An Epidemiological Study of Exhaustion in the Context of Chronic stress. Concept, Cortisol, Causes and Consequences

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AN EPIDEMIOLOGICAL STUDY OF EXHAUSTION IN THE CONTEXT OF CHRONIC STRESS

Concept, Cortisol, Causes and Consequences

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Abstract

The interest in exhaustion has increased rapidly during the last few decades in many developed countries. In Sweden, prevalence of exhaustion increased by 50 percent on average between 1989 and 2005, and recent data reveals that exhaustion still remains at this higher level. Scientifically, exhaustion is not clearly defined. Chronic stress is acknowledged to give rise to exhaustion, but specific mechanisms involved have generally been overlooked in stress research. The relatively new concept of "hypocortisolism" in this context, referring to low levels of circulating cortisol, and observed in disorders featuring exhaustion, should be of interest. Hypocortisolism has also been suggested to comprise a mechanism for development of stress-related disease that challenges the previous general view of stress pathophysiology. The main objective of this thesis was to evaluate whether exhaustion as concept may be helpful in elucidating stress mechanisms. The four included Papers explored the discriminant validity of exhaustion in relation to depression and anxiety; HPA activity in exhaustion; associations with psychosocial work stressors; and significance for onset of a "stress-related disease", i.e. cardiac disease. Two study populations were used. For Papers I, III, and IV, analyses were performed on data from the Malmö Shoulder and Neck Study (N = 12,607); prospective data on coronary heart disease for Paper IV was obtained through data linkage. For Paper II, a working population sample (N = 78) was analysed. Exhaustion was assessed by means of the (inverted) SF-36 vitality measure. In Paper I, exhaustion emerged separately from depression and anxiety in factor analysis, supporting the conceptual integrity of exhaustion. In Paper II, HPA dysregulation in terms of a flattened diurnal cortisol rhythm (due to lower morning cortisol) was found in exhaustion. In Paper III, relationships with work-related stressors were demonstrated. Finally, in Paper IV, the contribution of exhaustion, independent from depression and anxiety, in development of coronary heart disease was indicated in men. The findings point to a unique and potentially important role of exhaustion in stress theory. It may, however, be important to focus gender in search of relevant concepts and mechanisms for development of stress-related disease. The search for preventive measures should be essential in future research.

Key words: chronic stress, cortisol, depression, exhaustion, gender, HPA activity, psychosocial

To Mattias and Svante, for being in my life,
and to Tanja and Björn, for having made it

”Vägen till klokhet är stenlagd med dumheter”

Marit Paulsen

(“The road to wisdom is paved with stupidities”)

Abbreviations

BMI	Body Mass Index
CFS	Chronic fatigue syndrome
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
DSM	Diagnostic and Statistical Manual of Mental Disorders
GHQ	General Health Questionnaire
HPA	Hypothalamo-Pituitary-Adrenal
ICD-10	International Classification of Diseases, tenth revision
MBI	Maslach Burnout Inventory
MBI-GS	MBI General Survey
MDCS	Malmö Diet and Cancer Study
MSNS	Malmö Shoulder and Neck Study
OR	Odds ratio
PTSD	Posttraumatic stress disorder
S	Synergy index
SF-36	Medical Outcomes Study Short Form questionnaire (36 items)
VE	Vital exhaustion
VED	Vital exhaustion and depression
WHO	World Health Organization

List of publications

This thesis is based on the following publications, which will be referred to by their Roman numerals:

I Lindeberg, SI, Östergren PO, Lindbladh E. Exhaustion is differentiable from depression and anxiety: evidence provided by the SF-36 vitality scale. *Stress: International Journal on the Biology of Stress* 2006; 9(2):117-23.

II Lindeberg SI, Eek F, Lindbladh E, Hansen ÅM, Östergren PO, Karlson B. Exhaustion measured by the SF-36 vitality scale is associated with a flattened diurnal cortisol profile. *Psychoneuroendocrinology* 2008; 33(4):471-7.

III Lindeberg SI, Rosvall M, Choi B, Canivet C, Isacsson SO, Karasek R, Östergren PO. Psychosocial working conditions and exhaustion in a working population sample of Swedish middle-aged men and women. *European Journal of Public Health* 2011; 21(2):190-6.

IV Lindeberg SI, Rosvall M, Östergren PO. Does exhaustion predict coronary heart disease? *Manuscript submitted for publication.*

Contents

Introduction

During the last few decades, the scientific interest in exhaustion has increased rapidly. Exhaustion is, however, not a clearly defined scientific concept, and several different but apparently overlapping constructs featuring exhaustion co-exist in the scientific literature, as well as in the diagnostic classification systems. Furthermore, chronic stress is acknowledged to give rise to exhaustion, but specific mechanisms involved have generally not been defined in stress research. The main focus of this thesis was to delineate exhaustion as it appears in normal populations, and explore its significance for the onset of a "stress-related disease" (cardiac disease).

Definition of exhaustion

In the Oxford English dictionary (9th edition, 1995), exhaustion has been defined as "1. the act or an instance of draining a thing of a resource or emptying it of contents; the state of being depleted or emptied. 2. a total loss of strength or vitality". In the scientific literature exhaustion is generally used interchangeably with fatigue, and they will here be considered as synonyms. Fatigue has been described as a poorly defined feeling, referring to a subjective symptom of malaise and aversion to activity, or to objectively impaired performance (Sharpe and Wilks 2002). Fatigue and exhaustion have, however, been used in somewhat different contexts, fatigue being the preferred term in medical literature, whereas exhaustion seems to be more commonly used in the psychological literature. This would relate to that fatigue is often used in terms of a symptom, whereas exhaustion more denotes a state of its own (paralleling the medical term "idiopathic (unexplained) fatigue"). A PubMed search (March 2011) illustrates the predominance of fatigue over exhaustion in medical literature; the former had 53,491 hits, and the latter 10,745. There is another semantic difference between exhaustion and fatigue, in terms of severity, in that exhaustion can be conceived of as more severe than fatigue. Olson (2007) suggested that tiredness-fatigue-exhaustion should be considered as three distinct states, exhaustion being the most severe one, along an adaptation continuum, indicating different degrees of adaptation to stressors. In this thesis, however, no such conceptual separation between exhaustion and fatigue is made. Exhaustion will here be explored in a psychosocial and biological

stress context. The choice of the term “exhaustion” (and not fatigue) as the principal terminology used to describe the phenomenon under study for this thesis, was motivated by the theoretical overlap with some, primarily psychological, constructs of “exhaustion”, such as burnout and vital exhaustion, and also guided by a wish to facilitate interdisciplinary dialogue.

Epidemiology of exhaustion

Most general population studies of exhaustion or fatigue have used single-item questions, and prevalence varies with definition and measurement used. Prevalence rates varied from 7 to 45 percent in a number of community-based studies (Lewis and Wessely 1992). Fatigue is one of the commonest presenting symptoms in primary care, estimated to constitute the main complaint in 5-10 percent of patients (Sharpe and Wilks 2002). Exhaustion is often found to be about two to four times more prevalent in women than in men, whereas most studies have not revealed any consistent variation with age, except that fatigue is uncommon before adolescence (Lewis and Wessely 1992; Sharpe and Wilks 2002; Evengård et al 2005; Ranjith 2005). Exhaustion has been associated with lower socio-economic groups (Ranjith 2005), but in one study this was apparent mainly in men (Loge et al 1998).

Swedish national surveys give a perhaps unique possibility to explore trends in experience of exhaustion over time. Between 1980 and 1989, the prevalence of exhaustion, as denoted by having difficulties getting going in the morning and at the same time being strikingly tired during the days as well as the evenings (measured by three questions), during the past two weeks, did not change, with a prevalence of around 4 percent in men and 8 percent in women. However, by 2005, prevalence had gradually increased by around 50 percent on average. In men, exhaustion increased only in those younger than 55 years old, and in women in those younger than 75. Older men (55-84 years) and women (75-84 years) had become less fatigued during this time period. Prevalence of exhaustion increased gradually with younger age, and in 16-24 year old young men, the prevalence tripled between 1989 and 2005, whereas it doubled in women in this age-group (Table 1). Considering these striking increases, which only appeared in younger individuals, it should be clear that exhaustion is not particularly related to aging and disease. New data on prevalence of exhaustion from the years 2008 and 2009 (not previously published) show that the prevalence is still high; in women, the average prevalence seems to be unchanged since 2005, and in men it may even have increased, appearing in all age-groups except for the youngest (Table 1).

Table 1. Prevalence of exhaustion[1] in Swedish men and women in 1980-81, 1988-89, 1996-97, 2004-05, and 2008-09[2]

	Men					Women				
	80-81	88-89	96-97	04-05	08-09[2]	80-81	88-89	96-97	04-05	08-09[2]
Age										
16-24	3.0	3.0	5.4	8.6	5.8	7.6	7.5	10.2	15.3	12.3
25-34	4.1	3.9	7.7	8.4	9.9	10.3	9.0	14.6	17.0	15.2
35-44	3.8	4.2	5.1	6.7	9.0	7.6	8.1	11.6	14.4	14.5
45-54	4.5	4.1	4.5	6.1	8.4	10.3	8.4	10.9	12.0	15.4
55-64	4.6	4.2	3.2	4.5	5.2	7.7	7.3	7.7	11.0	11.5
65-74	3.8	3.1	3.6	2.4	5.0	6.6	4.5	7.9	8.6	6.7
75-84	7.0	5.3	5.1	4.4	6.3	11.4	7.8	8.9	9.0	10.0
All aged 16-84	**4.2**	**3.9**	**5.0**	**6.2**	**7.2**	**8.7**	**7.7**	**10.5**	**12.8**	**12.6**

[1]Difficulties getting going in the morning and strikingly tired during the days as well as evenings during the past two weeks. [2]These years telephone interviews replaced interviews at personal visits, which may have affected the results. Source: Statistics Sweden, *Health and Medical care 1980–2005;* and Statistics Sweden, Living Conditions Survey, year 2008-2009.

Medical and psychological constructs featuring exhaustion

Neurasthenia

Neurasthenia was probably the first clinical term for a condition of exhaustion, and the history of neurasthenia should be of interest. The first two scientific publications on neurasthenia, also referred to as nervous exhaustion or nervous prostration, respectively, were published in America in 1869, one by a neurologist, Beard, and the other by a psychiatrist, Van Deusen. Wessely et al (1998) described that during the 19th century, neurasthenia rapidly "spread" from America to Europe, especially to France and Germany. By 1900, a French doctor wrote that "the name of neurasthenia was on everybody's lips, the fashionable disease". The primary symptom of neurasthenia was chronic fatigue, or, as it was put at that

time, the “cardinal characteristic being an inordinate sense of physical or mental fatigue”. The most common manifestation was either a “neuromuscular weakness” or an “unusually rapid exhaustion” which “mainly affects the mental activities; the power of attention becomes quickly exhausted and the capacity for perception is paralysed”. Be it mental or physical, the fatigue “comes early, is extreme and lasts long” (all citations from Wessely et al 1998). Beard, who initially had the most influence on the understanding of neurasthenia, regarded it as a physical disease, and the term “nervous exhaustion” actually alluded to a notion of depletion of energy in the central nervous system (Bankier et al 2001). A failure of cerebral blood supply was also a popular explanation. The increased demands on the system could result from overwork, or be the result of toxic, metabolic, or infective insults. The doctrine of overwork linked neurasthenia with a variety of changes in society. Medical authorities viewed overwork as the agent by which the nervous system became exhausted (which could be purely physical, mental, or a mixture of both). Initially, neurasthenia had been sustained by the belief that it was a condition of the most successful people in society. But by 1900, awareness increased that not only were women and the lower classes susceptible to the condition, they were becoming the majority of cases. The difficulties to measure fatigue and the lack of discrete neuropathological lesions challenged the organic view of neurasthenia, and neurasthenia became regarded as more likely to result from idleness than overwork, reflected in the increased emphasis on activity and exercise, instead of the classic rest cure. The concept of neurasthenia was kept at first, but viewed as a psychological, rather than a physical, illness. Leading psychiatrists like Freud, Bernheim, and others continued to believe in a physical neurasthenia, characterised by that it was not amenable to psychotherapy, but they thought it was rare. Later, neurasthenia was replaced by the new psychiatric diagnoses, mainly by the new concept of depression. Neurasthenia was considered “perhaps minor, attenuated, atypical, masked, but always forms of anxious melancholia” (Wessely et al 1998). The neurasthenia concept thus gradually disappeared, and formal interest had disappeared by 1960 in the US and UK, leading to the diagnosis being dropped out from the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in 1980. The concept was still in use, however, in countries such as China, Japan, the Netherlands, Germany, Eastern Europe, and the former Soviet Union (Wessely et al 1998; Bankier et al 2001), and the diagnosis is still provided as a psychiatric diagnosis in WHO’s International Classification of Diseases (ICD-10; diagnosis code F48.0, also Fatigue syndrome). Wessely et al (1998) pointed out the striking similarities between neurasthenia and more recent medical constructs such as chronic fatigue syndrome, claiming that the latter should not be considered as a new disease.

Chronic fatigue syndrome, fibromyalgia and posttraumatic stress disorder

Although clinically defined as separate disorders, the substantial overlap between chronic fatigue syndrome and fibromyalgia is well recognised (Wessely et al 1999; Clauw 2009; Kato et al 2009; Gottfries et al 2009). These disorders also share features with posttraumatic stress disorder, in terms of symptoms and co-morbidity, as well as derangements in physiological parameters (Heim et al 2000; Fries et al 2005). The pathogenesis of chronic fatigue syndrome and fibromyalgia remains largely unknown, and these disorders are, together with other frequently co-morbid disorders, such as irritable colon syndrome and tension headache, commonly referred to as "functional somatic syndromes" (Wessely et al 1999; Kato et al 2009; Tak and Rosmalen 2010).

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) was defined as a clinical disease in 1988 by the US Centers for Disease Control and Prevention, after that a sudden interest among clinicians and the public emerged in the mid 1980's (Holmes et al 1988). Diagnostic criteria for CFS were revised in 1994; CFS is defined by persistent or relapsing fatigue lasting 6 or more months, in combination with a number of symptoms featuring self-reported impairments in concentration and short-term memory, sleep disturbances, headaches, sore throat, tender lymph nodes, musculoskeletal pain, and post-exertion malaise, which cannot be explained by another medical or psychiatric cause, although presence of psychiatric disorders is not an exclusion criterion (Fakuda et al 1994). The fatigue, which often is of acute onset, following a viral infection or psychological stress, has a poor spontaneous recovery at 18 months, and its prevalence has been estimated to be around 0.5 percent in primary care (Parker et al 2001). Prevalence may be even higher in the general population (two percent or more), and around four times as common in women compared with men (Evengård et al 2005). Discussion of its nature and causes has been heated; many psychistrists have emphasized its association with psychiatric disorders, whereas sufferers have maintained that their fatigue has a physical cause (Lewis and Wessely 1992; Parker et al 2001). Several viruses, of which Epstein-Barr Virus was the first, have been thought to be associated with the development of chronic fatigue syndrome, but none has been confirmed as etiologic factor. Recently, a report that a retrovirus (xenotropic murine leukaemia virus-related virus; XMRV) was associated with CFS (Lombardi et al 2009) received great interest, but it has been pointed out that subsequent studies did not confirm this association (Menéndez-Arias 2011). The diagnostic code for CFS renders some confusion; although chronic fatigue syndrome is the consensus term in the scientific literature, to be preferred before other existing terms, of which

myalgic encephalomyelitis (ME) is most common, CFS is not included in the ICD-10 (or in the DSM). Instead, CFS is diagnosed as Postviral fatigue syndrome (ICD-10 diagnostic code G93.3, also Benign myalgic encephalomyelitis; Gottfries et al 2009), classified under neurological disorders (but CFS has mainly been treated within the clinical context of infectious disease care). This diagnosis is more commonly used in countries such as the US and UK, than in for example Sweden (Lundin 2009).

Fibromyalgia

Fibromyalgia is a condition marked by chronic widespread pain, and multiple symptoms and co-morbidities including fatigue, sleep disturbances, morning stiffness, subjective swelling, paresthesias, numbness, cognitive dysfunction, depressive episodes and anxiety (Wolfe 1986; Clauw 2009; Riva et al 2010). Formal criteria for fibromyalgia were established in 1990 by the American College of Rheumatology (Wolfe et al 1990), consisting of history of widespread pain, combined with pain present in at least 11 of 18 tender point sites on digital palpation. At least two to four percent of the adult population may be affected by this disease, and the incidence peaks between age 30 and 50 years; the female-to-male ratio has been estimated to 5-9:1 (Wolfe 1986; Riva et al 2010), but may be lower (3-4:1) in the general population (Kato et al 2009). Fibromyalgia is included as a diagnosis in the ICD-10 under rheumatological disorders and "other soft tissue disorders, not elsewhere classified" (M 79.7).

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) has over the years been labelled "combat exhaustion" or "combat fatigue", "stress syndrome", and "traumatic war neurosis", amongst many other descriptive labels. PTSD, formally defined in the early 1980's, is classified as a psychiatric disorder (ICD-10 diagnosis code F43.1, under "Reaction to severe stress, and adjustment disorders"). In contrast to CFS and fibromyalgia, as well as most other psychiatric disorders, the etiology of PTSD has been defined. PTSD is characterized by a pattern of symptoms arising in the aftermath of a trauma or stressful event (of either brief or long duration), which cause significant functional impairment and distress to the individual. The onset of disease follows the trauma with a latency period that may range from a few weeks to months, or even years (Vitzthum et al 2009). Typical features include episodes of repeated reliving of the trauma in intrusive memories ("flashbacks"), dreams or nightmares, occurring against a persistent background of a sense of emotional blunting, detachment from other people, unresponsiveness to surroundings, anhedonia, and avoidance of activities and situations reminiscent of the trauma.

PTSD is associated with high rates of comorbidity, presented by a spectrum of common clinical features such as sleep disturbance, depression, anxiety, irritability, difficulty in concentrating, fatigue, suicidality, chronic pain, and hyperarousal. It is estimated to affect 8-9 percent of individuals in the population at some point in their lives, and more than one-third of cases continue to meet diagnostic criteria after many years (ICD-10; Vitzthum et al 2009; Cukor et al 2010; Kaplan et al 2010).

Burnout

Burnout is mainly viewed as a stress and crisis concept, and has been of major interest to occupational and social psychologists (Hallsten et al 2005). It is generally agreed that the core feature of burnout is exhaustion, and "burnout" and "exhaustion" are often used interchangeably in the burnout literature. The most frequently used construct of burnout is the one developed by the American social psychologist Christina Maslach. Her initial conceptualisation of burnout during the 1970's had its roots in caregiving and service occupations, in which the relationship between provider and recipient was regarded as a core feature. Feelings of "emotional exhaustion" were seen as the key aspect of burnout, described as depletion of emotional resources leading to that "workers feel they are no longer able to give of themselves at a psychological level" (Maslach et al 1996; Maslach et al 2001). The Maslach Burnout Inventory (MBI) was constructed in the 1980's, leading to a shift in burnout research from being descriptive in nature, to a more systematic quantitative research. Factor analytic study of the MBI led to that burnout was defined as a three-dimensional syndrome, consisting of *emotional exhaustion*, *depersonalization* (negative or cynical attitudes or feelings about one's clients), and *reduced personal accomplishment*. The field of industrial-organisational psychology also took interest in burnout, viewing it as an individual stress response, "job stress". The view that burnout was unique to human service professionals shifted after reports that it was prevalent also in other types of occupations. Therefore, in the 1990's the MBI – General Survey (MBI-GS; Maslach et al 1996), to be used in all occupations, was constructed. According to Maslach and co-workers, the three components yielded by the MBI-GS burnout construct, now labelled *exhaustion*, *cynicism*, and *reduced personal efficacy*, are conceptualised in slightly broader terms compared with the initial three-dimensional definition, in that they are conceptualised with respect to the job, and not just to the personal relationships that may be a part of that job. The exhaustion component still represents the basic individual stress dimension of burnout, now referring to feelings of being overextended and depleted of one's emotional and physical resources, and is the most widely reported and most thoroughly analysed dimension of the MBI burnout construct (Maslach et al

2001). Some burnout researchers, of which the Israelian organisational psychologist Arie Shirom has been most prominent, have questioned Maslach's second and third components (cynicism and personal inefficacy) as parts of the burnout definition, arguing that (work) exhaustion is the core meaning of burnout. The two other MBI components would instead reside in different conceptual domains, cynicism constituting a specific coping style following exhaustion, and reduced personal efficacy overlapping the concept of self-esteem (Kristensen et al 2005; Shirom and Melamed 2006; Melamed et al 2006).

An early alternative conceptual approach to burnout was developed by the Israelian and American, respectively, psychologists Ayala Pines and Elliott Aronson, viewing it as "a state of physical, emotional and mental exhaustion caused by long term involvement in situations that are emotionally demanding", and an end result of a gradual process of disillusionment (Pines and Aronson 1981; Pines 1993). Thus, Pines and Aronson did not consider burnout as a specifically work-related condition, but regarded work as one possible cause of burnout. Or, put in another way, when people try to find meaning in their life through work and feel that they have failed, the result is burnout (Pines 1993). Pines too constructed a burnout measure, which has been criticised to gauge depression and anxiety besides exhaustion (Melamed et al 2006). The Swedish psychologist Hallsten agrees with the notion of burnout as arising in different contexts, such as work, family, education, or job search, as long as the context is important for a person's self-esteem or self-worth (Hallsten et al 2005).

Burnout was thus not originally considered as a clinical entity, and has mainly been assessed in working populations. In ICD-10, burnout (or State of vital exhaustion, Z73.0) is classified under "Factors influencing health status and contact with health services", which do not refer to clinical diagnoses. However, "clinical burnout" is occasionally addressed in the scientific literature. In Sweden, from the late 1990's and onwards, burnout or exhaustion became a concern for the health care system, and was considered to be a major cause of the rapidly increasing numbers of individuals on sickness absence. In Sweden, therefore, and as only country, "exhaustion syndrome" was added to ICD-10 as a psychiatric disorder (F43.8, "other reactions to severe stress") in 2008, by The Swedish National Board of Health and Welfare. Diagnostic criteria (defined in 2003) include physical and mental symptoms of exhaustion during two weeks or more, following one or more identifiable stress factors that have lasted for at least six months; substantial lack of mental energy in the form of reduced initiative, reduced endurance, or an extended time for recovery after mental stress; at least four of the following symptoms, i.e. concentration or memory difficulties, reduced ability to handle demands or to work under time pressure, emotional instability or irritability, disturbed sleep, physical weariness or fatigability, physical symptoms such as pain, chest pain, palpitations, stomach complaints, dizziness, or sound

hypersensitivity; and symptoms should cause significant suffering or declined function at work, socially, or in other important respects (The Swedish National Board of Health and Welfare 2003). It has been acknowledged that this syndrome is difficult to distinguish from chronic fatigue syndrome (Gottfries et al 2009).

Vital exhaustion

The Dutch psychologist Ad Appels has studied what was initially called a syndrome of vital exhaustion and depression (VED; Appels 1980; Falger and Appels 1982; Appels and Mulder 1984), later only vital exhaustion (VE; Appels et al 1987; Appels et al 1993), as a risk-factor for coronary heart disease. This research was based on that cardiologist had noticed that in the months prior to a cardiac event, many patients had visited a physician, and that "undue fatigue or lack of energy" was the most common symptom (Appels 1997). In order to measure this state, the Maastricht Questionnaire was developed (Appels et al 1987). Vital exhaustion has been described as feelings of excess fatigue, hopelessness, listlessness, loss of vitality, loss of libido, increased irritability, and problems with sleep, reflecting a state of mental and physical exhaustion (Appels and Mulder 1988). Appels and co-workers were aware of that most clinicians interpreted these feelings as a side effect of manifest or subclinical heart disease, but Appels (1980) proposed a dynamic model, in which chronic self-induced stress arises when "a basically insecure person tries to get as much appreciation or narcissistic supply from his environment as possible by striving very hard", leading to overburdening and exhaustion, especially when coping with problems and conflicts he cannot bring under control. Other descriptions of the process leading to vital exhaustion (and depression) have been learned helplessness (Falger and Appels 1982), and a conservation-withdrawal response following prolonged exposure to stress (Appels 1997). Appels and co-workers have claimed that a state of vital exhaustion is not equal to depression, arguing that guilt and low self-esteem are missing, and that fatigue and loss of vitality constitute dominant features (Appels 1990; van Diest and Appels 1991; Kopp et al 1998). But the construct is frequently separated into components of depression and fatigue (Appels et al 2000b; Williams et al 2010), and other researchers describe it as "a measure of fatigue and depression" (Prescott et al 2003; Bergelt et al 2005; Kornerup et al 2010).

Stress theory

The stress concept can be formalised with two ideas. The first is that the body has a surprisingly similar set of physiological responses (summarised as the stress response) to a broad array of stressors (a "stressor" is anything that can elicit the

stress response), and the second is that chronic stress can influence development of disease (Sapolsky 2004, p. 8). The stress response can be mobilised not only in response to actual physical or psychological events, but also in anticipation of them. This latter type of stress, often referred to as "psychosocial", is thought to be most important in today's society as the main source of chronic stress.

The stress concept has its roots in the works of mainly two scientists, namely the physiologist Walter B Cannon (1871-1945), and the endocrinologist Hans Selye (1907-1982). Cannon described the notion of homeostasis (physiological steady-state, or bodily internal balance). He was the first to recognise the role of adrenaline, noradrenaline, and the sympathetic nervous system. He also formulated the well-known "fight-or-flight" response, stating that animals, including humans, react to threats with a general discharge of the sympathetic nervous system, priming the animal for fighting or fleeing. He regarded this response to be a purely beneficial mechanism by which the body could adapt to challenge (Sapolsky 2004, p. 12). Selye was the pioneer in the discovery of glucocorticoids (cortisol in humans, but Selye's research was mainly conducted on animals), and their functions during stress. He also put much effort into delineating and popularising the stress concept. His main message during his life-long research career in this field was that stress, when continuing for a longer time, participated in the development of disease. He called this process the General Adaptation Syndrome (GAS), or, later, the stress syndrome. According to Selye, "stress" is reflected by the sum of non-specific (i.e. non-specifically induced) changes of the body in response to demand that occur at any one time, whereas the stress syndrome encompasses all non-specific changes as they develop throughout time during continued exposure to stressors. This syndrome was described as including three stages: the initial "alarm" stage (or phase), which would be equivalent to Cannon's fight-or-flight response; the second "adaptation" or "resistance" phase, defined as the successful mobilisation of the stress response system and the reattainment of homeostatic balance; and the third and final stage of "exhaustion" (Selye 1978; see also p. 32).

A decade ago, Taylor and co-workers proposed that the "fight-or-flight" response is mainly a male stress response, and that "tend-and-befriend" better describes what the female stress response is about, although the same physiological stress response described for "fight-or-flight" would appear initially also in women. Tend and befriend refers to a propensity to show protective responses toward offspring, and affiliate with others, in response to threat. The underlying bio-behavioural mechanism of tend-and-befriend would draw on the attachment-caregiving system, with oxytocin, estrogen, and endogenous opioid peptide mechanisms at its core (Taylor et al 2000). Differences in stress management styles between the genders, women being more prone to seek social support, are considered supportive of the tend-and-befriend view, and although this view may

seem to challenge classic stress theory, there is acceptance of the idea that the body does not respond to stress merely by preparing for aggression or escape, and that important gender differences in the physiology and psychology of stress exist (Sapolsky 2004, p. 33).

The stress response

According to (classic) stress theory, the core of the stress response is built around preparing the muscles for heavy activity ("fighting or fleeing"), and therefore one of the main purposes of the stress response would be the rapid mobilisation of energy (glucose and simple forms of proteins and fats) from storage sites, and the inhibition of further storage. The stress response is also described as what the body does to re-establish homeostasis after that a stressor has put you out of homeostatic balance (Sapolsky 2004). The sympathetic nervous system is a first means by which the brain mobilises activity in response to a stressor. The sympathetic nervous system originates in the brain, with nerves projecting out via the spine and throughout the body. The chemical messengers adrenaline - secreted from the adrenal medulla - and noradrenaline - secreted by all other nerve endings - activate various organs, particularly the cardiovascular system. Another important way to mobilise activity is through the secretion of glucocorticoids by activating the hypothalamo-pituitary-adrenal (HPA) system (Figure 1). The hypothalamus in the brain secretes an array of releasing hormones into the hypothalamic-pituitary circulatory system in response to a stressful stimulus, the main such releaser being CRH (corticotropin releasing hormone). CRH triggers the pituitary to release ACTH (corticotropin), which in turn triggers glucocorticoid release by the cortex of the adrenal glands. Whereas adrenaline acts within seconds, glucocorticoids back its activity up over the course of minutes or hours (by for example activating brainstem neurons that stimulate sympathetic arousal, as well as enhancing the effects of adrenaline and noradrenaline on the heart). The secretions of the HPA system and the sympathetic nervous system account for the main part of the activity in the body during the stress response. Other hormones that are released during stress are glucagon from the pancreas, which together with glucocorticoids and the sympathetic nervous system raise circulating levels of glucose; prolactin from the pituitary, which for example suppresses reproduction during stress; endorphins and enkephalins from the pituitary and the brain, which help blunt pain perception; and vasopressin (antidiuretic hormone) from the pituitary, which together with other related hormones block diuresis to counteract potential loss of blood volume (through dehydration or hemorrhage). Heart rate, blood pressure, and breathing rate increase so that nutrients and oxygen can be transported to the critical muscles as rapidly as possible, and digestion, growth, tissue repair, and reproduction are inhibited through the inhibition of hormones such as insulin,

growth hormone, estrogen, progesterone, and testosterone in order to optimise the energy use (Sapolsky 2004).

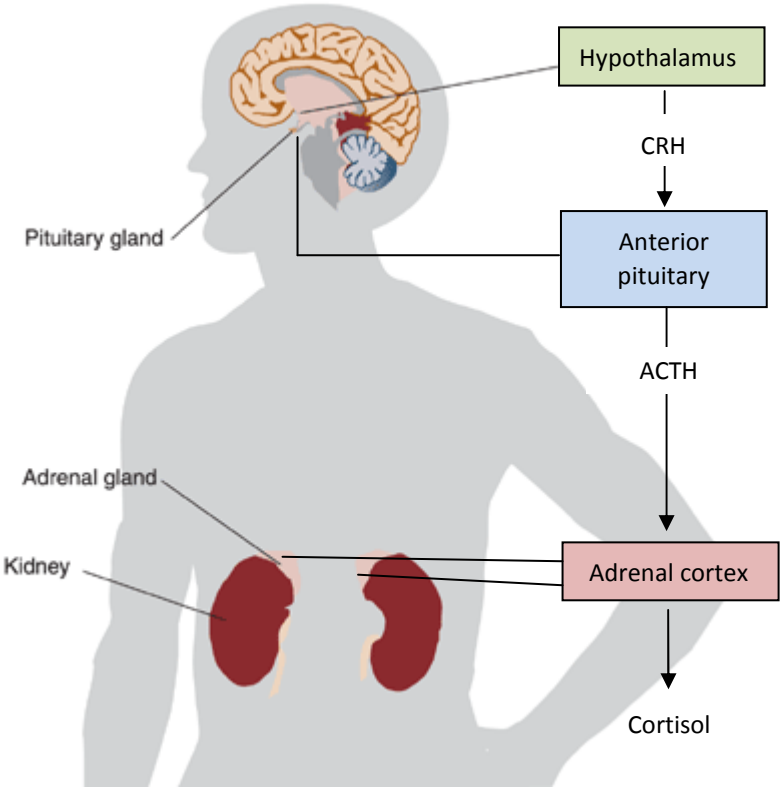

Figure 1. The Hypothalamo-Pituitary-Adrenal (HPA) system. Source of figure (here modified): National Institute on Alcohol Abuse and Alcoholism (NIAAA).

Hypocortisolism

Whereas it is well established that stress can cause excess levels of glucocorticoids in the body, there is less consensus on how low glucocorticoid levels, or "hypocortisolism", fits into the picture. Hypocortisolism has predominantly been observed in disorders - reported in about 20-25 percent of the patients - that feature fatigue or chronic pain, often in combination, such as chronic fatigue syndrome, fibromyalgia, posttraumatic stress disorder, and atypical depression

(Heim et al 2000; Fries et al 2005; Riva et al 2010). However, hypocortisolism, with cortisol concentrations decreasing further during periods of heightened stress, has also been noted in medically healthy people living in conditions of chronic stress, and in women with a history of early life stress in terms of childhood abuse (Heim et al 2000; Zarkovic et al., 2003; Raison and Miller 2003). Hypocortisolism is thought of as hyporesponsiveness, or hypoactivity, on different levels of the HPA axis, and has mainly been indicated by lower basal urinary, plasma or salivary cortisol concentrations. However, the low-dose dexamethasone suppression test (DST; acting on the pituitary level) has been suggested to be the most sensitive measure of hypocortisolism (Fries et al 2005). In the DST, a low dose of a synthetic cortisol analogue (dexamethasone) causes suppression of cortisol levels in normal healthy individuals, whereas an even stronger suppression of cortisol ("super-suppression") has been found in hypocortisolaemic individuals. This is thought to reflect an enhanced feedback sensitivity of the HPA axis. The etiology of hypocortisolism is not clear, but it has been suggested that hypocortisolism develops after prolonged periods of stress-induced HPA hyperactivity axis and excessive glucocorticoid release (Fries et al 2005).

The close relationship between hypocortisolism and fatigue is known from Addison's disease, which is a primary defiency in the production of cortisol (most commonly due to autoimmune destruction of the adrenal cortex). Profound fatigue is a principal symptom of this disease.

Disturbed diurnal cortisol rhythm

Besides absolute levels of cortisol in terms of "higher" or "lower", another studied feature of stress and cortisol pattern is the diurnal cortisol variability, or the level of disruption of the normal diurnal (circadian) cortisol rhythm. The normal diurnal rhythm of cortisol release is that cortisol levels are the lowest at night, and that levels markedly rise and peak in the morning around awakening, with subsequent gradual decline in cortisol levels throughout the day. More evenly distributed cortisol levels during the day, as compared with the normal rhythm, are referred to as a flattened diurnal cortisol profile, or low cortisol variability. A decade ago, Sephton et al (2000) demonstrated that the lack of a normal diurnal cortisol rhythm (but not absolute levels of cortisol), was associated with shorter survival time in metastatic breast cancer. It has been suggested that circadian rhythm may be an indicator of the regulatory competence of stress response mechanisms (Sephton and Spiegel 2003). The implications of a disturbed diurnal cortisol rhythm are, however, not clear, in terms of whether it is an effect of HPA axis dysfunction, and what mechanisms then may be involved, or rather reflects disturbance of other hormonal systems (Sapolsky 2004, p. 177; Kumari et al 2011).

From stress to disease

Sapolsky (2004) stated that if the stress response is repeatedly turned on, or if the stress response cannot be turned off, leading to too much sympathetic nervous system arousal and too much secretion of cortisol, the stress response can eventually become damaging, increasing the risk of getting a disease, or, more specifically, increasing the risk that the bodily defences are overwhelmed by the disease. Examples of diseases that are recognised as being promoted by stress are cardiovascular disease, obesity, diabetes (particularly type 2), functional gastrointestinal disorders, ulcers, depression, musculoskeletal pain disorders, osteoporosis, and possibly cancer. Specific stress pathophysiological mechanisms differ between the diseases. The leading pathological mechanism of cardiovascular disease is atherosclerosis, which includes thickening of walls in the arteries (atherosclerotic plaques) as a result of a build-up of fatty materials such as cholesterol, and an inflammatory response in the artery walls. Chronic stress can enhance atherosclerotic plaque formation by increasing the blood-pressure and thereby increasing the odds of blood vessels being damaged and inflamed. The mobilisation of energy into the bloodstream increases the likelihood that circulating fat and cholesterol stick to the inflamed injury sites. Furthermore, the sympathetic nervous system makes the blood more viscous, and platelets more likely to clump together and adhere to atherosclerotic plaques (Sapolsky 2004, p. 43).

One frequently discussed potential route through which stress may promote disease, is by influencing the immune system. Glucocorticoids are wellknown to suppress the immune system, by for example stopping formation of new lymphocytes in the thymus. They also inhibit the release of protein messengers like interleukins and interferons (cytokines), making circulating lymphocytes less responsive to an infectious alarm, and they cause lymphocytes to leave the circulation for storage in immune tissues, or even destroy them. Most of the glucocorticoid effects are against T cells, rather than B cells, meaning that cell-mediated immunity, including cytokine release, is more disrupted than antibody-mediated immunity. During the first few, up to thirty, minutes after the onset of a stressor, many aspects of immunity, in particular innate immunity and inflammation, are enhanced. After one hour, immune function is back to baseline, and it is only with major stressors of longer duration, or with really major exposure to glucocortiocids, that the immune system does not just return to baseline, but decreases into a range that qualifies as immunosuppressing (40 to 70 percent below baseline). Although evidence may suggest that stress-induced immuno-suppression increases the risk and severity of some diseases, such as the common cold, AIDS, and colon cancer (but no overall suggestion that stress increases the risk of cancer in humans is made), the connection may be relatively weak and its importance exaggerated (Sapolsky 2004, p. 145).

Raison and Miller (2003) have argued against the generally agreed upon predominant role of excess levels of cortisol in disease development. Their principal message was that insufficient glucocorticoid signalling – in simple terms due to either of two major pathways, i.e. low availability of cortisol (hypocortisolism) or reduced glucocorticoid receptor sensitivity – may be central in the process between stress and disease. The latter pathway would be predominant in states characterised by HPA hyperactivity, such as major depression, indicating that a dichotomy between "hypo-" and "hyper"-cortisolism may, under some circumstances, not be crucial in understanding disease-promoting mechanisms in relation to the HPA system. Insufficient glucocorticoid signalling is suggested to be critical in affecting the immune system, prinicipally in terms of unrestraining inflammation, but also to enhance sympathetic nervous system responses, and CRH secretion, the latter with subsequent alterations in activity, appetite, and sleep. Examples of pathologies that may be influenced by these mechanisms are posttraumatic stress disorder, major depression, chronic fatigue syndrome and fibromyalgia (with proinflammatory cytokines and "sickness behaviour" as common denominator), insulin resistance and diabetes, osteoporosis, and cardiovascular disease (Raison and Miller 2003). This view may also contribute to explain one of the "persistent paradoxes" in stress research (Sapolsky 2004, p. 158), i. e. that autoimmune disease is worsened by stress, and observations that repeated stressors enhance immune activation.

However, there is no consensus on a disease-promoting role of hypocortisolism. Instead, a potential beneficial effect of hypocortisolism was suggested by Fries et al (2005). Hypocortisolism would then constitute a protective response, dampening the damaging effects of cortisol in response to daily hassles, at the expense of negative symptoms such as stress sensitivity, pain, and fatigue.

Depression and anxiety

Depression and anxiety are often conceived of as internal psychological responses to chronic stress (Lepore 1995), or as stress-related conditions (Bunker et al 2003). Psychologically, both depression and anxiety are believed to involve cognitive distortions, but a discrepancy between the disorders can be said to be that in the face of stressful challenges, depressed are more likely to underestimate their ability to deal with the challenge and give up ("learned helplessness"), whereas an anxiety-prone person is still attempting to mobilise coping responses (Sapolsky 2004, p. 300-4; p. 319). The link between stress and clinical depression is well acknowledged. The first few depressive episodes experienced by an individual may typically be reactive to a major stressor, but from about the fourth depressive episode, the stress-depression link seems to be weaker, and depression is more likely to appear regardless of experience of stressors (Sapolsky 2004, p. 292). The

link may also go in the other direction; people who are prone to depression tend to experience stressors at a higher rate, for example by interpreting social interactions as signs of rejection (Sapolsky 2004, p. 291). Depression and anxiety constitute separate diagnostic entities, but are frequently co-morbid and highly correlated in both unselected and clinical samples (Beuke et al 2003).

Depressive episodes

In ICD-10, depression (depressive episode, F32) is, depending upon the number and severity of symptoms, specified as mild (F32.0), moderate (F32.1), severe without psychotic symptoms (F32.2, major depression), or severe with psychotic symptoms (F32.3). A fifth category is referred to as other depressive episodes (F32.8), including atypical depression and "masked" depression. ICD-10 describes depressive episodes as a lowering of mood, reduction of energy, and decrease in activity, in which capacity for enjoyment, interest, and concentration is reduced. Marked tiredness after even minimum effort is common, and sleep is usually disturbed and appetite diminished. Self-esteem and self-confidence are almost always reduced, and, even in the mild form, some ideas of guilt or worthlessness are often present. The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" ("vegetative") symptoms (most pronounced in severe depression), such as early morning awakening, depression being worst in the morning, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. In severe depression, suicidal thoughts and acts are common (ICD-10).

Atypical depression

The term atypical depression, which was introduced in the early 1960's, has been used variously to denote depression with the following characteristics: non-endogenous depression, anxiety state, reversed vegetative symptoms, chronic pain, bipolar features, and interpersonal rejection sensitivity (Davidson 2007). Consistency across or within types has not been impressive, why the characteristics distinguishing atypical depression from other depressive subtypes still are ambiguous (Davidson 2007; Pae et al 2009). Reversed vegetative symptoms refer to a reversal of the "typical" vegetative symptoms seen in depression, including increased (instead of decreased) appetite, weight, and sleep. These symptoms are, together with mood reactivity (mood improvement in response to positive events), leaden paralysis (arms or legs feeling heavy), and rejection sensitivity, included as diagnostic criteria in the DSM; Davidson 2007). One feature of atypical depression has been described as profound inertia and fatigue (Gold and Chrousos 1999), or as domination of the "psychomotor" features

of the depressive disorder, in terms of an “incapacitating physical and psychological exhaustion” (Sapolsky 2004, p. 294). Other reported discrepant features against major (“typical”) depression are responsiveness to other types of antidepressants (Davidson 2007; Pae et al 2009), physiological hypocortisolism (indicated by low CRH levels and DST super-suppression) instead of hypercortisolism (Gold and Chrousos 1999; Davidson 2007), reversed diurnal variation (i.e. feeling worse as the day progresses), as well as having more of trouble falling asleep at night, and not waking up early in the morning (Pae et al 2009). Up to 40 percent of patients with clinical depression may have atypical depression, and this subtype has been reported to be more common among younger, as well as female, depressed patients (Davidson 2007; Pae et al 2009).

Anxiety disorders

In anxiety disorders, the dominant symptoms include sudden onset of palpitations, chest pain, choking sensations, dizziness, and feelings of unreality (depersonalization or derealization). In ICD-10, anxiety disorders are categorised as phobic anxiety disorders (F40), in which anxiety is evoked predominantly in certain well-defined situations, and other anxiety disorders (F41), which include panic disorder, generalised anxiety disorder, and mixed anxiety and depressive disorder. Panic disorder includes recurrent attacks of severe anxiety, and a secondary fear of dying, losing control, or going mad is often present; generalised anxiety disorder includes generalised and persistent ("free-floating") anxiety, as well as complaints of persistent nervousness, trembling, muscular tensions, sweating, lightheadedness, and epigastric discomfort, and fears that the patient or a relative will shortly become ill or have an accident are often expressed; mixed anxiety and depressive disorder is referred to when symptoms of anxiety and depression are both present, but neither is clearly predominant (ICD-10).

Chronic stress and cardiac disease

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in both men and women in the industrialised world, and is frequently studied as outcome in stress epidemiology. It is an established view that, besides factors such as an unhealthy diet, smoking, and physical inactivity, chronic stress and the experience of emotional factors may promote the development and clinical manifestation of CHD. Social isolation and lack of social support, as well as depressive disorders, the latter ranging from mild (subclinical) to classic major depression, are the chronic stressors and emotional factors that have received the strongest evidence for being long-term risk-factors for CHD (Bunker et al 2003; Sapolsky 2004; Rozanski et al 2005). Other stress concepts such as work-related

stressors and marital stress were considered likely to promote CHD in one review (Rozanski et al 2005), whereas Bunker et al (2003) stated that work-related stressors, as well as type A behaviour, hostility, and anxiety disorders have received less evidence, or none (as in the case of type A behaviour), for being risk-factors for CHD. The role of exhaustion in CHD development remains unclear. Although several studies have demonstrated that vital exhaustion predicts CHD (Appels and Mulder 1988; Prescott et al 2003; Williams et al 2010), these results are difficult to interpret due to the inclusion of depressive symptoms in the vital exhaustion construct (Prescott et al 2003; Kent and Shapiro 2009).

Coronary heart disease is more common among men, which for example in Sweden means that the risk of dying from heart disease is 60-70 percent higher for men than for women. It is also more common - about double the risk - among people with a low education compared with those with a high education. In Europe, CHD is ten times as common among Eastern European men as it is among French men, and it is about 40 percent as common in Sweden as in southern Europe. Mortality in CHD has decreased markedly in most Western European countries and North America during the last few decades, but it has recently been reported that in the US, this decrease slowed down after the year 2000, and for women the mortality has even increased. The reason for this is probably the increasing prevalence of overweight and obesity, diabetes, high blood-pressure, and the metabolic syndrome (Norberg and Danielsson 2009).

The concept of exhaustion in stress theory and research

Selye conceptualised exhaustion as a final stage in the “stress syndrome”, but this notion was, at least up until recently, not acknowledged in stress research. Furthermore, stress-related fatigue has generally not been defined in terms of specific stress mechanisms, but would simply be due to expending too much energy when activating the stress response too often (Sapolsky 2004, p. 62). Selye described that the exhaustion phase arose following lack of “adaptation energy”, the amount or reserve of which was genetically inherited; when all adaptation energy was used, “irreversible, general exhaustion and death” would follow (Selye 1978, p. 81). This notion was derived from animal experiments, in which rats, although successfully adapted to stressful conditions such as long-term exposure to cold, would eventually succumb to an early death if the stressor continued for an extended time (several months; Seye 1978, p. 112-3). The notion of the exhaustion phase was (to my knowledge) not clearly defined or elaborated in humans, but seems to have mainly involved a speeding up of the aging process and emergence of “wear-and-tear diseases, diseases of civilization”, which he thought

were primarily due to stress (Selye 1978, p. 430). According to Sapolsky, Selye believed that disease can emerge during the exhaustion stage because of depletion of the stores of hormones secreted during the stress response, but that it is now known that it is very rare that any of the crucial hormones are actually depleted during even the most sustained of stressors (Sapolsky 2004, p. 12-3). However, instead of absolute depletion of stress hormones, a relative deficiency or insufficiency during the course of chronic stress may be at hand, as suggested by Raison and Miller (2003).

It is the mission of this thesis to explore whether exhaustion may be a useful concept in stress theory, in terms of elucidating some of the mechanisms during chronic stress. In epidemiology, burnout and vital exhaustion have theoretically been linked to the final exhaustion phase in Selye's stress syndrome, as well as to hypocortisolism and subsequent coronary heart disease (Maslach and Schaufeli 1993; Appels 2004; Melamed et al 2006). This thesis will consider if a conceptualisation/operationalisation of exhaustion as a non-contextual state, which does not comprise the concept of depression, may be better suited to represent what could be referred to as an "exhaustion stage" during chronic stress. The discriminant validity of such an operationalisation of exhaustion would therefore need to be determined. HPA activity in exhaustion in normal populations requires exploration, and the assumed relationship between chronic stressors and exhaustion needs to be established. Finally, it should be explored if exhaustion contributes to development of coronary heart disease, independently of the potential contribution of depression.

Aims

General aim

The general aim of this thesis was to explore aspects of exhaustion as a potentially unique state related to chronic stress and disease.

Specific aims

- To explore the discriminant validity of exhaustion, as assessed by the SF-36 vitality scale, in relation to depression and anxiety (Paper I)
- To investigate HPA activity in exhaustion (Paper II)
- To explore associations between stressors in the working life and exhaustion (Paper III)
- To investigate the unique contribution of exhaustion to coronary heart disease (Paper IV)

Materials and methods

Study populations and designs

Two study samples were used in this thesis. The Malmö Shoulder and Neck Study cohort, comprising an urban middle-aged general population sample, was used for analyses in Papers I, III and IV; analysis for Paper II was conducted on data from a smaller working population sample (see Table 2 for an overview of objectives, samples, designs, and methodologies in Papers I-IV).

Papers I, III and IV

The Malmö Shoulder and Neck Study (MSNS) was designed as a prospective questionnaire-based cohort study with a follow-up period of one year. The main aim was to study mechanical and psychosocial exposures in the workplace on the incidence of shoulder and neck complaints (Östergren et al 2005). The MSNS cohort was a sub-cohort of the Malmö Diet and Cancer Study (MDCS), a population-based investigation focusing relationships between dietary factors and cancer incidence (Figure 2). Men and women living in the city of Malmö (approximately 230,000 inhabitants by the year of 1991) in the south of Sweden on January 1, 1991, and born between 1926 and 1945 (i. e. 45 – 65 years old), were first selected as background population for the MDCS (Berglund et al 1993); in 1995 the MDCS was extended to also include men born between 1923 and 1925, and women born between 1923 and 1950 (74,138 individuals in all). Recruitment took place between 1991 and 1996 through two parallel means: community-directed invitation (via posters and pamphlets in public places, advertisements in public transport buses, face-to-face contacts with people visiting the yearly city festival and at work sites, with women attending for mammography, with organisations for immigrants, and with different occupational groups such as policemen and health service staff; 18 percent were recruited this way), and personal invitation (82 percent) to randomly selected individuals in the background population (Manjer et al 2002). 5,233 individuals were excluded due to identification problems, death, move, or communication problems (language or mental retardation), leaving 68,905 eligible subjects. Of these, 28,098 subjects completed the baseline examination, corresponding to a participation rate for the total MDCS cohort of 40.8 percent (Manjer et al 2001; Manjer et al 2002). A

selection bias investigation indicated better self-reported health in participants than in non-participants, and demonstrated that overall mortality was substantially higher in non-participants both during and following recruitment (Manjer et al 2001).

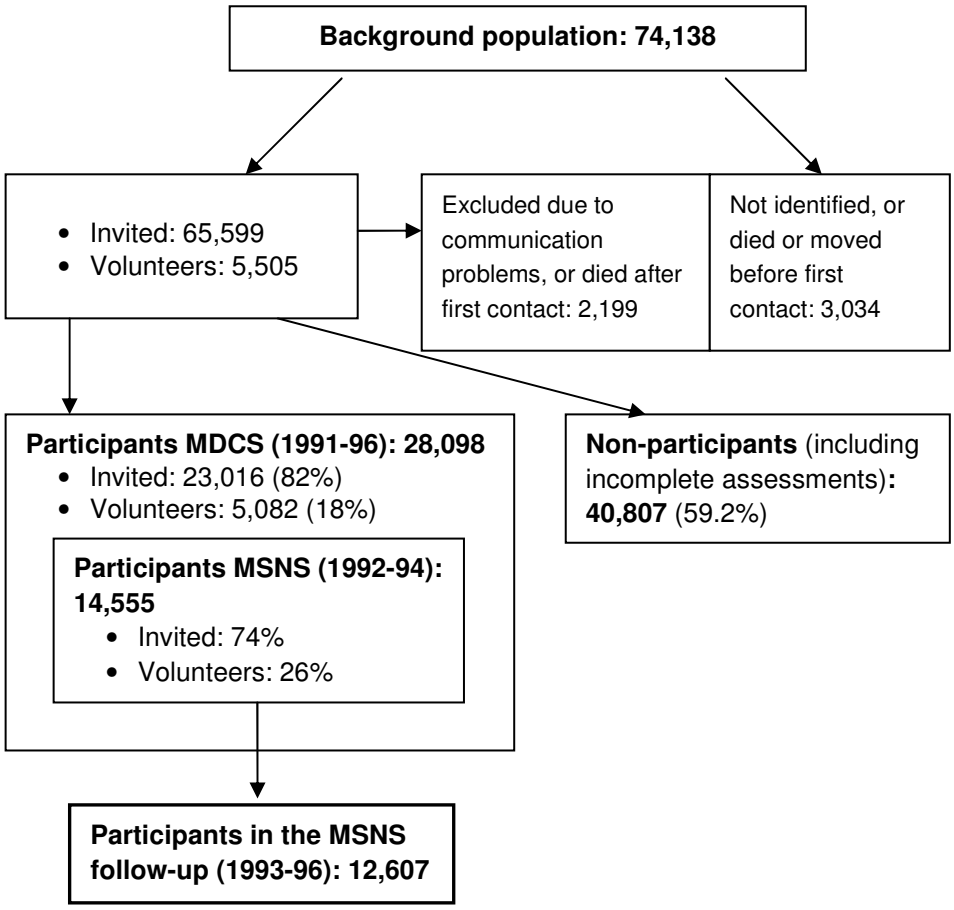

Figure 2. Recruitment procedures and participation in the Malmö Diet and Cancer Study (MDCS) and the Malmö Shoulder and Neck Study (MSNS). (Modified after Lindström 2000 and Manjer et al 2001).

The MSNS cohort consists of the participants who completed the baseline examination of the MDCS between February 1992 and December 1994 (N = 14,555), during which period items assessing for example work exposures and pain were included in the questionnaire. Out of the 14,555 MSNS participants, 74

percent had been personally invited and 26 percent had been invited through community-directed communication, as described above. After about one year (mean follow up time 403.1 days, standard deviation 48.9), a follow-up questionnaire was mailed to all 14,555 participants, of whom 12,607 (5,593 men and 7,014 women) responded; response rate 86.6 percent (Östergren et al 2005). Since the exhaustion measure used in this thesis was included in the MSNS follow-up questionnaire, and not in the baseline questionnaire, only those participating in the follow-up were eligible for analysis. In Paper I, analysis was performed on the total MSNS follow-up sample (N = 12,607), using cross-sectional data. The study population in Paper III included 5,001 vocationally active (working minimum 30 hours a week) who were not sick-listed at baseline; work exposure data from both baseline and follow-up were used. For Paper IV, participants from the total sample, without prior registered or self-reported cardiovascular event, and with complete data on exhaustion (N = 12,208), were included.

Paper II

The study sample for Paper II was derived from a cohort study aimed to explore risk-markers of occupational stress. The participants in this cohort (N = 437) were initially recruited during the year 2001, from five companies constituting seven workplaces, all located in the southern part of Sweden. These work-places were identified with the assistance of the local Labour Inspectorate and on the basis of possible high workload. The companies included one high school, one telecommunication company (located at three different geographical positions but with similar work tasks, i.e., customer service), one regional social insurance office, one pharmaceutical company, and one wood industry (Hansen et al 2006). The baseline examination, including survey assessment and cortisol sampling, took place at the location of each workplace. Results presented in Paper II were cross-sectional, based on the first follow-up assessment, performed between May 2004 and November 2005. Included were employees at four (N = 265) of the five work-sites (excluding the high-school), since only these participants received a questionnaire including the SF-36 vitality scale, used for the measurement of exhaustion in this thesis. After agreement of participation in the follow-up, the study subjects received by post a study questionnaire and a saliva sampling kit, along with a pre-stamped envelope to be used after completion of the survey assessment and cortisol sampling. Eighty-four individuals (32 percent) responded to this part of the follow-up assessment. Six were excluded due to corticosteroid medication or invalid cortisol samples, leaving 78 participants (57 women and 21 men), aged 26-63 years, eligible for Paper II.

Table 2. Objectives, study samples, designs, outcomes, and statistical analysis methods in Papers I-IV

Paper	Objective	Study sample	Design	Outcome	Analysis
I	Exploration of discriminant validity of exhaustion, as assessed by the SF-36 vitality scale, in relation to depression and anxiety	MSNS, general population sample *N* = 12,607	Cross-sectional data	-	Factor analysis
II	Explore HPA axis activity in exhaustion	Working population sample *N* = 78	Cross-sectional data	Cortisol levels and variability	ANOVA MIXED Model
III	Explore associations between psychosocial working conditions and exhaustion	MSNS, working sub-sample *N* = 5,001	Longitudinal exposure data, cross-sectional design	Exhaustion	Logistic regression analysis
IV	Explore exhaustion as independent predictor of coronary heart disease	MSNS, general population sample CVD-free *N* = 12,208	Prospective design	Coronary heart disease	Cox regression analysis

MSNS = Malmö Shoulder and Neck Study Cohort.
CVD = cardiovascular disease

Measures

Exhaustion

The SF-36 vitality scale was used for measuring exhaustion. The 36-item Short-Form (SF-36) Health Survey is a quality-of-life instrument constructed to survey health status and was designed for use in clinical practice and research, health policy evaluations, and general population surveys. The SF-36 includes one multi-item scale for measurement of each of eight health concepts: physical functioning; role limitations because of physical health problems; bodily pain; social functioning; general mental health; role limitations because of emotional problems; vitality (energy/fatigue); and general health perceptions (Ware and Sherbourne 1992). The eight SF-36 scales have been observed to define two distinct physical and mental health clusters in factor analytic studies of both general and patient populations, and cross-culturally. The vitality scale correlates moderately with both the physical health and the mental health component, with a higher correlation with the mental health component (Ware et al 1998).

The original (American) vitality items are: "How much of the time during the past 4 weeks Did you feel full of pep?, Did you have a lot of energy?, Did you feel worn out?, and Did you feel tired?. Response alternatives are 1 – All of the time, 2 – Most of the time, 3 – A good bit of the time, 4 – Some of the time, 5 – A little of the time, and 6 – None of the time.

In the MSNS, the vitality and the general mental health scales from the SF-36 were included (see Appendix, Figure 1), but no other SF-36 subscale. The translation into Swedish was made from the British version of SF-36 (Brazier et al. 1992; received from the Whitehall study) by the researchers conducting the MSNS. The British SF-36 vitality scale contains the following items: "How much of the time during the **past 4 weeks,** Did you feel full of life?, Did you have a lot of energy?, Did you feel worn out?, and Did you feel tired?". In Paper II, the standardised Swedish version of the SF-36 vitality items (Sullivan and Karlsson 1994) was used (see Appendix, Figure 2); no other SF-36 subscale was included in that study questionnaire. After data collection, the last two vitality item scorings were reversed, yielding an exhaustion ("inverted vitality") score in the positive direction, with a possible score range of 4-24. One percent did not respond to one or more of the vitality items in the MSNS, while there was no missing data concerning this measure in Paper II.

Validity of the exhaustion measure

Internal reliability of the SF-36 vitality scale has been shown to be high, with a Cronbach's alpha of 0.85 in Sweden and the UK, and 0.87 in the US (Sullivan and Karlsson 1994). In the study sample for Paper II, Cronbach's alpha was 0.89.

In the MSNS (Papers I, III, IV), the SF-36 vitality scale was not identical to the standardised version of the SF-36 vitality scale (Sullivan and Karlsson 1994). This concerns mainly the first item ("*full av livslust*" - approximately "full of a lust for life" in English - as compared with "*riktigt pigg och stark*" - word by word translation would be "really alert and strong" - in the standardised version). The Cronbach's alpha for the vitality scale in the MSNS (N = 12,607) was 0.81, thus exhibiting good internal reliability (i. e. alpha >70). Item-total correlations were also satisfactory (Table 3).

Table 3. Corrected item-total correlations and Cronbach's alpha if item deleted for the inverted vitality scale in the MSNS (N = 12,607). Alpha for total scale 0.81.

Vitality item	Corrected item-total correlation	Cronbach's alpha if item deleted
(not) Full of life	0.62	0.76
(not) A lot of energy	0.65	0.75
Worn out	0.56	0.79
Tired	0.68	0.74

In the MSNS follow-up questionnaire, two other questions concerning exhaustion, not analysed in the Papers, were included (response alternatives Almost never or never/Sometimes/Often/Very often or always):

1. How often do you feel *physically exhausted* at the end of the day? and

2. How often do you feel *emotionally or mentally exhausted* at the end of the day?

Correlations between these item scores and the inverted vitality score (continuous) were similar for men and women. Inverted vitality correlated slightly more with emotional/mental exhaustion than with physical exhaustion (Table 4). This may seem to be in coherence with previously found correlations for the vitality scale with physical and mental health dimensions of the SF-36 (Stansfeld et al 1997; Ware et al 1998).

Table 4. Correlations between inverted SF-36 vitality continuous scores and scores of the physical and emotional or mental exhaustion items in men (*N* = 5,593) and women (*N* = 7,014) in the Malmö Shoulder and Neck Study.

Exhaustion score	A	B	C
A Inverted vitality	—	0.53	0.56
B Physical	0.51	—	0.46
C Emotional/mental	0.54	0.45	—

Correlation coefficients underneath the diagonal represent males, and coefficients above the diagonal represent females. All correlations were significant at the .01 level.

The discriminant validity of exhaustion, as assessed by the SF-36 vitality scale (in the MSNS), in relation to depression and anxiety was analysed in Paper I (p. 54-55). Results of factor analysis including the vitality items and a measure of psychiatric illness (the General Health Questionnaire, GHQ, see p. 49) supported the validity of the exhaustion measure, although the first item slightly overlapped the depression factor. In order to further explore the validity of the exhaustion measure used in Papers I, III and IV, additional factor analysis is presented here. When the SF-36 general mental health items were included in the factor analysis, besides the vitality and GHQ items, the four vitality items loaded on one factor, not overlapping any other factor, together with three of the mental health items. One SF-36 mental health item (A very nervous person) loaded on the anxiety factor, and one (Down in the dumps) loaded mainly on the depression factor, seemingly in accordance with face validity of these items (Table 5). The factorial overlap between the SF-36 subscales would seem coherent with previous psychometric validation of the SF-36 (Stansfeld et al 1997; Ware et al 1998). The fact that two SF-36 mental health items did load mainly on the depression and anxiety factors, respectively, may seem to reduce the likelihood that an "instrumental effect" influenced the apparent discrimination between the vitality items and psychiatric illness, i.e. that loadings on separate factors were due to separate measurements.

When the above described physical and emotional/mental exhaustion items were included instead, the vitality items loaded together with these two additional exhaustion items on one factor, separate from the depression and anxiety factors. However, the first vitality item loaded nearly as strongly on the depression factor as it did on the exhaustion factor (Table 6). It can be concluded that the first vitality item is somewhat representative for depression, indicating that the particular wordings of this item in the MSNS are not optimal, but that the discriminant validity of this exhaustion measure yet would seem satisfactory.

TABLE 5. Varimax rotated factor analysis of the inverted vitality and mental mealth items, and the GHQ-30 items in the total MSNS sample (*N* = 12,607).

	Factors				
	1	2	3	4	5
Inverted SF-36 vitality					
(not) Full of life			**0.74**		
(not) A lot of energy			**0.74**		
Worn out			**0.52**		
Tired			**0.65**		
Inverted SF-36 mental health					
A very nervous person	**0.47**				
Down in the dumps		**0.45**	0.40		
(not) Felt calm and peaceful			**0.68**		
Downhearted and blue	0.42		**0.52**		
(not) A happy person			**0.68**		
GHQ Anxiety items					
Lost much sleep over worry	**0.74**				
Constantly under strain	**0.71**				
Scared or panicky	**0.54**	0.48			
Everything on top of you	**0.60**	0.43			
Nervous and strung-up	**0.64**	0.41			
GHQ Depression items					
Thinking of yourself as worthless		**0.75**			
Life entirely hopeless		**0.76**			
Life not worth living		**0.74**			
Nerves too bad	0.42	**0.58**			

Factor loadings for "other GHQ-30 items", not pre-defined as either depression or anxiety, are not shown. Only coefficients ≥ 0.40 are shown.
Bolded coefficients indicate each item's strongest loading.

TABLE 6. Varimax rotated factor analysis of the inverted vitality items, the physical and emotional/mental exhaustion items, and the GHQ-30 items in the total MSNS sample (*N* = 12,607).

	Factors				
	1	2	3	4	5
Inverted SF-36 Vitality					
(not) Full of life		0.46			**0.50**
(not) A lot of energy					**0.56**
Worn out					**0.72**
Tired					**0.78**
Exhausted at the end of the day					
Physically exhausted					**0.74**
Emotionally/mentally exhausted					**0.61**
GHQ Anxiety items					
Lost much sleep over worry	**0.75**				
Constantly under strain	**0.71**				
Scared or panicky	**0.55**	0.44			
Everything on top of you	**0.60**	0.43			
Nervous and strung-up	**0.64**	0.42			
GHQ Depression items					
Thinking of yourself as worthless		**0.76**			
Life entirely hopeless		**0.79**			
Life not worth living		**0.76**			
Nerves too bad	0.43	**0.59**			

Factor loadings for "other GHQ-30 items", not pre-defined as either depression or anxiety, are not shown. Only coefficients ≥ 0.40 are shown.
Bolded coefficients indicate each item's strongest loading.

Distributions of inverted vitality scores and exhaustion in the MSNS

The inverted vitality score was normally distributed in both men and women (Figure 3).

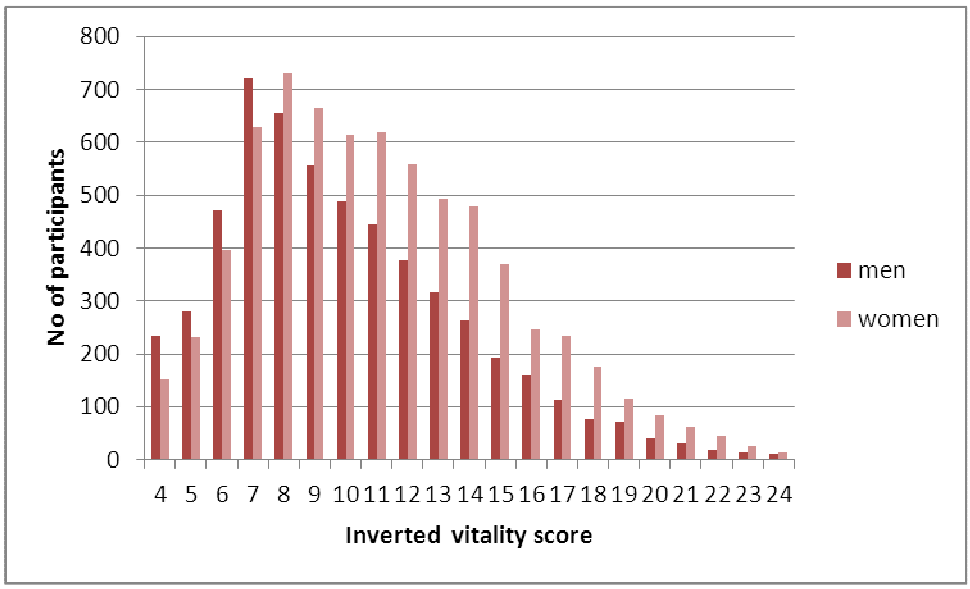

Figure 3. Frequency distribution of the inverted SF-36 vitality score in men (*N* = 5,593) and women (*N* = 7,014) in the Malmö Shoulder and Neck Study.

In Papers II and III, an arbitrarily defined cut-off of ≥ 16, indicating decreased energy and feeling tired and worn out "a good bit of the time" or more during the past two weeks, was used to define exhaustion cases. Prevalence of exhaustion in the MSNS cohort (*N* = 12,607) was 12.3 percent; 9.6 percent in men (*N* = 5,593) and 14.3 percent in women (*N* = 7,014). Mean inverted vitality score was 18 in exhausted men and women, compared with 9.5 in non-exhausted. Within the exhausted group, the item assessing *not* A lot of energy obtained the highest scores, followed by Tired, *not* Full of life, and Worn out in descending order (Figure 4).

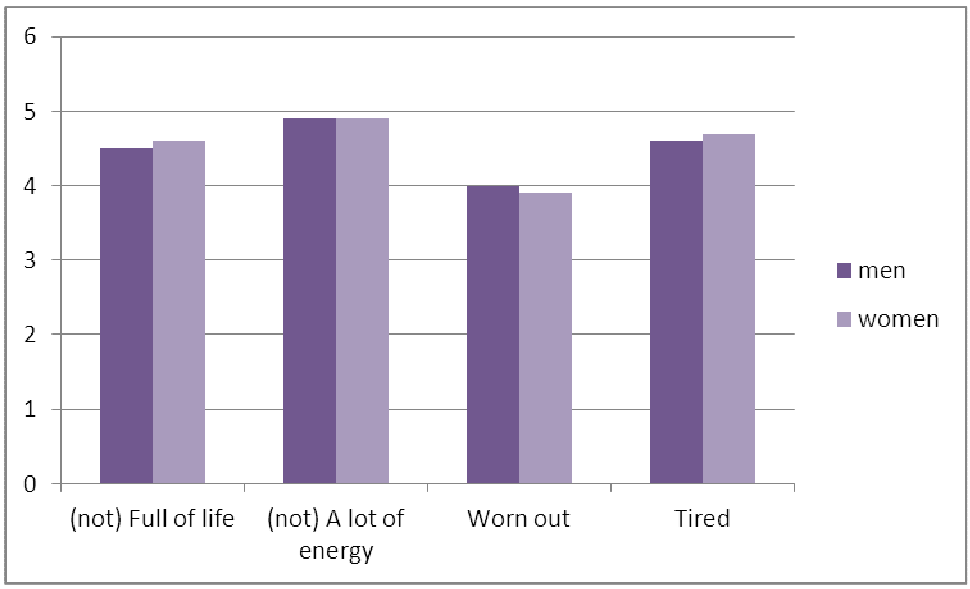

Figure 4. Individual inverted vitality item scores in men (*N* = 536) and women (*N* = 1000) defined as exhausted (total inverted vitality score ≥ 16).

There was a trend towards exhaustion being more common in the younger age-groups than in the older, in both men and women (Figure 5). In men, exhaustion was more common in manual than non-manual socio-economic groups, while the opposite trend appeared in women (Figure 6). Those who were unmarried or not cohabiting were more exhausted (15.5 percent cases in men and 17.7 percent in women) than those who were (8.3 and 12.9 percent). Foreign-born were also more exhausted (18.1 and 23.7 percent) than those born in Sweden (8.5 and 13.3 percent).

The prevalence of exhaustion did not differ essentially across seasons for men (9.5-9.9 percent; highest during the winter season, December through February). In women, the differences were larger, ranging between 13.0 percent (summer) and 15.9 percent (spring), whereas during autumn and winter, exhaustion levels were average (14.1 and 14.4 percent).

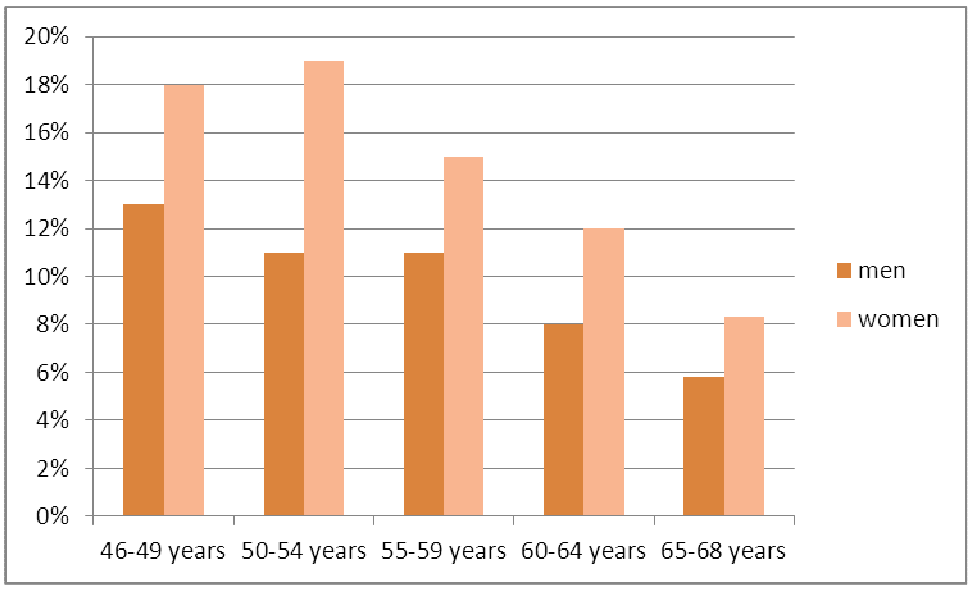

Figure 5. Prevalence of exhaustion in different agegroups in men and women in the Malmö Shoulder and Neck Study (*N* = 12,607).

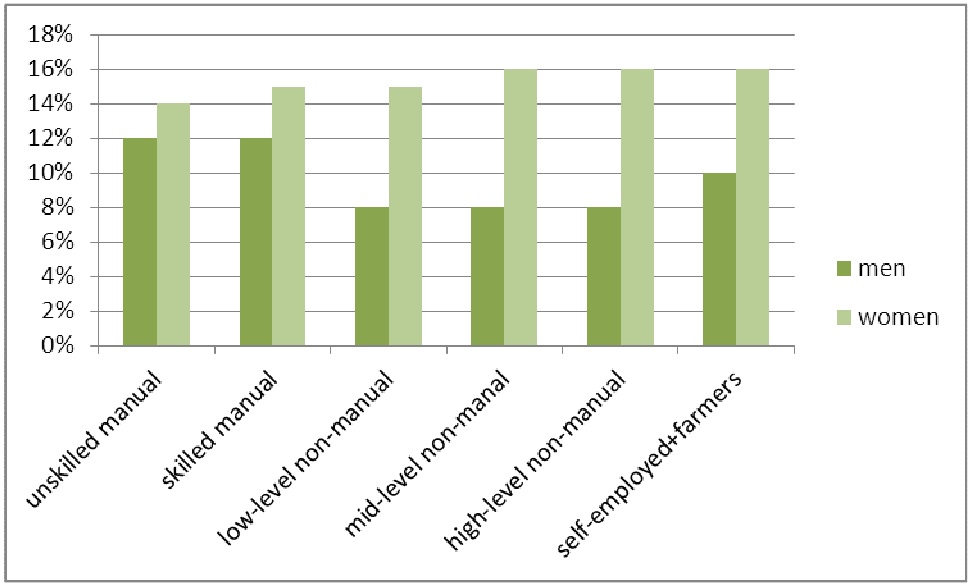

Figure 6. Prevalence of exhaustion in different socioeconomic groups in men and women in the Malmö Shoulder and Neck Study (*N* = 12,607).

Psychiatric illness

The 30-item General Health Questionnaire (GHQ-30; Huppert et al 1989) was used for assessing depression and anxiety in Papers I and IV. The GHQ was developed as a screening instrument for detecting non-psychotic psychiatric illness. It exists in many versions, such as the GHQ-60, the GHQ-28, and GHQ-12 (the figures indicate each version's number of items). The GHQ-28 was developed from the GHQ-60 by means of factor analysis, yielding four different scales: Somatic symptoms, Anxiety and insomnia, Social dysfunction, and Severe depression (Goldberg and Hillier 1979). Four of the depression items, and five of the anxiety and insomnia items, from the GHQ-28 are included in the GHQ-30. These were defined as "depression" and "anxiety" items, respectively, and displayed as such in the tables in Paper I, but all 30 GHQ items (using continuous Likert scoring, 0-1-2-3) were included in the factor analyses.

In Paper IV, five items (Thinking of yourself as worthless, Life entirely hopeless, Life not worth living, Nerves too bad, and Losing confidence in yourself) were included in the measurement of depression, and nine items (Lost much sleep over worry, Constantly under strain, Scared or panicky, Everything on top of you, Nervous and strung-up, Restless, disturbed nights, Could not overcome your difficulties, Life a struggle all the time, and Taking things hard) were used as measure of anxiety (continuous Likert scored). All pre-defined (in Paper I) depression and anxiety items were thus included, together with additional GHQ-30 items that loaded on the respective factor in both sexes in Paper I.

Cortisol

Saliva cortisol was measured for Paper II. The participants were instructed to collect saliva at three pre-specified time points on an ordinary workday: at awakening, 30 minutes after awakening, and at 2100h, and to mark the exact sampling time at a label attached to the sampling tube. They were instructed to refrain from brushing their teeth after awakening until they had obtained the second saliva sample, primarily in order to prevent the saliva sampling swabs from contamination of gingival micro-bleeding, and to refrain from smoking and having a heavy meal one hour prior to saliva sampling. The saliva samples were to be kept frozen until they were sent to the research department. For determination of cortisol in saliva, a competitive radioimmunoassay was used.

Diurnal variation of salivary cortisol, or cortisol variability, was defined as the difference between the maximum morning cortisol concentration (the highest measured concentration out of the two morning samples) and the evening cortisol concentration.

Psychosocial working conditions

In Paper III, psychosocial working conditions were analysed in terms of chronic stressors. The research field of work stress has been dominated by the demand-control-support model, which contains two main hypotheses: the "job strain hypothesis" and the "iso-strain hypothesis". The job strain hypothesis proposes that workers who are exposed to a combination of high job demands and low control at work (referred to as a "job strain" situation) have an increased risk of psychological strain and stress-related disease. The iso-strain hypothesis predicts that when job strain is combined with low job support (referred to as isolated strain, or "iso-strain"), the risk increases further. There is not consensus on whether these hypotheses are defined by additive effects between exposures, or by interactive effects (de Lange et al 2003). In Paper III, both additive effects and interaction (synergy) between exposures were defined to support the job strain and iso-strain hypotheses.

Job demands and job control were assessed by a Swedish version of the Karasek Job Content Questionnaire (JCQ), including five (Work fast, Work hard, Excessive work, Insufficient time, Conflicting demands) and six (Learn new things, Job requires skills, Job requires creativity, Non-repetitious work, Freedom as to how to work, Freedom as to what to do at work) items, respectively.

The job support scale was composed of six items oriented toward the atmosphere of the workplace: There is a calm and pleasant atmosphere at my workplace, There is a good fellowship, My workmates support me, If I have a bad day, I'm met with acceptance, I get on well with my supervisors, and I get on well with my workmates). The job demands, control, and support variables were dichotomised into high and low categories at their baseline means.

Coronary heart disease

In Paper IV, information on cardiovascular events, including fatal and non-fatal coronary events and stroke, was obtained by data linkage with national and local registers (the Swedish Hospital Discharge Register and the Cause-of-death Register from the Centre for Epidemiology at The Swedish National Board of Health and Welfare; and the Stroke register of Malmö (STROMA) at the Cardiovascular epidemiology research group, Clinical Research Centre, Scania University Hospital, Malmö). During follow-up, 374 men and 197 women experienced a coronary event, 571 in all, of which 11.4 percent were fatal.

Statistics (Papers I–IV)

Paper I

Factor analysis, including the inverted vitality and GHQ items, was performed. Both orthogonal (Varimax), resulting in statistically uncorrelated factors, and oblique (Promax) rotation, which allows the factors to be correlated, were used. The number of factors was determined by including principal components with eigenvalues greater than 1. Analyses were performed on the total sample, and also on the total sample stratified by sex, age groups, country of birth, and socioeconomic status. Since the presence of a somatic disorder might lead to exhaustion, and thus perhaps influence the relationship between exhaustion and depression and anxiety, respectively, further analysis was performed on a sub-sample excluding persons who at the baseline examination reported having a history of either of the following disorders, i. e. myocardial infarction, stroke, claudicatio intermittens, high blood-pressure, diabetes, thyroid disease, gastric ulcer, renal calculus, cancer, asthma, rheumatoid arthritis, or inflammatory bowel disease.

Paper II

Due to positively skewed distributions and heteroscedastic variances (proportional to the level of measurements) of cortisol data, the diurnal cortisol variability was ranked and the cortisol concentrations were logarithmically transformed before entering them into statistical analyses. For exploration of differences in diurnal cortisol variability between exhausted and non-exhausted subjects, univariate analysis of variance (ANOVA) was performed. Categorical predictor was group (exhausted or non-exhausted). Gender, age, awakening time (i. e., the time of the first sample), self-reported chronic disease, BMI, and daily smoking were introduced as covariates in the model in the first step, as well as the two-way interaction group by gender in order to examine possible differential associations between cortisol variability and exhaustion among males and females. In the second step, total daily medication, use of oral contraceptives or estrogens, thyroid medication, and antidepressants (created as four separate variables) were introduced as covariates one by one.

Differences in mean diurnal cortisol levels between exhausted and non-exhausted groups were examined in a repeated measures model specified in the general linear MIXED models module. The model was solved using the restricted maximum likelihood (REML) method. Categorical predictors were group (exhausted or non-exhausted) and time of day (three levels). Interactions and covariates (see above), here including also the two-way interaction group by time of day in order to

examine possible differential cortisol patterns between groups, were introduced in the model (same procedure as previously).

In addition, ANOVAs (same procedure as in the ANOVA described above) were performed in order to explore group differences in cortisol concentrations at each of the three sampling times.

Paper III

Initial interaction analysis demonstrated effect measure modification by sex on the association between exposure variables and exhaustion, and therefore all subsequent analysis was performed by gender split. Logistic regression analysis of longitudinal exposures of work characteristics (high or low at both baseline, T1, and follow-up, T2, or change from high or low, respectively, between T1 and T2) was performed.

A large number of covariates, representing potential confounders of, or mediators in, the relationship between working conditions and exhaustion, were controlled for. These included age, socioeconomic status, marital status, nationality, smoking, alcohol consumption, self-reported history of disease, pain, number of work hours per week, physical strain at work, number of housework hours per week, physical strain in housework, and having children living at home. The two other psychosocial working conditions were also controlled for in order to explore independent effect of each working condition.

Potential interactions (adjusted for age) between demands and control, and between job strain and job support, were tested using cross-sectional exposures at follow-up, as well as longitudinal exposures. In the latter case, only participants who did not change exposure from high to low, or vice versa, between follow-up and baseline were included in the analyses; this yielded a sub-sample of 2,976 men and women for investigating interactions between demands and control, and a sub-sample of 3,128 for interactions between job strain and job support. The "Rothman synergistic interaction methodology" (Figure 7) was used. A synergy index equal to unity ($S = 1$) represents additive effects of exposures without interaction. Synergy is defined to be present if the effect of both exposures is more than additive compared with their independent effects ($S > 1$), and antagonism represents a combined effect that is less than additive ($S < 1$). Confidence intervals (95%) for the synergy indexes were calculated.

$$S = \frac{OR(AB) - 1}{[OR(Ab) - 1] + [OR(aB) - 1]}$$

Figure 7. Calculation of synergy index (S). OR = Odds ratio; Ab = exposed to one factor; aB = exposed to the other factor; AB = exposed to both factors.

Paper IV

Initial interaction tests showed that depression and anxiety, but not exhaustion, interacted with sex in the prediction of coronary heart disease, and therefore analyses were performed by gender-split. The Cox regression model was used to assess contributions to the occurrence of coronary heart disease. The assumption of proportional hazards was assessed by graphical inspection of the estimated log-survival curves.

For comparison of predictive properties between different symptom scores, continuous summed scores of exhaustion, depression, and anxiety were used as independent variables. Analyses were adjusted for age, traditional risk-factors for cardiovascular disease, socioeconomic status, and for the other symptom scores, separately as well as simultaneously.

Due to a priori concern that the first exhaustion item may in fact represent a depressive symptom, thus potentially biasing the results, additional analysis was conducted after exclusion of this item.

For exploration of a dose-response relationship between exhaustion and coronary heart disease, grouped categories of the exhaustion score (4-8, 9-11, 12-15, 16-24) were used. Cut-offs were arbitrarily chosen while keeping number of endpoints in each category sufficient. Analyses were adjusted for age, traditional risk-factors for cardiovascular disease, socioeconomic status, and depression and anxiety.

Results and conclusions

Paper I: Exhaustion is differentiable from depression and anxiety: evidence provided by the SF-36 vitality scale

Results

The principal component analysis of the inverted vitality and the GHQ-30 item scores yielded five components with an eigenvalue > 1. In the orthogonal Varimax rotated solution, the first factor was defined as anxiety, the second as depression, the third and fourth as non-labeled GHQ factors, and the fifth factor was defined as exhaustion. All four vitality items loaded substantially on the exhaustion factor, while the GHQ items all loaded on other factors (Table 7). The first vitality item ("*full av livslust*") slightly overlapped the depression factor (factor loading 0.399). An oblique Promax rotated solution confirmed the groupings of variables found in Varimax rotation, and showed that correlations between the exhaustion factor and the depression and anxiety factors were 0.48 and 0.54, respectively (Table 8). Throughout analyses stratified by sex, age, country of birth, and socioeconomic status, the inverted vitality items still loaded heavily on a separate factor distinct from the GHQ factors. In women, the first vitality item overlapped slightly more with depression (factor loading 0.44) than in men (factor loading 0.35). The results remained virtually unchanged after removal of persons having a history of somatic disorder.

The previously identified GHQ depression and anxiety items (Goldberg and Hillier 1979), respectively, loaded mainly on their own factors in the total sample, although three of the five anxiety items ("scared or panicky", "everything on top of you", and "nervous and strung-up") overlapped the depression factor, and one of the four depression items ("nerves too bad") overlapped the anxiety factor (Table 7).

Conclusion

Exhaustion as measured by the SF-36 vitality scale appeared to comprise a homogeneous entity distinguishable from depression and anxiety. This seemed to be valid also for different socio-demographic strata, and independently of presence of disease. There was some indication that the first vitality item might also reflect depression, which was considered to be due to the particular wordings of this item in the MSNS dataset (not applicable to standardised versions).

TABLE 7. Varimax rotated factor analysis of the inverted SF-36 vitality items and the GHQ-30 items in the MSNS follow-up sample (*N* = 12,607).

	Factors				
	1	2	3	4	5
Inverted SF-36 Vitality					
(not) Full of life		0.40			**0.64**
(not) A lot of energy					**0.70**
Worn out					**0.66**
Tired					**0.76**
GHQ Anxiety items					
Lost much sleep over worry	**0.76**				
Constantly under strain	**0.72**				
Scared or panicky	**0.55**	0.47			
Everything on top of you	**0.61**	0.44			
Nervous and strung-up	**0.65**	0.42			
GHQ Depression items					
Thinking of yourself as worthless		**0.77**			
Life entirely hopeless		**0.78**			
Life not worth living		**0.75**			
Nerves too bad	0.43	**0.59**			

Factor loadings for "other GHQ-30 items", not pre-defined as either depression or anxiety, are not shown. Only coefficients ≥ 0.40 are shown.
Bolded coefficients indicate each item's strongest loading.

TABLE 8. Correlations between factors identified in Promax rotated factor analysis, total sample (*N* = 12,607)

Factor	1	2	3	4	5
1. Anxiety	1.00				
2. Depression	0.64	1.00			
3. Unlabeled factor (GHQ)	0.54	0.58	1.00		
4. Unlabeled factor (GHQ)	0.53	0.49	0.63	1.00	
5. Exhaustion	0.54	0.48	0.42	0.44	1.00

Results

Twenty respondents (26 percent) scored 16 or above on the inverted SF-36 vitality score and were thereby designated as belonging to the exhausted group. Strikingly, none in the exhausted group reported any daily medication, whereas in the non-exhausted group, 26 percent medicated on a daily basis. ANOVA revealed that diurnal cortisol variability differed significantly between exhausted and non-exhausted groups ($p = 0.038$). The observed difference in cortisol variability was derived mainly from the second morning sample, whereas evening cortisol levels did not differ between the groups (Figure 8). The repeated measures mixed model analysis showed no significant difference in mean diurnal cortisol output between exhausted and non-exhausted groups ($p = 0.33$). Neither were there significant differences in cortisol concentrations at each sampling time ($p > 0.2$).

Conclusion

Exhausted individuals exhibited physiological features compatible with a flattened diurnal cortisol rhythm. Morning cortisol (awakening response) was lower in exhausted, but not to a statistically significant degree.

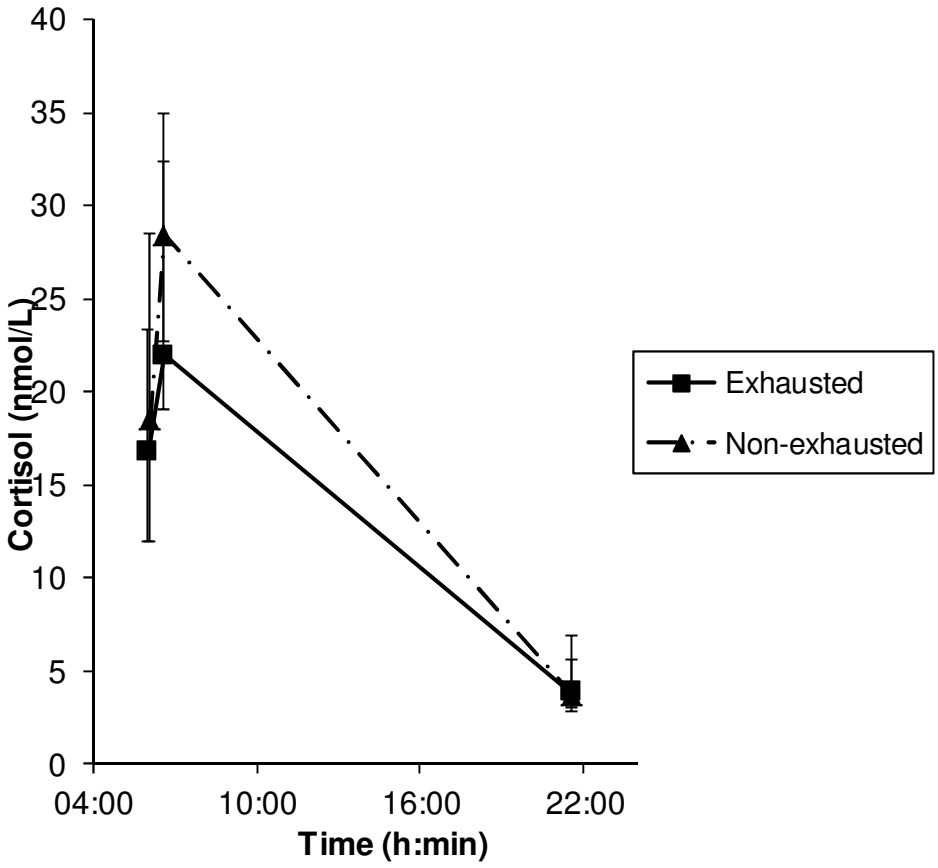

Figure 8. Diurnal cortisol profiles for exhausted (n = 20) and non-exhausted (n = 58) groups. Displayed are median cortisol concentrations and 25th and 75th percentiles at awakening, 30 minutes after awakening, and in the evening.

Paper III: Psychosocial working conditions and exhaustion in a working population sample of Swedish middle-aged men and women

Results

In this working population sample, exhaustion was twice as common among women (16 percent) as among men (8 percent). "Consistent job strain", i.e. a combination of high job demands and low control at both baseline and follow-up, was reported by 14 percent of the women and 7.5 percent of the men. Consistent iso-strain was reported by 6.5 percent of women and 3.6 percent of men (not reported in Paper III).

High psychological job demands, low job control, and low job support at both baseline and follow-up (consistent adverse exposures) were independently associated with exhaustion in both men and women. The strongest associations were found for low job support. Associations for adverse exposure reported only at either baseline or follow-up were less clear or absent (Table 9).

Additive effects between high job demands and low job control, and between job strain and low job support, were observed in both men and women. Synergy was most evident in women, but indicated also in men (Table 10 and 11).

Conclusion

Job demands, job control, and job support all seemed to exert independent main effects on exhaustion in both men and women, although causal effects would need to be further established in future research. More long-term exposure to adverse psychosocial working conditions exhibited stronger association with exhaustion. The job strain and iso-strain hypotheses were supported for both men and women, but synergy between exposures was most evident in women. Gender differences in prevalence of, and synergy between, exposures to adverse psychosocial working conditions may explain some of the higher prevalence of exhaustion in women in this sample, but continued exploration of other stressors and explanations should be of interest.

Table 9. Odds ratios (95% confidence interval) for associations between longitudinal exposures of psychosocial working conditions and exhaustion

Working condition	Exposure at T1-T2	n	Model 1	Model 2
			Men (*N* = 2,555)	
Job demands	Low-Low	833	1.0	1.0
	High-Low	297	1.0 (0.6-1.8)	0.8 (0.4-1.5)
	Low-High	337	1.5 (0.9-2.5)	1.3 (0.8 -2.3)
	High-High	1088	2.0 (1.4-2.9)	1.5 (1.0-2.3)
Job control	High-High	1490	1.0	1.0
	Low-High	185	0.8 (0.4-1.5)	0.7 (0.3-1.5)
	High-Low	312	1.3 (0.8-2.0)	1.3 (0.8-2.1)
	Low-Low	568	1.7 (1.2-2.3)	1.6 (1.1-2.3)
Job support	High-High	1169	1.0	1.0
	Low-High	297	1.8 (1.1-2.9)	1.6 (1.0-2.8)
	High-Low	293	1.3 (0.7-2.3)	1.2 (0.7-2.2)
	Low-Low	796	3.3 (2.3-4.6)	2.7 (1.9-4.0)
			Women (*N* = 2,446)	
Job demands	Low-Low	899	1.0	1.0
	High-Low	254	1.3 (0.9-2.0)	1.1 (0.7-1.8)
	Low-High	344	1.8 (1.2-2.5)	1.6 (1.1-2.3)
	High-High	949	2.5 (1.9-3.2)	1.9 (1.4-2.5)
Job control	High-High	938	1.0	1.0
	Low-High	203	1.6 (1.0-2.4)	1.8 (1.2-2.9)
	High-Low	356	1.3 (0.9-1.9)	1.3 (0.9-1.9)
	Low-Low	949	1.9 (1.5-2.4)	1.8 (1.4-2.4)
Job support	High-High	1182	1.0	1.0
	Low-High	227	1.9 (1.3-2.9)	1.8 (1.1-2.7)
	High-Low	350	2.4 (1.7-3.3)	2.1 (1.5-3.0)
	Low-Low	687	3.6 (2.8-4.7)	3.0 (2.3-4.0)

T1 = baseline, **T2** = follow-up
Model 1: adjusted for age
Model 2: adjusted for age, socioeconomic status, nationality, smoking, alcohol consumption, no. of working hours per week, physical strain at work, no. of housework hours per week, physical strain in housework, children living at home, disease, pain, and the two other psychosocial working conditions

Table 10. Synergy indexes (S; 95% CI) for interactions between job demands and job control ("job strain") in relation to exhaustion in male and female working sub-samples of the MSNS

	Cross-sectional exposures at follow-up	
	Men (*N* = 2,555)	Women (*N* = 2,446)
Job strain	*n* = 439 S = 1.7 (0.8-3.6)	*n* = 686 S = 2.2 (1.0-4.5)
	Longitudinal exposures	
	Men (*N* = 1,549)	Women (*N* = 1,427)
Job strain	*n* = 191 S = 1.6 (0.6-3.9)	*n* = 340 S = 2.0 (1.0-4.0)

Table 11. Synergy indexes (S; 95% CI) for interactions between job strain and low job support ("iso-strain") in relation to exhaustion in male and female working sub-samples of the MSNS

	Cross-sectional exposures at follow-up	
	Men (*N* = 2,555)	Women (*N* = 2,446)
Iso-strain	*n* = 243 S = 1.4 (0.7-2.7)	*n* = 380 S = 1.8 (1.2-2.9)
	Longitudinal exposures	
	Men (*N* = 1,651)	Women (*N* = 1,477)
Iso-strain	*n* = 93 S = 2.1 (0.9-4.7)	*n* = 158 S = 2.0 (1.1-3.6)

Paper IV: Does exhaustion predict coronary heart disease?

Results

In men, while exhaustion tended to predict coronary heart disease (CHD), depressive symptoms acted in the direction of being protective against CHD, which was statistically significant in the fully adjusted model. No clear association between anxiety and CHD was observed in men. In women, all symptom scores predicted CHD in age-adjusted analysis. Depression and anxiety were strong predictors of CHD in women, with effects remaining statistically significant after adjustment for traditional cardiovascular risk-factors and exhaustion, but not for each other (Table 12). Exclusion of the first exhaustion item strengthened the association between the exhaustion score and CHD in both men and women. Exhaustion now significantly predicted CHD also in men (age-adjusted HR = 1.04**,** 95% CI 1.01-1.08, $p = 0.026$ for test for trend), due to that the excluded item tended towards a protective association with CHD in men (HR = 0.97, 95% CI 0.90-1.06).

In age-adjusted analysis, a significant trend for the association between exhaustion categories and CHD was observed in women, although a somewhat weakened association was indicated in the highest category. In men, only the highest exhaustion category was associated with CHD (which would explain the lack of statistical significance for the continuous exhaustion score seen in Table 12). In men, adjustment for symptoms of depression or anxiety strengthened the association between exhaustion and CHD, whereas in women, the association was further attenuated by these adjustments, and no clear association between exhaustion and CHD was observed in the fully adjusted model (Table 13).

Conclusion

Although exhaustion may predict coronary heart disease in both men and women, the unique contribution of exhaustion was apparent only in men. Further studies would be required in order to confirm these results. Depression unexpectedly appeared as protective against coronary heart disease in men, and these results underscore the necessity of treating exhaustion and depression as different concepts, and to continue to explore potential gender differences in their effects on coronary heart disease.

Table 12. Risk of first coronary heart disease by exhaustion, depression, and anxiety continuous summed symptom scores (risk by 1-point scale score increase) in 5,061 men and 6,734 women in the Malmö Shoulder and Neck Study cohort. Results from Cox regression analyses shown as hazard ratios with 95% confidence intervals. *P*-values represent significance testing for test for trend.

		Model 1	Model 2	Model 3
Symptom score				
		Men		
Exhaustion		1.02 (0.99-1.05)	1.00 (0.97-1.03)	1.02 (0.99-1.06)
	P-value	0.13	0.89	0.20
Depression		0.98 (0.94-1.02)	0.96 (0.92-1.00)	0.94 (0.88-1.00)
	P-value	0.34	0.060	0.049
Anxiety		1.00 (0.98-1.02)	0.99 (0.97-1.01)	1.00 (0.97-1.04)
	P-value	0.82	0.37	0.91
		Women		
Exhaustion		1.05 (1.01-1.09)	1.02 (0.99-1.06)	0.98 (0.93-1.03)
	P-value	0.007	0.21	0.39
Depression		1.08 (1.04-1.12)	1.06 (1.02-1.11)	1.03 (0.97-1.11)
	P-value	0.000	0.008	0.35
Anxiety		1.04 (1.02-1.07)	1.04 (1.01-1.06)	1.03 (0.99-1.08)
	P-value	0.001	0.009	0.16

Model 1 adjusted for age
Model 2 adjusted for age, diabetes, hypertension, BMI, smoking, alcohol consumption, physical activity, and socioeconomic status
Model 3 adjusted for the above covariates, depression, anxiety, and the two other symptom scores

Table 13. Risk of first coronary heart disease (CHD) by exhaustion sum category (the lowest exhaustion category is reference) in 5,061 men and 6,734 women in the Malmö Shoulder and Neck Study cohort. Results from Cox regression analyses shown as hazard ratios (95% confidence intervals).

		Men	
Exhaustion score	**n/cases**	**Age-adjusted**	**Adjusted for all[1]**
4-8	2188/164	1	1
9-11	1370/96	1.03 (0.80-1.32)	1.00 (0.76-1.31)
12-15	1040/73	1.05 (0.79-1.38)	1.06 (0.77-1.44)
16-24	463/41	1.49 (1.06-2.11)	1.62 (1.05-2.50)
Test for trend		*P* = 0.091	*P* = 0.14
		Women	
Exhaustion score	**n/cases**	**Age-adjusted**	**Adjusted for all[1]**
4-8	2101/51	1	1
9-11	1851/56	1.41 (0.96-2.06)	1.16 (0.78-1.73)
12-15	1832/64	1.78 (1.23-2.58)	1.07 (0.69-1.64)
16-24	950/26	1.54 (0.96-2.49)	0.60 (0.32-1.14)
Test for trend		*P* = 0.007	*P* = 0.33

[1] Adjusted for age, diabetes, hypertension, BMI, smoking, alcohol consumption, physical activity, socioeconomic status, depression, and anxiety

General discussion

The main objective of this thesis was to explore aspects of exhaustion as a potential stress concept. Exhaustion was assessed in normal populations, through self-reports of decreased energy and feeling tired or worn out, by means of the SF-36 vitality measure. In Paper I, exhaustion, as assessed by this measure, appeared as a homogeneous entity separate from depression and anxiety. In Paper II, HPA dysregulation in exhaustion was found, and in Paper III, relationships with work-related stressors were demonstrated. Finally, in Paper IV, the independent contribution of exhaustion in development of coronary heart disease was indicated in men. The findings point to a unique and potentially important role of exhaustion in stress research. The grounds for conveying this notion will be discussed in more detail in the following sections.

The exhaustion concept

It has been proposed that exhaustion, or fatigue, like many other medical conditions, is best viewed as a continuum (from mild to severe, including clinical syndromes). That would imply that exhaustion is not something one "gets" or not, the question is rather how much of it one has. The continuous distribution of exhaustion scores in the general population (demonstrated also in Figure 3), is considered to support this notion (Lewis and Wessely 1992; Sharpe and Wilks 2002; Kant et al 2003). It is also the basic notion of exhaustion in this thesis (and parallels the generally acknowledged view of a continuum between depressed mood or subclinical depressive symptoms, and major depression). It should be clear that this view acknowledges that the severe end of the exhaustion spectrum is to be considered a disease, which is as important as any other disease in search of prevention and treatment (Wessely et al 1999). I will hereafter refer to such clinically defined diseases as functional somatic syndromes (including primarily chronic fatigue syndrome and fibromyalgia), or clinical fatigue syndromes (also including posttraumatic stress disorder, PTSD), in order to distinguish them from exhaustion as defined and studied in this thesis.

Exhaustion has also been argued to be best viewed as a uni-dimensional construct (Lewis and Wessely 1992; Michielsen et al 2004), despite the fact that many authors conceive of it as multidimensional, including components such as for

example emotional exhaustion, physical fatigue, reduction in activity, reduction in motivation, and mental or cognitive fatigue. A notion of dividing exhaustion into physical and mental components is often expressed, but there is no consensus about such contrast (Michielsen et al 2004). Exhaustion, as assessed by the vitality scale, correlated similarly with "physical" and "emotional or mental" exhaustion (Table 4). Interestingly, Studts et al (2001) reported that ten subscales, aimed to measure cognitive, affective, somatic, and general aspects of fatigue, all loaded on the same factor in factor analysis. Åhsberg et al (2000) found in structural equation modelling a general dimension, "lack of energy" (including the expressions *worn out*, *spent*, *drained*, and *overworked*), that was latent to the other dimensions "physical exertion", "physical discomfort", "lack of motivation", and "sleepiness" in their fatigue construct. The uni-dimensional operationalisation of "general" exhaustion, applied in this thesis, would thus seem supported.

There has been a long debate on whether exhaustion and its syndromes - from neurasthenia to burnout - is something else than depression (Wessely et al 1998; Maslach and Schaufeli 1993). Today this appears to be more or less generally agreed upon (Huibers et al 2007). Paper I would also seem to support this notion, considering that the exhaustion items loaded on a single factor separate from the depression and anxiety factors. However, exhaustion did correlate to a fairly high degree with depression and anxiety (r 0.48 and 0.54, respectively). Furthermore, factor analysis with eigenvalue exceeding unity criterion, the method applied in Paper I, has been used for assessing dimensionality within one construct, and the method has been claimed to exaggerate the number of dimensions (Michielsen et al 2004). Therefore, the apparent overlaps between exhaustion and depression and anxiety merit a further discussion. A recent study by Kato et al (2009) seems to answer some of the questions concerning their aetiologies, focusing non-shared environmental (including individual experiences such as stress) and genetic factors. By the use of a genetically informative general population sample of female twins (from The Swedish Twin Registry) and structural equation modelling, they were able to show that a predominantly genetic pathway, which particularly contributed to both major depression and generalised anxiety disorder, also was related to chronic impairing fatigue, but to a lesser degree. Fatigue was more strongly influenced by another pathway (predominantly determined by environmental factors), which also was related to chronic widespread pain, irritable bowel syndrome, and recurrent headache (functional somatic syndromes), but not to depression and anxiety. In addition, and in contrast to depression and anxiety (for which only shared genetic factors were found), fatigue (as well as the other functional syndromes) was partly explained by unique genetic factors. Thus, the psychiatric disorders depression and anxiety seem to be more etiologically connected with each other, than they are with chronic impairing fatigue. These results would appear coherent with results in Paper I, considering that symptoms

of depression and anxiety were more overlapping (in terms of more factorial overlap, as well as stronger correlation, $r = 0.64$) than these states were with exhaustion. The results in Paper IV further support that exhaustion should be conceptually differentiated from depressed mood, since evidence of their opposite effects on coronary heart disease in men was demonstrated (whereas symptoms of depression and anxiety were more similar in their influence on coronary heart disease in both men and women). In summary, evidence supports both the conceptual integrity of exhaustion, as well as its genetically and environmentally determined relationship with depression and anxiety. Thus, although closely related, exhaustion also seems to appear unrelated to depression and anxiety, and to be more etiologically influenced by chronic stress than by genetics, as compared with psychiatric illness.

The basic notion of exhaustion as investigated in this thesis, in terms of denoting energy decrease and loss of vitality during chronic stress, should seem essentially coherent with notions of burnout and vital exhaustion (Maslach and Schaufeli 1993; Appels 1997; Maslach et al 2001; Appels 2004; Melamed et al 2006). However, both burnout and vital exhaustion seem to lack some conceptual clarity, and to be burdened with methodological difficulties. Burnout is mainly defined as work-related (Maslach et al 2001; Kristensen et al 2005; Shirom and Melamed 2006), but distinguishing features of burnout in relation to other stress-related exhaustion states seem unclear. Initially, interpersonal interaction processes (in relation to clients or recipients) had a key role in the definition of burnout, but were seemingly abandoned (Maslach et al 2001). Kristensen et al (2005) defined the key feature of burnout as the attribution of fatigue and exhaustion to work, but they also included "personal burnout" in their inventory, in order to assess non-contextual exhaustion; thus, burnout could also be non-work-related, contrary to their initial conception, adding to the confusing ambiguity of the term burnout. Similar ambiguity, i.e. burnout as both specifically work-related and non-contextual, has been expressed by Shirom and Melamed (Shirom and Melamed 2006; Melamed et al 2006). Furthermore, from a stress theoretical point of view, it is generally agreed that stress-related states have a multifactor pathogenesis, why an exploration of other potentially contributing factors to burnout should be of interest. Such an exploration is difficult to conduct when the construct is pre-defined (and operationalized) as work-related. The methodological difficulties with the operationlization of burnout in epidemiological studies, in terms of yielding potentially overestimated associations between work stressors and burnout, were discussed in Paper III. However, a conceptualisation of burnout as "a state of physical, emotional and mental exhaustion caused by long term involvement in situations that are emotionally demanding", and not inherently work-related (Pines and Aronson 1981; Pines 1993), is in line with the notion of exhaustion as defined in this thesis, but such a conception of burnout is rare.

Finally, despite the fact that vital exhaustion has been claimed to constitute something else than "depressed mood", or "depressive symptomatology", and to be characterised by excess fatigue and loss of vigour (van Diest and Appels 1991; Kopp et al 1998), vital exhaustion has still been referred to as "depressive symptomatology" (Appels et al 2000a; 2000b), adding to the confusion of this concept. The theoretical conceptualisation of vital exhaustion recently outlined (notably, now mainly referred to as "exhaustion"; Appels 2004) is clearly equivocal to the notion of exhaustion in this thesis. Yet, the original operationalization of "vital exhaustion and depression" has not been modified, and many researchers refer to it as a measure of fatigue and depression (Prescott et al 2003; Bergelt et al 2005; Kornerup et al 2010). The results of Paper IV imply that different vital exhaustion "components" (fatigue and depression) ought to be explored separately in prediction of disease.

Exhaustion and cortisol

Considering the widespread evidence of hypocortisolism in clinical fatigue syndromes, it has often been assumed that exhaustion would be associated with low cortisol levels. In investigating this notion in non-clinical samples, measures of burnout have been predominant, rendering inconclusive results because both high and low cortisol levels, as well as null-findings, have been indicated (Mommersteeg et al 2006; Bellingrath et al 2008). Nicolson and van Diest (2000) found a tendency for that vital exhaustion, after exclusion of depressed subjects, was associated with lower diurnal cortisol. The study design for Paper II, assessing cortisol only in the morning and evening, did not primarily address the issue of daily cortisol output. Lower morning cortisol, which generally is considered to indicate hypocortisolism (Heim et al 2000; Fries et al 2005; Bellingrath et al 2008; Tak and Rosmalen 2010), was found in exhausted subjects compared with non-exhausted, but these results were not statistically significant. Evening levels did not differ between groups. It could, however, be demonstrated that exhaustion was associated with flattened diurnal cortisol rhythm. This finding has subsequently been replicated (using the SF-36 vitality scale) by Kumari et al (2009).

Bellingrath et al (2008) demonstrated stronger cortisol suppression in the DST in exhaustion, as indicated by measures of burnout emotional exhaustion and vital exhaustion in a sample of teachers (excluding subjects with psychiatric disorders), although they were unable to find statistically significant associations with basal cortisol levels (measured seven times during the day). The basal cortisol patterns for the two measures of exhaustion were almost identical, with lower levels during the first hour after awakening, and during the rest of the day levels practically did not differ between exhausted and non-exhausted groups. Of note, these results (referring to morning and evening results) were very similar to the results in Paper

II. It has been estimated that in order to demonstrate hypocortisolism in terms of basal cortisol levels in clinical samples, at least 155 study subjects in each case and control group would be required (Tak and Rosmalen 2010). Therefore, the statistical null-findings in Paper II (including 78 individuals in total), as well as in the study by Bellingrath et al (2008), which included 135 individuals in total, would seem expected. It has also been proposed that the DST is a more sensitive measure of hypocortisolism (Heim et al 2000; Fries et al 2005). This may seem even more relevant when measuring exhaustion in normal populations, possibly involving even subtler dysregulation of basal cortisol levels, and is supported by the findings presented by Bellingrath et al (2008).

Results from the Whitehall II study presented by Kumari et al (2009), using the SF-36 vitality scale for the assessment of exhaustion in a large-scale older community-based population (originally forming an occupational cohort, 49 percent were retired), should be of particular interest. Besides flattened diurnal rhythm, they found significantly lower cortisol concentrations in the two morning samples in exhausted subjects, thus confirming the morning sample results in Paper II. However, bedtime cortisol concentrations were significantly higher in exhausted subjects (as were afternoon levels, but not to a significant degree). Overall cortisol levels (measured six times during the day) were lower in exhausted compared with non-exhausted, but this difference was not formally tested. The DST was not performed. Interestingly, this precise cortisol pattern, i.e. flattened diurnal rhythm, lower morning cortisol, and higher evening cortisol, was recently suggested to be particularly related to the experience of fatigue and chronic pain (functional somatic symptoms; Tak and Rosmalen 2010). Taken together, evidence points to that exhaustion in non-clinical samples is associated with HPA dysregulation in terms of flattened diurnal rhythm and hypocortisolism.

Comparison with HPA activity in depression, and other chronic stress states

In clinical samples, although results are not universal, a hyperactive HPA axis has frequently been found in severely depressed patients and to a lesser extent in outpatients and mildly depressed patients, measured through, for example, higher cortisol levels, or "hypercortisolism" (found in 40 – 60 percent of cases), failure to suppress cortisol secretion after administration of dexamethasone (DST non-suppression), and higher cortisol in the morning (Gillespie and Nemeroff 2005; Handwerger 2009; Vreeburg et al 2009). High morning cortisol (awakening response) has been observed in subjects with current as well as remitted major depression, and was therefore suggested to indicate increased biological vulnerability for major depression (Vreeburg et al 2009). Miller et al (2007) conducted a meta-analysis of HPA activity during chronic stress, as defined by

persistent circumstances (lasting at least one month) that would normatively be appraised as threatening and exceeding coping resources. The meta-analysis showed evidence of significantly higher post-dexamethasone cortisol (and non-significantly higher afternoon/evening cortisol; no other HPA function data was available) in those who after exposure to chronic stress developed major depression, as compared with those who did not, results which are in line with findings from psychiatric patient samples.

Miller et al (2007) also reported that individuals who after exposure to chronic stress had developed PTSD, were more likely to exhibit lower total daily cortisol output (hypocortisolism), lower morning cortisol, higher afternoon/evening cortisol, as well as lower post-DST cortisol (super-suppression), as compared with chronically stressed without PTSD. This cortisol pattern is coherent with the pattern found in exhaustion by Kumari et al (2009). Regarding non-clinical states, Miller et al (2007) also investigated "subjective distress" (not specified) in relation to chronic stress, and found that it was associated with HPA dysfunction in terms of cortisol levels being lower in the morning, higher in the afternoon/evening (suggesting that a flattened diurnal rhythm also is at hand), and overall higher during the day (hypercortisolism; there was no data on post-DST cortisol). This pattern was similar to that in chronic stress states in general, which also were associated with significantly lower morning cortisol levels, higher concentrations of afternoon/evening cortisol, a flatter diurnal rhythm, and hypercortisolism, as well as more pronounced suppression of cortisol in the DST.

Bellingrath et al (2008) assessed associations between HPA axis activity and measures of depression and anxiety (besides exhaustion) in their working teachers sample, and, as for exhaustion, lower post-DST cortisol appeared for depressive symptoms (but not for anxiety), in combination with non-significant associations with basal cortisol levels; however, since the focus of the study was other constructs, and therefore participants with psychiatric disorders had been excluded, depressed mood assessed in that study would be different from assessments of depressed mood in the general population, making it difficult to interpret the results. No association between depressive symptoms and diurnal cortisol rhythm was found in the Whitehall II study (Kumari et al 2011). Other studies of HPA activity in association with depressive symptoms, as measured in non-clinical populations, with a proper study design, seem to be lacking.

A few words need to be said about anxiety and cortisol; although anxiety disorders have been associated with increased cortisol (Abelson et al 2007; Vreeburg et al 2010), this is not considered to be the usual response to anxiety, which mainly is associated with excess sympathetic activation (Sapolsky 2004, p. 319).

In summary, there is consistent evidence for that clinically defined depression is associated with hyperactivity of the HPA axis, thus presumably contrasting HPA

activity in exhaustion. However, HPA activity in depressed mood as measured in non-clinical samples remains to be further explored, although the apparent lack of studies in this field may reflect null-findings. Furthermore, low morning cortisol, flattened diurnal rhythm, high afternoon/evening cortisol levels, and enhanced post-dexamethasone cortisol suppression may be generally appearing during chronic stress, irrespective of presence of hypo- or hypercortisolism, as implicated by the findings by Miller et al (2007). It should, however, be noted that half of the included studies in the meta-analysis measured only one type of HPA function, why it is difficult to know if the different types of HPA dysfunction really were co-occurring. Moreover, since presence or prevalence of exhaustion in the chronic stress states included in the meta-analysis were unknown, the associations of exhaustion with low morning cortisol and post-dexamethasone suppression, as compared with chronic stress states not involving exhaustion, also were unexplored. The specificity of these HPA dysfunctions to hypocortisolism, as previously suggested (Heim et al 2000; Fries et al 2005; Bellingrath et al 2008; Tak and Rosmalen 2010), may thus need to be further established.

Development of hypocortisolism (and exhaustion)

Different theories regarding emergence of hypocortisolism appear to exist. Some researchers seem to suggest that some people (for some unknown or unmentioned reason) have a "defect" in cortisol secretion (Sapolsky 2004, p. 200), which may represent a pre-existing vulnerability (McEwen and Kalia 2010), and therefore are more susceptible to developing disorders such as functional somatic syndromes. An alternative view is that hypocortisolism is secondary to the illness (the fatigue syndrome) itself (Cleare 2004a; 2004b; McEwen and Kalia 2010), whereas still others suggest that a hypofunctional HPA axis is related to chronic stress, and may occur due to a "switch" from HPA axis hyper- to hypofunction (Fries et al 2005; van Houdenhove et al 2009). It has been described that a majority of chronic fatigue patients describe the onset of their symptoms as "a loss of resilience", or a "crash", sharply contrasting their premorbid state, which may have been characterised by a high level of activity, achievement, overcommitment, perfectionistic traits and perseverance, often in the face of accumulating adversity and emotional burden, or during or after an exhausting viral infection (van Houdenhove et al 2009). According to Fries et al (2005), this model is supported by animal data, where rats were exposed to a prolonged period of chronic stress by restraining them repeatedly over a period of 3 weeks. During the stressful period, the animals showed a hyperreactive HPA axis, but two weeks after termination of the chronic stressor, the animals were hypocortisolaemic compared to non-stressed animals. Furthermore, in the meta-analysis by Miller et al (2007) it was concluded

that one of the most robust findings was a negative association between time since onset of the stressor and HPA axis activity, i. e. longer time was associated with morning cortisol, daily volume, ACTH, as well as postdexamethasone cortisol all being lower (which could not be explained by presence of PTSD), suggested to support a model of initial stress system activation followed by diminished activity over time. Self-adjusting abilities in terms of negative feedback systems (down-regulation of specific receptors, reduced biosynthesis or depletion at several levels of the HPA axis, and/or increased negative feedback sensitivity to glucocorticoids) have been suggested to play a significant role in survival of the organism by counteracting the enduring increased levels of glucocorticoids, and protecting the organism against their possible harmful effects. Failure in these self-adjusting abilities ("over-adjustment") has been suggested to be a cause of hypocortisolism, and an enhanced pituitary feedback (reduced ACTH response) to be the primary, or most common, adaptational mechanism underlying hypocortisolism (Heim et al 2000; Fries et al 2005). Different severity grades along the "exhaustion continuum" may, however, involve different types of adaptation; in primarily healthy individuals with a history of early life stress, hypocortisolism seemed to result as an end organ (adrenal gland) adaptation to a sensitised (exaggerated) stress response at the level of the pituitary and/or the hypothalamus (Raison and Miller 2003).

The direct link between chronic stress and hypocortisolim, as well as the reversibility of hypocortisolism, in medically healthy individuals, would seem demonstrated by Zarcovic et al (2003), in that very low cortisol levels (even fulfilling criteria for Addison's disease) during exposure to severe chronic stress due to ongoing war, returned to normal after termination of the war. Kumari et al (2009) showed that HPA dysregulation (low waking cortisol and flattened diurnal rhythm) in older healthy and non-exhausted individuals predicted exhaustion two to four years later, but that exhaustion did not predict HPA dysregulation (one to three years later), thus pointing to that physiological stress level dysregulation precedes exhaustion, and not the other way around. The relevance of HPA dysregulation and exhaustion beyond clinical contexts would seem to be sustained by these findings.

Causes of exhaustion

Few studies have explored potential causes of exhaustion. Pavlikowska et al (1994) found in a population based study of fatigue that the most common attribution for fatigue (40 percent) was psychosocial, such as work, family, or lifestyle. The second commonest attribution (17 percent) was psychological distress, mainly anxiety or depression, and the third commonest (15 percent) was physical causes (for example surgery or anemia). The two latter attributions

(psychological and physical), as well as pregnancy, were associated with higher degree of fatigue than were psychosocial attributions. In Paper III, it was demonstrated that psychosocial working conditions, in terms of high job demands, low job control, and low job support, were associated with exhaustion. These results were in agreement with some previous cross-sectional and prospective investigations.

Women generally report more health problems than men do, and this seems to be true also for exhaustion, often found to be at least twice as common in women (Sharpe and Wilks 2002). Prevalence of exhaustion was higher in women than in men in the Malmö Shoulder and Neck Study (MSNS) cohort, but higher in men in Paper II. Considering the low response rate (32 percent) and the small number of participants, the latter result should, however, be interpreted with caution. In the total MSNS sample, exhaustion was about 1.5 times as common in women (Paper IV), and among the vocationally active twice as common (Paper III). The reason for this gender difference is not known, and rarely investigated. In Paper III, whereas high demands and low job support were somewhat more common in men, low job control was about 1.5 times more common in women, seemingly in accordance with findings from previous studies of women's working conditions (Lundberg 2002). Consequently, job strain also was more common in women than in men (14 versus 7.5 percent), as was iso-strain (6.5 versus 3.6 percent), which may explain some of the found gender difference in exhaustion levels.

It has however been pointed out that women's stress to a higher degree than men's, seems to be related to a combination of work and family life (Lundberg 2002). Studies of physiological stress responses, supporting this notion, have shown that women who are employed full-time have elevated stress levels off work compared with men, and a greater spill-over of stress between work and home conditions, which has been attributed to women's traditional primary responsibility for household and children. Furthermore, women seem to react more to "family matters" (such as children's health check-ups) than to situations related to performance (Lundberg 2002). These stress response differences mainly concerned the sympathetic nervous system, whereas gender differences in cortisol levels are considered less pronounced (Lundberg 2002). In a study by our research group of how role conflict between work and family (work interfering with family and family interfering with work) was associated with exhaustion (performed on the same study sample as Paper III), it was, quite surprisingly, shown that men more often than women reported that work interfered with family, whereas women more often reported that family interfered with work. (It was discussed that these reports may have reflected that, although both domains (work and family) would be considered important by both genders, it was the most prioritised domain that interfered with the less prioritised domain.) However, work-to-family conflict in particular was associated with higher risk for exhaustion in women, and the two

types of conflict together contributed to a larger part of the variance of exhaustion in women than in men (Canivet et al 2010). These results may seem to be coherent with the "tend-and-befriend" theory; i.e., just like lack of social support ("befriending") has been found to be more stressful for women, as reviewed by Taylor et al (2000), an experienced inadequacy to "tend" may also render more stress in women, although both lack of support and work-to-family conflict are stressful also for men.

Potential causes of, or contributing factors to, exhaustion discussed so far involved current life stressors. Other plausible causes of exhaustion - not explored in this thesis - concern early life stress. The relevance of early life experiences for the risk of becoming exhausted is indicated by evidence that abused children have an increased risk of developing both hypocortisolism (without defined disease), and clinical fatigue syndromes (Heim et al 2000; Raison and Miller 2003). This seems to be true also for atypical depression, which shares many features with functional somatic syndromes, in that childhood sexual abuse and childhood neglect have been reported to be significantly more common in atypical than in "typical" depression (Davidson 2007).

Exhaustion and disease development

Although it is well acknowledged that chronic stress contributes to a variety of diseases, mechanisms still remain to be elucidated. Elucidating the potential role of exhaustion in this process may contribute to the understanding of how stress influences disease development.

Exhaustion and depression

It is often assumed that exhaustion precedes depression, whereas the opposite has been considered more difficult to explain (Skapinakis et al 2004). However, a depressive episode could be regarded as a chronic stressor, which would make the latter relationship seem plausible. Skapinakis et al (2004) and Huibers et al (2007) found that fatigue and depression both predicted each other. Depression was somewhat more likely to predict fatigue, especially with time, suggesting that they become more and more intertwined, or create a "vicious cycle". Huibers et al (2007) suggested that the social isolation and loss of interest associated with depression would render the individual inactive and lead to physical deconditioning and (increased) fatigue. Samples included 66 and 55 percent women, and potential gender differences were not explored. It is not known from these studies whether exhaustion predicted first-incident depression, or vice versa, which should

be of interest considering that stress may precede only the first depressive episodes (Sapolsky 2004, p. 292).

Marin and Menza (2005) pointed out that studies have found that three quarters or more of patients who are improved by either psychotherapeutical or pharmacological antidepressant treatment, still complain of residual fatigue, which was considered to not only significantly deteriorate quality of life, but also to constitute a major risk-factor for chronicity and relapse of depression. This may seem to be in line with the above mentioned results, and with the notion of a vicious cycle between exhaustion and depression. The importance of paying attention to, and addressing treatment of, both depression and fatigue was emphasised (Marin and Menza 2005; Huibers et al 2007).

Exhaustion and functional somatic syndromes

Exhaustion may be seen as a predisposing factor to functional somatic syndromes, corroborated by findings in a working population, in which exhaustion seemingly predicted chronic fatigue syndrome (Huibers et al 2004). It has been hypothesised that HPA axis hypofunction in functional somatic syndromes, primarily exemplified by the chronic fatigue syndrome, is linked to a fundamental and persistent dysregulation of the neurobiological system (van Houdenhove et al 2009). A characteristic of exhaustion, as defined in this thesis, may be that it is more of a reversible state, which may be in line with the notion of exhaustion and clinical fatigue syndromes as varying degrees along a continuum. In the study by Huibers et al (2004), half of the initially exhausted participants were no longer exhausted, according to study criteria, four years later. Van Houdenhove et al (2009) suggested that functional somatic syndromes may result from a disturbed balance, evolving over time, between glucocorticoid and inflammatory signalling pathways. A hypofunctional HPA axis may lose its immune-restraining capacity, which, after for example a stress system challenge in terms of physical or mental effort, may lead to excessive proinflammatory cytokine release, affecting the brain to provoke a pathological "sickness response": flu-like malaise, light fever, lethargy, hyperalgesia, sensory hypersensitivity, low mood, sleepiness, concentration problems and social withdrawal. This type of "sickness behaviour" was suggested to have evolved to "force" the individual to change priorities and behaviour in order to promote recovery; the exact mechanisms underlying such a neuroendocrine–immune disequilibrium are not known, but may hypothetically involve impaired glucocorticoid receptor functioning by early trauma, or stress-related immune activation (van Houdenhove et al 2009).

Exhaustion and cardiovascular disease

As previously mentioned, in epidemiological studies, the predictive role of exhaustion has mainly been investigated by means of the vital exhaustion construct, and therefore the unique contribution of exhaustion to disease, independent from the potential contribution of depression, has not been established. In Paper IV, exhaustion seemed to predict coronary heart disease in both men and women, but independence from depression and anxiety in doing so was demonstrated in men. Vital exhaustion has primarily been investigated as a predictor of coronary (ischemic) heart disease, but recently, Kornerup et al (2010) investigated its prospective association with stroke (which shares many etiological mechanisms with coronary heart disease). Interestingly, they found that while vital exhaustion significantly predicted ischemic (but not hemorrhagic) stroke in women, it tended towards being protective against ischemic stroke in men. These results can be compared with results in Paper IV, indicating a protective effect of depressive symptoms on development of coronary heart disease in men, while predicting the same disease in women. The importance of exploring predictive effects of exhaustion and depression independently of each other should be apparent. Moreover, predictive properties of either (vital) exhaustion or depression have rarely been investigated with a gender-perspective, which seems highly warranted in future research. In Paper IV, depressive symptoms in women predicted coronary heart disease independently of exhaustion, but not vice versa. It is possible that in women, exhaustion and depression are more similar or intertwined states, in terms of pathophysiological features, or more closely linked to each other over time, which remains to be elucidated in future research.

Discussed mechanisms of the potential influence of exhaustion on coronary heart disease have mainly involved promotion or disinhibition of one of the key factors in atherosclerosis development, namely inflammation (Appels 2004; Paper IV). Considering the well-known suppressive effects of cortisol on immune function, hypocortisolism in exhaustion would appear as a plausible pathophysiological pathway, mediated by increased inflammation. Inflammation may also contribute to altered glucose metabolism leading to insulin resistance, diabetes, and obesity (Raison and Miller 2003), known to promote coronary heart disease. Enhanced responses of the sympathetic nervous system are also suggested to follow hypocortisolism (Raison and Miller 2003), thus promoting heart disease. Rosmond and Björntorp (2000) demonstrated that low cortisol variability (flattened diurnal rhythm) was associated with a number of risk-factors for cardiovascular disease and diabetes type 2. Notably, this cortisol pattern was also associated with substantially lower morning and diurnal cortisol levels, as well as DST super-suppression, but these HPA dysfunctions were not in focus in that study.

According to Kumari et al (2011), no prospective study in normal populations has succeeded in linking either high or low cortisol levels with cardiovascular events,

and in a few patient population studies, both high and low levels were associated with adverse outcomes. In their very recent study, Kumari et al (2011) reported from the Whitehall II study that flattened diurnal rhythm, but not cortisol awakening response, was prospectively associated with mortality in cardiovascular disease (CVD; all diseases of the circulatory system were included) in both men and women. Higher bedtime cortisol seemed to explain this association. Full adjustment for potential confounders was not performed due to sample size. Adjustment for exhaustion (measured by the SF-36 vitality scale) somewhat increased the association between diurnal rhythm and CVD, and only marginally decreased the association between bedtime cortisol and CVD (whereas separate adjustments for smoking, obesity, and fasting glucose actually increased the association). As previously mentioned, causes or mechanisms of flattened diurnal cortisol rhythm are unknown. Stress-related elevations during a stressful day, long-term changes in circadian regulation, or impaired central negative feedback sensitivity of the HPA axis have been suggested (Kumari et al 2011).

The paper by Kumari et al (2011) also reported that exhaustion significantly, and independently of cortisol pattern, predicted cardiovascular deaths (bedtime cortisol-adjusted HR, 95% CI = 2.37, 1.12-5.04). Their findings thus do not seem to support that flattened diurnal rhythm, low morning cortisol, or high bedtime cortisol mediate a potential causal effect of exhaustion on cardiovascular death. Considering that cortisol levels in exhaustion during basal conditions may be only subtly lower or normal (or even higher), a decreased ability to physiologically respond to acute stressors - in terms of enhanced negative feedback of the HPA axis, as indicated by post-DST cortisol super-suppression (Fries et al 2005) - may be a crucial implication of exhaustion. This notion seems to be supported by some previous studies. Kristenson et al (1998) reported that low peak cortisol response to a laboratory stress setting was significantly related to high baseline cortisol and vital exhaustion, and to smoking, and concluded that an inability to respond to acute stress may be an independent risk-factor for coronary heart disease. Dahlgren et al (2004) formed two comparison groups based on level of increase in morning cortisol response during a week of high work stress, as compared with a low stress week; group one consisted of those who exhibited higher morning cortisol response during high stress than during low stress, and group two of those with a lower response. During the low stress week, overall diurnal cortisol levels were higher in group two than in group one. Within group two, cortisol levels did not differ significantly between high stress and low stress weeks, except for morning cortisol, whereas within group one, significantly higher cortisol levels were measured during high stress compared with low stress. Group two reported higher workload, fatigue, and exhaustion during both weeks as compared with group one, whereas levels of perceived stress, depression, and anxiety did not differ significantly. It was concluded that level of exhaustion may modulate the response to stress, in terms of suppressing morning cortisol. Acute stress is known to induce immune activation and inflammation, and the stress response, mainly

cortisol, helps counteract this immune response (Raison and Miller 2003; Sapolsky 2004). Thus, concerning potential stress pathophysiological pathways, unrestrained inflammation during heightened (acute) stress, due to inability to adequately mobilise the stress response, could be a mediating pathway between exhaustion and cardiovascular disease. The DST may be helpful in resolving these issues.

Exhaustion and other diseases

Interestingly, in the paper by Kumari et al (2011), exhaustion, but not flattened diurnal rhythm or bedtime cortisol, was reported to significantly (and independently of cortisol pattern) predict non-cardiovascular deaths, HR (95% CI) = 1.72 (1.31-2.25). There was no information on what diseases caused this mortality, but cancer may have been a major cause. However, in a study on the prospective association between vital exhaustion and cancer, vital exhaustion showed a clear tendency towards being protective against this disease (Bergelt et al 2005). Clearly, future research will need to elucidate these issues. Although very preliminary and non-adjusted, why exhaustion may have merely reflected a symptom of manifest disease, the findings by Kumari et al (2011) may seem to support a notion of exhaustion as an important concept in stress theory in general.

Implications for future research and prevention

The role of exhaustion in development of disease, both cardiovascular and other, and mediating mechanisms remain to be further elucidated in future research. Inability to respond to acute stressors, due to enhanced negative feedback of the HPA axis, could be central, why assessment of post-dexamethasone cortisol is suggested in order to explore potential mediating physiological mechanisms. Focusing potential differences between the genders seems warranted, and exploration of other stress physiological systems than those discussed here, and in line with the suggested tend-and-befriend response in women, could be fruitful. Furthermore, although still merely suggestive, there is gathering evidence that, at least in men, exhaustion may be more important than depression as risk-factor for coronary heart disease (Appels et al 2000b; Kop et al 2002; Paper IV). Such a suggestion challenges the today well-acknowledged scientific notion that depression predicts coronary heart disease in both men and women. It has even, quite boldly, been suggested that the well-documented association between physical inactivity and coronary heart disease may be confounded by a higher prevalence of depression in physically inactive (Rugulies 2002). Another bold suggestion, in line with results in this thesis, would perhaps be that in men, associations between depression and coronary heart disease are confounded by

exhaustion. To date, it has not been shown that even successful treatment of depression (psychotherapeutical and/or pharmacological) has substantially prevented coronary heart disease (Frasure-Smith and Lespérance 2010). Considering that residual fatigue in depression may be very common, it could be explored if the suggested additional treatment strategies for residual fatigue (which included cognitive interventions, graded aerobic exercise, dose reduction or discontinuation of fatigue-inducing antidepressants, and pharmacological interventions such as dopaminergic antidepressants (buproprion), stimulants, thyroid preparations, and modafinil; Marin and Menza 2005), may have preventive effects against coronary heart disease.

A randomised intervention study of exhaustion, in order to decrease the risk of new cardiac events, was undertaken by Appels (2004). Treatment included reduction of stressors, support of recovery and rest, relaxation exercises, stimulation of physical exercise, and treatment of hostility. This treatment reduced the risk of being exhausted at 18 months follow-up by 55 percent, and the risk of being depressed by 53 percent. It also reduced the risk of suffering from anginal complaints by 29 percent. However, the intervention did not succeed with its main purpose, to reduce the risk of new coronary events. Nearly half of all new cardiac events occurred within six months, which in some cases was even before start of intervention, and evidence suggested that longer-term beneficial effects of the intervention were at hand. However, at present, preventive measures targeting other lifestyle factors than stress (diet, physical activity, smoking) may be considered more important in prevention of cardiovascular disease.

Since this thesis mainly concerns a phenomenon that appears to be commonly occurring in the general population, a focus on primary prevention would seem appropriate. Early prevention is also more likely than secondary prevention to be efficient in hindering chronic stress and exhaustion. An obvious target for intervention is child maltreatment and abuse, which is well-known to cause life-long suffering, and may predispose to adult exhaustion and fatigue syndromes (Heim et al 2000; Raison and Miller 2003). But other circumstances early in life may also be important, and it has been suggested that attachment style should be considered in future research in order to understand development of vulnerability to functional somatic syndromes (van Houdenhove 2009). According to attachment theory, as outlined by Bowlby (1907-1990) and Ainsworth (1913-1999), attachment style is thought to evolve through parent-child interactions during the first few years in a child's life, and to be relatively stable for most people throughout their lives. It has been hypothesised that the attachment behavioural system is intimately linked to the biology of the stress response, including appropriate excitation of a stress response, and its modulation when the stressor has passed, in both children and adults (Maunder and Haunter 2008). This notion may be well in line with the well-recognised fact that people habitually

differ in how they psychologically modulate their stress responses. Such differences are considered very important in understanding why some people are more prone towards stress-related diseases than others, and they are thought to be not only genetically determined, but also influenced by environmental factors early in life. Interestingly, as an example of this environmental influence, observed in the animal world, Sapolsky (2004, p. 316) described that genetically determined "high-reactivity" traits in infant monkeys could be completely prevented if these infants early in life were fostered by "atypically nurturing mothers", which was suggested to indicate the importance of "mothering style". The connection to attachment theory seems obvious, and research on parent-child interactions and attachment style influencing stress responses in humans is warranted. Hypothetically, promotion of secure attachment may prevent not only exhaustion, but also other types of stress-related distress and disease, a research area which should be of great interest in the future.

Conclusions

- The notion of conceiving exhaustion as a unique concept, separate from the other stress-related states depression and anxiety, is supported.

- Exhaustion is probably associated with specific HPA dysregulation, involving flattened diurnal cortisol rhythm and hypocortisolism.

- Psychosocial working conditions seem to contribute to exhaustion. Other causal or contributing factors, including early life stress, need further exploration.

- Exhaustion appears to predict coronary heart disease, but its unique developmental influence on this disease, independent from depression and anxiety, may occur mainly in men.

- These findings point to a unique and potentially important role of exhaustion in stress research. Potential gender differences in development of stress-related disease need to be focused in future research. Further research is warranted in order to find effective preventive measures of chronic stress and exhaustion.

Summary in Swedish

Intresset för utmattning har ökat både i Sverige och internationellt under de senaste årtiondena. Utmattning som begrepp är oklart definierat vetenskapligt, och det finns olika benämningar på utmattningstillstånd, som till exempel den något gammalmodiga benämningen neurasteni, som ännu finns kvar som diagnosklassifikation (där även benämnt ”trötthetssyndrom”), kroniskt trötthetssyndrom, som är mer uppmärksammat i anglosaxiska länder, och utbrändhet (burnout), som framförallt studerats i psykologisk forskning. Överlappningen är betydande, och det verkar som att kulturella influenser avgör vilken benämning som hamnar i fokus i ett enskilt land. I Sverige tog intresset fart i slutet på 1990-talet, med siktet framför allt inställt på arbetsrelaterad utbrändhet och de eskalerande sjukskrivningarna, som ledde fram till att den internationellt unika diagnosen utmattningssyndrom infördes i Sverige år 2008.

Fokus för denna avhandling är dock inte primärt patienter med kliniska utmattningstillstånd, utan koncentreras istället på utmattning så som den ter sig i en allmänbefolkning. Återkommande frågeundersökningar utförda av Statistiska Centralbyrån (SCB) bekräftar bilden av att utmattning (i termer av att ha svårt att komma igång på morgonen, och samtidigt vara påfallande trött under dagen såväl som på kvällen under de senaste två veckorna) ska ha ökat. Mellan 1989 och 2005, efter att ha legat stabilt under 1980-talet, ökade förekomsten av utmattning med hela 50 procent i genomsnitt. Ökningen var störst i yngre åldersgrupper, med mer än en fördubbling i åldern 16-24 år. Nya data från SCB insamlade åren 2008-09, som inte tidigare publicerats, visar att denna höga nivå (7 procent bland män och 13 procent bland kvinnor) verkar kvarstå. Att sådan trötthet inte är direkt knuten till åldrande och sjukdom ter sig därför uppenbart, och stämmer väl med teorin att kronisk psykosocialt betingad stress ger upphov till utmattning. De specifika fysiologiska mekanismerna för sådan utmattning har generellt inte definierats inom stressforskningen. Men under det senaste årtiondet har det utkristalliserats ett mönster av att låga kortisolnivåer, istället för höga som traditionellt varit förknippat med kronisk stress, kan förekomma både i olika kliniska utmattningstillstånd, och under utdragen stress hos i övrigt friska individer. Det har också argumenterats att låga kortisolnivåer skulle kunna vara en bidragande orsak till stressrelaterad sjukdom, som till exempel hjärtkärlsjukdom.

Syftet med denna avhandling var att epidemiologiskt undersöka utmattning i en stresskontext. Utmattning mättes med ett antal frågor (se Appendix), och definierades som avsaknad av energi och en känsla av att vara trött och utsliten under en hel del av tiden, eller mer, de senaste fyra veckorna. Malmö Nack-skulderstudien användes för analyserna i tre av de fyra delarbetena som ingår i denna avhandling. Måttet på utmattning ingick i den studiens ettårsuppföljning, som innefattar en allmänbefolkning bestående av 12 607 individer mellan 46 och 68 år boende i Malmö vid tiden för baslinjeundersökningen (1992-94). I denna medelålders stadspopulation uppfyllde 10 procent av männen och 14 procent av kvinnorna kriterierna för utmattning. I ett fjärde delarbete, som analyserade sambandet mellan kortisolnivåer och utmattning, användes en mindre arbetande population.

Depression och ångest anses vara stressrelaterade tillstånd, och är flitigt använda som utfall i epidemiologisk stressforskning. Gränsdragningen mellan depression och utmattning är inte helt tydlig. I det första delarbetet analyserades om utmattning kan anses vara ett eget tillstånd, skilt från depression och ångest. Utmattningsfrågorna föll i analyserna ut som en egen homogen entitet, skilda från frågor om depression och ångest som ingick i samma frågeformulär. Resultaten styrkte uppfattningen att utmattning kan skiljas från depression och ångest. De styrkte samtidigt utmattningsmåttets psykometriska validitet.

Låga kortisolnivåer har återkommande observerats hos individer med olika kliniska utmattningssyndrom, men kopplingen till utmattning i en normal-befolkning har varit mindre tydlig. Det andra delarbetet analyserade kortisolnivåer relaterade till utmattning i en liten (78 individer) arbetande population. En så kallad ”platt kortisolkurva”, som har associerats med kronisk stress i tidigare studier, kunde påvisas. Utmattade uppvisade något lägre kortisolnivåer på morgonen, men inte till en statistiskt säkerställd nivå.

De allra flesta studier som analyserat samband mellan kronisk stress på arbetet och utmattning har använt sig av utbrändhet som utfallsmått. Eftersom sådana mått kopplar utmattningen direkt till en dålig arbetsmiljö så kan de anses mäta både exponering (arbetsmiljö) och utfall (utmattning), och därmed överskatta sambanden mellan arbete och utmattning. En sådan koppling till arbete finns inte i denna avhandlings utmattningsmått, och syftet med tredje delarbetet var därför att analysera sambanden mellan psykosociala arbetsförhållanden (krav, kontroll och stöd på arbetet) och utmattning. Resultaten visade att det fanns samband mellan alla tre typerna av arbetsförhållanden och utmattning, och att sambanden var starkare ju längre de dåliga förhållandena hade pågått, det vill säga om de rapporterades både vid baslinjeundersökningen och vid uppföljningen ett år senare.

Den sista delstudien analyserade om utmattning är en riskfaktor för framtida hjärtinfarkt. Tidigare studier som analyserat detta samband har i de flesta fall använt ett mått på utmattning som också innehåller frågor om depression. Eftersom depression anses utgöra en riskfaktor för hjärtinfarkt, och eftersom utmattning är tätt associerad med både depression och ångest, testades effekten av utmattning på hjärtinfarkt oberoende av en eventuell samtida effekt av depression och ångest. Det visade sig att utmattning hade ett samband med framtida hjärtinfarkt hos både män och kvinnor, men att en oberoende effekt verkade finnas enbart hos män. Ett oväntat fynd var att depression uppvisade en tydlig tendens att vara skyddande mot hjärtinfarkt hos män. Detta samband var statistiskt signifikant efter att ha kontrollerats för associerade traditionella riskfaktorer för hjärtinfarkt (till exempel rökning, övervikt, högt blodtryck, etc.) och för utmattning. Det skulle kunna vara så att de samband mellan depression och hjärtinfarkt som påvisats hos män egentligen beror på samtidig utmattning, men det är något som får undersökas vidare i framtida studier.

Slutsatsen var att det finns fog för att anse att utmattning är ett unikt eller eget kroniskt stresstillstånd, skilt från andra tillstånd som depression och ångest, och att utmattning kan spela en viktig roll i utvecklingen av sjukdom. Låga kortisolnivåer och en otillräcklig förmåga att mobilisera den fysiologiska stressresponsen under ökad stress är tänkbara komponenter i utvecklingen av utmattning och sjukdom.

Framtagandet av preventiva åtgärder borde vara värdefullt. Negativa händelser under barndomen har visat sig ha samband med låga kortisolnivåer och olika trötthetssyndrom senare i livet, varför en viktig inriktning skulle kunna vara att förhindra att stresskänslighet uppstår tidigt i livet. Ett särskilt intressant område kan vara att studera om och hur anknytningsmönster och stresskänslighet hör ihop.

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Appendix

HM3	**I vilken utsträckning har Du under de senaste fyra veckorna:** *Markera ett svar för varje fråga!*	Hela tiden	Större delen av tiden	En hel del av tiden	En del av tiden	Ganska liten del av tiden	Inte alls
	a) känt Dig full av livslust?	☐	☐	☐	☐	☐	☐
	b) varit en mycket nervös person?	☐	☐	☐	☐	☐	☐
	c) känt Dig så under isen att inte något kunde muntra upp Dig?	☐	☐	☐	☐	☐	☐
	d) känt Dig lugn och fridfull?	☐	☐	☐	☐	☐	☐
	e) haft massor av energi?	☐	☐	☐	☐	☐	☐
	f) känt Dig nedstämd och sorgsen?	☐	☐	☐	☐	☐	☐
	g) känt Dig utsliten?	☐	☐	☐	☐	☐	☐
	h) varit en lycklig person?	☐	☐	☐	☐	☐	☐
	i) känt Dig trött?	☐	☐	☐	☐	☐	☐

Figure 1. The SF-36 vitality (items a, e, g, and i) and general mental health (items b, c, d, f, and h) scales included in the follow-up questionnaire of the Malmö Shoulder and Neck Study.

Frågorna här handlar om hur du känner dig och hur du haft det under de senaste fyra veckorna.
Ange för varje fråga det svarsalternativ som bäst beskriver hur du känt dig.

Hur stor del av tiden under de senaste fyra veckorna . . .	Hela tiden	Största delen av tiden	En hel del av tiden	En del av tiden	Lite av tiden	Inget av tiden
har du känt dig riktigt pigg och stark?	☐	☐	☐	☐	☐	☐
har du varit full av energi?	☐	☐	☐	☐	☐	☐
har du känt dig utsliten?	☐	☐	☐	☐	☐	☐
har du känt dig trött?	☐	☐	☐	☐	☐	☐

Figure 2. The SF-36 vitality items from the questionnaire for Paper II.