



PhD thesis

Rikke Hinge Carlsson

2015

**Physiological stress reactions: Intervention of psychosocial
work environment – distress and rehabilitation**

Department of Occupational and Environmental Medicine

Bispebjerg Hospital



**Bispebjerg
Hospital**

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Academic advisor: Åse Marie Hansen

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Department of Occupational and Environmental Medicine

Bispebjerg Hospital

Faculty of Health and Medical Sciences

University of Copenhagen

This PhD thesis is based on the following original papers:

Study I

Carlsson RH, Hansen ÅM, Kristiansen J, Nielsen ML, Blønd M, Netterstrøm B

“Workplace reorganization and changes in physiological stress markers”

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Study II

Carlsson RH, Hansen ÅM, Kristiansen J, Nielsen ML, Blønd M, Netterstrøm B

“Changes in Allostatic Load during workplace reorganization”

Submitted

Study III

Carlsson RH, Hansen ÅM, Netterstrøm B

“Measuring Allostatic Load during a stress treatment intervention”

Submitted

Supervisors

Åse Marie Hansen, PhD, Professor

Department of Public Health

Faculty of Health

University of Copenhagen

Denmark

Affiliated to the National Research Centre for the Working Environment

Bo Netterstrøm, MD, DSc

Department of Occupational and Environmental Medicine

Bispebjerg Hospital

Denmark

Evaluation Committee

Naja Hulvej Rod, MS, PhD, Professor

Department of Public Health

University of Copenhagen

Denmark

Tores Theorell, MD, Professor

Institute for Stress Research

Stockholm University

Sweden

Nanna Hurwitz Eller, MD, DSc

Department of Occupational and Environmental Medicine

Bispebjerg Hospital

Denmark

List of abbreviations

AL	= Allostatic Load
HPA	= Hypothalamic-Pituitary-Adrenal
CORT0	= Cortisol at Awakening
ACR	= Awakening Cortisol Response
DHEAS	= Dihydroepiandrosterone-Sulfate
SBP	= Systolic Blood Pressure
DBP	= Diastolic Blood Pressure
HRV	= Heart Rate Variability
TPw	= Total Power, work
TPs	= Total Power, sleep
LF/HFw	= Low Frequency/High Frequency, work
LF/HFs	= Low Frequency/High Frequency, sleep
HBA1C	= Glycated Haemoglobine
TCHOL	= Total Cholesterol
HDL	= High Density Lipoprotein Cholesterol
BMI	= Body Mass Index
WHR	= Waist-Hip-Ratio
CRP	= C-Reactive Protein
IL6	= Interleukin 6
FIBR	= Fibrinogen
HRV	= Heart Rate Variability
RTW	= Return to Work
SCL92	= Symptom Check List-92
GSI	= Global Severity Index
CBT	= Cognitive Behavioral Therapy
ERI	= Effort Reward Imbalance
OSH	= Organizational changes, Stress and Health

Preface

This PhD thesis concludes the project “Physiological stress reactions: Intervention of psychosocial work environment – distress and rehabilitation” and was carried out at the Department of Occupational and Environmental Medicine, Bispebjerg Hospital and at the Department of Public Health, Faculty of Health, University of Copenhagen. The project is was funded by the Danish Working Environment Research Fund and aims to investigate physiological stress reactions of long-term stress.

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1. Introduction

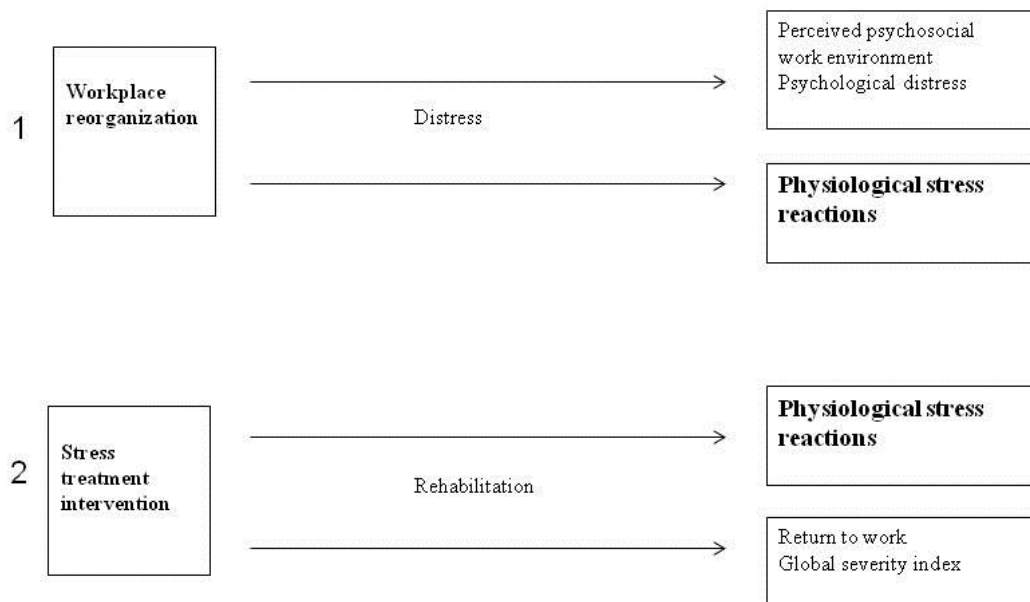
Stress is the individual response to a stressor, and a stressor is the exposure releasing the stress response. The type of stressor can be psychological, physical, chemical, or biological. A stress condition is characterized by an activation of different biological systems together with mental and behavioural processes. Still the definition of stress is unclear. Walter Cannon popularized the concept of homeostasis and used stress to refer to external factors that disrupted homeostasis. Moreover, he coined the term “fight or flight” to describe an animal’s response to a threat (Cannon 1932), later recognized as the acute stress response of a general adaptation syndrome, postulated by Hans Selye to be a universal stress response among vertebrates and other organisms. He asserted that prolonged exposure to stressors resulted in “diseases of adaptation” (Selye 1936). Although the definition is still discussable, it is important to distinguish between acute and chronic stress, the latter also referred to as long-term stress. Acute stress is natural and important, whereas long-term stress might have negative consequences from a personal and social point of view.

The physiological reactions of acute stress are well known and are essential to protect the body and adapt to the environment. Probably, the same physiological mechanisms are involved in the reactions of long-term stress (Sapolsky 2004) (Chrousos 2009). Acute and long-term stress reactions promote adaptation via responses of neural, cardiovascular, autonomic, immune, and metabolic systems, including several physiological markers (McEwen 2008). All of these systems operate through allostasis defined by Sterling and Eyer as the regulatory process of maintaining physiological stability (Sterling, Eyer 1981). The term allostatic load (AL) describes the lack of recovery or the result from chronic overactivity or underactivity of allostatic systems (McEwen 1998).

It is well documented that impaired psychosocial work environment increases the risk of developing cardiovascular disease (Eller et al. 2009) (Backe et al. 2012) and depression (Bonde 2008) (Netterstrom et al. 2010). Moreover, other diseases, such as allergy, asthma, and various autoimmune conditions, seem to aggravate (Agarwal, Marshall 2001) (Chrousos 1995) (Marshall 2011). The pathological mechanisms linking impaired psychosocial work environment and disease may be prolonged physiological stress reactions.

This thesis covers the physiological stress reactions (physiological stress markers and AL) of both distress and rehabilitation during two different types of intervention related to psychosocial work environment: 1. Workplace reorganization and 2. Stress treatment intervention (Figure 1).

Figure 1. Design PhD thesis

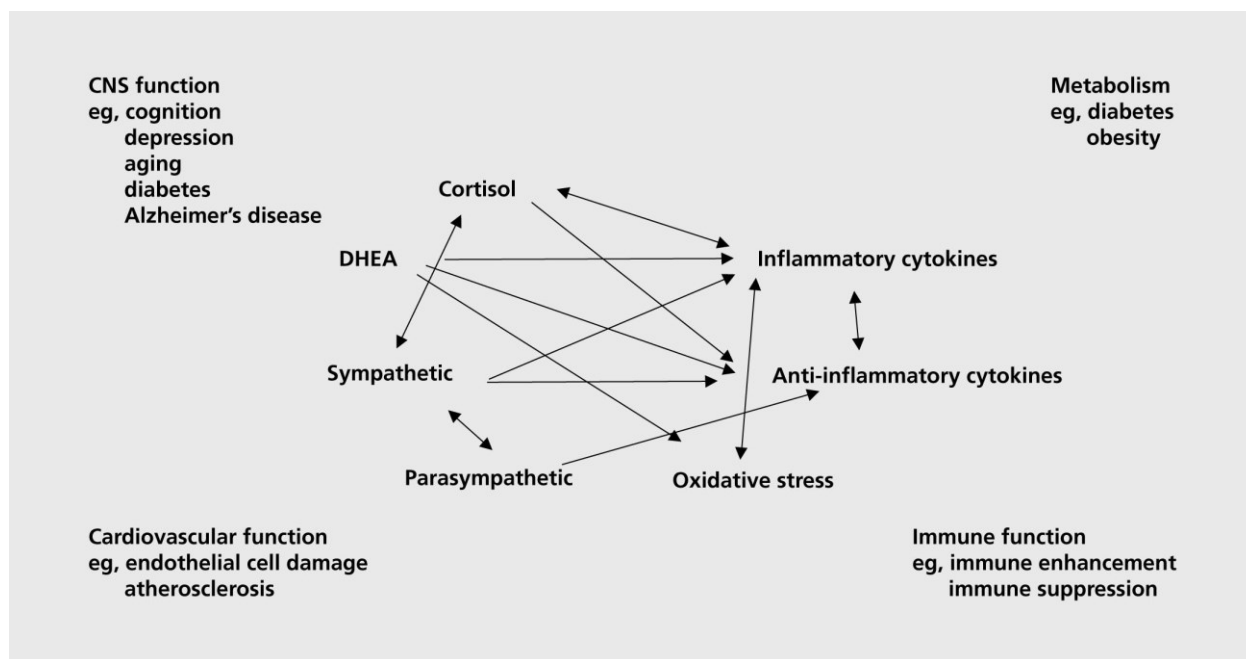


1.1 Physiological stress reactions

1.1.1 Physiological stress markers

The sympathetic-adrenal-medullary axis' release of catecholamines and the hypothalamic-pituitary-adrenal (HPA) axis' secretion of glucocorticoids initiate stress reactions, and cortisol and adrenalin are the major stress hormones often thought of in connection with stress. However, the reactions involve other important hormones/mediators as pro- and anti-inflammatory cytokines that regulate each other and are also regulated by glucocorticoids and catecholamines. Moreover, the parasympathetic nervous system, that opposes the sympathetic nervous system and has an anti-inflammatory effect, also plays an important role in the stress reactions. The interaction between all these hormones and mediators is very complex and interconnected in a non-linear network (McEwen 2008) (Juster, McEwen & Lupien 2010) (figure 2).

Figure 2. Nonlinear network of mediators of allostasis involved in the stress response



(McEwen 2008)

Primary mediators refer to stress hormones and their antagonists in conjunction with pro- and anti-inflammatory cytokines. Primary effects of these mediators are both central functions of the stress response and the influence on peripheral functions resulting in secondary outcomes of the

cardiovascular, metabolic, and immune/inflammatory system (Chrousos 2009). If the stress response continues this may result in a culmination of physiological dysregulation in the form of disease referred to as tertiary outcome (Juster, McEwen & Lupien 2010) (McEwen, Wingfield 2003). Figure 3 describes physiological stress reactions and more specifically, the different biological systems and physiological markers included in this thesis to reflect primary mediators/effects and secondary outcomes (figure 3).

Figure 3. Physiological stress reactions

	Description	Expected stress reaction
Primary mediators/effects		
Neuroendocrine system	Mediation of secondary outcomes Facilitation of cognitive functions Inhibition of vegetative functions Activation of counter-regulatory feedback loops	
- Cortisol (salivary) Cortisol at Awakening (CORT0) (nmol/l) Awakening Cortisol Response (ACR) (nmol/l)	Principal glucocorticoid hormone secreted by the adrenal cortex 2-15% of cortisol released remains unbound/free, only free cortisol in saliva Circadian rhythm, increase in the early morning hours (awakening cortisol), peaking 30 min after awakening (awakening cortisol response), decreases steadily, lowest evening/night Influence on metabolic catabolism (gluconeogenesis, glycogenolysis, lipolysis)	↑
- Dihydroepiandrosterone-sulfate (DHEAS) (μmol/l)	An adrenal-derived steroid and precursor of sex-hormones Present in the blood largely as its sulfated derivative, DHEAS Antagonist to the effects of cortisol and has a regenerative and protective role during acute stress (Lennartsson 2013)	↓
Secondary outcomes		

Cardiovascular system	Increased cardiovascular tone (heart rate and blood pressure) Increased oxygenation (nutrition of brain, heart and skeletal muscles)	
- Blood Pressure Systolic Blood Pressure (SBP) (mmHg) Diastolic Blood Pressure (DBP) (mmHg)	The peak pressure reached in the arterial system is systolic blood pressure, the lowest pressure as the heart relaxes is diastolic blood pressure Hypertension is defined as systolic blood pressure of ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg	↑
- Heart Rate Variability (HRV) Total Power, work (TPw) (m^2) Total Power, sleep (TPs) (m^2) Low Frequency/High Frequency, work (LF/HFw) (ratio) Low Frequency/High Frequency, sleep (LF/HFs) (ratio)	Rhythmic changes in heart rate over time Used to measure parasympathetic influence on the heart	↓
Metabolic system	Increased metabolism in the form of catabolism and inhibition of reproduction and growth	
- Glycated Haemoglobine (HBA1C) (mmol/l)	A marker of average blood glucose levels over the previous months Indicator of poorer control of diabetes mellitus associated with increased risk of cardiovascular disease	↑
- Total Cholesterol (TCHOL) (mmol/l)	Circulates in lipoproteins and most important function is formation and permeability of cell membranes The sum of high-, low- and very low-density lipoprotein-cholesterol High concentrations associated with coronary heart disease	↑

- High Density Lipoprotein Cholesterol (HDL) (mmol/l)	Transport cholesterol from blood to primary liver Protective effect against coronary heart disease	↓
- Body Mass Index (BMI) (kg/m ²)	Measure of body fat based on height and weight (mass, kg/height, m ²)	↑
- Waist-Hip-Ratio (WHR) (ratio)	Ratio of circumference of waist to that of the hips “Apple-shape” associated with higher health risk than “Pear-shape”	↑
Immune/inflammatory system	Increase of detoxification of metabolic products and foreign substances Activation of counter-regulatory feedback loops (inclusive of immune-suppression)	
- Interleukin 6 (IL6) (µmol/l)	Major initiator of acute phase response and primary determinant of CRP production Pro- and anti-inflammatory actions	↑
- C-Reactive Protein (CRP) (mg/l)	Indicator of acute inflammation, rises up to 50,000 fold An acute phase reactant and very useful as a general inflammation marker It is an object of discussion whether the clinical applicability of CRP regarding risk of cardiovascular disease is useful in the light of newer quantification techniques to improve the sensitivity of this marker in contrast to the point of view that CPR is a too non-specific marker (Salazar et al. 2014)	↑
- Fibrinogen (FIBR) (µmol/l)	Acute-phase reactant that responses to infection, chronic inflammation, smoking, environmental factors Can convert to fibrin, a structural component of blood clots and indicate increased risk of cardiovascular disease	↑

(Fink 2010)(Chrousos 2009)

Several studies have investigated the association between psychosocial work environment and physiological stress markers. Some markers such as cortisol are more investigated than others.

However, the association between psychosocial work environment and cortisol is inconsistent across studies (Karlson B et al 2012). In a review of 147 eligible studies, Chida et al found positive association between an increase of awakening cortisol response and job stress (Chida, Steptoe 2009). DHEAS is an antagonist to the effects of cortisol, and in a Swedish study, the authors found perceived stress at work to be associated with attenuated DHEAS response during acute psychosocial stress in the form of Trier Social Stress Test. Moreover, the ratio between the cortisol and DHEAS production during the test were highest in participants reporting higher perceived stress at work (Lennartsson et al. 2013).

In relation to the cardiovascular system, blood pressure or hypertension is frequently investigated. A recent review pointed out a relationship between psychosocial work environment and hypertension. However, the author also put focus on the problematic aspects of the subject such as different models for measuring and assessing effect and varying time spans and outcome variables (Rosenthal, Alter 2012). The result of this review corresponds to other studies (Steenland et al. 2000), (Sparrenberger et al. 2008). The clinical relevance of HRV is the association with cardiovascular disease (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996) indicating that a low HRV may be associated with increased cardiovascular disease-related morbidity and mortality (Kristal-Boneh et al. 1995). A recent review evaluated and summarized the evidence of the association between psychosocial work environment indicated by several work-stress models and HRV. The authors found workplace stressors to associate with low HRV and more specifically, a decreased neural vagal control of the heart indicating diminished adaptation of the autonomic nervous system (Jarczok et al. 2013). HRV might link to cardiovascular disease through factors related to the metabolic syndrome (Thayer et al. 2010).

Various physiological changes define the metabolic syndrome of which insulin resistance is the primary metabolic defect. In addition, the syndrome includes abdominal obesity, dyslipidaemia, and hypertension. In a prospective follow-up study from 2005 using data from the Whitehall II study, the authors observed a significant association between high job strain and metabolic syndrome (Chandola, Brunner & Marmot 2006). Concerning the specific physiological markers related to the metabolic system and included in metabolic syndrome, a Danish study found only HBA1C to associate significantly with impaired psychosocial work environment (Hansen et al. 2009).

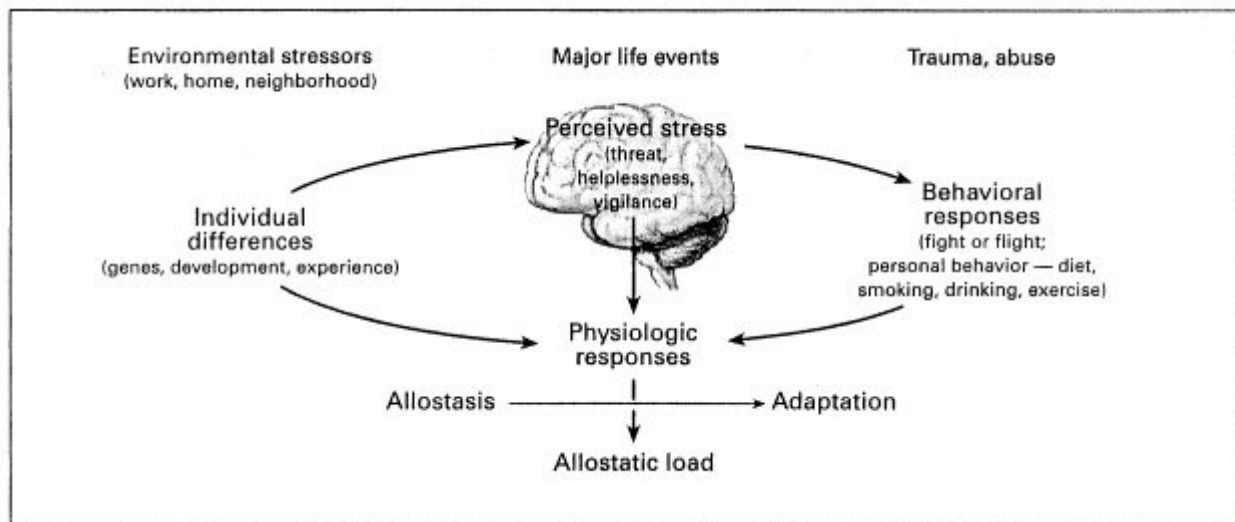
Markers of the immune/inflammatory system might be involved as both primary mediators and secondary outcomes (Juster, McEwen & Lupien 2010). A recent review investigated the possible association between psychosocial job stress and immune parameters in blood, saliva, and urine, concluded from 56 different studies. The authors found job stress to be associated with various immune parameters indicating disrupted immune function (Nakata 2012). An earlier review by Glaser noted an association between long-term stress and an increased risk of infectious disease. Moreover, numbers of cases with delayed wound healing and risk of reactivation of latent infections such as herpes virus increased (Glaser, Kiecolt-Glaser 2005). Concerning the more specific physiological markers related to the immune/inflammatory system, different studies found positive association between psychological distress and CRP and IL6 (Owen et al. 2003) (Kiecolt-Glaser et al. 2003) (Janicki-Deverts et al. 2008) (Hintikka et al. 2009). A Danish review stated that increased FIBR was a potential candidate for a physiological effect associated with adverse psychosocial work environment (Hansen et al. 2009).

1.1.2 Allostatic Load

Physiological systems activated by stress can protect and restore the body, and the ability to physiologically adapt to the environment is of importance for the health. Different terms describe the concept of physiological equilibrium. Homeostasis means “steady state” and homeostatic systems such as blood pH and body temperature must be maintained within narrow ranges of normal values (Cannon 1932). Allostasis means “the ability to achieve stability through change” and allostatic systems have, in contrast to homeostatic systems, much broader boundaries, also expanding outside normal values (Sterling, Eyer 1988). In other words, allostasis differs from homeostasis by operating with dynamic rather than static biological set-points (Schulkin 2003). The concept of allostasis and AL emphasizes the non-linear and complex interactions of multiple mediators and also include behavioural and physiological consequences of the individual response to a long-term stressor (figure 4). McEwen and Stellar defined AL as “wear and tear” or strain on the body produced by repeated ups and downs of physiologic response under challenge predisposing the organism to disease (McEwen, Stellar 1993). AL represents the cumulative physiological dysregulation and can incorporate multiple stress sensitive allostatic systems involving relevant physiological markers. Different studies have shown this comprehensive measure to better predict future health risks than any single factor on its own (Seeman et al. 2001) (Karlmanjla et al. 2002). The AL model includes measures of multi-systemic interactions among

primary mediators and effects, relevant markers representing secondary outcomes and thereby detection of individuals at high risk of tertiary outcomes also called allostatic overload (Juster, McEwen & Lupien 2010).

Figure 4. The stress response and development of Allostatic Load



(McEwen 1998)

The MacArthur Studies of Successful Aging provided the first steps towards an operational definition of AL by using a count-based AL including 10 physiological markers. First, they dichotomized each marker as score “1” for markers falling within the highest or lowest quartile associated with increased risk of disease or poorer health, or as score “0” for scores falling within the other three quartiles. Then they summed the scores of all markers into a cumulated AL score (0-10). The design of the measure of AL summarized levels of physiological activity across a range of relevant regulatory systems in relation to disease risks; SBP and DBP (cardiovascular activity), WHR (metabolic, glucocorticoid activity), HDL and TCHOL (atherosclerotic risk), HBA1C (glucose metabolism), DHEAS (HPA axis antagonist), cortisol (HPA axis activity), and norepinephrine and epinephrine (sympathetic nervous system activity). The cross-sectional findings showed high AL to be related to lower functioning, poorer cognitive performance and weaker physical performance. At follow-up after 3 years, high AL at baseline showed significantly greater declines in cognitive and physical functioning and increased risk of cardiovascular disease (Seeman

et al. 1997). They found the same results after a 7-year follow-up and moreover, a relation between AL and increased risk of all-cause mortality (Seeman et al. 2001). A recent review detailed the existing measures of AL and noted “the group AL index” defined by Seeman et al as the traditional and still most often used measure (Juster, McEwen & Lupien 2010). However, it is important to have in mind that this traditional measure was first operationalized to predict cognitive and physical functioning, disease, and mortality in ageing studies. Therefore the division of the range into clinically high-risk and low-risk levels may be too coarse for other purposes. It might also be interesting to focus on the distribution of values in the low-risk levels and observe physiological changes within individuals as a predictor of disease later in life (Seplaki et al. 2005).

Subsequent research in this area has developed to focus also on psychosocial work environment and AL. Several studies have shown empirical substantiation for this relationship (Juster, McEwen & Lupien 2010) (Beckie 2012). In a German study of industrial workers, an association between increased job demands and high AL was found (Schnorpfeil et al. 2003). Another study among Chinese industrial workers observed an association between low job control and increased glucolipid AL (Li, Zhang & Wang 2007) and in a sub-study of the same cohort, an association between high job demands and, low decision latitude and high AL (Sun et al. 2007). In another German study including female schoolteachers, there was observed association between great effort-reward imbalance and modestly high AL (Bellingrath, Weigl & Kudielka 2009), and in a Swedish study association between lack of recovery from work stress and increased AL was observed (von Thiele, Lindfors & Lundberg 2006b). A later Swedish study on the same data showed association among middle aged women and high AL for work in the health care sector rather than for work within in information technology (Hasson, Von Thiele Schwarz & Lindfors 2009). In studies investigating burnout or exhaustion as a consequence of stressful working conditions, a study among Dutch telecom managers showed no relation between AL and burnout or exhaustion (Langelaan et al. 2007). In contrast to this, another study among healthy, educated, Canadian workers showed relation between increased AL and high frequency of burnout symptoms (Juster et al. 2011). All of these studies used cross-sectional designs.

1.2 Intervention

1.2.1 Workplace reorganization

Employees confront with increasing numbers of organizational change at work at different levels ranging from minor daily stressors related to changes in technology and workplace practices to

major upheavals of mergers, downsizing, and restructuring (Sikora PB, Beaty ED, Forward J 2004) (Di Nunzio D, Hohnen P, Hasle P et al 2009).

A major reorganization of non-state public offices took place in Denmark on 1 January 2007. Before reorganization, the non-state public sector in Denmark had two levels of administration: The counties and the municipalities. After reorganization, most of the 14 counties and 275 municipalities merged into larger units; the 14 counties merged into five regions, and the 275 municipalities merged into 98. Typically, 2-4 units merged, but one county experienced only minor changes compared to the rest and 25 municipalities remained unmerged.

Research in this area has shown workplace reorganization to cause impaired psychosocial work environment and have negative health consequences (Kivimaki et al. 2000) (Kivimaki et al. 2001) (Netterstrom, Hansen 2000). More specifically, the health effects of different types of intervention during workplace reorganization have been investigated in two different reviews. Egan et al. investigated the health and psychosocial effects of increasing employee participation and control through workplace reorganization including 18 studies and identified evidence suggesting that some organizational-level participation interventions may benefit employee health (Egan et al. 2007). Closely related to this review, Bambra et al. investigated the health and psychosocial effects of changes in work environment through task structure work reorganization. They found that task-restructuring intervention that increased demand or decreased control had a negative effect on health (Bambra et al. 2007). A recent Danish review including 17 studies, both cross-sectional and longitudinal, observed an association between organizational change and elevated risk of mental problems in 11 of 17 studies. However, the authors concluded the review to provide insufficient evidence of this association and that more studies of long-term effects are required (Bamberger et al. 2012). Workplace reorganization may cover both workplace expansion and downsizing, of which the latter can involve job insecurity. There is evidence for an association between job insecurity and poor health although much of the research is limited to cross-sectional studies and self-reported outcomes (Sverke, Hellgren & Naswall 2002) (Laszlo et al. 2010) (Kim et al. 2012). Different studies investigated downsizing and found this kind of workplace reorganization to have negative health consequences in the form of increased sickness absence (Vahtera, Kivimaki & Pentti 1997) (Kivimaki et al. 2001). A review investigating downsizing and health found that 85% of the included studies indicated negative effects on health (Quinlan, Bohle 2009). Concerning workplace expansion, a Swedish study found a relationship between workplace expansion and an

increased risk of long-term sickness absence and hospital admissions. The strongest association was among women in the public sector (Westerlund et al. 2004).

Studies investigating the association between workplace reorganization and physiological stress reactions are few. In a Danish study evaluating the physiological effects of changes in workplace reorganization due to outsourcing of bus routes, the results suggested that the change in psychosocial work environment led to prolonged stress among employees and that urinary cortisol, HBA1C, DHEAS, and ambulatory measurements of blood pressure were useful measures (Netterstrom, Hansen 2000). These physiological stress reactions of workplace reorganization correspond with different other studies. In a study investigating the effect of downsizing, the authors observed a possibly flattened circadian cortisol rhythm indicating physiological dysfunction (Hertting, Theorell 2002). In another study investigating job insecurity, there was observed an increase in blood pressure among women who lost job security and a decrease in body mass index among women reporting chronic job insecurity (Ferrie et al. 2002). Finally, a cross-sectional Swedish study investigated the relation between job insecurity and AL and found that job insecurity was unrelated to AL. However, the results also showed that job insecurity was related to poor self-rated health and increased morning cortisol levels (Naswall, Lindfors & Sverke 2012).

1.2.2 Stress treatment intervention

The result of different studies documents a relationship between impaired psychosocial work environment and the prevalence of mental disorders, such as depression, anxiety, adjustment disorders, and other stress-related conditions (Andersen, Nielsen & Brinkmann 2012) (Netterstrom et al. 2008). Furthermore, long-term stress associates with loss in productivity, short- and long-term sick leave and early retirement (Cancelliere et al. 2011) and places a substantial burden on the economics of many developed countries (Goetzel et al. 2004) (Henderson, Glozier & Holland Elliott 2005) (van der Klink, van Dijk 2003). Therefore, the interest in evaluation of the effects of stress management intervention on the Return to Work (RTW) is growing, and reviews and evaluation studies have found positive effects on the RTW rate through such interventions (Blonk, Brenninkmeijer & Lagerveld 2006) (Franche et al. 2005) (van der Klink, van Dijk 2003).

In the period June 2010 to September 2010, general practitioners in the Capital region of Denmark received an invitation to refer patients with stress symptoms to an intervention study based on the effects of a multidisciplinary stress treatment program. The program targeted stress reduction and RTW and included participants on sick leave. The stress treatment intervention significantly

reduced symptom levels measured by scores on the Symptom Check List-92 (SCL92) used to calculate the Global Severity Index (GSI) (Olsen, Mortensen & Bech 2004a) and increased the RTW rate in the intervention group compared with a control group (Netterstrom, Friebel & Ladegaard 2013). This result corresponds to two meta-analyses including studies on intervention directed at members of the working population and concluding stress management intervention to be effective compared to no treatment (van der Klink et al. 2001) (Richardson, Rothstein 2008). A recent review of existing systematic reviews assessed the effectiveness of individual, organizational, and mixed interventions on mental health and absenteeism as outcomes. Concerning individual intervention, the review concluded Cognitive Behavioural Therapy (CBT) to improve mental health (Bhui et al. 2012). The stress treatment intervention consisted of stress-coping sessions based on CBT and was directed to both the worker and the workplace, inspired by Swedish experiences (Arnetz et al. 2003) (Anderzen, Arnetz 1999) (Anderzen, Arnetz 2005). Moreover, an 8-week mindfulness-based stress reduction programme developed by Jon Kabat-Zinn (Kabat-Zinn et al. 1992) was part of the intervention and in previous research showed to have a positive effect on mental health symptoms (Fjorback et al. 2011) (Baer 2003) (Greeson 2009).

Few studies have investigated the association between stress treatment intervention and physiological stress reactions. In a study by Mommersteeg et al., a psychotherapeutic intervention led to a significant reduction in burnout complaints and to an increase of initially low morning cortisol levels (Mommersteeg et al. 2006b). A recent study by some of the same authors showed that a mindfulness-based stress reduction intervention might help reduce blood pressure levels and blood pressure reactivity to stress (Nyklicek et al. 2013). No studies so far have investigated the relation between stress treatment intervention and AL.

1.3 Conclusions leading to the aim of this thesis

- Impaired psychosocial work environment increases the risk of developing disease (Eller et al. 2009) (Backe et al. 2012) (Bonde 2008) (Netterstrom et al. 2010).
- Several physiological markers have been investigated in relation to psychosocial work environment but the results are inconsistent (Karlson B et al 2012) (Rosenthal, Alter 2012) (Jarczok et al. 2013) (Hansen et al. 2009).
- Several studies have found association between impaired psychosocial work environment and AL but most of them by use of cross-sectional designs (Beckie 2012).
- Few studies have investigated the physiological stress reactions of distress during a workplace reorganization and rehabilitation during a stress treatment intervention.

2. Aim of the thesis

The aim of this thesis is to investigate physiological stress reactions (physiological stress markers and AL) of both distress and rehabilitation during two different types of intervention: 1. Workplace reorganization and 2. Stress treatment intervention.

Study I

The study “Workplace reorganization and changes in physiological stress markers” aims

- to investigate changes in physiological stress markers as a consequence of workplace reorganization.
- to investigate changes in the perceived psychosocial work environment (job strain, effort-reward imbalance (ERI)), in psychological distress (stress symptoms, perceived stress), and the association between changes in these psychological markers and changes in the physiological stress markers.

Study II

The study “Changes in Allostatic Load during workplace reorganization” aims

- to investigate changes in AL during workplace reorganization.
- to investigate the association between changes in the perceived psychosocial work environment (job strain, ERI) and psychological distress (stress symptoms, perceived stress) and changes in AL.

Study III

The study “Measuring Allostatic Load during a stress treatment intervention” aims

- to investigate changes in AL during a stress treatment intervention.
- to investigate the association between changes in AL, and RTW and changes in GSI.

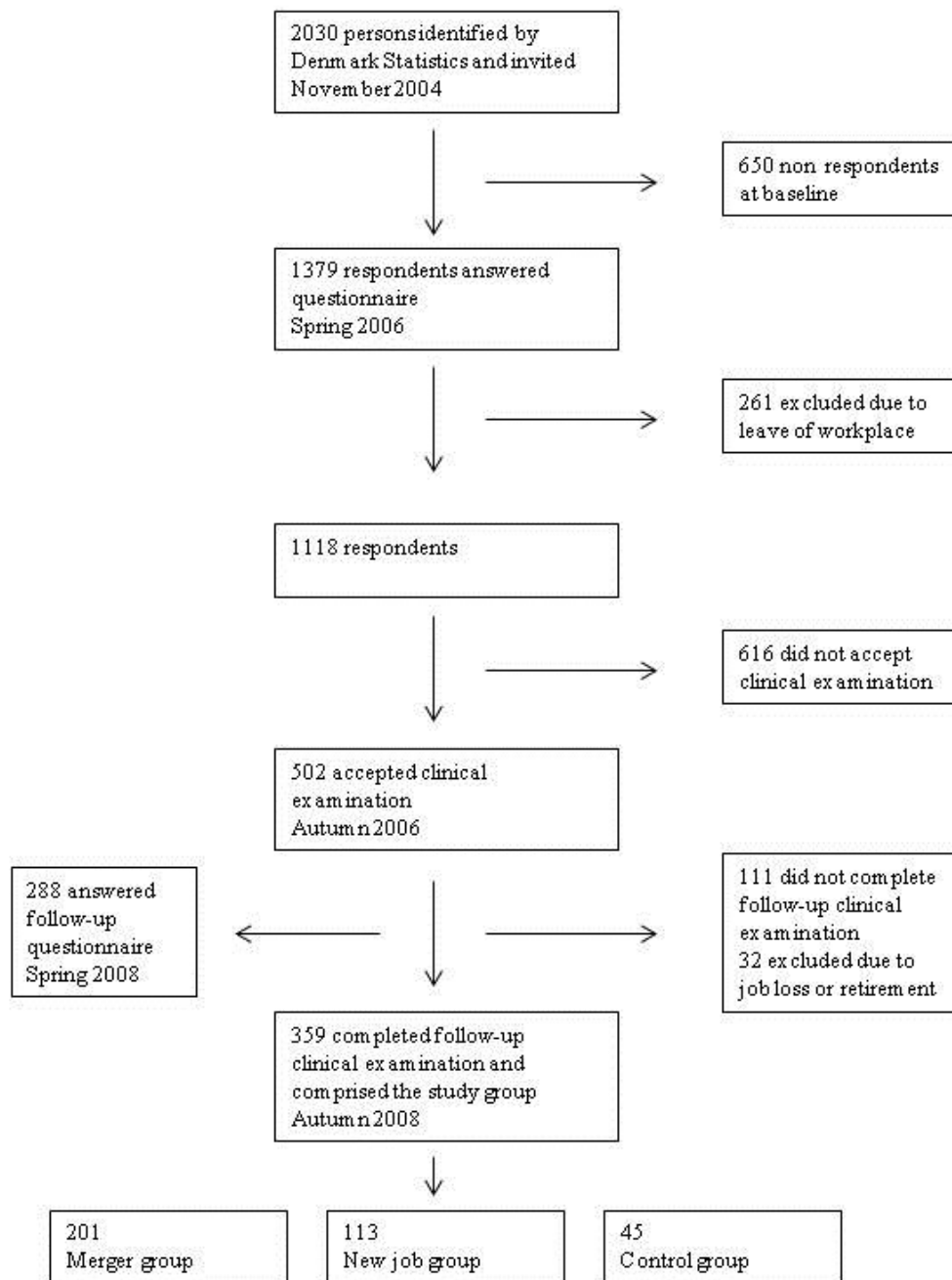
3. Material and methods

3.1 Workplace reorganization (study I and II)

3.1.1 Design and population

The study Organizational changes, Stress and Health (OSH) included white-collar employees in the administration of five municipalities and two counties based on the knowledge of the impending mergers. Four municipalities and one county merged with others, while one municipality and one county remained unmerged with only minor changes in tasks. We used data from questionnaires and clinical data collected in spring and autumn 2006 and 2008. The study group comprised 359 participants, 265 women and 94 men. The original design of the OSH study was based on cases and controls in the form of merging or not. From the information given in the questionnaire about workplace in spring 2006 and in autumn 2008, we divided the participants into three reorganization groups: 1. Merger, 2. New job, and 3. Control. Of the 359 participants, 201 employees from the four municipalities and one county that merged with other units on 1 January 2007 formed the merger group. The new job group consisted of 113 participants who got new jobs outside the organization during follow-up. The control group consisted of 45 participants employed in the one municipality and the one county that did not merge with other units, and who also answered in the questionnaire to have the same job tasks before and after the reorganization (figure 5).

Figure 5. Flowchart workplace reorganization



3.1.2 Physiological assessment (study I and II)

According to known physiological stress responses (McEwen 2008), we included physiological stress markers of the neuroendocrine, the cardiovascular, the metabolic, and the immune/inflammatory system (figure 3). The collection of physiological data took place in cooperation with the laboratory at Hillerød Hospital and with the National Research Centre for the Working Environment, Denmark.

The neuroendocrine system

For determination of DHEAS in serum, we used a radio immune assay (Siemens Medical Solutions Diagnostics AB, Mölndal, Sweden). To measure salivary cortisol the participants received Salivette® cotton swabs and instructions to collect the first sample immediately after awakening, while still in bed, and another sample 30 minutes after awakening. The samples were kept frozen at minus 20 degrees until analysis was carried out according to the manufacturer's specifications with a competitive radioimmunoassay (RIA) (Spectria Cortisol Coated Tube RIA, purchased from Orion Diagnostica, Espoo, Finland). This method was evaluated and the performance validated by inter-laboratory comparison schemes (Hansen et al. 2003).

The cardiovascular system

Casual blood pressure, systolic and diastolic, was measured at clinical examination. For practical reasons and equipment limitations only some of the participants completed measurements of HRV (110 women and 45 men). The data of ambulatory ECG's in relation to HRV were recorded using a 3-lead LifeCard CF Holter monitor (Delmar Reynolds Medical Inc., Irvine, CA, USA) over approximately 18 hours. We selected ECG of 15 min. during work and sleep and chose the period of work to start at 2 pm and the period of sleep to start 45 min. after going to sleep (information from a questionnaire) for all participants. By spectral analysis of the 15 min. ECG during work and sleep, we derived frequency domain HRV after visual inspection and filtered for possible outliers and artefacts (ectopic beats, falsely detected beats, etc.). The RR-intervals with a frequency of 4 Hz were re-sampled, the time series linearly detrended, and the spectral components of the HRV by Welch's averaged, modified period gram method (Hamming window size 256 points, 50% overlap) estimated. Like the variables of HRV, TP was defined as the area under the spectral power density function in the range 0.003-0.4 Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology 1996). The ratio between power in LF range (0.04-0.15 Hz) and power in HF range (0.15-0.4 Hz) was calculated. The ratio, LF/HF has

been used in a large number of studies as an indicator of the autonomic balance because an increase in LF/HF reflects changes in autonomic modulation of cardiac rhythm in the direction of more sympathetic activity relative to parasympathetic activity (Pagani et al. 1986). We used the variables TP and LF/HF at work and sleep.

The metabolic system

Standard procedures were used to analyse blood samples of HBA1C, HDL and TCHOL. Weight, height and waist/hip circumference were measured at clinical examination to calculate BMI and WHR.

The immune/inflammatory system

For the determination of IL6, we used an enzyme-linked immune assay (R&D Systems, Minneapolis, USA) and Westgard control charts to document that the analytical method remained under analytical and statistical control (Westgard et al. 1981). As reference, we used material from NIBSC Code No 89/548 (NIBSC, Hertfordshire, England). Blood samples of CRP and FIBR were analysed following standard procedures.

3.1.3 Measuring Allostatic Load (study II)

According to earlier studies investigating AL (Juster, McEwen & Lupien 2010), we measured AL of the neuroendocrine system, the cardiovascular system, the metabolic system, the immune/inflammatory system and a cumulated AL score based on these four systems including 13 physiological markers. Since we wanted to investigate changes in AL, we focused on the distribution of values in both low-risk and high-risk ranges. We divided each marker in octiles by cutpoints and scored them 1-8. Higher score reflected higher AL. We used cutpoints from data in 2006 to divide data from 2006 and 2008 into octiles. In addition, we calculated the score of the four biological systems as a mean score of the included physiological markers. To reflect the cumulative physiological burden, we calculated the mean score of the four systems in an overall AL index.

3.1.4 Perceived psychosocial work environment (study I and II)

To measure the effect of workplace reorganization on perceived psychosocial work environment we included two of the most used and tested models to describe the perceived psychosocial work environment, Karasek's and Theorell's job demand-control model (job strain) (Karasek, Theorell 1990) and Siegrist's effort-reward imbalance model (ERI) (Siegrist et al. 2004). We used dimensions of demand and control from a 17-item questionnaire partially derived from the job

content questionnaire (Karasek et al. 1998) and dimensions of effort and reward from four questions evaluating effort and seven questions evaluating reward.

3.1.5 Psychological distress (study I and II)

To investigate the effect of workplace reorganization on psychological distress, we derived variables of stress symptoms from the COPSOQ questionnaire (Kristensen et al. 2005) including 10 items reflecting respectively physiological symptoms (heart beat rate, headache, dizziness, stomach ache, pain in the body), cognitive symptoms (difficulty with remembering, difficulty in taking decisions, difficulty with thinking clearly), and psychological symptoms (being irritable, feeling sad).

The variable perceived stress was measured by one question: “Stress means a situation in which a person feels tense, restless, nervous or anxious or is unable to sleep at night because his/her mind is troubled all the time. Do you feel this kind of stress these days?” (Elo, Leppanen & Jahkola 2003).

3.1.6 Covariates

In study I, we adjusted for baseline value (2006) of the relevant physiological markers and covariates that could influence on physiology such as gender, age, and physical activity in leisure time (less or more than 4 hours per week) Moreover, we adjusted for occupation (technician, academic, clerk, consultant, other) since we investigated work-related stress. In study II, we adjusted for baseline value (2006) of AL and gender according to recent studies on AL and gender differences (Juster et al. 2011) (Mair, Cutchin & Kristen Peek 2011). Moreover, we investigated the influence of age and socioeconomic status (SES) since it is well known that low SES incurs great risk of increased AL (Szanton, Gill & Allen 2005).

3.1.7 Statistical

In study I, we examined changes in both the physiological markers, perceived psychosocial work environment and psychological distress during the reorganization in hierarchical linear regression analyses by use of mixed models. We examined the physiological markers, perceived psychosocial work environment and psychological distress as dependent and explaining variables, time index and reorganization groups as fixed factor variables and potential confounders as covariates in different models - unadjusted and adjusted for covariates. To investigate the association between changes in physiological markers and perceived psychosocial work environment/psychological distress, we examined each physiological marker as dependent variable adjusted for reorganization groups as

fixed factor variable, covariates, and changes in the different markers of perceived psychosocial work environment and psychological distress in different models using mixed models. We analysed the physiological markers, job strain, ERI, stress symptoms, and perceived stress as continuous variables, reorganization groups as a three-level group variable, gender as a dichotomized variable, age as a continuous variable and occupation as a five-level group variable.

In study II, we calculated cutpoints of octiles for each physiological marker and recoded these ranges into an AL score 1-8 with high score reflecting high AL according to knowledge about stress reactions of the individual markers. To start with, we computed the AL score for each of the four biological systems as a mean score of the included physiological markers in each system. Then we computed the overall AL score as a mean score of the different systems. We examined the changes in AL during reorganization in hierarchical linear regression analyses with AL as dependent and explaining variable, time index and reorganization groups as fixed factors and potential confounders as covariates by use of mixed model. We examined different models adjusted for covariates and baseline values/changes in the markers of perceived psychosocial work environment and psychological distress to investigate the association between changes in AL and changes in perceived psychosocial work environment and psychological distress. We analysed AL, job strain, ERI, stress symptoms and perceived stress as continuous variables, reorganization groups as a three level group variable, gender as a dichotomized variable, age as a continuous variable and SES as a five-level group variable.

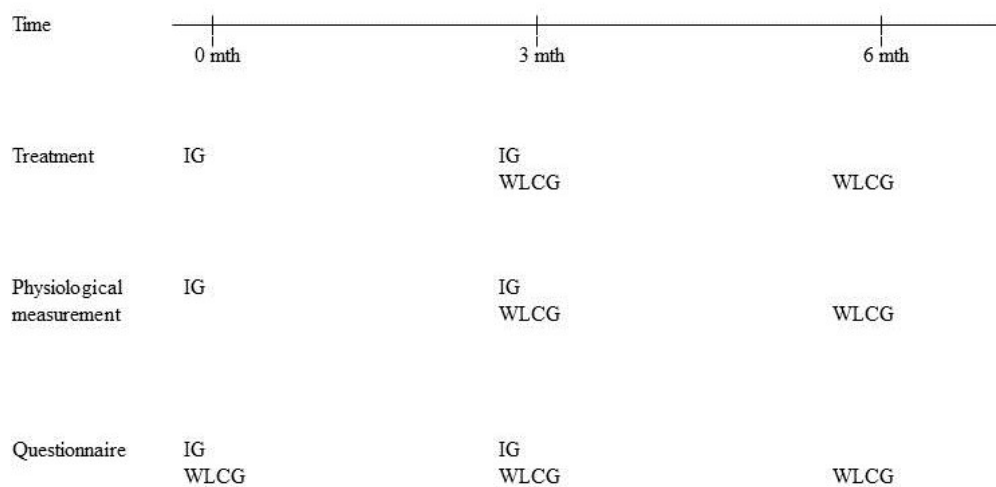
3.2 Stress treatment intervention (study III)

3.2.1 Design and population

The study Copenhagen Stress Treatment Project was based on the effects of a multidisciplinary stress treatment program including an initial medical and a psychological interview, a personality test, a clinical examination, eight individual stress treatment consultations with a physician or psychologist during three months, advocated dialogue with the workplace as an opportunity, and a psychiatrist assessment if necessary. In addition, the participants were offered a group-based mindfulness course of eight 2-hour sessions once a week (Kabat-Zinn et al. 1992). The inclusion criteria were full time or part time sick leave, employment or self-employment, significant symptoms of stress during months and motivation to participate. The exclusion criteria were current abuse of alcohol or psychoactive stimulants, major psychiatric disorder and significant somatic disorder assumed to be the primary cause of the stress condition. We included participants from two

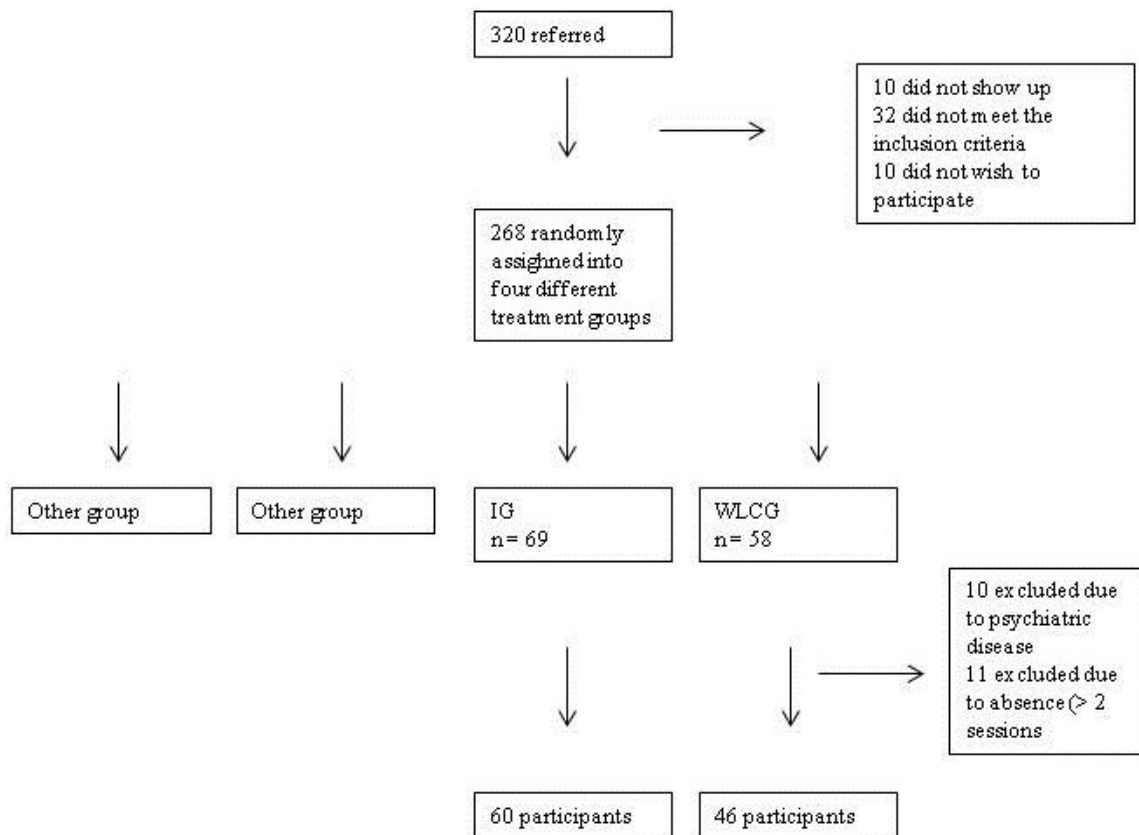
individual groups: An intervention group (IG) that received treatment immediately, and a waitlisted control group (WLCG) that received treatment after three months of waiting. The WLCG did not serve as a control group in study III due to measurements of physiology at different points of time in the two groups. Questionnaires and clinical data were collected before and after treatment in the two groups (figure 6).

Figure 6. Design stress treatment intervention



The study group comprised 106 participants, 60 participants in the IG and 45 in the WLCG (figure 7).

Figure 7. Flowchart stress treatment intervention



3.2.2 Physiological assessment

As described in section 3.1.2.

3.2.3. Measuring Allostatic Load

As described in section 3.1.3.

3.2.4 Return to Work

In another study based on the same data, a significantly higher RTW rate in the IG was observed compared to the WLCG after the stress treatment intervention (Netterstrom, Friebel & Ladegaard 2013). Therefore, we included RTW as a potential mediator. We assessed sick leave status after treatment at the final session for the IG and the WLCG from five possible treatment outcomes: 1.

Working full time, 2. Increased working hours, 3. Unemployed but available in the labour market, 4. Unemployed and on sick leave and 5. No changes in sick leave. We recoded the RTW variable as: Full-time work, yes = 1 and/or 3 and no = 2, 4 and/or 5.

3.2.5 Global Severity Index

We included also GSI as a potential mediator since GSI was investigated in the same study and found to decrease significantly more in the IG compared to the WLCG (Netterstrom, Friebe & Ladegaard 2013). The SCL92 is a 92-item self-administered questionnaire that measures psychological symptoms. The items are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely much) and the time frame is referred to as “the past week”. The sum of all 92 items constitutes the GSI (Olsen, Mortensen & Bech 2004b).

3.2.6 Covariates

We adjusted for the same covariates as described in study II.

3.2.7 Statistical

In study III, we investigated the IG and the WLCG separately. We examined the changes in AL during stress treatment intervention in hierarchical linear regression analyses with AL as dependent and explaining variable, time index as fixed factors, and potential confounders as covariates by use of mixed model. Moreover, we examined different models adjusted for covariates, RTW, and changes in GSI to investigate the association between changes in AL, and RTW and changes in GSI. We analysed AL as a continuous variable, gender as a dichotomized variable, age as a continuous variable, SES as a five-level group variable, RTW as a dichotomized variable and GSI as a continuous variable.

4. Results

4.1 Workplace reorganization (study I and II)

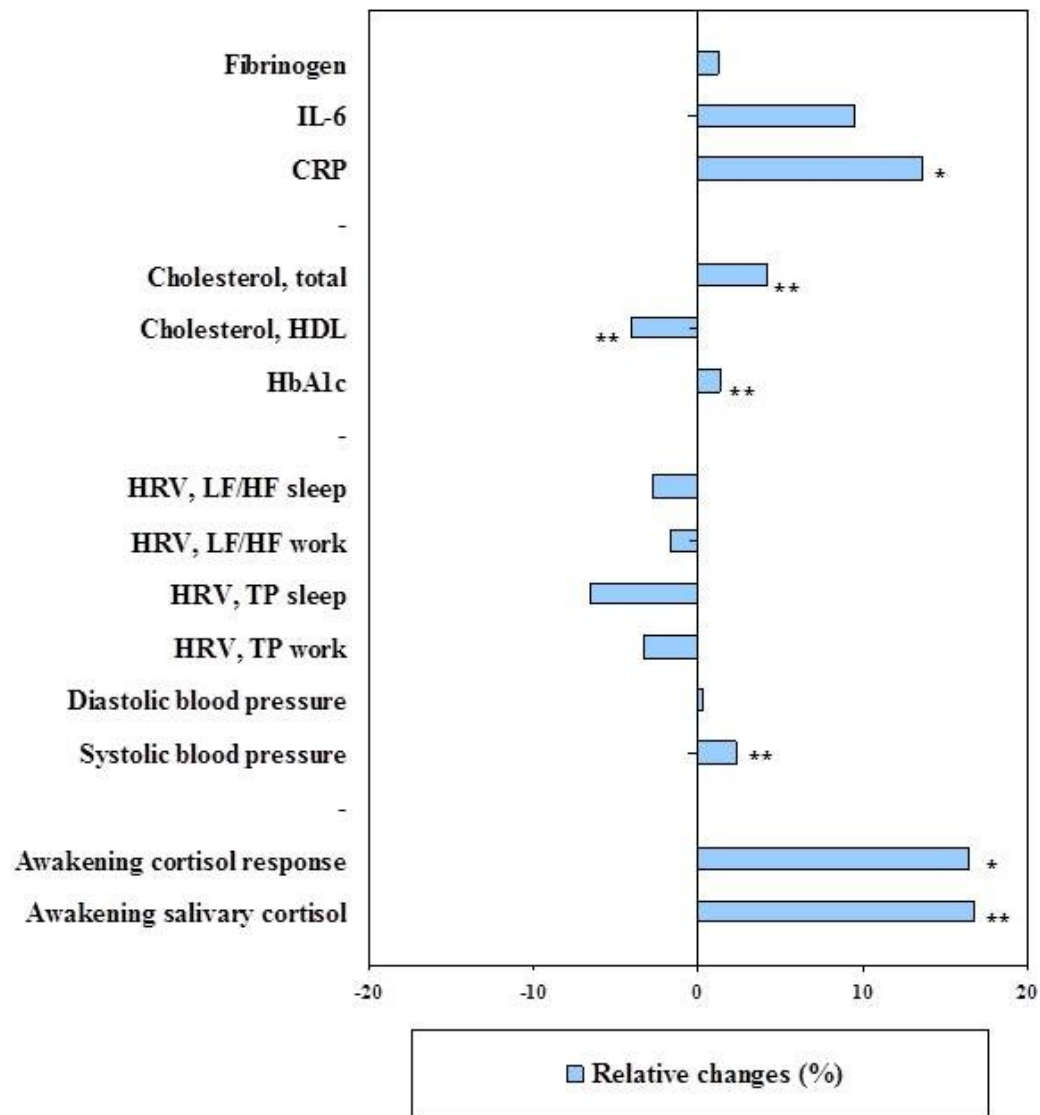
4.1.1 Main results (study I)

In the whole study group, we observed significant changes in the expected directions of several physiological markers during workplace reorganization: SBP (3.2, SE (0.9), $p<0.01$), S0 (1.6, SE (0.4), $p<0.01$), ACR (1.3, SE (0.5), $p=0.01$), HBA1C (0.07, SE (0.01), $p<0.01$), TCHOL (0.2, SE (0.04), $p<0.01$) and CRP (0.3, SE (0.1), $p=0.04$) increased, whereas HDL (-0.07, SE (0.01), $p<0.01$) decreased (figure 8). When we investigated changes in the physiological stress markers in the different reorganization groups, we observed only a significant increase of CRP (0.3, SD 0.09, $p<0.01$) in the merger group compared with the control group and a significant increase of IL6 in the merger group (0.03, SD 0.09, $p<0.01$) and the new job group (0.03, SD 0.1, $p<0.01$) compared with the control group.

The association between workplace reorganization and changes in perceived psychosocial work environment and psychological distress showed no significant change in job strain (-0.05, SE 0.07, $p=0.47$) and ERI (-0.01, SE 0.02, $p=0.77$) but a significant increase of stress symptoms (0.5, SE 0.2, $p=0.01$) and perceived stress (0.3, SE 0.07, $p<0.01$) in the whole study group. We observed no difference between the different reorganization groups.

Furthermore, we investigated the association between changes in the physiological stress markers and perceived psychosocial work environment and psychological distress. We observed no significant association, neither in the whole study group nor between the different reorganization groups.

Figure 8. Relative changes in mean values of physiological stress markers during workplace reorganization (*p<0.05, **p<0.01).



4.1.2 Additional results (study I)

We investigated whether changes in BMI was associated with the observed changes in the physiological markers and found that BMI increased significantly during the workplace reorganization but could not explain the changes in the physiological markers.

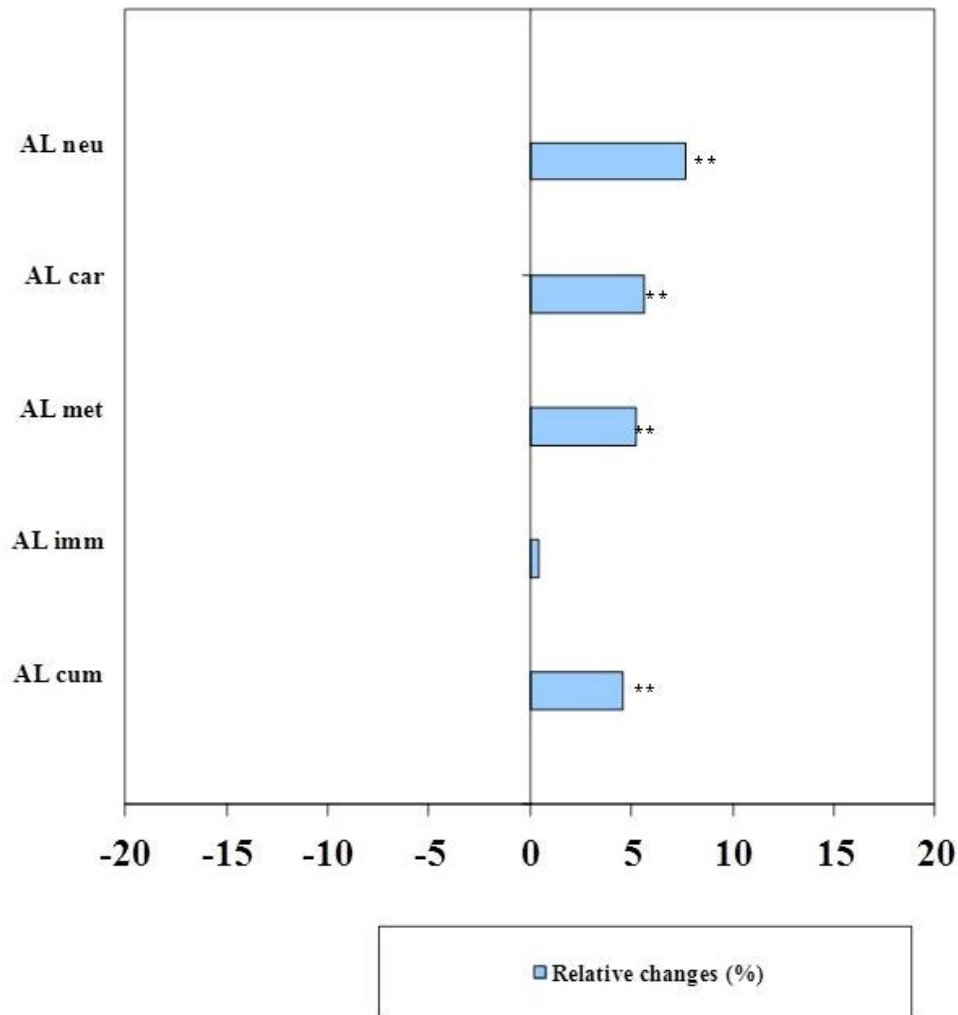
4.1.3 Main results (study II)

AL increased significantly during reorganization in the whole study group (0.20, SE 0.04, $p < 0.01$) and more specifically, AL increased significantly in the cardiovascular system (0.25, SD 0.08, $p < 0.01$), the metabolic system (0.23, SD 0.04, $p < 0.01$) and the neuroendocrine system (0.33, SD 0.06, $p < 0.01$) (figure 9).

When we investigated the different reorganization groups, we observed a tendency to significant increase in the merger group (0.10, SD 0.06, $p = 0.07$) compared with the control group and in details, we observed a significantly higher increase of AL in the merger group compared with the control group in the immune system (0.46, SD 0.13, $p < 0.01$) and a tendency of significant higher increase in AL in the merger group compared with the control group in the neuroendocrine system (0.17, SD 0.09, $p = 0.07$).

We did not find significant association between the observed changes in AL, and changes in the markers of psychosocial work environment and psychological distress in neither the whole study group nor in the reorganization groups.

Figure 9. Relative changes in mean values of AL during workplace reorganization (* $p < 0.05$, ** $p < 0.01$).



4.1.4 Additional results (study II)

In the procedure of constructing a cumulative measurement in the form of AL, we tested both the traditional method of Seeman et al. (Seeman et al. 1997) (Juster, McEwen & Lupien 2010) and octiles. The rationale of using octiles was twofold. Firstly, we studied healthy people at work and wanted to observe small physiological changes also in the low-risk levels. Secondly, most

physiological markers have a SD of approximately 10%, which is close to octiles (Hansen, Garde & Persson 2008).

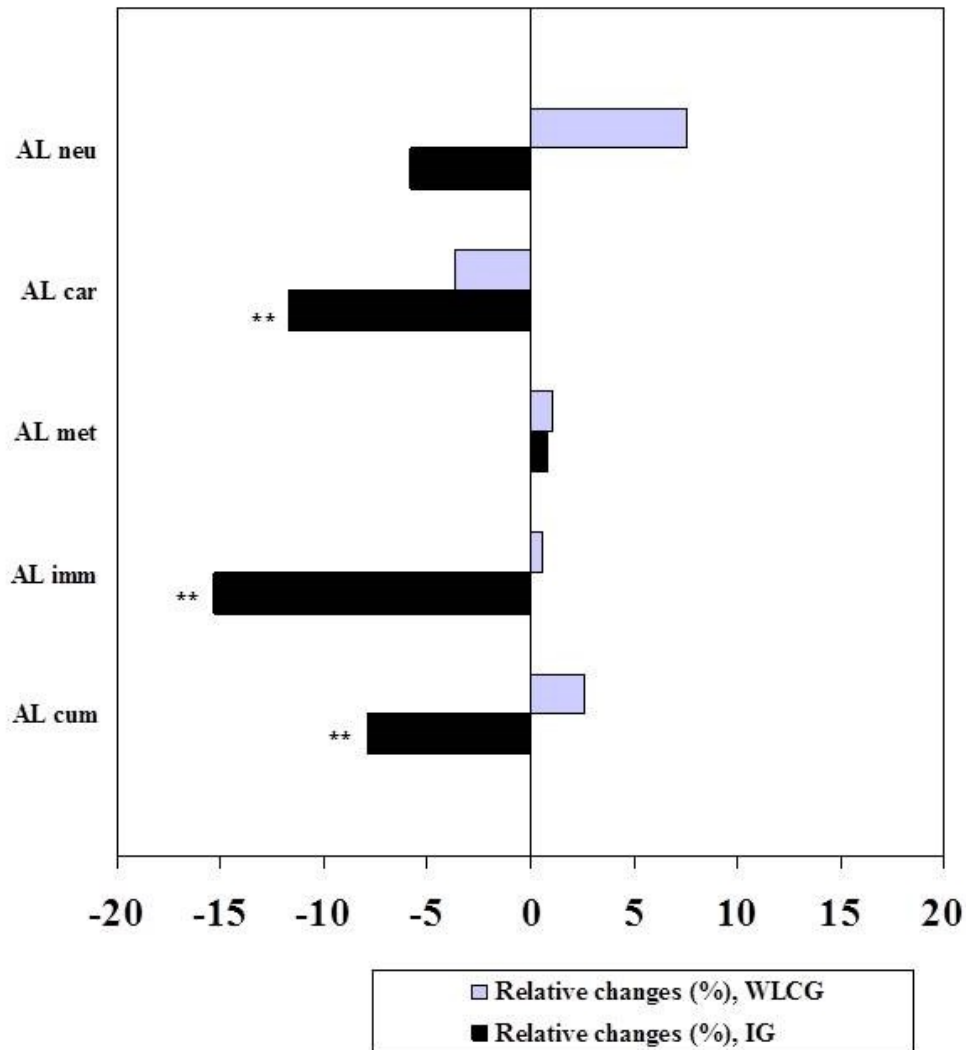
4.2 Stress treatment intervention (study III)

4.2.1 Main results

We investigated changes in AL in the IG and the WLCG during stress treatment intervention and observed a significant decrease in AL (-0.35, SE 0.09, $p<0.01$) in the IG, but no significant changes (0.05, SD 0.10, $p=0.64$) in the WLCG. In details, we observed an insignificant decrease in AL of the metabolic system, a borderline significant decrease of the neuroendocrine system (-0.25, SD 0.16, $p=0.07$), and a significant decrease of the cardiovascular system (-0.50, SD 0.12, $p<0.01$) and the immune system (-0.70, SD 0.20, $p<0.01$) in the IG. In the WLCG, we observed no significant changes in AL except from a borderline significant increase of AL in the neuroendocrine system (0.35, SD 0.18, $p=0.10$) (figure 10).

We observed no significant association between the changes in AL and RTW and changes in GSI.

Figure 10. Relative changes in mean values of AL during a stress treatment intervention in the IG and WLCG (*p<0.05, **p<0.01).



4.2.2 Additional results

Since the WLCG is not a control group due to physiology measured at different points of time, we first investigated the two groups together and found a significant decrease in AL (-0.15, SD 0.07, p=0.04) during the stress treatment intervention.

5. Discussion

5.1 Main findings

During workplace reorganization we found a significant increase in several physiological markers (study I) and in AL (study II) in the whole study group, but we only found a significant increase in the merger or new job group compared with the control group in two physiological markers (IL6, CRP) and a tendency of significant increase in AL in the merger group compared with the control group. Moreover, psychological distress increased significantly (study I) in the whole study group but did not differ significantly between the reorganization groups. During the stress treatment intervention, AL decreased significantly only in the IG (study III) that also decreased significantly in GSI (Netterstrom, Friebel & Ladegaard 2013). Neither the significant changes in psychological distress (study I) nor GSI (study III) were significantly associated with the changes in physiological markers (study I) and AL (study II and III).

The lack of association between changes in physiological and psychological markers in all three studies could indicate either limitations of the clinical implications as stated in a study observing the same result (Mommersteeg et al. 2006b), or that some people react to stress in a psychological way and others in a physiological way, depending on individual differences. These individual differences might be explained by personality and coping that both play independent and interactive roles in influencing physical and mental health (Carver, Connor-Smith 2010). An important distinction among coping responses is between approach and avoidance (Skinner et al. 2003). Since the approach coping strategies are efforts to deal with a stressor or related emotions and include both problem- and emotion-focused coping. The emotion-focused coping includes a wide range of responses, ranging from self-soothing to expression of negative emotions and focus on negative thoughts. The approach coping strategies has been connected to the extravert personality, and some view extraversion as reflecting relative sensitivity of a general approach system (Elliot, Thrash 2002) (Caspi, Roberts & Shiner 2005). This type of personality and coping strategy might reflect individuals reacting in a psychological way but not a physiological way. They are problem-focused, have the ability to express emotions, and are willing to report problems, as for example work-related problems. Opposite this, the avoidance coping response involves an attempt to escape from feelings of distress, and denial creates a boundary between reality and the person's experience (Carver, Connor-Smith 2010). The personality trait of neuroticism includes vulnerability to experiences of anxiety and general distress and has been linked to the avoidance temperament

(Caspi, Roberts & Shiner 2005). This kind of personality type can also be related to the type D personality, a profile referring to a general propensity to psychological distress characterized by the combination of negative affectivity and social inhibition. Type D has been shown to associate with a threefold increased risk of adverse cardiovascular outcomes (Denollet, Conraads 2011). The avoidance coping strategy, neuroticism and type D personality all together, might reflect the individuals only reacting in a physiological way. They actually feel threatened but deny these negative feelings and have decreased ability and willingness to report problems, also work-related. This type of reaction is only useful in the short term and will have to be dealt with eventually or be expressed in another way such as physiological reactions that might predict cardiovascular disease later in life. The grounding of the stress response in approach versus avoidance also matters physiologically. Approach coping styles have been related to low overall levels of cortisol, more favourable diurnal cortisol rhythms, and fast recovery to normal patterns after a stressor (Mikolajczak et al. 2007) (O'Donnell et al. 2008) (Sjogren, Leanderson & Kristenson 2006). Contrary to this, lower immune functioning among HIV patients has been linked to avoidance tendencies in the form of difficulty in recognizing and expressing emotions (Temoshok et al. 2008). These results support the idea of individual reactions to stress influenced by personality and coping strategies. However, the different coping strategies and personality traits play interactive roles and these concepts are complicated (Carver, Connor-Smith 2010). Moreover, there are several competing theories, and the effect of stress-induced cortisol level elevations on affective state should be mentioned. Different studies have shown that elevated cortisol levels in stressful situations are associated with an attenuated negative emotional arousal (Het, Wolf 2007)(Het et al. 2012) (Fischer et al. 2000), meaning that the stress-induced cortisol response might help to cope with the emotional load of the situation by preventing an emotional overload. This is in accordance with McEwen's AL model suggesting that an inadequate stress response facilitates emotional disturbances (McEwen 2003).

5.2 Workplace reorganization (study I and II)

5.2.1 Design

We investigated the original design of both mergers and controls but observed only a significant difference between the reorganization groups concerning two physiological markers of the immune system and a tendency of significant difference between the reorganization groups concerning AL. This could indicate that all employees involved in the reorganization were affected whether they

were merging or not. This finding corresponds to an earlier study on downsizing suggesting that “layoff survivor sickness”, a negative reaction among survivors instead of relief, is the typical experience (Noer 1993). Probably reorganization involves the same mechanisms.

Another perspective for discussion is the timing of measuring both physiological and psychological markers. The measurements in autumn 2006 might not reflect the participants’ true baseline but instead a physiological and psychological stress condition caused by knowledge about the reorganization to come and thereby negative expectations. This corresponds to the results of qualitative interviews effectuated after the workplace reorganization (http://www.bispebjerghospital.dk/NR/rdonlyres/41AACAC0-994D-4DDA-AC86-127637B55F35/0/OSH_SlutrapportAMFF.pdf). In addition, the collection of data in autumn 2008 might have been too late to reflect the actual stress condition. This problem illustrates the difficulties and uncertainties about the time perspective of both physiological and psychological reactions of long-term stress in relation to exposure.

5.2.2 Selection bias

The 650 non respondents and the 261 excluded due to leave of work place might have been less motivated to participate due to a stress condition and lack of energy. However, the reason for not participating could also be explained by not having the time and not finding it necessary to participate due to motivation and energy to work or change job. These possible explanations might have caused selection bias and could have had influence on the results. A number of 111 participants did not complete the clinical follow-up and reported poorer health, more stress and higher sickness absence at baseline compared to the included participants. Among the physiological markers only ACR was significantly higher among the non-participants. This may cause an underestimation of the true effect. Moreover, we excluded 32 participants that completed the follow-up but lost their job or retired in the period. These non-participants were significantly older as a natural explanation of retirement and had a significantly higher WHR and HbA1C probably related to the higher age. Last, the unequal distribution of men and women (94 men and 265 women) should be taken into account when drawing conclusions from the results.

5.2.3 Outcome measures

We included biological systems and physiological markers according to known physiological stress responses (McEwen 2008) and the use in earlier studies (Juster, McEwen & Lupien 2010), and observed physiological changes corresponding to expected physiological stress reactions (Chrousos

2009) (Sapolsky 2004). The fact that not all the included physiological markers present a linear correlation between increase of values and higher risk of disease can be discussed. Regarding BMI, underweight might also have negative health consequences and low values of ACR have shown to be correlated with negative health consequences in the form of burnout (Kudielka, Bellingrath & Hellhammer 2006)), although the results in this area are inconsistent (Mommersteeg et al. 2006a). In this study, the included participants were healthy workers assumed not to suffer from burnout, thus all being normal- or overweight. Moreover, it may be argued that physiological changes do no harm and can be seen as normal fluctuations caused by different life events. However, according to the theory of AL, several episodes of strain on the body produced by repeated ups and downs of physiologic responses can predispose the organism to disease (McEwen, Stellar 1993).

The explanation of an increase in psychological distress but with no effect on the perceived psychosocial work environment could be that the workplace reorganization did not affect the investigated factors of the psychosocial work environment such as job strain and ERI but only the experience of being a part of a major reorganization (study I). Another explanation could be that some people may have had benefit whereas others may have had disadvantage with regard to these two dimensions, and that these two groups balance one another in the total study population.

5.2.4 Comparison with previous findings

The results corresponds with previous studies investigating the association between workplace reorganization in the form of downsizing (Hertting, Theorell 2002), job insecurity (Ferrie et al. 2002), and changes in physiological markers. Also the association between workplace reorganization and psychological distress corresponds to previous findings (Swaen et al. 2004) (Lavoie-Tremblay et al. 2010). However, research investigating the relation between workplace reorganization and AL is sparse. A recent cross-sectional Swedish study found that job insecurity was unrelated to AL (Naswall, Lindfors & Sverke 2012). Therefore, this thesis contributes to the limited research in this area, and the longitudinal design and workplace reorganization as a natural intervention is its main strength.

5.3 Stress treatment intervention (study III)

5.3.1 Design

The lack of AL measurements at study start in the WLCG is the main limitation. However, the study was designed this way to avoid bias in the form of being taken care of and having some kind

of treatment. The reason why we observed no significant changes in AL in the WLCG during treatment could be that the WLCG recovered already during the three months of waiting. Confirming this, two-thirds of the WLCG reported to have received some type of treatment from a psychologist or their general practitioner during the time of waiting (Netterstrom, Friebel & Ladegaard 2013). Moreover, the RTW increased and the GSI decreased during the time of waiting in the WLCG. However, the groups did not differ in physiology overall at start of treatment. Therefore, we assume the WLCG to have higher levels in AL compared to the IG at study start caused by either a higher physiological stress level at that point of time or perhaps a higher physiological level in general. This corresponds to baseline characteristics that showed longer duration of sick leave, higher moderate/severe depression rate and higher mean GSI in the WLCG at study start compared to the IG (Netterstrom, Friebel & Ladegaard 2013). This worse condition might also explain why the WLCG did not recover to the same physiological level as the IG despite of the waiting period and treatment.

5.3.2 Selection bias

We excluded 21 participants that were significantly younger ($p > 0.05$) with a mean age of 39.1 years than the final 106 included participants (mean age of 43.5 years). Due to the limited number of participants and unequal distribution between men ($n=22$) and women ($n=84$), we analysed men and women together. These factors should be taken into account when conclusions from the results are made although adjustment for gender had no influence.

5.3.3 Outcome measures

AL is a useful measurement to integrate individual physiological differences and observe a cumulative physiological burden. Throughout the first operational definition of AL this measure was investigated as an exposure to predict cognitive and physical functioning, disease, and mortality in ageing studies. Later, the AL measure was investigated as an outcome associated with impaired psychosocial work environment. The studies related to both ageing and work used only single measurements of AL and most often the traditional measure of Seeman et al. (Seeman et al. 1997). The aim of this thesis is to investigate changes in AL. Therefore, the methods of study II and III focus on the distribution of values in both high-risk and low-risk ranges as recommended in a recent review for future perspectives of AL (Juster, McEwen & Lupien 2010). We use an AL score based on octiles advantageous to assess small, but relevant changes in AL. Moreover, the same review suggests interventions on AL (McEwen, Stellar 1993) as the next stage in AL research. This

thesis aims to investigate changes in AL both during distress and rehabilitation – the latter to investigate whether AL is reversible.

The concept of AL has been criticized for only reflecting the metabolic syndrome, but the AL index has shown to predict mortality and physical functioning more uniformly than its clusters or constituents in the form of neuroendocrine markers versus metabolic syndrome markers (Seeman et al. 2001). Furthermore, the AL index includes markers reflecting the immune system. In study III, we observe significant reactions in AL of the cardiovascular and immune/inflammatory system in contrast to significant reactions in AL of the neuroendocrine and metabolic system in study II. The different time aspects of measuring AL, three months versus two years, might explain this difference, since primary mediators/effect (neuroendocrine and immune/inflammatory system) dominate in the short term and secondary outcomes (metabolic system) in the long term.

RTW was not significantly associated with the decrease in AL during treatment and a possible explanation could be that those who returned to work were still in a stress condition but had to start work again due to different circumstances. The fact that the decrease in GSI during treatment is not significantly different between the participants that returned work compared to the participants still on sick leave confirms this.

5.3.4 Comparison with previous findings

No studies so far have investigated the relation between stress treatment intervention and AL. A Swedish study investigated the association between self-rated recovery from work stress and biologic dysregulation in terms of AL, and found that insufficient recovery might result in high AL (von Thiele, Lindfors & Lundberg 2006a). Besides the intervention design making it possible to investigate physiological changes over time and the significant improvement in the clinical condition of the participants as main strengths, this study opens a new perspective of AL that might contribute to better understanding and use (Juster, McEwen & Lupien 2010).

6. Conclusion

In conclusion, the studies of this thesis show significant changes in physiological stress reactions of both distress and rehabilitation during workplace reorganization and a stress treatment intervention. However, a limitation of the results when comparing the different reorganization groups in study I and II, and the lack of control group in the stress treatment intervention in study III, should be taken into account. Altogether, this leaves the conclusion unclear and the clinical implications limited.

7. Perspectives for future research

Physiological stress reactions might not be as noticeable as the psychological reactions but can still predict disease later in life. Therefore, both conditions should be taken seriously. The findings of this PhD thesis indicate that physiological markers and AL might be useful measurements to understand and observe the physiology of both distress and rehabilitation but further investigation in this area is needed.

8. English summary

Background

Stress is the individual response to a stressor and a stressor the exposure releasing the stress response. The type of stressor can be psychological, physical, chemical, or biological, and in this case psychological stressors are studied. A stress condition is characterized by an activation of different biological systems together with mental and behavioural processes. The distinguishing between acute stress (minutes, hours) and chronic stress (days, years) also referred to as long-term stress is important. Acute stress is natural and important whereas long-term stress might have negative consequences from a personal and social point of view. The physiological reactions of acute stress are well known, and probably the same physiological mechanisms are involved in the reactions of long-term stress. It is well documented that impaired psychosocial work environment increases the risk of developing cardiovascular disease and depression and aggravates other diseases, such as allergy, asthma, and various autonomic conditions. The linking pathological mechanisms may be prolonged physiological stress reactions. Therefore, the aim of this thesis is to investigate physiological stress reactions during two different types of intervention related to psychosocial work environment: 1. Workplace reorganization and 2. Stress treatment intervention.

Methods

A major reorganization of non-state public offices was effectuated in Denmark on 1 January 2007. In 2006 and 2008, we collected clinical and questionnaire data from 359 participants, 265 women and 94 men employed in five municipality and two county administrations. Since only four out of five municipalities and one out of two counties merged with others, we defined different reorganization groups: 1. Merger group, 2. New job group (participants who got new jobs outside the organization during follow-up), 3. Control group. To reflect stress reactions of the neuroendocrine, cardiovascular, metabolic, and immune/inflammatory system, we included different physiological markers. As a cumulative physiological measurement, we calculated Allostatic Load (AL) based on 13 of these markers. We analysed changes in physiological markers and AL from 2006 to 2008, changes in perceived psychosocial work environment (job strain, ERI), psychological distress (stress symptoms, perceived stress), and the association between these physiological and psychological markers.

Furthermore, we used data from an intervention study based on a multidisciplinary stress treatment program, where the participants decreased significantly in Global Severity Index (GSI) and increased return to work (RTW) during the intervention. We included 106 participants from two individual groups - an intervention group (IG), that received treatment immediately, and a waitlisted control group (WLCG,) that received treatment after three months of waiting, and collected questionnaire and clinical data before and after treatment. We analysed changes in AL and the association between these changes, and RTW and changes in GSI.

Results

We observed a significant increase in several physiological stress markers and AL during workplace reorganization in the whole study group during workplace reorganization but only a significant increase in the merger or new job group compared with the control group in two physiological markers and a tendency of significant increase in AL in the merger group compared with the control group. Moreover, the finding is that psychological distress increases significantly in the whole study group but does not differ significantly between the reorganization groups. We observe no significant association between changes in the physiological and psychological markers. During the stress treatment intervention we observe a significant decrease in AL in the IG, but not in the WLCG. Neither RTW nor the significant changes in GSI are significant associated with the changes in AL.

Conclusion

In conclusion, we observe significant changes in several physiological markers and AL in the expected directions during both distress related to a workplace reorganization and rehabilitation related to a stress treatment intervention. However, limitations of the results, when comparing the different reorganization groups and the lack of control group in the stress treatment intervention, should be taken into account. Altogether, this leaves the conclusion unclear and the clinical implications limited.

Perspectives

From this result physiological markers and AL might be useful measurements to understand and observe the physiology of both distress and rehabilitation but further investigation in this area is needed.

9. Danish summary / Dansk resumé

Baggrund

Stress er det individuelle respons på en stressor, og en stressor er den påvirkning, der udløser responset. Stressoren kan være af både psykologisk, fysisk, kemisk eller biologisk art – i denne sammenhæng psykologisk. Stresstilstanden er karakteriseret ved en aktivering af forskellige biologiske systemer samt mentale og adfærdsmæssige processer. Forskellen mellem akut stress (minutter til timer) og kronisk eller langvarig stress (dage til år) er vigtig. Akut stress er naturligt og nødvendigt, mens langvarig stress kan have negative konsekvenser ud fra et personligt såvel som samfundsmæssigt synspunkt. Det akutte fysiologiske stressrespons er velkendt, og højst sandsynligt er de samme fysiologiske mekanismer involveret i et langvarigt respons. Det er veldokumenteret, at dårligt psykosocialt arbejdsmiljø øger risikoen for kardiovaskulær sygdom og depression og forværrer andre sygdomme som allergi, astma og forskellige autoimmune tilstande. De mellemliggende patofysiologiske mekanismer kan være langvarige fysiologiske stressreaktioner. Derfor er formålet med denne afhandling at undersøge fysiologiske stressreaktioner i forbindelse med to interventioner relateret til psykosocialt arbejdsmiljø: 1. Arbejdspladssomstrukturering og 2. Stressbehandling.

Metode

En omfattende omstrukturering på det kommunale område blev effektueret i Danmark d. 1. januar 2007. I 2006 og 2008 indsamlede vi kliniske data og spørgeskemadata fra 359 deltagere, 265 kvinder og 94 mænd, der var ansat i administrationen i fem kommuner og to amter. Da kun fire ud af fem kommuner og en ud af to amter fusionerede med andre, definerede vi forskellige omstruktureringsgrupper: 1. Fusionsgruppen, 2. Nyt job-gruppen (deltagere der fik nyt job uden for det kommunale område i løbet af omstruktureringen) og 3. Kontrolgruppen. For at belyse stressreaktioner i det neuroendokrine, kardiovaskulære, metaboliske og immunologiske/inflammatoriske system inkluderede vi forskellige fysiologiske markører. Som et samlet fysiologisk mål beregnede vi Allostatic Load (AL) baseret på 13 af disse markører. Vi analyserede ændringer i fysiologiske markører og AL fra 2006 til 2008, ændringer i selvoplevet psykosocialt arbejdsmiljø (krav/kontrol modellen og ERI) og psykologisk stress (stresssymptomer, selvoplevet stressniveau) og sammenhængen mellem disse fysiologiske og psykologiske faktorer. Ydermere anvendte vi data fra et interventionsstudie baseret på et multidisciplinært stressbehandlingsprogram, hvor deltagernes Global Severity Index (GSI) faldt signifikant, og

Return to Work (RTW) steg i løbet af interventionen. Vi inkluderede 106 deltagere fra to individuelle grupper - en interventionsgruppe, der fik behandling med det samme, og en ventelistegruppe, der fik behandling efter at have ventet tre måneder, og indsamlede spørgeskema og kliniske data før og efter behandling. Vi analyserede ændringer i AL i løbet af behandlingen og sammenhængen mellem ændringer i AL og RTW og ændringer i GSI.

Resultater

Vi finder en signifikant stigning i flere af de fysiologiske stressmarkører og AL i hele deltagergruppen samlet i løbet af arbejdspladsomstruktureringen, men ser kun en signifikant stigning i to fysiologiske markører og en tendens til signifikant stigning i AL i fusionsgruppen eller nyt job-gruppen sammenlignet med kontrolgruppen. Desuden stiger psykologisk stressniveau signifikant i hele deltagergruppen samlet, men ikke signifikant forskelligt i de tre omstruktureringsgrupper. Vi observerer ingen signifikant sammenhæng mellem ændringerne i de fysiologiske og psykologiske markører. I løbet af stressbehandlingsinterventionen observerede vi et signifikant fald i AL i interventionsgruppen men ikke i ventelistegruppen. Hverken RTW eller signifikante ændringer i GSI viser signifikant sammenhæng med ændringerne i AL.

Konklusion

Samlet set viser studierne i denne afhandling signifikante ændringer i flere fysiologiske markører og AL i de forventede retninger i forbindelse med henholdsvis stress og en arbejdspladsomstrukturering, og rehabilitering og en stressbehandlingsintervention. Dog må der tages højde for, at sammenligningen mellem de forskellige omstruktureringsgrupper i forbindelse med arbejdspladsomstruktureringen og en manglende kontrolgruppe i forbindelse med stressbehandlingsinterventionen begrænser resultatet. Samlet betyder dette, at konklusionen og den kliniske forståelse er uklar.

Perspektiver

Ud fra dette resultat kan fysiologiske markører og AL måske være egnede mål til at forstå og observere fysiologien i forbindelse med stress og rehabilitering, men yderligere forskning indenfor dette område er nødvendig.

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