

# PERCEIVED CHRONIC STRESS, HEALTH AND COGNITION

Lena Öhman

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## ABSTRACT

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The aim of this licentiate thesis was to examine consequences of chronic stress for stress-related diseases and to investigate the chronic stress – cognition relationship.

In the first study data covering ten years was used from the Betula Prospective Cohort Study (Nilsson et al., 1997). Based on the ratings on a stress scale, matched samples between 40 and 65 years of age were divided into a high and low stress group. The reported incidence of cardiovascular, diabetes, psychiatric, tumor, and musculoskeletal diseases was assessed five and ten years after a baseline assessment. The incidence of diseases five years after baseline assessment showed no differences between the groups. After ten years, there was a higher incidence of psychiatric diseases in the high stress group as well as a significant effect for tumors. These results indicated that moderately elevated stress levels may have an impact on psychiatric diseases, especially depression, and possibly also some tumor diseases, but it was concluded that prolonged moderate stress does not appear to be very harmful to health in general.

In the second study cognitive performance was studied in chronic stress outpatients and matched controls. A battery of cognitive tests assessing processing speed, attention, episodic-, semantic- and working memory was used. Performance decrements for the chronic stress patients were found in episodic memory, particularly in learning across repeated trials, and in tasks requiring divided attention under either encoding or retrieval of words. Performance differences were also seen in aspects of working memory, mental tempo, semantic access (letter fluency) and prospective memory. It was concluded that executive functioning may be suboptimal in chronic stress patients and that letter fluency and prospective memory tests can be useful as clinical tools when evaluating chronic stress states.

Taken together, the findings indicate that there is no clear association between moderately elevated chronic stress and increased incidence of stress related diseases, whereas certain cognitive functions such as executive functioning appear vulnerable to chronic stress.

This thesis for the licentiate degree is based on the following studies:

Öhman, L., Bergdahl, J., Nyberg, L., & Nilsson, L.-G. Longitudinal analysis of the relation between moderate long-term stress and health. (submitted)

Öhman, L., Nordin, S., Bergdahl, J., Slunga Birgander, L., & Stigsdotter Neely, A. Cognitive function in outpatients with perceived chronic stress. (submitted)



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Umeå, January, 2006

Lena Öhman



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# Perceived chronic stress, health and cognition

Lena Öhman

## INTRODUCTION

To stay healthy is a main goal for the individual, but personal wellbeing is also of economical and structural interest for the society. In Sweden there is a dramatic increase in sick leave. Many workers are soon reaching retirement age, and there is increasing unemployment among young people who have not yet set themselves up at the labor market. In the Swedish society work is one of the most important sources to gain distinction and perceive life satisfaction. According to the Swedish General Social Insurance Agency a high percent of the fast growing long-term sick-leave during the last decade is related to psychosocial poor health. Therefore several reports and evaluations have been performed in order to analyze and eliminate potential causes (Hallsten, Bellaagh, & Gustafsson, 2002; SOU, 2003). According to these reports, contributing factors could have both inter- and intra-personal origin, such as bad working environment, severe family situations and inappropriate personal coping strategies leading to chronic stress.

## BACKGROUND

### General stress: Development and definitions of the concept

The stress concept is full of ambiguity; it could both refer to the cause (stressor) and the reaction (stress response) to an event. A stressor is considered as the main cause of stress, and could be of either physical or psychological nature. A stressor disturbs the bodily homeostasis and a stressor causing stress for one person is not automatically causing the same response in another person, because people deal with stressors in different ways. Therefore, stress response is the outcome of a person's interaction with the surrounding environment. This interaction is a complicated process involving several factors of psychological and physiological nature, and it also involves environmental factors such as social support, perceived control and satisfaction in life and in the working situation. Good physical health, certain genetic factors, and life style could mitigate the negative effects of the stress response (McEwen, 1998).

Cognitive appraisal is, according to Lazarus and Folkman (1984), the psychological evaluation of the person-environmental relationship to figure out how stressful an event is for a given person. Coping is the psychological ability to handle stressful events and generated emotions, and considerable individual variability exists in the way individuals adapt to stressful events (McEwen, 1999). The stress response is functional in physical situations when an appropriate action could terminate the stress response, but it can get dysfunctional in our modern society because of various psychosocial stress factors (McEwen, 2000) If the adaptation is dysfunctional, repeated stress responses accelerate cortisol secretion. Chronic stress refers to the individual's state of body and mind, if exposed to high-level stress during a prolonged period of time. With this state follows a change in activation of the hypothalamic-pituitary-adrenal (HPA)-axis, which regulates the

cortisol proportion in the blood. Chronic stress is thought to be a major factor behind the burnout syndrome (Schaufeli & Enzmann, 1998).

In 1936, Selye introduced the *General Adaptation Syndrome* that followed especially critical situations and reflects the physiological attempt to adapt toward these challenging conditions. In 1949, Walter Cannon further described the stress response as a logic effect of a stressor and that it over time has contributed to human survival. He also describes *the fight and flight response* to acute stress, and the concept *homeostasis* was coined by him.

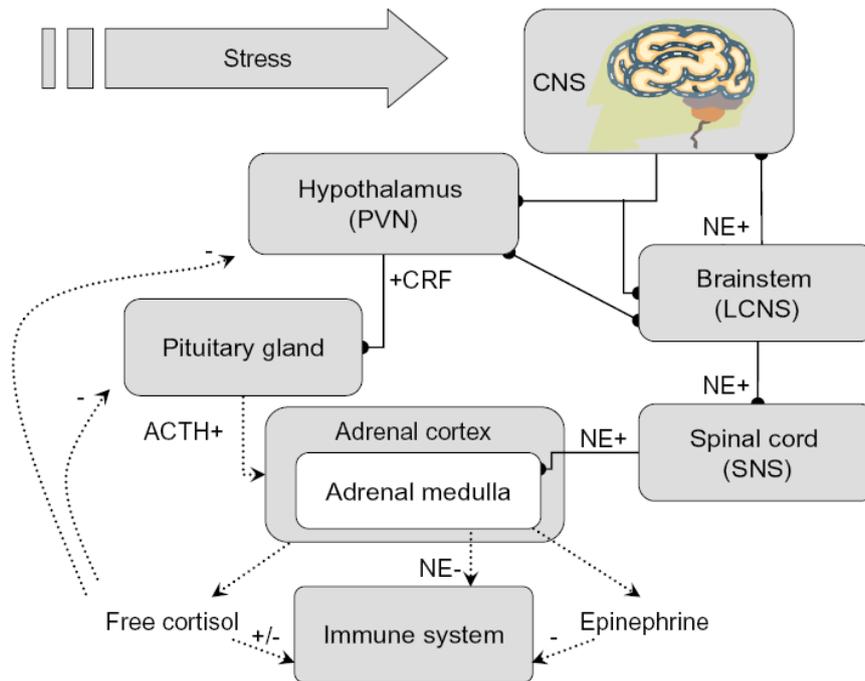
In the early 1960's, a new discovery was made. It was found that neuropeptides could access the brain in rodents and thereby affect cognition and behavior, and that a feedback system regulated the hormone response (de Kloet, 2000). Before that, scientists in the area thought that hormones could only affect the peripheral nervous system and had no access to the brain. McEwen and collaborators (1968) further discovered that corticosteroids affected the rodent brain, especially the hippocampus, which was the region containing most receptors for corticosteroids. These discoveries established the stress-hippocampus link (Lupien & Lepage, 2001).

The concept of allostatic load (McEwen, 2000), referring to the cost the body has to pay for equilibrium, is important in understanding the process that can result in chronic stress states. Allostasis, the physical mechanism to cope with stressors, has normally a protecting function, but if there is no adequate adaptation and the body has no chance to rest, these processes become detrimental. These compensation actions in organs, which normally are working in the favor of homeostasis, are then putting them at risk for developing both physical and psychiatric stress related diseases (de Kloet, Vreugdenhil, Oitzl, & Joëls, 1998).

## Stress and the autonomic nervous system

The sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) are systems belonging to the autonomic nervous system (ANS), connected via brainstem nuclei to the central nervous system (CNS; Elenkov, Wilder, Chrousos, & Vizi, 2000; see Figure 1). ANS regulates the reflex activities in heart, vessels, adrenals, and digestive tract. The main purpose of the ANS is to maintain homeostasis. SNS and PNS activate antagonistically depending on situation. A continuously ongoing basal function preserves sympathetic and parasympathetic tone. The SNS has connections with the whole body, except skeletal muscle fibers. Sympathetic activation at basal level includes regulation of blood pressure and heart rate. The homeostasis could be disturbed by stressors like getting cold, oxygen depletion, muscular strain, severe pain, and psychological factors as emotional excitement. Parasympathetic or cholinergic activation increases heart rate, digestion, contraction of pupil, bladder, and colon.

In the stress response both the sympathetic-adrenal-medulla (SAM) system and the HPA-axis are activated. There are interactions between these two systems such that norepinephrine (NE) from the SAM system could stimulate the activity in the HPA-axis, and corticotrophin-releasing factor (CRF) in the HPA-axis could on the other hand influence the SAM system's release of NE (Gold, Drevets, & Charney, 2002). However, exactly how is not yet clearly understood.



*Figure 1.* Interacting stress response in immune and neuroendocrine systems. The central nervous system (CNS) simultaneously activates the sympathetic-adrenal-medulla (SAM) system and the hypothalamic-pituitary-adrenal (HPA)-axis. Corticotrophin-releasing factor (CRF) from the parvo-ventral nucleus (PVN) stimulates the pituitary gland to release adrenocorticotrophic hormone (ACTH) and affecting adrenal cortex to release cortisol. Activated locus-coeruleus-noradrenergic system (LCNS) in brainstem, release norepinephrine (NE) which arouses the CNS, and activates the sympathetic nervous system (SNS) by noradrenergic fibers, releasing NE. NE affects target organs including adrenal medulla releasing NE and epinephrine, and is acting suppressing on the immune system. High cortisol levels mainly acts inhibitory on the immune system, and on the HPA activation in a feedback loop. Solid lines, neural circuits; dotted lines, hormonal influences; +, activation; -, inhibition.

## The SAM system

Directly when the SNS is activated by stress, there is a sympathetic stimulation of target organs (Figure 1), also called *the fight and flight response*. NE releasing sympathetic fibers origin in cranial nerves and reach out to stimulate target organs (fully described in Elenkov et al., 2000), and these are rapidly activated by second messenger systems in postsynaptic tissues. The SAM system is activated to release catecholamines (CAs) into the blood: NE (which has more long going effects on target organs) and epinephrine hormone. CAs is mainly immuno-suppressive upon anabolic functions like growth, reproduction and gastrointestinal functions. The SAM activation increases pupils, perspiration, heart rate and lung function, depletion of energy stores, and contraction of blood vessels, in a body prepared to take action.

## The HPA-axis

Brain structures and flow involved in the HPA-axis are schematically drawn in Figure 1. In the stress response, CRF is secreted from hypothalamic parvo-ventral nucleus (PVN) into the pituitary portal circulation. This leads to release of adrenocorticotrophic hormone (ACTH) from the pituitary gland into the circulating blood, and is in a few minutes

transported to receptors in the adrenal cortex. Depending on the level of ACTH the adrenal cortex secretes corticosteroids, mainly cortisol (Lupien & Lepage, 2001). Normally, the HPA-axis is inhibited through a negative feed-back loop, which regulates cortisol levels back to normal. Release of CRF, ACTH and cortisol helps to down-regulate stress hormone release, but if the axis has become dysfunctional the feedback does not work. This leads to chronic high levels of cortisol, which may induce neuropathological effects (de Kloet, Joëls, & Holsboer, 2005). The effects of cortisol are most devastating on the hippocampus, because of its high density of cortisol receptors, and that the hippocampus is important regarding cognitive functions.

Five percent of the cortisol is free circulating and the rest is tied to proteins. Receptors for cortisol are mainly sited in hippocampus, but are also present in amygdala, pituitary gland, hypothalamus, and pre-frontal cortex (Alderson & Novack, 2002). Two types of receptors in the brain are activated in a complex network by these corticosteroids, mineralcorticoid receptors (McRs) and glucocorticoid receptors (GcRs). McRs are cited in limbic system, mainly hippocampus, and mediates basal memory consolidation. GcRs are widely spread in the brain, both sub-cortical and in pre-frontal cortex. Cortisol is easily tied to McRs, and when all McRs are involved, GcRs are connected to reach physiological balance, and binding to GcRs inhibits the cortisol release in the HPA-axis (Lupien & Lepage, 2001).

When cortisol levels are repeatedly elevated due to stress, both receptor types are fully occupied, and consolidation of new memories and learning are impaired (Alderson & Novack, 2002; de Kloet, Oitzl, & Joëls, 1999; McEwen & Sapolsky, 1995). HPA dysregulation with chronically high cortisol levels induces neural density loss, dendritic shrinkage in hippocampal CA3 region, and a negatively affected neurogenesis (McEwen, 1999; Lupien & Lepage, 2001). Prefrontal cortex is in the same way affected by chronic high cortisol levels, causing a reorganization of dendrites and thereby fewer synaptic connections (Wellman, 2001).

Chronic increased cortisol levels in blood causes changed activity of GcRs in the brain over time (Gold et al., 2002), it inhibits the feedback loop, and the circadian rhythm with normal morning rise of cortisol is disturbed, leading to an obliterated curve. In even severer outcomes, as in PTSD, there could be a high CRF activation in combination with hypocortisolism (de Kloet et al., 2005).

## The immune response

The immune response is mediated in two ways, by immune cells themselves or by immune cell products like antibodies, defending the body against microorganism (antigen) attacks. White blood-cells, lymphocytes and leucocytes, are transported to their target by circulating blood, and act as the main supervisors of the immune response (Cohen & Herbert, 1996).

Acute stress consolidates immune functions to prepare for a rapid fight or flight response, but states of long-term psychological stress reduces the functions of the immune system (Figure 1; Elenkov et al., 2000). Changes are seen on a cellular level, where chemical messengers from CNS, endocrinal organs and the immune cells are down-regulated due to CAs and corticosteroids. A consequence is a lower communication between the CNS and the immune system, leading to higher risk for inflammation and cancer (Reiche, Nunes, & Morimoto, 2004). Cells in the immune system have receptors for neurotransmitters, neuropeptides, neurohormones, and adrenal hormones. The immune and neuroendocrine system (including the HPA-axis and the SAM system), interact with common mediators and receptors, and are both regulated by the brain. Cytokines are proteins secreted by inflammatory leukocytes and act locally as intercellular mediators. Receptors for both cytokines and adrenal hormones

are found in various places in the brain, and responses to psychological emotions and high chronic stress use the same neurological system as the immune response do (O'Connor, O'Halloran, & Shanahan, 2000; Reiche et al., 2004).

## **Health: Consequences of stress**

The main purpose of the two adaptation systems, the neuroendocrine and the immune system, is to maintain homeostasis. When the adaptation is not working there is a strain on bodily functions (McEwen, 2000). With chronic stress comes a multi-integration of different diseases worth considering: physical disorders like cardiovascular diseases, such as arrhythmia, hypertension and increased risk of coronary heart disease, metabolic changes like insulin resistance, high cholesterol values, and obesity; mental disorders like anxiety, depression, and sleep disturbance (Björntorp, Holm, Rosmond, & Folkow, 2000; Melamed, Kushnir, & Shirom, 1992, Nilsson, Nilsson, Hedblad, & Berglund, 2001).

Cortisol normally enhances the transport of serotonin both in neural tissue and by lymphocytes, but in chronically stressed or depressed individuals the transport limits is reached due to dysregulation of HPA-axis and serotonin levels in synapses are down-regulated. This in turn leads to impaired serotonergic activation, which provides a link between chronic stress and depression (Tafet et al, 2001). Further, nociceptive stimulus is one of many stressors activating the HPA axis and some of the hormones that are active in the stress response are also active in the pain response. Therefore a dysfunctional HPA-axis may also be the common link between chronic pain and depressive states (Blackburn-Munro & Blackburn-Munro, 2001).

## **Cognition: Consequences of stress**

Hippocampus is necessary for declarative memory, which is the memory we could deliberately access and verbally refer to (Squire, 1992). The stress-hippocampus-prefrontal link, refer to the high density of GcRs in hippocampus, which are easily activated by stress, and its further direct connections to prefrontal cortex including a high density of GcRs as well (Lupien & Lepage, 2001).

Working-memory performance is subserved by the prefrontal cortex and foremost sensitive to acute elevations of cortisol (Lupien & Lepage, 2001), while declarative memory consolidation processes are highly affected by corticosteroid influence on synaptic connections in both hippocampus and prefrontal cortex. Long-term potentiation (LTP) refers to a strengthened nerve impulse due to repeated activation, contributing to long-term memory (de Kloet et al., 1999). The consolidation process seems to be cortisol dose dependent, following a reversed u-curve; the best condition for a prolonged LTP is when all the McRs and some of the GcRs are activated.

It has long been known that prolonged periods of physical and psychological stress have aversive effects on the structure and circuitry of the brain, notably the hippocampus and prefrontal cortex (Lupien & Lepage, 2001; McEwen, 1998; Radley et al., 2004). Research examining the effects of chronic exposure of stress hormones on cognition has found impairment of declarative memory, and in aspects of working memory tasks (Alderson & Novack, 2002; Lupien & Lepage).

Earlier research in working-age samples on cognitive functions associated to chronic stress, has not found generally decreased performance, but selective impairment in non-verbal memory, visual and auditory attention (Sandström, Nyström Rhodin, Lundberg, Olsson, & Nyberg, 2005), suggesting frontal cortex dysfunctions, and that chronically

stressed have reduced capacity in tests taxing executive functions. Another study shows that episodic memory during a divided attention task was initially normal in a treatment and control group with high elevated stress levels. After an affect-focused intervention the performance in the treatment group remained at normal level, but was lowered in the control group (Bergdahl, Larsson, Nilsson, Riklund Åhlström, & Nyberg, 2005).

Not only cognition may be affected by the stress-hippocampus-prefrontal link, there are also prefrontal-cortical projections to control limbic functions, regulated by dopaminergic system. These connections, which regulate motivation and goal directed behavior, are using mostly the same receptors as the stress responses do, and are therefore closely related to the HPA-axis and the SAM system (Tafet & Bernardini, 2003). Dopamine is further involved in pre-frontal connections, critical for executive functions such as focusing, planning and making judgments (Moghaddam, 2002; Robbins, 2005).

## RESEARCH OBJECTIVES

The overall goal of the two studies was to study effects of perceived long-term stress, both in a cross-sectional and in a longitudinal way. The objective in the first study was to longitudinally examine consequences of long-term moderately elevated levels of stress for various health outcomes. To address this issue, data covering ten years, were used from the Betula study.

The objective of the second study was to further examine the chronic stress - cognition relationship by comparing patients with chronic stress with controls by means of a broad array of standard neuropsychological tests.

### The Betula study

The Betula prospective cohort study, named after the Latin name of the birch tree (*Betula*), has figuratively speaking its roots in the northern Swedish town, Umeå. The Betula study has recently been carried out for the fourth time, all-encompassing over 4,000 participants. Each participant is randomly drawn from the population registry of Umeå. The first test wave 1988-1990 (T1) was followed by tests every five year (see Table 1). For each subsequent test wave (T2, T3, T4) a new sample was recruited to control for effects of repeated testing. The purpose of the study is to longitudinally examine several variables of cognition and health, and the main focus is on development of memory function and health during adult life span and when growing old, especially regarding early signs of dementia. The test battery includes interviews, questionnaires, and neuropsychological assessments. The examination was conducted by trained testers in two separate test-sessions, each approximately 90-min long. The first test session included health variables and the second test session memory variables (for further description of the study see Nilsson et al., 1997; Nilsson et al., 2004).

Table 1.

*Overview of study design in the Betula study: age-cohorts, test-samples and birth-years. Grey areas are sub-samples involved in Study I*

Test Wave	Sample	Age Cohort														
T1 1988-1990	S1 (n=1000)				35	40	45	50	55	60	65	70	75	80		
	S1 (n=872)					40	45	50	55	60	65	70	75	80	85	
T2 1993-1995	S2 (n=997)			35	40	45	50	55	60	65	70	75	80			
	S3 (n=966)					40	45	50	55	60	65	70	75	80	85	
	S1 (n=727)						45	50	55	60	65	70	75	80	85	90
T3 1998-2000	S2 (n=684)			40	45	50	55	60	65	70	75	80	85			
	S3 (n=830)					45	50	55	60	65	70	75	80	85	90	
	S4 (n=563)		35	40	45	50	55	60	65	70	75	80	85	90		
	S1 (n=560)						50	55	60	65	70	75	80	85	90	95
T4 2003-2005	S3 (n=670)						50	55	60	65	70	75	80	85	90	95
	S5 (n=562)	35	40	45	50	55	60	65	70	75	80	85	90	95		
Year of Birth		1968-70	1963-65	1958-60	1953-55	1948-50	1943-45	1938-40	1933-35	1928-30	1923-25	1918-20	1913-15	1908-10		

## The Stress Clinic

The patients in Study II had stress related health problems and signs of exhaustion and were after screening referred to the Stress Clinic at NUS (Norrlands Universitets Sjukhus), from surrounding health centers and were included in the medical treatment project: Rehabilitation for Stress-Related Disease and Burnout (REST), with the main purpose to evaluate a method of group-based behavior-modification treatment. All patients had an appointment with a physician, a psychologist, and a nurse for further medical examinations before entering the project. From January to May 2003, the patients in Study II, a sub sample of the proposed participants in the REST project, were additionally examined with neuropsychological tests. Most patients, compared to a matched control sample, complained about cognitive dysfunction and the test battery was including several types of tests to evaluate the relationship between chronic stress and cognitive performance in different modalities,

## EMPIRICAL STUDIES

### Study I: Longitudinal analysis of the relation between moderate long-term stress and health

This study was based on three test waves of the Betula study: 1993-1995 (T2), 1998-2000 (T3), and 2003-2005 (T4), see Table 1 (Nilsson et al., 1997; Nilsson et al., 2004). The objective was to study long-term consequences of moderately elevated perceived stress for various health outcomes known to be linked to HPA-axis dysregulation such as

cardiovascular and metabolic conditions (Kopp & Réthelyi, 2004; Korte, Koolhaas, Wingfield, & McEwen, 2005; Öhlin, Nilsson, Nilsson, & Berglund, 2004), immune system and musculoskeletal syndromes (Blackburn-Munro & Blackburn-Munro, 2001; Reiche et al., 2004), and psychiatric conditions (Kopp & Réthelyi; Pedersen, Wan, & Mattson, 2001; Reiche et al.). In this study, sub-samples of two non-clinical population-based samples, sample 1 (S1) and sample 3 (S3) were used. The sub-samples included individuals between 40 and 65 years of age (N=565) from S1 and S3 in the test occasion T2 (baseline). The aim was to study a working-aged sample, not yet retired, to assess components of health that not were affected by the aging population's health problems. Perceived general stress was measured by using a stress scale rated from 0 to 10 with the endpoints 0= not stressed at all, and 10= much stressed. The participants who rated stress from 0 to 4 at baseline and five years after baseline (T3) were included in the low-stress group and those who rated from 5 to 10 were included in the high-stress group. The high – low divide was motivated by the mean stress ratings in T2-T4 (high, the mean rating + 1std up to 10; low, 0 up to the mean rating). The stress measure used in the present study was validated with the Perceived Stress Questionnaire (PSQ) (Levenstein et al., 1993). The stress level was continuously normal in the low-stress group and continuously elevated in the high-stress group from baseline to T3 and T4. After matching for age, gender, and education level the high-stress group finally included 137 subjects and the low-stress group 211 subjects.

At the baseline measure the high-stress group reported significant higher frequency of sleeping problems, fatigue, anxiousness, and mood symptoms. The high-stress group also reported significantly higher frequencies of psychiatric and musculoskeletal conditions at baseline. A repeated measure of stress level and diseases was performed in three test occasions: baseline (T2), T3, and T4. A questionnaire was administered to measure background variables and in an interview the presence of stress related symptoms and treatment of various diseases during the previous five years were recorded. The following diseases were registered at baseline, five (T3), and ten years (T4) after baseline: cardiovascular, diabetes, tumors, psychiatric, and musculoskeletal. The incidence of diseases five years after the baseline assessment showed no differences between the high and low-stress group, but a tendency of higher incidence of psychiatric diseases was observed in the high-stress group. Ten years after baseline there was a significantly higher incidence of psychiatric diseases and tumors in the high-stress group, although the number of tumor cases was low. The cumulative incidence of diseases across the test events five and ten years from baseline showed a pattern of higher incidence in the high-stress group for all five diseases (Figure 2). Although moderate elevated stress level may have a negative impact on health such as psychiatric diseases, especially depression, it still seems that the presence of prolonged moderate stress do not appears to be harmful to health during shorter time intervals.

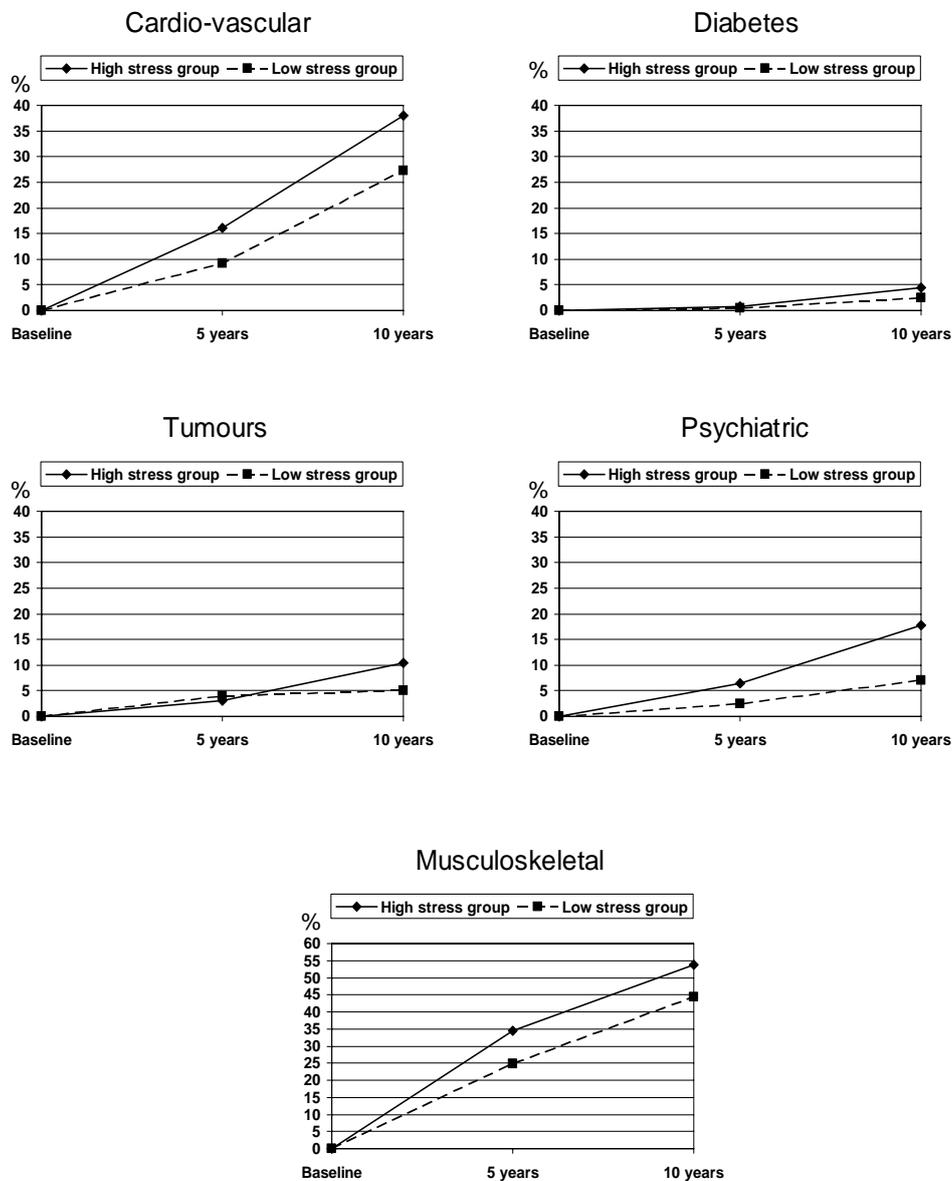


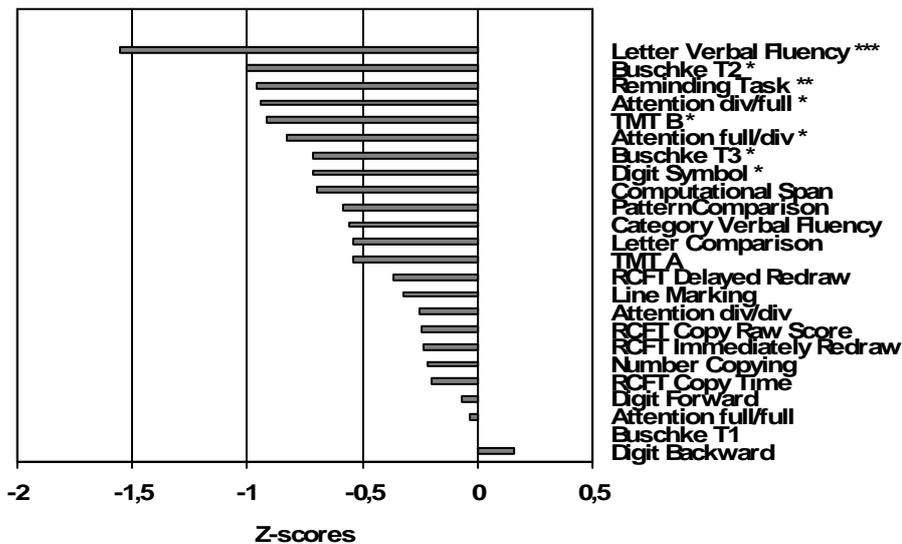
Figure 2. Cumulative incidence of diseases five and ten years after baseline.

## Study II: Cognitive function in outpatients with perceived chronic stress

The chronic stress – cognition relationship was studied with a broad array of neuropsychological tests assessing attention/executive function, working memory, episodic memory, and semantic memory. Extended tests of episodic memory functioning and its relation to attention and/or executive control were performed. There was also of interest to study which cognitive measures that were reliably associated with chronic stress. Nineteen chronic stress outpatients, 13 women and 6 men, and a matched control group (n=19) were included in this study. The patients were recruited to the Stress Clinic, Department of

Occupational and Environmental Medicine, Umeå University, Sweden. Attention and processing speed were assessed with four tasks: Digit symbol from WAIS-R (Wechsler, 1987), Trail Making Test A (TMT A) (Lezak, 1995; Reitan, 1992), Pattern Comparison and Letter Comparison (Salthouse & Babcock, 1991), and Motor Speed Test (Salthouse, 1993). The working memory was measured with: Computational Span (Salthouse & Babcock), Digit Span forward and backwards from WAIS-R (Wechsler), Trail Making Test B (TMT B; Lezak, 1995; Reitan). Regarding testing of episodic memory Free-recall task (Buschke, 1973), Full and Divided Attention examination (Murdock, 1965; Nyberg, Nilsson, Olofsson, & Bäckman, 1997), Rey Complex Figure Test (RCFT; Rey, 1941), and a prospective memory task (Mäntylä & Nilsson, 1997) were administered. To test the semantic memory the Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1989) was used in order to assess letter and category verbal fluency. The intention with choosing this test battery was to assess complex cognitive performance connected to different cognitive domains.

The results showed a significant overall multivariate effect of group indicating lower performance on several cognitive tasks for the chronic stress group. For illustrative purposes, the relative performance of the chronic stress patients across tasks is displayed in Figure 3, portraying the means for the chronic stress group expressed in Z-scores. As can be seen from the figure, a pattern of preserved and inferior performance is observed. The tests of attention and processing speed revealed that the chronic stress patients performed lower on digit symbol tasks compared to the controls and regarding the working memory the chronic stress patients performed worse on the TMT B. The episodic memory testing revealed that learning across trials was compromised in the chronic stress patients relative to the controls. Both the patients and the controls performed equally well in the full encoding/full retrieval and divided encoding/ divided retrieval condition, whereas the performance of the chronic stress patients dropped compared to the controls from full encoding/full retrieval to the divided encoding/full retrieval condition. The chronic stress patients also performed at a lower level in the prospective memory task. The semantic memory tests showed that the chronic stress patients performed worse on letter fluency compared to the controls. Taken together, the results showed that the chronic stress patients demonstrated suboptimal performance on eight of the cognitive measures. Six of these eight cognitive measures were included to study which of the cognitive tests best separated the groups into chronic stress patients and controls (two of the tests were excluded because of high correlations with two other episodic tests). A logistic regression analyze revealed that letter fluency and the prospective memory task best distinguished between chronic stress patients and controls. Conclusively, in this clinical study of patients in working-age suffering from long-term high stress, there was no general impairment in cognitive functions, but aspects of executive functioning was selectively affected compared to matched controls.



\* =  $p < .05$ , \*\* =  $p < .01$ , \*\*\* =  $p < .001$ , according to ANOVAs

Figure 3. Mean performance of the chronic stress patients relative to controls across the cognitive tasks expressed in Z-scores.

## GENERAL DISCUSSION AND CONCLUSIONS

The main goal in this thesis was to evaluate effects of perceived long-term stress in working-age, both cross-sectional and longitudinally. In Study I, potential health consequences of moderately elevated stress over time was studied using data from the Betula study. The Betula study keeps a wide longitudinal data base which makes it possible to study cross-sectional changes in individuals and in groups over time. In keeping with previous findings, it was found that psychiatric diseases, commonly depressive states, were closely related to prolonged elevated stress (de Kloet et al., 2005; Gold et al., 2002). At the baseline measurement (T2), five and ten years prior to the second (T3) and third (T4) measurement in Study I, significantly more subjects reported psychiatric and musculoskeletal problems in the high-stress group compared to those with low stress. To further study the incidence of disease, only those that did not report any disease at baseline were included. The result showed that the high-stress group developed significantly more psychiatric diseases over the following test waves (T3, T4) compared to the low-stress group. These findings indicate that elevated prolonged stress could be important in development of depressed states. Speculatively, personality traits such as insufficient coping strategies could increase the vulnerability to stress. The pattern of cumulatively increasing incidence of diseases, seen in Figure 2, consolidates the interaction that has been suggested between neuroendocrinological and immune systems (Reiche et al., 2004). The relation between high stress and cancer diseases should, however, at present be regarded tentative due to small groups, potentially insufficient self-reports and vague classification of tumors.

The objective of the second study was to study the chronic stress - cognition relationship. The results were based on a cross-sectional comparison of a patient group suffering from chronic stress and matched controls on several neuropsychological tests. A main conclusion of Study II was that executive control functions are negatively affected in

chronic stress. Support for this conclusion was, for example, provided by results from the selective reminding task, in which one could see a lowered performance when a strategy for re-learning was required. In the divided attention task there was a decrease in the ability to allocate attention during dual-task conditions. In the prospective memory task there was a decreased ability to update the memory of the task to remember (McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999; Kliegel, Eschen, & Thöne-Otto, 2004). In the letter fluency task there was a difficulty in fluently coming up with words. Letter fluency requires creative strategic search, while category fluency more depends on knowledge-based semantic memory systems (Martin, Wiggs, Lalonde, & Mack, 1994). All these patterns of performance by the stress patients are reflective of suboptimal executive control processes related to the stress-hippocampus-prefrontal link (Lupien & Lepage, 2001).

The results of Study II underscore the need to use memory measures that are sufficiently demanding and evaluate several components of memory as well as executive control. In particular, the results indicated that it would be of value to include tests of word fluency and possibly also prospective memory. In keeping with the present findings, previous studies of cognitive impairment in chronic stress samples of working-age have not revealed generally decreased performance, but selective impairment such as lowered episodic memory during a divided attention task (Bergdahl et al., 2005) and impairment in non-verbal memory and visual and auditory attention in burnout patients (Sandström et al., 2005). Collectively, these findings are indicative of frontal cortex dysfunction. Likewise, research on post traumatic stress disorder has also shown selective deficits in prefrontal mediated tasks (Koenen et al., 2001).

An objection to the conclusion that chronic elevated stress has negative effects on cognition could be that the stress patients generally have lower levels of motivation. However, as the performance in the patient group was not generally poorer, not dropping over time, and rather selective to specific cognitive domains and task conditions, this objection may not implicate serious consequences for Study II.

In conclusion, the present results support the following more general conclusions regarding the interaction between moderate chronic stress, health and cognition. First, psychiatric illness (notably depression) was the health condition that was most affected by moderately heightened stress levels. Second, cognitive impairment was task-dependent, with fairly pronounced decreases on cognitive functions mediated by prefrontal regions. The observed link between stress and health as well as between stress and cognition suggests that a dysfunctional HPA-axis is a common factor behind a variety of problems among chronically stressed. At the same time, it should be noted that these studies generally present relatively small effects, suggesting that prolonged moderate stress may not be as harmful to health and cognition as may have been expected on basis of studies of individuals suffering from more severe stress. However, future studies are necessary to further examine how moderately elevated chronic stress in working-age interact with cognition and health.

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