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PhD thesis

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

Department of Occupational and Environmental Medicine

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PhD thesis

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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

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List of abbreviations

ERI = Effort Reward Imbalance

GSI = Global Severity Index

RTW = Return To Work

SCL92 = Symptom Check List-92

CBT = Cognitive Behavioral Therapy

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

Preface

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

First of all, I would like to thank you my excellent supervisors Bo Netterstrøm and Åse Marie Hansen. Thank you to Bo, for giving me the chance to work with the area of stress, for useful discussions and knowledge about this subject, for believing in me and for the perfect support through all the years I have worked on this project. Thank you to Åse, for taking extra good care of me in the last period of this project and for always being positive and always having the time and energy to give constructive support.

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Rikke Hinge Carlsson

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1. Introduction

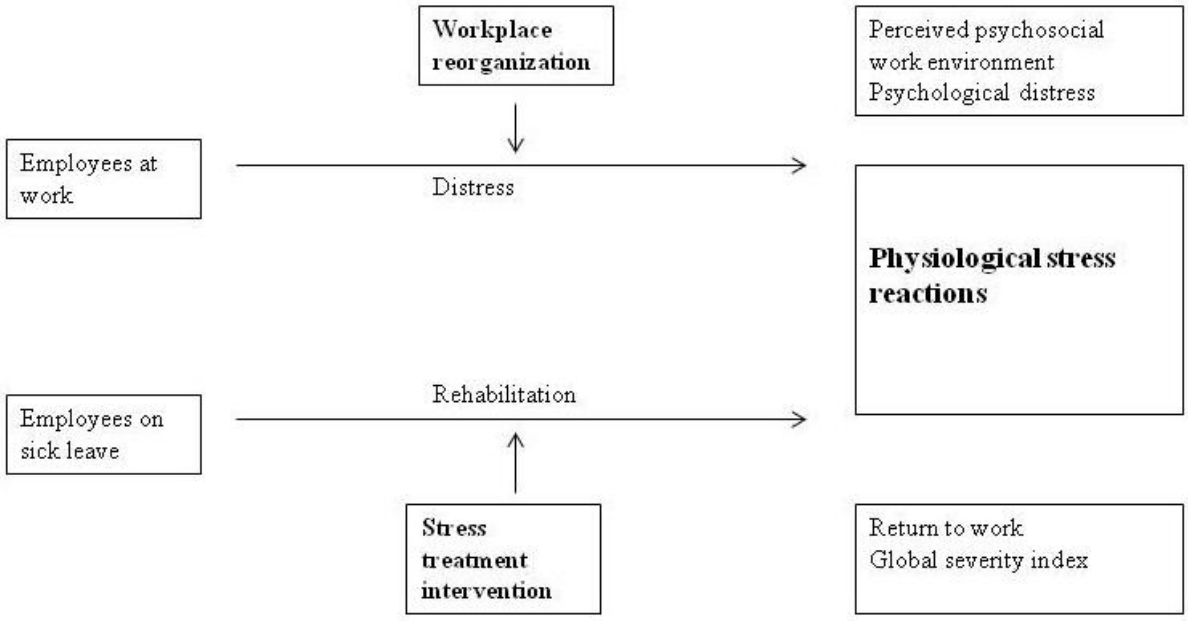
Stress is the individual response to a stressor and a stressor the exposure releasing the stress response. The type of stressor can be psychological, physical, chemical or biological. A stress condition is characterized by an activation of different biological systems together with mental and behavioral 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 adaption" (Selye 1936). Although the definition is still discussable it is important to distinguish between acute and chronic stress, 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 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 a 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 interventions of psychosocial work environment: 1. Workplace reorganization and 2. Stress treatment intervention (Figure 1).

Figure 1. Design PhD thesis

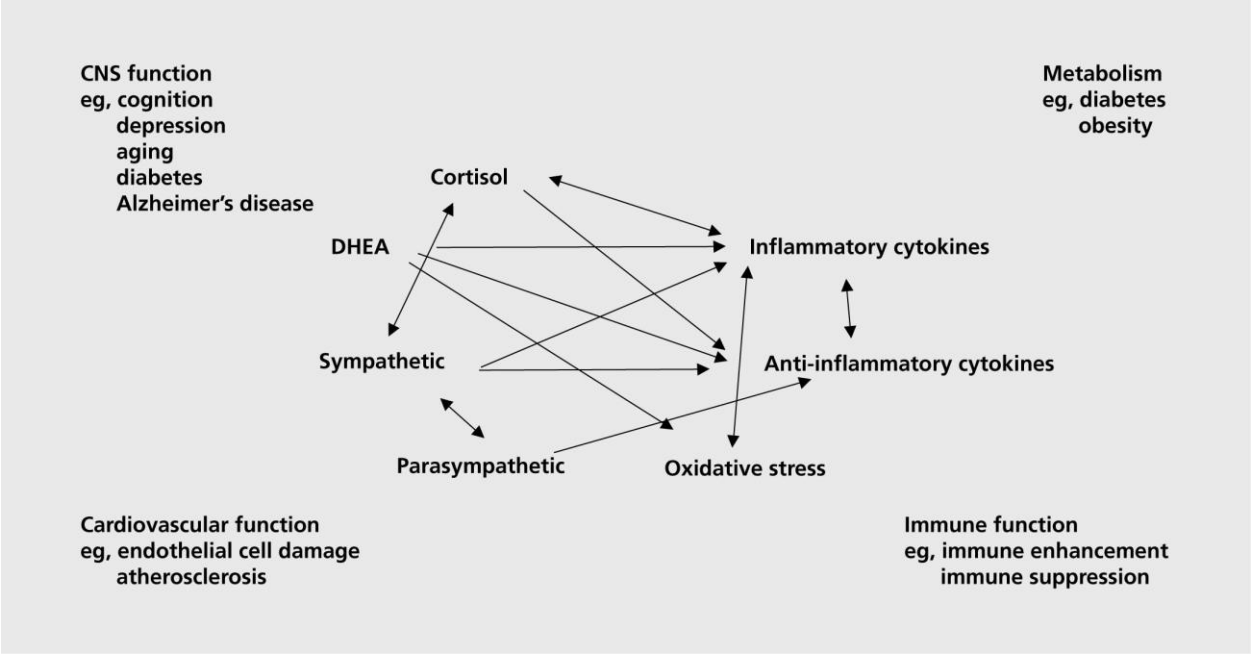


1.1 Physiological stress reactions

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 the 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 interactions between all these hormones and mediators are 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 continue this may result in a culmination of physiological dysregulations 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 specific, 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 Exact function unclear but stressful events tend to lower levels	↓
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 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	Measure of body fat based on height and	↑

(BMI) (kg/m^2)	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 (include 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 Used as a very rough proxy for cardiovascular disease	↑
- 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 (`Kristenson, M`, `Garvin, P`, `Lundberg, U` 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).

In relation to the cardiovascular system, blood pressure or hypertension is frequently investigated. A recent review concluded evidence pointing to 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, varying time spans and

outcome variables (Rosenthal, Alter 2012). This association corresponds to other studies (Steenland et al. 2000) (Sparrenberger et al. 2008). The clinical relevance of HRV is the association with cardiovascular disease (Anonymous1996) 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. They found workplace stressors to associate with low HRV and more specific a decreased neural vagal control of the heart indicating diminished adaptivity of the autonomic nervous system (Jarczok et al. 2013). Moreover, HRV might link to cardiovascular disease through factors related to the metabolic syndrome (Thayer et al. 2010).

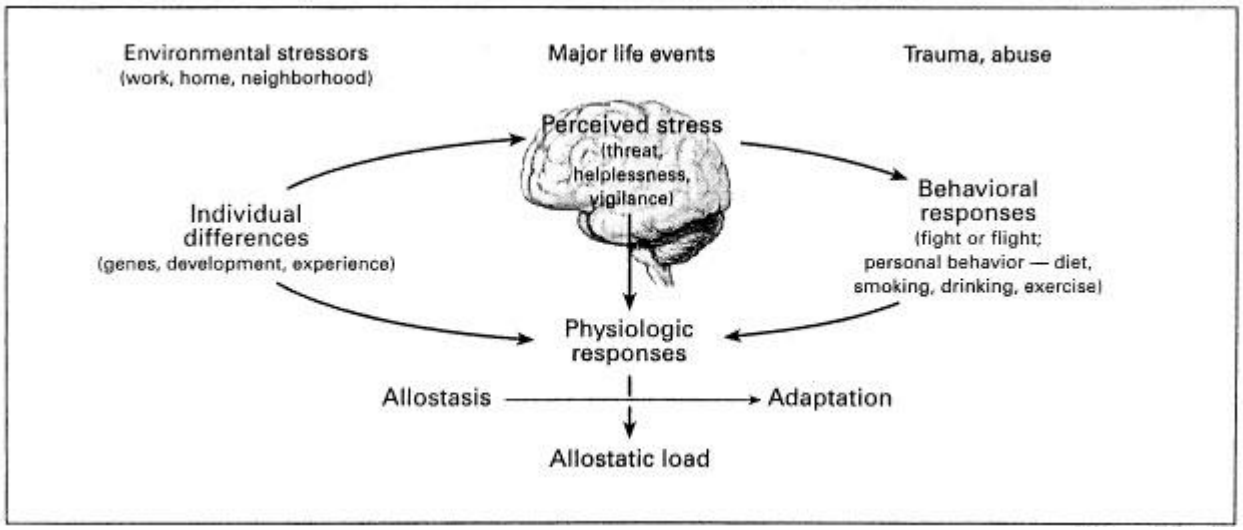
Various physiological changes define the metabolic syndrome of which insulin resistance is the primary metabolic defect. In addition, the syndrome includes abdominal obesity, dyslipidaemia and hypertension. In a prospective follow-up study from 2005 using data from the Whitehall II study, the authors 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 significant 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 including 56 different studies. The authors found job stress to be associated with a various immune parameters and NK cell immunity the most robust, 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, delayed wound healing and the 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 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 behavioral 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) (Karlamangla 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 in score "1" falling within the highest or lowest quartile associated with increased risk of disease or poorer health or score "0" 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 AL to be related to lower functioning, poorer cognitive performance and weaker physical performance. At follow-up over 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 this 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).

Later, the research in this area 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, they found an association between increased job demands and high AL (Schnorpfeil et al. 2003). Another study among Chinese industrial workers observed an association between lower job control and increased glucolipid AL (Li, Zhang & Wang 2007) and in a sub-study of the same cohort, an association between higher job demands, lower decision latitude and higher AL (Sun et al. 2007). In another German study including female schoolteachers, they observed association between greater effort-reward imbalance and modestly higher AL (Bellingrath, Weigl & Kudielka 2009), and in a Swedish study association between lack of recovery from work stress and increased AL (von Thiele, Lindfors & Lundberg 2006b). A later Swedish study on the same data showed association between working in the health care sector rather than in information technology and higher AL among middle-aged women (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 Interventions

1.2.1 Workplace reorganization

Employees confront with increasing organizational changes at work at different levels such as minor daily stressors related to changes in technology and workplace practices, and major upheavals of mergers, downsizing and restructuring (Sikora PB, 2004) (Di Nunzio D, 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 specific, the health effects of different interventions 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 to the work environment through task structure work reorganization. They found that task-restructuring interventions 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, where 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) (Cheng GHL, 2008) (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 changes 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, they 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, and moreover physician-diagnosed symptoms of ill-health. 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 document 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 a loss in productivity, short- and long-term sick leave and early retirement (Cancelliere et al. 2011), and place 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 interventions 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 including 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 of interventions directed at members of

the working population and concluding stress management interventions 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 interventions, the review concluded Cognitive Behavioral Therapy (CBT) to improve mental health (Bhui et al. 2012). The stress treatment intervention consisted of stress-coping sessions based on CBT and directed at both the worker and 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 a part of the intervention and in previous research shown 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 significant reduction in burnout complaints and increase of initially lowered morning cortisol levels (Mommersteeg et al. 2006b). A recent study of 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 aims of this thesis

- Impaired psychosocial work environment increases the risk of developing disease, and long-term physiological stress reactions might be the linking mechanism (Eller et al. 2009) (Backe et al. 2012) (Bonde 2008) (Netterstrom et al. 2010).
- Several physiological markers has been investigated in relation to psychosocial work environment but the results are inconsistent (`Kristenson, M`, `Garvin, P`, `Lundberg, U` 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 (Juster, McEwen & Lupien 2010) (Beckie 2012).
- Few studies have investigated the physiological stress reactions of distress during a workplace reorganization and rehabilitation during a stress treatment intervention.

2. Aims of the thesis

The aim of this thesis is to investigate physiological stress reactions of long-term stress.

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 mediating effect of these factors on changes in 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 mediating effect of workplace reorganization status and personal involvement in the reorganization.

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 mediating effect of RTW and GSI.

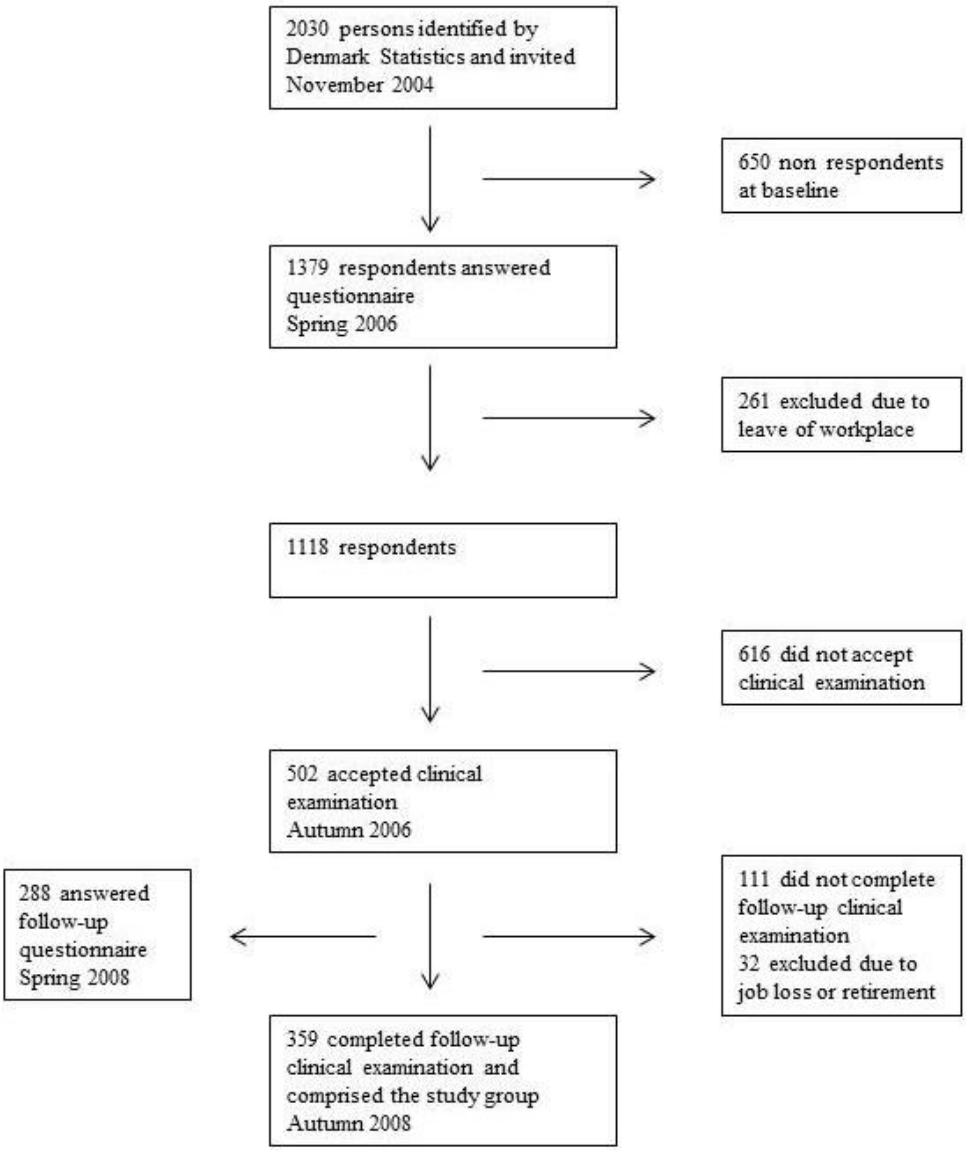
3. Material and methods

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 questionnaire and clinical data collected in spring and autumn 2006 and 2008. The study group comprised 359 participants, 265 women and 94 men (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 was in cooperation with the laboratory at Hillerød Hospital and 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 limited equipment only some of the participants completed measurements of HRV (110 women and 45 men). The data of ambulatory ECG`s in relation to HRV was recorded using a 3-lead LifeCard CF Holter monitor (Delmar Reynolds Medical Inc., Irvine, CA, USA) over approximately 18 hours. By spectral analysis of 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. As variables of HRV, TP was defined as the area under the spectral power density function in the range 0.003-0.4 Hz (Anonymous1996). The ratio between power in the LF range (0.04-0.15 Hz) and power in HF range (0.15-0.4 Hz) was calculated. We used the variables TP and LF/HF at work and sleep where TP is an indicator of the parasympathetic activity and LF/HF an indicator of the sympathetic activity.

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 a 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 Workplace reorganization status

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 employed in 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 in the questionnaire also answered to have the same job tasks before and after the reorganization.

3.1.5 Perceived psychosocial work environment (study I)

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 et al. 1998)

and Siegriest'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.

3.1.6 Psychological distress (study I)

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 beating, headache, dizziness, stomach ache, pain in the body), cognitive symptoms (difficulty with remembering, difficulty in taking decisions, difficult to think clearly), and psychological symptoms (been irritable, felt 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).

3.1.7 Personal involvement in the reorganization (study II)

We used two questions from the questionnaire in spring 2008 to reflect personal involvement in the workplace reorganization. One item concerned the influence on planning: "Did you have influence on planning the changes concerning your job tasks during reorganization" with three response categories: 1. "Influence on planning", 2. "No influence on planning" and 3. "No changes during reorganization". Another item concerned humane consideration: "Was any humane consideration taken during reorganization" and three responds categories: 1. "Humane consideration", 2. "No humane consideration" and 3. "No changes during reorganization".

3.1.8 Covariates

In study I, we adjusted for gender, age, occupation (technician, academic, clerk, consultant, other), physical activity in leisure time (less or more than 4 hours per week), BMI and workplace reorganization status according to the original design of OSH.

In study II, we analysed men and women separately according to recent studies on AL and gender differences (Juster et al. 2011) (Mair, Cutchin & Kristen Peek 2011). Moreover, it is well known that lower socioeconomic status (SES) incurs greater risk of increased AL (Szanton, Gill & Allen 2005). Among women, we found an equal distribution on all social classes, whereas 80% of the

men were in social class 1 and 2. Therefore, we adjusted for SES as a potential confounder only among men. Last, we investigated the influence of age.

3.1.9 Statistical

In study I, we examined the analysis of changes in both the physiological markers, perceived psychosocial work environment and psychological distress during the reorganization in hierarchical linear regression analyses with explaining variables and potential confounders as covariates by use of mixed models. We analysed both the physiological markers, job strain, ERI, stress symptoms and perceived stress as continuous variables.

In study II, we calculated cutpoints of octiles for each physiological marker and recoded these ranges into an AL score 1-8 with higher score reflecting higher AL according to knowledge about stress reactions of the individual markers. First, we computed the AL score for each of the four biological systems as a mean score of the included physiological markers in each system. Second, 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 by use of mixed model both as a raw model without adjustment and models adjusted for workplace reorganization status, influence on planning, humane consideration and potential confounders. We analysed AL and confounders as continuous variables and workplace reorganization status, influence on planning and humane consideration as categorized variables.

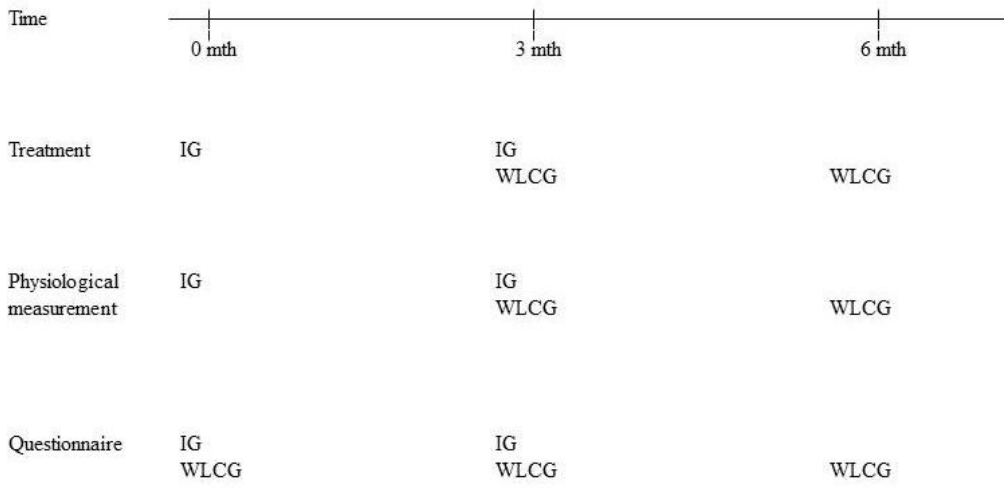
3.2 Stress treatment intervention (study III)

3.2.1 Design and population

The study Copenhagen Stress Treatment Project was based on the effects of a multidisciplinary stress treatment program including initial medical and psychological interview, personality test, clinical examination, eight individual stress treatment consultations with a physician or psychologist during three months, advocated dialogue with the workplace as an opportunity and psychiatrist assessment if needed. 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

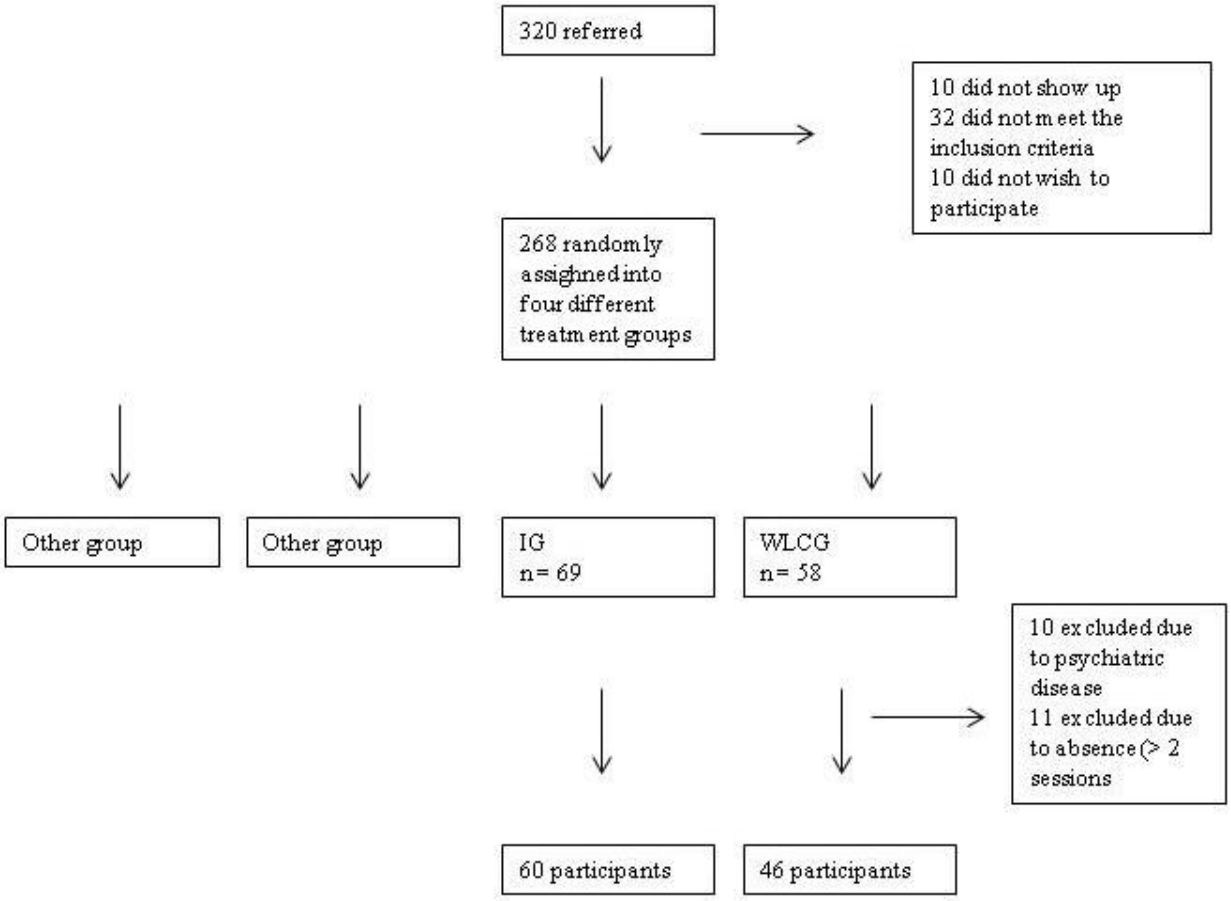
distributed on two groups: An intervention group (IG) that received treatment immediately, and a waitlisted control group (WLCG) that received treatment after three months of waiting (figure 6).

Figure 6. Design stress treatment intervention



The study group comprised 106 participants, 60 participants in the IG and 45 in the WLCG. Questionnaire and clinical data were collected before and after treatment (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 on the same data, a significant 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 labor 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, Friebel & Ladegaard 2013). The SCL92 is a 92-item self-administered questionnaire that measure psychological symptoms. The items are rated on a 5-point Likert scale ranging from 0 (not at all) to 4 (extremely) and the time frame referred to "the past week". The sum of all 92 items constitutes the GSI (Olsen, Mortensen & Bech 2004b).

3.2.6 Covariates

Due to the small size of the material and number in each group, we analyzed women and men together in the analyses but took gender into account by calculating the AL score of the selected physiological markers by use of different cut points for women and men. Moreover, we included age and physical activity since both groups increased the level of physical activity during treatment. The participants did not differ in SES overall, so we did not include this covariate.

3.2.7 Statistical

In study III, we used the same statistical methods as in study II but included other variables. To investigate the mediating effect of RTW and GSI on the changes in AL, we analysed RTW as a dichotomized fixed factor variable and GSI as a continuous covariate variable.

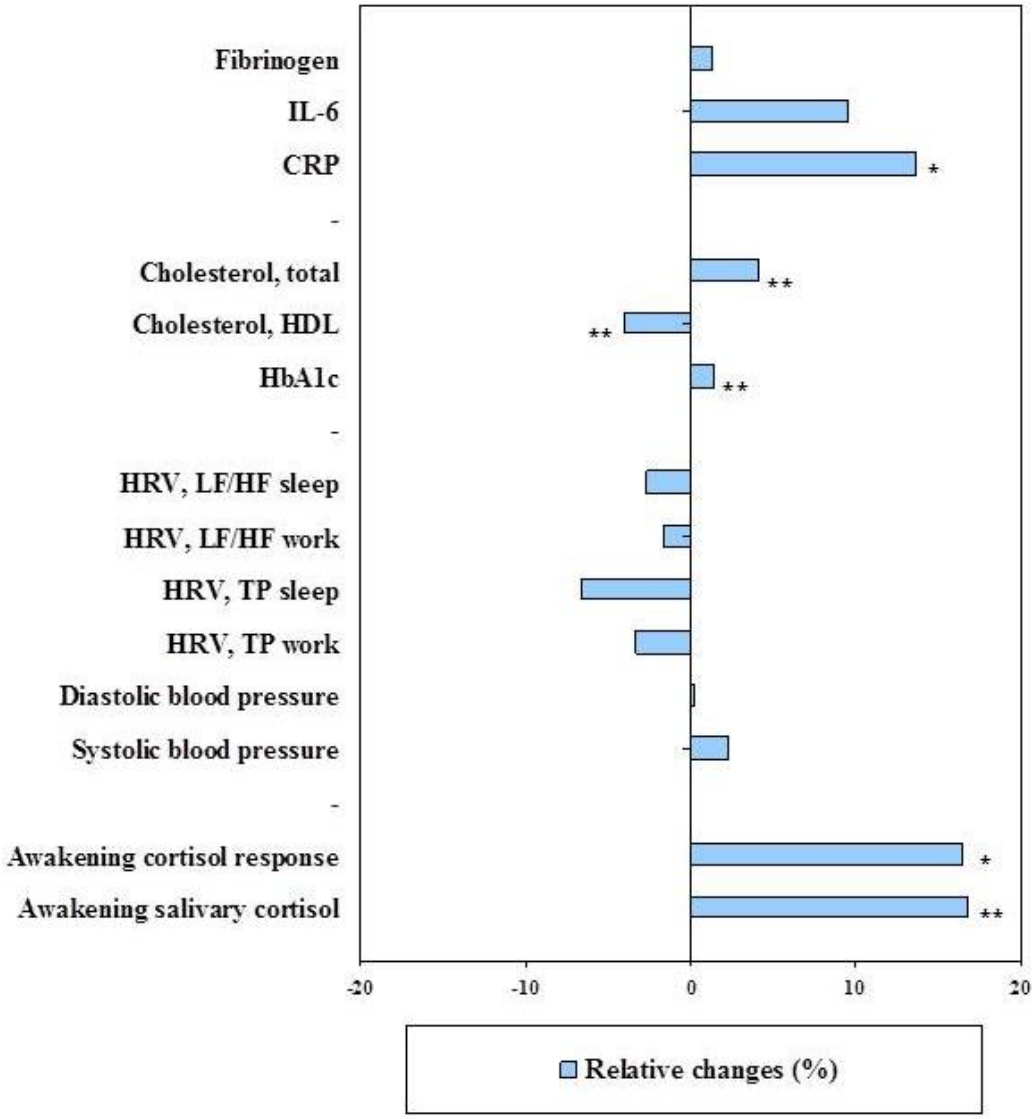
4. Results

4.1 Workplace reorganization (study I and II)

4.1.1 Main results (study I)

We investigated changes in the physiological stress markers during reorganization and observed significant changes in the expected directions of several physiological markers: 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. The association between workplace reorganization and changes in perceived psychosocial work environment and psychological distress showed no 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). Finally, we investigated the mediating effect of changes in perceived psychosocial work environment and psychological distress on changes in the physiological stress markers and found only perceived stress to have significant influence (p=0.03) on change in SBP during reorganization though the change was still significant (2.7, SE (0.9), p=0.03) after adjustment. Adjustment for covariates did not influence the results (figure 8).

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



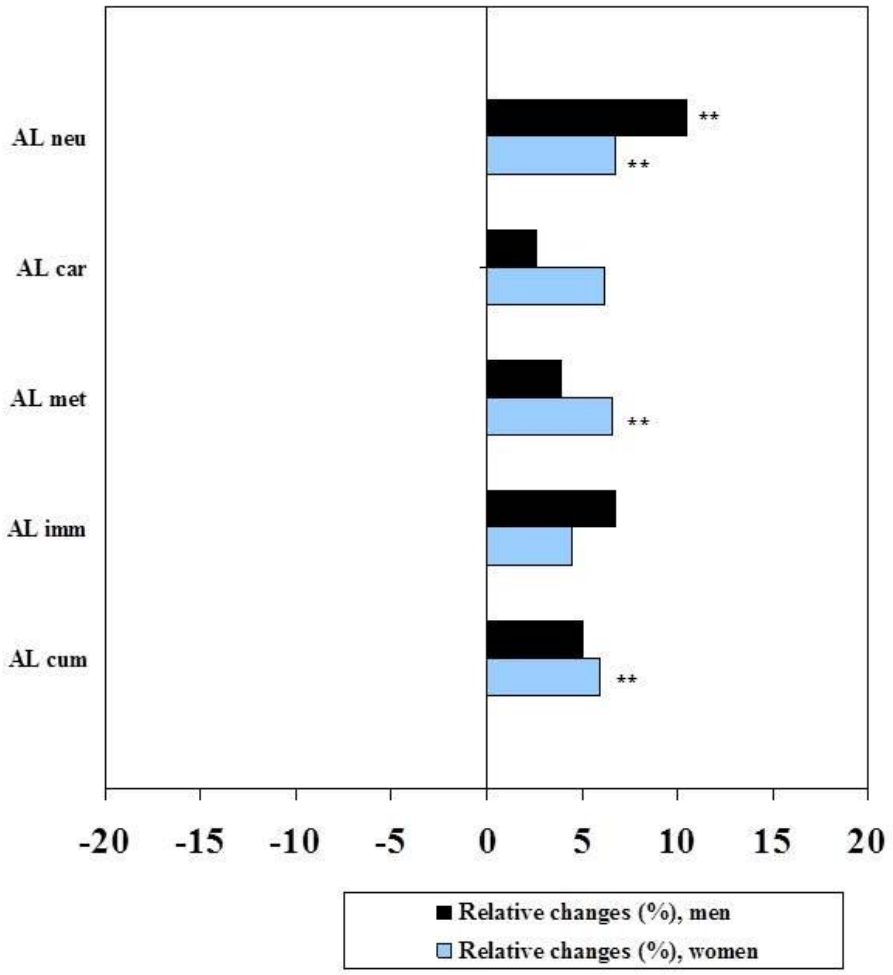
4.1.2 Additional results (study I)

Before we included reorganization groups as a covariate, we investigated the original design and found no significant differences between the groups in changes of both the psychological and physiological stress markers.

4.1.3 Main results (study II)

AL increased significantly during reorganization among women (0.27, SE 0.09, p<0.01), but neither adjustment for reorganization group nor any of the personal involvement factors had any mediating effect. Among men, AL increased insignificantly. When we adjusted for reorganization groups, the increase was significantly higher in the merger group (0.94, SE 0.28, p<0.01) and the new job group (0.60, SE 0.28, p<0.05) compared with the control group. However, none of the covariates influenced the results significantly. More specific, AL of the neuroendocrine and metabolic system increased significantly among women and the neuroendocrine system among men (figure 9).

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



4.1.4 Additional results (study II)

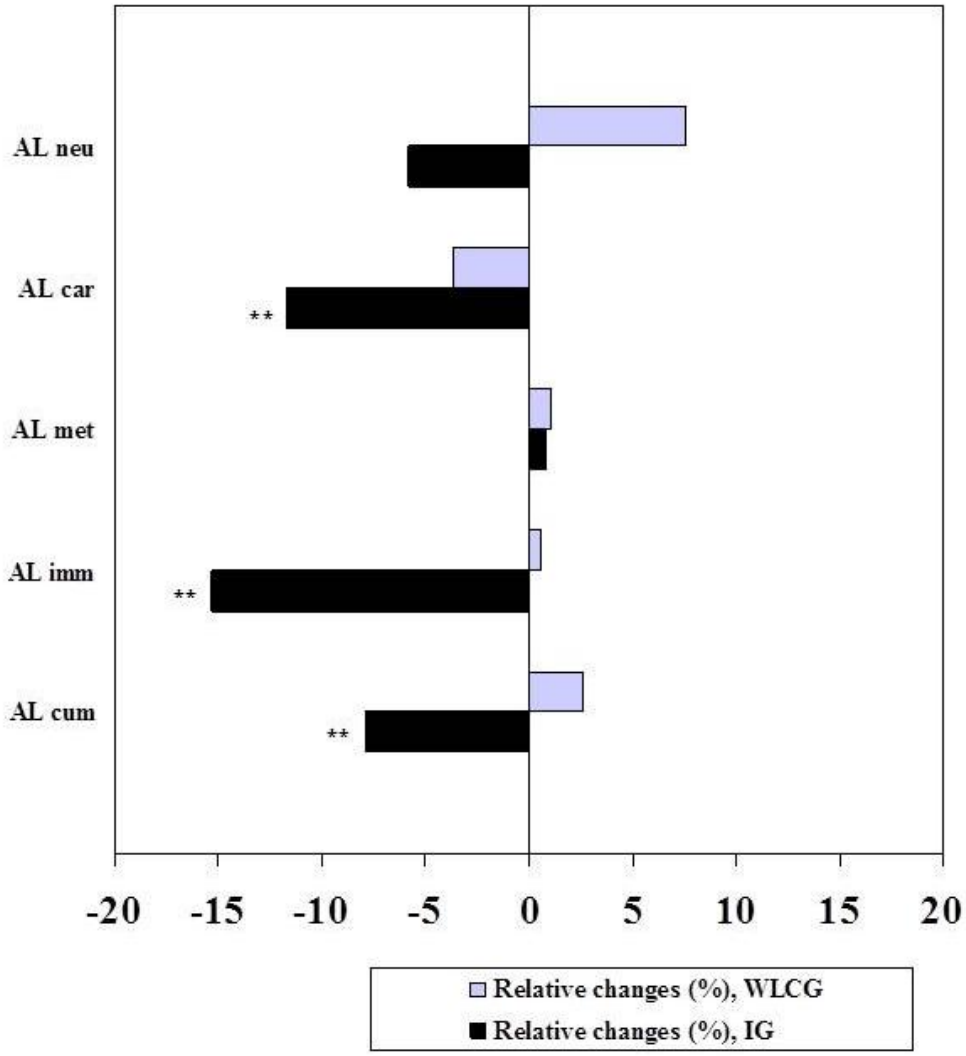
In the procedure of constructing a cumulative measurement in the form of AL, we tested both the traditional method of Seeman et al. (Seeman et al. 1997) (Juster, McEwen & Lupien 2010) and octiles. The rationale of using octiles was twofold. Firstly, we studied healthy people at work and wanted to observe 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 treatment and observed a significant decrease in AL (-0.34, SE 0.09, $p<0.01$) in the IG but no significant changes (0.12, SD 0.10, $p=0.28$) in the WLCG. RTW had a borderline significant influence ($p=0.05$) on the decrease in AL in the IG, but the participants that had returned to work after the stress treatment intervention did not differ significantly from the participants that were still on sick leave. GSI had no influence on the decrease in AL in any of the groups. Adjustment for covariates did not influence the results. In details, AL of the cardiovascular and immune system decreased significantly in the IG (figure 10).

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



4.2.2 Additional results

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

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) among women. Moreover, psychological distress increased significantly (study I). During the stress treatment intervention, AL decreased significantly in the IG (study III) that also decreased significantly in GSI (Netterstrom, Friebel & Ladegaard 2013). Neither psychological distress (study I) nor GSI (study III) had a mediating effect on changes in physiological markers and AL.

These findings 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, also called engagement and disengagement (Skinner et al. 2003). Approach coping strategies are efforts to deal with the 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 extraversion 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 the individuals reacting in a psychological way but not a physiological way. They are problem-focused and have the ability to express emotions. 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 neuroticism personality 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, the 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 which are 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 matter physiologically. Approach coping styles has been related to lower overall levels of cortisol, more favorable diurnal cortisol rhythms, and faster 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 with several theoretical approaches (Carver, Connor-Smith 2010).

5.2 Workplace reorganization (study I and II)

5.2.1 Design

We investigated the original design of both mergers and controls but found no difference between the groups. 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, was 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 actually 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

A number of 111 participants did not complete the clinical follow-up and reported poorer health, more stress and higher sickness absence at baseline. 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 consequence of retirement and had a significantly higher WHR and HBA1C probably related to the higher age. The unequal distribution of men and women (94 men and 265 women) should be taken into account when drawing conclusions from the results although the strongest results were among women.

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 in 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). Here, the included participants were healthy workers assumed not to suffer from burnout and all 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 no effect on the perceived psychosocial work environment could be that the 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). Therefore, we also expected personal involvement in the reorganization to reflect this experience but perhaps the validity of the questions or recall bias can explain the lack of influence on the physiological changes (study II).

5.2.4 Compared with previous findings

The results correspond with previous studies investigating the association between workplace reorganization in the form of downsizing (Hertting, Theorell 2002) and job insecurity (Ferrie et al. 2002) and changes in physiological markers. Also the association between workplace reorganization and psychological distress correspond 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 the 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 taking 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. 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) confirming this theory. 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 would 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 correspond 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 analyzed 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 was to investigate changes in AL. Therefore, the methods of study II and III focused 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 used an AL score based on octiles advantageous to assess small, but relevant changes in AL. Moreover, the same review suggested interventions on AL as the next stage in AL research. This thesis aimed 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 observed 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 did not influence 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 was not significantly different between the participants that returned work compared to the participants still on sick leave confirms this.

5.3.4 Compared 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.

6. Conclusion

In conclusion, the studies of this thesis showed significant changes in physiological stress reactions of both distress and rehabilitation during workplace reorganization and a stress treatment intervention. Perceived stress increased significantly during workplace reorganization and GSI during the stress treatment intervention but neither of these factors could explain the physiological changes. Whether the clinical implications of this finding are limited or people react to stress in either a physical or psychological way due to individual differences leave the conclusion unclear. Also limitations in the design of both studies should be taken into account.

7. Perspectives for future research

Physiological stress reactions might not be as noticeable as the psychological reactions but can 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, especially longitudinal studies, 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, in this case psychological. A stress condition is characterized by an activation of different biological systems together with mental and behavioral 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 was to investigate physiological stress reactions of long-term stress in relation to two different interventions of 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. 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 analyzed changes in physiological markers and AL from 2006 to 2008 and moreover, changes in perceived psychosocial work environment (job strain, ERI) and psychological distress (stress symptoms, perceived stress). We investigated the mediating effect of these factors and personal involvement in the reorganization on the physiological changes. 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 an intervention group (IG) that received treatment immediately and a waitlisted control group (WLCG) that received treatment after three months of waiting. We analyzed changes in AL and the mediating effect of GSI and RTW.

Results

We observed a significant increase in several physiological stress markers and AL during workplace reorganization. Moreover, psychological distress increased significantly but had no mediating effect on the physiological changes. During the stress treatment intervention, we observed a significant decrease in AL in the IG but not in the WLCG. Neither RTW nor GSI had influence on this result.

Conclusion

In conclusion, we found 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, a significant increase in psychological distress during reorganization and a significant decrease in GSI during stress treatment could not explain the physiological changes. This could indicate that some people react to stress in a psychological way and others in a physiological way depending on individual differences. Limitations in design of both studies should be taken into account.

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, especially longitudinal studies, is needed.

9. Danish summary / Dansk resumé

Baggrund

Stress er det individuelle respons på en stressor og en stressor den påvirkning, der udløser responset. Stressoren kan være af både psykologisk, fysisk, kemisk eller biologisk art – i denne sammenhæng psykisk. 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 var formålet med denne afhandling, at undersøge fysiologiske stressreaktioner i forbindelse med langvarig stress ud fra to interventioner relateret til psykosocialt arbejdsmiljø: 1. Arbejdspladsomstrukturering 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. 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 samt ændringer i selvoplevet psykosocialt arbejdsmiljø (krav/kontrol modellen og ERI) og psykologisk stress (stresssymptomer, selvoplevet stressniveau). Derudover undersøgte vi den medierende effekt af disse faktorer og personlig involvering i omstruktureringen. 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 en interventionsgruppe, der fik behandling med det samme og en ventelistegruppe, der fik behandling efter at have ventet tre mdr. Vi analyserede ændringer i AL i løbet af behandlingen og den medierende effekt af GSI og RTW.

Resultater

Vi observerede en signifikant stigning i flere af de fysiologiske stressmarkører og AL i løbet af arbejdspladsomstruktureringen. Desuden steg psykologisk stressniveau signifikant i løbet af omstruktureringen men havde ingen medierende effekt på de fysiologiske ændringer. I løbet af stressbehandlingsinterventionen observerede vi et signifikant fald i AL i interventionsgruppen men ikke i ventelistegruppen. Hverken RTW eller GSI havde nogen indflydelse på dette resultat.

Konklusion

Samlet set viste 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 kunne en signifikant stigning i selvoplevet psykologisk stress i forbindelse med arbejdspladsomstruktureringen og et signifikant fald i GSI i forbindelse med stressbehandlingsinterventionen ikke forklare de fysiologiske ændringer. Dette kunne indikere, at nogle mennesker reagerer psykologisk og andre fysiologisk i forbindelse med stress afhængig af individuelle forskelle. Der bør tages højde for begrænsninger i designet af begge studier.

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 og særligt longitudinelle studier er nødvendig.

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11. Reference list

"Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology", 1996, *Circulation,* vol. 93, no. 5, pp. 1043-1065.

`Kristenson, M`, `Garvin, P`, `Lundberg, U` (ed) 2012, *The Role of Saliva Cortisol Measurement in Health and Disease*, Bentham Science Publishers.

Agarwal, S.K. & Marshall, G.D.,Jr 2001, "Stress effects on immunity and its application to clinical immunology", *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology,* vol. 31, no. 1, pp. 25-31.

Andersen, M.F., Nielsen, K.M. & Brinkmann, S. 2012, "Meta-synthesis of qualitative research on return to work among employees with common mental disorders", *Scandinavian journal of work, environment & health,* vol. 38, no. 2, pp. 93-104.

Anderzen, I. & Arnetz, B.B. 2005, "The impact of a prospective survey-based workplace intervention program on employee health, biologic stress markers, and organizational productivity", *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine,* vol. 47, no. 7, pp. 671-682.

Anderzen, I. & Arnetz, B.B. 1999, "Psychophysiological reactions to international adjustment. Results from a controlled, longitudinal study", *Psychotherapy and psychosomatics,* vol. 68, no. 2, pp. 67-75.

Arnetz, B.B., Sjogren, B., Rydehn, B. & Meisel, R. 2003, "Early workplace intervention for employees with musculoskeletal-related absenteeism: a prospective controlled intervention study", *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine,* vol. 45, no. 5, pp. 499-506.

Backe, E.M., Seidler, A., Latza, U., Rossnagel, K. & Schumann, B. 2012, "The role of psychosocial stress at work for the development of cardiovascular diseases: a systematic review", *International archives of occupational and environmental health,* vol. 85, no. 1, pp. 67-79.

Baer, R. 2003, "Mindfulness training as a clinical intervention: a conceptual and empirical review", *Clin Psychol Sci Pract,* vol. 10: 125-143.

Bamberger, S.G., Vinding, A.L., Larsen, A., Nielsen, P., Fonager, K., Nielsen, R.N., Ryom, P. & Omland, O. 2012, "Impact of organisational change on mental health: a systematic review", *Occupational and environmental medicine,* vol. 69, no. 8, pp. 592-598.

Bambra, C., Egan, M., Thomas, S., Petticrew, M. & Whitehead, M. 2007, "The psychosocial and health effects of workplace reorganisation. 2. A systematic review of task restructuring interventions", *Journal of epidemiology and community health,* vol. 61, no. 12, pp. 1028-1037.

Beckie, T.M. 2012, "A systematic review of allostatic load, health, and health disparities", *Biological research for nursing,* vol. 14, no. 4, pp. 311-346.

Bellingrath, S., Weigl, T. & Kudielka, B.M. 2009, "Chronic work stress and exhaustion is associated with higher allostastic load in female school teachers", *Stress (Amsterdam, Netherlands),* vol. 12, no. 1, pp. 37-48.

Bhui, K.S., Dinos, S., Stansfeld, S.A. & White, P.D. 2012, "A synthesis of the evidence for managing stress at work: a review of the reviews reporting on anxiety, depression, and absenteeism", *Journal of environmental and public health,* vol. 2012, pp. 515874.

Blonk, R., Brenninkmeijer, V. & Lagerveld, S. 2006, "Return to work: a comparison of two cognitive behavioral interventions in cases of work-related psychological complaints among self-employed", *Work and Stress,* vol. 20.

Bonde, J.P. 2008, "Psychosocial factors at work and risk of depression: a systematic review of the epidemiological evidence", *Occupational and environmental medicine,* vol. 65, no. 7, pp. 438-445.

Cancelliere, C., Cassidy, J.D., Ammendolia, C. & Cote, P. 2011, "Are workplace health promotion programs effective at improving presenteeism in workers? A systematic review and best evidence synthesis of the literature", *BMC public health,* vol. 11, pp. 395-2458-11-395.

Cannon, W. (ed) 1932, *The wisdom of the body*, New York: Norton.

Carver, C.S. & Connor-Smith, J. 2010, "Personality and coping", *Annual Review of Psychology,* vol. 61, pp. 679-704.

Caspi, A., Roberts, B.W. & Shiner, R.L. 2005, "Personality development: stability and change", *Annual Review of Psychology,* vol. 56, pp. 453-484.

Chandola, T., Brunner, E. & Marmot, M. 2006, "Chronic stress at work and the metabolic syndrome: prospective study", *BMJ (Clinical research ed.),* vol. 332, no. 7540, pp. 521-525.

Chida, Y. & Steptoe, A. 2009, "Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis", *Biological psychology,* vol. 80, no. 3, pp. 265-278.

Chrousos, G.P. 2009, "Stress and disorders of the stress system", *Nature reviews.Endocrinology,* vol. 5, no. 7, pp. 374-381.

Chrousos, G.P. 1995, "The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation", *The New England journal of medicine,* vol. 332, no. 20, pp. 1351-1362.

Denollet, J. & Conraads, V.M. 2011, "Type D personality and vulnerability to adverse outcomes in heart disease", *Cleveland Clinic journal of medicine,* vol. 78 Suppl 1, pp. S13-9.

Egan, M., Bambra, C., Thomas, S., Petticrew, M., Whitehead, M. & Thomson, H. 2007, "The psychosocial and health effects of workplace reorganisation. 1. A systematic review of organisational-level interventions that aim to increase employee control", *Journal of epidemiology and community health,* vol. 61, no. 11, pp. 945-954.

Eller, N.H., Netterstrom, B., Gyntelberg, F., Kristensen, T.S., Nielsen, F., Steptoe, A. & Theorell, T. 2009, "Work-related psychosocial factors and the development of ischemic heart disease: a systematic review", *Cardiology in review,* vol. 17, no. 2, pp. 83-97.

Elliot, A.J. & Thrash, T.M. 2002, "Approach-avoidance motivation in personality: approach and avoidance temperaments and goals", *Journal of personality and social psychology,* vol. 82, no. 5, pp. 804-818.

Elo, A.L., Leppanen, A. & Jahkola, A. 2003, "Validity of a single-item measure of stress symptoms", *Scandinavian journal of work, environment & health,* vol. 29, no. 6, pp. 444-451.

Ferrie, J.E., Shipley, M.J., Stansfeld, S.A. & Marmot, M.G. 2002, "Effects of chronic job insecurity and change in job security on self reported health, minor psychiatric morbidity, physiological

measures, and health related behaviours in British civil servants: the Whitehall II study", *Journal of epidemiology and community health,* vol. 56, no. 6, pp. 450-454.

Fink, G. (ed) 2010, *Stress Science Neuroendocrinology*, Elsevier, Oxford.

Fjorback, L.O., Arendt, M., Ornbol, E., Fink, P. & Walach, H. 2011, "Mindfulness-based stress reduction and mindfulness-based cognitive therapy: a systematic review of randomized controlled trials", *Acta Psychiatrica Scandinavica,* vol. 124, no. 2, pp. 102-119.

Franche, R.L., Cullen, K., Clarke, J., Irvin, E., Sinclair, S., Frank, J. & Institute for Work & Health (IWH) Workplace-Based RTW Intervention Literature Review Research Team 2005, "Workplace-based return-to-work interventions: a systematic review of the quantitative literature", *Journal of Occupational Rehabilitation,* vol. 15, no. 4, pp. 607-631.

Glaser, R. & Kiecolt-Glaser, J.K. 2005, "Stress-induced immune dysfunction: implications for health", *Nature reviews.Immunology,* vol. 5, no. 3, pp. 243-251.

Goetzel, R.Z., Long, S.R., Ozminkowski, R.J., Hawkins, K., Wang, S. & Lynch, W. 2004, "Health, absence, disability, and presenteeism cost estimates of certain physical and mental health conditions affecting U.S. employers", *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine,* vol. 46, no. 4, pp. 398-412.

Greeson, J.M. 2009, "Mindfulness Research Update: 2008", *Complementary health practice review,* vol. 14, no. 1, pp. 10-18.

Hansen, A.M., Garde, A.H., Christensen, J.M., Eller, N.H. & Netterstrom, B. 2003, "Evaluation of a radioimmunoassay and establishment of a reference interval for salivary cortisol in healthy subjects in Denmark", *Scandinavian Journal of Clinical and Laboratory Investigation,* vol. 63, no. 4, pp. 303-310.

Hansen, A.M., Garde, A.H. & Persson, R. 2008, "Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: a review", *Scandinavian journal of clinical and laboratory investigation,* vol. 68, no. 6, pp. 448-458.

Hansen, A.M., Larsen, A.D., Rugulies, R., Garde, A.H. & Knudsen, L.E. 2009, "A review of the effect of the psychosocial working environment on physiological changes in blood and urine", *Basic & clinical pharmacology & toxicology,* vol. 105, no. 2, pp. 73-83.

Hasson, D., Von Thiele Schwarz, U. & Lindfors, P. 2009, "Self-rated health and allostatic load in women working in two occupational sectors", *Journal of health psychology,* vol. 14, no. 4, pp. 568-577.

Henderson, M., Glozier, N. & Holland Elliott, K. 2005, "Long term sickness absence", *BMJ (Clinical research ed.),* vol. 330, no. 7495, pp. 802-803.

Hertting, A. & Theorell, T. 2002, "Physiological changes associated with downsizing of personnel and reorganisation in the health care sector", *Psychotherapy and psychosomatics,* vol. 71, no. 2, pp. 117-122.

Hintikka, J., Lehto, S.M., Niskanen, L., Huotari, A., Herzig, K.H., Koivumaa-Honkanen, H., Honkalampi, K., Sinikallio, S. & Viinamaki, H. 2009, "Unemployment and ill health: a connection through inflammation?", *BMC public health,* vol. 9, pp. 410-2458-9-410.

Janicki-Deverts, D., Cohen, S., Matthews, K.A. & Cullen, M.R. 2008, "History of unemployment predicts future elevations in C-reactive protein among male participants in the Coronary Artery Risk Development in Young Adults (CARDIA) Study", *Annals of Behavioral Medicine : A Publication of the Society of Behavioral Medicine,* vol. 36, no. 2, pp. 176-185.

Jarczok, M.N., Jarczok, M., Mauss, D., Koenig, J., Li, J., Herr, R.M. & Thayer, J.F. 2013, "Autonomic nervous system activity and workplace stressors--a systematic review", *Neuroscience and biobehavioral reviews,* vol. 37, no. 8, pp. 1810-1823.

Juster, R.P., Bizik, G., Picard, M., Arsenault-Lapierre, G., Sindi, S., Trepanier, L., Marin, M.F., Wan, N., Sekerovic, Z., Lord, C., Fiocco, A.J., Plusquellec, P., McEwen, B.S. & Lupien, S.J. 2011, "A transdisciplinary perspective of chronic stress in relation to psychopathology throughout life span development", *Development and psychopathology,* vol. 23, no. 3, pp. 725-776.

Juster, R.P., McEwen, B.S. & Lupien, S.J. 2010, "Allostatic load biomarkers of chronic stress and impact on health and cognition", *Neuroscience and biobehavioral reviews,* vol. 35, no. 1, pp. 2-16.

Juster, R.P., Sindi, S., Marin, M.F., Perna, A., Hashemi, A., Pruessner, J.C. & Lupien, S.J. 2011, "A clinical allostatic load index is associated with burnout symptoms and hypocortisolemic profiles in healthy workers", *Psychoneuroendocrinology*, vol. 36, no. 6, pp. 797-805.

Kabat-Zinn, J., Massion, A.O., Kristeller, J., Peterson, L.G., Fletcher, K.E., Pbert, L., Lenderking, W.R. & Santorelli, S.F. 1992, "Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders", *The American Journal of Psychiatry*, vol. 149, no. 7, pp. 936-943.

Karasek, R., Brisson, C., Kawakami, N., Houtman, I., Bongers, P. & Amick, B. 1998, "The Job Content Questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics", *Journal of occupational health psychology*, vol. 3, no. 4, pp. 322-355.

Karlamangla, A.S., Singer, B.H., McEwen, B.S., Rowe, J.W. & Seeman, T.E. 2002, "Allostatic load as a predictor of functional decline. MacArthur studies of successful aging", *Journal of clinical epidemiology*, vol. 55, no. 7, pp. 696-710.

Kiecolt-Glaser, J.K., Preacher, K.J., MacCallum, R.C., Atkinson, C., Malarkey, W.B. & Glaser, R. 2003, "Chronic stress and age-related increases in the proinflammatory cytokine IL-6", *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 15, pp. 9090-9095.

Kim, I.H., Muntaner, C., Vahid Shahidi, F., Vives, A., Vanroelen, C. & Benach, J. 2012, "Welfare states, flexible employment, and health: a critical review", *Health policy (Amsterdam, Netherlands)*, vol. 104, no. 2, pp. 99-127.

Kivimaki, M., Vahtera, J., Ferrie, J.E., Hemingway, H. & Pentti, J. 2001, "Organisational downsizing and musculoskeletal problems in employees: a prospective study", *Occupational and environmental medicine*, vol. 58, no. 12, pp. 811-817.

Kivimaki, M., Vahtera, J., Pentti, J. & Ferrie, J.E. 2000, "Factors underlying the effect of organisational downsizing on health of employees: longitudinal cohort study", *BMJ (Clinical research ed.)*, vol. 320, no. 7240, pp. 971-975.

Kristal-Boneh, E., Raifel, M., Froom, P. & Ribak, J. 1995, "Heart rate variability in health and disease", *Scandinavian journal of work, environment & health,* vol. 21, no. 2, pp. 85-95.

Kristensen, T.S., Hannerz, H., Hogh, A. & Borg, V. 2005, "The Copenhagen Psychosocial Questionnaire--a tool for the assessment and improvement of the psychosocial work environment", *Scandinavian journal of work, environment & health,* vol. 31, no. 6, pp. 438-449.

Kudielka, B.M., Bellingrath, S. & Hellhammer, D.H. 2006, "Cortisol in burnout and vital exhaustion: an overview", *Giornale italiano di medicina del lavoro ed ergonomia,* vol. 28, no. 1 Suppl 1, pp. 34-42.

Langelaan, S., Bakker, A.B., Schaufeli, W.B., van Rhenen, W. & van Doornen, L.J. 2007, "Is burnout related to allostatic load?", *International Journal of Behavioral Medicine,* vol. 14, no. 4, pp. 213-221.

Laszlo, K.D., Pikhart, H., Kopp, M.S., Bobak, M., Pajak, A., Malyutina, S., Salavecz, G. & Marmot, M. 2010, "Job insecurity and health: a study of 16 European countries", *Social science & medicine (1982),* vol. 70, no. 6, pp. 867-874.

Lavoie-Tremblay, M., Bonin, J.P., Lesage, A.D., Bonneville-Roussy, A., Lavigne, G.L. & Laroche, D. 2010, "Contribution of the psychosocial work environment to psychological distress among health care professionals before and during a major organizational change", *The health care manager,* vol. 29, no. 4, pp. 293-304.

Li, W., Zhang, J.Q. & Wang, S. 2007, "Research progress on allostatic load as a measurement of the effects of chronic stress", *Zhonghua lao dong wei sheng zhi ye bing za zhi = Zhonghua laodong weisheng zhiyebing zazhi = Chinese journal of industrial hygiene and occupational diseases,* vol. 25, no. 8, pp. 500-502.

Mair, C.A., Cutchin, M.P. & Kristen Peek, M. 2011, "Allostatic load in an environmental riskscape: the role of stressors and gender", *Health & place,* vol. 17, no. 4, pp. 978-987.

Marshall, G.D.,Jr 2011, "The adverse effects of psychological stress on immunoregulatory balance: applications to human inflammatory diseases", *Immunology and allergy clinics of North America,* vol. 31, no. 1, pp. 133-140.

McEwen, B.S. 2008, "Central effects of stress hormones in health and disease: Understanding the protective and damaging effects of stress and stress mediators", *European journal of pharmacology,* vol. 583, no. 2-3, pp. 174-185.

McEwen, B.S. 1998, "Stress, adaptation, and disease. Allostasis and allostatic load", *Annals of the New York Academy of Sciences,* vol. 840, pp. 33-44.

McEwen, B.S. & Stellar, E. 1993, "Stress and the individual. Mechanisms leading to disease", *Archives of Internal Medicine,* vol. 153, no. 18, pp. 2093-2101.

McEwen, B.S. & Wingfield, J.C. 2003, "The concept of allostasis in biology and biomedicine", *Hormones and behavior,* vol. 43, no. 1, pp. 2-15.

Mikolajczak, M., Roy, E., Luminet, O., Fillee, C. & de Timary, P. 2007, "The moderating impact of emotional intelligence on free cortisol responses to stress", *Psychoneuroendocrinology,* vol. 32, no. 8-10, pp. 1000-1012.

Mommersteeg, P.M., Heijnen, C.J., Verbraak, M.J. & van Doornen, L.J. 2006a, "Clinical burnout is not reflected in the cortisol awakening response, the day-curve or the response to a low-dose dexamethasone suppression test", *Psychoneuroendocrinology,* vol. 31, no. 2, pp. 216-225.

Mommersteeg, P.M., Keijsers, G.P., Heijnen, C.J., Verbraak, M.J. & van Doornen, L.J. 2006b, "Cortisol deviations in people with burnout before and after psychotherapy: a pilot study", *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* vol. 25, no. 2, pp. 243-248.

Nakata, A. 2012, "Psychosocial job stress and immunity: a systematic review", *Methods in molecular biology (Clifton, N.J.),* vol. 934, pp. 39-75.

Naswall, K., Lindfors, P. & Sverke, M. 2012, "Job insecurity as a predictor of physiological indicators of health in healthy working women: an extension of previous research", *Stress and health : journal of the International Society for the Investigation of Stress,* vol. 28, no. 3, pp. 255-263.

Netterstrom, B., Blond, M., Nielsen, M., Rugulies, R. & Eskelinen, L. 2010, "Development of depressive symptoms and depression during organizational change--a two-year follow-up study

of civil servants", *Scandinavian journal of work, environment & health,* vol. 36, no. 6, pp. 445-448.

Netterstrom, B., Conrad, N., Bech, P., Fink, P., Olsen, O., Rugulies, R. & Stansfeld, S. 2008, "The relation between work-related psychosocial factors and the development of depression", *Epidemiologic reviews,* vol. 30, pp. 118-132.

Netterstrom, B., Friebel, L. & Ladegaard, Y. 2013, "Effects of a multidisciplinary stress treatment programme on patient return to work rate and symptom reduction: results from a randomised, wait-list controlled trial", *Psychotherapy and psychosomatics,* vol. 82, no. 3, pp. 177-186.

Netterstrom, B. & Hansen, A.M. 2000, "Outsourcing and stress: Physiological effects on bus drivers", *Stress Medicine,* vol. 16, pp. 149-160.

Noer, D. (ed) 1993, *Healing the wounds: overcoming the trauma of layoffs and revitalizing downsized organizations,* Jossey-Bass, San Francisco.

Nyklicek, I., Mommersteeg, P.M., Van Beugen, S., Ramakers, C. & Van Boxtel, G.J. 2013, "Mindfulness-based stress reduction and physiological activity during acute stress: a randomized controlled trial", *Health psychology : official journal of the Division of Health Psychology, American Psychological Association,* vol. 32, no. 10, pp. 1110-1113.

O'Donnell, K., Badrick, E., Kumari, M. & Steptoe, A. 2008, "Psychological coping styles and cortisol over the day in healthy older adults", *Psychoneuroendocrinology,* vol. 33, no. 5, pp. 601-611.

Olsen, L.R., Mortensen, E.L. & Bech, P. 2004a, "The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample", *Acta Psychiatrica Scandinavica,* vol. 110, no. 3, pp. 225-229.

Olsen, L.R., Mortensen, E.L. & Bech, P. 2004b, "The SCL-90 and SCL-90R versions validated by item response models in a Danish community sample", *Acta Psychiatrica Scandinavica,* vol. 110, no. 3, pp. 225-229.

Owen, N., Poulton, T., Hay, F.C., Mohamed-Ali, V. & Steptoe, A. 2003, "Socioeconomic status, C-reactive protein, immune factors, and responses to acute mental stress", *Brain, behavior, and immunity,* vol. 17, no. 4, pp. 286-295.

Quinlan, M. & Bohle, P. 2009, "Overstretched and unreciprocated commitment: reviewing research on the occupational health and safety effects of downsizing and job insecurity", *International journal of health services : planning, administration, evaluation*, vol. 39, no. 1, pp. 1-44.

Richardson, K.M. & Rothstein, H.R. 2008, "Effects of occupational stress management intervention programs: a meta-analysis", *Journal of occupational health psychology*, vol. 13, no. 1, pp. 69-93.

Rosenthal, T. & Alter, A. 2012, "Occupational stress and hypertension", *Journal of the American Society of Hypertension : JASH*, vol. 6, no. 1, pp. 2-22.

Sapolsky, R.M. 2004, *Why zebras don't get ulcers*, 3. ed. edn, Times Books, New York.

Schnorpfeil, P., Noll, A., Schulze, R., Ehlert, U., Frey, K. & Fischer, J.E. 2003, "Allostatic load and work conditions", *Social science & medicine (1982)*, vol. 57, no. 4, pp. 647-656.

Schulkin, J. 2003, "Allostasis: a neural behavioral perspective", *Hormones and behavior*, vol. 43, no. 1, pp. 21-7; discussion 28-30.

Seeman, T.E., McEwen, B.S., Rowe, J.W. & Singer, B.H. 2001, "Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging", *Proceedings of the National Academy of Sciences of the United States of America*, vol. 98, no. 8, pp. 4770-4775.

Seeman, T.E., Singer, B.H., Rowe, J.W., Horwitz, R.I. & McEwen, B.S. 1997, "Price of adaptation--allostatic load and its health consequences. MacArthur studies of successful aging", *Archives of Internal Medicine*, vol. 157, no. 19, pp. 2259-2268.

Selye, H. 1936, "A syndrome produced by diverse nocuous agents", *Nature*, vol. 138, no. 32.

Seplaki, C.L., Goldman, N., Glei, D. & Weinstein, M. 2005, "A comparative analysis of measurement approaches for physiological dysregulation in an older population", *Experimental gerontology*, vol. 40, no. 5, pp. 438-449.

Siegrist, J., Starke, D., Chandola, T., Godin, I., Marmot, M., Niedhammer, I. & Peter, R. 2004, "The measurement of effort-reward imbalance at work: European comparisons", *Social science & medicine (1982)*, vol. 58, no. 8, pp. 1483-1499.

Sjogren, E., Leanderson, P. & Kristenson, M. 2006, "Diurnal saliva cortisol levels and relations to psychosocial factors in a population sample of middle-aged Swedish men and women", *International Journal of Behavioral Medicine*, vol. 13, no. 3, pp. 193-200.

Skinner, E.A., Edge, K., Altman, J. & Sherwood, H. 2003, "Searching for the structure of coping: a review and critique of category systems for classifying ways of coping", *Psychological bulletin*, vol. 129, no. 2, pp. 216-269.

Sparrenberger, F., Fuchs, S.C., Moreira, L.B. & Fuchs, F.D. 2008, "Stressful life events and current psychological distress are associated with self-reported hypertension but not with true hypertension: results from a cross-sectional population-based study", *BMC public health*, vol. 8, pp. 357.

Steenland, K., Fine, L., Belkic, K., Landsbergis, P., Schnall, P., Baker, D., Theorell, T., Siegrist, J., Peter, R., Karasek, R., Marmot, M., Brisson, C. & Tuchsen, F. 2000, "Research findings linking workplace factors to CVD outcomes", *Occupational medicine (Philadelphia, Pa.)*, vol. 15, no. 1, pp. 7-68.

Sterling, P. & Eyer, J. 1981, "Biological basis of stress-related mortality", *Social science & medicine.Part E, Medical psychology*, vol. 15, no. 1, pp. 3-42.

Sterling, P. & Eyer, J. 1988, "Allostasis: A new paradigm to explain arousal pathology" in *Handbook of life stress, cognition and health*, eds. S. Fisher & J. Reason, NY: Wiley, , pp. 629.

Sun, J., Wang, S., Zhang, J. & Li, W. 2007, "The association between job stress and allostatic load in a large sample of chinese employees", *Work & Stress*, vol. 21, pp. 333-347.

Sverke, M., Hellgren, J. & Naswall, K. 2002, "No security: a meta-analysis and review of job insecurity and its consequences", *Journal of occupational health psychology*, vol. 7, no. 3, pp. 242-264.

Swaen, G.M., Bultmann, U., Kant, I. & van Amelsvoort, L.G. 2004, "Effects of job insecurity from a workplace closure threat on fatigue and psychological distress", *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*, vol. 46, no. 5, pp. 443-449.

Szanton, S.L., Gill, J.M. & Allen, J.K. 2005, "Allostatic load: a mechanism of socioeconomic health disparities?", *Biological research for nursing*, vol. 7, no. 1, pp. 7-15.

Temoshok, L.R., Waldstein, S.R., Wald, R.L., Garzino-Demo, A., Synowski, S.J., Sun, L. & Wiley, J.A. 2008, "Type C coping, alexithymia, and heart rate reactivity are associated independently and differentially with specific immune mechanisms linked to HIV progression", *Brain, behavior, and immunity*, vol. 22, no. 5, pp. 781-792.

Thayer, J.F., Verkuil, B., Brosschot, J.F., Kampschroer, K., West, A., Sterling, C., Christie, I.C., Abernethy, D.R., Sollers, J.J., Cizza, G., Marques, A.H. & Sternberg, E.M. 2010, "Effects of the physical work environment on physiological measures of stress", *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*, vol. 17, no. 4, pp. 431-439.

Vahtera, J., Kivimaki, M. & Pentti, J. 1997, "Effect of organisational downsizing on health of employees", *Lancet*, vol. 350, no. 9085, pp. 1124-1128.

van der Klink, J.J., Blonk, R.W., Schene, A.H. & van Dijk, F.J. 2001, "The benefits of interventions for work-related stress", *American Journal of Public Health*, vol. 91, no. 2, pp. 270-276.

van der Klink, J.J. & van Dijk, F.J. 2003, "Dutch practice guidelines for managing adjustment disorders in occupational and primary health care", *Scandinavian journal of work, environment & health*, vol. 29, no. 6, pp. 478-487.

von Thiele, U., Lindfors, P. & Lundberg, U. 2006a, "Self-rated recovery from work stress and allostatic load in women", *Journal of psychosomatic research*, vol. 61, no. 2, pp. 237-242.

von Thiele, U., Lindfors, P. & Lundberg, U. 2006b, "Self-rated recovery from work stress and allostatic load in women", *Journal of psychosomatic research*, vol. 61, no. 2, pp. 237-242.

Westerlund, H., Ferrie, J., Hagberg, J., Jeding, K., Oxenstierna, G. & Theorell, T. 2004, "Workplace expansion, long-term sickness absence, and hospital admission", *Lancet*, vol. 363, no. 9416, pp. 1193-1197.

Westgard, J.O., Barry, P.L., Hunt, M.R. & Groth, T. 1981, "A multi-rule Shewhart chart for quality control in clinical chemistry", *Clinical chemistry*, vol. 27, no. 3, pp. 493-501.

Papers