole [105-107]. Furthermore, presenteeism (i.e., being present at work in spite of somatic or psychological illness, often resulting in reduced productivity) is a major cost-driver for chronic stress [106], indicated to reduce output by at least as much as absenteeism [108]. For the afflicted individual, chronic stress can lead to increased medical expenses and decreased income [106]. Total societal costs for work-related stress in western countries have been conservatively estimated to range between US $221 million to $187 billion annually [109]. Costs related to productivity loss have been found to be the largest contributors to the total costs, with direct medical and healthcare costs constituting remaining costs [109].

2.1.5 Potential risk- and protective factors

2.1.5.1 Childhood adversity and intrapersonal factors

Adverse childhood environment and trauma can predict the onset of a range of adult psychiatric disorders [110, 111], and can affect afflicted individuals susceptibility to stress [112-114]. In a Swedish study, traumatic life events (both in childhood and in adulthood), post-traumatic stress disorder (PTSD), and attention deficit hyperactivity disorder (ADHD), were indicated to be significantly associated with burnout and long term sick leave due to stress [115]. Further, personality type characterized by high neuroticism has been found to moderate how effectively an individual copes with stress, and is associated with increased stress exposure, interpersonal conflict, and burnout [99, 116, 117]. Factors such as low self-esteem [34, 118], low self-efficacy [119], and perfectionism [120] have also been indicated to increase the risk of chronic stress.

2.1.5.2 Work-related factors

Work-related factors affecting stress and mental health have received a lot of attention in stress research. Two influential models are the job demand-control model [121] and the effort-reward imbalance model [122]. According to these models, high demands at work in combination with low control, or imbalance between personal effort and the rewards received for those efforts (e.g., job security, monetary rewards), are associated with high job strain (stress). A large body of research based on these models has established these work-related conditions (and the resulting job strain), as risk factors for mental health problems and cardiovascular disease [122-125]. Studies have also found high demand-low control and high effort-low reward to be associated with burnout [126, 127] and symptoms of ED [128].

2.1.5.3 Lifestyle- and behavioral factors

Individual behavioral changes (e.g., down-prioritizing leisure time, social withdrawal, and excessive worry) have been identified as important in potentiating and exacerbating negative health outcomes due to stress [129-131]. In fact, a study of consecutively recruited adult patients in primary care indicated that lifestyle factors (e.g., exercise, sleep, social support, recovery, and self-care skills) explained significantly more of perceived stress than demographic factors (age, gender, employment, marital status, and education) [132]. In that

study, sleep and recovery showed the strongest inverse relationship with perceived stress [132]. This is in line with a large body of empirical research indicating that deficiency in recovery, including sleep, is a risk factor for the development of chronic stress and mental ill health [9, 131, 133].

Recovery can be defined as the process of mental and physical deactivation, or unwinding, after an episode of effortful expenditure [9]. Recovery has been studied both in terms of extrinsic activities (e.g., watching TV, spending time with friends, and physical exercise) and in terms of intrinsic experiences of recovery (e.g., relaxation and being able to "switch off" thoughts about stressors) [131]. Rumination and excessive worry have been found to impede recovery by prolonging the effect of stressors, and thereby increase the risk of exhaustion and fatigue [134, 135]. A recently published study of a randomized controlled trial showed that a psychological intervention specifically aimed at increasing recovery activities in a sample suffering from chronic stress was effective in reducing symptoms compared with a waitlist control condition [136]. Further, a randomized controlled trial of an internet-based treatment for stress-related insomnia indicated that the waitlist-controlled improvement in sleep found in the treatment group was mediated by an increase in number of recovery activities that, in turn, was associated with lower perseverative cognitions [137].

Besides recovery and sleep, physical activity and social support are are commonly suggested to compose protective elements in the development of chronic stress. For example, there seems to be an inverse relationship between leisure time physical activity on the one hand, and stress and life dissatisfaction on the other hand [138]. A prospective study in a sample of Swedish healthcare workers and social insurance officers found that physical activity can reduce the incidence of burnout [139]. Another study indicated that a 12-week aerobic training intervention in addition to a 24-week multimodal rehabilitation programme may have beneficial effects on episodic memory performance in patients with ED compared with those who received no aerobic training in addition to MMR [140].

Social support, i.e., existing within a social context in which one experiences a feeling of belonging and support, is likely an important factor for mental health and quality of life in general [141]. Sheldon Cohen presented the "buffering hypothesis" based on the growing interest in the role of interpersonal relationships in protecting people against the possible adverse health effects of stressful life events. This hypothesis states that psychosocial stress is more likely to have deleterious health effects for those in lack of social support, whereas the effects of stress will be decreased for individuals with stronger support systems [142]. Even though empirical support of an interactive effect of social support on job stress is, in general, limited [124], some studies have found social support to mitigate perceived stressors [143] and reduce the risk of burnout [144]. A systematic review found that a lack of social support in the workplace was associated with more symptoms of ED and depression [128].

To summarize, many factors may interact to constitute risk- and protective factors in the development of chronic stress, including early life adversities, intrapersonal factors, work-related factors, and a range of lifestyle and behavioral factors. In the following, lifestyle and

behavioral factors will be of primary focus, because these may be relevant in the maintenance of chronic stress, and often constitute main treatment targets in cognitive behavioral therapy (CBT).

2.1.6 Maintaining mechanisms – a cognitive behavioral approach

Although it is important to map risk factors in the development of chronic stress (not least to potentiate broad preventative measures), risk factors are imprecise when it comes to predicting exactly *who* will develop a stress-related disorder. As a complement to researching risk factors, cognitive and behavioral approaches have focused on increasing knowledge of what maintains psychopathology once it is established. To date, there is no single coherent and comprehensive psychological model with established empirical support for chronic stress. However, given the large overlap of chronic stress with anxiety and depression, it is plausible that chronic stress can be conceptualized within a similar framework to that which is used for anxiety and depression, a framework based on learning theory and/or cognitive information processing theory. In this section, I will give a brief account of these theories, followed by a proposed cognitive behavioral model for chronic stress.

2.1.6.1 Learning theory

Learning theory (which consists of a wide range of concepts and principles that will not be comprehensively described here) has the overall aim to explain learning processes. Two principals are of central importance: *Respondent conditioning* and *operant conditioning*. Respondent conditioning (sometimes called Pavlovian conditioning) refers to learning by association. For example, Linda experiences a high level of stress during a meeting with her employer, in which she is asked to complete a report until the next morning (she gets palpitations, breaks out in sweat, and feels dizzy). By respondent conditioning, previously neutral stimuli (such as the room in which they sit or the work clothes that Linda is wearing) may become conditioned to the eliciting stimulus and in themselves elicit a similar stress-reaction at a later time [145]. In other words, Linda's reaction may be generalized to situations or objects that previously did not elicit stress. With this type of generalized learning, exposure to stressors has the potential to increase exponentially (not only was the meeting stressful, but now Linda feels stressed about work the next time she puts on her work clothes), potentially resulting in repeated and and prolonged stress-reactions.

Operant conditioning refers to learning by consequences. As proposed by B.F. Skinner (1902-1990), our behaviors are, to a large degree, governed by whether they are positively or negatively reinforced or punished [146]. Reinforcement increases the likelihood of a behavior by means of reducing an aversive experience (negative reinforcement) or by increasing a desired experience (positive reinforcement). Continuing with the example above: After the meeting with her employer, Linda decides to work late and cancels her evening plans. Her stress-reaction subsides quickly (negative reinforcement), and she feels pride in that she is a trusted employee that is able to problemsolve effectively (positive reinforcement). The consequences of Lindas behavior increase the likelihood that she will behave in a similar

manner the next time she is asked to meet a difficult deadline. Although beneficial in the short run, operant behavior can prohibit new learning experiences (such as investigating what would happen if she declared that the deadline was too short, if she asked for help, or simply refused). Respondent and operant learning interact and perpetuate each other, and, in the long run, influence lifestyle choices that may cause negative health consequences.

2.1.6.2 Cognitive information processing theory

Whereas learning theory broadly speaking concerns how contextual factors govern behavior, cognitive theory focuses on the role of mental processes, such as attention, memory, perception, and problem solving, in affecting our emotions and behaviors. This is evident in the transactional model of stress, for example, which posits that it is the individuals *perception* of a threat or stressor that affects the emotional response and leads to a range of behaviors – not necessarily the stressor in and of itself [2]. When Linda is asked to complete a task at work, for example, her automatic cognitive response is "*I must do an excellent job*" and "*If I fail my boss she will find out that I am a looser and I may get fired*". These thoughts play a significant role in Linda's emotional reaction and behavior. Clearly, perceptions and interpretations are not always "correct" when it comes to evaluating a threat and anticipating events. When a person is experiencing high stress, anxiety, or depression, information processing can become biased [147, 148]. When under stress, for example, attention may be directed towards further threats, and it becomes increasingly difficult to sort and evaluate impressions [149, 150].

In summary, a cognitive behavioral approach to chronic stress implies that both dysfunctional behavioral patterns and biased information processing play a role in the development and maintenance of symptoms.

2.1.6.3 A proposed CBT model for chronic stress

Taking a cognitive behavioral approach to chronic stress points to the importance of analyzing contextual factors of behaviors and thoughts that are incompatible with recovery, and of analyzing dysfunctional avoidance behavior that may reduce the individual's resources to handle demands. Figure 2 presents a model of the maintenance of chronic stress, as proposed by Niclas Almén [151]. The model illustrates how thoughts, emotions, physiological reactions, and behaviors intimately interact and maintain chronic stress once symptoms have already accumulated. Importantly, these maintaining factors often differ from the factors that were central in the initial development of chronic stress. Hence, symptoms may not subside automatically even if the initial stressors are removed.

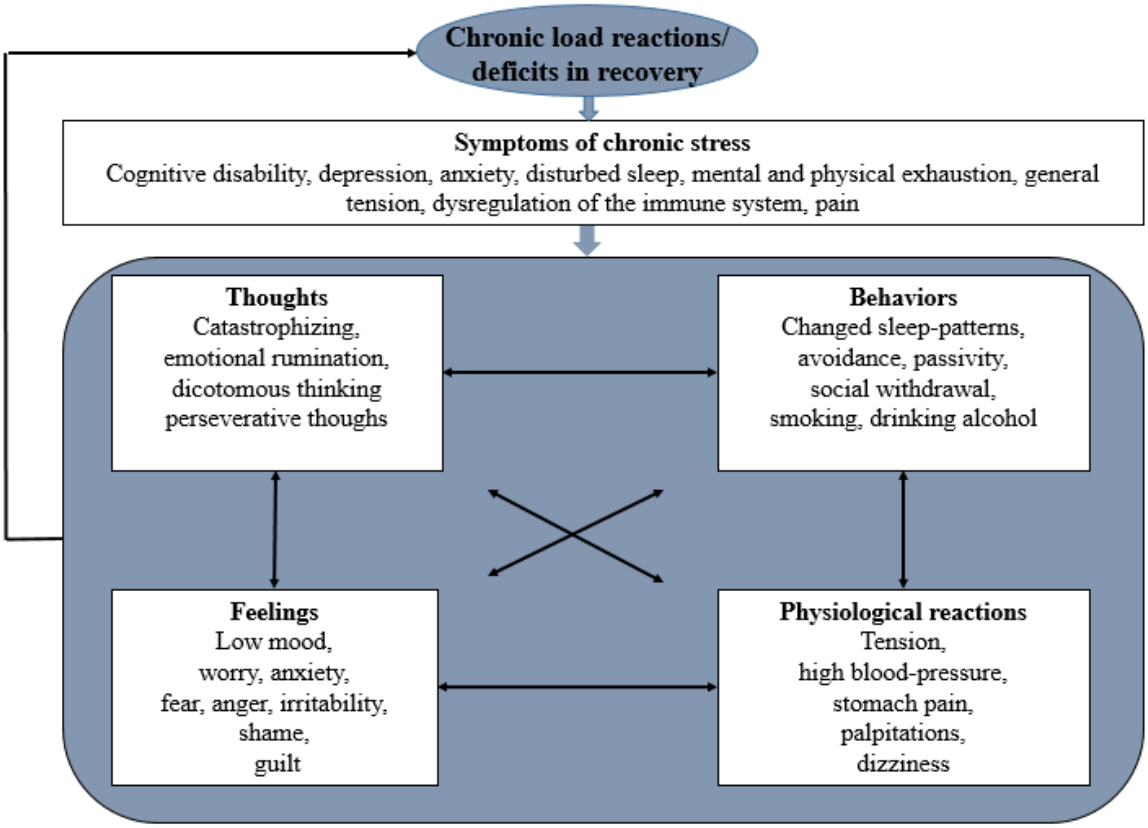

Figure 2. Maintaining model of chronic stress, adjusted and translated with permission from Niclas Almén [151].

Let us look at an example for clarification. John struggled with high job demands for an extended period (several months), while also having small children at home that needed care after working hours. His every day life was full of potential stressors with limited room for recovery. He successively experienced increased tension, disturbed sleep, and fatigue (which, under the circumstances, would be considered normal). These symptoms, in turn, became stimuli for new stress-reactions. At work, for example, John noticed that he had a hard time focusing, and tasks took longer to complete. Not performing at his regular high capacity triggered worry and a feeling of inadequacy. To cope with this, he cut out breaks at work, and opened the computer at home in the evenings to complete what he had not finished. While this temporarily reduced his stress (negative reinforcement), Johns new habits made it more difficult for him to fall asleep. He struggled with perseverative rumination about his life and how he should handle his job. Lying in bed ruminating made John feel that he was actively trying to solve the situation (positive reinforcement). However, increasing fatigue made it more difficult for him to engage in his family, which led to conflicts with his wife (an additional stressor). John began to stay late at work to avoid his wife and the negative emotions evoked by their arguments (negative reinforcement).

Ironically, John's reaction to his situation and his symptoms led to a negative spiral of more symptoms and less recovery. As is common in patients with anxiety and depression, John engaged in behaviors to alter, avoid or control his emotional responding rather than adaptive strategies to deal with the stressful situations [152]. Previous recovery activities, such as taking a lunchbreak with collegues, going to the gym, spending time with family and friends, or

watching a movie at night, came to be directly punished in that they increased Johns feelings of inadequacy, physical tension, and biased cognitions (e.g., *"If I take a break I won't finish work on time and they will think I'm a slacker"*).

In summary, emotional, cognitive, and behavioral responses to chronic stress often perpetuate each other and maintain symptoms by further obstructing recovery. Once this chain of events has begun to live its own life, removing external stressors (by, for example, sick leave) can be a necessary, but often insufficient, solution for symptom reduction. The model proposes that interventions targeting the cognitive and behavioral responses to chronic stress may be helpful in breaking the chain of increased stress-exposure, deficits in recovery, and health-damaging behavior.

2.2 COGNITIVE BEHAVIORAL THERAPY

Cognitive behavioral therapy (CBT) is an umbrella term for psychological treatments that are based on learning theory and/or cognitive psychology. CBT specifically targets patterns of unhelpful behaviors and ways of thinking, and has the overarching treatment goal of improving functioning and achieving symptom reduction by helping patients to alter dysfunctional cognitions and maladaptive behavioral patterns [153]. To date, CBT is by far the most rigorously researched psychological treatment method for a range of mental disorders, with meta-analyses of randomized controlled trials yielding large effect sizes in the treatment of anxiety disorders [154], depression [155], and insomnia [156].

Meta-analyses indicate that CBT may also be a promising treatment method to reduce stress in the working population [157-160]. However, as pointed out by the authors of these meta-analyses, most interventions are applied on a general population of employees rather than on those in need (i.e., that are clinically referred or suffer from high levels of stress and burnout). Indeed, CBT for clinical populations suffering from chronic stress or stress-related disorders has been significantly less studied. Three meta-analyses [64, 161, 162] and one systematic review [163] have evaluated the effect of interventions (mainly CBT) for chronic stress or stress-related disorders. These found no significant effect on symptoms compared with control conditions, but reported low confidence in results due to the limited number of studies eligible for inclusion, limitations in methodological quality of studies, and heterogeneity of studies with regard to treatment content, length, extent, and type (individual or group) of interventions.

In summary, although there is evidence to suggest that CBT can be effective in reducing anxiety, depression, insomnia, and stress, there are important knowledge gaps regarding whether CBT is effective in reducing symptoms in populations suffering from chronic stress in general and stress-related disorders in particular.

2.2.1 Common treatment techniques and protocols

Before we move on to reviewing studies of CBT for chronic stress, I want to present some common treatment techniques included under the CBT umbrella, and present the form and

content common to CBT protocols for chronic stress (including the protocol used in the present research project).

2.2.1.1 Behavioral activation

Behavioral activation is a brief, goal-directed and activating treatment, originally developed for patients with depression [164]. The goal of behavioral activation is to improve mood by means of decreasing negatively reinforced avoidance behavior and increasing behavior that is positively reinforced [165]. Because avoidance and reduced value-driven behavior (i.e., behavior that is in line with what is intrinsically important to an individual) is common to many mental disorders (not only depression), behavioral activation has been suggested to be broadly integrated into psychotherapy [166], also for patients with AD [167]. In a study investigating burnout-depression overlap in schoolteachers, the authors concluded that treatment for depression may be helpful for individuals identified as "burned out" [168].

2.2.1.2 Exposure

Exposure is a therapeutic technique to enable new learning by means of systematically approaching feared stimuli (internal, such as thoughts, feelings and physiological responses, and external, such as physical places and objects) in the absence of the associated aversive event. Building on Linda as an example, she comes to a point where she is afraid to go to work because she thinks she would collapse (which happened on a previous occation). The workplace has become a conditioned stimulus associated with fear. Exposure would imply repeatedly approaching the workplace, learning that the workplace in itself does not cause a collapse. Although it is unknown exactly how exposure excerpts its effect, research suggests that the conditioned response (e.g., fear) may not be completely extinguished. Rather, by means of so called *inhibitory learning*, the conditioned stimulus (e.g., the workplace) continues to be associated with fear on the one hand, but also with safety [169].

Exposure therapy has been shown to be an effective treatment strategy for anxiety disorders [154], and given that anxiety is common in patients with stress-related disorders, it is plausible that patients with stress-related disorders could also benefit from this therapeutic technique. Examples of specific stress-related fear- and avoidance patterns that could be helped by exposure are: Fear of making a mistake or of not performing as well as usual (perfectionism), fear of assertiveness (e.g., stating ones mind or turning down an offer), or fear of symptoms. Fear of symptoms or health deterioration is common in patients with stress-related disorders and feeds avoidance of activities and behaviors that may be health promoting, such as physical activity, making an appointment, or meeting with a friend.

2.2.1.3 Cognitive restructuring and behavioral experiments

Cognitive restructuring is a technique based on information-processing theory, with the aim to affect obstructive emotions and symptoms by means of cognitive reappraisal. Cognitive reappraisal is achieved by identifying dysfynctional beliefs and thoughts that are believed to maintain emotional distress, and then to challenge these beliefs to generate more functional

thinking patterns [148]. For example, Linda holds the belief that "*If I go to work I will surely collapse, and everybody at work will think that I am weak and laugh at me*". By investigating, for example, the likelihood of this aversive event, and what would be the worst thing that could happen if the aversive event occurred, Linda might reappraise her belief and subsequently decrease her fear.

One common way of challenging dysfunctional thoughts is by conducting *behavioral experiments.* Behavioral experiments imply that a person explicitly tests target cognitions by confrontation with anxiety-provoking situations [147]. In the example of Linda, she might visit the workplace to find out whether or not she collapses. She might experiment with showing weakness at work (such as faking a collapse or talking about her health problems) to investigate how her collegues react to her (do they laugh?).

2.2.1.4 Form and content of common face-to-face CBT protocols for chronic stress

Both group CBT [170-179] and individual CBT [170, 180-186] have been evaluated for chronic stress. Group interventions tend to vary greatly in length, with a range of between 8 to 30 sessions spread over a period of 8 weeks to 1 year. In general, each session lasts for about 2-3 hours and includes between 6 to 12 participants. Individual CBT interventions comprise approximately 6 to 10 hours total treatment time, spread over 5 to 16 weeks. Whereas many interventions are administered by psychologists or psychotherapists, other professional categories are also used, such as "labor experts" [180], "stress-management consultants" [171], and occupational physicians [186].

Treatment content is quite similar to what is commonly found in protocols for stress-reduction in non-clinical samples (see, for example, [157]). All protocols include psychoeducation about stress. Most often, cognitive restructuring is the main techniques used, coupled with, for example, time-management or problem solving skills, lifestyle interventions (e.g., establishing daily routines or promoting physical activity), communication skills training, and some kind of relaxation strategy. Generic CBT techniques such as behavioral activation and exposure are rarely employed, at least not explicitly. For example, although some protocols express having an "activating approach" (which is equated with graded exposure) [180, 186], I have found only two studies that specifically mention including exposure techniques in the treatment [172, 178].

When a primary aim of the intervention is to support sick-listed patients back to work, specific components are often included in the CBT for this purpose. Interventions include identification of obstacles for return to work, gradual increases in working hours, and optional meetings with employers [179, 180, 182, 184, 186]. Some studies investigate multidisciplinary treatment approaches and add interventions alongside CBT, such as qigong [179] and mindfulness-based stress-reduction [184].

2.2.1.5 Multimodal rehabilitation

Multimodal rehabilitation (MMR) is a complex intervention with the aim to provide rehabilitation and improve functioning in those with chronic health conditions. MMR consists

of varying interventions delivered by different health professional categories, and usually incorporates group treatment (based on CBT) given parallel to, for example, physical activity, vocational rehabilitation and, potentially, antidepressant treatment [30, 64, 187]. In Sweden, MMR is the recommended treatment for ED [30], even though evidence of the effectiveness of this type of extensive and costly treatment program is limited. As pointed out in a recent narrative review, the interpretation of MMR studies is complicated by the fact that it is not a uniform concept and can include a range of different treatment modalities [187].

2.2.1.6 The protocol used in this research project

The CBT protocol used in the studies included in this thesis has been developed over years of clinical practice at Gustavsbergs primary care clinic in Stockholm, Sweden. A basic assumption of the treatment is that stress is a natural and necessary part of life, but that negative health consequences may result from insufficient recovery in combination with maladaptive behaviors adopted in response to sustained stress (see section 2.1.6.3). Independent of symptoms and functional ability, a goal of the treatment is to support patients in developing a daily balance between effortful expenditure and recovery, in order to improve coping capacity and support patients in becoming active agents in their own lives. Table 2 summarizes the treatment components, as well as the main exercises worked with throughout treatment. Although the treatment incorporates both cognitive and behavioral components, it is primarily behaviorally oriented.

The treatment begins with psychoeducation about acute and chronic stress, as well as common behavioral patterns that may maintain symptoms. It is important to explain and normalize psychological and physiological reactions, because studies have shown that negative beliefs about stress can predict somatic symptoms and moderate the affective response to real life stressors [78, 188, 189].

The treatment then moves on to target deficits in recovery by encouraging identification and scheduling of idiosyncratic recovery activities, as well as by introducing a short relaxation exercise. As a means of supporting recovery, one session is dedicated to giving psychoeducation about sleep [190] together with empirically supported interventions for improved sleep (sleep hygiene and stimulus control) [156, 191].

The next step in the treatment involves work to identify central life values (i.e., what kind of a person do I want to be, and what is genuinely important to me?) within different areas of life (e.g., relationships, leisure time, occupational). Values constitute the motivational basis from which behavioral repertoires can successively be adapted to include more positively reinforcing and health promoting behaviors. From module 4 and onward, the treatment essentially incorporates the brief behavioral activation treatment for depression (BATD) as developed by Lejuez and collegues [165]. Additionally, exposure techniques [192] are taught in module 6 to help patients deal with difficult emotions and impulses that may arise when working with behavior change, and break fear-avoidance patterns related to, for example, assertiveness, perfectionism, and excessive worry.

Table 2. *Overview of treatment content in CBT for stress-related disorders*

Module	Theme	Main exercises
1	Introduction to CBT and psychoeducation about stress	Monitoring daily activities and experiences (diary) Functional analysis
2	Learning recovery techniques and practicing relaxation	
3	Dealing with disturbed sleep	
4	Identifying values and breaking them down into concrete activities/behaviors	
5	Behavioral activation, taking steps	Scheduled recovery Practicing relaxation
6	Exposure, dealing with difficult emotions, breaking fear-avoidance patterns	
7	Continued behavior change toward life balance and health	Challenging unhelpful behavioral patterns, taking new steps Behavioral activation and
8	Continued behavior change toward life balance and health	
9	Identifying and challenging core cognitive assumptions	
10	Communication skills, assertiveness training	
11	A summary of the treatment	
12	Maintaining gains and relapse prevention	

CBT, Cognitive behavioral therapy

Towards the end of the treatment (modules 9 and 10) core cognitive assumptions (i.e., insistent beliefs about, for example, how one *should* behave to be socially accepted) are identified. Such assumptions have likely been helpful during other periods in life, but for patients suffering from chronic stress they may maintain behavioral patterns that obstruct recovery and desired behavioral change. Strategies for helpful communication when under stress are taught and practiced. These include strategies for self-assertion (i.e., clearly communicating ones needs or opinions), strategies for giving and receiving critique, and listening to another person.

Through self-monitoring and work with functional analyses throughout the treatment, patients identify their own maladaptive stress-related cognitions and behavioral patterns that are believed to maintain symptoms of chronic stress. They are encouraged to plan their days to include a variety of effortful activities, value-driven activities, and recovery activities. Upon completing the treatment, patients create a plan to maintain gains and prevent relapse.

In the current research project, the treatment was evaluated both as an individual face-to-face treatment and as an ICBT. In both formats, modules were presented in a consequtive order and patients had weekly communication with their therapists (licenced clinical psychologists). In the ICBT, therapists and patients communicated exclusively via the treatment platform, and because treatment content was conveyed through text in the platform, communication mainly included feedback on exercises as well as support in problem solving and treatment adherence.

Of note, upon converting the treatment from the face-to-face protocol to the internet platform, two sessions were added (modules 7 and 8 in Table 2). These included no new information but were designed to further support patients in working with the behavioral changes that were identified as important in the previous modules.

2.2.2 Randomized controlled trials of face-to-face CBT

In this section I will give an overview of the existing evidence for face-to-face CBT for chronic stress and stress-related disorders. The studies reviewed are exclusively randomized controlled trials of adult, clinical populations (i.e., participants have undergone clinical assessment and are not recruited solely based on elevated symptom levels on a self-rating scale).

2.2.2.1 Treatment effect on symptoms

In most studies, CBT has been found superior to waitlist control conditions pre- to posttreatment [175, 176, 178, 184, 185]. Studies that have compared CBT with "no treatment" control groups (in which patients were clinically assessed and then free to seek other help), however, have generated mixed results: One study indicated that CBT was significantly superior to no treatment [183], but two studies found no differences between groups regarding symptom reduction [181, 182]. Of note, in these studies approximately half of patients in the control groups received psychological treatment outside of the studies.

Studies that have explicitly compared CBT with other active treatments and/or treatment-as-usual (TAU), have generated a rather consistent pattern of findings: Symptoms have reduced in all treatment arms over time, but no significant interaction effects have been found (i.e., there appears to be no specific effect of CBT) [170, 173, 177, 179, 184]. This was the case when, for example, cognitively oriented group CBT was compared with psychodynamic group therapy and with TAU [173], when CBT (including work place interventions) with added qigong was compared with qigong only [179], and when CBT was compared with a work-focused CBT and TAU [180]. When a multidisciplinary treatment including CBT, work-place dialogue, and mindfulness-based stress-reduction was compared with TAU (12 conventional, individual sessions with a psychologist) and a WLC, the treatment was no more effective than TAU, but both CBT and TAU were more effective than the WLC in reducing symptoms [184].

There are some exceptions to the pattern described above. When group CBT was compared with a physical activity intervention and TAU, CBT was found to be more effective than physical activity in improving general health in patients (even at the 6- and 12-month follow-ups), and also in reducing burnout ratings pre- to posttreatment compared with TAU [171]. However, on all other outcomes (of note, no primary outcome was reported) no significant differences were found between groups. In a study in which CBT was compared with a placebo group intervention for sick-listed men, CBT was found to be significantly more effective on all symptom domains pre- to posttreatment [172].

It is difficult to interpret and draw conclusions from the relatively limited number of randomized controlled trials that have been conducted of CBT for chronic stress. Studies use differently defined populations, different outcome measures (rarely specifying a primary outcome), and different treatment approaches (e.g., "Work-focused CBT", or multidisciplinary treatment programs of which CBT is a part). Further, several methodological issues limit conclusions. For example, studies using three treatment arms tend to include small sample sizes, thus limiting power to detect true differences between interventions [170, 171, 173, 177]. Some studies suffer from substantial attrition [170, 173, 179], from low treatment adherence, and from the fact that patients to a large extent receive treatment outside of the study [e.g., 179, 182-184].

2.2.2.2 Treatment effect on sick leave

Because chronic stress is often defined, in part, by inability to work (i.e., sick leave), and a majority of studies require sick leave for inclusion [171, 173, 179, 182-184], days on sick leave or rate of return to work is often a central outcome in randomized controlled trials of face-to-face treatment for chronic stress. Evidence of the effect of CBT on sick leave for individuals with chronic stress is mixed. Some studies have found interventions based on CBT principles to facilitate return to work or lead to full work resumption faster than control conditions [184, 186, 193]. Others, however, have not [170, 183]. In a study by Blonk and colleagues [180], an intervention administered by labor experts that combined CBT principles with interventions targeting increased work resumption was found to reduce time to partial and full return to work compared with only CBT. Willert and colleagues found that CBT compared with a waitlist control was effective in reducing self-reported absenteeism, but registry-based data on sick leave did not show significant differences between groups [194].

In a Cochrane Review of interventions to facilitate return to work in adults with AD, authors found moderate quality evidence that CBT did not reduce time to partial or full return to work compared with no treatment [162]. However, interventions directly aimed at supporting return to work by means of problem solving (often based on CBT-principles) were found to significantly enhance partial return to work at 1-year follow-up compared with non-guideline based care [162]. A recent meta-analysis of tertiary interventions for chronic stress found a significant overall effect of CBT on partial return to work compared with controls [64]. One meta-analysis of psychological interventions (including CBT) for CMDs (including stress-related disorders), found a small but significant effect of treatment on sick leave [195]. In this meta-analysis there were no differences in effect between interventions with a primary aim of reducing symptoms and those which aimed directly at supporting return to work [195].

2.2.2.3 Summary of evidence base

In summary, research on CBT for chronic stress and stress-related disorders is limited and results are mixed. The lack of internationally congruent diagnostic terms and assessment procedures, heterogeneity in interventions and outcomes, and methodological limitations, makes it difficult to interpret results and draw conclusions about the effect of CBT for patients

with stress-related disorders. More adequately powered, methodologically sound randomized controlled trials are needed.

2.2.3 Therapist-guided internet-based CBT

There is a high demand for CBT amongst patients with mental health problems, but access to treatment is generally limited [196]. To overcome the gap between demand and access, delivering treatment via the internet has emerged as a viable option over the past 20 years [197]. The main idea of therapist-guided internet-based CBT (ICBT) is to help individuals accomplish the same cognitive- and behavioral changes as with conventional CBT, but treatment content is delivered via the internet by means of self-help texts and other multimedia tools. In ICBT, patients generally communicate with their therapist weekly throughout the treatment by asynchronous, email-like text messages in the treatment platform. However, studies have increasingly investigated different forms for therapist support, such as only providing support upon the request of the participant (so called adherence-focused support) [198, 199]. Self-guided internet-based treatments (i.e., with no therapist support except for, perhaps, technical support) have also been investigated [200-202], but most studies point to the importance of therapist support for treatment effectiveness [203, 204] as well as for optimizing adherence and preventing drop out [205, 206].

ICBT has been shown to be efficacious for anxiety disorders [207, 208] and depression [207, 209], and is indicated to be equally effective as face-to-face CBT in treating these conditions [210, 211]. Because ICBT often requires less than 10 minutes of therapist time weekly per patient [197], ICBT can be a resource efficient alternative to face-to-face CBT, with additional benefits including increased availability of treatment to patients in rural areas, and that patients can access the treatment outside office hours.

2.2.3.1 What do we know about ICBT for chronic stress?

The short answer to this question is: Not very much. When it comes to ICBT for stress-reduction, significantly less research has been carried out compared with face-to-face CBT. Even so, two meta-analyses and one review have been conducted of web- and computer-based interventions to reduce stress, jointly pointing to a potential positive effect of ICBT in reducing stress in heterogeneous samples [204, 212, 213]. Whereas the meta-analysis conducted by Stratton et al. [213] included interventions for a broad range of mental health problems in employees, Heber et al. [204] specifically investigated the effect of interventions aimed at reducing stress. In that meta-analysis, ICBT was found to reduce level of perceived stress with small to moderate effect sizes compared with waitlist control conditions. Interventions generally lasted between 6 and 12 weeks, and were most often self-guided. Many of the included studies had a high risk of bias and there was moderate heterogeneity between trials [204]. Of note, however, some individual studies with high methodological rigor investigated the effect of ICBT for stress-reduction in employees with elevated levels of stress, generating large effect sizes on symptoms of stress and significant effects on a range of secondary mental health outcomes [198, 200, 214].

As is the case for most studies of face-to-face CBT for stress-reduction, samples studied in trials of ICBT are often unselected, non-clinical (or with elevated symptoms as assessed by self-rating scales), and have rarely undergone formal assessment with respect to somatic and psychiatric morbidity. Hence, although there are promising indications of ICBT for stress-reduction, generalizability of findings to those suffering from chronic stress or stress-related disorders may be limited.

I have found only two randomized controlled trials that have investigated ICBT for clinical samples of chronic stress. In one of the studies, the effect of a brief (four modules) CBT based on relaxation, time management, mindfulness, and strategies to cope with interpersonal difficulties, was compared with a waitlist control condition for individuals with AD [215]. AD was determined using a self-rating scale to assess the ICD-11 diagnostic criteria. Participants had full access to modules and the intervention was completely self-guided. In that study (N = 284), 52% of participants never completed a single excersise, and 86% of participants failed to complete follow-up assessment. Hence, although a completers-analysis indicated a moderate waitlist-controlled effect size on AD symptoms in the intervention group, no firm conclusions can be drawn regarding the efficacy of the intervention. The second study tested the efficacy of ICBT for a clinically assessed sample of managers diagnosed with any condition included in the section F43 *Reaction to severe stress, and adjustment disorders* in the ICD-10 (including ED). The treatment content was somewhat similar to that of the ICBT investigated in the present thesis (see section 2.2.1.6). Results indicated that the intervention generated large effects on symptoms of stress and exhaustion compared with an attention control group, and effects were maintained at a 6-month follow-up [216].

As for sick leave, no ICBT study aimed at reducing stress has, to my knowledge, assessed sick leave objectively (i.e., by use of registry data). Work-related outcomes are sometimes addressed in terms of, for example, self-rated absenteeism and presenteeism. On these outcomes, most studies have found no effect of ICBT compared with waitilist control conditions [198, 214, 216]. An exception was in the study by Ebert et al. [200] in which self-guided internet-based stress-management was found to produce a small but significant effect on presenteeism six months after treatment completion.

In summary, although ICBT is indicated to be efficacious in treating many mental disorders, and is likely efficacious in reducing stress in mixed samples, more large scale randomized controlled trials are needed to test the efficacy of ICBT for clinical samples diagnosed with stress-related disorders.

2.2.4 Health economic effects

Health economic evaluations are important to provide decision makers with information about which treatments give maximum effect in relation to their cost [217]. Without knowledge of cost-effectiveness, there is a risk that healthcare resources are used inefficiently, and that fewer can be offered treatment [218]. The question of costs in relation to effects may be of particular

importance when it comes to treatment for ED, given that the recommended multimodal rehabilitation programs imply high costs and lack evidence of effectiveness [219].

Two common forms of health economic analyses are cost-effectiveness and cost-utility analyses. Cost-effectiveness concerns the association between costs and disease-specific effects (such as remission rates), whereas cost-utility concerns the association between costs and more general outcomes that are meaningful regardless of clinical condition (such as health-related quality of life). To estimate cost-effectiveness and cost-utility, incremental cost-effectiveness ratios (ICERs) and cost-utility ratios (ICURs) are usually calculated. ICERs and ICURs are the difference in costs between two conditions, divided by the difference in condition effect (i.e., remission rates or health-related quality of life, respectively) [217]. Analyses can be conducted from the perspectives of different stakeholders, such as society, the healthcare system, or the clinic. Because the amount of money a decision maker is willing to pay for, for example, one additional patient in remission, it is crucial in determining whether a new treatment is to be adopted or not, cost-effectiveness and cost-utility are usually expressed in terms of different willingness to pay (WTP) scenarios.

Although there are indications that work-site mental health interventions for stress-reduction may yield a positive cost-benefit ratio (i.e., monetary benefits, not in relation to clinical outcomes), health economic studies of interventions aimed at reducing stress generally suffer from low methodological quality, and evidence of cost-effectiveness and cost-utility is lacking [220]. I have found only two health economic evaluations of internet-based interventions aimed at reducing stress in employees with elevated work-related stress [221, 222]. Both of these studies indicated that the interventions had approximately 70% probability of being cost effective compared with waitlist control conditions, from an employer's perspective [221] and from a societal perspective [222], at a WTP of 0. Although these results are promising, to the best of my knowledge, no study to date has conducted a health economic evaluation of CBT (or ICBT) for patients diagnosed with AD or ED.

2.2.5 Mediators of change

Although CBT is indicated to be effective in reducing stress and stress-related symptoms (see, for example, [157]), there are to date large knowledge gaps regarding what factors in treatment contribute to bringing about these changes. The mixed results found across studies investigating CBT for chronic stress suggest that not all patients are sufficiently helped, and that there is substantial room for improvement of interventions.

One way of improving treatment outcomes is by identifying central mechanisms by which treatments work. Treatment mechanisms refer to the chain of events or processes that explain how therapeutic change comes about [223]. The identification of mechanistic processes can lead to more effective treatments by means of explicitly developing strategies to target those mechanisms [224]. The first step to uncover treatment mechanisms is often to identify mediators of treatment effect. A mediator can be defined as an intervening variable that

statistically accounts for the relationship between an independent variable (such as treatment) and a dependent variable (such as perceived stress) [223].

Only a few studies have conducted mediation analyses within randomized controlled trials of CBT for stress-reduction. In a study by Lloyd, et al. [225], increased psychological flexibility (i.e., the ability to focus on the current situation and take action in spite of difficult thoughts or feelings) was found to mediate reduction in emotional exhaustion in a non-clinical sample that underwent a brief, waitlist-controlled group intervention. Another study found improved emotion regulation to mediate the effect of a waitlist-controlled ICBT on level of perceived stress in a sample of employees with elevated levels of stress [198]. Yet another study investigated putative mediators of change by an internet-based intervention with the aim to improve recovery from work-related strain in teachers with sleeping problems [226]. Results indicated that the treatment, compared with a waitlist control, fostered an increase in recovery activities which in turn were related to lower perseverative cognitions (worry and rumination) and a subsequent reduction in disturbed sleep (the main outcome measure). Recently, our research group found that a reduction in impaired sleep partly mediated the effect of face-to-face CBT (the intervention described in section 2.2.1.6) compared with an active control condition (RTW-I) on symptoms of exhaustion in patients diagnosed with ED [227].

To summarize, although there is very limited knowledge to date regarding what factors bring about change in CBT for chronic stress, cognitive factors (such as psychological flexibility and perseverative cognitions), emotion regulation, and increased recovery (e.g., by improved sleep) are indicated to be potentially important treatment targets for symptom reduction by CBT.

2.3 SUMMARY AND CURRENT DIRECTIONS

It is clear that, although a bountiful body of research exists when it comes to understanding stress as a psychophysiological phenomenon and its relationship to clinical correlates and potential risk- and maintaining factors, there are important knowledge gaps when it comes to treatment. Most studies have evaluated interventions in work-settings using heterogeneous, non-clinical samples [157-160]. Few randomized controlled trials of interventions targeting stress-related disorders have been conducted. There is large heterogeneity between trials (regarding inclusion, interventions, and outcome measures), results are mixed, and many methodological issues remain to be solved before a solid evidence-base can be built for any one protocol targeting AD or ED [64, 161-163].

In clinical settings, patients suffering from chronic stress and stress-related disorders are many in number, yet few receive psychological treatment. Finding highly accessible, and efficacious, treatments that can be disseminated on large scale is of importance to meet patient demand and reach out to the many individuals who may perceive barriers to seeking help. There is vast support for the effectiveness of ICBT for many mental health conditions [197], and there are indications that ICBT might also be effective in reducing stress and exhaustion [198, 214, 216]. In fact, internet-based interventions have been suggested to be particularly suitable for patients diagnosed with AD, because the low treatment threshold and high accessibility could counteract the development of more severe mental health conditions [228]. However, to date only very few randomized controlled trials have investigated the efficacy of ICBT for patients with stress-related disorders.

Whereas treatment recommendations for AD generally suggest brief interventions [167, 228], treatment guidelines for ED in Sweden encompass a multitude of interventions, such as MMR [30], and sick leave recommendations are up to one year [41]. The differential recommendations, not based on a solid empirical ground, have great implications for societal and healthcare costs as well as for the care that patients receive. Irrespective of whether interventions are effective or not, outcomes should always be placed in the context of costs for the individual and for society as a whole in order to make wise choices as to which treatments to implement [229]. There is a dire need for health economic trials investigating cost-effectiveness and cost-utility of interventions before treatment recommendations are given.

Because most interventions for chronic stress consist of "packages" of treatment techniques (even when under a common umbrella of CBT), more knowledge is needed as to *how* the treatments work, that is, which specific factors or processes mediate treatment effect? To date, knowledge about mediators and mechanisms of change in the treatment of chronic stress is limited. This staggers the improvement of existing protocols and the development of new treatment strategies [224]. More studies investigating putative mediators of treatment effect in randomized controlled trials are needed to bring the field of intervention research forward for stress-related disorders.

3 AIMS OF THE THESIS

The overarching aim of the present thesis was to build and expand on the limited knowledge base regarding CBT as a treatment for stress-related disorders by further investigating clinical efficacy, cost-effectiveness, and mediators of change in treatment.

3.1 STUDY I

The aim of Study I was to evaluate the effectiveness of disorder-specific CBT, a return-to-work intervention (RTW-I), and a combination of the two (COMBO) for patients on sick leave due to a common mental disorder (CMD). We hypothesized that CBT, alone or as part of COMBO, would be superior to the RTW-I in reducing symptom severity, and that the RTW-I, alone or as part of COMBO, would be superior to CBT alone in reducing days on sick leave. For the purpose of the present thesis, the aim of Study I was also to evaluate the effect of a new CBT protocol used to treat patients with AD or ED, conditions for which no evidence-based treatment protocols exist. The main hypothesis was that CBT for these stress-related disorders would be superior to the RTW-I in reducing symptom severity.

3.2 STUDY II

The aim of Study II was to evaluate the CBT protocol for stress-related disorders used in Study I, when delivered as a therapist-guided internet-based intervention (ICBT). We hypothesized that, compared with a waitlist control condition (WLC), ICBT would result in significant improvements in level of perceived stress as well as in a range of other health related outcomes. We also investigated whether ICBT would have an effect on functional impairment and self-rated work ability compared with the WLC.

3.3 STUDY III

The aim of Study III was to evaluate cost-effectiveness of ICBT from a societal perspective and from a healthcare perspective. Data on clinical outcomes and resource utilization was collected in tandem with Study II. We hypothesized that, compared with the WLC, ICBT would generate improvements at no or low net costs pre- to posttreatment, thereby making the treatment cost effective.

3.4 STUDY IV

In Study IV we aimed to further investigate the role of sleep impairment in mediating the effect of CBT on symptoms in patients with stress-related disorders (for our previous findings, see [227]). Based on data collected in Study II, we hypothesized that a reduction in impaired sleep would mediate the effect of ICBT on level of perceived stress and exhaustion compared with the WLC. We also aimed to explored whether a potential mediated effect would be moderated by participants' level of impaired sleep at baseline.

4 THE EMPIRICAL STUDIES

Studies I and II in this thesis were randomized controlled trials conducted with different samples. In Study I, a broader sample of patients with CMDs was included, of which a majority (72%) were diagnosed with AD or ED. Because CBT for stress-related disorders is the primary focus of this thesis, the overall results from Study I will be complemented by results from a recently published subgroup analysis of patients with stress-related disorders based on Study I (not included in the thesis) [230]. In Study II, only patients with a principal stress-related disorder of AD or ED were included. Studies III and IV are based on data from Study II. Table 3 summarizes the sample characteristics of patients with stress-related disorders in respective trial.

Table 3. *Overview of demographic characteristics of patients diagnosed with AD or ED in the randomized controlled trials of Study I and Study II in this thesis*

Demographic variables		**Study I** *N*=152[a]	**Study II** *N*=100
Gender	Women, *n* (%)	132 (86.8)	85 (85.0)
	Men, *n* (%)	20 (13.2)	15 (15)
Age	Mean age (*SD*)	43.7 (9.2)	47.2 (8.8)
	Range	23-64	26-65
Principal disorder	AD, *n* (%)	25 (16.4)	53 (53.0)
	ED, *n* (%)	125 (82.2)	47 (47.0)
Mean duration[b]	Mean years (*SD*)	0.6 (0.4)	1.6 (1.3)
Highest education[c]	College/University	85 (55.9)	91 (91.0)
	Secondary school 2-3 years, *n* (%)	58 (38.2)	9 (9.0)
	Compulsory school 9 years, *n* (%)	10 (6.6)	0 (0.0)
Psychotropic medication	Antidepressants, *n* (%)	32 (21.1)	11 (11.0)
	Anxiolytics, *n* (%)	17 (11.2)	2 (2.0)
	Hypnotics, *n* (%)	39 (25.7)	17 (17.0)
Received intervention	CBT[d], *n* (%)	52 (34.2)	50 (50.0)
	RTW-I, *n* (%)	49 (32.2)	N/A
	COMBO, *n* (%)	51 (33.6)	N/A
	WLC, *n* (%)	N/A	50 (50.0)

Note: Study I consisted of primary care patients who were on sick leave due to a stress-related disorder. Study II consisted of a nationally recruited sample that was self-referred. AD, adjustment disorder; ED, exhaustion disorder; CBT, cognitive behavioral therapy; RTW-I: Return-to-work intervention; COMBO, combination of CBT and RTW-I; WLC, waitlist control condition.

[a]Total number of patients with stress-related disorders in Study I. The total study sample, including patients with social anxiety disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, major depressive disorder, and insomnia, was *N*=211.

[b]In Study I, Mean duration refers to disorder and was established through clinician assessment, whereas in Study II, Mean duration was self-rated by patients and refers to stress-related symptoms.

[c]Education level was assessed differently in Study I and Study II, why any higher education after secondary school here is referred to as "College/University".

[d]Face-to-face or via internet.

4.1 STUDY I: COGNITIVE BEHAVIOURAL THERAPY AND RETURN-TO-WORK INTERVENTION FOR PATIENTS ON SICK LEAVE DUE TO COMMON MENTAL DISORDERS: A RANDOMIZED CONTROLLED TRIAL

4.1.1 Methods

4.1.1.1 Procedure and inclusion

Study I was a multisite parallel randomized controlled superiority trial in which 211 consecutively recruited primary care patients on sick leave due to a CMD were randomized to either (1) CBT, (2) RTW-I, or (3) COMBO. Potential patients were referred to the study by general practitioners at four primary care clinics that were part of the study, and subsequently underwent a structured assessment procedure conducted by a licenced psychologist which included the Mini International Neuropsychiatric Interview [MINI; 231].

Inclusion criteria were: (a) age 18 to 65, (b) being on sick leave (50-100% of full time) for at least one month but no longer than six months due to a CMD (specified as AD, ED, social anxiety disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, major depressive disorder, or insomnia), (c) a score of 4-6 on the 0-8 scored clinician-administered Clinician's Severity Rating [CSR; 232], (d) if on medication for a CMD, this had been stable for at least three months, (e) low risk of suicide, (f) no current self-harm, dementia, bipolar disorder, psychosis, or eating disorder, (g) no current substance abuse, and (h) ability to read Swedish.

Of the total sample, 152 patients (72%) were diagnosed with a primary stress-related disorder (i.e., AD or ED).

4.1.1.2 Outcomes

Primary outcomes were (a) psychiatric symptom severity assessed using the CSR [232] at post-treatment and at 6- and 12-months after randomization, and (b) net days of sick leave one year after randomization, data collected from the registry of the Swedish Social Insurance Agency. Secondary generic outcome variables were depression, anxiety, perceived stress, quality of life, and work ability.

Although not reported in Study I, disorder specific self-rating scales were also administered at the different assessment points. Patients with AD and ED reported level of perceived stress using the 14-item Perceived Stress Scale [PSS, 233], and patients diagnosed with ED reported symptoms of exhaustion using the 22-item Shirom-Melamed Burnout Questionnaire [SMBQ, 234]

4.1.1.3 Treatments

The CBT protocols used were disorder-specific protocols for respective CMD. In lack of evidence-based treatments for stress-related disorders, patients diagnosed with AD or ED were

treated with a CBT protocol developed by our research group that had been tested in clinical practice since 2007. A central aim of that treatment was to help patients achieve a balance between effortful expenditure and recovery in every day life, by scheduling idiosyncratic recovery activities and practicing relaxation, but also by incorporating traditional CBT components such as behavioral activation and exposure techniques to support patients in making value-driven and healt-promoting behavioral changes. Please see section 2.2.1.6 for a detailed description of the treatment. The treatment consisted of 9-13 weekly individual sessions.

The RTW-I was a psychological intervention with the primary aim of supporting patients in taking steps toward a sustainable and healthy work situation. The treatment was developed by our research group and focused on establishing early contact with the employer [235] and planning graded exposure to the work place [186]. The RTW-I consisted of four central modules: (1) conceptualization, (2) psychoeducation (3) planning, and (4) monitoring adherence to the plan. In the conceptualization module, causes for sick leave were investigated, as were work-related goals and perceived barriers to return to work. The patient received information about the national social security system, the employers responsibilities, and medical guidelines for prescribing sick leave. Pros and cons with sick leave were discussed. Pychoeducation was based on a cognitive behavioral approach and included topics such as behavioral activation, exposure, and problem solving, with the specific aim to support patients in approaching work life and dealing with difficult emotions and situations related to the work place. Modules 3 and 4 were based on gradual exposure to the work place, and included optional meetings with the employer and other parties involved in the sick leave process, such as the Social Insurance Agency and the general practitioner. The purpose of such meetings was to create a plan for sustainable work resumption and to support the patient in following that plan. The RTW-I consisted of 7-11 individual sessions that could be spread over a period of up to 20 weeks.

The COMBO combined CBT and the RTW-I, starting with three RTW-I sessions (modules 1-3) and then monitoring the RTW progress parallel to administering the complete CBT protocol. Depending on which disorder-specific CBT protocol was administered, the COMBO could vary in length between 10 and 25 sessions, spread over a maximum of 25 weeks.

4.1.1.4 Statistical analyses

Mixed-effects models were used to analyze differences between conditions in symptoms and days on sick leave. Effect sizes for symptoms were calculated using Cohen's *d.* To analyze net days on sick leave, we used full day equivalents, adjusted for days on sick leave one year before randomization.

4.1.2 Results

All treatments were associated with large reductions in symptom severity and secondary symptom outcomes pre- to posttreatment (d = 0.8-2.5). CBT was significantly superior to the RTW-I in reducing symptom severity (CSR; Cohen's d = 0.4). No significant differences were

found between COMBO and CBT or COMBO and the RTW-I. Improvements were maintained to the 1-year follow-up. At that time, however, there were no longer any significant differences in symptom severity between treatments. There were no significant differences in net days of sick leave between treatments one year after randomization.

4.1.2.1 Subgroup analysis of patients with stress-related disorders

Subgroup analyses (published separately, please see [230]) of patients with stress-related disorders showed that the CBT protocol developed for this patient group was significantly superior to the RTW-I in reducing symptom severity pre- to posttreatment, with a moderate between-group effect size of Cohen's $d = 0.53$. There was no significant difference between the COMBO and the RTW-I or between the COMBO and the CBT on this outcome. Within-group effect sizes on symptoms of perceived stress were large in all treatment groups ($d = 1.20$-1.67) pre- to posttreatment, as were effect sizes on symptoms of exhaustion (reported only by patients with ED; $d = 1.50$-2.04). There were significant interaction effects between time (pre- to posttreatment) and group (CBT, RTW-I, COMBO) indicating that patients in the COMBO reduced their level of perceived stress significantly more than patients in the RTW-I with a small to moderate between group effect size ($d = 0.48$). CBT was superior in reducing symptoms of exhaustion in patients with ED compared with patients with ED in the RTW-I ($d = 0.38$). No differences were found between treatments with regard to net days on sick leave, and one year after randomization there were no longer any significant differences between treatments on symptom severity or on self-rated symptoms of perceived stress and exhaustion.

4.1.3 Conclusions

Disorder-specific CBT was indicated to reduce symptom severity in sick-listed patients with CMDs at a faster pace than a work-focused psychological intervention (RTW-I). The RTW-I did not contribute to reduced net days on sick leave to the 1-year follow-up compared with CBT. Because a large majority of patients with CMDs in Study I were diagnosed with a stress-related disorder, it is plausible that findings are representative of this patient group. Indeed, this was confirmed in a separately published post hoc subgroup analysis [230]. Because this was the first randomized controlled trial in which the CBT protocol for stress-related disorders was evaluated, results need to be replicated. Seeing that stress-related disorders account for the largest increase in new sick leave spells [61] and for the longest sick leave periods in Sweden [72], further investigation into interventions that may prevent and shorten sick leave periods is warranted.

4.2 STUDY II: INTERNET-BASED COGNITVE BEHAVIORALTHERAPY FOR CHRONIC STRESS: A RANDOMIZED CONTROLLED TRIAL

4.2.1 Methods

4.2.1.1 Procedure and inclusion

Study II was a randomized controlled efficacy trial in which 100 individuals diagnosed with AD or ED were randomized to ICBT (n = 50) or to a WLC (n = 50). Participants were recruited nationally via a newspaper ad and via social media. Primary inclusion criteria were (a) age 18–65, (b) a primary diagnosis of AD or ED, (c) no substance abuse or dependence in the past six months, (d) no current or past psychosis or bipolar disorder, (e) no suicidal ideation (f) if on medication with a monoamine agonist, this had been stable in the past month, and (g) no on-going psychological treatment.

Inclusion criteria were assessed by a licensed psychologist using information collected in a telephone-conducted clinical interview comprising the MINI [231], and data obtained from an online screening. Randomization was stratified based on disorder (AD or ED) to ensure equal distribution of AD and ED across treatment conditions and enable subgroup analyses.

4.2.1.2 Outcomes measures

The primary outcome measure was the 14-item PSS [233]. Secondary outcome measures included the 22-item SMBQ [234], which was used to assess symptoms of exhaustion, and a range of other outcome variables such as depressive symptoms, anxiety, insomnia, and quality of life. Further, we assessed functional impairment and work ability. All outcome measures were self-report questionnaires filled in online before treatment start (pre), after the 12 week treatment phase (post), and (for the ICBT group only) 6 months after treatment (6MFU).

4.2.1.3 Treatments

The ICBT was a 12-week intervention delivered via a secure web platform where psychoeducation, worksheets, and exercises were presented primarily through text. Patients received weekly online support from an assigned therapist who gave gradual access to modules. Treatment content was almost identical to the treatment protocol used in Study I, and is described in detail in section 2.2.1.6 in the background of this thesis. Like in Study I, the treatment included work to increase daily recovery and improve sleep, as well as behavioral activation and exposure techniques to break fear-avoidance patterns. Patients in the WLC received no treatment during the 12-week main phase of the trial. They were immediately crossed over to ICBT after the 12-week treatment phase.

4.2.1.4 Statistical analyses

Continuous outcomes were analyzed using mixed-effect modeling, where the main statistical parameter of interest was the interaction effect of time (pre- to posttreatment) and study group

(ICBT vs. WLC). Subgroup analyses were conducted for AD and ED respectively. Within- and between-group effect sizes were calculated using Cohen's *d*, and the proportion of patients with clinically significant improvement on the outcomes perceived stress (PSS) and exhaustion (SMBQ) were calculated using the criteria proposed by Jacobson and Truax [236]. All analyses were based on an intention to treat approach.

4.2.2 Results

Data loss was very limited at post treatment (1 of 50 in ICBT and 2 of 50 in the WLC did not complete self-rating scales) and at the 6MFU (3 of 50 in ICBT did not complete self-rating scales). Patients in ICBT on average completed 9.2 out of 12 modules (*SD* = 3.2). Average therapist time spent per week and patient was a little over 7 minutes over the course of treatment.

Figure 3 illustrates the improvement on the PSS, which is indicative of the general pattern on almost all symptom outcomes measured in the study. Compared with the WLC, the ICBT led to large improvement in the primary outcome perceived stress (Cohen's *d* = 1.09), and moderate to large improvement in all secondary symptom domains compared with the WLC. At posttreatment, 62% of patients in ICBT met criteria for clinically significant improvement on the PSS, as compared with 10% in the WLC. On the outcome measuring exhaustion, 48% of patients in the ICBT made a clinically significant improvement, compared with 6% in the WLC. All improvements were maintained to the 6MFU. No significant differences were found between groups (ICBT vs. WLC) on measures of functional impairment or work ability.

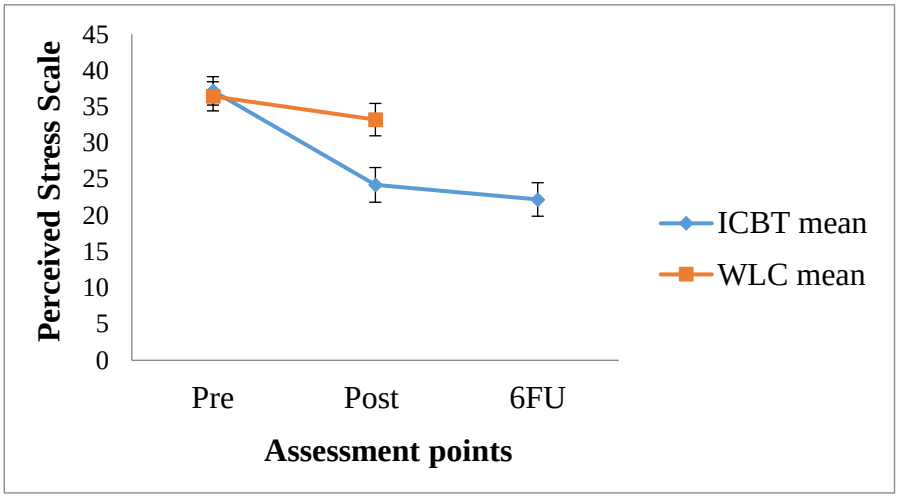

Figure 3. Course of improvement on the primary outcome measure PSS-14. Error bars represent 95% Confidence Intervals. ICBT, Internet-based cognitive behavioral therapy; WLC, waitlist control; Pre, before treatment; Post, after treatment; 6FU, six-month follow-up.

4.2.2.1 Subgroup analysis of AD and ED

Subgroup analyses of respective diagnostic group (AD and ED) indicated that patients with both disorders benefitted greatly from the treatment. At baseline, patients with ED suffered from significantly more severe symptoms and level of disability compared with patients diagnosed with AD. Nevertheless, they reduced symptoms of perceived stress, exhaustion, and impaired sleep with waitlist-controlled effect sizes ranging from d = 1.22 to 1.27 at posttreatment. For patients with AD, corresponding effect sizes ranged from d = 0.88 to 0.95. No significant interaction effects of diagnostic groups were found on outcomes, with the exception of self-rated health (on this outcome, only patients with ED made a statistically significant improvement). No significant differences were found between groups with regard to treatment completion or treatment satisfaction.

4.2.3 Conclusions

The ICBT protocol for stress-related disorders is indicated to be efficacious in reducing symptoms and increasing quality of life in a national sample diagnosed with AD or ED. The large effect sizes coupled with the minimal therapist time required and the relative simplicity of the treatment, suggest that ICBT could be a highly cost effective treatment with the potential to substantially increase treatment accessibility to those most in need. Because the WLC was crossed over to treatment after the 12-week main phase of the trial, no conclusions can be drawn about long-term effects of the ICBT. Studies using larger sample sizes and longer follow-up periods may be needed to establish the potential effect of ICBT on functional impairment. Regarding work ability, results from Study II are in line with findings in Study I, as well as with previous studies indicating that decreased symptoms are not necessarily related to perceived work ability or return-to-work after sick leave [237-239].

4.3 STUDY III: COST-EFFECTIVENESS OF THERAPIST-GUIDED INTERNET-BASED COGNITIVE BEHAVIORALTHERAPY FOR STRESS-RELATED DISORDERS: SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

4.3.1 Methods

4.3.1.1 Procedure and inclusion

This was a within-trial cost-effectiveness and cost-utility analysis with a time-perspective of 12 weeks (pre- to posttreatment), conducted from a societal and from a healthcare perspective. Data was collected in tandem with the randomized controlled trial described in Study II. Nationally recruited participants (N = 100) diagnosed with AD or ED were included and randomized to a 12-week ICBT (n = 50) or to a WLC (n = 50).

4.3.1.2 Outcomes and measures

Remission rate was the primary clinical outcome for the cost-effectiveness analysis, operationalized as clinically significant improvement on the primary outcome 14-item PSS according to the Jacobson and Truax [236]. The EuroQol Questionnaire 3L version (EQ-5D), which measures health-related quality of life [240], was used for the calculation of cost-utility. The self-rated Trimbos and Institute Medical Technology Assessment of Costs Questionnaire for Psychiatry [TIC-P; 241] was used to measure resource utilization, from which societal and healthcare costs could be evaluated. Health outcomes and costs were surveyed pre- and posttreatment and (only in the ICBT group) at the 6MFU. For the cost-effectiveness and cost-utility analysis, only the pre- to posttreatment assessments were used. All costs were converted to US $ from the Swedish Krona.

4.3.1.3 Treatments

Please see section 4.2.1.3.

4.3.1.4 Statistical analyses

Incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs) were calculated based on remission rates and health-related quality of life respectively, using bootstrap sampling (5000 replications). The probability of the treatment being cost effective (compared with the WLC) at different willingness to pay (WTP) scenarios was investigated. Several sensitivity analyses were conducted to support the robustness of results.

4.3.2 Results

The ICBT was more likely than the WLC to generate higher remission rates and slightly larger reductions in societal costs pre- to posttreatment. From a societal perspective, ICBT had a 60% probability of being cost effective at a WTP of $0, and a 96% probability of being cost effective at a WTP of $1000 for one additional patient in remission (see Figure 4, solid line). A

sensitivity analysis indicated that the ICBT would be cost effective even if the intervention cost was tripled (see Figure 4, dotted line). The cost-utility analyses supported the superiority of ICBT compared with the WLC from a societal perspective.

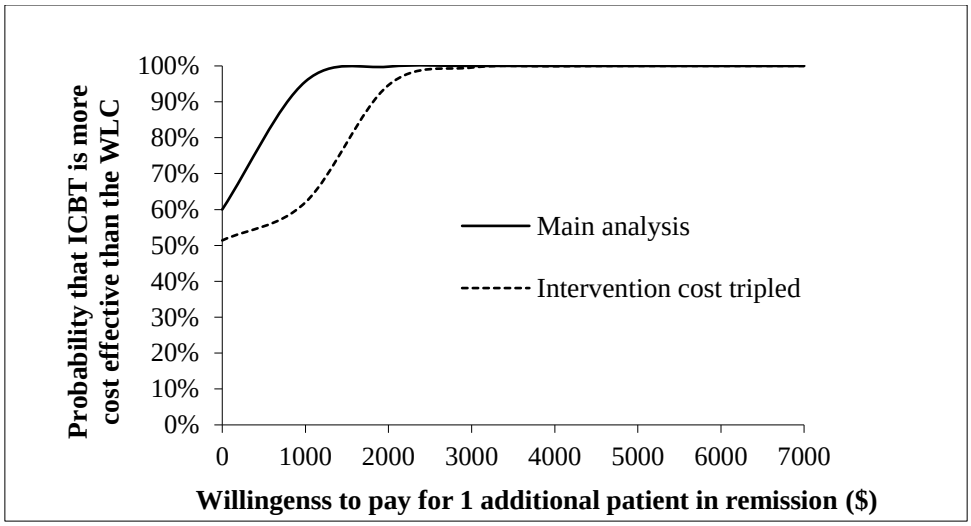

Figure 4. Cost-effectiveness acceptability curve from a societal perspective comparing internet-based cognitive behavioral therapy (ICBT) with a waitlist control condition (WLC) over the 12-week treatment period. Note: Solid line represents the probability of ICBT being cost effective under normal circumstances. Dotted line represents the probability of ICBT being cost effective based on a sensitivity analysis in which a 3-fold higher intervention cost was used.

Taking a healthcare perspective (i.e., including only direct medical costs), the ICBT had a 97% probability of being cost effective given a WTP of $1000 for one additional patient in remission. Subgroup analyses showed that, although the ICBT was cost effective both for patients with AD and ED, it was more so for patients with AD. For these patients, there was a 92% probability that ICBT was more cost effective than the WLC at a WTP of $0. The corresponding probability for patients with ED was 38%, although this probability increased to 80% given a WTP of $1000. Sensitivity analyses supported the robustness of results, and pointed to the significance of reduced costs for presenteeism, as seen in the ICBT group compared with the WLC, in rendering treatment cost-effectiveness.

4.3.3 Conclusions

ICBT is likely to be a cost effective treatment compared with a WLC for individuals diagnosed with AD or ED, both from a societal and from a healthcare perspective. Most probably, ICBT leads to substantial symptom improvement at no net societal costs in a period of only 12 weeks. Even though some costs are associated with administering the treatment, the high scalability of ICBT means that the costs are likely to be quickly returned to society. The indication that ICBT may significantly reduce costs related to presenteeism is encouraging and merits further investigation.

4.4 STUDY IV: THE MEDIATING ROLE OF SLEEP IN INTERNET-BASED COGNITVE BEHAVIORALTHERAPY FOR CHRONIC STRESS: RESULTS FROM A RANDOMIZED CONTROLLED TRIAL

4.4.1 Methods

4.4.1.1 Procedure and inclusion

Study IV was based on the randomized controlled trial conducted in Study II. Nationally recruited participants (N = 100) diagnosed with AD or ED were included and randomized to a 12-week ICBT (n = 50) or to a WLC (n = 50).

4.4.1.2 Outcomes and putative mediator

The putative mediator investigated in Study IV was impaired sleep, as measured with the Insomnia Severity Index [ISI; 242]. Impaired sleep was assessed weekly over the course of treatment (week 1 to 11), as were the stress-related outcomes the PSS [233] and the SMBQ [234].

4.4.1.3 Treatment

Please see section 4.2.1.3.

4.4.1.4 Statistical analyses

We employed a parallel process latent growth modeling strategy within a structural equation framework to examine treatment effect on the growth trajectory of the outcomes (PSS and SMBQ) via the growth trajectory of ISI. Accurate confidence intervals based on the asymmetric confidence interval method (bias-corrected bootstrapping of 2000 samples) were constructed. We also conducted moderated mediation analyses to investigate whether the strength of the mediated effect was moderated by participants' initial level of sleep impairment.

4.4.2 Results

A total of 84% of the sample reported some sleep difficulties pre-treatment (a score of 10 or above on the ISI) and 52% of the sample scored 16 or higher on the ISI which indicates clinical insomnia [243]. The waitlist-controlled effect size on the ISI at posttreatment assessment was large (Cohen's d = 1.05). Tests of the indirect effects (based on the parallel process latent growth models), indicated that the larger reduction in perceived stress and exhaustion associated with the ICBT compared with the WLC, was mediated by a reduction in impaired sleep (PSS: $\alpha\beta$ = -0.44, 95% $CI_{asymmetric}$ [-0.92, -0.14]; SMBQ: $\alpha\beta$ = -0.08, 95% $CI_{asymmetric}$ [-0.15, -0.04]). Level of impaired sleep at baseline predicted the size of the mediation effects such that, for patients with a higher level of impaired sleep at baseline, the mediated effect of sleep on stress and exhaustion was accentuated.

4.4.3 Conclusions

Improving sleep quality may be of importance for achieving successful treatment outcomes in ICBT for chronic stress in the form of AD and ED. This finding may be particularly pertinent for individuals with pronounced sleep impairment upon initiating treatment. Although the design of Study IV does not allow conclusions to be drawn regarding which treatment components contributed to the reduced sleep impairment, it is plausible that treatments aimed at reducing chronic stress could benefit from including interventions that specifically target sleep impairment, as this could play a role in overall symptom reduction.

4.5 ETHICAL CONSIDERATIONS

Study I and II were approved by the regional ethics committee in Stockholm, Sweden, and were judged to comply with international ethical guidelines for human research. All patients provided written informed consent and were informed of their right to leave the study at any time without penalty, judgement or further clarification. The studies were conducted in line with the Declaration of Helsinki Ethical Principles and were preregistered at ClinicalTrials.gov (identifiers NCT01636791 and NCT02540317) in order to protect against publication bias.

4.5.1 On the issue of random allocation

Random allocation to interventions may constitute an ethical dilemma in that participants may be assigned to a harmful intervention or be denied interventions with known positive effects. The specific CBT protocol used for patients with AD and ED in Study I and Study II lacked prior scientific evidence of its efficacy, and potential harmful effects were unknown. However, several studies of CBT for stress-reduction in heterogeneous populations have shown promising results, and more than 10 years of clinical evaluation of the CBT protocol for patients with stress-related disorders at Gustavsbergs primary care clinic suggest that the treatment is acceptable as well as efficacious. Taking into account that no evidence-based treatments exist for AD and ED, it was deemed important to test the efficacy of CBT for these specific disorders.

In Study I, 141 of the 211 primary care patients suffering from CMDs were offered the best available treatment for their respective disorders. However, 67 of the 211 patients were randomized to an experimental treatment consisting of a novel return-to-work intervention (RTW-I). This is a deviation from national guidelines and is an important ethical consideration. However, only a minority of patients with CMDs that seek healthcare in in Stockholm receive evidence-based treatment. Our hope was that the general CBT-based psychoeducation that RTW-I offered, together with support in dealing with work-related difficulties, would contribute to improving patients' well-being. We argued that the study had the potential to contribute to important knowledge regarding how best to treat patients with CMDs and how to support their return to work.

In Study II, 50% of participants were randomized to a WLC. When suffering from clinical levels of stress-related symptoms, waiting for three months might be difficult and there is a risk that symptoms deteriorate. Furthermore, the use of a WLC can be criticized for providing a favorable comparison. However, a WLC may represent a somewhat realistic scenario in such that no treatment guidelines exist for AD or ED, and many suffering individuals never get access to psychological treatment. To the best of my knowledge, Study II was one of the first studies of ICBT for AD and ED, and we therefore argued that it was reasonable to assess whether the treatment was efficacious before comparing to an active control. Before inclusion, all participants were informed that participation in the study meant that they would either be offered to initiate treatment immediately, or after 12 weeks. Because both groups were required to fill in weekly questionnaires about their mental health status, potential deterioration and suicide risk could be detected by study psychologists, in which case patients were contacted via telephone for suicide assessment.

4.5.2 Treatment side-effects

To date, knowledge about potential side effects of CBT for stress-related disorders is limited. To learn more, participants in both Study I and II were, at posttreatment, asked to document adverse events related to the treatment. In line with proposed recommendations to counteract negative side effects of treatment (which include monitoring, flexible contact with the therapist and flexible treatment schedule) [244], participants' self-rated symptoms were monitored weekly throughout treatment in Study I and II, to enable quick detection of potential deterioration. Further, participants in Study II could contact their therapist at any time and expect a reply within 48 hours, and they could independently choose when and where to work with their treatment. Based on our clinical impressions of working with the treatment, the clinical gains of treatment clearly overshadow the negative effects.

4.5.3 Handling of data

All participants in Study I and II gave their written informed consent upon being included in the study, and all information that could be considered private (e.g., sick leave status and psychiatric symptoms) was handled confidentially and according to clinical routine practice and healthcare legislation. All self-rating scales were administered electronically, and data was entered and accessed using randomly generated passwords. Data was stored on an encrypted server using 128-bit SLL encryption to protect against hacking. Results of the studies were exclusively presented at group level to protect the integrity of individual participants.

5 DISCUSSION

5.1 MAIN FINDINGS

Studies I and II in this thesis indicate that a relatively brief CBT protocol can be efficacious in reducing psychiatric symptoms and increasing quality of life in patients diagnosed with AD or ED, both when delivered as a face-to-face treatment compared with another psychological treatment (RTW-I) and when delivered as an ICBT compared with a WLC. There were no differences between the face-to-face CBT and the RTW-I in net days of sick leave one year after randomization (Study I; see also [230]), and the ICBT was not superior to the WLC in increasing self-rated work ability (Study II).

In Study III, we found that the substantial symptomatic improvement by ICBT was not associated with any net societal cost compared with the WLC, and the treatment was cost effective both from a societal and from a healthcare perspective in a period of only 12 weeks. Reduced sleep impairment was found to stastistically mediate the effect of ICBT on symptoms of stress and exhaustion, suggesting that impaired sleep might be an important target in the treatment of stress-related disorders (Study IV).

5.1.1 Treating stress-related disorders with CBT

5.1.1.1 Face-to-face CBT

Findings from Study I are encouraging. The CBT protocol for stress-related disorders generated within-group effect sizes on symptoms of stress and exhaustion that are comparable with effect sizes found in previous studies on established CBT protocols for anxiety disorders [154] and depression [155]. Further, we found the CBT to be significantly superior to another psychological intervention (RTW-I), reducing symptom severity pre- to posttreatment with a moderate between-group effect size (d = 0.53). This finding is rather rare, because although several randomized controlled trials of CBT for chronic stress have found significant symptom reduction between pre- and posttreatment, most have failed to establish the superiority of CBT compared with other active control conditions [245]. Why is this?

It is possible that the absence of between-group interaction effects in most previous trials can be partly explained by methodological limitations such as small sample sizes [e.g., 170, 173, 177], high drop out rates [170, 173, 179], or patients engaging in treatment outside of the study [e.g., 179, 182-184]. It is also possible that an explanation can be found in different treatment content and somewhat different populations. For example, in the study by Sandahl et al. [173], the treatment included only cognitive interventions, and participants (who had been on sick leave over 90 days upon inclusion) were assessed to suffer from “work-related depression”. Meta-analyses of interventions for work-related stress have found an inverse relationship between number of sessions/ number of treatment components and effect size [157, 159]. If this finding is applicable also to the treatment of chronic stress, it is possible that the absence of between-group interaction effects in some studies can be understood by the fact that interventions have

been very comprehensive. For example, Stenlund et al. [179] evaluated the effect of an intervention that comprised over 140 hours total treatment time over a period of one year, including both CBT and qigong. This intervention did not generate superior effects on symptoms compared with qigong only. Similarily, Netterström et al. [184] found TAU (12 individual sessions with a psychologist) to be equally effective in reducing symptoms as an intervention consisting of CBT, work-place diaglogue, and mindfulness-based stress-reduction. Hence, in speculation, it it possible that some interventions have included *too many* sessions or *too many* components. Indeed, in Study I we found that when CBT was combined with the RTW-I (COMBO), it was no longer superior to the RTW-I alone. Clinical experience from the trial suggested that the COMBO was too extensive or complicated both for patients and therapists, possibly diverting attention from treatment components in the CBT that were believed to target important mechanisms in stress-related disorders (e.g., recovery).

The fact that both the CBT and the RTW-I reached equivalent sub-clinical symptom levels at the 1-year follow-up is in line with findings from previous trials [e.g., 171, 183]. This suggests that, even though symptoms of chronic stress may subside over time with different types of interventions (or by natural course), CBT might substantially shorten the suffering of patients by increasing the pace at which symptoms of stress and exhaustion are reduced.

In summary, although the existing evidence base for CBT in treating stress-related disorders is still rather, findings from Study I indicate that patients with stress-related disorders might benefit greatly from a relatively brief, structured CBT protocol delivered in a primary care context, where most patients first seek help [52]. More well powered, randomized controlled trials investigating CBT for stress-related disorders are warranted. Preferably, the effectiveness of CBT should be further established before additional components are added, because complex interventions makes it more difficult to descipher which components may be central for symptom reduction.

5.1.1.2 ICBT

The ICBT tested in this thesis (Study II) generated larger between-group effect sizes compared with the pooled effects of other internet- or computer-based programs for stress (as evaluated in a meta-analysis) in terms of stress symptoms (d = 1.09 vs. 0.45), depression (d = 0.67 vs. 0.34), and anxiety (d = 0.57 vs. 0.32) [246]. One reason for this may be that previous internet-based studies of interventions to reduce stress have largely used non-clinical or undiagnosed samples. With lower symptom severity at baseline there is a risk of floor effects, and without clinical assessment samples are likely heterogeneous which could generate high variance in symptom levels. There are indications that greater symptom severity moderates the effect of ICBT, predicting higher response- and remission rates compared with patients with lower symptom severity [247, 248].

Even though only a very limited number of studies of ICBT for stress-related disorders have been conducted, there are some methodologically sound studies of ICBT in which participants had elevated levels of stress [198, 214] to which we can compare our results, and one study in

which ICBT was evaluated for managers diagnosed with stress-related disorders according to the ICD-10 [216]. Compared with these studies, effects on mental-health outcomes found in Study II are generally equivalent. However, the ICBT in the present thesis generated a larger controlled effect size on impaired sleep (d = 1.05) compared with the other studies (d = 0.34-0.52). It is possible that this difference can be attributed to the early interventions targeting increased recovery and disturbed sleep in our ICBT protocol. A lack of recovery during the day has been shown to increase the risk of disturbed sleep [249], and self-reported sleep quality has been found to be improved by a single session of psychoeducation regarding sleep in a primary care sample compared with a WLC [190].

In the studies by Heber et al. [214] and Ebert et al. [198], no clinical assessment was conducted, and thus it is possible that their samples included participants suffering from other mental health problems not specifically related to chronic stress. In the study by Persson Asplund et al. [216], the ICBT protocol was evaluated in a sample of distressed managers rather than in a broader clinical population. In such, findings from Study II complement previous research on ICBT for stress-reduction by providing evidence that ICBT can be efficacious in reducing symptoms also in a national sample diagnosed with AD or ED. Results need to be replicated and future studies should compare ICBT to active control conditions.

5.1.2 Does CBT have an effect on work-related outcomes?

Although the primary aim of this thesis was to investigate the efficacy of CBT in terms of symptom reduction in patients with stress-related disorders, the fact remains that stress-related disorders are a very common cause for sick leave, often resulting in extended sick leave periods [47, 72]. Hence, questions regarding how sick leave can be prevented and how return to work can be facilitated are inevitably important.

5.1.2.1 Face-to-face CBT

There are indications that a combination of CBT techniques and interventions focusing on the work situation can be helpful to support return to work for patients on sick leave due to stress-related disorders and other CMDs [180, 186, 250], perhaps more so than CBT alone [180]. Hence, in Study I, we hypothesized that the RTW-I (alone or in combination with CBT) would be superior to CBT as a stand-alone treatment in reducing sick leave for sick-listed patients with CMDs. Contrary to our expectation, however, sick leave reduced to the 1-year follow-up in all treatment arms. This was the case also when analyzing data from patients in the subgroup diagnosed with stress-related disorders [230]. Because no untreated control group or TAU was included in the design, we do not know whether all patients in Study I reduced sick leave more than patients in general would under usual care circumstances or whether a reduction in sick leave might be expected (independent of treatment) over the course of a year.

Meta-analyses of the effect of treatment (including CBT) on sick leave in general populations with CMDs have found only small effects [195, 251], and in samples with stress-related disorders (where comparisons are most often made with care-as-usual) results have been mixed

[64, 162]. Hence, because Study I included three comprehensive treatments, it is possible that it was underpowered to detect differences in sick leave. Further, seeing that a majority of patients were diagnosed with ED, it is also possible that factors such as national sick leave recommendations affected length of sick leave. In Sweden, sick leave recommendations for ED are generous compared with those for other CMDs, ranging from 6 months to 1 year [41]. Benefits and regulations have been shown to strongly affect sick leave [252], and the absence of a between-group effect on sick leave in Study I might suggest that guidelines constitute a stronger predictor of this outcome than does specific treatment content. Of note, the separately published subgroup analysis indicated that, for patients in Study I that were diagnosed with other CMDs than stress-related disorders (i.e., depression, anxiety disorders or insomnia), there was a strong effect on sick leave in the RTW-I compared with disorder-specific CBT [230]. These results are very interesting, but because the subgroup was small (n = 59) and heterogeneous, they should be interpreted with causion and be considered provisional.

In summary, evidence is limited when it comes to the efficacy of any psychological intervention in reducing sick leave in patients with stress-related disorders. More randomized controlled trials using large sample sizes and long follow-up periods are warranted. Also, an important question for future studies is whether CBT could prevent sick leave for patients with stress-related disorders. In a study by Hägglund, et al. [219], face-to-face CBT was found to prevent sick leave for patients with CMDs who were not on sick leave upon commencing treatment. For those who were already on sick leave at treatment start, CBT did not have an effect on this outcome. If these findings are applicable to patients specifically diagnosed with stress-related disorders remains to be investigated.

5.1.2.2 ICBT

In Study II, the effect of ICBT on self-rated work ability was explored. Results indicated that the treatment did not lead to improvement in this outcome compared with the WLC. Interestingly, however, analyses of cost changes pre- to posttreatment in Study III (based on data collected in Study II) indicated a significant between-group interaction effect in favor of the ICBT on costs related to work cutback due to presenteeism. In other words, patients in the ICBT reported a significant decrease in number of days worked when ill across the 12-week treatment phase, leading to reduced costs for production loss compared with the WLC.

Although promising, previous research suggests that the relationship between symptom reduction and work-related outcomes is generally weak [237-239]. Most previous studies of ICBT for stress-reduction have not found an effect on self-reported absenteeism or presenteeism, in spite of large symptom reduction [198, 214, 216]. Hence, whether ICBT for stress-related disorders can reduce work cutback due to presenteeism needs further investigation. Future studies of ICBT for stress-related disorders would also benefit from incorporating objective measures of sick leave using registry data.

5.1.3 Can AD and ED be treated with the same protocol?

This is an important question, because treatment recommendations for AD and ED tend to differ markedly. Most researchers within the field of AD, for example, agree that the first-line treatment should be a brief, low-intensive psychological intervention, such as self-help or internet-based treatment [e.g., 163, 167, 228]. For ED, however, the Swedish National Board of Health and Welfare recommends extensive, multimodal treatment [30]. Indeed, clinical trials of ED have sometimes comprised up to 140 hours of treatment over periods of up to one year [e.g., 179]. The differential treatment recommendations are not based on any strong empirical ground, yet they hold important clinical and health economic implications.

By stratifying randomization based on diagnosis in Study II, we were able to evaluate the effect of ICBT for patients with AD and ED separately. Findings suggested that the relatively brief ICBT was efficacious both for patients with AD and ED. Completion rate and treatment satisfaction did not differ between the diagnostic groups. Even though patients with AD consistently reported better mental- and physical health compared with ED, patients with ED gained just as much, if not more, from the intervention (as indicated by larger between-group effect sizes on almost all outcomes in the ED subgroup).

So where does this leave us when it comes to treatment recommendations? The finding that ICBT was beneficial for patients with AD is in line with existing clinical recommendations. The finding that patients with ED gained such symptom relief from the ICBT is, however, rather surprising. One possible explanation could be that ICBT is a highly structured format, which might counteract therapist drift and thereby compensate for the limited amount of therapist contact [253]. It is also possible that patients with ED in Study II sought help in an earlier phase of symptom development compared with patients in some previous studies, as indicated by the relatively low rate of sickness absence (approximately 30%) in that subgroup. Of note, however, the relatively brief CBT protocol was indicated to be efficacious also when delivered to consequtively recruited primary care patients on sick leave due to stress-related disorders, of which 82% were diagnosed with ED [230].

Taken together, our findings suggest that both patients with AD and ED can benefit greatly from the CBT protocol investigated in this thesis. Although patients did not significantly improve their functional impairment or work ability compared with the WLC in Study II, findings hold important clinical implications: An easily accessible, relatively short ICBT can significantly reduce suffering and increase quality of life in a large and highly disabled group of patients. If implemented in primary care, more patients could be treated earlier in the symptom development without increased societal costs. Although results need to be replicated, our findings suggest that it may be time to rethink the necessity of extensive, multimodal care for patients with ED, at least as a first-choice intervention. Regarding AD, future studies should investigate whether these patients might respond to a lower-dose intervention (e.g., ICBT consisting of 6 modules rather than 12), and whether treatment of AD might prevent the development of more severe disorders such as ED.

5.1.4 Cost-effectiveness of ICBT

To the best of my knowledge, the health economic analysis of ICBT for the stress-related disorders AD and ED conducted in this research project is the first of its kind. Findings are in line with cost-effectiveness estimates presented in meta-analyses of ICBT for various clinical conditions [210, 254], and also with two recently published health-economic studies of cost-effectiveness of ICBT for stress-reduction in employees with elevated levels of self-rated stress [221, 222]. These two studies found support for the cost-effectiveness of ICBT compared with waitlist control conditions from an employer's perspective [221] and from a full societal perspective [222], with similar probabilities as found in Study III (>60% probability at a WTP of 0 for an additional improvement). Interestingly, in those studies, as in ours, cost-effectiveness was driven largely by a reduction in costs for presenteeism in ICBT. This is a promising finding because costs for presenteeism tend to be high in samples with chronic stress [106, 108]. Taken together, results provide preliminary evidence of cost-effectiveness of ICBT for stress-reduction from different stakeholder perspectives (the society, the employer, and the healthcare clinic) and for somewhat different populations with stress-related problems.

As a sensitivity analysis in Study III we characterized heterogeneity in our findings by investigating whether the cost-effectiveness of ICBT differed in the diagnostic groups AD and ED. Characterizing heterogeneity is a criterium in the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [255], and yet is often overlooked in health economic trials [256]. Findings suggested that, even though ICBT was cost effective in both diagnostic groups, it was clearly more so for patients with AD. These results can be understood by the fact that patients with ED made smaller cost changes relative to their controls than did patients with AD (although both diagnostic groups made large symptomatic improvements by ICBT). Seeing that patients with AD overall had lower symptom severity and functional disability compared with ED, a possible conclusion from these finding could be that offering treatment to patients early on in the development of chronic stress might be beneficial in terms of optimizing treatment cost-effectiveness and preventing increased societal costs. However, the fact that ICBT was highly cost effective also for patients with more severe symptoms of chronic stress (ED) is encouraging.

Cost-effectiveness based on the comparison between different treatments regarding the relation between costs and, for example, remission rates, has a high clinical value. However, the cost-utility of a given treatment, where costs are placed in relation to more generic health-related outcomes (such as QALYs), lends itself more easily to comparisons across clinical trials and clinical conditions, and is therefore often preferred by economists [256]. Thresholds of what can be considered value for money have been developed to guide economic decisions in healthcare, ranging from approximately US $26 000 per QALY in the United Kingdom to US $50 000 per QALY in Australia and the United States [256, 257]. In our study, we found that the probability of cost-utility of ICBT from a societal perspective was the same as that of cost-effectiveness (60% at a WTP of $0). This probability rose to 71% at a WTP of $25 000. Although thresholds of this type are increasingly criticized [257, 258], they give a frame of reference indicating that

ICBT for stress-related disorders as evaluated in Study III can likely also be considered to render cost-utility for patients with AD and ED.

5.1.5 Sleep as a putative mediator of change in ICBT

The finding from Study IV, that a reduction in impaired sleep mediated the effect of ICBT on symptoms of stress and exhaustion, is in line with results from a previously published study by our research group [227]. In that study, reduced sleep impairment was found to partially mediate the effect of face-to-face CBT (the same protocol as used in Study IV) on symptoms of exhaustion in sick-listed patients with ED [227]. In Study IV, we were able to extend findings also to patients diagnosed with AD, and propose that reduced sleep impairment mediates the effect of treatment not only on symptoms of exhaustion but also on perceived stress. The fact that CBT in the present study was delivered via the internet as opposed to face-to-face, supports the growing body of evidence suggesting that these two delivery formats may generate equivalent effects [211]. Our results are also in line with findings from prospective studies that indicate the importance of sleep in the prevention and rehabilitation of chronic stress [e.g., 133, 259].

Disturbed sleep is very common in patients with stress-related disorders. Indeed, more than half of participants in the ICBT trial scored 16 or higher on the ISI at baseline, which is indicative of clinical insomnia [243]. Importantly, however, although the waitlist-controlled effect size on the ISI pre- to posttreatment was large (d = 1.05), it is unclear precisely which treatment components that contributed to this effect. It is possible that the interventions targeting improved sleep (i.e., psychoeducation about sleep, sleep hygiene, and stimulus control) early in the ICBT played an important role reducing sleep impairment. There is empirical support for the efficacy of these interventions in the treatment of insomnia [156, 191]. However, Santoft et al. [227] found improved sleep to mediate the effect of face-to-face CBT on symptoms of exhaustion even though, in that study, interventions specifically targeting sleep were optional and delivered towards the end of treatment. Also, other ICBT protocols have generated equivalent effects on perceived stress and exhaustion as found in our ICBT trial, without directly targeting disturbed sleep (and finding only small to moderate effect sizes on the ISI) [198, 214, 216].

Hence, there are likely different pathways through which sleep and other stress-related symptoms can be improved. Santoft et al. [227] argued, for example, that the reduced sleep impairment found in that study possibly could be attributed to the comprehensive focus on increasing daytime recovery in the treatment (by, for example, scheduling recovery activities, structuring the day, and practicing relaxation). A lack of recovery during the day has been found to increase the risk of disturbed sleep [249], and an intervention focusing solely on daytime recovery was found effective in reducing symptoms of stress and exhaustion compared with a WLC [136]. Further, putative mediators that were not measured in Study IV, such as emotion regulation that has previously been suggested to mediate reduction in stress by ICBT [198], may be intimately related with sleep. For instance, consistent sleep has been indicated to be

important for emotional self-regulation [260], and impaired sleep can lead to increased emotional reactivity [261-263].

A limitation to Study IV was that we were unable to analyze how change in symptoms was temporally sequenced, meaning that we do not know whether change in sleep preceded change in symptoms of stress and exhaustion or vice versa. Nevertheless, against the backdrop of previous research, our findings suggest that improving sleep in patients with stress-related disorders may be of importance to reduce symptoms of stress and exhaustion. Given that the evidence base for treating insomnia is strong [156] whereas support for the treatment of chronic stress is still rather weak, it may be reasonable to recommend treatment protocols for chronic stress to include empirically supported interventions for improved sleep. This recommendation is substantiated by evidence from meta-analyses that interventions to improve sleep can be effective also in reducing secondary psychiatric symptoms [264, 265]. Further, self-help CBT for insomnia has been found to reduce perceived stress and day time fatigue with moderate to large within-group effect sizes in individuals with insomnia and comorbid mental health problems [266], and one study showed that ICBT for insomnia was as efficacious as ICBT for depression in reducing depression severity in patients diagnosed with both depression and insomnia [267].

5.2 GENERAL METHODOLOGICAL ISSUES

5.2.1 Control conditions and follow-up

Both randomized controlled trials in this thesis (Study I and II) have some limitations with regard to the control conditions used. In Study I, it was a limitation that no untreated or treatment-as-usual control condition was included. The inclusion of an untreated control group would have generated valuable information about sick leave that could be compared with results from other studies or to primary care in general. For patients with stress-related disorders, who received the new CBT treatment developed by our research group, an untreated control condition would also have generated important information regarding the impact on symptoms of CBT for stress-related disorders. This being said, including a fourth treatment arm in Study I would have reduced power to detect differences between groups. A much larger sample size would have been required, which was not feasible for practical and economic reasons.

In Study II, the ICBT was compared with a WLC that, for ethical reasons, was crossed over to treatment immediately after the experiemtal phase. This was a limitation because it precluded comparisons between conditions at the 6MFU and did not enable control over potential confounders between posttreatment and the 6MFU. The use of a WLC was motivated by the fact that research on CBT for stress-related disorders, particularly in the form of ICBT, is still in its early stages. We wanted to protect against basic threats to internal validity, such as spontaneous remission and regression towards the mean, and also reduce the risk of type-II error [268]. Further, because access to psychological treatment is generally limited, and waiting for three months is likely to be a common scenario for patients who struggle with mental health

problems [196], we considered a WLC to represent a realistic scenario for patients with stress-related disorders.

5.2.2 Assessment procedures and measures

Measuring stress in general is a challenge, given the complexity of the concept [269]. Assessing and measuring stress-related disorders is also associated with some specific challenges. For example, few structured clinical interviews include diagnostic modules for AD, and even though specific measures of AD have begun to emerge (structured clinical interviews and self-report questionnaires), these have so far been insufficiently validated (for a summary, please see [25]). ED, being a Swedish diagnosis, is not included in structured clinical interviews such as the MINI (used in the current thesis). The Karolinska Exhaustion Disorder Scale [KEDS; 43] was developed to specifically measure symptoms characteristic of ED. However, this is a self-rating questionnaire and not a diagnostic tool. Further, the fact that the KEDS is almost exclusively used in Sweden makes it difficult to compare results with those reported in international studies of chronic stress.

In the present thesis, we used well-validated self-rating scales for all symptom outcomes. To assess perceived stress and symptoms of exhaustion we used the PSS and the SMBQ respectively. The PSS, although not a disorder-specific scale in any sense, is the most commonly used measure of perceived stress [270] and is often used as a primary outcome measure in clinical trials of chronic stress. As for the SMBQ, although it is a measure of the burnout construct, it has shown high correlation with other measures of chronic stress [55, 271], and the fact that it is frequently used as an outcome measure in international studies of chronic stress enables comparisons across trials.

To further our understanding of the stress-related disorders AD and ED, it would have been valuable to conduct structured clinical assessment in Study II, both at posttreatment and at the 6MFU, using the CSR to assess symptom severity at the different assessment points (as in Study I). This would also have enabled further comparisons between the efficacy of CBT as a face-to-face treatment (in Study I) and as an ICBT (in Study II) in which we used slightly different samples. Due to practical and economic factors, however, this was not feasible.

Regarding the assessment of impaired sleep as a putative mediator (Study IV), the ISI is a commonly used measure that has illustrated acceptable internal consistency (Cronbach's $\alpha = 0.86$ in our sample) as well as good convergence with clinical evaluation of sleep disturbance severity and sensitivity to detect changes in treatment [243]. Nevertheless, future studies might complement this measure with the use of objective sleep measures [272].

5.2.3 Generalizability

In the clinical studies included in this thesis, a large majority of patients with stress-related disorders were middle-aged, highly educated women (see Table 3). This limits generalization of findings to the full spectrum of individuals suffering from stress-related disorders. Whereas the effect of gender on outcome in CBT is generally limited [273], level of education has been found to predict outcome in guided self-help CBT [274], and it is possible that this could be the

case also for ICBT. This being said, the demographics of our samples are similar to other clinical trials of chronic stress [e.g., 38, 184, 214], and may be representative of those who are most prone to seeking help in healthcare settings. More studies are needed investigating how to reach out to other groups of individuals suffering from stress-related disorders that may feel stigmatized in the healthcare system or encounter other obstacles to seeking and receiving help.

5.3 FROM HERE ON AND FORWARD

5.3.1 Regarding the effectiveness of CBT

As has been noted throughout this thesis, there are no evidence-based treatments for chronic stress in general or for stress-related disorders specifically. Even though this thesis has contributed to the relatively limited research regarding CBT as treatment for stress-related disorders, more randomized controlled trials are needed, using different recruitment strategies, different control conditions, and long-term follow-up of outcomes. I encourage other research groups to further investigate the protocol used in the present thesis as a face-to-face treatment, as an internet-based treatment, and also as a group treatment. Group treatment for stress-reduction is recommended by the Swedish National Board of Health and Welfare [30] as one of many interventions for ED, and is commonly used in clinical settings as a means of increasing treatment access and reducing costs. When it comes to costs, future trials should routinely include robust economic evaluations so that effects of different treatment formats can be placed in relation to their costs and enable wise decisionmaking regarding how best to use limited healthcare resources while providing the most effective treatment.

5.3.2 Regarding sick leave interventions

More studies need to investigate what interventions could effectively target work-related outcomes such as improved work ability, reduced presenteeism, and reduced sick leave. Even though psychological interventions may have some effect on sick leave compared with control groups [195, 251], the evidence base for any particular type of return-to-work intervention is limited. Prevention of sick leave is likely equally important to study. There are indications that CBT may prevent sick leave for patients with CMDs who are not on sick leave upon initiating treatment [219]. This finding needs to be replicated and tested in samples specifically diagnosed with stress-related disorders. Further, organizing work- and school environments to promote mental health could be of importance to reduce the risk of chronic stress and subsequent sick leave. To date, however, evidence for the effect of primary interventions targeting organizations is limited [158, 275].

5.3.3 What works for whom?

Even though we found the “treatment package” investigated in this thesis to be effective in reducing symptoms for many patients with stress-related disorders, there is clearly room for improvement. AD and ED together constitute a group with a broad range of symptoms and level

of disability, potentially incorporating different symptom trajectories. Studying moderators and mediators of treatment effect could help to descipher what works for whom, and enable the development of more streamlined and tailored treatment strategies. Indeed, transdiagnostic and tailored CBT delivered via the internet holds promise for the treatment of anxiety and depression, and can effectively deal with comorbidity [276]. Future studies might compare the structured ICBT used in the present thesis with other formats for delivering the treatment. Factorial trial designs, in which different treatment modules can be compared within the same study, could be an effective approach [197].

Given the plethora of constructs used to operationalize chronic stress in the international research litterature (and now, new diagnostic criteria for AD in the ICD-11 that differ markedly from DSM-5 criteria [e.g., 163]), it is possible that a more process-based approach to studying interventions for chronic stress and stress-related disorders is a promising avenue for future studies.

5.3.4 Dissemination and implementation

Even though ICBT has repeatedly been shown to be an effective treatment for a wide range of psychiatric disorders [210], studies indicate that most people still would prefer face-to-face interventions to internet-based therapy [277]. Specifically for more severe symptom levels, there seems to be negative attitudes amongst patients as well as amongst clinicians and stakeholders (such as insurance companies) when it comes to internet-based treatment [197]. This may constitute a hurdle in the dissemination and implementation of ICBT in regular healthcare settings. It is possible that there is a general lack of knowledge and understanding of the positive effects of ICBT, that could partly be overcome by education and training.

From the perspective of different stakeholders, a blended treatment approach (i.e., using internet-based interventions as a complement to face-fo-face interventions) is often preferred to ICBT as a stand-alone intervention [278]. Many randomized controlled trials of ICBT include no face-to-face contact with the therapist, and assessments are usually conducted via the telephone [197]. In contrast, a blended approach for patients with stress-related disorders in a healthcare setting might include coming to the clinic for somatic and psychological assessment, receiving face-to-face information and education about ICBT, and establishing a contact with the therapist. During ICBT, patients would have the possibility to book a physical session at the clinic if needed. Upon completing ICBT, patients would again visit the clinic to follow up treatment gains or possible deterioration, and discuss the need for potential further interventions. This procedure is in line with a stepped care approach, which is a model of healthcare delivery that is indicated to be an effective and resource-efficient way to treat CMDs in primary care [e.g., 279].

Treatment within a stepped care model has been suggested to be particularly suitable for patients diagnosed with AD [167]. Because AD has a potentially transient nature, brief internet-based interventions may be a good first-line treatment for this patient group [228]. Results from Study II indicate that also patients with ED can benefit greatly from a relatively brief ICBT. For

patients that are not in remission, it is possible that individual face-to-face treatment should conduce a next step in the treatment process, involving other healthcare professionals when needed. The central benefit of a stepped care model is that, because many patients are likely to be helped by less intense treatment, clinicians have time to administer more complex treatments for those in need, without the need for long waits or unneccesary referrals.

5.3.5 Concluding remarks

The studies in this thesis provide support for the efficacy of a relatively short and easily administrated CBT protocol for symptom reduction in patients with AD and ED. We provide preliminary evidence that the treatment can be effective also when delivered via the internet as a therapist-guided intervention, and that this format can be a cost effective alternative compared with waiting for treatment for 12 weeks. Finally, we found impaired sleep to be a putative mediator of treatment effect in ICBT, which might guide the development of future treatment strategies.

This thesis is hopefully the first of many to come that will specifically target treatment for stress-related disorders in a primary care context, where many individuals seek and recieve help. Throughout the work with my doctoral project, I have been startled by the limited number of high quality, randomized controlled trials within the area. I plead for effectiveness studies, dismantling studies, and clinical implementation studies. I, for one, will continue to further build knowledge within this domain.

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