Stress Management Interventions and Predictors of Long-term Health

Prospectively Controlled Studies on Long-term Pain Patients and a Healthy Sample from IT- and Media Companies

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Dissertation presented at Uppsala University to be publicly examined in Hörsalen, Ingång D 1, Dag Hammarskjölds väg 17, Uppsala, Wednesday, October 19, 2005 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English.

Abstract

This thesis reports on the effects of stress management on long-term pain patients and on a healthy sample from IT and media companies; two groups that are commonly exposed to high stress levels. Even if there are important differences between these two groups, there are similarities such as the necessity for effective stress management. Stress-related and musculoskeletal disorders are major public health issues in most industrialized countries and are expected to become increasingly common during the coming decades. The pathogenic plastic changes in the CNS and immune system caused by long-term stress pose severe burdens to individuals, organizations as well as society in general. Thus, stress management may be essential to maintain and improve long-term health and wellbeing and to proactively counteract stress-related ill-health.

This thesis is based on four papers: Paper I assessed the effects of massage as compared to relaxation tapes in long-term pain patients. Paper II validated some of the Visual Analogue Scale questions that were to be used in paper III and IV. Paper III assessed the effects on mental and physical wellbeing and biological stress markers from a web-based stress management and health promotion tool. Paper IV aimed at mapping out predictors for trends (improvement vs. worsening) in self-rated health (SRH) over a period of one year.

The overall results indicate that individually focused stress management interventions in long-term pain patients as well as on a healthy, working population may have short-term beneficial effects on psychological and physiological stress, health and wellbeing. On a long-term basis the beneficial changes seem to revert. In paper four, it is indicated that the stress management intervention is not a significant predictor of long-term changes in SRH. Rather, other factors such as health perception, sleep quality and sense of coherence predicted improvement in SRH over time.

Keywords: stress, health promotion, stress management, public health, psychosocial, self-rated health, pain, intervention, web, Internet, TNF-alpha, DHEA, NPY, CGA

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urn:nbn:se:uu:diva-5944 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-5944)
To my lovely parents, wife, son and family.

Science is organized knowledge. Wisdom is organized life.
Immanuel Kant 1724-1804

Wisdom is the supreme part of happiness.
Sophocles 496-406 B.C.

Happiness is nothing more than good health and a bad memory.
Albert Schweitzer 1875-1965

It is not stress that kills us; it is our reaction to it.
Adopting the right attitude can convert a negative stress into a positive one.
Hans Selye 1907-1982

Science is a wonderful thing if one does not have to earn one's living at it.
Albert Einstein 1879-1955
This thesis is based on the following four papers, which will be referred to in the text by their Roman numerals.


II Hasson D, Arnetz BB, Validation and findings comparing VAS vs. Likert scales for psychosocial measurements, *Submitted manuscript*, 2005.


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Abbreviations

ACTH  Adrenocorticotropic hormone
ADH   Antidiuretic hormone/vasopressin
ANCOVA Covariated analysis of variance
ANOVA Analysis of variance
CgA   Chromogranin A
CNS   Central nervous system
CRH   Corticotropin releasing hormone
DHEA  Dehydroepiandosterone
FSH   Follicle stimulating hormone
HPA   Hypothalamic-pituitary-adrenal
HPG   Hypothalamic-pituitary-gonadal
IT    Information technology
LH    Luteinizing hormone
NGF   Nerve growth factor
NPY   Neuropeptide Y
NS    Non significant
SD    Standard deviation
S.E.M Standard error of the mean
SRH   Self-rated health
SA    Sympathetic-adrenomedullary
TNFα  Tumour necrosis factor α
VAS   Visual analogue scale
Introduction

This thesis reports on the effects of stress management on long-term ill patients and on a healthy population. The long-term ill population consisted of a common primary healthcare patient group; patients suffering from the stressful condition of “diffuse” long-term musculoskeletal pain\(^1\) [1]. Stress management was used as a rehabilitation intervention aiming at decreasing pain and improving quality of life. The healthy population was derived from employees at IT and media companies. Stress management was introduced and used as a proactive intervention for health promotion and stress prevention. These populations both have in common that they are frequently exposed to various sources of acute and long-term stress.

Stress-related and musculoskeletal disorders are major public health issues in most industrialized countries and are expected to become increasingly common in the coming decades [2-6]. According to the World Health Organization (WHO), mental ill-health and stress-related disorders are the major overall causes of premature death in Europe [7]. Several of the most frequent diseases in adults can in 40-70\% of the cases be related to the burden of long-term stress combined with an adverse and unhealthy lifestyle [8, 9]. Besides the fact that stress has an association with decreased attention on bodily symptoms and signals, lifestyle is often affected in a negative way. Stress increases the risk of accidents at work and leisure time as well as destructive behaviours such as drug/tobacco/alcohol abuse, poor eating habits and lack of physical activity [10]. Moreover, stress-related disorders have a negative economic impact, disrupt work and home life and might even increase suicide risk [11]. Apart from the human suffering, it has been estimated that the costs in the European Union for the mental health issues amounted to 325 billion euro in the year 2000 [3]. Mental ill-health may, according to the WHO, be caused by a combination of biological, social, psychological and stressful circumstances [7].

Interestingly enough, too great or too little stress exposure seems to decrease life expectancy if individuals that are exposed to mild stress are used as reference group. This might be due to the fact that mild stress may stimulate anabolic and defensive bodily systems, that are activated in order to

\(^1\) Long-term pain is defined by the International Association for the Study of Pain (IASP) as “pain which has persisted beyond normal tissue healing time”, taken, in absence of other criteria, to be 3 months.
handle potentially more severe stressors [12, 13]. This indicates that moderate stress may be protective and even strengthening for various bodily processes on a long-term basis. The susceptibility for stress-related disorders seems to be related to both genetic and psychosocial environmental factors from early childhood [9].

Aims of the papers

The aim of paper I was to assess the possible effects of commonly used stress management techniques, i.e. massage as compared to relaxation tapes, in stressful conditions of “diffuse” and long-term musculoskeletal pain. Paper II focused on validating some of the visual analogue scales (VAS), e.g. self-rated health (SRH) and mental energy, which were to be used in paper III and IV. The aim of paper III was to assess the possible effects on mental and physical well-being and biological stress markers from a web-based stress management and health promotion tool. Paper IV aimed at mapping out predictors for trends (improvement vs. worsening) in SRH over a period of one year.

Stress

A brief introduction to the complexity of stress

Stress, in relation to biological, individual and societal conditions, is a thrilling field to study. In spite of hundreds of thousands of scientific publications within this field of research, there seems to be a long way before a complete understanding of implications, effects and optimal application for the individual, organization and society is beginning to be within reach. The knowledge about stress is burdened with several contradictions and new insights within different disciplines supersede each other constantly.

To mention one of many examples, it is now known that the neurotransmitter serotonin, which is involved in the stress response, can bind to 14 different receptors and thus mediate several diverse physiological and psychological effects [14]. This means that hormones such as neurotransmitters can have many different, and sometimes contradictory, functions. Add to this the constant strive of an organism to achieve homeostasis (physiological balance), which means that several mechanisms and bodily systems may be activated in order to fill a certain function. If attempts are made to disturb the preset homeostasis of the body (even if it is dysfunctionally set), e.g. through medication, one has to consider these compensatory mechanisms. For example, there are at least five ways for the body to regulate blood pressure. If
one bodily system is inhibited, it is not uncommon that another is activated to fill the same function. Thus, from a holistic perspective, it seems as if there are not many simple connections when facts are more thoroughly investigated. Just as life itself, stress is a multidimensional subject that constantly and rapidly grows and develops within all its inherent dimensions.

Definition
The actual word “stress” was originally adapted from physics by Walter Cannon [15]. It is most commonly used as a metaphor with a wide range of individualized, contextualized and momentary meanings attributed to it. As the case is with many expressions, there is no single, generally agreed upon definition. So the word “stress” has numerous different meanings within scientific contexts as well as in everyday life. Furthermore, the word “stress” is commonly used in popular cultures to describe numerous self-diagnosed physical and mental ailments, the severity of which often depends on subjective perceptions [16]. One important distinction, however, may be to clarify if stress is a cause (stressor) or an effect (stress response) of a certain event [17].

A “stressor” is a factor that contributes to a physiological and/or mental stress reaction. Anything can be a stressor for a given individual and it may be so for different reasons. It can be everything from hormonal changes to various kinds of mental, emotional, physical, psychological, environmental and socioeconomic challenges. Most definitions of stress have in common that stress is an adaptive response to a combination of or any of these challenges, resulting in physiological and behavioural reactions mediated and regulated by the brain [17].

Biological aspects
The biological stress system includes a multitude of components that regulates neural, endocrine and immune responses that are adaptively activated during stress. The central components are located in the hypothalamus and the brain stem, which receive external and internal input. Thereafter, appropriate responses are exerted via the endocrine hypothalamic-pituitary-adrenal (HPA) axis and the neural sympathetic-adrenomedullary (SA) and parasympathetic systems [15].

From a biological and psychological point of view, stress is a complicated process, which occurs as a result of various stimuli and conditions. Stress itself is a neutral process that aims at maintaining the homeostasis, which is an essential and dynamic state of physiological balance. In fact, stress is the response of the cell and organism to challenges that may threaten the homeostasis [12, 15]. If the homeostasis is altered, which among other things include changes in the acid-base and salt balance, body temperature and
blood oxygen levels, there is a risk of disease. A major change can even cause death. As a result of stress then, biological as well as behavioural adjustments occur. The process to achieve stability (homeostasis) through change is called “allostasis” [14, 17-22]. This process of maintaining homeostasis occurs in all bodily organs, all the way down to the cellular level [12]. Allostasis represents the body’s long-term efforts to protect itself although it may be harmful from some points of view. Allostasis involves the long-term regulation of the autonomic nervous system, HPA axis, cardiovascular, metabolic and immune systems, as a response to internal and external stress [18, 22].

The autonomic nervous system

The autonomic nervous system consists of the sympathetic and parasympathetic nervous systems and regulates vital functions of the body. It is not consciously controlled, although certain events, such as emotional stress, fear, sexual excitement, and alterations in the sleep-wakefulness cycle change the level of autonomic activity. One of the most important functions is to maintain the homeostasis and coordinate responses to external stimuli [23, 24].

The central purpose of the stress response, which is mainly governed by the sympathetic nervous system, is to shift focus from long-term to immediate needs, and thus mobilize energy to the body parts requiring it the most. In acute and physically stressful situations this response is usually well adapted to its purpose. The muscles need more oxygen, especially the muscles in the legs. So the breathing frequency increases to boost blood oxygen levels, and the heartbeat increases to deliver oxygen to the larger muscle groups. The blood vessels contract to minimize bleeding, should a physical injury occur. According to the same principle the blood coagulates more rapidly. All these effects are governed by the sympathetic and parasympathetic nervous systems, which control a wide range of physiologic functions, including cardiovascular tone, respiration, skeletal muscle and adipose tissue metabolic activity and gastrointestinal function. These systems exert their effects through the adrenal medulla that secretes adrenaline and noradrenaline into the blood. These catecholamines also potentiate ACTH-stimulated cortisol production. Furthermore, in connection to the stress response a multitude of hormones are secreted by different glands and blood glucose levels increase. During acute stress the brain also releases endorphins, which partly act as natural pain relievers [14, 15, 23].

Generally, the sympathetic and parasympathetic nervous systems counteract each other. Whereas the sympathetic nervous system for instance triggers arousal and the above described stress response, the parasympathetic nervous system induces muscle relaxation, slows the heart rate, lowers the blood pressure, stimulates gastrointestinal movements and secretions, aids absorption of nutrients, protects the retina from excessive light, and empties the
urinary bladder and rectum. Thus, the parasympathetic nervous system primarily governs recovery processes through preservation of energy and maintenance of organ function during restful periods [23, 24].

**The HPA axis**

Next, the HPA axis is involved. It coordinates the central nervous system (CNS), glands and immune system in order to achieve balance. Corticotropin releasing hormone (CRH) is the main central regulator of the HPA axis and it induces production and secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH, in turn, stimulates secretion of glucocorticoids from the adrenal gland, which is the end-organ of the HPA axis. A prolonged stress exposure contributes to functional changes in the adrenal gland, as it responds quite rapidly to sustained stimulation with hypertrophy and hyperplasia. Consequently, in long-term stress, high levels of glucocorticoids and relatively low levels of ACTH are commonly observed. So the elevated glucocorticoid secretion is maintained in spite of low or normal ACTH levels [15, 23]. This feature is a splendid illustration of adaptation of the stress response.

Glucocorticoids exert their effects through broadly distributed intracellular receptors in almost all body tissues. Furthermore, the secretion is partly regulated through a negative feedback system. Glucocorticoid secretion affects a wide range of bodily functions, i.e. metabolism of carbohydrates, fat, electrolytes and water, alters immune responses and inhibits inflammatory reactions, effects on bone and connective tissue, and neuropsychiatric effects. Long-term exposure to pathologically elevated glucocorticoid levels may cause impairments in these bodily functions [25].

**Acute and long-term stress**

A qualitatively and quantitatively appropriate stress response depends on the fine-tuning of the whole stress system. The exposure to acute and long-term stress may contribute to both positive and negative consequences. Regardless of which, long-term stress has a catabolic effect in the body and mind as it affects the balance between anabolic and catabolic processes [9]. Consequently, a prolonged stress reaction, without sufficient recovery may dysregulate a number of bodily systems, including the HPA axis and change behavioural patterns of individuals. This dysregulation is called “allostatic load” and results from long-term overactivity or underactivity of the allostatic systems [18, 22]. When the HPA axis functions as it should, there is enough energy and focus to handle a stressor or crisis. When allostatic load causes it to be dysregulated, there might be an over-secretion or under-secretion of different hormones, which over time may lead to increased physical and psychological wear and tear and exhaustion [14, 26]. These events are some of the fundamental features in the development of stress-related disorders and diseases.
Another system that is affected by stress is the immune system. As moderate stress and certain acute stressors seem to enhance it, long-term stress may impair it [26-28]. Short-term physical or mental stress, challenge or physical activity increases the secretion of certain immune markers in the blood and different classes of immune cells become more active. It seems as if this enhanced immunity is mediated via glucocorticoids in collaboration with the sympathetic nervous system. Paradoxically, the glucocorticoids, among other things, also contribute to the degeneration of the immune system during long-term stress. In addition, the hormones of the sympathetic nervous system, such as \( \beta \)-endorphins, contribute to the inhibition of the immune system during stress, even if the mechanisms for this are not completely established. Considerable amount of energy is used to degenerate the immune system during long-term stress; body tissue shrivels and cells die. However, the stress induced inhibition of the immune system could well be a side effect of another more appropriate adaptive mechanism [26].

Socioeconomic perspectives

Social and individual differences in response patterns to social and environmental stressors seems to be determined by several factors, including birth weight, financial prerequisites, and conditioned oversensitivity or insensitivity [29]. It seems as if the long-term, optimally beneficial stress response with regard to health, relates to living and work environments typical of those with a favourable financial and material situation. This optimal stress response is characterized by a rapid reversion to a restful state after stress activation and thereby a strong resistance against stress-related disorders. If an individual has adequate resources to manage stress and to affect his/her environment, the level of demands does not seem to be associated with health-related risks [29, 30].

According to findings from studies of industrialized countries, the mortality rates are strongly correlated with socioeconomic inequalities within each country [31]. A lower socioeconomic status generally increases the risk of stress-related disorders and premature death. The inbuilt paradox in this is that even in countries with a high level of social welfare, a lower socioeconomic status seems to be a considerable stress factor, also after adjusting for traditional risk factors, such as smoking, obesity and lack of physical activity [32]. However, the social inequity in health is smaller in such countries than in countries with a low level of social welfare [33]. The remaining effect of social class in countries with a high level of social welfare may be explained by an existing component of relativity, which implies that a lower social status certainly affects health and stress level on a high abstraction level, e.g. within a country or society. However, this relativity component is also present at lower levels of abstraction, i.e. all the way down to the organizational level. The fact that civil servants with the second highest position has been
shown to have worse health than those with top positions indicates that it can be due to a relatively lower social status rather than an absolute one [29].

Finally, an important issue where researchers have been divided in their opinion concerns the causality about whether a lower social status contributes to ill-health or vice versa. Marmot and co-workers [29, 34] however, imply that there is sufficient evidence to assert that a substantial part of the relationship arises because the social environment impacts biology to cause disease.

Psychosocial stress

Psychosocial stressors usually relate to psychological, social, individual or environmental circumstances that repeatedly induce a stressful experience [35]. The health and wellbeing of an individual or group is strongly associated with the ability to adaptively and successfully cope with the strains and challenges of life. The detrimental health effects of psychosocial stressors are primarily mediated by two main processes:

a) Self destructive and unhealthy behaviour that may emanate from insufficient behavioural/emotional/psychological/social coping.

b) Enhanced neuronal/immune/neuroendocrine activation.

Unhealthy behaviour, poor financial and material situation, severe life events, traumatic stress and regular exposure to a stressful environment all of which are more common in lower social classes are considered to be possible causes of social health inequalities in modern society.

Psychosocial stress could be related to poor living and working conditions, threat of unemployment (or actual unemployment), reduced income and unstable social network. Under such circumstances feelings of anger, dissatisfaction and hopelessness are more common, more intense and extended over time, which in turn increases stress even more [36].

There is now comprehensive scientific evidence on the relationship between long-term psychosocial stress and morbidity/mortality in cardiovascular disorders. Some of the major psychosocial stressors are social isolation, depression, low socioeconomic status, hostile behaviour and lack of control and support in combination with high demands at work. Moreover, an extended period of life events may contribute to similar effects [10, 37, 38]. At the same time, other factors, such as drug abuse, poor nutritional and physical activity habits, high blood pressure and harmful blood lipids also increase the risk for cardiovascular disorders. However, these health issues can also be a consequence of long-term stress exposure and moderated by social and personality factors [10].

In spite of the extensive evidence for the association between long-term exposure to psychosocial stressors and ill-health, there is a need for more
research on this topic. Knowledge on specific pathologic mechanisms is still limited. Modern health problems often emanate from complicated series of patterns, where individual factors interact with the physical and psychosocial environment during a long time period before the symptoms are manifested. The fact that these symptoms build up during such a long time makes it more difficult to determine the underlying mechanisms with certainty [10, 30].

Stress and disease

In spite of rapid development in the field of stress research, it is difficult to generalize the bodily reactions to stress. The behavioural reactions, however, seem to be somewhat easier to generalize. In any case, the stress response affects all bodily systems, e.g. reproduction, growth, metabolism and immunity. The vulnerability of these systems is substantially determined by genetic factors, but also by experiences early in life and concurrent environmental factors [15, 39-41].

The acute/short-term stress response is generally adaptive as it provides short-term protection and may increase chances for survival in certain situations. However, long-term stress, emanating from a combination of lifestyle factors, disease, behavioural, psychological, social and environmental aspects, contribute to gradual and almost imperceptible pathological changes that develop over months and years. Thus, the stress response may be critical for short-term survival but is also a major contributor to catabolic and aging processes of individuals. A consequence of the wear and tear of long-term stress may be a wide range of disorders and diseases, including cardiovascular disorders and stroke, fibromyalgia and other musculoskeletal disorders and pain conditions, fatigue disorders, burnout, depression and a wide range of anxiety, cognitive and mental disorders, gastrointestinal disorders, metabolic disorders, autoimmune disorders such as asthma and rheumatism or depressed immune system resulting in for example long-lasting cold or other infections. Long-term stress may contribute to the development and worsening of all these disorders and may also indirectly be involved in the development of several other pathogenic patterns and diseases, such as cancer [5, 14, 15, 18, 20, 26, 39-45].

In summary, long-term stress may contribute to mental and physical disease, and conversely long-term disease may alter the stress response in a pathological way. Whereas the acute stress response is necessary for restoration of homeostasis, the excessive/prolonged or maladaptive/dysregulated response to stressors is self-destructive and pathogenic [15, 39-41].
Prevalence

Long-term pain
Long-term pain is strongly related to stress (see the section “Stress and pain”). Furthermore, pain is the most common symptom in adults and the chief complaint in 40% of primary care visits [46, 47]. Long-term pain and other musculoskeletal syndromes are complex and stressful phenomena that constitute an ever increasing challenge to health care in general and especially to primary health care. Typically, these kinds of long-term disorders are very difficult to treat and patients are often burdened with several diagnoses, low socioeconomic status and other unfavorable conditions. In addition to enormous human suffering, long-term pain also constitutes an economic burden to society [4, 48-50].

The prevalence figures from epidemiological studies on long-term pain in the general population vary from 5-49%. The prevalence increases with age and women are more often affected than men. With regard to muscle pain, it has been estimated that up to 85% of the population will suffer from muscle pain [4, 5, 46-50]. The prevalence of specific diagnoses is more difficult to estimate. This fact, and the large variation in prevalence figures, is most likely due to the fact that there have been differences between studies in methodology as well as classification principles for pain. Furthermore, there are cultural differences in wording of diagnoses and assumed causes for pain. Diagnoses and their criteria also tend to vary over time [48, 49].

If the utilization of health care is used as an indicator of clinical relevance, 10-15% of the general population suffers from clinical long-term pain. This fact, in relation to the higher general prevalence figures, may indicate that many more individuals suffer in silence, without utilizing health care resources. Rather, they manage their own symptoms. However, the few percent seeking health care for long-term pain often consume a disproportionate amount of health care resources. 10% of the patients consume up to 75% of the resources. Furthermore, these patients are also subject to high sickness absenteeism and are more likely to go on early retirement [4, 49].

Stress-related disorders
To my knowledge, no studies to this date have estimated the total prevalence of all stress-related disorders combined. Considering the fact that long-term stress is a partial or main contributor to several of the most common diseases and disorders, it is self-evident that the prevalence of stress-related disorders is high. Long-term stress and comorbid diseases constitute a significant proportion of disability worldwide. The WHO report Global Burden of Disease [6] estimates that mental ill-health, including stress-related disorders, will be the second leading cause of disability by the year 2020. The primary cause is
cardiovascular disorders, which in fact are also related to or caused by long-term stress [2, 3, 6, 11]. Individuals suffering from high stress exhibit decline in physical and mental functioning, high sick leave, work impairments and are high consumers of health care services. Prevalence figures for stress-related mental disorders vary between 10-30%, and for different kinds of work related stress up to 60%. Various sources have estimated that up to 75% of primary health care visits are stress-related [2, 3, 11, 51-53]. However, prevalence of these kinds of disorders is difficult to exactly determine due to changes and differences in study methodology, diagnostic criteria and assessment tools [2, 11, 54].

Stress and pain

Physiological pain may be an adaptive and essential early warning system for possibly harmful stimuli [55]. Pain comprises sensory as well as emotional/affective dimensions and is often accompanied by desires to end, reduce or escape it [45, 56, 57]. Pain per se, may be an important stressor and there seems to be a bidirectional association between exposure to stress and sensitivity to pain [5, 58, 59]. Whereas acute stress seems to produce decreased sensitivity to pain (analgesia), prolonged exposure may generate increased sensitivity to pain (hyperalgesia) [57, 59]. Furthermore, several studies have shown psychosocial stress to be associated with musculoskeletal disorders, or even to be a contributing cause of it [5, 42, 60]. Long-term pain impacts wellbeing like any uncontrollable stressor in the sense that pain that has not been alleviated has evidently not been controlled. Consequently, the generalization of pain-related stress to disability and depression may mirror the phenomenon of learned helplessness [61].

Mechanisms

Stress and pain affect and are affected by the same neural pathways and brain structures [45, 60]. Several mechanisms have been proposed to explain the relationship between stress and regulation of muscle pain [5, 45, 55, 58, 59]. Short-term moderate stress exposure, such as physical activity, may increase vasodilatation and muscle blood flow. As a result, pathogenic metabolites and inflammatory substances are removed, which yields a protection against muscle pain. Furthermore, the increase in sympathetic activity may improve performance of fast-contracting muscles, whereas the catecholamines exert the opposite effect on slow-contracting muscles. Additionally, mental stress seems to produce vasoconstriction and thus reduced blood flow. The lack of sensitivity to bodily signals, such as fatigue and muscle tension, during mental stress, may contribute to a long-term and pathogenic overload on some muscle fibres [5, 58].
Furthermore, it has been suggested that a major mechanism of long-term pain is neuronal plasticity, i.e. the capacity of neurons to change their function, profile or structure, in the pain transmission system [45, 55, 58]. Plastic changes easily occur in the CNS through repeated stimulation, which may lead to either habituation (decreased response/sensitivity) or sensitization (increased response/sensitivity) [62]. There are two kinds of plasticity that are responsible for pain and hypersensitivity; modulation and modification. Modulation refers to reversible changes in the excitability of the peripheral and central neurons. Modification represents long-lasting alterations in the expression of neurotransmitters/receptors/ion channels or changes in structure, connectivity and survival of neurons. These changes may cause major modifications in the pain system, distorting its normal stimulus-response patterns [55].

The plastic changes, which also are affected by psychological factors, may eventually lead to irreversible structural changes in central pain pathways [45, 55, 58, 60]. One important change, central sensitization, opens silent synapses, which render more neurons to respond to weak mechanical stimuli and enlarged receptive fields. As a consequence, the projective area of the muscle in the CNS may expand and referral muscle pain may occur. These alterations probably constitute important steps in the transition from acute to long-term pain. Additionally, metabolic changes in sensory spinal neurons also seem to be important in this process [55, 58].

Interestingly, stress-induced pain sensitivity, and analgesia for that matter, can be classically conditioned. So a neutral stimulus that has previously been associated with a painful stimulus, can elicit disproportionately painful sensations [57]. This fact may be especially important with regard to the development of work-related stress and pain issues. What is more, emotional characteristics may determine whether stress-induced pain sensitivity is elicited or not. For example, a high anxiety level induces and enhances pain sensitivity, whereas decreased or low anxiety through drugs, behavioural interventions or coping produce pain relieving effects. Anxious individuals also seem to focus more on their fears and problems. High somatic anxiety and harm avoidance have been found in patients with fibromyalgia, a pain disorder related to long-term stress. Consequently, normal cognitive performance is interrupted and the cognitive capacity is absorbed in enhanced processing of the stressor, e.g. pain. Furthermore, excessive psychological demands and life events, lack of control and poor social support are all factors that have been associated with development of musculoskeletal pain [57, 63-67]. Thus, psychological factors seem to be important mediators of the plastic changes that occur in the transition from acute to long-term pain. Long-term alterations in the secretion of several hormones, in combination with emotional (pain unpleasantness/stress/depression) and behavioural factors, seem to be involved in this process [4, 45, 55-58, 60].
Neurotransmitters involved in the regulation of stress and pain

There are a multitude of neurotransmitters involved in the regulation of stress and pain. All the mechanisms of action and effects of these are very complicated to elucidate. This is partly due to the fact that each hormone may have several different, and sometimes opposing, effects in different parts of the body and CNS. Furthermore, much information needs to be discovered, clarified and confirmed in order to fully understand the role of each, and the interplay between different neurotransmitters.

Some of the important hormones involved in the pain regulating processes are the pain-inhibiting endogenous opioids (endorphin, enkephalin, dynorphin), oxytocin, noradrenaline, dopamine, serotonin, CRH, and endogenous pain-producing substances such as substance P and neuropeptide Y (NPY) (both inhibitory and stimulating effects), nerve growth factor (NGF), bradykinin, prostaglandines (PGE2), and high concentrations of potassium [42, 55, 58-60, 68-73]. To better comprehend the mechanisms in the interaction between stress and pain, some of these neurotransmitters will be described. It is important to bear in mind that, since there are a variety of receptor types, a neurotransmitter can have more than one action and thus several different and sometimes contradictory effects [74].

Corticotropin releasing hormone (CRH)

Stressors stimulate the release of CRH throughout the brain [70]. CRH is an important mediator of the stress response, including stress-induced analgesia. It also acts on numerous brain structures that are involved in the regulation and processing of pain. CRH can produce analgesia that is independent from the release of β-endorphin through actions at multiple levels of the peripheral and central nervous systems [70].

In a review by Lariviere and Melzack [70] evidence is provided that CRH can indeed induce analgesia at all levels of the neuraxis, i.e. both centrally and peripherally. However, it seems as if inflammation is crucial in order for CRH to evoke local analgesia. Furthermore, the pain relieving effects of CRH seem to be especially relevant with regard to long-term pain.

The role of CRH in the modulation of pain has important implications for the relationship between stress and pain. The consequences of acute and long-term stress exposure, however, are often the opposite. Hence, whereas acute stress may produce analgesia, long-term exposure to stress may result in hyperalgesia, i.e. increased sensitivity to pain. These differences may be related to alterations in central CRH neurotransmission as well as central response to CRH secretion [70].

Endogenous opioids

Prolonged pain and fear are the most powerful activators of the endogenous opioid-mediated modulating system. The same system is activated as a result
of a multitude of stressful conditions. For example, some soldiers that were wounded in battle require little or no analgesic medicine, due to stress-induced analgesia [68, 75].

There are mainly four groups of endogenous opioids; endorphin, enkephalin, dynorphin and nociceptin, all of which include a number of substances in each group. Most of the effects of the endogenous opioids are largely unknown [72]. However, it is known that they are involved in a multitude of bodily functions including behaviour, pain regulation (inhibition/analgiesia), stress and social status (homeostasis), tolerance and dependence, learning and memory, eating and drinking, alcohol and drug abuse, endocrine functions, sexual activity and reproductive function, mental illness and mood, seizures and neurological disorders, neurophysiology, general activity and locomotion, gastrointestinal, renal and hepatic functions, cardiovascular responses, respiration and thermoregulation and immunological responses [76]. Endogenous opioids affect the pituitary secretion of gonadotropin (LH and FSH), prolactin, ACTH, vasopressin (ADH), and oxytocin [77]. β-endorphin, enkephalin as well as dynorphin have pain inhibiting effects [72].

β-endorphin is especially important, since during stress it is both co-released with ACTH from the pituitary and secreted in the brain. It mediates stress-induced analgesia and regulates neuroendocrine functions. CRH, which is a major coordinator of the stress response, stimulates the release of β-endorphin. Moreover, β-endorphin seems to be involved in the regulation of LH in the HPG axis and ACTH in the HPA axis. The suppressive effects of stress and CRH on the reproductive system are most likely mediated by β-endorphin. Additionally, it may be important in limiting the HPA axis response during stress [68, 77].

There are reasons to believe that parts of the opioids’ analgesic effects are mediated via secondary stimulation of serotonin secretion in the descending pain pathways [72].

Sensory stimulation increases levels of enkephalin (low-frequent stimulation) and dynorphin (high-frequent stimulation) [72]. Enkephalins inhibit secretion of substance P, which results in fewer pain impulses to the brain [75]. Furthermore, dynorphin is a potent vasoconstrictor [73]. Nociceptin has been shown to have both analgesic and anti-opioid effects and to influence stress-induced secretion of pituitary hormones [78].

Oxytocin

Oxytocin is a hormone that can be released from the pituitary by different kinds of positive experiences, such as pleasant touch and social interaction, breast feeding and via oestrogen. Oxytocin has several effects. It stimulates contraction of the uterus during labour and the secretion of milk during breast feeding. Furthermore, it has a soothing, anti-depressive and anxiolytic effect and stimulates social interactive behaviour and bonding between
mother and child and male and female. Thus, it seems to physiologically counteract some of the catabolic effects of stress and to reduce pain. Additionally oxytocin seems to promote learning, the ability to recognise other individuals, increase maternal behaviour, increase pain threshold and may stimulate sexual behaviour. Since oxytocin is broken down quickly in the blood flow, the long-term effects are probably mediated via secondary mechanisms, which indicate that oxytocin initiates regulating mechanisms in the hormonal and nervous systems of the body [79].

Virtually every acute stressor has been shown to markedly increase secretion of oxytocin. There is no well established explanation for this, but there are indications that it may have a regulating effect on ACTH or an adaptive effect in the body and brain [80]. Uvnäs Moberg [79] indicates that oxytocin counteracts the negative effects of stress partly through its role as a hormone, but also as a neurotransmitter in a micro nervous system that emanates from hypothalamus. There, oxytocin mitigates the function that triggers the fight-flight reaction. Moreover, oxytocin seems to indirectly promote nutrition storing, growth and healing through activation of the parasympathetic nervous system and other mechanisms.

**Serotonin and Noradrenaline**

Noradrenaline and serotonin have several effects in the body apart from being important neurotransmitters in the brain and modulating pain. In the brain these neurotransmitters are involved in the regulation of stress, mood, emotions, depression, anxiety and sleep. Their release in the CNS can inhibit or increase the sensation of pain, and through secondary mechanisms also the perception of pain [42, 60, 68, 69, 71, 73, 81, 82]. Furthermore, noradrenaline is involved in the regulation of cognition and attention and modulates certain motor movements. Serotonin can, in the circulation, contribute to either vasodilatation or vasoconstriction, depending on condition or area of circulation. Moreover, it can regulate pain threshold through the endogenous opioids [42, 60, 68, 69]. The increase in pain sensitivity during long-term stress is partly mediated via the effect of serotonin on the release of substance P [42, 59]. Both serotonin and noradrenaline have pain relieving effects through inhibition of spinal nociceptive neurons [72, 75].

**Dopamine**

Dopamine is a neurotransmitter in the CNS that modulates the actions of other neurotransmitters. It influences numerous brain functions, ranging from control of movement to higher cognitive functions and reward mechanisms. Physical as well as psychological stress increases the secretion of dopamine. The exact role of dopamine in the stress and coping responses is not yet completely established. However, dopamine is known to be involved in the initiation and progress of several neurological psychiatric disorders, such as Parkinson, schizophrenia and psychotic disorders [83, 84].
Dopamine seems to be involved in stress-induced analgesia in acute stress and increased sensitivity to pain in long-term stress. Exposure to various kinds of stressors, including psychological, stimulates the release of dopamine via the release of substance P and endogenous opioids [59, 68].

**Neuropeptide Y (NPY)**

NPY is widely distributed in the central and peripheral nervous systems. In the autonomic nervous system, although not in the brain, NPY is mostly located in noradrenergic neurons, from which it is released by high-frequency stimulation. It augments the vasoconstrictor effects of noradrenaline and circulating NPY increases with severe exercise. It is involved in the regulation of homeostasis, food intake, metabolic functions, sleep, emotions, stress response and pain. NPY mediates both analgesia and hyperalgesia through central and peripheral mechanisms and it is also involved in the perception of pain. Moreover, it has been reported to have a soothing, anxiolytic as well as antidepressive effect in the central nervous system [69, 73, 85-87]. The anxiolytic effects of NPY are probably mediated by Y1 receptors in the amygdala and involve inhibition of CRH. Moreover, NPY inhibits HPA activity and is thereby effective in reducing secretion of CRH, ACTH and cortisol. Additionally, NPY has been found to promote and improve sleep, which is important for stress-related recovery. These sleep promoting effects of NPY are suggested to be mediated through reduction in sleep latency as well as modulation of stage 2 and REM sleep [86].

**Substance P and Nerve Growth Factor (NGF)**

Substance P is present in neurons throughout the central and peripheral nervous systems. It has multiple biological effects in the cardiovascular, respiratory, gastrointestinal, immune and autonomic nervous systems and has been implicated in several pathological processes. Substance P is a powerful, if not the primary, mediator of pain, but also a modulator of central stress responses and anxiety [42, 69, 71, 73, 88-90]. It is released in response to noxious stimuli or injury, and increases and facilitates the conduction of pain signals to the brain. It has been shown that substance P causes an increase in the size and number of mechanosensitive receptive fields involving nociceptive neurons, and thus lowers the threshold for postsynaptic potentials. However, it has also been shown that substance P can be released in response to anxiety and fear and increase the perception of pain [88, 89]. Additionally, substance P is a mediator of inflammation as it has a strong vasodilating and permeability increasing effect, which causes an increase in local microcirculation and oedema [42, 58, 69, 88].

Substance P also has an inhibitory effect on the HPA axis and a stimulatory effect on the sympathetic nervous system. Serotonin secretion seems to stimulate the synthesis of substance P in the brain. As a result, when serotonin levels decrease, so does substance P in the brain. However, at the same
time it increases in the cerebrospinal fluid (whereas serotonin decreases) rendering widespread and increased sensitivity to pain. Hence, there seems to be an inverse relationship between brain and spinal cord concentrations of substance P and serotonin seems to inhibit the release of substance P in the spinal cord. Thus, it has been implicated that substance P is one of several mediators of increased sensitivity to pain [42, 73].

NGF (Nerve Growth Factor) is thought to facilitate the growth of substance P containing neurons and to be involved in the process of neuroplastic changes. NGF may be crucial to initiate and prolong painful syndromes [69, 73].

**Work-related stress**

Work-related stress level is determined by several dimensions. With exception of individual, genetic and socioeconomic factors, work-related stress includes everything from physical and hygiene factors such as work environment and salary, to psychosocial and management factors. There are a number of psychosocial models of work-related stress, which in summary assert that work-related stress is caused by a combination of high demands, low control and low support [38, 91], high effort and low reward [92, 93], understimulation or overstimulation [94] and/or by misfit between environmental demands, opportunities, and expectations and the abilities, needs and perceived outcomes for an employee [43].

**Consequences of work-related stress**

Stress affects organizations in various ways. Too little stress may lead to understimulation, boredom and sleepiness for the employees as well as the organization as a whole. Individual and organizational efficiency, performance and productivity are low. Optimal stress levels, however, render excellent chances of creativity, flexibility and good performance. In contrast, overstimulation due to information overload, lacking efficiency and/or poor leadership may result in hype, loss of creativity and flexibility, inability to make effective decisions, confusion and even collapse [43, 95].

Work-related stress can manifest itself in various ways for individuals. There can be emotional manifestations, such as anxiety, depression and feelings of hopelessness and helplessness. Cognitive manifestations may occur, including difficulties to concentrate, recollect, learn new things, be creative and make decisions. Finally, there can be behavioural and physiological manifestations, rendering pathogenic health behaviours that may influence virtually every bodily organ or system [43]. Furthermore, individuals may exhibit high rates of tension, anger, anxiety, depression, mental fatigue and sleep disturbances [96].

Direct costs for high stress is absenteeism and tardiness, strikes and work stoppages, dysfunctional turnover and more mistakes. Indirect costs include:
a) loss of vitality, responsiveness and resiliency; b) low morale and motivation, and high dissatisfaction; c) various kinds of communication problems and conflicts; d) erroneous decisions and impaired judgement; e) decreased organizational quality and social relations; f) physical and verbal aggression and violence; g) lost opportunities [43].

## Stress measurement

Stress is a multifactorial, complex variable that commonly shows large variations on a short-term as well as long-term basis. Mainly two methods are used to diagnose stress: physiological markers and questionnaires. The validity of different methods to measure and diagnose stress is a great challenge for various reasons. For one part, there is a basic issue concerning the definition of stress, which might differ between and within various scientific disciplines. This evokes questions about the validity of different assessment methods. What do they really measure and what do they reflect? Do they really measure what they intend to measure? What are the most valid and suitable indicators of short- and long-term stress? These are all questions to which there are no completely established answers yet. According to Noble [97], a thorough stress-oriented medical history assessment is currently the best way to measure stress and its effects. If time permits, the patient may be inquired about stressful life events, work events, finances, marital problems, natural disasters, etc, and note their effects. These events can also be listed by the patient before the meeting, along with their self-rated ability to cope with the problems.

### Physiological measures

There are a multitude of both psychological and physiological factors that could be measured and there is no general consensus about which variables that should be measured (and sometimes how). Physiological measures may range from various biological markers to measurements of heart rate, blood pressure, heart rate variability, body mass index, etc. The physiological measures provide the advantage of being rather objective compared to self-ratings. However, it is not always easy to determine which variables to choose and how to interpret the results. For example, a low cortisol level can be a positive as well as a negative sign. In the first scenario, it could imply that the individual is relaxed and in the second scenario the bodily systems are exhausted and can thus not produce more. Hence, a randomly obtained result may represent a peak, any intermediate stage of a change or a valid result that corresponds to the aim of the assessment [97]. In addition, mild stress, such as that of the blood sampling itself may elevate some of the rapidly reacting stress hormones.

Furthermore, for many of the stress-related hormones, such as cortisol, immune markers and sex hormones, it is essential to consider seasonal fluc-
tuations and natural variation in daily cycles [67, 98]. Many of these hormones are secreted in episodic bursts during the day and night, and levels are sometimes subject to negative feedback regulation. Finally, many of the anabolic and catabolic stress hormones, involving HPA and HPG axis as well as the immune system, are intertwined in a complex and not completely established manner. The stress-related hormones inhibit and stimulate the secretion of each other in different ways depending on a multitude of circumstances.

Questionnaires
Numerous questionnaires are used to diagnose and assess different aspects of stress [97]. Most of these tests are time consuming and sometimes difficult to handle and interpret for the researcher as well as the clinician. Furthermore, there are a great number of non-validated questionnaires that are commonly used in the commercial world.

An important aspect, especially when using questionnaires, is the fluctuating nature of stress on both a daily and long-term basis. One of the most common means of obtaining information in psychosocial research is through retrospective self-ratings [99]. Most questionnaires typically ask the respondents to assess various aspects of health and stress during the last month or year. Only few scales, including both VAS and Likert scales, ask the respondents to rate their feelings in the present moment. Although retrospective self-ratings provide valuable information, there is evidence that they are susceptible to numerous recall biases and cognitive errors [99, 100]. The current state at the time of filling out the questionnaire most likely impacts on the rating of the past month [99, 101].

In unpublished analyses from study II, different retrospective self-ratings were compared with present moment ratings of the same variable (Table 1). There were strong and highly significant time-related correlations. For example, respondents who scored high on the VAS for present health status also scored high on the corresponding VAS for health during last month and during last year. The same pattern was found for the Likert based items.

In general, it is reasonable that correlations are moderate when comparing questions with different rating intervals. Ratings of the current situation tend to be more polarized than retrospective ratings that summarize a longer time period. While current ratings are more affected by immediate mood status, retrospective ratings often include and account for both positive and negative recollections of the specified time period [99, 100]. However, the strong time-related correlations found in study II imply that, to a large extent, the present state seems to affect the retrospective ratings. Consequently, retrospective self-ratings might not be representative assessments of a longer time period, e.g. the last month or last year when measuring fluctuating variables, such as psychosocial exposures. This would furthermore result in decreased
correlation between retrospective ratings and both slow and rapidly reacting biological stress-markers.

Table 1. Time-related correlations and shared variance ($r^2$) within VAS and Likert items (N=633)

<table>
<thead>
<tr>
<th>Likert or VAS items</th>
<th>Spearman's rho</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health right now vs. last month (VAS)</td>
<td>.91**</td>
<td>.83</td>
</tr>
<tr>
<td>Health right now vs. last year (VAS)</td>
<td>.77**</td>
<td>.59</td>
</tr>
<tr>
<td>Health last month vs. last year (VAS)</td>
<td>.81**</td>
<td>.66</td>
</tr>
<tr>
<td>Health right now vs. last month (Likert)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health right now vs. last year (Likert)</td>
<td>.67**</td>
<td>.45</td>
</tr>
<tr>
<td>Health last month vs. last year (Likert)</td>
<td>.72**</td>
<td>.52</td>
</tr>
<tr>
<td>Sleep right now vs. last half-year (VAS)</td>
<td>.78**</td>
<td>.61</td>
</tr>
<tr>
<td>Sleep right now vs. last year (VAS)</td>
<td>.70**</td>
<td>.49</td>
</tr>
<tr>
<td>Sleep last half-year vs. last year (VAS)</td>
<td>.91**</td>
<td>.83</td>
</tr>
<tr>
<td>Concentration ability right now vs. last month (VAS)</td>
<td>.89**</td>
<td>.79</td>
</tr>
<tr>
<td>Concentration ability right now vs. last year (VAS)</td>
<td>.75**</td>
<td>.56</td>
</tr>
<tr>
<td>Concentration ability last month vs. last year (VAS)</td>
<td>.83**</td>
<td>.69</td>
</tr>
<tr>
<td>Stress right now vs. last month (VAS)</td>
<td>.78**</td>
<td>.61</td>
</tr>
<tr>
<td>Stress right now vs. last year (VAS)</td>
<td>.53**</td>
<td>.28</td>
</tr>
<tr>
<td>Stress last month vs. last year (VAS)</td>
<td>.69**</td>
<td>.48</td>
</tr>
<tr>
<td>Energy right now vs. last month (VAS)</td>
<td>.82**</td>
<td>.67</td>
</tr>
<tr>
<td>Energy right now vs. last year (VAS)</td>
<td>.63**</td>
<td>.40</td>
</tr>
<tr>
<td>Energy last month vs. last year (VAS)</td>
<td>.72**</td>
<td>.52</td>
</tr>
</tbody>
</table>

** p<.01 (2-tailed)

The results of paper II imply that single VAS questions can, in some cases of uniform construct, replace a single-item Likert scale or be used instead of multi-item Likert scales. This is especially relevant when assessing fluctuating variables that preferably should be measured repeatedly over time since retrospective self-ratings might not be representative assessments of a longer time period [102]. Moreover, single items in contrast to multiple-item indices, would be facilitating and time-saving for the researcher as well as the respondents and most likely enhance our ability to better understand the relationships between stressors of every day life, biological mechanisms and health.
Stress management and health promotion

Every individual is repeatedly exposed to stress during a lifetime and has to handle or “cope” with it [13, 103]. However, what is perceived as very stressful for one individual may not at all be stressful to another. So coping may be described as our actions and thoughts to handle or improve the negative aspects of a stressful situation [103]. These actions and thoughts, in turn, are of course influenced by the subjective appraisal and experience of a stressor, which is influenced by personality, emotions and other moderating situational and environmental factors [104].

Factors that generally seem to obstruct successful coping and thus health on a long-term basis are: avoidance strategies, destructive self-focus, procrastination and hostility. Factors that usually correspond or relate to constructive coping are: active coping, social support, sense of coherence, humour, distraction, relaxation and forgiving. Moreover, the building and managing of interpersonal relationships seems to be of importance for successful coping with a wide range of life stressors [104]. However, considering the complexity of coping processes, it is impossible to assure that some coping strategies are “good” whereas others are not. Rather, it is a combination of several different factors that will determine whether the outcome of the coping will be successful for an individual on a long-term basis or not [103].

Active coping, which is generally beneficial to health on a long-term basis, may be achieved by different kinds of stress management interventions. According to DeLongis and Preece [103], an important first step is to appraise the situation in a positive yet realistic manner. Then, fragmentation of a stressor into what aspects could be changed and what has to be accepted may facilitate the identification of potentially appropriate coping strategies. Coping strategies that include support, information and skills training have often proved to be effective.

Finally, it should be acknowledged that a healthy lifestyle from an early age may be one of the best approaches to reduce the negative consequences of stress on health [8]. Thus, educational institutions could contribute significantly to public health by supplying educational, behavioural, motivational, and life skills health promotion and stress management programs. IT-based learning systems or self-help interventions that optimise the interactive possibilities of multimedia may well be valuable resources for such programs. These tools could for example provide behavioural guidance as well as means to consolidate theoretical understandings [8].

Stress management interventions

There are a multitude of different stress management interventions and approaches that are offered to the public by various sources, including conven-
tional medicine and complementary and alternative medicine. Stress management interventions have been developed for work-related stress as well as a multitude of disorders, including long-term pain conditions and mental ill-health [95, 96, 105-112]. These interventions include various approaches that aim at reducing stress, improving coping, increasing self-confidence and decreasing vulnerability to stress. As a result, one can manage challenges and problems with less stress and more adaptive responses. Numerous techniques may be utilized for this purpose, including for example self-management skills, relaxation training, psychoeducation, cognitive behavioural therapy, behaviour modification, social support, problem solving, time management and physical activity [43, 95, 96, 105-113].

A number of studies have provided evidence that the implementation of stress management interventions may have several beneficial effects for individuals and organizations [43, 95, 96, 105-113]. One beneficial consequence of stress management may be an increased sense of control. This sense of control is important and generally adaptive for health, whereas the need for control may under some circumstances be maladaptive and lead to inflexibility in coping with difficult problems [61]. Many stress management interventions have the effect of enhancing perceived control, which may be especially important with regard to behavioural treatment of long-term pain.

It may improve physical and mental health, increase work satisfaction, as well as reduce organizational risks and costs of workplace ill-health, and thereby increasing organizational profits. Furthermore, it may facilitate reintegration of individuals into work after injury or sick leave as well as limit the impact and chronicity of different disabilities [43, 105, 107-109]. For example, cognitive interventions have been found to increase both physical and functional performance in subjects suffering from long-term pain [114-116]. These beneficial effects are probably due to the fact that unhelpful cognitions and beliefs are major contributors to the maintenance and progress of long-term pain [45, 60, 71].

Furthermore, pain generally increases stress and anxiety and thereby cognitions. If the pain is successfully treated stress and anxiety may be reduced, which in turn may cause a further reduction in pain. This pain-relieving cycle, however, is not so easy to achieve in diffuse long-term pain, which is commonly difficult to treat. Stress and anxiety levels are often high and may also increase over time in long-term pain patients. Often, the heightened stress and anxiety level is due to ineffective pain treatment. Consequently, patients often anticipate continued pain, which increases anxiety and stress even more. However, as mentioned before, stress and anxiety per se may contribute to the development and worsening of long-term pain and increase pain sensitivity. Therefore, an improved understanding of the underlying mechanisms as well as sources of stress and anxiety may be of importance in order to achieve optimally beneficial treatment effects [5, 42].
Massage

The word massage includes and describes a multitude of diverse techniques for manipulation of soft tissue. Massage is a frequently utilized method that has been assessed as a sole or partial treatment for a wide variety of different diseases and disorders [117, 118]. In a review by Field et al [117], it was indicated that massage renders some common effects that are elicited irrespectively of what kind of disorder that is treated. These effects were reduction in pain, anxiety, depression and stress hormones. Another review, by Moyer et al [118], reports on several mechanisms that may contribute to the beneficial effects of massage. These mechanisms were reported to be:

- The gate control theory of pain reduction.
- Influence on neurotransmitters, e.g. oxytocin, endorphins and serotonin.
- Mechanical effects, e.g. improved blood circulation.
- Promotion of parasympathetic activity and recovery, e.g. through increased relaxation and sleep improvement.
- Interpersonal attention.

However, with the exception of pain trials, very few studies have assessed the long-term effects of massage at a long-term post-intervention follow-up. In order to be able to draw reliable conclusions about possible long-term beneficial effects, there is a great need for prospectively controlled randomized clinical trials.

Self-help approaches

As the word implies, self-help relates to interventions that teach individuals how to help themselves. Frequently, books are used, but there are various modes of self-help, nowadays also including interactive websites and tape-recordings. Interestingly, self-help interventions have proved to be effective measures for numerous issues and render similar and equally beneficial effects as interpersonal face-to-face approaches [119, 120]. There are some indications that a combination of different modes of self-help, e.g. combination of a book and videotape or audiotape, may result in much better effects (more than doubling of effect sizes) compared to a single mode [119]. Furthermore, self-help seems to be more suitable and therefore produce better effects for some conditions and individuals than others [120]. The following section will describe some commonly utilized self-help techniques that have proved to be powerful for individual stress management.

Relaxation

Relaxation exercises aim at counteracting the physiological consequences of stress by decreasing sympathetic activity and increasing parasympathetic
activity [109]. Different kinds of physical and mental relaxation techniques, such as progressive relaxation [121] and breathing techniques, are the most commonly utilized and scientifically most thoroughly assessed stress management procedures (see references below). In most, if not all, relaxation exercises breathing techniques are utilized. Relaxation is usually either a part of a multimodal intervention or a sole measure. It is a practical method that is easily performed and implemented in different settings. In general, beneficial effects of relaxation have been reported. These effects include reduction in anxiety, stress, depression, headache, fatigue, acute and long-term pain, increased job performance and improved sleep quality [96, 105, 107-113].

Cognitive behavioural techniques
Cognitive behavioural techniques, such as cognitive restructuring and problem solving, aid individuals to manage stress by altering thoughts and emotions. One desired effect is that individuals appraise how their thinking styles and emotions affect behaviour. New insights and new perspectives may change emotions and thoughts that will beneficially alter behaviour. Indeed, various kinds of cognitive behavioural techniques have proved to be effective in stress management. Cognitive techniques have often been used together with other stress management interventions and are thought to be an essential ingredient to achieve the most effective results [51, 95, 96, 105, 107-109, 112, 122].

Psychoeducation and time management
Two other common and important ingredients in stress management programs are psychoeducation and time management. Psychoeducation refers to information about stress as well as psychological and physiological reactions to different kinds of stressors. This may help participants to better understand various reactions, thinking patterns and symptoms and thereby reduce stress. Furthermore, stress- and health-related information may render insights as well revealing solutions to specific problems. For example, information about coping strategies and stress management may be provided (see references below).

Time management techniques aim at increasing efficiency in time usage through structured solutions, and thereby saving time and reducing stress. An experience of time deficiency is common among stressed individuals, especially with regard to work-related stress. Thus, time management techniques may have important implications for work-related efficiency, stress level and recovery, as increased efficiency may save energy and counteract unnecessary stress. Both psychoeducation and time management are commonly utilized methods in multimodal stress management programs [95, 96, 106-110, 122].
Organizational stress management interventions

It has been repeatedly shown that there are significant associations between psychosocial workplace stress and the prevalence of musculoskeletal and stress-related disorders [91, 123]. At the same time, there are some indications that organizationally focused interventions may improve employee health and the psychosocial situation at work, as well as reduce work-related stress and thereto related ill-health. For example, studies have reported beneficial effects on employee health of organizational changes directed at optimizing demands combined with increasing control and social support or by just providing educational programs for managers. Furthermore, improvement of work organization may reduce sick leave and staff turnover [91, 123, 124]. Thus, organizational interventions may be an important ingredient for effective and successful stress management and health promotion. However, it is crucial that the organizational changes are supported by both the top and local management as well as the employees in order to be optimally efficient. Moreover, a participatory approach seems to be essential to obtain positive results [123].
Methods

The four papers in this thesis are based on three separate studies:

*Paper I*: was based on the data from study I. It assessed two stress management interventions, i.e. massage and relaxation-tape recordings, on patients suffering from “diffuse” long-term pain.

*Paper II*: was based on data from study II and was conducted to validate some of the VAS that would be used in study III.

*Paper III and IV*: were based on data from study III. The so called HealthIT-study assessed a proactive web-based stress management and health promotion tool on a healthy population from IT and media companies.

The three studies were conducted in different settings and on different populations. Consequently, different methodological designs and approaches were used.

Designs

Papers I, III and IV were based on two randomized prospectively controlled intervention studies. Measurements were conducted at baseline, post-intervention and at a long-term post-intervention follow-up. Paper II had a cross-sectional design. In all the papers, data was analyzed on group level. Hence, it was not possible to identify the outcome of single individuals based on the presented results.

Participants

*Paper I*

Background characteristics of the study participants are presented in Table 1 (paper I). 129 patients fulfilling the study criteria, i.e. the IASP (International Association for the Study of Pain) definition of long-term pain [1], were carefully examined by their primary care physician and asked if they wanted
to participate in a study concerning the efficacy of two different treatment methods for long-term pain. After informed consent was obtained, all of the patients enrolled in the study. A criterion for patient involvement in the study was that the condition was not due to any specific disease treatable by, for example, surgery. Pain should have existed for at least 3 months.

Patients were consecutively randomized into either of the two study groups: massage and tape-recorded mental relaxation. A certified physiotherapist invited the referred patients to an introductory visit in her office.

The participants were characteristic of the long-term pain patients commonly seen in primary health care settings. Many of them suffered from depression and had several other somatic and/or psychiatric diagnoses. Some of the participants had a history of unemployment and many were immigrants.

**Paper II**

Background characteristics of the respondents are presented in Table 1 (paper II). Participants were recruited via two web sites; one web site of the centre of environmental ill-health and stress (www.ceos.nu) at the Academic Hospital in Uppsala and one site offering a stress management and health promotion tool (www.pql.se) previously developed in a research project at Uppsala University. The invitation to participate in the study was posted in the news section on the main page of the web sites and interested visitors could click on a link to receive some more information. Furthermore, 3016 randomly selected registered users of the website www.ceos.nu received an e-mail asking them as to their interest to participate in the present study. The participants were informed that a questionnaire was to be validated and that their participation was voluntary and anonymous.

There were approximately 13,400 visits from about 2,700 unique individuals (some individuals visited the sites on a regular basis) at the websites during the two-week duration of the study. 805 individuals chose to participate in the study, out of which students, unemployed, individuals on sick-leave and pensioners were excluded in order to make the population more homogenous with regard to socioeconomic factors. Thus, the final number of participants was 633.

**Paper III and IV**

Baseline socioeconomic characteristics of the participants are presented in Table 4 (paper III). In collaboration with a White-Collar Union (Sif) and a Swedish Employers' Association (Almega), ten companies insured by the study’s source of funding Alecta (an occupational pension plan company) were asked as to their interest in participating. The management departments of six out of the ten asked companies were interested. Informed of the basic inclusion criteria, i.e. minimum group of ten individuals and access to economic production data, 2-4 departments within each company were chosen
and asked by the company management as to their interest in participating. The managers of the selected departments in turn asked their employees whether they were interested in participating.

There is no information on the exact number of employees that were asked to participate in the study. An exception was one of the media companies where 95 out of 100 possible participants chose to participate. In general there was also a great interest from the other departments and similar participation rates are therefore estimated.

Altogether, 317 participants from 22 departments/units in four information technology and two media companies enrolled in the study. Fourteen participants were excluded because of communication-related problems (n=7), change of mind to participate or quit their job before initiation of the study (n=7). Thus, 303 persons finally participated in study III (papers III and IV), out of which 26 participants (8.6%) dropped out. The reasons for dropping out were job termination (n=7), change of workplace (n=2), Foreign Service or moving abroad (n=6) or other reasons (n=11). There were no significant differences in dropout rates between the groups (6.9% in the intervention group vs. 9.8% in the reference group, p between groups = n.s.). With regard to study III, there were no statistically significant differences between the intervention and reference group in socioeconomic background or psychophysiological measures at baseline.

Interventions

In papers I, III and IV, classical stress management techniques were utilized with the aim of decreasing unwanted stress and consequently also for pain reduction in paper I. The procedures as well as interventions will be more thoroughly described below.

Paper I

At the first visit, individual patients received information about the aim of the study. Information was given about the design of the study as well as the specifics of the treatment. Finally the patients were asked to fill out the first questionnaire. In cases of language difficulties, a translator was hired.

The certified physiotherapist, who was specialized in massage, treated patients in the massage study group. The massage group patients received 6-10 sessions, each lasting 30 minutes. The patients were treated 1-3 times a week. Patients who participated in less than 6 treatments were considered dropouts. Patients in the massage group received an average of 7 treatments. Patients in this group typically exhibited severe sensitivity/touch-alloynia, due to the long-term pain. The massage was therefore adapted to meet the pain threshold of the patients. Under no circumstances was the massage considered painful or uncomfortable. Exceptions were made in the cases where
patients showed distinctive myofascial trigger points, which were treated by “trigger point technique”, implying that the therapist applied pressure at these tender areas which could be uncomfortable but not unbearable.

Patients in the relaxation tape group were instructed by the same physiotherapist as in the massage group to listen to a progressive relaxation [121] audiotape twice a week during five weeks. In short, the tape instructed the participants to systematically tense and relax the muscle groups of the body accompanied by slow and regular breathing. A calendar was given to follow frequency of training. In order to ensure that the participant learned the proper relaxation technique the physiotherapist guided the patients through a relaxation exercise at the first visit.

At the final treatment in the massage group, and after 5 weeks in the relaxation tape group, the patients filled out the second questionnaire. In the relaxation tape group the audiotape and calendar were returned on this occasion. Three months after the last treatment a final questionnaire was mailed to the patients.

**Paper III and IV**

Table 1 in paper III and IV provides a detailed description of the web-based tool and illustrates similarities and differences in the features that were offered to the intervention and reference group respectively. A web-based tool for health promotion and stress management was developed and offered all participants real-time monitoring of perceived current health and stress status, a diary and information about stress and health (Table 1, paper III and IV). In addition, participants in the intervention group were offered web-based cognitive exercises, aiming at decreasing unwanted stress and promoting health and recovery through health promotion initiatives. The exercises included techniques for relaxation, time management, cognitive reframing and a chat. Thus, the only things that distinguished the groups were the addition of the cognitive exercises and the chat in the intervention group. The web-based tool was developed by the researchers and most techniques are commonly utilized techniques in cognitive and behavioural psychology and stress management. These techniques were modified so that they could become more or less self-instructing to be used for self-help purposes.

The web-based tool and the exercises were not pilot tested before the study. However, the tool as well as exercises were chosen and adjusted on the basis that they had to be time efficient in order to be utilized. It was hypothesized that basic demands for regular usage were instant feedback on the questionnaire and that the measurement and exercises could be used rapidly. Consequently, it was decided that regular or daily monitoring should not take more than 20-40 seconds. Moreover, every exercise was labelled with information of time for accomplishment (time span 1-60 minutes). Some of the cognitive exercises, e.g. improving self-confidence, were designed such
that they consumed 5-10 minutes when learning and then could be conducted in a matter of seconds when utilizing.

Most exercises were presented in three different modes; on the web-site as plain text, as a downloadable PDF-file (sometimes including descriptive images), and as an interactive flash animation, guiding the participant with image and sound through the exercise. Since the intervention for both groups was completely web-based it could only be accessed online. All information was however printable, which made it possible for the participants to print material of interest and thus intervene elsewhere. Exposure to the intervention for both groups could only be logged via the number of logins to the website.

Evaluation

Questionnaires were compiled and used to evaluate the results in all papers. Additionally, physiological markers were sampled in papers III and IV for a more “objective” assessment. The assessment methods for each paper will be further described below.

Questionnaires

Paper I

Each patient thus filled out a questionnaire (Table 2) on three separate occasions: before the first intervention session, immediately after the termination of the intervention period, and at follow-up three months later. The questionnaire covered the following areas: age, gender, smoking habits, country of birth, marital status, and profession. In addition, self-rated health, consumption of medicine and the two indices mental energy (items regarding mental and cognitive wellbeing) and muscle pain were used.

Both indices have been used in a number of prior studies [125, 126]. The constructed indices all had Cronbach’s alpha of >0.7 with individual factor loadings of 0.5 or higher. Each index consisted of a number of questions to which participants were asked to respond on a 3- or 4-graded Likert scale concerning the frequency of occurrence or intensity of specific symptoms. Higher scores indicate a more beneficial outcome. The indices mental energy and muscle pain and most of the questions have previously been validated [125, 126]. In addition, SRH was measured using a single 5-graded Likert scale. SRH is one of the most widely used single measures of perceived current health status [127-135].
### Table 2. Questions and indices covered by the questionnaire in paper I

<table>
<thead>
<tr>
<th>Item/index</th>
<th>Answer alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background questions</strong></td>
<td></td>
</tr>
<tr>
<td>Age, gender, smoking habits, country of birth, marital status, and profession.</td>
<td></td>
</tr>
<tr>
<td><strong>Self-rated health</strong></td>
<td></td>
</tr>
<tr>
<td>How have your health been during the past month?</td>
<td>Very bad - quite bad - fairly well - quite good - very good.</td>
</tr>
<tr>
<td><strong>Mental energy (index)</strong></td>
<td></td>
</tr>
<tr>
<td>Check one of the following options if you have experienced any of the below inconveniences during the past week: Tiredness, Restlessness/irritation, Anxiety/worry, Melancholy, Concentration difficulties, Difficulties to sleep.</td>
<td>No – Yes, some time – Yes, many times – Yes, daily.</td>
</tr>
<tr>
<td><strong>Consumption of medicine</strong></td>
<td></td>
</tr>
<tr>
<td>Check one of the following options if you have used any of the following medicines during the last week: Analgesics, Sedatives, Hypnotics, Anti-depressants, Complementary medicine.</td>
<td>Never – Sometimes – Every day.</td>
</tr>
<tr>
<td><strong>Muscle pain (index)</strong></td>
<td></td>
</tr>
<tr>
<td>Check one of the following options of how much inconvenience with the following body-parts you have experienced during the past week: Head, Neck, Shoulders, Arms/hands, Upper part of the back (thoracic region), Lower part of the back (lumbar region), Legs/feet, General muscle pain.</td>
<td>No inconveniences – Little inconvenience (tension/tiredness) – More inconvenience (some body-parts ache sometimes) – Much inconvenience (constant pain).</td>
</tr>
</tbody>
</table>

### Paper II

The questionnaire with Likert and VAS based response alternatives consisted of socioeconomic background as well as stress- and health-related questions. The background questions included age (<20, 20–30, 31–45, 46–60, >60 yrs), gender (male vs. female), marital status (married/co-inhabiting/live-apart vs. single), educational level (primary school, high school, academic degree (BS, BA), and higher academic degree), income (<$12 000, $12–30 000, $30–45 000, >$45 000 pr annum), occupation (working, pensioner, sick-leave, student, unemployed) and financial situation (very poor – very well). The stress- and health-related questions included the single item on SRH [127-135], the Karolinska Sleep Questionnaire (KSQ) [136], the indices mental energy and work-related exhaustion from the Quality Work Competence (QWC) questionnaire [125, 126] as well as newly constructed single VAS and Likert based items to be compared. Items, topics and indices covered by the questionnaire are presented in Table 2 (paper II).
Paper III and IV

A questionnaire was compiled and included about 100 questions concerning socioeconomic status, consumption of caffeine drinks, expectations about the research project, self-rated health (SRH), stress and wellbeing at work as well as during leisure time, health economics and performance at work (Table 2, paper III and IV). Most of the questions were presented as Visual Analogue Scales (VAS) and some, concerning health economy, work time, basic daily functioning and symptoms of ill health, were presented as multiple-choice questions. Most of the newly constructed single VAS questions were based on previously validated Likert-based items or indices [93, 125, 126, 137-139]. Participants filled out the questionnaire online at baseline (before the initiation of the study) and at the end of the six-month intervention.

Physiological markers

Paper III and IV

The complete list of biological markers analyzed in the current study is presented in Table 3 (paper III and IV). More biological markers of general nature, such as general blood status, were collected for overall health matters or all-purpose profiling. These markers were not analyzed in the present study. Furthermore, P-substance P, S-IL-1beta and P-endothelin were also collected. However, in the first measurement there was not enough blood collected to render the exact results needed for more sensitive analyses of these variables, resulting in the decision to not include them in the analyses of paper III and IV. Thus, the biological markers analyzed in these papers were only the ones that could be related to various stress-related hypotheses.

Blood samples were collected from study participants between 7.00-11.30 am at each specific worksite (or nearby). Questionnaires were filled out during the same time period (usually same day or week) in order for the outcome of the blood and questionnaire data to be as comparable as possible. The exact time for blood sampling was recorded for each participant at baseline and at the end of the study so that the blood could be collected at the same time (± 15 minutes). Participants were instructed not to eat or drink (except water), nor use nicotinic substances at least ten hours before blood sampling. The blood samples were analyzed by the Karolinska University Hospital laboratory that is qualified by SWEDAC (Swedish Board for Accreditation and Conformity Assessment) that accredits laboratories in the medical sector according to the standard ISO/IEC 17025.
Statistical analyses

Variables were assessed for normality using Kolmogorov-Smirnov test. Changes over time (time, group and group x time) were assessed using two-way analysis of variance/covariance (ANOVA/ANCOVA). ANCOVA adjusts for initial differences so that the results more precisely reflect possible intervention effects, and thus permits a more sensitive analysis compared to regular analysis of variance (ANOVA). The increase in sensitivity arises from the fact that the covariance reduces the error term (within-group variability) against which intervention effects are compared. Furthermore, ANCOVA is not very sensitive to small deviations from a normal distribution [140]. In the papers using ANCOVA, baseline values of the assessed variables were used as covariates. Analyses were in some cases, such as in analyses of sex hormones, stratified with separate analyses of the gender groups.

Correlation analyses were utilized (Intraclass correlations and Spearman’s rho) to assess agreement and associations between various variables. Moreover, t-tests/one-way ANOVAs and/or marginal homogeneity tests were utilized to detect possible differences in absolute levels of group means or scores respectively.

In paper I, only parametric methods were used since calculations were based on multiple-item Likert indices. However, the following papers mostly included single VAS, which can be treated as an interval or ordinal scale [141-143]. Also considering that some variables were not normally distributed, both parametric and non-parametric tests were used in papers II, III and IV. In general, both analytic strategies yielded similar results. In paper III, it was decided that changes over time and differences between the groups would only be considered in cases where both parametric and non-parametric tests unanimously were statistically significant. For the non-parametric analyses, new variables (so called Δ variables) based on change between the first and second measurements were constructed. Differences between the groups were then assessed using a Mann-Whitney U test. In paper III and IV, logistic and linear regression (only paper IV) was used to model the probability of changes in the Δ variables (dependent variables).

Statistical significance was set at p<.05 (two-tailed) for all analyses.

Ethical approval

Paper I was approved by the ethics committee of Karolinska Institute. Papers II-IV (included in the same research project) were approved by the ethics committees of Uppsala University (Dnr 01-188) and Karolinska Institute (Dnr 01355).
Results

Paper I
At the end of the intervention, there was a significant improvement in the three main outcome measures: SRH, mental energy, and muscle pain in the massage group as compared to the relaxation group. However, at the 3-month post-intervention follow-up, there was a significant worsening in the outcome measures (time x group effect p<0.05) back to initial rating levels in the massage group as compared to no changes in the relaxation group (Figures 1-3 and Table 2, paper I).

Predictors of post-intervention improvement in SRH were study group (massage more beneficial than relaxation tapes), being born in a Nordic country, lower initial muscle pain and lower baseline health. This model explained 38% of the variance (Table 3, paper I).

Improvement in mental energy was predicted by study group (massage more beneficial than relaxation tapes), lower baseline mental energy and being born in a Nordic country. This model explained 29% of the variance (Table 3, paper I).

Predictors of improvement in muscle pain were study group (massage more beneficial than relaxation tapes), being born in Nordic country, higher baseline health and baseline mental energy, more initial muscle pain. Altogether, this model explained 25% of the variance (Table 3, paper I).

Paper II
The single VAS and single Likert items measuring the same construct were highly correlated, whereas there were moderate to strong correlations between the single VAS and the Likert indices (Table 4, paper II). Thus, respondents who scored high on the VAS for the variable “self-rated health” also tended to score high on the corresponding Likert based item. However, in spite of a moderate to strong correlation, there were statistically significant differences in absolute levels in seven out of eleven assessed variables. A lower shared variance (r²) between the two compared scales might explain some of these differences in absolute levels. Intraclass correlations and differences in absolute levels are presented in Table 4 (paper II).
There appeared to be systematic end-aversion bias in scorings on the Likert scales. A larger percentage of the respondents tended not to mark the two extreme ends of the Likert scales as compared with scorings on the corresponding VAS. Thus, on the Likert scales but not the VAS, respondents seemed to mark the three middle response categories more often, suggesting end-aversion bias.

**Paper III**

At the end of the 6-month intervention period, the intervention group had improved significantly as compared to the reference group on ratings of perceived ability to manage stress, sleep quality, mental energy, concentration ability, social support and competence usage at work (2-way ANCOVA, p<.05 time x group effect). With the exception for competence usage at work, all these changes and differences between the groups remained significant when applying the non-parametric Mann-Whitney U test (p<.05, two-tailed). Figures 3a-i (paper III) illustrate changes in self-rated measures and biological markers over time between the intervention and reference groups, respectively. Results shown are covaried for baseline scores of the depicted outcome variable. SRH increased significantly in both groups, with no differences between the groups (2-way ANCOVA, p<.0001 time effect; time x group effect non-significant). The results of the gender stratified variables were not different from the ones obtained when analyzing the non-stratified data.

Concerning the analyzed blood samples, the levels of the sulphated metabolite of the hormone dehydroepiandosterone (DHEA-S) decreased significantly in the reference group, with no changes in the intervention group. The levels of Neuropeptide Y (NPY) increased significantly in the intervention group compared to the reference group. CgA (chromogranin A) and ACTH (adrenocorticotropic hormone) decreased significantly in the intervention group as compared to the reference group. The levels of the immune marker TNFα decreased significantly in the reference group as compared to the intervention group (2-way ANCOVA, p<.05 time x group effect). With exception for ACTH, all these changes in biological markers and differences between the groups remained significant when applying the non-parametric Mann-Whitney U test (p<.05, two-tailed).

The logistic regression was used to predict the quartile exhibiting most improvement or beneficial change. The regression models correctly predicted 72.5-80.3% of changes of the various outcome measures. Improvement or beneficial changes in stress management (OR 2.213, 95% CI 1.162-4.215), mental energy (OR 2.194, 95% CI 1.107-4.346), social support (OR 2.752, 95% CI 1.432-5.287), NPY (OR 1.934, 95% CI 1.032-3.623) and TNFα (OR 3.185, 95% CI 1.637-6.196) were significantly predicted in the
intervention group compared to the reference group (Tables 5 and 6, paper III). Thus, the intervention group was approximately two to three times more likely to exhibit the highest improvement quartile in stress management, mental energy, social support, NPY and TNFα. These predictions remained significant even after adjustment for age, gender, annual income, education, marital status, work related factors that might disturb the relationships, i.e. working hours per week, working atmosphere, work intensity and number of breaks during a working day and all the remaining dependent variables. Beneficial changes in sleep quality, concentration ability, DHEA-S and CgA were not significantly predicted by group in the logistic regression analysis. The frequency of logins to the web was not a significant predictor of changes in any of the dependent variables.

Paper IV
There was a significant difference in baseline ratings of SRH between the participants maintaining/improving and those worsening in SRH. Participants worsening in SRH had a higher (better) baseline mean or rank compared to those maintaining/improving (75.4, SD 17.6 vs. 60.4, SD 21.4; p<.0001).

There was a significant improvement for both study groups (intervention vs. reference) between the first and last measurement (0-12 months) and no statistically significant difference between the groups (time effect p<.0001, time x group effect NS). Thus, both groups improved ratings of SRH over time (Figure 1, paper IV).

Criterion validity was assessed using Spearman’s Rank correlation test. Baseline SRH significantly correlated with numerous variables that are known to be related, indicating good overall criterion validity (Table 5, paper IV). In the logistic as well as linear regression baseline level of SRH was a major predictor of trends in SRH (OR=.29, 95% CI .139-.620, p=.001) (Tables 6a-b, paper IV). Hence, participants in the top SRH quartile at baseline were approximately 3.4 times more likely to exhibit worsening in SRH. Furthermore, in the logistic but not in the linear regression, the number of logins significantly predicted maintenance/improvement in SRH (OR=2.6, 95% CI 1.044-6.308, p=.04). Thus participants with highest number of logins (top quartile) to the web site were approximately 2.6 times more likely to exhibit maintenance or improvement in SRH. The logistic regression model correctly predicted 67.1% of changes in SRH. In addition to lower baseline ratings of SRH, the linear regression identified higher baseline ratings of sleep quality and sense of coherence as significant predictors of improvement in SRH. Altogether, this model accounted for 27.3% of the explained
variance. Socioeconomic variables were not significant predictors in any of the regression models.
General discussion

Both long-term pain patients and employees at IT and media companies are populations that are commonly exposed to high stress levels. Even if there are important differences with regard to socioeconomic factors, life situation and environment between these two groups, there are similarities that should not be neglected. For example, the necessity for effective stress management that can be utilized on a daily basis or on demand may be essential for maintaining or improving long-term health and wellbeing in these groups. The pathogenic plastic changes in the CNS and immune system caused by long-term stress may pose severe burdens to these individuals as well as organizations and society at large. So for humane, ethical and economic reasons it is essential to proactively develop humane support features for such “high-stress” groups.

The overall results indicate that individually focused stress management interventions in long-term pain patients as well as in a healthy, working population may have short-term beneficial effects. On a long-term basis the beneficial changes seem to revert. In paper IV, it is indicated that the intervention is not a significant predictor of long-term changes in SRH. Rather, there seem to be other factors, such as health perception, sleep quality and sense of coherence that predict improvement in SRH over time.

Interestingly, no physiological markers were predictive of future SRH, as changes in SRH was mainly affected by cognitive perceptions and sleep. It has not yet been established what SRH really represents, although there have been many speculations. However, SRH is a well established and potent independent predictor of future health outcomes. The findings of paper IV could be important for a better understanding of the concept SRH. Furthermore, there are three specific areas on which interventions could focus in order to maintain and enhance health over time.

One important finding of the present thesis is that ratings of sleep quality and/or energy improve in the intervention group vs. reference group (papers I and III) together with related systematic findings in biological markers (paper III) and other self-ratings (papers I and III). There is emerging evidence suggesting that sleep alterations can modulate the stress-health relationship. Acute and long-term stressors are associated with subjective and objective measures of sleep disturbances [53, 144, 145]. Thus, improvements in sleep quality might mediate some of the stress protective and health pro-
moting effects found in the intervention group in paper III and possibly also in paper I. Furthermore, paper IV confirmed that sleep quality may be a predictor of future SRH or health outcomes.

**Stress management intervention effects**

The short-term beneficial effects found in papers I and III is a common finding in stress management intervention studies. Apart from the fact that many studies do not conduct a long-term post-intervention follow-up, those that do generally fail to maintain or present only modest beneficial treatment effects. Furthermore, the point in time for post-treatment follow-up differs substantially between studies, as it ranges from three days to over one year [107, 108, 113, 146].

Post-treatment worsening in musculoskeletal symptoms is a common, but little understood phenomenon [146, 147]. This is a major problem since many patients are left with no long-term benefits from treatment. Perhaps stress management is more efficient for acute musculoskeletal pain than in long-term pain conditions, where pain maintenance is due to more complex mechanisms. Maybe different or multimodal treatment strategies are needed to achieve sustained long-term beneficial effects. Additionally, an intervention that focuses solely on individuals might have less ability to produce a lasting effect compared to interventions that also consider for example organizational aspects. Such multidimensional interventions could perhaps increase the possibilities for the participants to pursue beneficial effects of the individually focused intervention.

Indeed, it has previously been shown that organizationally focused interventions, such as educational programs for managers, may produce long-term beneficial health effects for employees [123, 124]. However, a multidimensional approach that combines individual and organizational interventions may take time to implement successfully. Therefore, potentially beneficial changes might neither be detected in the individuals nor in the organization until after several months or years; indicating the need for long intervention periods lasting at least over a year, as well as two or three repeated annual long-term post-intervention follow-ups. Thus, to achieve the desired sustained long-term effects in for example papers III and IV, a parallel focus on both individual and organizational stress management could have been helpful. The addition of an organizational approach could perhaps have enhanced and/or prolonged the effects of the individually tailored web-based intervention.

One major problem burdening stress management intervention research is the lack of similarity in settings, populations, methodology and statistical analysis strategy. Sometimes inappropriate statistics is used, and commonly there are very small sample sizes and sometimes high dropout rates. Furthermore, duration and frequency differ between interventions that have
been evaluated. In some studies there is no reference group against which effects may be contrasted [96, 107, 108, 110, 113]. This makes it difficult to compare and generalize findings of different studies, and consequently to establish firm conclusions. Moreover, different criteria of what constitutes a clinically or statistically significant result differ. In some cases, secondary findings or results from within group subscale analyses are used do draw conclusions. These analyses might well be useful for exploratory purposes, but are not equal or superior to analyses of total score or differences between groups [110].

Predictors of change in SRH

The strongest predictor of changes in SRH was baseline SRH in both paper I and IV. This might well be partly due to the unwanted statistical phenomenon of regression towards the mean [148-150] as lower initial SRH increased over time whereas higher initial ratings decreased. On the other hand, findings from previous prospective studies confirm the findings of this thesis, which implies that the results might be valid [135, 151]. For example, also Bailis and colleagues [151] found that SRH was, independently of other measures, the strongest predictor for SRH two years later. The predictive strength of SRH on future SRH and other health outcomes may indicate at least a short term stability of the measure itself and perhaps a low overlap with other possible predictors. Furthermore, as both this and most previous studies imply, clinical factors are less powerful predictors of SRH compared to other kinds of self-ratings.

Methodological considerations

There are some methodological considerations with this thesis that have to be addressed in order to assess the validity and generalizability of the results.

Questionnaires and validity

There are numerous established questionnaires, which have been recognized as both reliable and valid. Still, it is very common that researchers develop new instruments [107]. This is also true with regard to the HealthIT study (papers II, III and IV), in which the development of a new questionnaire was considered necessary. It was assumed that it would be too time-consuming and awkward for participants to fill out such an extensive questionnaire that would be required in order to cover all dimensions that were assessed with previously validated questionnaires.

However, some of the VAS items in the HealthIT questionnaire were validated against established Likert based items and indices in paper II. Moderate to strong correlations were found, indicating that at least some of the VAS items were comparable to established items/indices and some sin-
gle-items, such as SRH, might also be interchangeable. Furthermore, regarding the fact that objective markers (e.g. heart rate, blood pressure, blood samples, BMI), also were collected in the HealthIT study, it was possible to assert construct validity\(^2\) and criterion-related validity\(^3\). Content validity\(^4\) may constitute a problem for established instruments as well as new ones. The question about which dimensions that are captured by a questionnaire, item or index, or by different scale types (VAS vs. Likert) is not easy to answer. Please see paper II for a more thorough discussion on this topic.

**Regression towards the mean**

If regression towards the mean has occurred in either of the papers, it might be a limitation with regard to the internal validity [149, 152]. Thus, viable as the results may seem, they have to be interpreted with caution. However, considering past studies with similar findings, it is not likely either that there would be a total absence of significant beneficial changes in papers I, III and IV.

**Considerations with online measurements**

In this thesis, online measurement refers to web-based questionnaires, i.e. questionnaires that respondents fill out on an Internet website (online). Conversely, the term offline questionnaire refers to the traditional pen-and-paper based questionnaires. When using an online questionnaire there are numerous possible temporary factors, including technical issues, which might affect the test results. However, since the technology we utilized has been used and refined on thousands of individuals during the past years, all of the major issues have been solved.

In papers II-IV online questionnaires were utilized for assessment. This fact poses a question about the validity and generalizability of the present results to paper-based questionnaires and other online surveys. In general, online questionnaires seem to be valid and reliable. Furthermore, they exhibit psychometric properties and results similar to offline questionnaires [153-155]. However, sometimes online questionnaires yield different absolute levels compared to offline ones. For example, in a study by Andersson et al [153] the prevalence of depression and anxiety was marginally higher in online questionnaires compared with offline. This might be due to increased

\(^2\) Construct validity refers to the degree to which an instrument measures the construct under investigation, i.e. if a measure relates to other measures that theoretically or empirically should be related. For example, the association between self-rated psychological assessments and other theoretically or empirically related self-ratings or blood samples.

\(^3\) Criterion-related validity refers to the degree to which scores on an instrument correlates to some external criterion. The higher correlation, the higher validity.

\(^4\) Content validity refers to the degree to which an instrument adequately represents the content of the concept being measured.
self-disclosure, as there is evidence that individuals may be more honest and reveal more about themselves online than in face-to-face interactions [154]. In any case, it is important to consider the absolute level differences in cases where there are normative values or cut off points. These cannot be directly transferred from an offline to an online questionnaire.

In addition, it has been reported that subscales have loaded on other dimensions in online compared to offline surveys. However, online data collection neither statistically enhanced nor diminished the consistency of responses, nor compromised the integrity of the test [154, 155]. Nevertheless, this finding was not confirmed in paper II, where all scales and subscales loaded as expected. Thus, it is concluded that online questionnaires are suitable alternatives to offline questionnaires. Still, it is recommended that future studies should reassess validity for questionnaires to be converted for online use. Moreover, it is suggested that the findings of papers II-IV might be generalized to other online questionnaires. However, there is not conclusive evidence that the present results may be generalized to offline questionnaires.

Strengths and weaknesses

There were some strengths and some weaknesses with the studies in the present thesis that should be addressed.

Population, dropouts and compliance

A major weakness of the HealthIT study is that we have no exact number of potential participants. This fact might bias the results considering that the sample might not be representative for all the employees. However, in general there was a great interest among the employees of the enrolling departments to participate. In one of the departments, where we have the total number of potential participants, 95% enrolled. Similar participation rates are therefore estimated for the other departments. In any case, based on approximation of the total potential number of employees at each department, enrolment rate was most probably not less than 80% in the worst case scenario.

However, dropout rates were low and questionnaire response rates and compliance was high in all papers. High compliance usually means more reliable results and better intervention effects [113, 119]. In a meta-analysis of self-help treatment, it has been reported that dropout rates are generally 8.6% for reference groups and 9.7% for intervention groups [119]. These numbers are strikingly similar to the findings of paper III, even if the proportions were the opposite. Examples from previous assessments of stress management interventions commonly exhibit rather high dropout rates ranging

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5 Referring only to papers III and IV. Paper II was conducted on a different population.
between 30 and 70% [96, 107, 156-159]. In those cases it is difficult, if not impossible, to draw reliable conclusions.

A general problem with self-help approaches is the assessment of compliance. For example, in paper I it was not possible to measure true compliance for the mental relaxation tape group. However, previous studies have indicated a better compliance for electronic questionnaires than paper-based ones [160, 161]. Additionally, Stone et al [160] found that actual compliance of an electronic diary was 94% compared to 11-20% for the paper-based. Still, reported compliance was 90%, which implies that participants backfilled the paper diary (that was equipped with an electronic logging system). Since all participants in papers II, III and IV were logged, all measured compliance is true compliance. Nevertheless, due to the human factor, compliance could only be logged through the online questionnaire (responders vs. non-responders) and number of logins to the website (papers III and IV). Consequently, it is not known how much time each participant spent on the website and which exercises were utilized. This information is only available from the latter half of the intervention period. The issue of compliance assessment clearly has to be improved in future studies.

General strengths and weaknesses

In paper I it is a weakness that the pain conditions were not categorized into diagnoses. Categorization may have rendered useful information regarding whether any intervention was more or less respectively beneficial than the other for certain specific diagnoses.

A few IT-related problems occurred in the HealthIT study, but were solved along the way. Incorrect e-mail addresses to some participants complicated or made communication impossible.

A strength with the HealthIT study is that everything was completely web-based from the start. This means that the stress management tool was utilized and assessed via the same medium that was used for collecting self-ratings and other relevant background data. This automated, interactive self-help approach differs from previous studies of web-based interventions. Most commonly, other studies have been more similar with face-to-face counselling, where in addition to a website an active counterpart, often a psychologist, issues assignments and evaluations via e-mail. Consequently, the results of the present study might not be completely comparable with other assessments of web-based intervention studies.

Another perhaps relevant aspect is that the intervention was conducted and assessed in the “real world”, i.e. in authentic settings and not in artificial clinical settings. This might be important since the results could be generalized to authentic settings and everyday life.

Another strength of the HealthIT study (papers III and IV) was that the intervention and reference group were treated in the same way concerning
blood sampling, advice, web-based questionnaires, etc. The only thing that distinguished the groups was the addition of the interactive cognitive exercises and a chat for the intervention group. This indicates that the complete web-based health promotion and stress management system contributed to the beneficial effects on health, well-being and recovery. On the other hand, the minimal difference in the interventions between the study groups could have made it more difficult to detect relevant differences that perhaps would have been detected if the interventions would have been more different.

A possible weakness in paper III is that a multitude of items (57) and physiological markers (30) were analyzed, which makes it relevant to discuss the possible problem of mass-significance. To clarify this issue, percentages of significant findings out of the total number of analyses are presented here as well as in the discussion section of paper III. Altogether 87 parametric analyses were conducted in paper III on relevant VAS items and physiological markers. In 11 (13%) of these analyses significant results were obtained and 9 (10%) remained significant when non-parametric tests were used. Considering that the significant findings were grouped in psycho-physiologically meaningful ways, this might indicate that the results were not merely due to chance. However, the possibility of mass-significance still calls for a cautious interpretation of the results.

Ethical considerations

Users of self-help interventions are subjected to some potentially harmful pitfalls that must be addressed. First of all, it is of importance that information is correct and understandable so that misinterpretations are avoided to the greatest extent. If possible, all information and features should be tested, preferably in a pilot study. This was not possible in the present studies for financial reasons. However, information was proofread by several colleagues and friends and changes were made continuously if something needed to be adjusted or corrected.

Furthermore, just by participating in a stress management intervention, a false sense of safety may occur, which can lead to neglect or delay in handling potentially serious problems. On the other hand, in the present studies, both the long-term ill and the healthy population were supervised by trained medical personnel. In fact, in the HealthIT study, where blood samples were collected, some minor and major medical issues were retrieved. In those cases, participants were contacted and advised to visit a physician for a more thorough diagnosis and possibly treatment. In any case, all participants in the HealthIT study could access their blood sampling results online together with an explanation of each biological marker. All participants were urged to contact the researchers by mail or phone, should there be any questions or speculations, or if they wanted an oral explanation and comment. Generally,
however, if study participants or patients are not subject to medical assessments, they should be urged to undergo a thorough medical examination if necessary, when using self-help approaches.

Future implications

Stress management
Since stress is often a multidimensional problem, profound reflection may be needed for the successful implementation of a stress management intervention. Generally, it seems as if multi-component programs that consider different important dimensions, contribute to beneficial and sustained effects. It might also be important to consider that the effectiveness of stress management interventions may depend on the accuracy of the diagnosis, in which ever way it is derived. Stress can be diagnosed and assessed in various ways, including questionnaires, medical examinations, interviews, physiological markers, indirect observation or hard fact statistics such as sick leave [97, 107]. The most effective way of managing stress is to approach it at several levels focusing on individuals as well as organizations and society in general. It is important to focus on proactive prevention, as opposed to reactive prevention. Then focus on education and management strategies is desired. Finally, treatment of individuals already pathogenically affected by long-term stress is needed [106, 107].

Future research should focus more on predictors of stress management intervention effects. That could render more effective and focused interventions and generate important knowledge about moderators and mediators of successful stress management. Furthermore, it is important to elucidate what kind of stress management strategies are most effective and for whom.

Additionally, as most studies focus on the pathogenic aspects of stress [107], there is a need to focus on the salutogenetic factors as well. Effects of promoting a healthy lifestyle, thoughts and behaviour and enhancing coping resources may be important focus of future stress management and health promotion research.

Predictors of self-rated health
A multitude of possible predictors for SRH have been found in previous studies. This thesis confirms some of the previous findings. Future research should preferably focus on finding consistent patterns of predictors and explanations for changes and trends in SRH. An interesting aspect that could render valuable information is to assess predictors of individuals that fluctuate in SRH over time. It would be interesting to know if fluctuation per se in SRH is a salutogenic or pathogenic pattern on a long-term basis.
Conclusions

Stress management interventions
Before any firm conclusions can be drawn, these kinds of stress management intervention studies must be replicated and results confirmed. Preferably these studies should be conducted in similar settings, with comparable populations and mediums of intervention. It is important to conduct long-term post-intervention follow-ups, as these issues concern long-term conditions. The results of this thesis indicate that the stress management interventions utilized may have short-term beneficial effects. However, these effects do not seem to persist at the long-term post-intervention follow-up.

It is therefore important, and would be very interesting, to elucidate what factors, if any, and under which circumstances these kinds of interventions could render long-term beneficial effects. Duration of interventions, increased number of sessions or “booster sessions” and attention to organizational conditions may be significant aspects to consider. Furthermore, it would be interesting to elucidate which, if any, participants or groups benefit more and less respectively from these kinds of interventions.

Predictors of self-rated health
With regard to SRH, the results of this thesis and other studies indicate that SRH and other self-ratings are predictive of future subjective and objective health outcomes. However, the fact that different settings, types of population and methodology and statistical analysis strategies have been used in published studies examining SRH makes it difficult to compare results and therefore to draw reliable conclusions. This thesis cautiously implies that SRH is a major predictor of future SRH. In addition, other self ratings, such as sleep quality and sense of coherence might be predictors of future SRH and therefore possibly also of various future health outcomes.
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