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TRADITIONAL YOGA AND CLINICAL BURNOUT

Quality of life and biomarkers before and after treatment

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Quality of life and biomarkers before and after treatment

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To all previous and present Yogis

and

To my mother who always inspired, encouraged and supported me

"One thing I have learned in a long life: That all our science, measured against reality, is primitive and childlike – and yet it is the most precious thing we have."

"Bear in mind that the wonderful things you learn in your schools are the work of many generations. All this is put in your hands as your inheritance in order that you may receive it, honor it, add to it, and one day faithfully hand it on to your children."

Albert Einstein, 1897–1955

ABSTRACT

Background Stress-related disorders including clinical burnout (CB) are one of the main causes of sickness absenteeism in many Western countries. Little is known about the situation of CB patients, and objective markers are not used as an aid in clinical work with these patients. Moreover, evidence-based treatments are scarce to date. Yoga has shown an effect on stress, depression and anxiety, and might be an interesting treatment alternative.

Aims To understand the situation of patients with CB on sick leave (CBG), to investigate the effect of traditional yoga (TY) on patients with CB, and whether there are *subjective* and *objective measures* that can be used for screening, to diagnose CB, to follow the course and evaluate treatment effects.

Subjective measures

1. To describe health-related quality of life (HRQoL) in the CBG at baseline and compare to a healthy control group experiencing stress (HCG). 2. To explore the effect of psychological treatment with TY, mindfulness-based cognitive therapy (MBCT) and cognitive behavioural therapy (CBT) on HRQoL in the CBG.

Objective measures

1. To evaluate potential biomarkers for screening, diagnosis, to follow the course and to evaluate treatment effects in patients with CB on sick leave. 2. To compare the concentration of biomarkers in the CBG at baseline with that of biomarkers in the HCG at baseline. 3. To evaluate whether the 1 µg ACTH test can be used as a stress test.

Material and methods This thesis comprises 4 publications, derived from two randomized clinical trials (RCTs). Study population 1: The CBG, primary care patients (n=94, 12 men). Randomized to TY, MBCT or CBT. They received 20 weeks of group treatment, three hours per week, with additional homework for a minimum 4.5 hours per week. HRQoL was measured using SWED-QUAL questionnaire (S-Q). S-Q and biomarkers in blood and urine were sampled before and after treatment. Study population 2: The HCG, health care personnel (n = 88, 16 men). The HRQoL and biomarker baseline measurements for the HCG were used for comparison. HCG also provided data from the ACTH stimulation test. Article I presented a descriptive and comparative study of HRQoL at baseline. In Article II we explored the treatment effect of TY, CBT and MBCT measuring HRQoL pre- and post-treatment. Article III presented a hypothesis-generating and comparative study exploring biological markers in blood and urine for potential use as tools for screening, diagnosis, to follow the course and evaluate the treatment effects. Article IV presented a methodological study in which we explored whether the 1 µg ACTH stimulation test could be used as a tool to assess the capacity to respond to stress.

Results ***Subjective measures:*** (I) HRQoL in the CBG was low in general, and significantly lower in most subscales compared to the HCG. (II) Several S-Q subscale scores were normalized after treatment in all groups. Differences between the treatment groups were found in favour of TY and MBCT with a small effect size (ES). ***Objective measures:*** (III) All

biomarker concentrations were within the normal range at baseline in CBG. Compared to the biomarker concentrations in the HCG, the concentrations of the urinary hormones epinephrine, norepinephrine, dopamine, 5-hydroxyindoleacetic acid were significantly higher, while urinary cortisol concentrations were significantly lower. When comparing pre- and post-treatment concentrations for each treatment and for all treatments calculated together, testosterone and urinary epinephrine showed a significant decrease, while, estradiol showed a significant increase. (IV) The intravenous 1 µg ACTH stimulation test showed that the highest cortisol concentrations after injection were found at 30 and 40 min, and that the concentration curves for cortisol in serum and saliva were parallel at 30 and 40 min.

Conclusions In severely ill patients on sick leave and diagnosed with CB, ICD-10 code F43.8, ***subjective measures*** (HRQoL) showed a global decrease. After treatment small differences in effect size between groups were seen in several subscales, in favour of TY over MBCT and CBT, indicating differences in treatment effects. All groups showed large, significant improvements after treatment in HRQoL, presumably at least partly due to the treatments. ***Objective measures*** (biomarkers) showed potential biomarkers for screening and diagnosis (urinary catecholamines, urinary cortisol and 5-hydroxyindoleacetic), to follow the course and evaluate treatment effects (testosterone, estradiol and urinary epinephrine), and these warrant further investigation. The ACTH test could be a potential stress test, measuring the maximum concentration of cortisol in saliva after 1µg IV ACTH after 30 and 40 minutes solely. TY seems to be of interest to explore further for treatment and prevention. HRQoL and biomarkers can be used for screening and to follow the course, and warrant further investigation for the purpose of diagnosis and to evaluate treatment effects.

LIST OF SCIENTIFIC PAPERS

This thesis is based on the following original articles, referred to in the text by their Roman numerals.

I. **Astrid Grensman**, Bikash Dev Acharya, Per Wändell, Gunnar Nilsson & Sigbritt Werner. Health-related quality of life in patients with Burnout on sick-leave: Descriptive and comparative results from a clinical study. *International Archives of Occupational and Environmental Health.* 2016 Feb;89(2):319–29.

II. **Grensman A**, Acharya BD, Wändell P, Nilsson GH, Falkenberg T, Sundin Ö, Werner S. Effect of traditional yoga, mindfulness-based cognitive therapy, and cognitive behavioral therapy, on health related quality of life: a randomized controlled trial on patients on sick leave because of burnout. *BMC Complement Altern Med.* 2018 Mar 6;18(1):80.

III. **Astrid Grensman**, Bikash Dev Acharya, Per Wändell, Gunnar H Nilsson, Torkel Falkenberg, Sigbritt Werner. Potential biomarkers for screening, diagnosis and evaluation of treatment effect on clinical burnout: Descriptive and comparative results from a randomized control trial using psychological treatment. *Submitted.*

IV. **Astrid Grensman**, Bikash Dev Acharya, Per Wändell, Jan Sundquist & Sigbritt Werner. Salivary cortisol measurements for reliable numerical maximum concentration after the low dose 1 µg ACTH intravenously in healthy individuals. *Submitted.*

CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS

ACTH	Adrenocorticotropic hormone
ANS	Autonomous nervous system
CB	Clinical burnout
CBG	Clinical burnout group
CBT	Cognitive behavioural therapy
Cholesterol	Fasting plasma cholesterol
CRP	C-reactive protein, sensitive
DHEAS	Dehydroepiandrosterone-sulfate
ES	Exhaustion syndrome
GEE	General estimation equation
Glucose	Fasting plasma glucose
HbA1c	Glycated haemoglobin
HCG	Healthy control group
HDL	Fasting plasma high-density lipoprotein
HPA-axis	Hypothalamus-pituitary-adrenal-axis
HRQoL	Health-related quality of life
ICD-10	International classification of diseases, 10th version
LDL	Fasting plasma low-density lipoprotein
MBCT	Mindfulness-based cognitive therapy
MBI	Maslach burnout inventory
MRI	Magnetic resonance imaging
PNS	Parasympathetic nervous system
QoL	Quality of life
SHBG	Sex hormone binding globulin
SNS	Sympathetic nervous system
S-Q	Swedish health-related quality of life questionnaire, SWED-QUAL
T3	Triiodothyronine
T4	Thyroxine
TG	Triglycerides
TSH	Thyrotropin
u-5HIAA	Urinary 5-hydoxyindoleacetic acid
u-cortisol	Urinary cortisol
u-dopamine	Urinary dopamine
u-epinephrine	Urinary epinephrine
u-norepinephrine	Urinary norepinephrine
VISS	Medical and administrative support in primary care, Stockholm County Council, Sweden

1 BACKGROUND

1.1 Burnout

Work-related stress, including clinical burnout (CB), has for decades been a problem in many Western countries, resulting in increasing societal costs [1], and is today one of the leading causes of sickness absence in Sweden [2]. Persons experiencing CB have mostly been young to middle-aged women; however, the number of men affected is increasing [3]. It inflicts great suffering, with enormous indirect and direct costs at all levels of society, and it is still increasing [2, 4]. The concept CB has no clear definition [5], and so far no objective markers, i.e. biomarkers, are in use to aid in screening, diagnosis, following the course and evaluating treatment efficacy [6]. Evidence-based treatments are still scarce, although isolated studies have shown some effect on symptoms and return to work [7]. The course of clinical burnout is often long and many patients never fully recover [8]. Few random clinical trials (RCT) have been conducted in this patient group [7, 9, 10], and there is an urgent need for more knowledge on CB, a clear conceptualization, potential markers and suitable treatments.

Although the term/word burnout had been used previously in literature [11, 12], and a condition similar to burnout has been described in for example the Bible [13], and more recently in the novel *Buddenbrooks* [14], the concept of burnout was first coined by Freudenberg in 1974 in volunteers working with persons with drug addictions [15]. Shortly after Freudenberg coined the concept, Maslach, Jackson and Leiter wrote about burnout and also constructed the Maslach Burnout Inventory (MBI) [16, 17]. Their theory was that burnout develops as a result of the workplace situation. MBI measures the main components in burnout according to Maslach, i.e. cynicism and detachment, a reduced sense of personal accomplishment at work, and emotional exhaustion. The MBI is the questionnaire most often used in research. The MBI has no established cut-off level for burnout, which makes it difficult to use in a clinical setting. Other questionnaires, e.g. Shirom Melamed burnout questionnaire, have been used in previous research and have shown correlation with the ES diagnosis, but no cut-off level has been established yet [18].

As a diagnosis, burnout is not new, nor is it a new phenomenon. Previously the diagnosis neurasthenia was used, originating in the late 19th century and describing main features similar to burnout [5]. Burnout was initially a concept used by the social sciences, and not for diagnosis [5]. Later, studies on burnout have developed along two different lines; one focusing on treatment and one on the academic aspect, dealing with the underpinnings of burnout. Despite much research, the international scientific community has not yet established a clear definition and commonly accepted conceptualization [5].

In medicine, the need for a better understanding of burnout per se, diagnostic criteria and objective markers as well as the need for potential treatments, has been a driving force for research. The term CB is used frequently and in some countries, such as Sweden, Norway, Finland and the Netherlands, patients can be sick-listed for CB, but Sweden is the only

country using specific diagnostic criteria [5, 19, 20]. This is in part due to the need to qualify for sickness benefits as well as the need for diagnostic tools. In 2004, the National Board of Health and Welfare in Sweden established the diagnostic criteria for exhaustion syndrome (ES), ICD-10 code F43.8A (Table 1), which is used for CB in the Swedish context [8, 21]. In a recent study the diagnosis of ES was found to be the diagnosis which best corresponds to CB [22]. ES is characterized by emotional and physical exhaustion that cannot be restored by rest, cognitive disturbance, sleep disorders, emotional instability, difficulties with demands and physical symptoms like palpitation, dizziness or sensitivity to sounds (Table 1). The main features of ES with emotional and physical exhaustion correspond well to the main criteria of MBI [16]. In this thesis the term CB will be used for these patients. The course of CB tends to be long and many do not fully recover, or will live with a long-standing heightened sensitivity to stress, and relapse is common [19, 23]. There is no generally accepted clear definition of CB, which differs depending on the context and country [5]. It is also referred to by numerous names such as stress-related exhaustion disorder [22], chronic stress-induced exhaustion [7], chronic burnout syndrome [24], job-stress related depression [25] and neurasthenia [26]. Before ES was established in ICD-10, the code Z 73.0 was sometimes used to reflect "problems related to life management difficulty", but Z codes do not use diagnostic criteria and thus are less useful in a clinical setting. Furthermore, it is difficult to compare findings from patients diagnosed with Z 73.0[21]. The cause and a cure of CB have not yet been fully elucidated. Several theories have been proposed with different foci, both external and internal. Nonetheless, many agree on the definition that the resources of an individual do not meet the perceived demand [27, 28]. Long-standing stress exerts an effect via several pathways. First, stress affects the hypothalamic-pituitary-adrenal (HPA) axis and also the autonomic nervous system (ANS) [29]. It is not known why some persons are more susceptible, but performance-based self-esteem [30, 31] and genetic factors [32] have been found to have an impact. Research has also shown that sleep is a crucial factor for the development, maintenance and improvement of CB [33, 34], and that both work and personal factors contribute to CB [32, 35]; this is in concordance with the diagnostic criteria for ES. Furthermore, lowered self-efficacy [34] is also an important factor together with disturbed recovery [36-38], and occupational balance [39]. External factors, such as societal changes, downsizing in companies, resulting in very lean organizations with little extra capacity to handle unexpected events such as sick leave, have also been found to have an impact [40, 41].

Discussion is still ongoing as to whether CB is a separate diagnosis or is a form of depression [42]; nevertheless, today most agree that CB is a diagnosis in its own right, but that comorbidity with both anxiety and depression is common [7]. The main challenges for patients with ES are usually mental and physical exhaustion, and to lesser degree symptoms of depression. There is also a considerable overlap with other depression and anxiety diagnoses, myalgic encephalomyelitis/chronic fatigue syndrome, fibromyalgia, diabetes mellitus, hypothyroidism, chronic obstructive pulmonary disease, tick-borne encephalitis which must be ruled out before ES can be considered [43].

Table 1 Diagnostic criteria for exhaustion syndrome, ICD-10 code F43.8A.

A	Physical and mental symptoms of exhaustion with minimum 2 weeks duration. The symptoms have developed in response to one or more identifiable stressors which have been present for at least 6 months
B	Markedly reduced mental energy which is manifested by reduced initiative, lack of endurance, or increase of time needed for recovery after mental efforts
C	At least four of the following symptoms have been present most of the day, nearly every day, during the same 2 week period:
	a Persistent complaints of impaired memory
	b Markedly reduced capacity to tolerate demands or to work under time pressure
	c Emotional instability or irritability
	d Insomnia or hypersomnia
	e Persistent complaints of physical weakness or fatigue
	f Physical symptoms such as muscular pain, chest pain, palpitations, gastrointestinal problems, vertigo or increased sensitivity to sounds
D	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning
E	The symptoms are not due to the direct physiological effects of a substance (e.g. abuse of a drug, a medication) or a general medical condition (e.g. hypothyroidism, diabetes, infectious disease)

Translation from Glise et al., 2012.

1.2 Health, definition and policies for its promotion

Everybody wants to live a satisfactory life – with good health. The definition of health has changed over the years, and in 1984 the WHO introduced a new concept in which health is defined as "a resource for everyday life, not the objective of living" [44]. Moreover, health promotion is not just the responsibility of the health sector but goes beyond healthy lifestyle to well-being. Most countries have policies for promotion of health and quality of life (QoL), which also comprises health related QoL (HRQoL). In Sweden the government described the work for good and equal health as "a process which gives people possibilities to increase the control over and promote their health" [45].

In ancient times, Hippocrates and Galenos had a holistic view of health, which included both body and mind [46, 47]. Later, there was a division between these entities and subsequently the biomedical health definition was introduced [47]. Since then, enormous medical achievements have been made, especially in acute conditions. Recently, we have returned to a holistic approach to health and what a human being is. Much research is ongoing, and we have started to reveal the intricate interplay between body and mind, the differences in bodily functions and the ways to process and metabolize drugs, for example, with more individualized personal treatments. Moreover, people are highly flexible, and have more capacity to develop with different types of training, e.g. for psychiatric disorders such as

depression and anxiety. In addition, today we have the societal resources, a stable foundation due to long-term peace, economic resources and an increased understanding of psychiatric illness.

We have a highly sophisticated healthcare with advanced treatments and cures, and many more patients go through complicated surgical procedures, and also at a higher age. We live longer, both healthier and with severer diseases than ever before. Many patients live with chronic diseases, and with diseases that were previously incurable. We have advanced from a situation where survival and cure were the endpoints in research and clinic, to a situation where HRQoL has become increasingly important, after treatment or when living with different diseases, to such an extent that the goal in today's healthcare is the best possible HRQoL for patients with chronic diseases, after treatment or procedures and when on medication [48] .

One way of increasing HRQoL and coming closer to the health goals described by the WHO and governments around the world, is lifestyle interventions. Lifestyle interventions have become more and more interesting as an increasing number of positive effects have been demonstrated. Furthermore, medicines alone cannot address many of the health issues we face today when living with chronic diseases and after serious illness. Lifestyle interventions cannot be replaced by medicine – the effects of the two systems complement each other – and many lifestyle changes can be implemented by people by themselves. Although lifestyle is a broad concept without a clear definition, common aspects include having a good balance between activity and recuperation, sufficient sleep, healthy food, physical exercise, a non-sedentary life, "normal" weight, no smoking and a moderate alcohol. Yoga has been used as a lifestyle intervention for many years, and many yoga practitioners, both healthy and those living with disease, have described a good overall effect as well as an effect on specific symptoms such as stress, anxiety and depression [49]. Furthermore, yoga is a traditional system that has been used for many years to improve health and inner balance in the individual. Many patients today have a keen interest in how their mind and body function, an increasing wish to manage their situation themselves, and to be involved in their own treatment which is recommended [50]. They want to lower the risk of becoming ill and to avoid side effects of medication, for example in cancer treatment. Healthy individuals want to maintain their health throughout life and prevent the onset of disease. For this, methods such as yoga which can be practised freely, individually and in group are required, which can be a good base for future treatments if needed. Many persons are also interested in exploring whether yoga can be used more specifically as a treatment for, for example stress-related disorders.

1.3 Stress and the development of the concept of stress

Stress is an inevitable part of human life and the driving force of all human development, yet too much stress without proper recovery can lead to ill health, sick leave, disease and even death [51, 52]. Stress can be defined as anything that challenges our capacity and disturbs our

inner balance, our homeostasis. In the very beginning, the one-cell organism contracted and expanded as a reaction to stress in the form of light and darkness. Cold, heat, starvation, trauma, and attack are well-known stressors, as well as psychological stress, all exerting an impact on the individual[53]. Moreover, all positive events also cause stress. Claude Bernard wrote: "All the vital mechanisms … always have one purpose, that of maintaining the integrity of the conditions of life within the internal environment" [54]. Walter Cannon further developed these ideas into the concept of homeostasis. He also developed the concepts of the "fight or flight response" and the sympathetic-adrenal system, which are important in the understanding of stress [55, 56]. The fight or flight response means that you can react in two different ways when you are under attack; either fighting or fleeing. He also showed the importance of adrenaline in the stress response and for maintaining the equilibrium of homeostasis. Hans Selye introduced the expression stress and the concept of general adaptation syndrome [57]. Later, Mason argued that the role of emotions in stress reactions needs to be taken into account, which is in line with today's concept of stress [58]. When we relax on a daily basis, stress is not considered a problem, and yoga has shown to be an efficient tool for this [59].

In the development of CB two major stress systems are involved; the HPA-axis and the ANS [29, 60]. Much research is based on measuring cortisol, which is the end product when the HPA axis is stimulated [61]. Cortisol induces numerous changes in the body to prepare us for fight or flight; and is thus a potential marker for stress. Measuring cortisol concentration as an indicator of chronic stress has shown inconsistent results. This is probably due to a difference in time points when sampling. Initially when stressed, the concentration of cortisol will be high, returning to normal slowly, while with prolonged stress the concentration will be low with an insufficient response to stress [25]. Thus, it is crucial when interpreting results to know where the patient lies on the stress timeline [62-64]. Previous research has shown problems generating a sufficient cortisol response in the corticotrophin-releasing hormone (CRH) test after Dexamethasone pre-treatment. Decreased cortisol concentrations after the test were still present at follow-up 7 years later [25, 65]. The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) constitute the ANS, which is another system involved in the stress response. The ANS governs our inner organs and can only partly be influenced by our will [29]. Respiration rate, heart rate, digestion and papillary response are functions regulated by the ANS. The SNS and PNS usually counteract each other, i.e. in stressful situations the SNS is active, but using techniques that stimulate the PNS, the influence of the SNS diminishes. SNS can be described as a system which induces fast mobilization of resources, for example for fight, while PNS is a dampening system, which is more slowly activated. Respiration, an important factor in yoga practice [49, 66, 67], is one of the ANS functions that can be influenced by will. Furthermore, heart rate and blood pressure can be indirectly influenced by a change in the respiratory rate [66].

CB has been shown to induce changes in biomarker concentrations; nonetheless, biomarkers are not used in clinical practice [6, 68, 69]. Furthermore, CB has been shown to alter brain structures and function compared to healthy individuals [22, 70-73]. In imaging studies,

patients with CB exhibit dorsolateral prefrontal cortex thinning as well as thinning in the anterior cingulated cortex and left superior temporal gyros. Furthermore, changes in volume were found, with reduction of caudate and putamen volumes in the basal ganglia. In the patient group, perceived stress correlated with the reduced volumes of caudate and putamen, indicating causality [70]. Reduced volumes of caudate and putamen are involved in impaired cognitive functions such as attention, memory and executive functions. These findings resemble those found in persons with major life trauma which involves severe stress per se [70, 74]. Moreover, the thinning of grey matter in the prefrontal cortex and the altered functional connectivity are associated with impaired top-down regulation, i.e. an impaired ability to down-regulate negative emotions caused by, for example stress [71]. The cognitive impairments are often long-lasting, for months and even years. Some, but not all changes seem to be reversible in ES patients. A recent MRI study showed that the changes in the prefrontal cortex returned to normal together with a normalized caudate volume, while the increased volume of amygdala and the thinning of cortex of the left superior temporal gyrus seen, were unaltered after CBT treatment combined with breathing exercises, and full RTW in a group of ES patients [73]. Furthermore, the study indicated a correlation with perceived stress as well as increased vulnerability to stress in women. The follow-up MRI in this group was made approximately 2–4 years after the onset of ES. This highlights that in this severely sick group of patients some changes in cerebral areas involved in processing stress, are longstanding and even may persist [71, 73]. A recent study showed that the right amygdala, which is involved in stress processing, decreases in volume with the practice of yoga and meditation, and yoga might thus be a possibility to help these patients.

1.4 Measures

1.4.1 *Subjective measures* – HRQoL

Self-assessed QoL, which also comprises health-related quality of life (HRQoL), is known to reliably reflect the patient's situation [75]. This has made HRQoL increasingly popular, and many studies today use HRQoL as an outcome variable, alone or in combination with other measures, for example biomarkers. Information on HRQoL can be used to improve healthcare and decrease healthcare costs [48]. Burnout has been shown to have an impact on HRQoL in different groups, with lower scores the more severe the condition [76]. HRQoL in psychiatric patients and in patients with somatic diseases with psychiatric comorbidity have shown generally low scores [77, 78]. The reduction in HRQoL scores results from the symptoms and the reduced self-perceived abilities reported when filling in HRQoL questionnaires and seeing healthcare providers. The HRQoL questionnaire the Swedish Health-related Quality of Life questionnaire (SWED-QUAL) is comprised of subscales including sexual function and social interactions, which need to be explored to gain a broader picture of the situation in groups of patients such as those with CB [79]. Few studies were found that explored HRQoL in these severely ill patients diagnosed with CB [80].

1.4.2 *Objective measures* – Biomarkers

Potential biomarkers for screening, diagnosis, following the course and evaluating treatment effects were used as another outcome. Biomarkers in burnout have been of interest for a long time [6, 68, 81]. Objective markers are not currently used but could improve the possibilities to screen for and to diagnose CB, as well as to follow the course and to evaluate treatment effects. Few previous studies have been conducted on a uniformly diagnosed group of these severely ill patients. Furthermore, few randomized control trials (RCTs) have been conducted using well-defined treatments in the same patient group. We therefore wanted to explore the concentrations of biomarkers at baseline and to evaluate the change after treatment. The biomarkers were mainly those that have shown a change in previous stress research or in research on yoga or psychological research. In the Hatha yoga pradipika, one of the most important yoga texts, hormones and especially testosterone are said to be able to be regulated by pranayama and asanas [82].

1.4.3 *Objective measures* – Stress test

No stress test with measurement of cortisol is currently in use, but it might aid in diagnosis and evaluation of treatment effects. In psychosocial tests like the Trier Social Stress Test there is a habituation when repeated, which makes the test unsuitable in this setting [83]. Physiological tests, such as the insulin tolerance test, or the ACTH stimulation test used for diagnosing a cortisol deficiency, could be a possible alternative stress test in this setting.

1.5 Yoga

Yoga in the West, both the traditional and the many variations, have become increasingly popular over the last few decades as a means of improving and sustaining physical, mental and emotional well-being [84, 85]. Moreover, yoga has been listed by UNESCO as an intangible cultural heritage of humanity since 2016 [86]. The term yoga is a Sanskrit word meaning unification between the human spirit and the divine [87]. TY advocates a holistic approach to individual existence which functions as a single entity. TY is based on training to balance the “Deha” in order to develop a stable ground for meditation [82]. The Sanskrit term “Deha” means body, and as such comprises all parts of an individual: physical, mental, emotional and spiritual. The word spiritual denotes here a sense of an all-pervading feeling of benevolence.

In the West, we have generally applied 1) the physical aspect of the yoga practice, such as asanas (different physical movements and postures), and 2) pranayama (breathing exercises) and today 3) mental practices like meditation are more emphasized. Modern yoga tradition generally employs all three types of practices together.

The traditional yoga employed in this thesis is a gentle form of Ashtanga yoga and is practised by observing the original principles [82], which are:

- Performing gentle, slow movements, without much effort, respecting the body and breath, and not trying to change the breath.

- Slow breathing through the nose simultaneously with the movement.

- Trying to find the equilibrium within the stance or posture.

- Performing the exercises consciously, trying to be aware of the body, the movement and posture or stance while performing.

- Pausing in between the exercise repetitions, and trying to experience the effect on the body, emotions and feelings with an open mind that is non-judgemental and accepting.

According to yoga philosophy, human disease, in Sanskrit "Vyahdi", is considered to be caused partly by an imbalance of the three "Dhatus" or elements, known as Kapha, Vata and Pitta. In other words, disease occurs when one of these is in excess of that required. Furthermore, an imbalance in "Prahna", the vital energy that is regarded to be the sole cause of life, also contributes to disease [88].

An overarching principle in TY is similar to the idea of the self-healing capacity in medicine, in that TY philosophy on disease also states that TY uses this inherent self-restoring capacity [89]. Different physiological effects as well as the Western medicine placebo effect are utilized in yoga treatment. Another principle is that the yoga practitioner's awareness should be hold in the affected area, for example after trauma or pain in the knee, which is considered to stimulate the healing process [82].

Yoga when used as a treatment employs either individualized instructions or standardized protocols, as in this study [82]. Furthermore, each person performs the programme in a certain sequence. The yoga therapist strives to find the minimum of exercises to bring about the desired effect using synergistic effects from the exercises. Not only the exercises themselves but the order in which they are performed are important, in that one exercise will enhance the effect of the next [82, 90]. Furthermore, some aspects of the treatment will aim at a specific level, such as working on the cause of the illness, together with exercises that work at a more general level, to alleviate symptoms. This will indirectly have an impact on the cause. For example, in anxiety some asanas may be given targeting the cause, while relaxation may alleviate the symptoms. Over time, the repeatedly experienced relaxed state may have an indirect influence on the cause of the anxiety.

In TY practice it is said that 1% is theory, and 99% is training, which means that the person should understand why they are doing the exercise, and then try to understand what it means to them in their life, or situation, through their own experience while practising.

In the living yoga tradition in India, all types of yoga exercises are considered to have a medical effect if the previously mentioned principles are followed. This is irrespective of type, school or branch of yoga and whether it includes asanas, pranayama or meditation [91].

Yoga has proved to have an effect on hormones and stress markers [92-94], stress markers, mood, cognitive impairments, depression [95], anxiety [96, 97], stress [49, 98, 99], and on HRQoL, although not in our diagnosed patient group [100]. Furthermore, yoga has been used for rehabilitation after, e.g., acute myocardial infarction [101]. There is an increasing body of research, primarily on meditation, with results that are also considered applicable to movement-based contemplative practices like yoga. The yoga movements and postures together with the breathing exercises and meditation are thought to influence the nervous system, and to have multiple effects on various brain functions such as cognitive performance [102], emotion regulation [103], neuroplasticity [104], self-awareness [105], and attention modulation [106]. Thus yoga can be a plausible new treatment for cognitive improvement for this group of patients with cognitive impairments. Moreover, yoga has been shown to be neuroprotective [107], with a better effect the longer the duration of yoga practice. Yoga has also been shown to improve neuroplasticity [104]. Neuroplasticity is the brain's ability to rewire, the ability to reorganize itself, both physically and functionally due to behaviour, thinking and emotions, and it aids in changing and creating new behaviours. Furthermore, it is essential in promoting initiative and activity in depression, for example, in which patients often suffer from procrastination, the avoidance of doing a task by a given deadline.

In a longitudinal MRI study using mindfulness-based stress reduction, which includes asanas (physical postures) and meditation, the perceived stress decreased together with the density of the right baseolateral amygdala grey matter and improvements in the psychological state [108]. A meta-analysis of meditation, compiling results from MRI studies, showed that meditation-activated brain areas were involved in processing self-relevant information, self-regulation, focused problem-solving, adaptive behaviour and interoception. In expert meditators, meditation induced functional and structural brain modifications especially in self-awareness and self-regulation [105]. In regular long-term practitioners MRI revealed grey matter volume differences in the left hippocampus with a greater volume found in areas governing executive functions, specifically working memory, which has previously been shown to improve with yoga practice [105].

Yoga has been introduced in healthcare and programmes using for example mindfulness-based stress reduction, which also includes asanas (physical postures) and meditation [109], and yoga is used together with lifestyle interventions for patients with coronary arteriosclerosis [110].

Breathing is important for assimilating oxygen and to help eliminate the waste products from bodily processes, primarily carbon dioxide. Calm and deep breathing helps in this process. Oxygen is crucial in most processes in metabolism, and shallow breathing fills the respiratory tract only with approximately 0.2–0.5 L, but does not fill the entire lungs fully. This affects

the bodily functions, making them work less efficiently. It creates an overload to which the body tries to adjust, which is demanding and a form of stress. When breathing through the nose as in TY, the incoming air blends with nitric oxide formed in the sinuses. Nitric oxide dilates the blood vessels in the lungs and lowers the pulmonary artery resistance, which helps to take up more oxygen in the blood [111], which may further reduce the rate of breathing. Calm breathing makes the mind and body calm and reduces the stress experienced through an increase activation of the PNS [112]. Slow breathing, which uses more of the pulmonary capacity, and with a longer exhalation phase, has been shown to have multiple effects mediated through the PNS. In a recent study compiling the physiological evidence, the authors concluded that the effect of yoga is a result of activating the vagus nerve through calm breathing [112].

In medicine we know that our physical body has innate restorative capacities, capacities to adjust and repair. Bone heals after a fracture, and most wounds heal by themselves. Many infectious diseases and skin conditions get better over time. The body adapts, adjusts and can find new ways of functioning with the new condition. When something threatens/changes the homeostasis, the body reacts to restore the inner balance or, if this is not possible, to find another level of homeostasis. The body tries to find the resources from within and to support the parts or functions that need reinforcement for survival. We can even generate new nerve cells, which were previously considered to be impossible [113]. Several restorative and healing processes are known and have been delineated, but many are still unexplained; they are often called placebo or expectation effects [114].

TY works through additional physiological effects, besides the breathing. For example, the gentle movements increase the circulation and induce relaxation, thus enhancing the flow of nutrients, signal substances and oxygen to the tissues, simultaneously removing carbon dioxide and other waste products of cellular metabolism. Furthermore, when performing movements with awareness and attention, proprioceptive, kinaesthetic and interoceptive signals from the affected parts involved in the movement or posture reach the neural plexa, and signals are sent to adjust the movement or posture, and increase or decrease the muscular tone [106]. This interoceptive signalling helps the movements which are gentle, stimulating increased flexibility and muscle relaxation, which in turn enhances the blood circulation with the above-mentioned effects. Taken together, yoga seems to be an interesting treatment alternative, using other modalities than CBT, and thus may open up other possibilities for change.

1.6 Mindfulness and mindfulness-based cognitive therapy (MBCT)

Mindfulness-based cognitive therapy (MBCT) was developed from CBT to prevent depressive relapse [115]. The theoretical premise of MBCT is that depressive relapse is associated with lowered attention regulation together with other cognitive processes, especially rumination, i.e. repetitive, negative thinking and feeling that contribute to recurrence and relapse. MBCT targets cognitive reactivation [115]. The mindfulness

component also helps the patient to deal with experiential avoidance, i.e. avoiding painful feelings, thoughts and memories, and instead adopt an intentionally open, receptive and flexible attitude, being in the present moment. The evidence for effect as a relapse prevention is inconsistent, and seems to vary in different patient groups [116]. MBCT has shown an effect on active depression including treatment-resistant depression [117]. In this study MBCT was used as an additional new treatment.

1.7 Rehabilitation and cognitive behavioural therapy (CBT)

The recommended treatment in rehabilitation of patients diagnosed with CB is usually multimodal; using a bio-psychosocial model, i.e. psychological measures, usually CBT in groups or individually, and physical activity [43, 81]. Often, measures for improved sleep, coaching for return to work, stress management and body-awareness training are components of the treatment. The condition shows large individual differences and today individualized treatment is recommended in Sweden, for example by VISS, a medical and administrative support in primary health care [43]. Because no evidence-based treatments are available and, so far, only few studies have shown an effect from treatment on psychological complaints, the duration of sick leave and return to work [7], there is an urgent need for more studies on treatments.

The usual length of treatment in CB studies is 8–16 weeks [10] and, generally, the participants have been on sick leave for a maximum of 6 months prior to inclusion [10]. Currently, we do not know the optimal length of treatment, and relapse is common [7]. Some also claim that treatment has no effect, only time can heal [7]. Treatment for CB is usually given at specialist clinics and in occupational medicine, while less severe cases of stress-related illness are treated mostly in primary healthcare [43]. In previous studies CBT has shown an effect on depression, anxiety disorders, insomnia, symptoms of stress, and common mental disorders [118-120]. Psychological treatment has in a recent systematic review shown a small but significant decrease of sickness absence compared to care as usual [9], and CBT has shown an overall good effect on psychological complaints and HRQoL in patients with stress-related problems [121-123]. In a recent study, CBT + workplace intervention showed good effect on partial and full return to work [124].

Randomized controlled studies that have been conducted in patients with CB, in this diagnosed (ICD-code F34.8A, ES) and well-defined population on sick leave, are scarce [118, 119, 122], and a few are found in similar groups by different names, in clinical studies and in mixed samples [124-127]. To find possible ways to diagnose CB, to find more effective prevention and treatment, and to decrease the incidence of relapse, a deeper understanding of burnout per se, and of efficacious treatment components is needed that includes the patient perspective. Methods that can be used in different healthcare settings are urgently needed. Prevention and early intervention are comparatively easy to implement, can be less complicated and may lower costs [8]. Both yoga and MBCT are methods that have recently been introduced in diverse medical health care settings. Both healthcare personnel

and patients have shown great interest in these types of methods and what they can contribute, even more so because evidence-based methods for CB are lacking. CBT is a well-documented method and served as an active control group in the CBG. Group therapy could give lower therapy costs. Furthermore, participants can support each other, and group therapy may also increase the availability of therapy, as there is a lack of therapists. In addition, TY and MBCT can be practised at home and with occasional feedback delivered by a competent instructor under supervision. Furthermore, more available therapies will increase the opportunity to find suitable and individualized therapy, which is the recommended therapy in treatment guidelines in Sweden [43]. TY also give many health benefits besides stress reduction as the exercises encourage a healthy life style which CB patients warrant.

In TY there are many exercises and components similar to the techniques used in cognitive therapy. Furthermore, TY considers mindfulness not as a method but a state of mind which the yoga practitioner tries to reach in exercise.

2 AIMS AND HYPOTHESES

2.1 Aims

The overall aims of this thesis were to understand the situation of CB patients, to investigate the effect of traditional yoga on patients with CB on sick leave, and whether there are *subjective* and *objective measures* that can be used for screening and diagnose CB, to follow the course and evaluate treatment effects.

Subjective measures

To describe HRQoL in patients on sick leave with a diagnosis of CB, at baseline and in comparison with a HCG.
To explore the effect of TY, MBCT and CBT on HRQoL in patients with CB.

Objective measures

To evaluate potential biomarkers for screening, diagnosis, and for evaluation of treatment effects in patients with CB on sick leave.
To compare the concentration of biomarkers at baseline with the concentration of biomarkers in HCG.
To evaluate whether 1 µg ACTH test can be used as a stress test; to determine what would be the best time to sample cortisol after the injection in order to measure the maximum cortisol concentration; and to determine whether salivary cortisol can replace serum cortisol in the ACTH test.

2.2 Hypotheses

Subjective measures

That HRQoL in CBG would be low at baseline, and increase after psychological treatment with TY, MBCT and CBT.

That a better effect could possibly be found with TY.

Objective measures

That the biomarkers at baseline would be below or above the reference range in the CBG, and would show significant differences compared to the HCG at baseline.

That significant changes and trends would appear after treatment, with a potentially better effect with TY.

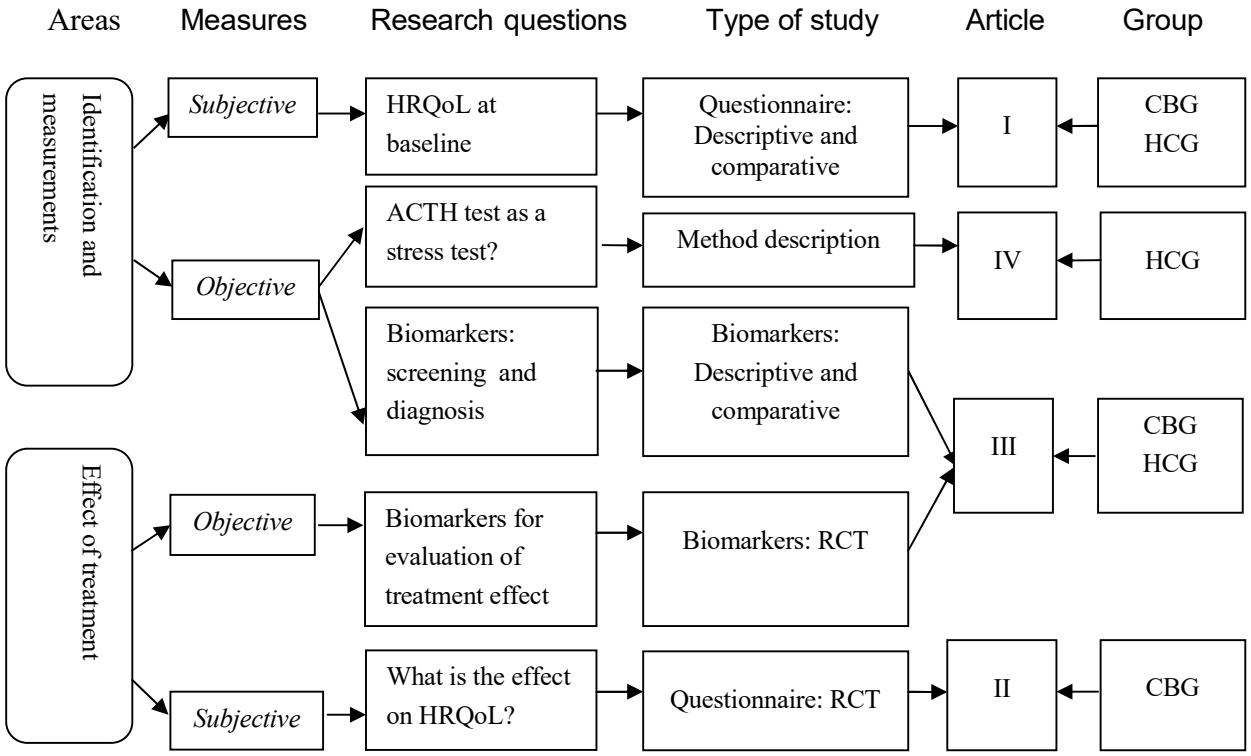
That the1 µg ACTH test could be used as a stress test.

In this thesis the results from the TY and CBT treatments will be discussed primarily, and MBCT to some extent.

2.3 Contents of thesis

Figure 1 illustrates the content of the thesis based on two published articles and two manuscripts.

2.3.1 **Figure 1** Content of the thesis



Health related quality of life (HRQoL), clinical burnout group (CBG), healthy control group (HCG), 1 µ Adrenocorticotropic test (ACTH test).

3 RESEARCH METHODS AND MATERIALS

3.1 Study population 1, the clinical burnout group (CBG)

3.1.1 Study population and inclusion

The patients were recruited chiefly from primary health care centres in Stockholm County Council, Sweden, as primary care is the health care setting where most CB patient primarily seek medical advice. The patient group came from a wide variety of occupations, mostly female white-collar workers. They were on sick leave, 50%, 75% or 100%, had a medically certified diagnosis by their family doctor and received sickness benefits, i.e. financial compensation. More than 90% of the patients had been on sick leave for a year or more. Altogether 702 patients applied to participate and were assessed for eligibility using an application form; subsequently, inclusion and exclusion criteria were confirmed over the phone (Table 2, for inclusion and exclusion criteria). In next step, 179 patients went through a psychological assessment to confirm the diagnosis of ES (Table 1) and psychiatric comorbidity. Finally, 119 patients were invited to participate (Figure 2, Flowchart). Of these 94 patients, 84 women, and 12 men, agreed to participate and they were allotted by block randomization to the treatment groups, women and men separately. Fourteen patients dropped out during the treatment.

Figure 2 Flowchart clinical burnout group

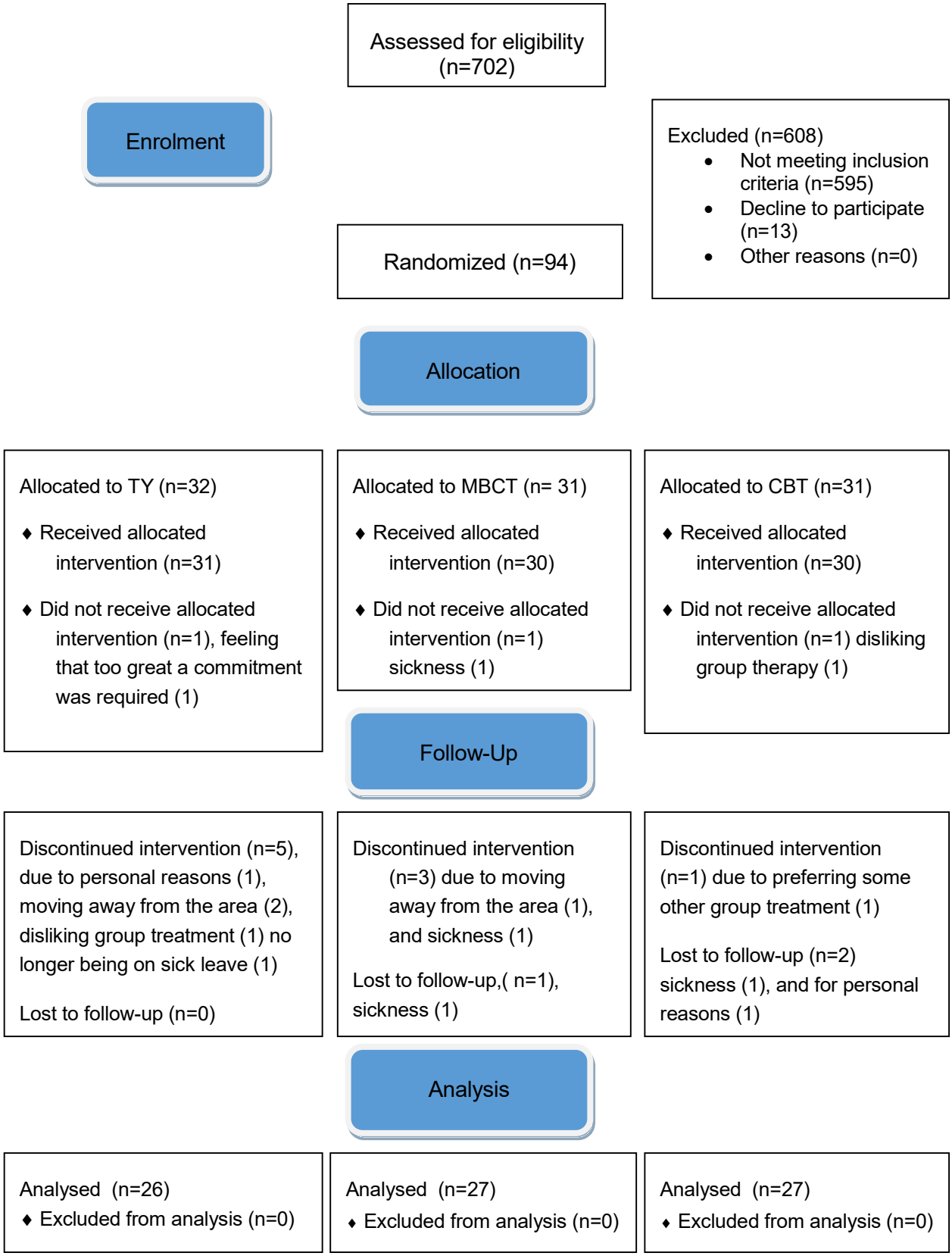


Table 2 Inclusion and exclusion criteria

Inclusion criteria
Aged 18 to 65 years
Being on at least 50% sick leave at the interview. Sick leave for a maximum of one year if on full-time sick leave at the interview, or for a maximum of three years if on part-time sick leave at the interview
Body mass index (BMI) of between 18 and 26
Meets the diagnostic criteria for Exhaustion Syndrome from the Swedish National Board of Health and Welfare, ICD 10 code; F43.8A
Exclusion criteria
Having other diseases that could give similar symptoms or hamper recovery
Not speaking Swedish well enough and not being well enough to participate in the study interventions
Using medication, including medicine containing glucocorticoids. Exceptions: antidepressants, sedatives, contraceptives and hormone replacement therapy. The patients were asked to take the same prescribed doses at both assessment times

3.1.3 Interventions

All three groups – TY, MBCT and CBT –received three hours of supervised group training per week. In addition, the participants practised on their own for 1–1½ hours, 3–4 times a week, including homework, for a total of at least 7 hours per week over five days. All participants followed this schedule, including the specific practices for each treatment arm stated below, for 20 weeks. All three groups practised various practical skills, such as formulating a self-motivated day-to-day activity chart and planning and executing a micropause as homework, see below, which was assessed during the following week's group session. The activity chart was used to help the patients create a realistic planning system. They planned the following day's activities the night before, and then during the day they endeavoured to follow their planned activities. In the evening they evaluated their work, rating how manageable their day had been and how they had felt emotionally during the day, thereby gradually coming to understand their limitations, i.e. validation [128]. During the micropause they tried for several minutes to be present with their bodily sensations and emotions while doing a brief practical task. This could, for example, be doing the dishes for a couple of minutes. The purpose of the micropause is to help the patients get closer to themselves with a deeper understanding of how they feel and how things affect them. The

groups consisted of 9–11 participants and three series of groups went through the programme. The instructor for all of the TY groups was a physician (AG), a trained TY teacher with many years of personal practice and of teaching TY. In the CBT groups, a licensed psychotherapist with extensive clinical experience in the field conducted the treatment. All three treatments were designed by the psychotherapist (BA), who is also a traditionally educated yoga teacher. The treatments were designed to suit the needs of the patients, expressed during the personal interviews.

Traditional yoga

The participants in this arm practised TY, a variation of Ashtanga yoga, which is a form of yoga with gentle movements and postures (asanas), breathing exercises and meditation (Table 3). The TY which was used in this study is mild and does not demand too much effort, considering the physical and mental state of the patients. The programme was designed specifically for this group of patients. Because they did not have much previous yoga experience, and to take into account their mental and physical state, the programme was introduced in two steps (Table 3). The overall purpose of the TY intervention was to help participants attain increased awareness of their own bodily sensations and emotional feelings.

The main components of TY were

1. Physical movements and postures (asanas); about 70%.

2. Breathing exercises; active and passive, about 20%.

3. Awareness: During all exercises, focus on feelings and bodily sensation was encouraged in order to understand and experience what was going on physiologically and emotionally.

4. Processing feelings by exercising the previous three components, so the individual gradually comes in contact with and becomes more aware of his or her feelings and emotions [33], and learns how to be present with and to experience difficult feelings and emotions instead of avoiding them.

Table 3 Exercises in the Traditional Yoga treatment

Exercises [82, 129]		
Name in Sanskrit (Name in English)	**Weeks 1–5**	**Weeks 6–20**
Padahastasana (Standing forward bend)	X	X
Supta pawanmuktasana (Knee-lock pose)	X	X
Bhujangasana (Cobra pose)	X	X
Ardha Salambhasana (Half grasshopper pose)	X	X
Digapranam (Salutation)	X	X
Vajrasana (Diamond pose)	X	
Breathing exercise	X	X
Vipareet Karan Mudra (Inverted pose)		X
Matsyasana (Fish)		X
Yoga Mudra (Sitting, forward bend)		X
Tadasana (Mountain pose)		X
Kapal Bati (Bellow breathing)		X
Chakki Chalanasana (Grind grain)		X
Meditation	X	X

Mindfulness-based cognitive therapy

The MBCT intervention was designed with the aim of teaching mindfulness and cognitive skills as a means to note distressing thoughts and feelings. They include: being aware of and recognizing one's own bodily sensations, attending to distressing thoughts and feelings by holding them in the present, and cultivating acceptance and self-awareness. These exercises possibly contributed to an awareness of a present-moment experience concomitantly with a compassionate, non-judgmental state. Additional skills, such as how to plan a satisfactory day by their own definition (using a self-motivated day-to-day activity chart), how to plan and execute micro-pauses, and how to accept negative feelings without being overwhelmed by them, were also on the agenda. Participants were taught to focus more on the emotional part of their feelings and less on their thoughts when they were practising mindfulness. Homework consisted of a protocol for measuring/observing negative feelings, body-mind awareness exercises, a day-to-day motivated chart, and instructions to follow a special theme for the week. All assignments and homework were assessed and analysed during the following week's group session.

Cognitive behavioural therapy

In addition to the day-to-day activity chart and the micropause, the CBT programme was comprised of various working components such as cognitive restructuring, applied relaxation technique, identifying stressors, coping with stress, and how to reduce the experience of daily stress. The homework included a protocol for negative thoughts, relaxation, and a special theme for the week. Each session had a specific theme, based on different cognitive and behavioural concepts and the theory behind the practical exercises, as well as working material and the specific homework assignment. Reports on the daily working chart were used for self-monitoring of day-to-day behaviour and reactions. The structure of a therapeutic session included formulating a jointly agreed work agenda for the group, a brief period of relaxation, reflections on the previous session, follow-up of the homework assignment, introduction of new themes, and preparation for the next homework assignment.

3.2 Study population 2, the HCG

3.2.1 Study population and inclusion

A group of 88 healthy participants (72 women and 16 men) who were working full-time and experiencing stress at work, but who did not fulfil the criteria for exhaustion syndrome, were used as the comparison group (HCG). They were chosen for the purposes of comparison, because the majority of the CBG had quite recently been in a situation similar to that of the HCG – working full-time and experiencing stress at work – and thus they were considered a suitable group for comparison. They were drawn from a previous study on stress management for health care personnel, and were recruited from May 2003 until December 2005 via self-referral from nine health care units in the Stockholm metropolitan area. The inclusion criteria for the HCG were the same as for the CBG, regarding age and weight. In addition, they were subjectively healthy, had no known diseases, and they were taking no medication, including hormonal contraceptives. None had endogenously elevated TSH and cortisol levels or had used exogenous glucocorticoids in any form during the last three months prior to the blood sampling and ACTH stimulation test. All women were premenopausal.

3.2.2 Measurements

The measurements were *subjective* and *objective*. Data were sampled at baseline for SWED-QUAL (I + II), and for biomarkers (III) in both the CBG and HCG. In the CBG, data were also collected after treatment (II + III). Data from the 1 µg ACTH stimulation test were derived from samples taken at baseline and after treatment in the HCG (IV). Blood sampling and the ACTH stimulation test were made in the follicular phase of the menstrual cycle.

3.2.2.1 *Subjective measures* – HRQoL (I +II)

As patient-reported HRQoL is a primary goal in today's healthcare, most studies explore some type of patient-reported outcome. In both our studies reflecting HRQoL, the Swedish health-related quality of life questionnaire, 1.0 (SWED-QUAL, Table 4) was used as primary outcome variable, employing the full version of this generic instrument [79]. SWED-QUAL is derived from the Medical Outcome Study (MOS) and SWED-QUAL is similar to SF-36 [130], although SWED-QUAL is based on subscales instead of a single global measure, which facilitates interpretation of the results. Furthermore, SWED-QUAL is a well-validated instrument in the Swedish general population. Moreover, SWED-QUAL is more extensive than SF-36, with several questions on social, cognitive and sexual functioning – aspects of life which are often affected in patients with burnout [131]. SWED-QUAL has been used in a wide range of studies on somatic as well as psychiatric conditions [78, 132]. It comprises 67 self-assessed questions on the present situation (now or the past week) grouped into 13 subscales, each with a separate index, from 0 (worst) to 100 (best possible). The subscales and descriptions are listed in Table 4. The questions are formulated negatively or positively, with four alternative answers such as No, not at all = 1, Yes, slightly = 2, Yes, fairly much = 3 or Yes, very much = 4. For some of the questions a Likert scale format is used with answers ranging from completely agree = 4 to completely disagree = 1. In addition, six questions on gender, age, having a partner or not, marital status, cohabiting and education level are included.

Table 4 Characteristics of subscales in SWED-QUAL

Subscale	Number of items	Description
Physical functioning	7	Extent to which health interferes with ability to perform physical activities (e.g., heavy manual work, sports, climbing stairs, dressing)
Satisfaction with physical functioning	1	Satisfaction with physical ability to do as wanted
Pain, frequency and intensity	6	Pain frequency, intensity and interference with activities of daily life (ADL), sleep and mood
Role limitation due to physical health	3	Extent to which physical problems interfere with ADL
Role limitation due to emotional health	3	Extent to which emotional problems interfere with ADL
Positive affect	6	Is a happy person, feels liked, emotionally in harmony, much to look forward to
Negative affect	6	Feels nervous, tense, down, sad, impatient, annoyed
Cognitive function	6	Concentration, memory, capacity to take decisions, confusion
Sleep quality	7	Problems with sleep initiation and maintenance, sleep adequacy and somnolence
General health perceptions	8	Health: prior and current, overall rating of health, immune defence, health worries
Satisfaction with family functioning	4	Satisfaction with family life in terms of cohesiveness, amount of support and understanding, amount of talking things over, overall happiness with family life
Satisfaction with partner functioning	6	Relation to spouse (or person felt closest to) in terms of saying anything wanted, sharing feelings, feeling close, being supportive
Sexual functioning	5	Lack of interest, inability to enjoy sex, difficulty becoming aroused, having orgasm (women), getting maintaining an erection (men)

3.2.2.2 *Objective measures* – biomarkers (III)

The objective outcome variables were 23 and 20 biomarkers for the CBG and the HCG, respectively. The biomarkers in blood and urine were selected from markers that have previously been used in stress research, in research on psychological treatments, or after yoga treatment. They were measured before and after five months of treatment with TY, MBCT or CBT. Adrenocorticotropic hormone (ACTH), prolactin, cortisol, dehydroepiandrosterone sulphate (DHEAS) testosterone, estradiol sensitive (estradiol), sex hormone binding globulin (SHBG), C-reactive protein, sensitive (CRP), thyrotropin (TSH), thyroxine (T4), triiodothyronine (T3), fasting plasma glucose (glucose), glycated haemoglobin (HbA1c), fasting plasma cholesterol (cholesterol), fasting plasma high-density lipoprotein (HDL), fasting plasma triglycerides (TG), urinary 5-hydroxyindoleacetic acid (u-5HIAA), urinary epinephrine (u-epinephrine), urinary norepinephrine (u-norepinephrine), urinary dopamine (u-dopamine) and urinary cortisol (u-cortisol) were analysed. Low-density lipoprotein (LDL) was calculated from total cholesterol, and the cholesterol ratio LDL/HDL was obtained.

3.2.2.3 *Objective measures* – ACTH stimulation test (IV)

The 1 µg ACTH stimulation test was performed in the morning, and the participants were instructed to fast starting at midnight and to refrain from alcohol, nicotine and caffeine-containing beverages. They were also asked to refrain from exertion leading to breathlessness 12 h prior to the test. Adherence to these guidelines was confirmed before the test. An intravenous cannula was inserted in an antecubital vein and kept patent with saline. The participants then rested for 30 min. ACTH (Synacthen®, Novartis Healthcare A/S, Copenhagen, Denmark, in the amount of 0.25 mg/ml) was freshly diluted to 1 µg/ml prior to use. After the 30 min rest period, baseline saliva and blood samples were collected (0 min). Immediately following collection of the blood sample at baseline (0 min), 1 µg ACTH was administered i.v. for one min, beginning no later than 0815 h. Saliva and blood samples were collected simultaneously at 20, 30, 40, 50 and 60 min following ACTH stimulation.

3.3 Statistics

3.3.1 Sample size CBG (II + III)

The sample size needed was estimated to be approximately 20–25 participants per group. The calculation was based on estimation, as when the study was designed there were no relevant studies in this field, and power analysis to determine the (effective) sample size was not possible. In a population (a cohort study) with diabetes type I and II the sample size was 40 persons per group with a power of 80% and $\alpha = 0.05$ based on a difference of 8 points on the SWED-QUAL subscale "general health perceptions", which is often used for comparison between groups and for sample size calculations [132]. Since the participants in our study had

a condition that was far worse than in the diabetic group, we assumed that the sample size could be smaller.

3.3.2 Sample size HCG (I + III + IV)

The sample size for a comparison between a group of people experiencing emotional ill health who were attending a mind-body medicine course and people in the general population was previously calculated to be 88 persons per group [133]. The calculations were based on an estimated difference of 7.5-scale points in the subscale general health in SWED-QUAL. In this study, the expected difference between the groups was larger. Thus, the number of persons needed per group could be smaller.

3.3.3 Statistics in each article

Article I: A Bonett-Price 95% confidence interval (CI) and median were calculated [134]. Also, Bonett-Price calculation for differences in medians was used to compare the subscale scores of the CBG with the subscale scores of the HCG to establish whether there were significant differences in scores. The significance level chosen was <0.05. Due to multiple comparisons, the Holm-Bonferroni correction was used in the statistical calculations for the outcome variables [135]. Effect size was calculated using Cohen's D, and in study I effect size was used to measure the relative difference in subscale scores between the CBG and the HCG. Effect size is the ratio of the mean difference in scores from the weighted SD and indicates whether a difference in subscale scores is clinically relevant or not. Cohen's D <0.2 is considered without importance, 0.2−<0.5 is a small difference, 0.5−<0.8 is a moderate difference, and ≥0.8 is a large difference. When Cohen's D is 1.0, the mean effect corresponds to the SD.

Missing data were found almost exclusively in items concerning "satisfaction with partner functioning" and "sexual functioning", and the proportions of persons not answering these items were 14 and 8%, respectively, in the HCG, and 14% for both items in the CBG, findings similar to those in previous studies [136].

Article II Wilcoxon's rank sum test [137] was used for comparison of the treatment groups' subscale scores at baseline and for comparison of the between-group treatment effect. Wilcoxon's sign rank was used for comparison of treatment effects [137]. Effect size was calculated using Cohen's D [138]. The median and the confidence interval were determined using the Bonett-Price calculation [134]. The significance level was set at < 0.05. Because there were multiple comparisons, the Holm-Bonferroni correction was used in the statistical calculations for the outcome variables [135].

Missing data were found, with few exceptions, in the subscales sexual function and partner functioning. This is in accordance with previous studies [136]. Those who did not answer

these items lived almost exclusively alone and had reported that they did not have a partner. The analyses were carried out according to the protocol.

Article III: The median and the confidence interval for the concentrations pre- and post-treatment were determined using the Bonett-Price calculation [134]. Student's T-test and Bonett-Price calculations were used for calculation of treatment effects within the groups and for all groups together as well as for comparison of the treatment effects between the groups and for the comparison between the healthy group and the treatment groups, all together [134, 139]. Student's T-test was used for normally distributed differences of concentration post- and pre-treatment, and Bonett-Price calculation was used for biomarkers with skewed distributed differences of concentration post- and pre-treatment [134, 139]. As this is a hypothesis-generating study the significance was set at two different levels: $P < 0.05$ and for trend $P \geq 0.05–0.20$. Also, for the same reason, no correction for multiple comparisons was made in the statistical calculations for the outcome variables.

Article IV: To determine the best time to measure the maximum response value, the number of maximum response values was calculated for each measure time; 20, 30, 40, 50 and 60 min after stimulation. The measure time with the most maximum response values was considered to be the best time to measure. Furthermore, the maxima at 30 or 40 min that were close to the maximum response value were considered to be the maximum response when calculating the number of maximum responses at each measure time. The median of the maximum concentration values at 20, 30, 40, 50 or 60 min was also compared to the median of the maximum concentration values at the time found to be the best time to measure, using the Fisher-Pitman permutation test, ($P < 0.05$) [140]. To compare the secretion of cortisol in serum and saliva, generalized estimating equation (GEE) was used to establish whether or not salivary and serum cortisol concentration curves were parallel [141]. GEE takes into account unequal variance and unstructured correlation, as was the case with the data used for GEE calculations in this study. We assumed unstructured correlation between measurements over time for each participant, and the calculation was made using the Huber-White sandwich estimator of variance ($P > 0.05$) [142].

Data analyses were conducted using the statistical program STATA versions 10.1, 11, 11.2 and 13 for Windows, StataCorp. (2009). Stata Statistical Software [143].

3.3.4 Statistical considerations

Subjective measures: **(I + II)** As the data are ordinal, the group-wise and between-group analyses of scores were done using non-parametric methods. To enable comparison with previous studies, percent increase and Cohen's D were calculated. An analysis using parametric methods was also carried out, and it yielded the same results for P-values. The results pre- and post-treatment differed slightly when presented as means instead of medians, but the general trend remained. Another phenomenon, "regression towards the mean", might have influenced the scores. For example, if SWED-QUAL is completed on a second occasion

in close proximity to the first, the scores tend to be closer to the mean. This could have influenced the scores to some extent in our group, but it is unlikely to have changed the results.

Objective measures: **(III)** Missing data were found mostly due to missing blood tests, non-adherence to the sampling instructions or problems at the laboratory when analysing. One participant fulfilled the diagnostic criteria for diabetes and the blood tests for fP-glucose and HbA1c were excluded from the analysis for that patient. The analyses of estradiol and DHEAS were made in premenopausal women without contraceptives and hormone replacement therapy only, and during the follicular phase of the menstrual cycle. The analysis of testosterone was made in all women, pre- as well as postmenopausal. The results for testosterone were reported as this is the most common to report, and as the results for testosterone and for bioactive testosterone were similar. The analyses were carried out per protocol. No serious adverse events occurred in the treatment groups.

3.3.5 Ethical considerations

The regional Ethical Review Board in Huddinge, Stockholm, Sweden, approved the studies included in this thesis. The studies were conducted in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All participants in both studies gave their informed written consent to participate.

When designing the study for the CBG, three different arms were chosen. Two new treatments with additional features were compared to CBT, which is the most common type of psychological support used as treatment for CB. In this study CBT was used as the active control group. No inactive control group was employed, as the longer you are on sick leave the more difficult it becomes to return to work. Also, recent data indicate that there might be a deterioration of the condition in an inactive control group [144].

The instructions for blood sampling and collection of urine might be complicated to understand and to follow for certain persons. This is true especially for patients with CB who often have cognitive impairments. Much emphasis was laid on encouraging an open and tolerant atmosphere for patients in order to make them feel free to phone for practical support and repeated instructions if necessary. Furthermore, they could call as many times as needed for a correct sampling, primarily of urinary collection. Blood sampling in both studies was conducted at laboratory by trained personnel in accordance with usual routines, and so was the ACTH test in study population 2, the HCG.

In the CBG a telephone interview was conducted with the persons who met the inclusion criteria in the application form, to confirm that the information was correct. That was done to minimize the number of persons who were denied inclusion after the personal interview, as we found that in many cases a denial was a great disappointment to the applicant, and often was perceived as personal failure. An explanation of why they were not considered for inclusion, and what they could do instead, was given to those applicants.

When filling in the questionnaires all the participants, both in the HCG and patients in the CBG, could do it at home, and at their own pace. They were encouraged to take their time and do it in several sessions if needed, to avoid answering mechanically. In the CB study the patients filled in the application form and questionnaires directly into the database. For the questionnaires, they used a personal code. In HCG the participants filled in questionnaires on paper.

Data in paper format (HCG study) (application forms, questionnaires and lab data) were anonymized and coded. All were kept in a locked storage during the active phase of the study. All were later on destroyed. Lab data, filled-in questionnaires and code keys for the HCG study were transferred into digital data files, stored at the department in encrypted areas on the disk. In the CB study only AG had access to these data. Data were presented at group level, to eliminate the risk that individual data would be identified. As few men participated and the spread in age was considerable, making it possible to identify individuals, individual data have not been transferred to public repositories, in order to protect their anonymity.

4 MAIN RESULTS

4.1 Sociodemographic data

Study populations 1 and 2: the CBG and the HCG (I–IV)

The CBG consisted mainly of middle-aged women with a high education (Table 5). Most of them had a partner and more than half of them were prescribed psychotropic drugs (anti-depressants, sleep-medication and tranquillizers), which at that time, was 5 times higher than in the general population (Table 5). Approximately 20% of these did not use their prescribed medicine, chiefly due to worry about side effects, no effect or a wish to handle the situation without medication. The majority were on full-time sick leave (Figure 3). A total of 92% of the patients had been on sick leave for 1 year or more at the start of the intervention. Of the patients in the CBG, 80% reported that they were sick because of work-related causes (Figure 4). The majority in the CBG were white-collar workers (Figure 5).

Figure 3 Sick leave

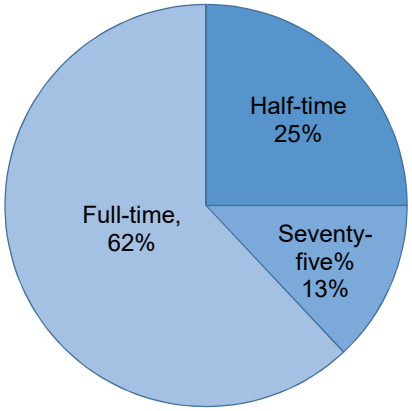


Figure 4 Reason for being sick

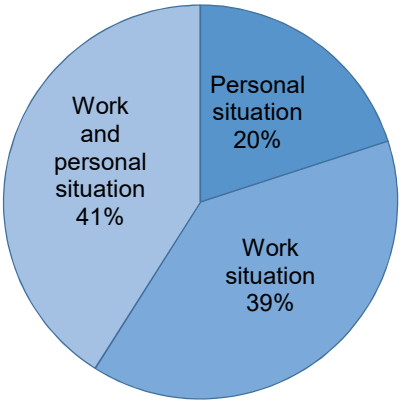
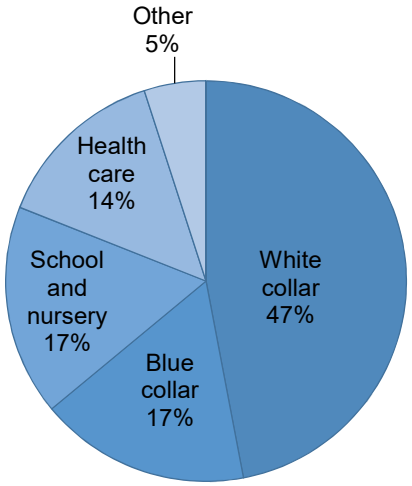


Figure 5 Occupation



All participants fulfilled the diagnostic criteria for ICD-10 code F43.8A (ES) and also the criteria for depression and anxiety. In the HCG the majority were women (Table 5). They reported that they were healthy but experienced stress, had no known diagnoses, and all were pre-menopausal, without medication or contraceptives. The CBG and the HCG were equal at baseline regarding sociodemographic variables. Both groups had higher education than the general population (Table 5). Fourteen patients withdrew from the CBG. The scores and sociodemographic variables of these patients were equal to the scores of the CBG patients who continued in the study.

Most of those who were not admitted to the study did not fulfil the inclusion/exclusion criteria, while the patients that declined to participate did so mostly as they felt that the study was too large a commitment.

Table 5 Sociodemographic data and medication for the clinical burnout group (CBG) compared to the healthy comparison group (HCG) and the Swedish population, women only.

	CBG	HCG	Swedish population[a]
Sociodemographic data, n	All [men] n=94 [12]	All [men] n=88 [16]	Women
Age, years, mean ± SEM	43.7 ± 0.97	40.0 ± 1.1	39–45
Education, years, %			
≤ 9 years	2	3	7
> 9–12 years	24	24	49
> 12 years	74	73	44
Having a partner, %	61	69	
Medication[b], psychotropic drugs prescribed, %	55	0	Approx. 10
Antidepressants, ATC NO6	42		
Sleep medication and tranquilizers, ATC NO5	27		
Painkillers, ATC NO2	4		

[a]The official Swedish population statistics in 2003–2008 from the National Board of Health and Welfare, and the National Social Insurance Board and Statistics Sweden are included for comparison in this table. [b] ATC code NO6, antidepressants; ATC code N05, sleep medication and tranquillizers and ATC code NO2, painkillers.

4.2 *Subjective measures,* HRQoL measured by SWED-QUAL

4.2.1 Article I, descriptive and comparative results

In today's healthcare, HRQoL is an important marker for the patients' perspective. It is known to predict future health, sick leave and mortality, and is the primary outcome variable in this thesis. At baseline, the CBG had low scores in 12 out of 13 subscales, with median scores ranging from 22–58 points (100 points=best possible health). These low scores were equal to or even lower than SWED-QUAL scores previously found in patients with severe psychiatric illness or chronic somatic diseases [78, 145]. The last subscale, "physical functioning", had a close to normal median score of 86 points. When the baseline scores were compared to the scores of the HCG, the scores were significantly lower in the CBG, $p <$ 0.001, in all subscales, including physical function. A median difference of 24–56 points was found for the subscales except for the subscale "physical functioning"; here the significant difference was only 10 points due to the above-mentioned higher baseline score. The largest median differences were found in subscales associated with the criteria for the diagnosis of ES, for example "role limitation due to emotional health", and "role limitation due to physical health" which measure the impairment in role functions, such as being a partner, parent or employee, because of decreased emotional and physical health (Table 6).

Furthermore, the subscales “positive affect”, “negative affect”, “general health”, “cognitive function” and “sexual functioning” were affected to a high degree. The two subscales that deal with social function – “satisfaction with family functioning” and “satisfaction with partner functioning” –were decreased to a lesser degree, indicating that many in the CBG felt that they had fairly good social support. Interestingly, considering that the subscale “physical health” was the subscale that showed the least decrease, “satisfaction with physical health” was low. The spread of the scores is indicated by the confidence intervals (CI) (Table 6). When comparing the CI of two groups, the results become more reliable if the CI’s are similar, as is the case in this study. Furthermore, the effect sizes were high, ranging from 0.85–2.01, and showed large differences between the two groups. Taking into account both measurements, the results indicate a severely lowered HRQoL in the CBG.

Table 6 SWED-QUAL scores in the clinical burnout group (CBG), in the healthy control group (HCG), and the median difference between the groups (scale scores, ranging from worst to best possible (0–100)). Test of difference, CBG vs HCG, all subscales $p < 0.001$.

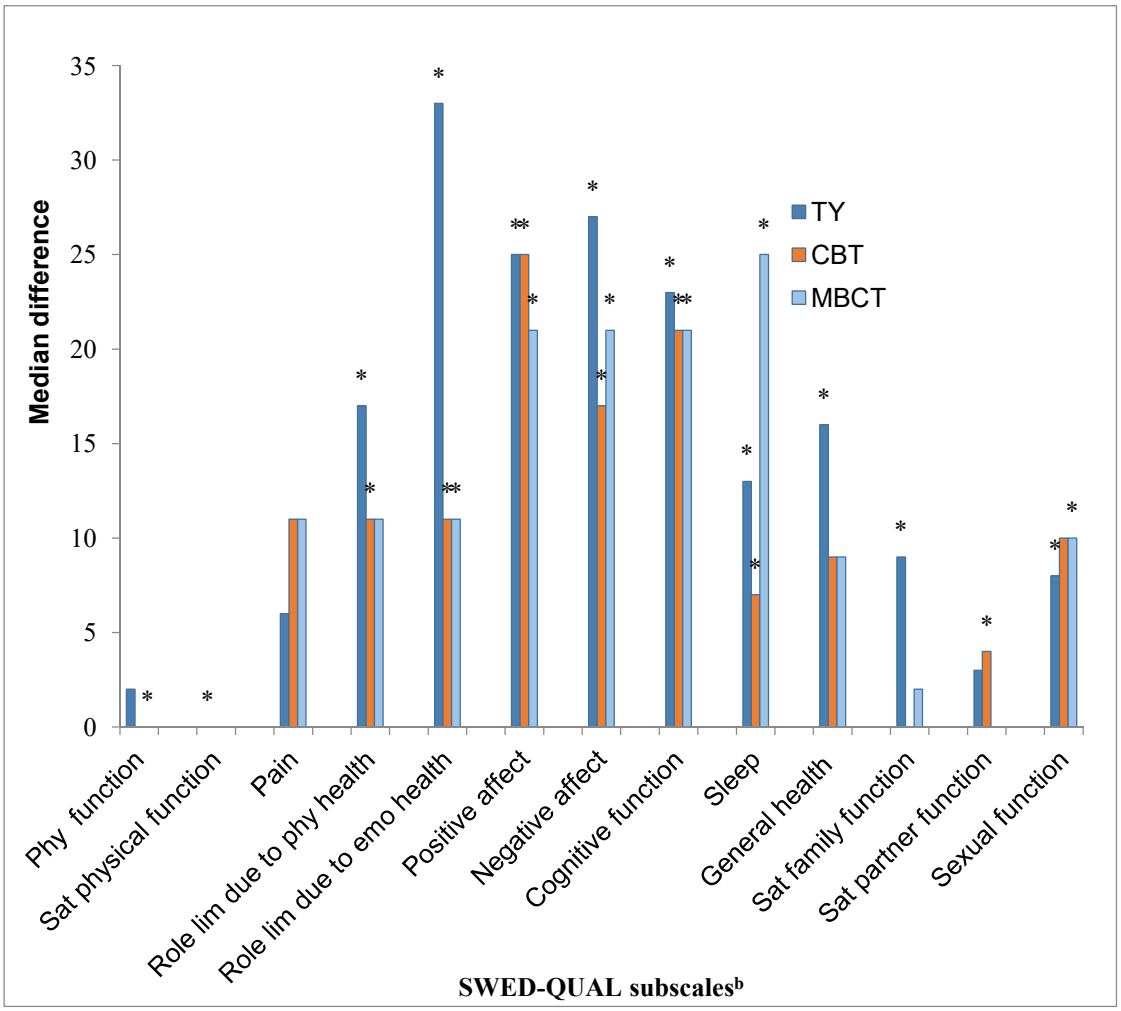
Subscale	CBG		HCG		Difference [b] CBG vs HCG		Test of difference
	Median (95% CI), n = 94 [a]		Median (95% CI), n = 88		Median (95% CI)		Effect size, Cohen's D [c]
Physical functioning	86	(81–90)	95	(93–99)	10	(4–15)	1.19
Satisfaction with physical functioning	33	(33–33)	67	(67–67)	34	(34–34)	1.17
Pain	58	(50–65)	85	(82–87)	27	(19–35)	1.15
Role limitation due to physical health	33	(27–39)	89	(78–100)	56	(44–68)	1.73
Role limitation due to emotional health	22	(11–33)	*78*	(67–89)	56	(41–71)	1.98
Positive affect	40	(31–48)	75	(67–83)	35	(24–47)	1.48
Negative affect	25	(19–31)	67	(61–73)	42	(33–50)	1.73
Cognitive function	25	(21–29)	79	(75–83)	54	(48–60)	2.01
Sleep	41	(34–48)	75	(68–82)	34	(24–48)	1.23
General health	44	(39–48)	91	(88–94)	47	(41–52)	2.01
Satisfaction with family functioning	50	(38–62)	79	(75–83)	29	(16–42)	0.89
Satisfaction with partner functioning	58	(52–65)	82	(80–84)	24	(17–30)	0.85
Sexual functioning	40	(33–47)	95	(88–102)	55	(45–65)	1.22

[a] = two persons with missing data. [b] Calculated by Bonett-Price. [c] =The effect size is the difference in scores between the healthy group and the study group divided by the pooled Standard Deviation (SD). An effect size > 0.8 is considered a large difference between the groups. [c] = Wilcoxon sign-rank test.

4.2.2 Article II, HRQoL in all and in each treatment group at baseline and after treatment

The next step was to calculate the median baseline scores with CI in all groups calculated together and in each treatment group, TY, MBCT and CBT. Furthermore, to calculate the difference between pre- and post-treatment scores. The results are shown in Figure 4 and Table 7. The results from all three groups showed that the HRQoL significantly improved after treatment. In TY 26 patients (5 men), and in both MBCT and CBT 27 patients in each (3 and 2 men respectively) were analysed. Ten subscales in TY and seven subscales in MBCT and CBT showed improvements, $p < 0.05$. The increases were especially found in the main domains covering aspects known to be affected in burnout, e.g. emotional as well as physical well-being, cognitive function and sleep. When calculating the median differences in scores post- and pre-treatment, they were found to be large in general. In TY the increase was from 0–27 points and in CBT from 4–25, and from 0–25 in MBCT. The ES was mainly medium or large. TY and MBCT showed a slightly better effect size than did CBT, measured by Cohen's D (Table 7).

Figure 6 Test of treatment effect (post-pre) [a] in SWED-QUAL [b] median, subscales scores, ranging from 0 (worst) to 100 (best) possible, after 20 weeks' treatment with Traditional Yoga (TY), Cognitive Behavioural Therapy (CBT) (control) or Mindfulness-based Cognitive Therapy (MBCT). Significant p-values, P < 0.05, and after Holm-Bonferroni correction are indicated by (*).



[a] Wilcoxon's sign-rank test was used for comparisons in each group.
[b] Swedish Health-Related Quality of Life Questionnaire.

Table 7 SWED-QUAL baseline median subscale scores ranging from 0 (worst) to 100 (best possible)[a], and test of treatment effect[b] per group and for all. Main results marked[c].

Subscale	All, n = 80			TY, n = 26			CBT, n = 27			MBCT, n = 27		
	Baseline, (CI)	P-value	ES	Baseline (CI)	P-value	ES	Baseline (CI)	P-value	ES	Baseline (CI)	P-value	ES
Physical well-being												
Physical functioning	86 (83-88)	**0.0003**	**0.36**	86 (81-90)	0.0207	**0.34**	90 (86-95)	0.4908	0.16	81 (74-88)	**0.0009**	**0.51**
Satisfaction with physical functioning	33 (33-33)	**0.0000**	**0.49**	33 (33-33)	**0.0031**	**0.52**	33 (16-50)	0.0185	**0.55**	33 (16-50)	0.0426	**0.39**
Pain	53 (45-61)	**0.0027**	**0.30**	50 (38-62)	0.0987	**0.29**	62 (49-76)	0.1631	0.14	33 (16-50)	0.0122	**0.55**
Role limitation due to physical health	33 (33-33)	**0.0000**	**0.59**	33 (18-48)	**0.0105**	**0.54**	33 (27-39)	**0.0043**	**0.65**	53 (42-63)	0.0362	**0.45**
Emotional well-being												
Role limit. due to emotional health	22 (11-33)	**0.0000**	**0.91**	11 (3-26)	**0.0006**	**0.93**	33 (22-44)	**0.0036**	**0.82**	33 (22-44)	**0.0004**	**0.99**
Positive affect	38 (31-44)	**0.0000**	**1.03**	40 (25-56)	**0.0009**	**1.05**	33 (17-50)	**0.0005**	**1.12**	42 (31-52)	**0.0011**	**0.90**
Negative affect	25 (19-31)	**0.0000**	**0.96**	33 (22-45)	**0.0000**	**1.0**	29 (21-38)	**0.0002**	**0.81**	21 (17-25)	**0.0001**	**1.07**
Cognitive function	25 (21-29)	**0.0000**	**0.91**	29 (14-44)	**0.0001**	**0.73**	25 (17-33)	**0.0001**	**0.9**	13 (2-23)	**0.0000**	**0.91**
Sleep	41 (36-47)	**0.0000**	**0.79**	36 (24-47)	**0.0008**	**0.69**	43 (34-52)	**0.0010**	**0.73**	46 (37-55)	**0.0002**	**0.97**
General health	50 (44-56)	**0.0001**	**0.47**	44 (37-51)	**0.0041**	**0.59**	50 (36-64)	0.0303	**0.45**	53 (34-72)	0.0658	**0.34**
Satisfaction with family functioning	46 (33-58)	**0.0000**	**0.60**	38 (15-60)	**0.0010**	**0.52**	40 (23-56)	0.2112	**0.32**	55 (35-75)	0.0097	**0.46**
Satisfaction with partner functioning	60 (54-66)	0.0041	**0.31**	58 (42-75)	0.0443	**0.21**	58 (47-70)	**0.0048**	0.18	67 (49-84)	0.4155	**0.20**
Sexual functioning	45 (40-50)	**0.0000**	**0.58**	45 (30-60)	**0.0019**	**0.5**	48 (29-66)	0.2119	**0.25**	40 (33-47)	**0.0009**	**0.62**

[a] Bonett-Price confidence interval (CI). [b]Wilcoxon sign-rank test and effect size (ES). Effect size, Cohen's D< 0.2 is considered as no effect, ≥ 0.2 < 0.5 a small effect, ≥ 0.5 < 0.8= a medium effect and ≥ 0.8= a large effect. [c] Significant ES and p-values after Holm-Bonferroni correction in bold and in marked areas.

4.2.3 Comparison of the treatments

The effect of the treatments was compared and a better effect from TY was found in altogether seven of the subscales, 5 when compared to CBT, and two when compared to MBCT, Cohen's D of 0.22–0.43 (Table 8). This might indicate a slightly better effect from TY than from CBT and MBCT in certain domains. TY had a larger increase in "negative affect" compared to CBT, $p = 0.09$ which probably in turn helped to increase "role limitation due to emotional health" more in TY compared to CBT, $p = 0.25$. MBCT had a better effect size than TY in two subscales (Table 8).

Satisfaction with the treatment: All patients reported that they were satisfied with the treatment and experienced a good effect.

Attendance: The yoga teacher and the psychotherapist recorded the attendance. Also, the patients in CBG executed the activity chart every day, and reported the exercises they had performed. Then they turned in their homework and activity chart to the psychotherapist or yoga teacher each week. The attendance for the groups was similar, with no significant difference, TY mean 69%, MBCT mean 75%, and CBT mean 70%.

Adherence: All three groups reported similar time spent on homework; in the TY mean 89.4 h, in the MBCT group 90.4 h, and 83 h in the CBT group.

Adverse events: At each session the patients were requested to report and discuss problems and adverse events, and if any, notes were taken. Moreover, the patients were asked to contact the therapist/yoga teacher if they had any concerns concerning the treatment. No major adverse events were reported.

Table 8 Comparison between the groups' treatment effects, measured by SWED-QUAL subscale scores, as p-values[a] and effect size[b].

Subscale	TY – CBT		MBCT – CBT		TY – MBCT	
	P-value	ES	P-value	ES	P-value	ES
Physical functioning	0.28	0.09	0.13	**0.44 M**	0.70	**0.29 M**
Satisfaction with physical functioning	0.82	0.06	0.89	-0.08	0.71	0.06
Pain	0.39	0.18	0.38	-0.07	0.66	0.13
Role limitation due to physical health	0.76	–0.02	0.47	**0.33 M**	0.75	0.04
Role limitation due to emotional health	0.25	**0.39 Y**	0.36	**0.32 M**	0.95	0.1
Positive affect	0.94	0.07	0.52	-0.17	0.70	**0.23 Y**
Negative affect	0.09	**0.43 Y**	0.19	**0.37 M**	0.65	0.09
Cognitive function	1.0	0.01	0.38	**0.32 M**	0.35	**0.28 M**
Sleep	0.40	0.16	0.16	**0.36 M**	0.66	0.16
General health	0.41	**0.26 Y**	0.88	0.04	0.69	**0.20 Y**
Satisfaction with family functioning	0.14	**0.22 Y**	0.32	0.15	0.46	0.07
Satisfaction with partner functioning	0.60	0.05	0.47	0.01	0.87	0.04
Sexual functioning	0.39	**0.31 Y**	0.48	**0.30 M**	0.91	0.09

[a] Wilcoxon rank-sum test. [b] Effect size (ES), Cohen's D< 0.2 is considered as no effect, ≥ 0.2 < 0.5 a small effect, ≥ 0.5 < 0.8= a medium effect and ≥ 0.8= a large effect. Significant ES and p-values after Holm-Bonferroni correction in bold.

4.3 *Objective measures,* Biomarkers and ACTH test

4.3.1 Article III, Biomarkers

The concentration of biomarkers at baseline in all treatments was calculated together and in each treatment group. Comparisons with the HCG, and with concentrations after treatment, were made in each treatment group at baseline and after treatment (III).

Before treatment, all biomarkers were within normal range in the CBG, both when all groups' concentrations were calculated all together and when each group's concentrations were calculated. When the results were compared to those of the HCG, urinary 5-HIAA, dopamine, epinephrine and nor-epinephrine showed significantly higher concentration, together with HbA1c, while urinary cortisol showed a significantly lower concentration (Table 9).

Table 9 Test of difference in concentration between CBG and HCG. Presented as p-value (P) and median for the numerical difference with 95% confidence interval (CI). The biomarkers that showed a difference or trend are presented here.

Biomarker[a]	**CBG, n=71–79 – HCG, n=21**	
	P	Diff
Cortisol (nmol/L)	**0.071**	71 (–6.11; 148.1)
Glucose (mmol/L)	**0.15**	–0.21 (–0.49; 0.074)
HbA1c (mmol/mol)	**<0.001**	–4 (–5.84; –2.16)
HDL (mmol/L)	**0.068**	0.2 (–0.015; 0.41)
U-5HIAA (µmol/d)	**< 0.001**	12.5 (7.47; 17.52)[e]
U-dopamine (nmol/d)	**<0.001**	520 (226.8; 813.20)
U-epinephrine (nmol/d)	**0.004**	10 (3.10; 16.90)
U-norepinephrine (nmol/d)	**<0.001**	92 (42.8; 141.18)
U-cortisol (nmol/d)	**<0.001**	–78.90 (–105.26; –52.54)

[a] Glycated haemoglobin (HbA1c), high-density lipoprotein (HDL).
[b] Bonett-Price was used to calculate the difference in median for the groups. **Significant** (<0.05) p-values in **bold underlined** and **trend** (p-values (≥0.05–0.2) in **bold** only.

The effect of psychological treatment

After treatment the concentrations of all biomarkers were stable and within the reference interval. The within-group effect of the treatments is shown, in all analysed together (study group) (n=71–79), and for each treatment group, TY, MBCT and CBT (Table 10).

When all the patients' concentrations were analysed together a significant change was seen in testosterone and urinary epinephrine (decrease) and in estradiol and glucose (increase). When the treatment groups were analysed separately, testosterone showed a significant decrease with CBT and MBCT, and a trend to decrease with TY. CBT showed a significant increase in estradiol and MBCT showed a significant decrease in dehydroepiandrosterone-sulphate (Table 10).

Treatment effects; calculated in the study group, n=71–79

A significant change in concentration (treatment effect), $P< 0.05$, was seen in four of the biomarkers (Table 10, column 1), with an increase in estradiol and a decrease in testosterone and in u-epinephrine (Table 2).

Results in each treatment group

Treatment effects of traditional yoga (TY), n=24–26

In the TY group no significant changes were found after treatment in any one of the 23 biomarkers (Table 2). A trend for an effect was seen in four biomarkers; a decrease in testosterone, LDL/HDL ratio and u-epinephrine (Table 2).

Treatment effects of Mindfulness-based Cognitive Therapy (MBCT), n=23–27

In MBCT, as in all analysed together, four biomarkers showed an effect. A decrease was found in DHEAS, testosterone and u-epinephrine (Table 10).

Treatment effects of Cognitive Behavioural Therapy (CBT), n=23–26

In CBT, three significant changes and three trends were found, with a decrease in cortisol and testosterone and an increase in estradiol (Table 10).

Table 10 Test of treatment effect (post – pre) in the study group (ALL), and in each group of treatment; traditional yoga (TY), mindfulness-based cognitive therapy (MBCT) and cognitive behavioural therapy (CBT). The biomarkers that showed an effect or a trend are presented here as p-value (P) and mean or median ([e]) for the numerical difference, with 95% confidence interval (CI).

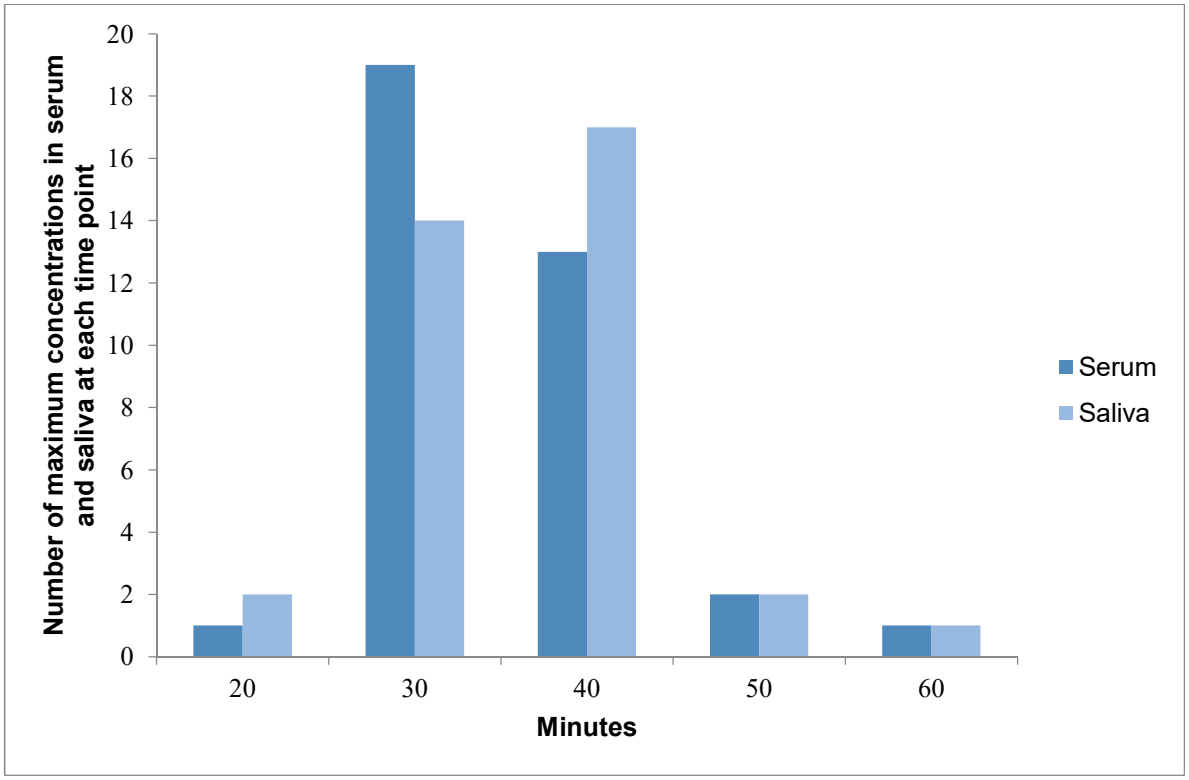
Biomarker[a]	Within-group treatment effect[b]							
	ALL, n=71–79[c, d]		TY, n=24–26		MBCT, n=24–27		CBT, n=23–26	
	P	(CI)	P	(CI)	P	(CI)	P	(CI)
Prolactin							**0.077**	–0.85 (–1,79; 0.09)[e]
Cortisol							**0.009**	–84.65 (–146.62; 22.69)
DHEAS[c]					**0.002**	–0.40 (–0.65; –15)[e]		
Testosterone[d]	**<0.001**	–0.15 (–0.20; –.10)	**0.077**	– 0.08 (–0.17; 0.01)	**<0.001**	–0.22 (–0.32; –0.12)	**0.024**	–0.13 (–0.24; –0.02)
Estradiol[c]	**<0.001**	48.5 (26.00; 1.00)[e]					**<0.001**	79.00 (43.64; 114.36)[e]
T4							**0.090**	–0.46 (–1.00; 0.08)
CRP					**0.19**	0.06 (–0.03; 0.15)[e]		
Glucose	**0.007**	0.13 (0.03; 22)	**0.089**	0.15 (–0.03; 0.33)	**0.036**	0.14 (0.01; 0.27)		
Cholesterol							**0.17**	0.20 (–0.91; 0.49)
HDL	**0.071**	0.05 (0.00;.10)						
LDL/HDL ratio			**0.054**	–0.20 (–0.40; 0.00)				
U-epinephrine	**0.012**	–4.09 (–7.25; –94)	**0.20**	–4.64 (–11.92; 2.64)	**0.012**	–5.43 (–9.55; –0.31)		
U-cortisol					**0.20**	–8.54 (–21.96; 0.89)		

[a] Concentrations given in (µg/L) for Prolactin; in (nmol/L) for Cortisol and Testosterone, in (µmol/L) for Dehydroepiandrosterone sulphate (DHEAS); in (pmol/L) for Estradiol, sensitive (Estradiol) and Thyroxine (T4); C-reactive protein, sensitive (CRP) (mg/L); in (mmol/L) for fasting plasma glucose (Glucose), fasting plasma cholesterol (Cholesterol) and high-density lipoprotein (HDL); no unit for low density lipoprotein/high-density lipoprotein ratio (LDL/HDL ratio), and given in (nmol/d) for 24 hours' urine collection of Epinephrine (U-epinephrine) and 24 hours' urine collection of Cortisol (U-cortisol). [b] T-test for comparisons in each group when normally distributed difference and Bonett-Price when the difference is skewed. **Significant** (<0.05) p-values **in bold underlined** and **trend** (p-values (≥0.05–0.2) **in bold only.** [c] In DHEAS and in estradiol only premenopausal women: n=18, n=17 and n=14–15 in TY, MBCT and CBT respectively. [d] In testosterone only women; n=21 in TY, and n=24 in both MBCT and CBT.

4.3.2 Article IV, ACTH stimulation test

In the ACTH stimulation test the majority of maximum responses in serum and saliva were found at 30 and 40 min (Figure 7).

Figure 7 Maximum responses in serum and saliva at 20 to 60 minutes.



When the 30 and 40 min times were calculated together, 30 out of 36 stimulations in serum and 29 out of 36 stimulations in saliva resulted in a maximum response after 30 or 40 min. Two additional stimulations, both in serum and in saliva, resulted in values after 30 or 40 min that were close to the maximum response value, with differences of 1.5 and 3.6 nmol/L in serum (0.2% and 0.5% difference) and 0.2 and 0.4 nmol/L in saliva (0.3% and 0.8% difference). Thus, 32 stimulations in serum and 31 in saliva had a maximum response or a response close to the maximum response after 30 or 40 min. No differences between sampling at 30 and 40 min compared to sampling at all times were found in serum ($P = 0.12$) or in saliva ($P = 0.06$), using the Fisher-Pitman permutation test. This indicates that sampling only at 30 and 40 min after stimulation was adequate for recording an individual's maximum response. The response values at 30 min were equal to the response values at 40 min both in serum ($P = 0.78$) and in saliva ($P = 0.85$), with a median difference of 0.1 nmol/L in serum and 1.1 nmol/L in saliva.

Parallel concentration curves

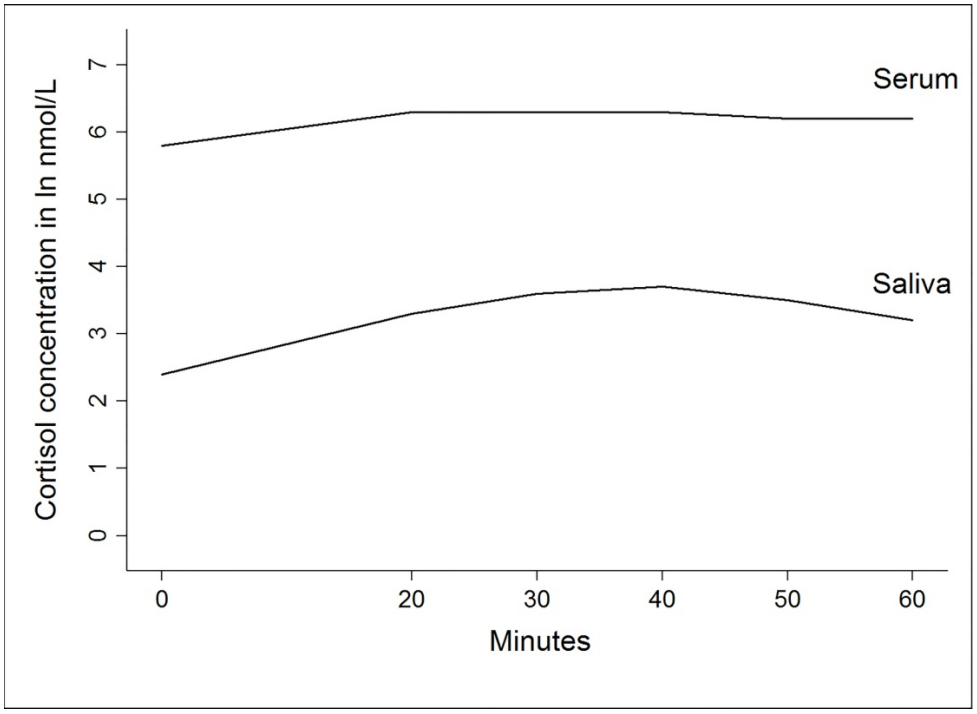
The concentration curves of cortisol in serum and in saliva were parallel at 30 and 40 min when calculated with GEE. In other words, salivary cortisol could replace serum cortisol in the ACTH stimulation (raw data, $P = 0.82$; raw data transformed into natural logarithms, $P =$

0.90) (Figure 8). Moreover, median cortisol concentrations were similar at 30 and 40 min for all participants, both in serum and in saliva (Table 2 and Figure 2)

Taken together, these findings suggested that sampling in saliva instead of serum at 30 and 40 min would be a reliable alternative for assessing an individual's maximum response after stimulation.

Furthermore, the medians of the maximum response values at 30 and 40 minutes were equal if the medians of the maximum response values were calculated at all times, $P = 0.1$ and $P = 0.06$, respectively. Cortisol concentration curves were parallel in serum and saliva at 30–40 min, $P = 0.83$.

Figure 8 Cortisol concentration curves over time for logarithmically transformed values showing parallelism in 30 and 40 minutes.



5 DISCUSSION

5.1 Main findings

Subjective measures: In this thesis the CBG were mostly women with high education, and were on sick leave due to job-related causes. They had a global decrease, comprising all areas of life covered by SWED-QUAL subscale scores. Their scores were lower than the HCG, and lower than or on a par with persons with severe psychiatric illness and chronic somatic diseases with psychiatric comorbidity. This indicates the severity of the situation, given that they recently had been healthy. The effect on HRQoL after 20 weeks' psychological group treatment was significant in 10 subscales in TY and in 7 subscales in MBCT and CBT, respectively, with normalized scores in many subscales in all groups. The largest improvements were seen in main domains known to be affected in burnout/CB and are probably due, at least in part, to the treatment. Better effect from treatment was seen in 7 subscales in favour of TY, with small effect sizes. ***Objective measures:*** The 23 biomarkers in blood and urine measured at baseline did not show any pathological concentrations according to current reference values. When compared to the concentrations of the HCG (20 biomarkers), the baseline concentrations of urinary catecholamines, 5-HIIA and cortisol were significantly lower and could potentially act as markers in future research. After treatment several potential markers were found that may be used to follow the course of CB, for evaluating psychological treatment in general or in one or more of the three treatment groups, such as testosterone, estradiol and urinary epinephrine. The 1 µg ACTH stimulation test can be used as a stress-test with sampling in saliva at 30 and 40 minutes, in saliva solely.

5.2 Socio-demographic data

The CBG was a clinical sample chiefly from primary health care centres, with a wide variety of professions, representing the situation in primary care where most of these patients initially are found. They were severely ill, on sick leave and they all had a concomitant depression and anxiety, which further aggravated their situation. Few clinical studies have been conducted in this patient group, which makes comparisons difficult. Moreover, burnout is most often evaluated by questionnaires, primarily MBI, and it is not known what scores might correspond to CB. This further complicates comparisons. Another factor is that most studies consider only work-related causes of burnout while the CBG studied in this thesis are diagnosed according to ICD-10 code F43.8 A, ES. ES also takes into account personal reasons for becoming ill, which was the sole cause in approximately 20% of the patients in the CBG, and as a part of the cause for being ill in another 41%.

The CBG had higher education than in the general population, but persons with higher education are known to have better health in common. However, the findings might be due to higher education opening opportunities for different types of occupations, with other work tasks and types of employment, which might lead to an increased risk of CB. Persons with lower education may have a higher total workload from work and home taken together, may

experience less social support, or may be too sick to manage to participate in treatment. The patients in the CBG had applied to take part themselves, mostly after they had received information at the primary health care centre; this indicates that they were highly motivated for treatment, which predicts a better outcome [146] .

All reported satisfaction with and effect from the treatment despite the fact that many patients at the inclusion interview had said that they actually wanted one of the other treatments. This is a more positive evaluation than expected but partly in line with previous research, which has shown that treatment works better if the participant is positive to the selected treatment, either based on their own wish or if they intellectually have understood and agreed with the underlying principle of the treatment, and actively participate in the treatment [146]. Here, at the interview they received a detailed description of each of the three treatment arms, which would have helped them to understand and agree with the treatment principles, and might explain their general satisfaction with the treatment. Besides, the discrepancy here might be due to the duration of the treatments, 20 weeks, which gave them time to establish new behaviours and get used to the exercises, enabling them to experience for themselves that the treatment worked, and because they were asked at the end of the treatment. Moreover, many patients request longer treatments. For example, in a recent study in a somewhat similar patient group, the patients were randomized to two groups. They received 6 and 2 sessions respectively over 12 weeks, and many patients reported that they would like to have more sessions/longer treatment. (Personal communication, Anna Nager, 3 December 2019). Furthermore, many reported that they had not been offered any other treatment at the primary healthcare centre, even though they were severely ill. In this situation, they might have seized the opportunity to receive treatment irrespective of whether the treatment was their first choice or not. Together, this could indicate that it is possible to influence several factors that are important for achieving a good outcome.

Few men applied to and participated in the study, and few men are diagnosed with CB; however, the number of men on sick leave for CB is increasing [2]. Men also tend to report less depression [147]. Explanations for this include the fact that women take more care of the home and children and are thus under more pressure than men; however, in the younger generation of today, many men take more responsibility in the family and are thus more likely to receive a CB diagnosis. The Swedish Work Environment Authority found recently that when men and women have the same work tasks, the amount of sick leave taken is the same [148]. A similar conclusion was drawn in a study based on descriptive data from the WHO MONICA study [149]. This study shows that about 13% of the study population (*n*=1000) which comprised healthy working individuals, with slightly more men, had a score > 4.0 on the Shirom Melamed Burnout Questionnaire which indicate CB. Shirom Melamed Burnout Questionnaire has been shown in other studies to be equivalent to a diagnosis of CB (ES) over a certain score. In working individuals in primary care, n= 345, the number of individuals indicating ES was 20% with approximately twice as many women as men [150]. Furthermore, several sectors dominated by female occupations have been subject to downsizing in the last few decades, resulting in a more pressed working situation, and more

women likely to be given a CB diagnosis. On the other hand, a recent study found partially reversible changes in different brain structures involved in stress processing, with more pronounced changes in women after equally perceived stress, indicating an increased sensitivity to stress in women [73].

5.3 *Subjective measures,* HRQoL

At inclusion, the CBG had lowered median scores in all subscales, thus affecting all areas of HRQoL; this has not been demonstrated before and highlights the severity of their situation. The scores were compared to the HCG group comprised of healthy working persons experiencing stress. Their situation had been very similar to that of the CBG until quite recently, and they were therefore considered to be a suitable comparison group. Despite the fact that the CBG had quite recently become ill, and that they were otherwise healthy, they had significantly lower median subscale scores than the HCG. The scores for the CBG were on par with or, for some subscales, even lower than for persons with severe psychiatric illness or chronic somatic disorders with psychiatric comorbidity [77, 78]. This was unexpected. Previous research has shown a somewhat similar pattern, with subscale scores lower than expected in a group of healthy persons in a course setting, reporting stress and a wish to change their lives [133]. In general, in both mental and somatic chronic diseases, there tends to be a habituation to the situation. Patients find ways to lead a reasonably good life with their illness, which can make subscale scores relatively higher. This indicates a better HRQoL than if the condition had onset recently. When the scores of the CBG were compared with the scores of a group of borderline patients, with at least two previous suicide attempts and in hospital after exacerbation of symptoms, the scores were on a par or, for some subscales, even lower [78]. The CBG had recently been leading a normal life, and probably had their usual concept of health fresh in their mind. On the one hand, poor sleep as experienced by these patients means that they tend to judge their situation more negatively due to emotional bias; this could, to some extent, have affected the subscale scores [151]. On the other hand, psychiatric patients have been shown to be credible reporters of their HRQoL [75].

5.3.1 Physical well-being

The subscale scores at baseline for “physical function” were comparatively high in all three groups, most probably because the patients were previously healthy and of an age with low concomitant morbidity. In a previous study, the same trend was seen in healthy individuals experiencing emotional ill-health and attending a mind-body-medicine course [133]. Other studies have shown that, initially, physical function is less affected in stressful situations compared to cognition and emotional well-being [152]. The other subscales on physical well-being showed an inconsistent pattern between the groups, with improvement in some subscales but not in others, despite the large improvements in emotional well-being. Individuals with burnout are more prone to negative affect and usually report a decline in mental health and somatic symptoms [153]. Furthermore, there is an inconsistent association between negative affect and objectivity when reporting health status [154]. Previous research

has found that high burnout, especially in persons scoring high on the emotional exhaustion component of MBI, corresponded to low HRQoL both mentally and physically [155]. In addition, a recent report on burnout suggests that physical health is also affected negatively in CB [156]. Taken together, we expected physical health to improve simultaneously with an improvement in emotional well-being. In TY, physical work in the form of gentle yoga movements was used together with awareness training, and this could have given the participants an accurate idea of their capacity and physical function. The subscale "physical functioning" showed a non-significant increase while the subscale "role limitation due to physical health" showed a significant improvement. As "physical functioning" also contains questions about physically demanding work, while "role limitation due to physical health" deals with the day-to-day situation in which the person is normally involved irrespective of how they feel, the improvement might have been experienced earlier. In the elderly at risk of cardiovascular disease, gentle yoga was found to improve the overall physical function and capacity in 83% of the participants [157]. The median scores for "physical functioning" in the CBT treatment group did not change, most probably because they had a high baseline subscale score. Relaxation was part of the CBT treatment in order to increase bodily awareness and, together with the cognitive strategies, was used to counteract the effects of burnout. However, it appeared not sufficient to improve "physical functioning". In previous research, CBT improved physical function in patients on sick leave for stress-related disorders, which is in contrast to our results. That study used SF-36, an HRQoL questionnaire similar to SWED-QUAL; however, the baseline scores were not reported in that study, which might explain this discrepancy [158]. All three groups reported a low, non-significant increase in scores in the subscale "pain", together with low, no and medium effect sizes in TY, CBT and MBCT, respectively, which was not anticipated. We had expected an improvement after treatment because pain is often an early symptom in stress-related disorders. On the other hand, perhaps because pain is a non-specific symptom it is the last of the symptoms to disappear. Because MBCT showed a significant increase in "physical functioning" we assumed it would affect the subscale "pain"; the low increase seen with TY might be due to the bodywork in the treatment which enabled them to come into contact with their physical pain and better assess it.

5.3.2 Emotional well-being and cognitive function

Emotional well-being comprised the subscales "negative affect", "positive affect" and "role limitation due to emotional health". This is the domain in which the largest improvements were observed. The improvements were found both when all groups were calculated together and when the groups were analysed separately (Table 7 + Figure 6). The effect from TY might be due to the fact that the participants tried to be aware of their bodily sensations and their emotions together with the rhythmic, regular breathing, and the gentle physical movements [159, 160]. These components have previously shown an effect on the autonomic nervous system, both the sympathetic and the parasympathetic systems, as well as on positive and negative emotions (affect) [106, 161, 162]. As TY uses a holistic approach, employing exercises from physical, emotional and cognitive domains in each exercise, this may have

enhanced the improvement in the emotional domain. In previous research CBT has also shown an effect on positive and negative affect [163, 164]. Cognitive function and emotions are closely connected, and there is a mutual influence. In burnout, memory, the ability to concentrate, the capacities to understand and to focus on day-to-day life are important aspects of cognitive function which are often compromised. Here, all three groups had a similar improvement in cognitive function although the methods were quite different, especially in the TY group which trained cognitive function in a different way from MBCT and CBT. This opens up possibilities to treat individuals that for various reasons cannot attend CBT or MBCT. This is in line with research in children diagnosed with ADHD who had improved day-to-day skills with an increased ability to focus and concentrate as well as increased social skills after yoga [165]. Cognitive function has also been shown to improve in breast cancer patients after yoga [166], and in menopausal women [167]. Furthermore, a large number of studies have shown that CBT has a good effect on various aspects of cognitive function, which is in line with our findings [33, 157].

5.3.3 Sleep

In all three groups the subscale "sleep" showed significant improvements. In previous studies TY is reported to have an effect on sleep, which may be due to the overall stress-reducing effect, relaxing, decreased negative effect and an improvement in body awareness. Yoga has in previous studies shown an impact on sleep disturbances, which support our findings. As sleep is known to be a crucial factor in the development of burnout the improvement might have helped to ameliorate the burnout symptoms. In a recent study improvement in sleep quality was one of the mediating factors in reduced symptoms of exhaustion [34]. CBT is a common therapy for sleeping problems, and has previously shown good effect in a group of depressed patients experiencing insomnia, which supports our findings [168]. TY showed a trend for a better effect than did CBT in the subscale "negative affect". This is in line with our hypothesis but additional studies are needed to explore this.

A general increase in HRQoL is not necessarily followed by an increase in work ability, but an improvement in the scores of subscales "role limitation due to emotional health" and "role limitation due to physical health" may indicate an increased capacity to work. These two subscales reflect how our role functions in life and at work are affected by how one feels physically and emotionally. Both TY and CBT showed large improvements in these subscales. Previously, some studies have been able to show increased return to work, lower sick leave or remission, using CBT as a stand-alone treatment or in combination with work-place interventions [7, 124, 169], but usually the treatments have been shorter (8–16 weeks) [10], and the effect sizes are often small. When the scores after treatment in TY and CBT were compared with the scores of HCG [131], both showed decreased median differences. The difference in subscale scores was no longer significant in ten subscales in the TY group, and in five subscales in the CBT group after median regression (data not shown). This might indicate a good effect of the treatment.

5.4 *Objective measures*, biomarkers

5.4.1 Biomarkers at baseline

None of the 23 biomarkers in the CBG showed a pathological level before treatment, i.e. had a concentration outside the current reference ranges. This is in accordance with earlier studies. Previous research has shown that biomarker concentrations at baseline are significantly higher or lower in stressed individuals than in non-stressed individuals and, with rare exceptions, within the reference range. However, we do not know whether these reference ranges can be applied in this setting or whether a low or high concentration within the reference range may be interesting in this group of patients.

The study in the CBG is one of the few studies that have explored biomarker concentration before and after well-defined psychological treatment in patients diagnosed with a medically certified diagnosis, ES, ICD-10 code F43.8A (Table 1). This means that direct comparison with previous research becomes difficult. In one study, patients were diagnosed based on psychometric rating scales, symptom scales and standardized medical examination and another used the ICD-10 code Z73.0. The ICD-10 group of Z-codes is defined as "Factors influencing health status and contact with health services", and these do not have any diagnostic criteria. The code Z 73.0, "State of vital exhaustion" was occasionally used to diagnose CB before ES was established, but direct comparisons with the CBG become difficult, which might explain some of the differences found here, for example concerning CRP, cortisol, HbA1c and u-epinephrine.

5.4.2 Comparison of the clinical burnout group, (CBG) with healthy working individuals experiencing stress (HCG) (III)

Cortisol

The adrenal hormone cortisol showed a trend (p=0.071) for a higher concentration in the CBG. In previous research, inconsistent results have been found, with decreased, increased or equal concentrations at baseline both in patients with "high burnout", i.e. severe burnout measured by psychometric instruments, and in patients with CB and other stress-related illness [69, 170, 171]. This might be due to "timing" i.e. the duration of the stress-related illness. How long the person has been sick is a crucial factor for the interpretation of the cortisol concentration when evaluating the level of burnout. This has been highlighted by several authors and could explain the contradictory results [62-64].

Adrenal and ovarian hormones

The adrenal and ovarian hormones estradiol, testosterone and their binding protein SHBG did not show any significant differences in concentration compared to the HCG. Testosterone showed a non-significant higher concentration. In a previous study a similar picture was seen, with significantly higher testosterone concentrations in persons on sick leave for affective stress-related mental disorders, compared to healthy people. When the results in that study

were compared to healthy individuals experiencing stress the increase was small, and non-significant, as in our study [172] .

Biomarkers for inflammation, and lipid and glucose metabolism

Lower levels of glucose and HbA1c were found in the CBG than in the HCG. Previous studies have shown higher HbA1c levels in persons with burnout [173, 174]. Both these study populations had milder burnout than those in the CBG.

Urinary hormones measuring stress

The 24-hour urine collection for the urinary hormones u-5HIAA, u-epinephrine, u-norepinephrine, u-dopamine and u-cortisol showed a significant difference for all hormones between the CBG and the HCG (Table 9). This might indicate that these hormones can be used as markers when studying CB in patients. In the CBG, all the urinary hormones showed higher secretion over 24 hours, except cortisol which showed a lower secretion. This was expected as the study group had been on sick leave for more than 12 weeks prior to the baseline measurements. Furthermore, they had experienced stress for a long period of time before being put on sick leave. Taken together, high u-catecholamines and low u-cortisol secretion was expected. In previous research, results have been contradictory. Moch et al. 2003 found lower u-cortisol in a group of burnout patients, even below the reference range, while there was no significant difference in the concentration of u-catecholamines [175]. In contrast, Traunmüller et al. 2018 found a lower concentration of u-norepinephrine, but not u-epinephrine, in persons diagnosed with burnout compared to a control group of healthy individuals working full-time [176]. The explanation could be that acute stress is high when working and dealing with a difficult situation, whereas the stress diminishes when on sick leave. A significantly higher concentration of u-5HIAA was found for the CBG compared to the HCG. Previous research has shown that patients with depressive disorder and stress, as in the CBG, have increased u-5HIAA which could explain the findings [177]. Furthermore, stress often precedes depression, and severe stress and depression often coexist in CB [21].

5.4.3 Hormonal changes after treatment within the CBG, n=71–79

The main effect was found in testosterone and in estradiol, both anabolic hormones, as well as in u-epinephrine. Testosterone decreased after treatment. Previous research has shown that middle-aged premenopausal women with chronic stress have higher u-testosterone than non-stressed women [178]. In another study testosterone was high in women on sick leave for psychosocial disorders, compared to healthy individuals [172]. Furthermore, exogenous testosterone has been shown to attenuate the integrated central stress response in healthy women [179]. In yoga studies, testosterone secretion in saliva increased after a single session of yoga in 23 healthy middle-aged and older women [180], and serum testosterone decreased in an RCT (n=90), after a holistic 12-week programme in women with polycystic ovarian syndrome [181], which is in line with our findings. This may indicate that testosterone is increased to mitigate the effect of stress, and thus decreases with a lowered level of stress, as

in our CBG. Besides, the concentration of testosterone is said be altered by yoga according to Hatha yoga pradipika, but how and in what way is not described [82]. In our study we could not determine whether the lowered testosterone was due to an impact on the adrenals, the ovaries, or on both. Estradiol measured in saliva has previously been shown to decrease in young women with elevated psychological stress, which is in line with our results [182]. As 95% of the estradiol is produced in the ovaries [183] we assume that the increased level after treatment was due to less suppression of the ovaries. Few studies have examined biological biomarkers after treatment especially in this well-defined, diagnosed group of CB patients. Moch et al. 2003 showed that prolactin, ACTH, u-cortisol, s-cortisol, DHEAS, glucose, TG, cholesterol, LDL, HDL, u-epinephrine and u-norepinephrine did not change after a 1–2-week stress management intervention programme [175]. The programme comprised diet, exercise and behaviour modification for 5–10 consecutive days. Follow-up was carried out monthly for 4 months. This is in line with our findings, except for u-epinephrine, although their treatment was shorter and their study population was small, n=16. Previously, cortisol has not shown any change after treatment when the cortisol awakening response was measured [184] and no change in diurnal serum cortisol secretion [185]. In another study DHEAS was shown to predict the development in health: an increase after treatment indicated a larger decrease in CB symptoms than for patients with a decrease in DHEAS concentration [186]. We could not verify their results since no comparison with burnout symptoms was made in our study.

5.4.4 Comparison within each treatment group n=23–27

Although biomarkers for measuring the effect of psychological treatment in general have not been established yet, we also studied the treatment effect in each of our treatment groups, to find out if differences in effect appeared. Here all three groups showed a decrease in testosterone, with a significant difference for MBCT and CBT and a trend in TY. Estradiol showed an increase in CBT. No previous studies have shown an effect on these anabolic hormones after treatment in patients with CB.

The most significant differences in biomarkers were found in MBCT and in CBT, while TY had several trends but no significant differences in biomarker concentrations. Why TY did not show an effect on a par with CBT and MBCT in this setting is noteworthy. All three treatment groups had a good effect on HRQoL [187]. Why the TY showed less effect on biomarkers remains to be elucidated. Concerning the biomarkers we at least know that the markers found can be explored in further research to follow the course of CB.

5.4.5 Comparison with other studies in similar patient groups

Previous studies in patients with CB have shown effects from psychological and stress-reducing interventions with our without workplace interventions, on psychological symptoms and QoL [7, 123], mostly shown marginal effects on sickness absenteeism and return to work [7] but also on burnout [188]. We cannot know for sure whether the changes found here in HRQoL and biomarkers are from the treatment, from time, i.e. a natural healing, from other factors like self-efficacy and intention to go back to work, or a

combination. However, a recent clinical study in patients with CB and diagnosed with ES showed significant improvement in return to work after rehabilitation, compared to wait-list controls at the one-year follow-up . These patients had been on sick leave for a mean of seven months, and a maximum one year at inclusion, which is slightly shorter than for our CBG. The authors concluded that the control group situation probably reflected the natural course of CB [126]. This indicates that treatment might have an effect in these patient and that healing is not just a matter of time, which has been proposed previously [7]. In another study, patients with CB showed a significant improvement after self-help combined with CBT face-to-face in a second step, compared to only self-help [169]. The CBT treatment in that study was disease specific and the results indicates that CBT as a stand-alone might help this group of people when a CBT protocol is used which is adapted to the patient group, as in our study. In another study, patients on sick leave and with adjustment disorder, received CBT alone or in a combination with integrated work aspects. Self-efficacy was measured at baseline and after 12 sessions with a therapist. Partial return was faster in the combined group and irrespective of level of self-efficacy, while full return to work was achieved to a higher degree in patients with high self-efficacy at baseline. This indicates that an individual evaluation of each patient should be performed and extra support in certain areas can give a better outcome. Moreover, with prolonged sick leave on full time, as in our CBG, and without much improvement, a rapid, spontaneous recovery becomes less probable. Furthermore, as these patients are at high risk of relapse, the treatments might help to increase the awareness of patterns and behaviours and give tools to better handle the work situation and life after the treatment period, which might reduce the risk of relapse. This is especially important as the risk of future sick leave and disability pension increases with repeated exposure to sick leave, as well as after long-term sick leave [189]. Furthermore, burnout is known to predict permanent work disability [190].

5.5 *Objective measures*, the intravenous 1 µg ACTH test

Sampling in saliva at 30 and 40 min is sufficient to reliably measure the maximum cortisol concentration following a 1µg ACTH test in a healthy population. Sampling both in serum and in saliva at only 30 and 40 min after the 1µg ACTH stimulation could be sufficient to record the maximum numerical response of an individual (figure 5). In addition, parallelism in the concentration curves of serum and salivary cortisol at 30 and 40 min ($P = 0.82$ and $P = 0.90$ for raw data and raw data transformed into natural logarithms) (Figure 6) implies that sampling in saliva could reliably replace sampling in serum in the 1µg ACTH test. The 1µg ACTH stimulation test has been used mainly in clinical, endocrinological settings to evaluate disturbances of the HPA axis and to diagnose somatic diseases. Since the HPA axis also mediates the body's response to a stress stimulus, the 1µg ACTH test may yield valuable information about an individual's ability to respond to stressful stimuli and provide a means to evaluate therapeutic psychological treatments and recovery. Based on our findings, sampling at 30 and 40 min would suffice to determine the maximum response, which would

be the highest value of the two samples. In addition, sampling only twice and only in saliva would be an alternative that is cost-effective, faster, and with non invasive sampling.

Previous studies have shown that stress may alter the function of the HPA axis, with altered cortisol secretion as an outcome following a DEX-CRH test, ACTH test, insulin-induced hypoglycaemia or standardized meal [25, 191, 192]. These findings support our proposal to use the ACTH test to diagnose stress-related disorders such as adjustment disorder and burnout, and to evaluate recovery and treatments. However, sampling, chiefly in plasma or serum but also in saliva, and at multiple times, is difficult to do in clinical practice or in large-scale studies. Our suggestion of using the 1μg ACTH test to sample in saliva and only twice would be an attractive alternative. The correlation between salivary and serum cortisol concentrations observed here has been reported earlier [193, 194], but no other study has shown that serum and salivary cortisol concentration curves were parallel at 30 and 40 min following ACTH stimulation, when the maximum response occurs, which supports the proposal to replace sampling in serum with sampling in saliva. Cortisol sampling in saliva instead of serum following stimulation tests with 1μg ACTH in healthy participants is in accordance with previous studies on both healthy participants and participants referred to endocrinological investigation with or without endocrine diagnoses [195, 196]. By contrast, Schindhelm et al. 2010 showed that sampling in saliva did not meet the criteria for sensitivity and specificity which sampling in serum or plasma did [197]. The Schindhelm study included 51 patients referred to ACTH testing as part of an endocrinological investigation to diagnose primary and secondary adrenal insufficiency, and sampling was performed only at baseline and at 30 min. When the test is used as a diagnostic tool, cortisol concentration should reach a value above the ≥ 500 nmol/L or ≥ 550 nmol/L cutoffs, depending on assay and sample time. Thus, the exact concentration value of the maximum response is not of interest. In stress research, however, where one is interested in the adrenal responsive capacity before and after different types of interventions, the exact value of the maximum response could be of interest. Therefore, the results of the study by Schindhelm et al. are not applicable when the ACTH test described here was evaluated for stress research. A possible explanation of the difference might be that sampling in the study by Schindhelm et al. was performed only once after stimulation (Fig. 4).

5.6 Strengths and limitations in the present dissertation

One of the strengths is that the CBG was a homogeneous group, and besides self-assessment, they were on sick leave for a medically certified diagnosis, using the ICD-10 code Exhaustion Syndrome, F43.8A. Furthermore the patients in CBG were recruited mostly from primary health care centres and they were a clinic sample with diverse occupations, reflecting the situation in occupational medicine and primary care. Few clinical studies were found in this particular group of severely sick patients. Strength is randomization to three well-defined psychological treatments, especially designed for this specific patient group. The *subjective measure* SWED-QUAL, a HRQoL questionnaire, has been use in several studies in the general population and is well validated. The questionnaire is generic, and the 13 subscales

allow for more specific analyses than if the questionnaire is global, which constitutes another strength in the study. Also, SWED-QUAL is generic and the questions cover many aspects of work and life and most components known to be affected in burnout. SWED-QUAL has in previous research shown to be stable over time in other patient groups, which might indicate that a change in scores reflect a real change [132]. A combination of *subjective* and *objective measures* was explored, which might give a better picture of the condition of the CBG. The *objective measures* with biomarkers have not been explored previously in this well-defined patient group, and before and after treatment.

Moreover, we used an active control group, which is recommended, as after a long, inactive period there are difficulties returning to work. Participating in a wait-list control group might mean that we withhold efficacious treatment from patients in need and maybe make it more difficult for them to return to their normal life and work. Also, an inactive control group in CB patients is rarely inactive, searching for all sorts of support, despite their severe condition, thus making it difficult to know what you are actually comparing with [198]. A somewhat similar situation emerges when "treatment as usual" is used as comparison because the treatment components, if any, may vary considerably. Besides, an inactive control group may deteriorate over time [144].

The limitations were that the number of patients in each treatment was small (n = 26–27). Furthermore no evaluation of the adherence to the treatment protocols was made, however, in each treatment arm, only one therapist was involved. Also, in most cases the patients were supposed to start work or work longer hours after the treatment was completed and many of the patients expressed worry and stress for that reason. The blood tests were taken and the questionnaire was filled out in this quite stressful situation, which might have influenced the results. The majority of the patients in the study were women, reflecting the situation at the primary health care centres. We do not know why more women are diagnosed with ES. One explanation may be that women often face a double workload with the main responsibility for housework. Moreover, a recent study found an increased vulnerability to stress in women, with larger structural brain abnormalities than in men in response to the same degree of perceived stress [73]. On the other hand, a report from 2014 showed that men are as likely as women to receive a diagnosis of ES, given that they have the same work situation [148]. The number of men with an ES diagnosis has increased during the past years [199]. In this study the group of men was too small to do a separate analysis of biomarker changes in men, and in men versus women after the three psychological treatments during ES.[200]

The patients in the CBG were highly motivated and thus we do not know how the treatment would have worked for patients with less or no motivation. Besides, having motivation also indicates that they were not the most ill patients. Maybe some patients have a worse condition or a social situation that may not give support during treatment, which makes it difficult to manage an extensive treatment like the treatments in CBG. Most of the patients reported that they previously had applied for but not received treatment for CB. This might mean that patients in the CBG, diagnosed with CB, had a more serious condition or more complicating

factors than usual in treatment, as at least one of several rehabilitation clinics during that period used diverse selection criteria.

CB is also a complex state which probably includes many factors that we so far do not take into consideration when we diagnose and treat these patients, and in Sweden the diagnostic criteria are currently under revision (personal communication, Anna Nager, 3 December 2019). Factors that might influence the process and need to be further explored are, for example, the expectancy of future work ability [201], how what you go back to at work affects [202], the feeling of self-efficacy [203], and how work-related reasons and the personal situation respectively affect the possibilities to return to work and life. The time also seems to be crucial. The importance of prevention has been stressed in many studies. Some changes in brain structures involved in stress processing have been shown to be reversible while others seem to be prevailing. At what point in the course of longstanding stress and CB these changes occur we do not know, nor to what extent they have an impact in a person's life after recovery. Some of these changes are similar to the changes seen in persons with early childhood trauma [53], indicating a non reversible condition. This stresses the importance of preventing and detecting these persons early and treating these persons before they become severely sick. Also, the situation at the workplace is important, and in the Netherlands the number of persons sick-listed has decreased after new regulations were introduced [204] together with new guidelines for treatment of AD in primary care and occupational settings [205]. Moreover, the companies were given greater responsibility for prevention, rehabilitation and financial responsibility for the employees' sickness benefits [206],

The results concerning biomarkers are not fully in line with the results for HRQoL. At baseline the biomarkers were lowered, but within reference intervals, while HRQoL was significantly lowered. Then, after treatment, TY was the treatment with the highest number of HRQoL subscales with a significant improvement, but it had no significant increases in biomarker concentrations after comparatively long time and treatment. This contradicts the hypothesis and warrants further investigation. The 1 µg ACTH test which measures cortisol after injection is a potential stress test with sampling only in saliva.

5.7 Conclusions

The CBG with patients on long-term sick leave, and diagnosed with CB had a global decrease in the *subjective measure* HRQoL. The scores were on a par with scores in patients with severe psychiatric disorder and chronic somatic diseases with psychiatric comorbidity, which indicates the severity of the situation for these patients.

Moreover, psychological treatment with TY, MBCT or CBT in-group showed a significant change in the majority of subscales, with the highest number of improved subscales (10 out of 13) in TY, and several of the subscales were normalized after the treatment period. Probably the improvements are due, at least to some extent, to the treatments. This suggests that the treatments can be used to reduce symptoms of stress and to increase HRQoL in stress-related disorders in general and more specifically in CB patients. TY seems to be a

possible treatment alternative to CBT. When comparing the effect of the treatments, a small effect size was found in favour of TY in 7 subscales, indicating a slightly better effect from TY in some aspects. The *objective measurement* with 23 analysed concentrations of biomarkers in the CBG showed a significant change compared to the HCG, indicating that physiological changes had occurred in these severely sick patients on sick leave, but not to such an extent that the biomarkers showed pathological concentrations, according to current reference ranges. Twenty-four-hour collection of the urinary hormones u-5HIAA, u-epinephrine, u-norepinephrine, u-dopamine, u-cortisol and HbA1c all showed a significant difference between the CBG and the HCG, and are potential biomarkers for diagnosis.

After 20 weeks of treatment in the CBG, testosterone, but also estradiol, DHEAS and u-epinephrine showed a significant difference pre-post treatment, and are potential biomarkers to follow the course, probably for evaluation of the effects of psychological treatment in general and for one or more of the three treatments, TY, MBCT and CBT groups. This remains to be evaluated in further research.

5.8 Implications for health care and future research

The results indicate that TY could be used at all levels in the health care system to improve HRQoL in stress-related disorders including CB, but more studies are needed with different types of control groups including a control group receiving a homogeneous "treatment as usual" and a wait-list control, to establish if, and to what an extent, the effects seen here are from the treatment.

It is not likely that a single marker or questionnaire alone can define and diagnose CB. Rather, a clinical examination together with biomarkers and questionnaires for burnout and HRQoL as well as psychiatric evaluation is probably necessary.

For treatment a similar situation is probably needed, with treatment components individually tailored for each patient, decided on in cooperation with the patient. Psychological treatment, physical activity, support for return to work, counselling for a healthy lifestyle concerning food, sleep and recuperation are probably necessary for a better balance in life and at work and to minimize the risk of relapse.

In future larger studies, the biomarkers found here can be used as outcome variables, to evaluate whether the hypotheses are true. If so, testing of the clinical usefulness of the biomarkers found is a possible next step. Furthermore, larger treatment groups are needed to ensure statistical significance for a smaller number of chosen parameters to confirm our findings. Also, filling out questionnaires and sampling blood and urine several times during the treatment and well before the finalizing of the study would be preferable. This should lower the risk that the stress of starting to work again or work longer hours influences the results. A follow-up period of 6–12 months, with treatment sessions maybe only once a month, together with sampling and filling out questionnaires at 6 and 12 months, could help to elucidate the effect of treatments on biological biomarkers in the long term.

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