



**Workplace Bullying, Stress Response and Long-term Sickness Absence-Exploring Mechanisms  
Results from Six Cohort Studies**

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Workplace Bullying, stress response and long-term  
sickness absence –  
Exploring mechanisms

FACULTY OF HEALTH AND MEDICAL SCIENCES  
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Workplace Bullying, stress response and long-term  
sickness absence –  
Exploring mechanisms



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Doctoral dissertation  
Section for Social Medicine  
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Tryk og grafisk tilrettelæggelse  
Grafisk – Københavns Universitet

The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation for public defence for the doctoral degree in medicine.

Copenhagen, 19 December 2017.

Ulla Wewer  
Head of Faculty

The Public defence will take place Thursday 21.6.2018 at 13.00 in the auditorium at Medicinsk Museion, Bredgade 2, Copenhagen.

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Åse Marie Hansen  
April 2017

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## **Preface**

The work for this dissertation started with an interest in how exposure to stressors in working life leads to disease. I focussed on the physiological stress response and started with a state of art report in Danish on Biomarkers of work-related stress in 1994 funded by Danish Working Environment Research Foundation (DWERF). The Director of National Research Centre for the Working Environment (NRCWE), Dr. Med, Ib Andersen (1983-2004), strongly supported the initiation of research in stress that included studying physiological mechanisms between the psychosocial working environment and stress related diseases. Together with my first PhD student, Professor Anne Helene Garde, NRCWE, I visited the research groups in the Nordic countries that work on psychosocial stressors and mechanisms leading to disease. We discussed the necessity of establishing a Nordic network on 'research in the physiological stress response as a mechanism leading to disease'. The gaps that we observed in our visiting the research groups were related to lack of validated laboratory methods for use in field studies. The gaps were specifically in relation to measurements of the physiological stress response in the working population. I initiated establishing a number of methods to study the physiological response to stressors. Furthermore, to enhance possibilities of knowledge exchange between the Nordic research groups I initiated two Nordic networks with the aim of getting an overview of research on physiological stress response in the Nordic countries in order to identify the gaps in this type of research and also to establish similar research in Denmark that will fill out the gaps. With support from Nordic Council of Ministers, we wrote a review on research on 'Physiological stress response in the Nordic countries' (1999-2001) and established a joint database on cortisol in saliva (2002-2005) a widely studied physiological response. The discussions in relation to the joint database underlined the importance of sampling procedures and validity of the measurement method. Within the frame of the Nordic network we initiated establishment of NIVA courses for PhD students and health professionals with the title: 'International Course on Biomarkers of stress in relation to Occupational Health' and held the course in 2002, and repeated it in 2006 and 2011. During the period from 1996 and onwards a number of methods for measuring the physiological stress response in field studies in the working population were established and validated. Ensuring compliance with sampling and validation of self-collected saliva samples we also performed stability studies of cortisol in saliva at different storage temperatures. All the basic knowledge of being able to include physiological responses in field studies of the psychosocial Working Environment and the physiological stress response was established in several papers and in a review with recommendations in 2008.

In 1999 salivary cortisol was used to assess physiological stress in a study on the association between stress and the intima media thickness together with Nanna Hurwitz Eller, Dr.Med., Ph.D., and Bo Netterstrøm, Dr.Med., Ph.D., both from Department of Occupational and Environmental Medicine, Bispebjerg University Hospital. This collaboration also involved a study on outsourcing and stress among bus drivers. In 2000 I was involved in a Swedish study on stressors at work and health, supported by the Labour Inspectorate, Sweden, and NRCWE and Director of NRCWE, Dr. Med. Palle Ørbæk (2004-2013), was the leader of this project. Workplace bullying emerged to be a strong stressor in the late 90'es and in the beginning of 2000. In the Swedish study the research group asked the participants about workplace bullying. Together with Professor Annie Høgh, Department of Psychology (IFP), University of Copenhagen, I initiated to study workplace bullying and health in the Swedish study. This study was the first full study on the association between workplace bullying and salivary cortisol. With the interest in workplace bullying and health effects as well as the results in the Swedish study, Annie Høgh, Eva Gemzøe-Mikkelsen, CRECEA, associate professor Charlotte Bloch,

Department of Sociology, and I initiated a research project on the Prevalence, risk factors, health outcome, and rehabilitation of workplace bullying. The project was funded by the DWERF and NRCWE. A part of the project focussed on the association between workplace bullying and early health effects in terms of salivary cortisol and sleep. Further, as a part of the project I initiated establishment of a Nordic Network on bullying at the workplace. The Network aimed at establishing a joint Nordic theoretical and methodological platform for research in workplace bullying.

The project on ‘Psychological RISK factors in the working environment and biological MEchanism for the development of stress, burn-out and depression study’ (PRISME) funded by DWERF was initiated in collaboration with Associate professor, Anette Kærgaard, Herning county Hospital, associate professor Linda Kærlev, Odense University Hospital, Professor Henrik Kolstad, Aarhus University Hospital, consultants Jane Frølund Thomsen and Sigurd Mikkelsen, Professor Jens Peter Bonde, Bispebjerg University Hospital, Professor Ole Mors and Professor Johan Hviid Andersen, Aarhus University, and Professor Reiner Rugulies, NRCWE. In the PRISME project I had the possibility to study to what extent low or high cortisol has an impact on poor sleep and whether poor sleep has an impact on salivary cortisol in population based studies. The Health Promotion study was initiated by Gisela Sjøgaard, professor, and Karen Sjøgaard, both Southern Danish University, and funded by the Ministry of Culture Committee on Sports Research and the National Board of Health under the Ministry of the Interior and Health. In this study I had the opportunity to study association between leisure-time physical activity and salivary cortisol.

We further studied whether there is a causal relation between workplace bullying and low cortisol leading to mental diseases when exposed to negative behaviour at work, in the MODENA project, funded by DWERF. The MODENA project was initiated in collaboration with Henrik Kolstad and associate professor Morten Willert, Aarhus University Hospital, Jane Frølund Thomsen, Sigurd Mikkelsen, Jens Peter Bonde, Bispebjerg University Hospital, Annie Høgh, IFP, and Reiner Rugulies, NRCWE. Finally, the project ‘Antecedents, mechanisms, and long-term consequences of negative social relations at work’, in which we use the MODENA cohort to merge with registers on among others sickness absence was established in collaboration with Annie Høgh and associate professor Ann-Louise Holten, IFP, and Anne Helene Garde and Reiner Rugulies, NRCWE. Two of the research questions are included in this thesis, i.e. if stress (quantitatively measured by psychological stress reactions) and sleep mediate the effects of negative social relations on Long-term sickness absence (LTSA). The project is financed by the Danish Independent Research Council and DWERF.

Åse Marie Hansen  
Copenhagen April 2017

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## List of Papers

### *Methodological issues in using salivary cortisol in field studies*

- I. Hansen ÅM, Garde AH, Christensen JM, Eller NH, Netterstrom B. Evaluation of a radioimmunoassay and establishment of a reference interval for salivary cortisol in healthy subjects in Denmark. *Scand J Clin Lab Invest.* 2003; **63**:303-310.
- II. Hansen ÅM, Garde AH, Persson R. Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: a review. *Scand J Clin Lab Invest.* 2008; **68**:448-458.

### *Workplace bullying and salivary cortisol*

- III. Hansen ÅM, Høgh A, Persson R, Karlson B, Garde AH, Ørbæk P. Bullying at work, health outcomes, and physiological stress response. *J Psychosom Res.* 2006; **60**:63-72.
- IV. Hansen ÅM, Hogh A, Persson R. Frequency of bullying at work, physiological response, and mental health. *J Psychosom Res.* 2011; **70**:19-27.
- V. Hogh A, Hansen ÅM, Mikkelsen EG, Persson R. Exposure to negative acts at work, psychological stress reactions and physiological stress response. *J Psychosom Res.* 2012; **73**:47-52.

### *Sleep and salivary cortisol*

- VI. Hansen ÅM, Thomsen JF, Kaergaard A, Kolstad, H, Kaerlev, L, Mors, O, Rugulies, R, Bonde, JP, Andersen, JH, Mikkelsen, S. Salivary cortisol and sleep problems among civil servants. *Psychoneuroendocrinology.* 2012; **37**:1086-1095.

### *Physical activity and salivary cortisol*

- VII. Hansen ÅM, Blangsted AK, Hansen EA, Sjøgaard K, Sjøgaard G. Physical activity, job demand-control, perceived stress-energy, and salivary cortisol in white-collar workers. *Int Arch Occup Environ Health.* 2010; **83**:143-153.

### *Workplace bullying, sleep and leisure-time physical activity (LTPA)*

- VIII. Hansen ÅM, Hogh A, Garde AH, Persson R. Workplace bullying and sleep difficulties: a 2-year follow-up study. *Int Arch Occup Environ Health.* 2014; **87**:285-294.
- IX. Hansen ÅM, Gullander M, Hogh A, Persson R, Kolstad HA, Willert MV, et al. Workplace bullying, sleep problems and leisure-time physical activity: a prospective cohort study. *Scand J Work Environ Health.* 2016; **42**:26-33.

### *Perceived stress and sleep as mediators between workplace bullying and long-term sickness absence (L TSA)*

- X. Grynderup MB, Nabe-Nielsen K, Lange T, Conway PM, Bonde JPE, Francioli L, Garde AH, Kaerlev L, Rugulies R, Vammen MA, Hogh A, Hansen ÅM. (2016) Does perceived stress mediate the association between workplace bullying and long-term sickness absence. *J Occup Environ Med.* 56(6): e226-230.
- XI. Nabe-Nielsen K, Grynderup MB, Lange T, Andersen JH, Bonde JP, Conway PM, Garde AH, Hogh A, Kaerlev L, Rugulies R, Hansen ÅM. (2016) The role of poor sleep in the relation between workplace bullying/unwanted sexual attention and long-term sickness absence. *Int Arch Occup Environ Health.* 89, 967-979.

### ***Abbreviations***

ACTH	= Adreno Cortico Tropic Hormone
AUC	= Area Under the Curve
AWI	= AWakening Index
BMI	= Body Mass Index
CAR	= Cortisol Awakening Response
CATS	= Cognitive activation theory of stress
CRH	= Corticotropin-Releasing Hormone
CS	= Cross sectional
CV	= Coefficient of variation
CVD	= CardioVascular Disease
DSI	= Disturbed Sleep Index
DWERF	= Danish Work Environment and Research Fund
HPA	= Hypothalamus-pituitary Adrenal
IFP	= Department of Psychology
KSQ	= Karolinska Sleepiness Questionnaire
LIPT	= Leymann Inventory of Psychological Terrorization
LTPA	= Leisure-time physical activity
LTSA	= Long-Term Sickness Absence
MDI	= Major Depression Inventory
MET	= Resting metabolic rate during quiet sitting
MODENA	= 'MObbing Depression and Negative behaviour' study
NAQ	= Negative Acts Questionnaire to measure workplace bullying, the operational method
NRCWE	= National Research Centre for the Working Environment
OR	= Odds Ratio
PRISME	= 'Psychological RISk factors in the working environment and biological MEchanism for the development of stress, burn-out and depression' study
PTSD	= Post-Traumatic Stress Disorder
RIA	= Radio Immune Assay
WBH	= Workplace Bullying and Harassment cohort

## **Introduction**

Data from the Work environment and Health survey in Denmark estimated that 10 to 12 per cent of the working population between 20 and 59 years of age have been subjected to bullying in the period 2005-2014 (79). Among these, approx. 2 per cent reported frequent bullying, that is, weekly or daily workplace bullying. Similar results have been reported in other countries (110, 125, 141). Bullying at work, according to most definitions, takes place when someone, repeatedly and over a long period of time (usually 6 months), is exposed to negative acts from one or several others, in a situation where he or she for different reasons may have difficulties defending him- or herself against these actions (41, 170, 198). Workplace bullying may take different forms. Direct bullying is aggressive acts that are aimed directly at the target, as for example teasing, scolding, spreading rumours, and threats (43, 135). Indirect bullying may take the form of social isolation or withdrawal of necessary information (43, 135). Bullying may be work-related (e.g. acts that make it difficult for the target to do his/her work) or personal (e.g. offending teasing, rumours, slander, or sexual harassment) (43, 135). One of the characteristics of bullying is the inequality in power between the perpetrator and the target (41). Either supervisors are directly involved or the bullying takes place between co-workers, where the perpetrator for some reason or another is stronger than the target. In some cases even subordinates, especially if acting in a group, may muster enough power to bully a supervisor (170).

Four decades ago severe behavioural and mental stress reactions among employees exposed to harassment or bullying at work was described by Brodsky (18). The bullied employees reported symptoms such as nervousness, irritability, chronic fatigue, insomnia, tension, memory problems, physical pains, aggression, depression, and self-hatred (18). A decade later, the legacy was taken up by Leymann (115). Since then the field of research has expanded greatly as have the number of studies documenting the detrimental effects of workplace bullying on targets' mental health problems and somatic symptoms (145). Both cross-sectional and prospective studies have consistently reported strong association between self-reported bullying at the workplace and a number of health-related outcomes such as sickness absence (16). Some individuals may even leave their job due to workplace bullying (76).

### ***Possible mechanisms of workplace bullying leading to health effects***

The link between workplace bullying and health effect is not fully understood. Workplace bullying is likely to make up a highly stressful situation characterized by lack of control. Attributions of control and predictability are important characteristics of the individual's appraisal processes (86, 111). While the link between cognitive processes and physiology is emphasized in transactional models such as the Cognitive Activation Theory of stress (CATS) and the allostasis model it is clear that the physiological consequences of bullying have been insufficiently examined and understood (134, 186). Theoretically, stress reactions may affect health either by a direct biological, prolonged physiological activation and lack of restitution, or by affecting health through life-style and health behaviours (126).

### ***Sleep problems as a pathway to disease***

A recent report from The Council on Health and Disease Prevention in Denmark stated that both poor sleep quality and short or long sleep durations are related to an increased risk for developing type 2 diabetes and that short sleep durations and poor sleep quality are related to an increased risk of developing cardiovascular diseases (82). Mental processes may lead to increased arousal and lack of recovery, which in turn may cause sleep problems (153, 166). The linkage between workplace bullying

and arousal is not direct as it entails mental processing, that may take different forms (e.g., worrying and difficulty controlling thoughts), and be extended over time (166). Poor sleep, e.g. sleep that is too short or that is otherwise disturbed, is a well-known response to stress in terms of increased physiological and psychological activation (53, 130). For job stressors also the anticipatory stress response plays a central role (4). Thus, in relation to workplace bullying, not only ruminations about what has happened may disturb sleep, but also worries about the following working day. No studies so far have investigated workplace bullying and subsequent sleep problems as a pathway to LTSA.

### ***Cortisol and relation to disease***

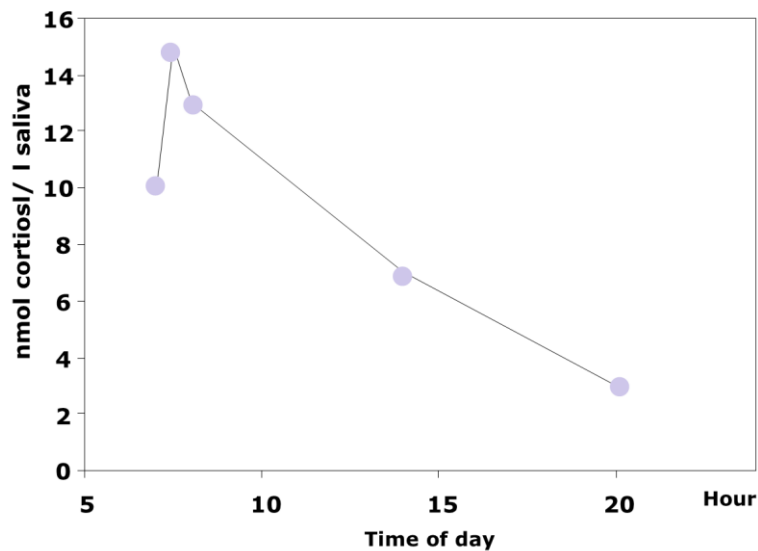
Cortisol is a widely used indicator for activation of the hypothalamus-pituitary-adrenal (HPA) axis in field studies, although several hormones are involved (eg, corticotropin-releasing hormone (CRH) and adreno-cortico tropic hormone (ACTH)). Cortisol is a steroid hormone, and is produced in humans in the adrenal cortex within the adrenal gland. The physiological effects of increased cortisol concentrations are, e.g. increased blood pressure, suppression of inflammation, and precipitate insulin resistance (7, 14, 190). It is known that prolonged and elevated concentrations of cortisol may lead to redistribution of body fat characterized by trunk obesity, hypertension, and type 2 diabetes as seen in Cushing's disease (190, 191). Neuroendocrine changes such as low cortisol levels has been shown to be associated with the underlying pathology of post-traumatic stress disorder (PTSD) (195). Also, patients with major depression exhibit higher concentrations of cortisol during the recovery period than non-depressed individuals (19). Recently, low cortisol concentration in saliva has also been linked to cardiovascular mortality (105). No studies have so far investigated the association between workplace bullying and salivary cortisol in field studies, and no studies have investigated salivary cortisol as a pathway to LTSA.

### ***Cortisol and psychological stress.***

Salivary cortisol has been widely used in research on mental stress, health and disease (22, 72, 83, 88). The conclusion from the review of Hjortskov et al 2004 showed both positive, and negative and no association between self-reported mental stress (72). A review by Chida et al from 2009 In 2009-11 the Scandinavian cortisol and stress network (Scancort) was formed, based on 20 researchers from the disciplines of public health, psychology, biology and medicine (98). The Scancort network aimed with this book to scrutinize if it was possible that different results of studies involving cortisol assessments were functions of differences in the theoretic assumptions made and the methods used (97). Studies on mental health measures, covering major depressive disorder, symptoms of depression, and symptoms of anxiety, burnout, and vital exhaustion (84) and perceived stress (63) were also reviewed. Only few studies were available on the association between somatic diseases and salivary cortisol and here the review concluded that a flat diurnal variation in cortisol (i.e. smaller deviation from morning peak to evening concentrations) seems to be the most typical finding in relation to somatic diseases (122). Which is in line with the findings of low cortisol levels may be associated with the underlying pathology of Post-Traumatic Stress Disorder (PTSD) (195) and a recent Danish study showed that low cortisol was associated with depression two years later (59).

### ***Cortisol secretion***

**Figure 1. Normal diurnal variation in salivary cortisol from wake-up until approx. 20:00 hours.**



Salivary cortisol is a simple, non-invasive, harm- and pain-free measure (97) that allows the longitudinal study of HPA-axis activity without substantial interference with the subject's normal habits and environment and can therefore be used in field studies (101)(Paper II). Since cortisol in saliva is stable for at least two weeks, it provides the possibility of self-sampling and mailing the samples by mail (Paper II). Cortisol is essential for human functioning as it is released in response to stress and low blood-glucose concentration. Cortisol functions to increase blood sugar through gluconeogenesis, to suppress the immune system, and to aid in the metabolism of fat, protein, and carbohydrates it also decreases bone formation (71). Cortisol secretion in saliva exhibits a distinct diurnal variation, with the highest concentration in the morning soon after awakening, when we need energy to be mobilised and lowest in the evening and night (Figure 1).

### ***Stress historically***

Workplace bullying is a severe stressor that is related to numerous adverse outcomes, such as depression and low quality of life (144).

Walther Cannon (1871-1945) used the term stress as being primarily equivalent to stimulus, and he focussed his experiments on the sympathetic nervous system and coined the term '*fight or flight response*' – non-specific simultaneous recruitment of bodily systems and stereotypic discharge of adrenaline and noradrenaline (20). He showed with his experiments on rats that stress impacted health if the organism is severely damaged by an acute non-specific stressor such as exposure to cold, surgical injury, or excessive muscular exercise (136). His theory states that animals react to threats with a general discharge of the sympathetic nervous system, priming the animal for fighting or fleeing – 'the fight or flight response' (also called the fight, flight, freeze, or fawn response (in PTSD), hyper-arousal, or the acute stress response) (136).

Hans Selye (1907-1982) proposed a three-stage model of physiological response to stress that develops over time, the first stage is the alarm phase lasting up to 48 hours, the second stage is the resistance

phase, which lasted up to one month, and the third phase is the exhaustion phase lasting more than one month (172). Selye defined stress as follows: “stress is the non-specific response of the body to any demand” (172). Selye suggested that the term stress should be used as a response within the organism to evocative agents, a stimulus response or an interaction between stimulus and response (124). The term ‘stressor’ was introduced by Selye in 1950 to differentiate between the outside exposure to the bodily response and stress as ‘the non-specific response of the body to any demand made upon it’ (124). Stressors constantly challenge a complex dynamic equilibrium, homeostasis, that is re-established by various physiological and behavioral adaptive responses (26).

Richard Lazarus and Susan Folkman suggested in 1984 that stress can be thought of as resulting from an "imbalance between demands and resources" or as occurring when "pressure exceeds one's perceived ability to cope" (112). This model, denoted the transactional stress model, the nature and severity of emotional reactions following exposure to bullying, may be a function of a dynamic interplay between event characteristics and individual appraisal and coping processes (111). Definitions of bullying at work commonly entail descriptions that emphasize prolonged exposure to interpersonal acts of a negative nature, with which the target is unable defend him or herself against (40, 198). These negative acts may be person-related and/or work-related (Paper V). Negative acts may make up a highly stressful situation characterized by lack of control (Paper V). Attributions of control and predictability are important characteristics of the individual's appraisal process (86, 111). In transactional models such as CATS (184) and the allostasis model (127) the link between cognitive processes and physiology is emphasized. It is the person's experience and evaluation of demands and expectancies of outcomes that determine whether the demands cause a stress response, which may affect the health (165). In CATS, coping with stressors is defined as positive outcome expectancy and is related to psychophysiology. In a stressful situation, it is not enough to have control, expectation of this control leading to a good result is necessary, if not, the individual may perceived the situation hopeless (165).

Four decades ago severe behavioural and mental stress reactions were observed among employees exposed to harassment or *bullying* at work (18). Two major biological systems are involved in the stress response. The locus coeruleus-noradrenaline/autonomic (sympathetic) nervous system (27) and the HPA axis are the major physiological stress response systems in the body (27, 57, 69, 126, 131, 162, 183). Moreover, the characterization of an individual's HPA axis activity, reactivity pattern to psychosocial stress as well as inter- and intra-individual variability, appears to be of major interest to shed light on workplace bullying and the stress reaction pattern following workplace bullying (70, 123).

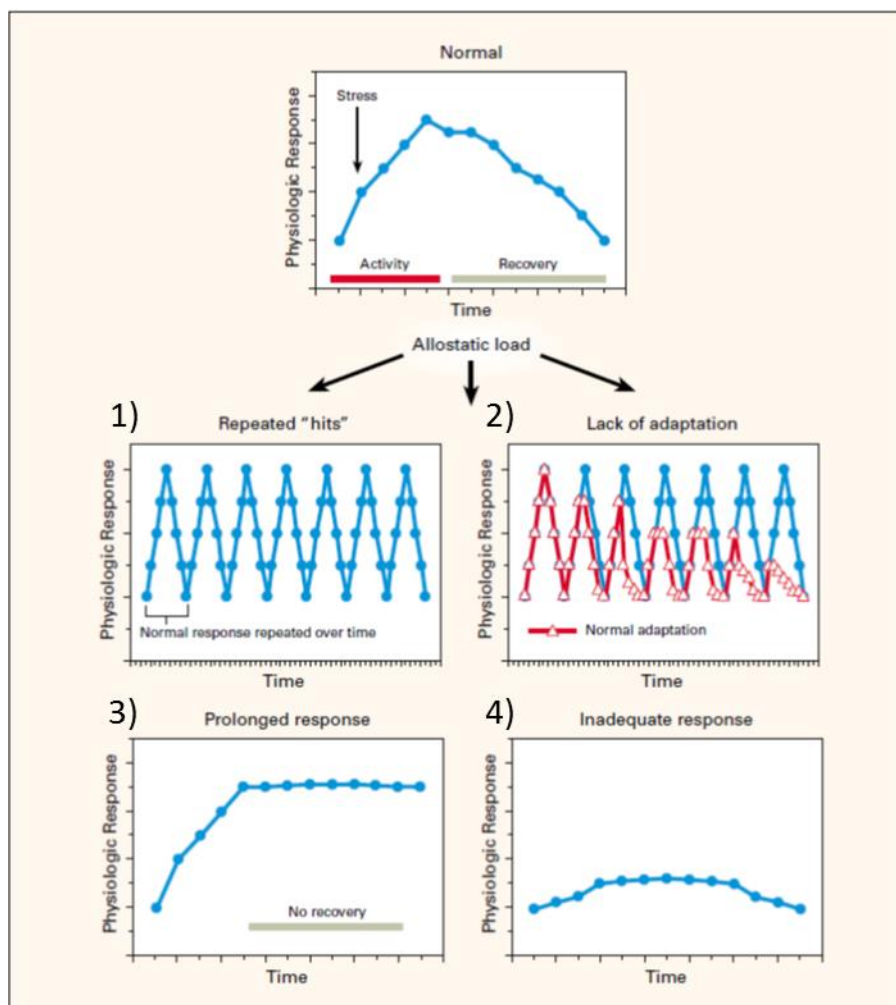
### ***Acute and chronic stress reaction and the HPA axis***

The physiological stress response to acute and chronic stress differs. The acute stress response is the bodily response to an acute stressor, and the response shuts down when the stressor is no longer present. McEwen also denotes this reaction allostasis, the ability to change allostatic (adaptive) systems, have much broader boundaries (126). Allostatic systems enable us to respond to our physical states (e.g., awake, asleep, supine, standing, exercising) and to cope with a variety of stressors (noise, crowding, isolation, hunger, extremes of temperature, danger, microbial or parasitic infection) (126). In modern life stressors including bullying may stem from the working environment.

The Trier Social Stress Test (TSST) is a laboratory procedure used to reliably induce stress in human research participants was created in 1993 at the University of Trier by Clemens Kirschbaum and colleagues. TSST was designed to exploit the vulnerability of the stress response to socially evaluative situations (91). To what extent the stress response is adequate may be tested in a TSST (8, 50, 85). The inventor of the TSST Clemens Kirschbaum and his research group have among other topics tested patients with chronic fatigue syndrome and found that they did not have an adequate salivary cortisol response compared to healthy controls (52).

According to McEwen, chronic stress reactions can take four different forms (Figure 2). The top graph is the normal response indicating an activation of the stress response followed by a recovery phase. Below the four different forms of chronic stress are shown: 1) multiple stressors repeated over a long period with an adequate stress response; 2) lack of adaptation which may occur if you do not have time to recover between stressors; 3) prolonged response due to delayed shut down of the physiological system; and 4) inadequate response in the glucocorticoid system, which may result in hyperactivity in other biological systems.

**Figure 2. Acute and chronic stress reactions.** (B. McEwen, New England Journal of Medicine 1998, 338(3), 171-179)

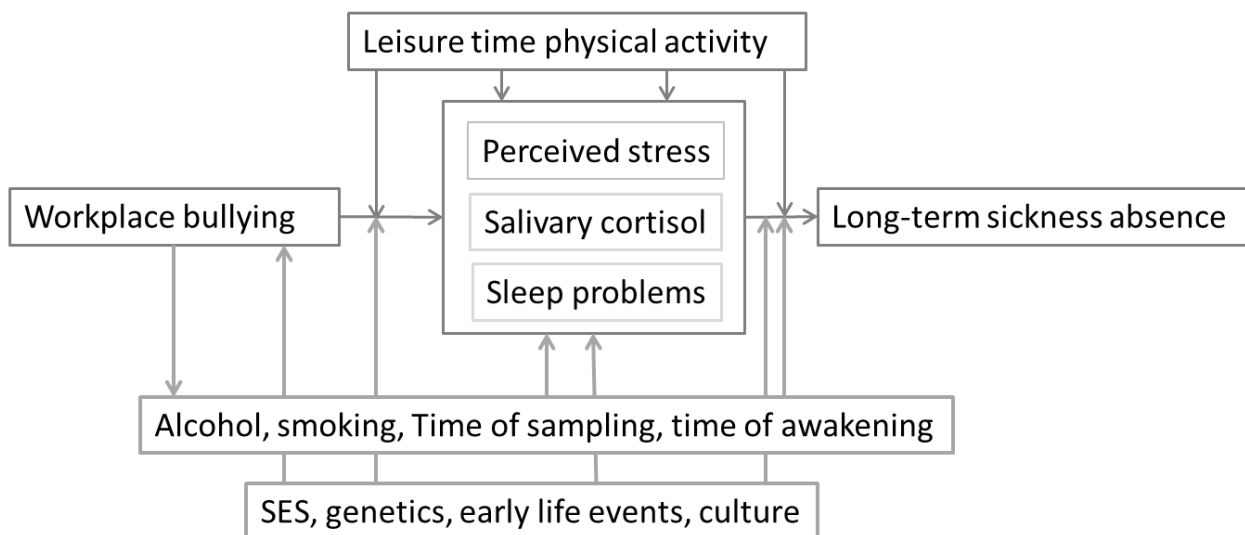


## Outline

To date, only few studies have investigated the association between workplace bullying and the physiological responses (102, 106) and sleep problems (95, 110, 141, 187, 201), not taking the Danish contribution into account. This thesis summarizes my research on bullying, stress responses and LTSA. The purposes of this thesis are to 1) to address methodological issues with respect to design, compliance and measurement validity when using salivary cortisol as a stress response in epidemiological studies, 2) investigate the associations between workplace bullying and the stress response, measured by perceived stress, salivary cortisol, and poor sleep, 3) explore if LTPA is a moderation in the association between workplace bullying and sleep, 4) finally, to explore possible pathways between workplace bullying and LTSA.

An overview of the overall model of the association between workplace bullying and health is described in figure 3.

**Figure 3. The conceptual model of the association between workplace bullying and health.**



### *Partial aims:*

#### *Methodological issues in using salivary cortisol in field studies*

Papers I and II are included in the thesis to address the importance of using valid measures when using field studies to study consequences of workplace bullying.

Paper I entitled *Evaluation of a radioimmunoassay and establishment of a reference interval for salivary cortisol in healthy subjects in Denmark:*

The purpose of Paper I was to perform a laboratory evaluation of a Radio Immune Assay (RIA) for determination of salivary cortisol and to establish a reference interval for salivary cortisol in healthy subjects in the morning and late afternoon on a working day. Furthermore, to estimate the contribution of ageing, Body Mass Index (BMI), gender, sick leave during the past year, alcohol, and smoking status to biological variation.

Paper II entitled *Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: A review:*



The purpose of Paper II was to provide a literature review of the current knowledge on these sources of variation in relation to the use of salivary cortisol in occupational field studies. Specifically, Paper II addresses the impact of:

- Biological variation related to time of sampling, within and between subject variation, and seasonal variation.
- Biological variation related to age, gender, and life style factors such as diet, medication, smoking, alcohol, and physical activity.
- Compliance with sample collection.
- Methodological variation relating to sampling and storage procedures (i.e. cotton versus polyester tampons and freezing of samples at different temperatures).

### ***Workplace bullying and salivary cortisol***

Papers III, IV and V are included to establish an association to physiological salivary cortisol widely used as physiological stress response

Paper III entitled *Bullying at work, health outcomes, and physiological stress response:*

The aim of Paper III was to investigate an association between bullying at work, self-reported health symptoms, and physiological stress response in targets of bullying and in employees witnessing bullying.

Paper IV entitled *Frequency of bullying at work, physiological response, and mental health:*

This study aimed to elucidate the relationship between bullying at work and cortisol secretion. Of particular interest was to examine whether frequently and occasionally bullied persons differed from non-bullied persons.

Paper V entitled *Exposure to negative acts at work, psychological stress reactions and physiological stress response:*

The overall aim of Paper V was to test an association between work-related negative acts, psychological and physiological stress-reactions and whether some negative acts are more related to physiological stress reactions than others.

### ***Sleep and salivary cortisol***

Paper VI entitled *Salivary cortisol and sleep problems among civil servants* is included to study the association between two physiological stress responses:

The purpose was to examine an association between sleep problems and salivary cortisol by using a cross-sectional design with repeated measures in a subsample three months later.

### ***Physical activity and salivary cortisol***

Paper VII entitled *Physical activity, job demand–control, perceived stress–energy, and salivary cortisol in white-collar workers* is included to explore the association between salivary cortisol and LTPA.

The aim of Paper VII was to examine the association between physical activity and perceived job demand, job control, perceived stress and energy, and physiological arousal reflected by morning and evening concentrations of cortisol in saliva among white-collar workers.

### ***Workplace bullying, sleep and LTPA***

Paper VIII is included to explore the association between workplace bullying and sleep and Paper IX is included to explore if LTPA, known to be helpful when exposed to stress, would decrease the effects of workplace bullying on sleep.

Paper VIII entitled *Workplace bullying and sleep difficulties: a 2-year follow-up study*:

The aims of the Paper VIII were to investigate whether being subjected to bullying and witnessing bullying at the workplace are associated with sleep difficulties, whether frequently bullied/witnessing have more sleep difficulties than occasionally bullied/witnessing, and whether sleep difficulties persist after two years among witnesses to bullying and bullied persons. For this thesis only result among workplace bullied are included.

Paper IX entitled *Sleep problems and workplace bullying: evaluation of the mediating and moderating effect of physical activity*:

The aims of this study were to prospectively examine (a) whether bullying increases the risk of sleep problems, and (b) whether the association between bullying and sleep problems is moderated by LTPA. To the best of our knowledge, no studies seem to have evaluated the possible moderating role of LTPA in relation to the association between workplace bullying and sleep problems.

### ***Perceived stress and sleep as mediators between workplace bullying and LTSA***

Finally Papers X and XI are included to explore pathways between workplace bullying and LTSA.

Paper X entitled *Does perceived stress mediate the association between workplace bullying and long-term sickness absence*:

This study aimed to examine whether perceived stress levels mediated the association between workplace bullying and subsequent LTSA, in a large cohort of Danish employees.

Paper XI entitled *The role of poor sleep in the relation between workplace bullying/unwanted sexual attention and long-term sickness absence*:

This study aimed to investigate whether poor sleep mediates and/or moderates the association between bullying and unwanted sexual attention, on the one hand, and LTSA on the other hand.

## **Workplace bullying in Denmark**

The Danish Work Environment Cohort Study shows a significant increase in the prevalence of bullying from 10.3 % in 2005 to 12.5 % in 2010 (79). The prevalence did not change markedly from 2012, where 11.8 % of a random sample of the working population reported to be bullied at the workplace to 2014, where 11.6 % reported to be exposed to workplace bullying.

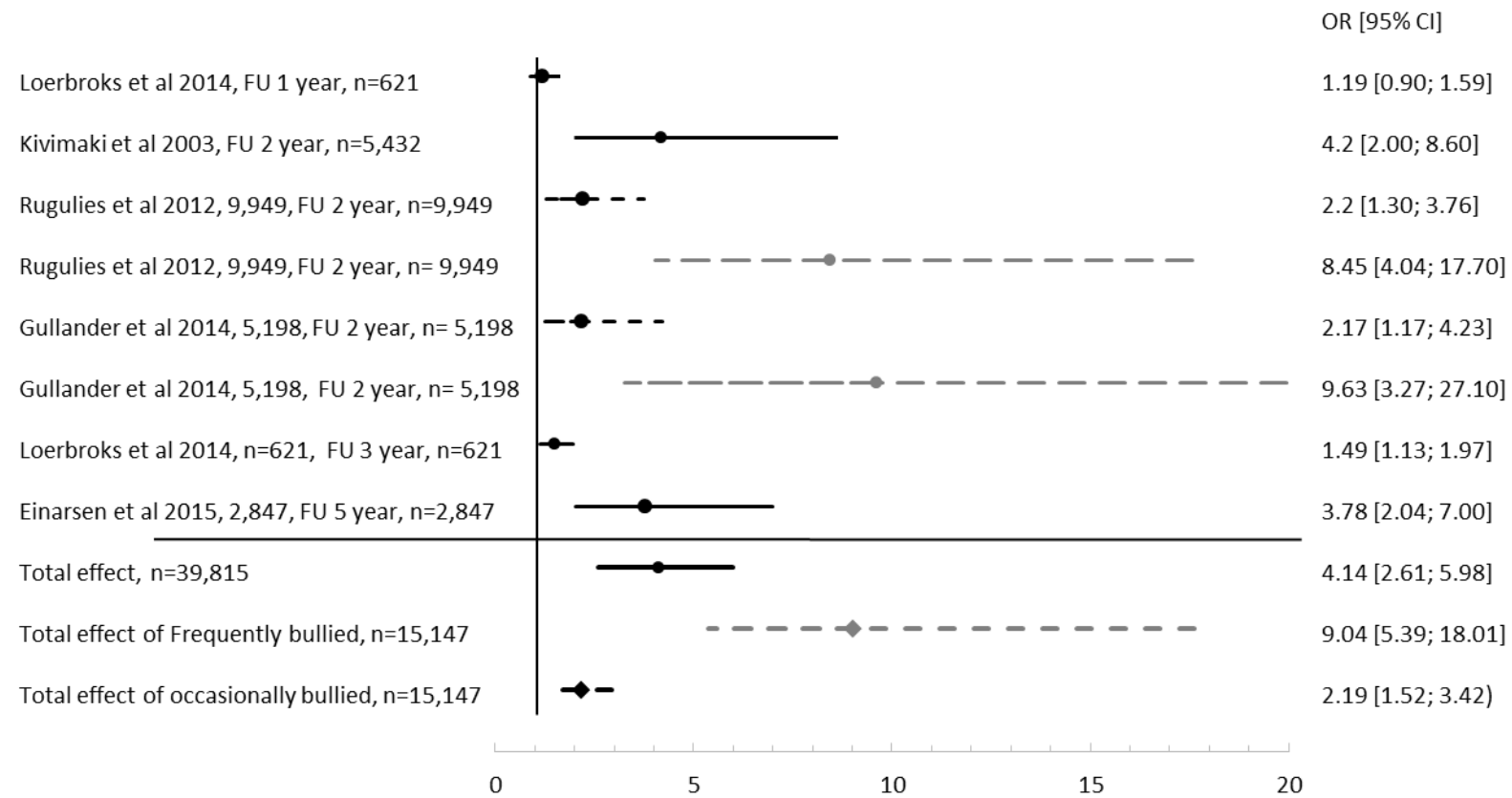
### ***Measuring workplace bullying***

In the above mentioned Danish national surveys of the working environment (79) the respondents are given a definition of workplace bullying before the questions, and according to most definitions this is, when someone is exposed to negative acts from one or several other persons repeatedly over a longer period of time (usually 6 months), where he or she for different reasons may have difficulties defending him- or herself against these actions (41, 170, 198). This common used method, the self-labelling method, entails asking the respondents whether they think they have been subjected to bullying or not, generally after having presented a definition of the term bullying (143). Another widely used method is the operational method that measures the frequency of exposure to negative acts (42, 116) and respondents are asked to indicate how often they have been exposed to a number of these negative acts during the past 6 months (143). The prevalence of bullying varies from 2 to 14.3% depending on which method is used (145). The use of the negative acts questionnaire (NAQ) allows to distinguish between different forms of bullying, such as work or person related negative acts and direct aggressive acts that are aimed directly at the target, as for example teasing, scolding, spreading rumours, and threats and indirect acts, denoted the (143). When using the operational method it is possible to test whether some negative acts are more detrimental than others. One problem with the self-labelling method could be that admitting to be a victim of bullying may imply disclosing one's weakness and inadequate coping, which is difficult for most people (39). Hence, if the negative behaviour is not perceived to be workplace bullying, the impact on health and wellbeing may not be present (39). A recent study by Gullander et al. (61) intended to overcome this bias by classifying workplace as workplace bullying workplaces by the number of witnesses. At workplaces where the percentage of witnesses were used to classify workplaces where bullying was reported, was not predictive of depression two years later (61). However, self-labelling of workplace bullying did predict depression two years later (61).

### ***Risk factors of workplace bullying***

Stressful and poorly organized work environments as well as deficiencies in leadership may facilitate work-related bullying, either directly or by creating a work climate in which bullying can flourish (3, 17, 46, 67, 116, 161). Workplace bullying is more frequent in organizations with a negative psychosocial work environment characterized by a negative social climate, many conflicts, a low level of information and control, a high level of role ambiguity, and role conflicts (77). When workplace stressors and interpersonal problems are not dealt with, they may escalate into bullying, resulting in high levels of psychological distress among those involved and even among those observing the bullying (178). In addition, targets of bullying often lack social support from co-workers and supervisors, which has been demonstrated that perceived low social support is related to distress and burnout, for instance in the relation between supervisors and subordinates (107, 113). This is unfortunate since a supportive work environment seems to be able to protect employees from some of the harmful effects of bullying (90, 159).

**Table 1. Workplace bullying and depression – cohort studies**



### ***Workplace bullying affects health***

The most studied health outcomes of workplace bullying are psychological symptoms and emotional reactions. Workplace bullying was shown to increase the risk of depression (44, 61, 75, 93, 119, 164, 168) in cohort studies (Table 1), but also increased burnout, anxiety, aggression (12, 64, 74, 121, 187), Cardiovascular Disease (CVD) (93), psychosomatic and musculoskeletal health complaints (13, 45, 93, 117, 142, 199). Table 1 only covers longitudinal studies on workplace bullying and depression or depressive symptoms. In a meta-analysis of the studies in table 1, an overall OR of depression or depressive symptoms was calculated to be 4.14 [95% CI: 2.61; 5.98]. Two studies also reported the frequency of workplace bullying (61, 168) giving an OR of 2.19 [95% CI: 1.52; 3.42] for occasionally bullied and 9.04 [95% CI: 5.39; 18.01] for frequently bullied. The studies on depression used different ways of measuring workplace bullying and depression and had different follow-up times. Depression were measured with new cases of depression (61), onset of major depression (168) and self-reported diagnosed depression two years later (93). Three studies used NAQ to measure workplace bullying and one-year follow-up (164), two-year (75) and five year follow-up (44). All studies showed increased risk of depression with workplace bullying independently of using depression, depressive symptoms or length of follow-up. One study adjusted for sense of coherence and depressive symptoms at baseline, resulting in the association became insignificant (75). Two studies showed that depression or depressive symptoms at baseline increased the risk of workplace bullying in two studies (75, 119). Thus, previous research indicated that workplace bullying increased the risk of depression, but also depression at baseline to increase the risk of being bullied at the workplace at follow-up.

### ***Workplace bullying and sickness absence***

Workplace bullying has been associated with both self-reported sickness absence (16, 33, 114, 138, 139, 179) and LTSA (28-30 days) in register based studies (28, 151, 181) (Table 2). Short-term sickness absence was described as self-reported measures from 3-8 days of sickness absence. One study used the salary system to estimate more than 14 days of sickness absence (182) and another study >15 consecutive days (81), and the cause was retrieved by contacting the general practitioner of the worker. One study characterized workplaces as bullying workplaces by the reports of workplace bullying and studied the OR of sickness absence in the workplaces with bullying compared to workplaces without bullying (92). The study measured sickness absence using both medically certified (spells of > 4 days) and self-certified (spells of 3 days) periods of sickness absence. The authors found that workplaces with reported bullying had higher sickness absence compared to the workplaces without reported bullying (92). None of these studies included possible pathways. We add to this evidence in two studies confirming that workplace bullying is a risk factor for LTSA (> 30 days) and further include possible pathways between workplace bullying and LTSA (Paper X and XI).

**Table 2. Workplace bullying and sickness absence**

Reference	Participants	Exposure	Outcome	Conclusion
Kivimäki et al. 2000 (92)	674 men and 4,981 women	Finnish hospital employees Work units with and without workplace bullying	Register based sickness absence: Self-certified, spells of 3 days Medically certified, spells of 4 days and more	Medically certified: Unadj/adj model: OR 1.09 [1.02-1.18]/1.03 [0.95-1.11] Self-certified: Unadj/adj model: OR 1.05 [1.00-1.10]/1.04 [0.98-1.10]
Voss et al. 2001 (188)	1,557 women/1913 men Mean age: 43/40	Employees at the Swedish post. Workplace bullying, self-labelling item	Swedish post's register of absenteeism Sickness events per 10,000 days. High event > 2 events per year	OR for workplace bullying among women: 1.91 [95%CI=1.31-2.77] Workplace bullying was not a risk factor among men.
Niedhammer et al. 2008 (138)	14,241 men and 10,245 women, age, CS	SUMER study, France Workplace bullying, self-labelling item (116)	Self-reported >8 days the previous year	Men: OR 1.37 [95%CI=1.20-1.56], for being bullied Women: OR 1.29 [95%CI[1.12-1.48]
Ortega et al. 2010 (151)	9,949 employees 95% women 18-64 years	Danish eldercare sector Workplace bullying, self-labelling item	Register based LTSA: Social transfer payment > 30 days of sickness absence	OR: 1.92 [95%CI=1.29-2.84]
Clausen et al. 2012 (28)	9,520 female employees in the Danish elder-care services	Danish elder-care services Workplace bullying, self-labelling item	Register based LTSA: Social transfer payment > 30 days of sickness absence	Workplace bullying HR: 2.26 [95% CI=1.50–3.42], mutually adjusted for threats, violence and unwanted sexual attention.
D'Errico et al. 2012 (33)	36,145 men and 24,618 women Age 15-64 years	Italian part of the Labour Force survey 2007 Bullying or discrimination	Sickness absence, the week before the survey, self-reported < 7 days	Men: OR 1.74 [95%CI=1.20-2.54], for being bullied Women: OR 1.97 [95%CI=1.38-2.80]
Niedhammer et al. 2013 (139)	14,881 men 14,799 women CS	31 European countries, European working condition survey. Workplace bullying, self-labelling item	Days of sickness absence the past year, self-reported	Men: OR 1.88 [95%CI=1.56-2.26], for being bullied Women: OR 1.55 [95%CI=1.32-1.82]
Janssens et al. 2014 (81)	2,983 middle-aged workers, 54% women (Belstress III study) Mean age: 43.	Belgium Bullying referring to isolation and destabilization (measured with nine items) (160).	>15 consecutive days, the cause was retrieved by contacting the general practitioner of the worker.	OR: 1.32 [95%CI=1.06–1.64]
Lesuffleur et al 2014 (114)	26,883 men and 20,079 women	SUMER study, France Workplace bullying, self-labelling item (116).	Self-reported >1 spell the previous year >2 spells >3 spells	Men: for being bullied and > 1/>2/>3 spells of sickness absence: OR 1.31 [95%CI=1.22-1.40]/ 1.98 [1.78-2.20]/ 3.15 [2.50-3.34] Women: OR 1.39 [95%CI=1.29-1.50]/ 1.93 [1.73-2.16]/ 2.89 [2.69-3.70]
Slany et al. 2014 (179)	16,120 men and 16,288 women	34 countries in Europe Workplace bullying, self-labelling item.	Sickness absence, the week before the survey, self-reported < 7 days	Men: OR 1.40 [95%CI=1.13-1.73], for being bullied Women: OR 1.89 [95%CI=1.59-2.25]
Suadicani et al. 2014 (182)	1,809 employees, 75% women. Mean age: 43	Danish hospital workers Workplace bullying, self-labelling item.	Sickness absence during the preceding year, salary system < 14 days	OR 0.50 [95%CI=0.33-0.77] for not being bullied compared to being bullied.

Reference	Participants	Exposure	Outcome	Conclusion
Stromholm et al. 2015 (181)	21,834 workers	Nord-Trøndelag Health Study (HUNT). Workplace bullying, self-reported.	Sickness benefit register of the Norwegian labour and welfare administration >28 days	OR: 1.34 [95% CI=1.07–1.67], adjusted for age, occupation, education, health, health-related risk factors, and previous sickness absence.
Bonde et al. 2016 (16)	WBH $\alpha$ cohort N=3,359 PRISME cohort N=4,489	Workplace bullying, self-labelling item with a definition.	Self-reported, sick-listed or unemployed; yes/no	Now and then bullied: OR 1.61 [1.0-2.6] Monthly, weekly, or daily bullied: OR: 2.49 [1.2-5.2]
Paper X	4,114 unique participants 6,331 observations across the two waves PRISME cohort	Workplace bullying, self-labelling item with a definition.	Register based LTSA: The Danish Register of Sickness absence compensation and Social transfer payments > 30 days of sickness absence	Workplace bullying > now and then to daily OR: 2.05 [95% CI=1.57-2.65] Workplace bullying > monthly to daily: OR: 2.22 [95% CI 0.92-4.01] A high vs. low perceived stress level predicted subsequent LTSA with an OR of 1.33 [95% CI=1.13-1.56]. Perceived stress explained 13% (95% CI=6-23%) of the total association between workplace bullying and LTSA
Paper XI	7,650 individuals contributing with 15,040 two-year WBH, PRISME, and MODENA# cohorts	Workplace bullying, self-labelling item with a definition.	Register based LTSA: The Danish Register of Sickness absence compensation and Social transfer payments > 30 days of sickness absence	Workplace bullying OR: 1.77; [ 95% CI=1.50-2.12] Disturbed sleep and difficulties awakening mediated 12.8% [95% CI=8.1-19.8%] of the association between bullying and LTSA. Poor sleep did not moderate the association between workplace bullying and LTSA

# MObbing Depression and Negative behaviour;  $\alpha$  Workplace Bullying and Harassment cohort

### ***Workplace bullying and sleep problems***

Sleep is a major path for restitution and vital for our mental and physical health (30, 148). Sleep has important homeostatic functions, and sleep deprivation is a stressor that may have consequences for the brain, for instance disturbed memory and cognitive functions as well as affected regulation of the neuroendocrine systems (128). The underlying anatomy of the stress response in the brain is closely interconnected with the anatomy that regulates sleep and wakefulness (6). Being exposed to stressful situations may cause disturbed sleep and less refreshing sleep (6, 55). Hence, it seems theoretically plausible that sleep difficulties may provide a link between work-related bullying and poor health. Only a few studies have examined whether an empirical association between measurements of bullying and sleep exists (95, 110, 141, 166, 187, 201) (Table 3). The oldest study just pointed out that the targets of bullying used sleep-inducing drugs and sedatives more often than did the respondents, who were not bullied (187). Two cross-sectional studies found that the contribution of workplace bullying to the burden of sleep disturbances may be substantial (141, 201). Lallukka et al. performed a five year follow-up study and found workplace bullying to be associated with sleep problems, but associations attenuated after factors related to the social environment, work, and health were simultaneously taken into account. A recent study supported this finding in first-time workplace bullied persons (95). Workplace bullying may not immediately cause sleep difficulties, but leads to prolonged activation that in turn may cause sleep difficulties (166). Paper VIII supported the association between workplace bullying and poor sleep.

The mutual relationship between bullying and psychological distress may indicate a vicious circle, where bullying and distress reinforce the negative effects of each other, i.e. bullying leads to mental health problems, which may act to worsen the target's situation or at least the perception of the work situation (44). Provided that sufficient rest and recovery follow stressful episodes (or serve to divide long-ranged stress episodes into shorter periods), it is generally presumed that humans may endure quite severe stress without developing poor health or long lasting mental health problems (131). A recent study showed that LTPA, relaxation, and detachment after work all reduced the need for recovery (29). Paper IX supported the finding that workplace bullying predicts sleep problems two years later and added to the existing knowledge to what extent high LTPA may reduce the hazardous effect of bullying on sleep two years later in two Danish cohorts of working men and women. No papers have so far studied if LTPA reduce the effect of workplace bullying on sleep.

### ***Sleep as a pathway to LTSA***

Further, lack of sleep is known to be associated with an increased risk of disease (30, 148). Recent studies have shown that insomnia predicts future sick leave and disability pension (176, 177). Poor sleep is associated with the risk of depression (200), cardiovascular disease (73), and type 2 diabetes (21). Therefore, in Paper XI we added to the existing knowledge to what extent sleep is a pathway between workplace bullying and sickness absence. Using LTSA (>30 days) as the outcome we found sleep to partly mediate the association between workplace bullying and LTSA.



**Table 3. Workplace bullying and sleep**

Reference	Participants	Exposure	Outcome	Conclusion
Vartia, 2001 (187)	CS: 949 85% women Man age: 40 years	Workplace bullying $\alpha$ (9 %) Leymann Inventory of Psychological Terrorization (LIPT)	Sleep inducing drugs and sedatives	The targets of bullying used sleep-inducing drugs and sedatives more often than did the respondents who were not bullied.
Niedhammer et al. 2009 (141)	CS: 4,562 women 3,132 men Mean age: 40 years	Workplace bullying (13% for women; 11% for men) LIPT, French version	Two items: evaluating difficulty initiating sleep and difficulty returning to sleep after experiencing a premature awakening. Response categories dichotomized: No (“no trouble at all,” “a little trouble”); Yes (“some trouble,” and “a great deal of trouble.”)	Although no conclusion about causality could be drawn from this cross-sectional study, the findings suggest that the contribution of workplace bullying to the burden of sleep disturbances may be substantial.
Lallukka et al. 2011 (110)	Five year FU: 5,399 women 1,247 men Age in 2002: 40 to 60 years	Workplace bullying $\S$ (5%)	4-item Jenkins questionnaire	Workplace bullying is associated with sleep problems, but associations attenuate after factors related to the social environment, work, and health are simultaneously taken into account
Rodriguez et al. 2011 (166)	4,068 employees from approx. 30 organizations	Belgium 9-item version of the NAQ questionnaire	Sleep quality measure by the Questionnaire on the Experience and Evaluation of Work	Workplace bullying was positively related to poor sleep quality in two randomly selected samples ( $r=.54$ , $p < .01$ for sample 1; and $r=.47$ , $p < .01$ for sample 2).
Ziemska et al. 2013 (201)	CS: 212 bullied (54 % women) 884 non-bullied (60 % women)	Workplace bullying (Method not given)	Sleep disorders (method not given)	OR of sleep disorders among bullied compared to non-bullied of 3.43 [2.30-5.13]
Kostev et al. 2014 (95)	CS: 2,625 patients 2,625 controls	Reporting first time workplace bullying during at least 12 month	Sleep disorders using primary care diagnoses (G47)	Following experiences of bullying sleep disorders were significantly more prevalent than in the control group
Paper VIII	Two year FU: 3,382 respondents (67 % women)	Workplace bullying, self-labelling item with a definition $\#$ .	Sleep problems during the past 4 weeks were assessed with six items from a modified version of Karolinska sleepiness questionnaire (KSQ) (5).	Being subjected to occasional bullying at baseline was predictive of subsequent sleep difficulties. Witnessing bullying at baseline did not predict sleep difficulties at follow-up.
Paper IX	Two year FU: 8,141 two-year episodes of which 587 were bullied	Workplace bullying, self-labelling item with a definition $\#$ .(116, 185)	Sleep problems during the past 4 weeks were assessed with six items from a modified version of KSQ (5).	The study found support for a higher risk of sleep problems among respondents reporting workplace bullying. Being physically active during leisure time reduced the association of workplace bullying with sleep quality but not with other sleep problems.

$\alpha$  Bullying is long-lasting, serious negative action and behaviour that is annoying and oppressing. It is not bullying if you are scolded once or someone shrugs his or her shoulders at you once. Negative behaviour develops into bullying when it is continuous and repeated. Often the target of bullying feels unable to defend him or herself.  $\S$  Mental violence or workplace bullying means isolation of a member of the organization, underestimation of work performance, threatening, talking behind one's back, or other pressurizing.  $\#$  Bullying takes place when employees are exposed to negative or offensive acts repeatedly over a longer period of time, which it is difficult to defend oneself against. CS=cross-sectional; FU=Follow-up.

### ***Perceived stress as a pathway to poor health***

Associations between psychological stress and disease have been established, particularly for depression, CVD, and HIV/ AIDS (31). This association may be due to prolonged psycho-physiological over-activation induced by repeated exposure to a stressor (132). In the long run exposure to stressors may lead to disease, through dysfunctions in bodily systems (132). Despite these empirical and theoretical reasons suggesting psychological stress as a potential mediator between workplace bullying and subsequent health problems and sickness absence, to our knowledge, no studies have examined such possible mediation (Paper X). Paper X adds to the existing knowledge whether perceived stress mediates the association between workplace bullying and subsequent LTSA, in a large cohort of Danish employees.

### ***Workplace bullying and stress response***

The stress response involves activation of the autonomic nervous system (ANS) and the HPA axis. Activation of ANS and HPA axis is also denoted the ‘fight and flight response’ (129). According to McEwen if activation of the ‘fight and flight response’ occurs too frequently, or if greatly prolonged negative effects of stress will occur, this may be negative for both health and survival (129). Role ambiguity and role conflicts may be a precursor for workplace bullying (46, 149, 178). Being exposed to constant exposure to adverse environments involving interpersonal conflict may be regarded as being under chronic stress (129). In this thesis workplace bullying is regarded as a severe stressor and salivary cortisol was used to mirror the activity in the HPA axis.

Cortisol is a natural energy-releasing hormone with a distinct diurnal rhythm being highest in the morning, and decreasing to the lowest level in the evening (Paper II). The regulation of cortisol can be disturbed in various ways such as high cortisol over a long period, a flat diurnal cortisol curve (i.e. low morning cortisol or high evening cortisol), or insufficiently secreted cortisol (26). Hence, salivary cortisol may be a potential biological indicator to measure how workplace bullying gets “under the skin”.

The association between salivary cortisol and workplace bullying was only studied in pilot study before my first study was published (102)/ Table 4. Kudielka and Kern found no significant differences in terms of both morning cortisol increase and cortisol day profile between the work day and the day off among 12 women and 4 men (aged 45, range 33-60) (102). However, the difference between the peak cortisol level in the morning and the lowest level in the evening showed a trend towards a lesser decrease at the work day ( $P = .10$ ) among people bullied at work (102). In 2012 Lac et al (106) performed a study among 41 patients and 28 psychologically healthy controls and did not find significant difference in Area Under the Curve (AUC) and Cortisol Awakening Response (CAR).

No large field studies have been conducted before my studies on salivary cortisol and workplace bullying was conducted (Papers III, IV and V).

**Table 4. Workplace bullying and cortisol in saliva**

Reference	Participants	Exposure	Outcome	Conclusion
Kudielka et al. 2003 (102)	Cases 12 women 4 men Age 18-65 years	Bullying was assessed with the German version of LIPT. Have you experienced within the last 6 months at least once a week 1 of 45 exactly defined psychologically stressful mobbing activities (140).	Saliva samples were collected after awakening and 30 min thereafter (= morning increase), as well as at 8 am, 11 am, 3 pm, 8 pm and 10 pm (= day profile) in Salivette®. Free salivary cortisol was assayed with an immunoassay (37).	There were no significant differences in terms of both morning cortisol increase and cortisol day profile between the work day and the day off. The difference between the peak cortisol level in the morning and the lowest level in the evening showed a trend towards a lesser decrease at the work day ( $P = .10$ ).
Le Lac et al. 2012 (106)	Cases/control 28/19 women 13/9 men Mean age: 46 years	Bullying was assessed with the LIPT method	Saliva samples were collected at awakening (7 am), 30 min and 60 min after awakening and then every 2 h from awakening to bed time: 9 am, 11 am, 1 pm, 3 pm, 5 pm, 7 pm, 9 pm and 11 pm. AUC and CAR were calculated. Free salivary cortisol were measured	There was no significant difference between cases and controls in cortisol levels at any time, or in AUC and CAR.
Paper III	294 women 143 men Age 18-65 years	QPS Nordic questionnaire (36): Have you been subjected to bullying or harassment at work during the past six months? Response categories yes/no.	Saliva samples were collected in Salivette® polyester tubes at awakening, 45 min after awakening, 8 h after awakening, and at 2000 h. Free salivary cortisol were measured using a radio immune assay (RIA) (Paper I)	Concentrations of cortisol in saliva were lower at awakening in bullied respondents compared to non-bullied respondents
Paper IV	1,413 women 531 men Mean age 45 to 50 years	Workplace bullying, self-labelling item with a definition#. (116, 185)	Saliva samples were collected in Salivette® cotton tubes at awakening, +30 min later, and at 20:00 hours. Free salivary cortisol were measured using a RIA (Paper I)	Frequently bullied persons reported poorer mental health and had a 24.8% lower salivary cortisol concentration compared with the non-bullied reference group.
Paper V	684 participants (67.2% women)	The revised Danish version of NAQ (42): exposure to 23 items on work- and person-related acts within the past 6 months. Response categories: 1=never, 2=now and then, 3=monthly, 4=weekly, 5=daily.	Saliva samples were collected in Salivette® cotton tubes at awakening, +30 min later, and at 20:00 hours. Free salivary cortisol were measured using a RIA (Paper I)	Direct harassment and intimidating behaviour are associated with psychological stress-reactions and a negative physiological stress response. Some negative acts are more detrimental than others.

# Bullying takes place when employees are exposed repeatedly over a longer period of time to negative or offensive acts, which it is difficult to defend oneself against.

## *Cohorts and methods*

Table 5 presents the cohorts used in this thesis.

*The atherosclerosis and work - study* (Papers I + II) was established to study the relation between cortisol in urine and saliva and intima media thickness (48). In relation to this study I established method evaluation to provide a quality assessment of the method. The study was also used to estimate a reference interval for salivary cortisol to be wiser on biological variations in salivary cortisol. This laboratory method was used for measurements of cortisol in saliva in the atherosclerosis and work study (Papers I and II), The Swedish study (Paper III), WBH (Papers IV and V), The PRISME study (Paper VI) and the Health Promotion study (Paper VII).

*The Swedish study (Paper III)* was established for the local Labour Inspectorate for routine evaluation of the working conditions. Guidelines for inclusion into the study were the following: (i) the workplaces should preferably have around 100 employees to ensure that our requests of participation would generate a reasonably large number of responding participants at each workplace, (ii) a variety of branches should be represented, and (iii) the data should be collected prior to the end of year 2001 (Paper III). The survey included measuring workplace bullying was measured by one question from the QPS Nordic questionnaire (36): “Have you been subjected to bullying or harassment at work during the past six months?” and one question about witnessing bullying: “Have you noticed anyone being subjected to bullying or harassment at your workplace during the past six months?” The response categories were “yes” or “no”. Also mental distress and psychosomatic symptoms over the past week, the present day included.

*The WBH study (Papers IV, V, VIII, IX and X)* was established to study health effect of workplace bullying and the relationship between bullying at work and cortisol secretion. To add knowledge from the results in the Swedish study it was of particular interest to examine whether frequently and occasionally bullied persons differ from non-bullied persons with regard to cortisol secretion. We measured bullying with the *self-labelling method* to classify workplace bullied respondents, witnesses to bullying, and perpetrators (143) (used in Papers IV, VIII, IX and X). The respondents were calibrated by use of a definition of bullying was listed ahead of the questions “*Bullying takes place when employees repeatedly over a longer period of time are exposed to negative or offensive acts, which it is difficult to defend oneself against*”. The three questions read: “*Have you been subjected to bullying at work within the past 6 months?*”, “*Have you witnessed bullying at work within the past 6 months?*”, “*Have you yourself bullied someone or participated in bullying someone at work within the past 6 months?*” All items were responded to on a five step scale: 1=never, 2=now and then, 3=monthly, 4=weekly, 5=daily (Paper IV). We also included the *operational method* to measure workplace bullying (42, 117) (used in Paper V). Of health measures we used somatic and cognitive symptoms from the Stress Profile questionnaire, developed by Setterlind and Larsson (173). We also measured stress symptoms the past four weeks using the second version of the Copenhagen Psychosocial Questionnaire (COPSOQII) (155) and depressive symptoms by 12 items from the Major Depression Inventory (MDI) (11). Sleep difficulties the past four weeks was measured by a modified version of KSQ (5). Two indexes disturbed sleep index (DSI) and awakening index (AWI) have been recommended by one of the inventors of the instrument (169) and used in previous research (158). DSI reflect lack of sleep continuity and AWI reflects feelings of unsatisfactory awakening and being insufficiently restored (65).

*Salivary cortisol and collection of saliva samples*

The saliva samples were collected during a workday. We asked the participants to collect saliva samples in Salivette® cotton tubes at awakening, 30 minutes after awakening, and at approx. 20:00 h. A written instruction emphasized that swabs should be kept in the mouth until thoroughly hydrated and to carefully fill in the exact time of sampling when collecting each saliva sample.

*The PRISME study (Paper VI)* was designed for prospective studies of job-related psychosocial determinants for major depression and other common mental disorders (94). The PRISME cohort comprised hospital and civil-service employees from workplaces in the Central Denmark Region.

Workplace bullying was measured as described above in the WBH cohort. In the PRISME study we as above used the KSQ (9) to measure sleep problems, and we two recommended indexes (DSI and AWI) as recommended by one of the inventors of the instrument (169). The participants were asked to rate their perceived stress level (4 items) based on Cohen's Perceived Stress Scale (32).

#### *Collection of saliva samples*

A written instruction emphasized that swabs should be kept in the mouth until thoroughly saturated (Paper VI). Saliva samples were collected in Salivette® cotton tubes 30 minutes after awakening and at approx. 20:00 h. Three month later saliva was sampled at awakening, +20 min. and +40 min. after awakening and at approx. 20:00 h.

*The health promotion study (Paper VII)* was part of a randomized controlled trial that was conducted as a prospective intervention study on health promotion between January 2005 and January 2006 (15). In this thesis only information on the association between leisure time physical activity and salivary cortisol was included.

#### *Leisure-time physical activity*

Physical activity was estimated by a Danish version of the IPAQ Long Form Questionnaire based on which the physical activity level can be quantified in METs, for more details see [www.ipaq.ki.se](http://www.ipaq.ki.se) and Paper VII.

#### *Collection of saliva*

The participants received written and oral information about sampling details. The participants were told not to brush their teeth before sampling. Saliva samples were self-monitored by use of Salivette® tubes with cotton tampons at awakening, 30 minutes after awakening, and approximately 14 hours after awakening. For more details see Paper VII.

*The MODENA study (Papers IX, X, + XI)* was based on two already established Danish cohorts, the WBH (Papers IV, V and VIII) and the PRISME study (61). In 2011 the WBH- and the PRISME cohorts were combined into a joint study as the MODENA cohort (Table 5).

#### *Measuring LTPA*

The participants were asked how many hours per week they were physically active during their leisure time. The response categories were: 1 = <2 hours/week; 2 = 2-4 hours/week of light physical activity, 3 = more than 4 hours/week light physical activity or 2-4 hours/week intense physical activity; and 4 = more than 4 hours/week intense physical activity. The validity of items on

physical activity was validated to a metabolic equivalent (MET) activity scale with a correlation of 0.74 by Aadahl and Jorgensen in 2003 (1).

#### *LTSA*

LTSA was defined in this study as a period of 30 or more continuous days of sickness absence. Information on sickness absence was obtained by linkage to the Danish register of sickness absence compensation benefits and social transfer payments (RSS) (154). In Denmark all employers are entitled to sickness absence compensation for employees that are absent for 30 or more continuous days, and such cases of compensation are registered in the RSS. All respondents who experienced a period of LTSA prior to the survey were excluded from the study populations in Papers X and XI. Thus, a participant experiencing a period of LTSA in 2006 would be excluded from the 2007 part of the study, but not from the 2009 part. The rest of the respondents were followed in the RSS for exactly 2 years after obtaining their questionnaire information, and periods of LTSA during this two-year period were recorded.

#### *Mediator perceived stress*

Perceived stress was included as a mediator in Paper X. The perceived stress score was dichotomized in a high or low perceived stress group split on the 50th percentile. Similarly, the total score was used to divide the participants into five perceived stress categories split on the 20th, 40th, 60th, and 80th percentile for use in the mediation analysis (Paper X).

Paper XI used questionnaire data from the WBH cohort (surveys in 2006 and 2008) (Paper IV) and the PRISME cohort (surveys in 2007 and 2009) (94)/ Paper VI. In 2011, an additional follow-up survey was conducted among the participants of the WBH and PRISME cohorts. For the follow-up in 2011 (the MODENA study (61)), we used the self-labelling method to measure workplace bullying. The item was preceded by the same definition as used in Papers IV, VIII, IX, and X.

#### *Unwanted sexual harassment*

Our questionnaire measured sexual harassment as unwanted sexual attention. Participants were asked the question: "Have you been subjected to unwanted sexual attention at work within the past 6 months?" (WBH) or "Have you been subjected to unwanted sexual attention at work within the past 12 months?" (MODENA) (Papers IV, VIII, IX, and X), which was followed by the following explanation: "Unwanted sexual attention is verbal or physical behaviour of sexual nature, which is unwanted, offensive, or hurtful, and without reciprocity". The response options were: "No", "Yes, daily", "Yes, weekly", "Yes, monthly", "Yes, sometimes", and "Yes, one time" (Paper IX).

**Table 5. An overview of Cohorts used in Papers I to XI.**

<b>Cohorts</b>	<b>Year</b>	<b>Participants</b>	<b>Purpose for the thesis</b>
The atherosclerosis and work – study (48) [Paper1]	1998	42 healthy men and 88 healthy women responding to public advertising.	Laboratory evaluation of a Radio Immune Assay (RIA) for determination of salivary cortisol and to establish a reference interval for salivary cortisol in healthy subjects in the morning and late afternoon on a working day.
The Swedish study [Paper III]	2001	294 women and 143 men employed in five companies constituting seven workplaces, all located in the Southern part of Sweden: a high school, a telecommunication company (located at three different geographical positions but with similar work tasks, i.e. customer service), a regional social insurance office, a pharmaceutical company, and a company within wood industry.	To examine the association between workplace bullying and salivary cortisol.
WBH [Papers IV, V, and VIII]	2006	7,358 women and men from public and private workplaces in Denmark were invited. Of these 3,363 responded to the questionnaire and 2,541 gave saliva samples.	To examine the association between workplace bullying, salivary cortisol, sleep and LTSA.
	2008	All responders and new employees invited to participate in 2008 (n=3,707) of which 2,237 responded.	To examine the association between workplace bullying, salivary cortisol, sleep and LTSA.
PRISME (94) [Paper VI]	2007	10,036 women and men, hospital and civil-service employees from workplaces in the Central Denmark Region were invited and 4,489 responded in 2007.	To examine the association between Workplace bullying, perceived stress, sleep and LTSA, and salivary cortisol and sleep.
	2009	All responders in 2007 were invited to participate in the 2009 wave and 3,232 responded 2009.	To examine the association between Workplace bullying, perceived stress, sleep and LTSA, and salivary cortisol and sleep.
The health promotion study (15) [Paper VII]	2006	Randomized controlled trial was conducted as a prospective intervention study on health promotion. A total of 549 public employees of which 389 gave saliva samples.	To examine the association between physical activity and physiological arousal reflected by morning and evening concentrations of cortisol in saliva.
MODENA (61) [Papers IX, X, + XI]	2011	MODENA built on the PRISME and WBH cohorts. In MODENA study all responders in the waves of PRISME waves (n=4,489) and WBH (3,707) giving a total of 8,196 invited. In the combined survey, we had 5,000 respondents to the questionnaire in 2011.	To examine the association between Workplace bullying, sleep and LTSA.

## Results and discussion

### *Methodological issues in using salivary cortisol in field studies*

#### *Paper I. Evaluation of a radioimmunoassay and establishment of a reference interval for salivary cortisol in healthy subjects in Denmark*

The purpose of Paper I was to perform a laboratory evaluation of a RIA for determination of salivary cortisol and to establish a reference interval for salivary cortisol in healthy subjects in the morning and late afternoon on a working day. Furthermore, to estimate the contribution of age, BMI, gender, sick leave during the past year, alcohol, and smoking status to biological variation. Paper I was included in this thesis to document the method performance and measurement variability that may lead to changes erroneously interpreted as effects. The laboratory method was shown to be applicable to measure salivary cortisol in saliva from healthy respondents. Paper I showed a large normal biological variation (e.g., diurnal variation, within-subject variation, and between-subject variation) as well as methodological variation (laboratory techniques, material specifications etc.), which has to be taken into account when planning a study where salivary cortisol is used a measure of stress reactions.

#### *Results on method performance*

The analytical method for determination of cortisol has been evaluated by a method evaluation design according to Christensen *et al.* (24) to estimate random and systematic effects, including intra- and inter-assay variation. Samples for the method evaluation in water were prepared according to the manufacturers specifications in the range of 2.1-89.1 nmol/L by use of certified reference material (CRM 921) from National Institute of Standards and Technology (Gaithersburg, USA). As described in Paper I the samples for the method evaluation in saliva were prepared by spiking pooled saliva samples with CRM 921. The method evaluation of the certified reference material in water did not show any bias of the method, i.e. recovery was 97% [CI: 94%; 100.9%]. We estimated the LOD (detection limit) was 1.59 nmol/L according to IUPAC (120). We estimated the ratio between analytical and within-subject variation ( $CV_a/CV_i$ ) to be 0.14, which indicated that the method was adequate for measurement in healthy subjects. We observed as expected that salivary cortisol revealed a distinct diurnal variation with the highest concentrations of cortisol in the morning. Reference intervals for samples at the time of awakening (range of time of awakening: 05:27-07:27h), 7.6-39.4 nmol/L for peak level in saliva samples collected 20 min after awakening (range: 05:47-07:47), and from LOD to 16.2 nmol/L for late afternoon samples (17:00-19:00). Reactivity (increase from awakening to 20 min after awakening), sometimes denoted CAR, was estimated to be 82% [CI: 2179; 345%] and recovery (decrease from 20 min after awakening to 18.00) to be 80% [CI: 51; 109%].

#### *Paper II. Sources of biological and methodological variation in salivary cortisol and their impact on measurement among healthy adults: A review.*

The purpose of Paper II was to provide a literary review of current knowledge on sources of variation in relation planning and run field studies, where salivary cortisol is used as a measure of stress reactions and when interpreting the results.

Paper II was included in this thesis to highlight and address the impact of:

- Biological variation related to time of sampling, within and between subject variation, and seasonal variation.
- Biological variation related to age, gender, and life style factors such as diet, medication, smoking, alcohol, and physical activity.
- Compliance with sample collection.



- Methodological variation relating to sampling and storage procedures (i.e. cotton versus polyester tampons and freezing of samples at different temperatures).

*Biological variation related to time of sampling, within and between subject variation, and seasonal variation*

Cortisol in saliva has a distinct diurnal variation with the highest concentrations in the morning peaking approximately 30-45 min. after awakening and declining throughout the day to the lowest in the evening just before going to bed (100, 163)/Papers I+II. Planning to collect saliva samples in large epidemiological studies use of self-sampling may be a challenge. Due to the distinct diurnal variation it is crucial to record the time of sampling for each sample taken (Paper II). Some studies sample at awakening, between 15 and 60 min. after awakening and after 18 hours (100)/Paper I. Other studies used sampling throughout the day with 2-6 hours between the sampling times (62, 66, 100, 133). A recent book evaluated the role of salivary cortisol in relation to health and disease (122). Salivary cortisol has been collected in various ways, such as 1) single time points, including means (or sums) of several single measurements; 2) deviations/slopes between 2 or more measurements; 3. AUC calculated from 2 or more measurements (122). Also seasonal variation has to be taken into account if a follow-up is planned. A recent study by Persson et al showed that cortisol varies over the year (156) with the highest concentration in the winter (November to March) and the lowest in summer (May to August).

*Biological variation related to age, gender, and life style factors such as diet, medication, smoking, alcohol, and physical activity.*

The importance of being aware of within and between subject variations related to gender, age, and life-style factors such as smoking, physical exercise, and alcohol intake (56) was also discussed in Paper II in assessment of associations to exposure to psychosocial working environment.

*Compliance with sample collection*

Clear instructions and compliance by the participants are needed to control for food intake, beverages, tobacco, alcohol, physical activity, medicine, sleep during the night before, and other confounders (122)/Paper II. An important factor when using self-monitoring was compliance with the requested time of sampling (38). A few methods have been used to measure compliance such as using electronic devices to track when participants actually accessed the cotton swab, or tampon. One study it was observed that 74% of the participants accessed the tampon according to the study protocol, which was significantly higher than participants, who were not informed of their sampling being tracked (99). Another study among participants, unaware of being monitored if they followed the protocol, 71% of participants complied with the protocol (193). The same study also showed that the persons, who were aware of being monitored the self-reported compliance were of 93%, which was consistent with the objective compliance of 90% (193). An interesting find was that the non-compliance participants had significantly lower morning cortisol values than the participants which complied with the sampling protocol (99, 193). In the studies in this thesis we used two ways of ensuring compliance. In one study the participants were provided a postcard or with an introduction of how to sample saliva and also to note on each sample at what time the samples were taken (Paper III). In follow-up and later studies (WBH, PRISME, and Health Promotion studies) a one-page sleep diary was provided and participants were asked to fill it in when they woke up (Papers III, VI, and VII). We tested the difference between the time stated as wake-up time by the respondents and the time noted on the first saliva sample. In the PRISME study, participants were asked to collect samples 30 min. after awakening (59). In total 70% of the participants collected their morning samples between 26 and 59 min. after awakening, 80% between 19 and 73 min after

awakening, and 90% between 9 and 102 min. after awakening (59). In the WBH study, we asked the participants to collect saliva samples at awakening, 30 min. after awakening, and at 20:00. We instructed the participants to have their saliva tubes placed near their bed, to take the first sample right at awakening. We observed a difference between awakening and first saliva sample of -32 min. [95% CI: -38; -26] and to the second samples -3 min. [95% CI: -10; 3] giving 29 min. in average between the two samples (data not published). The results may indicate that the participants take the sample right after awakening, but note awakening time in the sleep diary together with collecting of the 2<sup>nd</sup> saliva sample. Hence using awakening time from diaries to assess compliance to the sampling protocol may be an alternative method compared to the compliance found using electronic devices as used in previous studies (99, 193).

*Methodological variation relating to sampling and storage procedures (i.e. cotton versus polyester tampons and freezing of samples at different temperatures).*

It is of particular interest in cohort studies where multiple sampling of saliva takes place over a longer period of time, that the devices used for collecting saliva do not interfere with the sampling (Paper II). Salivette® is a widely used method for collection of saliva and most types of Salivette® it implies collecting saliva by means of a tampon, which is placed in the mouth until soaked with saliva. During the periods of my studies the tampons were produced by different materials and the different materials of a tampons have been found to influence the measurement of e.g. steroid components (174)/(Paper II). No studies so far addressed the potential interference that different tampons may have on the concentration of cortisol measured. In Paper II we report a laboratory study to test how shift in the tampon material affected the measurement of cortisol. The results showed that cotton tampons reduced the measured concentration of cortisol to 62% and detained more saliva than polyester (Paper II). A huge problem in collecting saliva from participant is the amount of saliva. After centrifugation of the Salivette®, recovery of saliva from polyester tampons were 95.8 (±1.1) % and from cotton tampons 54.7 (±2.3) % (Paper II). We further, we were experiencing that the company providing the assay changed antibody. The shift in the antibody of the analytical assay influenced the measurements with 12% difference (Paper II).

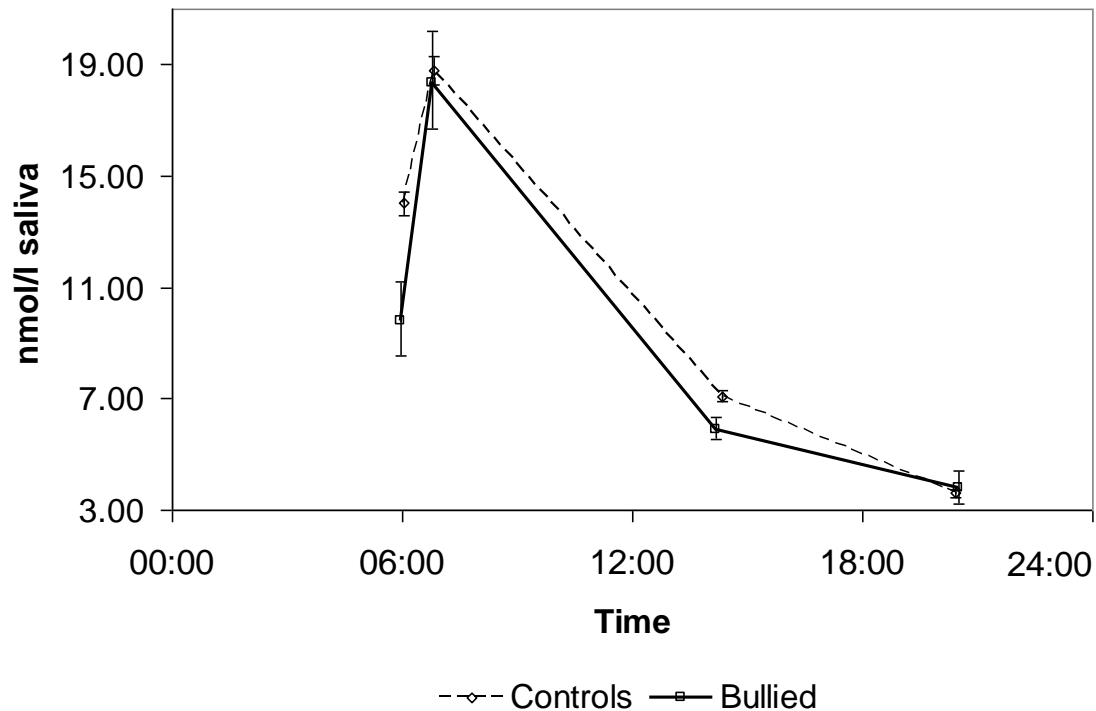
In follow-up cohort studies using self-sampling, it is of interest to know about storage time, both in term of time from collection till receiving the sample in the laboratory and in case of lack of funding for laboratory analyses so the samples have to be stored until sufficient funding is found. Garden and Hansen showed that saliva samples for cortisol measurement can be stored at room temperature for up to two week, three month at 5°C and at -80°C for up to one year (54)/ (Paper II).

***Workplace bullying and salivary cortisol***

*Paper III. Bullying at work, health outcomes, and physiological stress response*

Paper III investigated as the first field study the associations between workplace bullying and physiological stress response in targets of bullying. The hypothesised was that cortisol in the saliva is lower in employees subjected to bullying compared with non-bullied respondents.

**Figure 4. Concentrations of cortisol measured in saliva among bullied and non-bullied respondents (Paper III).**



Legend for figure 4. Concentrations of cortisol measured in saliva collected at awakening, 45 min after awakening, 8 hours after awakening, and at 2000 hours on a working day for bullied (n=22) and non-bullied respondents (n=371). The variance component analysis showed that concentration of cortisol in saliva was 30% [1-50%] lower in the morning and 7% [-2-82%] lower at 1400 in bullied respondents compared to non-bullied respondents.

Paper III presents an association between workplace bullying and the physiological stress response in terms of salivary cortisol. We observed that workplace bullying was associated with lower support from co-workers and supervisors. Further, this study demonstrated a different diurnal profile with lower concentration of cortisol in the saliva samples collected at awakening in bullied respondents compared to non-bullied respondents. The stress response is an essential and necessary physiological response to a challenge or threat. In this study the item on workplace bullying was responded to as yes or no, hence we did not have the opportunity to distinguish between degrees of workplace bullying. In line with other studies we observed a cross sectional association between being bullied and symptoms of depression, anxiety, somatisation, and changes in mental health. Paper III represents a novel approach since this is the first cohort study contributing with new knowledge on the associations between workplace bullying and physiological stress response. This study did not address the frequency of workplace bullying.

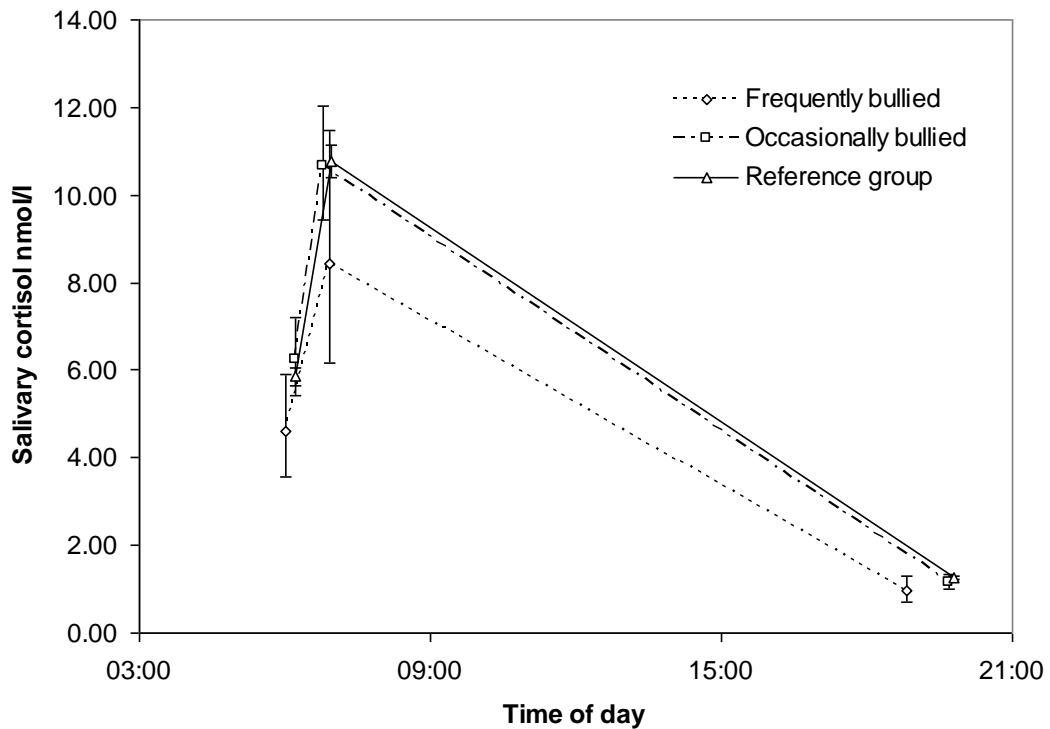
*Paper IV. Frequency of bullying at work, physiological response, and mental health.*

The aim of Paper IV was to study the relationship between workplace bullying and salivary cortisol. It was of particular interest to examine whether frequently and occasionally bullied persons differed from non-bullied persons.

In this cohort study among 1,944 employees at 55 workplaces we observed that 1.1% of the employees were frequently bullied and 7.2% occasionally bullied. Bullying occurred at 78% of the workplaces (43 workplaces), frequent bullying occurred at 40% of the workplaces. The frequently

bullied employees reported poorer mental health and had a 24.8% lower salivary cortisol concentration compared to their non-bullied colleagues (figure 5). Occasionally bullied employees had a poorer self-reported mental health, but their cortisol concentrations did not deviate from their non-bullied colleagues. The association remained significant even after controlling for age, gender, exact time of sampling, mental health, and duration of bullying.

**Figure 5. Cortisol in saliva during a working day among frequently and occasionally bullied respondents and non-bullied men and women (Paper IV)**



Legend for figure 5. Concentrations of cortisol measured in saliva collected at awakening, 30 min after awakening, and at 20:00 hours on a working day.

Paper IV study added ground breaking knowledge on the frequency of workplace bullying and salivary cortisol. Previous studies only included if the respondent reported yes or no to the time on workplace bullying (Kudielka and Paper III). In Paper IV we showed that only respondents reporting frequently bullied had lower salivary cortisol. Yet, the physiological response seems to underscore the possibility that bullying indeed may have measurable physiological consequences (Paper IV). Hence, the physiological response supports the mental symptoms found among the frequently bullied.

*Paper V. Exposure to negative acts at work, psychological stress reactions and physiological stress response.*

The aim of Paper V was to test the association between work-related negative acts, psychological stress-reactions and cortisol secretion, and to test whether some negative acts are more detrimental to health than others.

**Table 6. Association between negative behaviour and salivary cortisol (Paper V)**

	N	Unadjusted (a)		Adjusted (a,b)	
		% Change per score	p-value	% Change per score	p-value
Isolation	634	-4.26	0.232	-3.91	0.277
Direct harassment	632	-12.54	0.000	-12.18	0.001
Intimidating behaviour	634	-10.09	0.021	-9.62	0.030
Work-related	634	-4.80	0.106	-4.51	0.132

a) Models were adjusted for actual sampling time; b) Models adjusted for gender and age

In Paper V we used 23 items on negative behaviour at the workplace bullying to assess workplace bullying, also denoted the operational method. The result showed significantly lower concentrations of cortisol in subjects exposed to direct harassment and intimidating behaviour (Table 6/Paper V)). Paper V is the first study studying exposure to negative acts with salivary cortisol as the outcome. The results showed an association between low salivary cortisol among frequently bullied and not among occasionally bullied. Yet the present data suggests that being bullied frequently is associated with generally low cortisol secretion, but not a different diurnal profile. Indeed, there was no interaction between time-of-day and bullying status, and there were no difference between the groups as regards the derived measures, that is, the CAR and decline during the day, both of which have been used widely in psycho-physiological research (23, 103). Paper V found also the largest difference in the morning samples. Previous research showed with the largest difference between 20:00 to 05:00 hours among individuals with PTSD compared to controls (196). In Papers IV and V saliva samples were collected from awakening until approx. 20:00. In both Papers IV and V the largest difference were observed at awakening in bullied respondents compared to non-bullied. Bullied respondents perceive more PTSD symptoms than their non-bullied colleagues. Hence the results on Papers III, IV and V may be comparable to finding of individuals with PTSD (196)/Paper V. Also healthy individuals living under conditions of chronic stress and patients with several bodily disorders, including chronic fatigue syndrome also have been found to have lower concentrations of cortisol in the morning and in the evening compared to controls (69, 180). Paper V extended previous research by indicating that some negative acts (direct harassment and intimidating behaviour) are more detrimental than others.

In the Papers III, IV, and V, salivary cortisol was measured at the same time point as responding to the item of workplace bullying or negative acts at the workplace. The Papers were included to show the association between workplace bullying and salivary cortisol.

Measurement of workplace bullying is asked to ‘*in the past 6 or 12 month have you experienced workplace bullying*’. Hence, the reporting of workplace bullying covers at least the past 6 month, which may indicate a chronic exposure. Salivary cortisol may therefore reflect a long-term condition. Low morning cortisol in saliva was observed in Papers III, IV and V. In addition to higher self-reported symptoms of anxiety, depression, somatisation, and mental health problems compared to non-bullied respondents may thus point in the direction that the bullied respondents might develop more chronic symptoms. Traumatic events may threaten the perception of cognitive schemas or assumptions of the world as meaningful, controllable, and benevolent, and the self as worthy and capable of controlling external events (78, 80). Hence the results extend previous findings by showing that being subjected to bullying not only has psychological consequences, but

it may also have physiological consequences (Papers III, IV, and V). Gullander et al used a combined dataset of the PRISME and WBH studies to study to what extent being bullied was related to subsequent change in morning and evening salivary cortisol after discontinuance of workplace bullying, and they did not find decreased concentration of cortisol in saliva two years later (60). Gullander et al. only used two cortisol samples in the study, a morning sample (30 min. after awakening) and an evening sample. Further, according to Einarsen et al., a bullying episode lasts up to two years (44). Since cortisol is a marker of HPA-axis activity, and it seems reasonable to presume that chronic stress may lead to exhaustion and fatigue, it seems plausible that the measured cortisol concentrations at baseline could reflect a long-term condition that is associated either with a chronic stress reaction or with an exhaustion reaction (84, 137). Another explanation could be the mismatch between length between our questionnaire waves in the PRISME and WBH cohorts, which were two years. Because a bullying episode may last up to two years (44), the targets of bullying that were still at the workplace were recovered in the physiological response.

### ***Sleep and salivary cortisol***

*Paper VI. Salivary cortisol and sleep problems among civil servants.*

The purpose of Paper VI was to examine the association between sleep problems and salivary cortisol by using a cross-sectional design with repeated measurements in a subsample three-month later.

Paper VI showed that sleep problems during the past four weeks were associated with low morning and evening saliva cortisol concentrations: [ -3.1% per score of disturbed sleep ( $p=.009$ ); and -4.7% per score of awakening problems ( $p<.001$ )]. We did not find that sleep problems to be related with slope (the morning to evening change in cortisol levels). Further, awakening problems predicted lower cortisol (-7.51% per score;  $p=.003$ ) three month later. Disturbed sleep was associated with CAR and slope three month later (-7.84% and -8.24%) and awakening problems (-6.93%). We also found an association between disturbed sleep and increased AUC (3.77%). Paper VI also showed that low morning cortisol was associated with more sleep problems during a four-week period prior to sampling among 4,066 Danish civil servants. At follow-up three months later, those with sleep problems had a flattened cortisol profile. Those with awakening problems also had low salivary cortisol in general. Previous studies have reported a flattened cortisol profile associated with poor sleep measured as sleep duration (104, 189), whereas other reported increased salivary cortisol (58, 171, 194) or no change in cortisol (47, 49).

Poor sleep has been shown to inhibition of the stress system (25). Waye et al. (192) found that the lower morning cortisol values may be a result of increased cortisol secretion during night hours due to more wake-up times after sleep onset and, consequently, decreased HPA-axis activation after awakening. Other studies of work stressors showed that a high workload were related to increased sleepiness, impaired sleep and flattened the diurnal profile of cortisol secretion (34), low cortisol levels in the morning to be associated with sleepiness at awakening (35), low sleep quality and mood (192). Hence, the low cortisol among bullied may be due to poor sleep (10).

Paper VI was included in this thesis to show the association between salivary cortisol and sleep. Paper IV found that more sleep problems during four weeks period prior to sampling to be associated with lower levels of saliva cortisol in the morning and evening. Further, at follow-up three-month later, those with sleep problems had a flattened cortisol profile. In addition, those with awakening problems had lower salivary cortisol in general.

### ***Physical activity and salivary cortisol***

*Paper VII. Physical activity, job demand–control, perceived stress–energy, and salivary cortisol in white-collar workers.*

The aim of Paper VII was to examine the association between physical activity and perceived job demand, job control, perceived stress and energy, and physiological arousal reflected by morning and evening concentrations of cortisol in saliva among white-collar workers.

Paper VII was included in this thesis to test two hypotheses:

1. Physical activity is associated with a more dynamic cortisol time pattern.
2. Physical activity moderates the relations between perceived stress–energy and concentration of cortisol in saliva.

Participants, irrespectively of gender, reporting high degree of physical activity reported higher perceived energy compared to those who reported moderate and low degree physical activity ( $p = 0.001$ ). High concentrations of cortisol were associated with high perceived stress and high perceived energy. In the initial model, physical activity did not influence the concentration of cortisol in saliva (hypothesis 1). By including the interaction between perceived stress and perceived energy in the final model, we found that high perceived stress and energy were correlated low evening cortisol concentrations. The final model included physical activity. We found that physically active employees perceived more energy, and for men also with lower perceived stress, indicating a beneficial stress–energy response. We found an association between physical activity and higher concentration of salivary cortisol (factor = 1.007), mainly due to vigorous physical activity (hypothesis 2). Hence, vigorous physical activity may reduce stress and increase energy.

### ***Workplace bullying, sleep and leisure-time physical activity***

Paper VIII was included to test for association between workplace bullying and sleep difficulties two years later. Paper IX was included to investigate if LTPA influence the association between workplace bullying and sleep difficulties two years later.

*Paper VIII. Workplace bullying and sleep difficulties: a 2-year follow-up study.*

The aim of the Paper VIII was to investigate whether being subjected to workplace bullying was associated with more sleep difficulties at baseline and follow-up two years later. We also tested if frequently bullied have more sleep difficulties occasionally bullied.

Paper VIII found that workplace bullying were associated with sleep problems at baseline. Paper VIII also found that workplace bullying was associated with subsequent sleep difficulties among occasionally bullied (Table 7). Occasionally bullied had higher ORs of disturbed sleep (3.60 [95 % CI 1.31; 9.86]), unsatisfactory awakening (3.08 [95 % CI 1.16; 8.15]), and poor quality of sleep (5.22 [95 % CI 1.69; 16.09]) compared to non-bullied (model 1). The OR stayed significant when adjusting for age, gender, and BMI (model 2) and for lifestyle factor (smoking and alcohol/model 3). Adjusting for sleep difficulties at baseline diminished the ORs for disturbed sleep, unsatisfactory awakening, and poor quality of sleep and became statistically non-significant (Table 4/ model 4). Among frequently bullied the crude OR of quality of sleep was significant (poor quality of sleep 3.56 [95 % CI 1.09; 11.59]/model 1). The OR showed only small changes when adjusting for age, gender, BMI, smoking, and alcohol. Adjusting for sleep quality at baseline, the association between

occasionally bullied and sleep quality became in-significant (OR 2.04 [95 % CI 0.52; 7.97]/ model 4).

**Table 7. Risk of subsequent sleep difficulties among bullied at follow-up two years later**

	Not bullied	Occasionally bullied		Frequently bullied	
		OR	95% CI	OR	95% CI
N	1400	124		19	
<b>Disturbed sleep</b>					
Model 1: crude OR	<b>1.00</b>	<b>3.60</b>	<b>(1.31; 9.86)</b>	2.11	(0.71; 6.31)
Model 2: Adjusted for age, gender, and BMI	<b>1.00</b>	<b>3.77</b>	<b>(1.34; 10.65)</b>	1.98	(0.64; 6.13)
Model 3: Adjusted for age, gender, BMI, alcohol and smoking	<b>1.00</b>	<b>3.32</b>	<b>(1.16; 9.53)</b>	1.69	(0.53; 5.32)
Model 4: Adjusted for age, gender, BMI, alcohol, smoking and disturbed sleep at baseline	1.00	1.79	(0.49; 6.52)	1.24	(0.31; 4.99)
<b>Awakening problems</b>					
Model 1: crude OR	<b>1.00</b>	<b>3.08</b>	<b>(1.16; 8.15)</b>	2.47	(0.87; 7.00)
Model 2: Adjusted for age, gender, and BMI	<b>1.00</b>	<b>2.86</b>	<b>(1.06; 7.74)</b>	2.17	(0.75; 6.31)
Model 3: Adjusted for age, gender, BMI, alcohol and smoking	<b>1.00</b>	<b>2.83</b>	<b>(1.03; 7.75)</b>	2.25	(0.76; 6.61)
Model 4: Adjusted for age, gender, BMI, alcohol, smoking and awakening problems at baseline	1.00	2.07	(0.69; 6.26)	1.61	(0.49; 5.26)
<b>Quality of sleep</b>					
Model 1: crude OR	<b>1.00</b>	<b>5.22</b>	<b>(1.69; 16.09)</b>	<b>3.56</b>	<b>(1.09; 11.59)</b>
Model 2: Adjusted for age, gender, and BMI	<b>1.00</b>	<b>5.36</b>	<b>(1.73; 16.62)</b>	<b>3.72</b>	<b>(1.13; 12.21)</b>
Model 3: Adjusted for age, gender, BMI, alcohol and smoking	<b>1.00</b>	<b>5.11</b>	<b>(1.64; 15.89)</b>	<b>3.66</b>	<b>(1.11; 12.07)</b>
Model 4: Adjusted for age, gender, BMI, alcohol, smoking and sleep quality at baseline	1.00	2.83	(0.78; 10.32)	2.04	(0.52; 7.97)

Our finding of the cross-sectional association between workplace bullying is in line with a survey of the French working population by Niedhammer et al. that found that frequently bullied experienced more sleep disturbances, independently of self-rated health and depressive symptoms (141). However, Niedhammer et al. only assessed frequent' bullying (daily, almost daily and weekly), whereas our study both included assessment of occasionally bullied (monthly and now and then) and frequently bullied persons (Weekly and daily). In this respect, Paper VIII extends the previous findings by showing that also 'occasionally bullied' is a relevant group to study and include in preventive actions at the workplace. As frequently bullied people are more likely to leave their work (76) or take long-term sick leaves compared to non-bullied employees (151), the large group of occasionally bullied may constitute the group with the highest risk of chronic exposures and sleep disturbances. A recent longitudinal study found workplace bullying to be associated with sleep difficulties at follow-up five years later (110). Paper VIII confirms these findings with only two years follow-up in the raw analyses (Paper VIII). The risk of sleep difficulties among bullied respondents diminished and became statistically non-significant at follow-up when adjusting for sleep difficulties at baseline. However, it is questionable whether it is meaningful to adjust for baseline sleep difficulties. It could be expected that sleep become disturbed by intrusive thoughts and ruminations (150) both before and after specific bullying episodes. Hence, exposure to workplace bullying may trigger subsequent intrusive negatively coloured thoughts, and similar thoughts may be evoked in advance due to anticipations of becoming exposed to new bullying episodes at work. In this case, and as the item of workplace bullying is referred to the past 6-12



month, the sleep difficulties observed at baseline may be due to the workplace bullying. Therefore, adjusting for sleep at baseline could be an over-adjustment in the final analysis.

*Paper IX. Workplace bullying, sleep problems, and leisure-time physical activity: a prospective cohort study.*

The aim of Paper IX was to prospectively examine (a) whether bullying increases the risk of sleep problems, and (b) whether the association between bullying and sleep problems is moderated by LTPA. We expect that, among individuals who are high in physical activity during their leisure time, the association between bullying and sleep problems will be weaker compared to individuals, who are less physically active during leisure time. To our knowledge, no studies have evaluated the moderating role of LTPA in relation to the association between workplace bullying and sleep problems.

Paper IX found that workplace bullying at baseline was associated with overall sleep problems, awakening problems, lack of restful sleep, and disturbed sleep at follow-up. When adjusting for the sleep variables at baseline overall sleep problems, awakening problems, and lack of restful sleep remained significant but not disturbed sleep. Excluding depressed respondents at baseline the effect stayed significant with respect to awakening problems and lack of restful sleep. We did not find that LTPA moderated the association between workplace bullying at baseline and sleep problems at follow-up. We included analyses of follow-up sleep problems among four subgroups of workplace bullying at baseline and follow-up (1: not bullied at follow-up and baseline (reference); 2: bullied at follow-up and not at baseline; 3: bullied at baseline and not at follow-up; and 4: bullied at both baseline and follow-up). The respondents perceived more sleep problems at follow-up if bullied at any time.

In line with previous longitudinal studies on workplace bullying and sleep problems (110)/(Paper VIII) we found supportive evidence that exposure to workplace bullying increases the risk of sleep problems. In the prospective study by Lallukka et al. (110), excluding respondents with mental health problems and adjusting for sleep problems at baseline resulted in attenuation of the observed association between bullying and sleep problems. Our study showed similar findings as reported by Lallukka et al (110) when adjusting for baseline sleep problems and excluding respondents with depression. We also investigated across-time developments and observed that bullied respondents at baseline had overall sleep problems, awakening problems, lack of restful sleep, and disturbed sleep at follow-up, irrespectively reporting workplace bullying at follow-up (table 4/Paper IX). To which extend an increase of 0.04 to 0.07 more sleep problems with increase in frequency of bullying constitute clinical relevance is at this point difficult to assess. However, the overall results indicated that workplace bullying has an impact on the respondents' perceived sleep quality. We studied associations in the working population and did not expect to find severely poor sleepers.

We found no indication that LTPA at baseline moderated these associations. Thus, our research question that high LTPA would reduce the hazardous effect of bullying on sleep did not receive support.

In conclusion, Papers VIII and IX find in line with previous studies that workplace bullying is a risk of poor sleep. We also add to the existing knowledge across time developments of workplace bullying and observed that bullied respondents at baseline had sleep problems at follow-up, irrespectively of whether workplace bullying was also reported at follow-up. Paper IX is the first

study to investigate if LTPA reduces the effect of workplace bullying on subsequent sleep. We concluded that LTPA do not reduce the hazardous effect of bullying on sleep.

### ***Perceived stress and sleep as mediators between workplace bullying and LTSA***

*Paper X. Does perceived stress mediate the association between workplace bullying and long-term sickness absence.*

Psychological stress may be a potential mediator between workplace bullying and subsequent health problems and sickness absence. To our knowledge no studies have examined such possible mediation so far. To contribute bridging this gap, Paper X aimed at examining whether perceived stress levels mediated the association between workplace bullying and subsequent LTSA, in a large cohort of Danish employees.

Papers X and XI were included to study association between workplace bullying and LTSA and to which extent perceived stress, and sleep difficulties mediated the association.

The background for Paper X was that workplace bullying was found to be related to self-reported sickness absence (16, 33, 114, 138, 139, 179), and LTSA (28-30 days) in register based studies (28, 151, 181), and perceived stress (Papers III, IV and V). Perceived stress has been found to be associated with poor health (31). This association can be understood in the light of the Allostatic Load model (132), according to which prolonged and repeated stress leads to dysfunctions in bodily systems and to disease as a consequence.

In Paper X we show that workplace bullying is associated with high levels of perceived stress and that both workplace bullying and perceived stress were associated with an increased risk of LTSA during a two-year follow-up period. We also find that perceived stress partially mediated the association between workplace bullying and LTSA.

This study used data from previous cohorts described above, the PRISME cohorts collected in 2007 and 2009. We excluded all observations from participants with LTSA within the last two years before taking part in the study. We excluded all observations with missing information on one or more of the variables used in the analysis. A total of 4,114 unique participants contributed with 6,331 observations across the two waves of the study.

*Paper XI. The role of poor sleep in the relation between workplace bullying/unwanted sexual attention, and LTSA.*

Paper XI aimed to examine two possible mechanisms through which poor sleep may play a role in the relation between bullying/sexual harassment and LTSA.

The background for Paper XI due to the association between workplace bullying and poor sleep (95, 110, 141, 166, 187, 201)/(Papers VIII and IX). We hypothesized that poor sleep, partially mediated the association between workplace bullying and LTSA. Paper XI showed that workplace bullying was prospectively associated with LTSA. We found that workplace bullying was associated with LTSA ((OR 1.77; 95 % CI 1.50–2.12)). Only a small part of this association was mediated by poor sleep (AWE: 12.8 % (95 % CI 8.1–19.8)). Poor sleep increases the risk of depression (200), cardiovascular disease (73), and type 2 diabetes (21). Poor sleep also increases the risk of sickness absence (108, 109). However, no studies have shown that poor sleep partly mediates the association between workplace bullying and LTSA.

### **Methodological considerations**

The strength of these studies are that the analytical method used for measuring cortisol in saliva was evaluated in the laboratory performing the measures of salivary cortisol, using a certified reference material (Paper I). In the method evaluation, we estimated within-subject variation to be able to estimate the precision of the method. For this, we used criteria for clinical use, stating that a desirable precision could be defined as  $CV_a < 0.5 CV_i$  and an optimum performance could be defined as  $CV_a < 0.25 CV_i$  (51). The performance of the method showed  $CV_a/CV_i$  to be 0.14, indicating that the analytical variation in the method employed was adequate for use in measurements of healthy subjects. A reference interval for morning and evening salivary cortisol was established to validate the laboratory method for use among non-diseased individuals (Paper I). We followed the guidelines from EURACHEM, EURACHEM guidance Document No 1 (2), that stated that "*The validation of standard methods should not be taken for granted - the laboratory should satisfy itself that the degree of validation of a particular method is adequate for its purpose*".

In all studies where salivary cortisol was used concentrations of cortisol were analysed on a logarithmic scale due to non-normal (skewed) distributions and increasing variances with higher concentrations. We adjusted for the exact *time-of-sampling* to take into account the variance accounting for that the participants do not take the sample at the same time. The effect of the exact sampling time was evaluated by including the variable *exact-time-of-sampling* (categorical, linear, and squared) as continuous independent variables in the Papers I, III, IV, V, and VI.

### **Selection bias**

In the WBH study, the workplaces were recruited through advertisements on the websites of trade unions, employers' organizations, and trade networks etc. and the participants in the PRISME study was recruited from one region in Denmark. Hence the inclusion of workplaces could be due to having employees exposed to workplace bullying and may be prone to positive selection, and a thereby higher than normal prevalence of bullying (Paper IV). Recent Danish Work environment and Health surveys from 2010 to 2014 (79) between 10 and 12 per cent of the working population between 20 and 59 years report being exposed to workplace bullying. Also, a previous study with special focus on the psychosocial working environment in Denmark 6.7% reported occasional bullying, and 1.6% frequent bullying (152). Reporting workplace bullying in the WBH cohort showed same levels of workplace bullying (Papers IV, V, VIII, IX, X and XI). Hence, it seems unlikely that the WBH study should represent workplaces with unusually heavy or light bullying problems. Indeed, the fact that the bullied persons were well spread out across the workplaces as opposed to being clustered to a few workplaces seems to support such an interpretation (Paper IV).

Further, the response rates in the WBH and the PRISME cohorts were relatively low at baseline, approx. 45% (Papers IV, V, VI, VIII, IX, X and XI). This may cause that some invited individuals in the population were less likely to be included than others. In the PRISME study, very little indication of biased risk estimates due to low participation was found at baseline (87). At follow-up in the PRISME study 3,232 of invited respondents at baseline responded, giving a response rate of approx. 72%. Low participation in population-based follow-up studies may cause a biased estimation of health risk. In the PRISME cohort we found no indication of low participation rate at baseline distorts the estimates of associations between the work unit level of psychosocial work environment and mental health outcomes during follow-up (87). A drop-out analysis in the WBH study showed that more bullied respondents and witnesses as well as respondents reporting high

AWI refrained from responding to the questionnaire at follow-up (Papers VIII and IX). Hence, the association between workplace bullying and sleep difficulties is likely to be underestimated. Previous studies have indicated that frequent bullying is a stronger risk factor for LTSA than occasional bullying (28). In Paper X we only had 46 respondents reporting being frequently bullied (daily or weekly). We analysed data with respondents reporting monthly, weekly and daily bullying in one category in Paper X. We performed a sensitivity analysis only on cases of frequent bullying, i.e. weekly and daily (Paper X). The results showed very broad confidence intervals and very few statistically significant results, but the effects estimates pointed in the same direction as the main analysis the workplace bullying was associated with LTSA (Paper X).

The participants in Paper VII were recruited from 12 geographically differently located units of a Danish public administrative authority located in the eastern part of Denmark. Out of the 2,163 employees invited, 544 (99%) filled in the questionnaire, and 389 (71%) collected saliva samples at baseline. More than 50% of the white-collar workers were classified as highly physically active (i.e. high resting MET estimates during quiet sitting). It is estimated that approx. 40% of the Danish adult population do not fulfil the recommendations for physical activity by Danish National Board of Health (68). Hence this population is a very unusual distribution compared to the general population. However, the association between physical activity and salivary cortisol can hardly be affected by the selection bias in the population studies.

### ***Misclassification***

A major strength of the present thesis is that the exposure, workplace bullying, was measured in different ways, i.e. using the self-labelling and the operational methods (Papers III, IV, V, VIII, IX, X and XI). To admit being a target of bullying may be to admit to weakness and inadequate coping, which may be difficult for some respondents (39) and may lead to underreporting or missing data (175). The use of the NAQ to measure exposure to workplace bullying (42, 116) may be less prone to misclassification of exposure to negative behaviour at work (Paper V). It seems likely that bias due to failure to admit to being bullied would lead to an underestimation of the true associations since the targets would end up in the reference group and hence minimize the contrast between groups (Paper V). The reliability of using a single item to measure bullying has been discussed, i.e. underestimation of the number of bullied respondents (147). A recent study comparing different measures of workplace bullying has found that the correlation between bullying behaviour (measured by several negative acts) and a single item on bullying, when including a definition of workplace bullying, is high (42). However, the self-labelling method does not provide information on the nature and content of workplace bullying, and may not include persons who are frequently exposed to negative and unwanted behaviour but, for some reason, do not label themselves as being bullied (146). In Papers III, IV, VIII, IX, X, and XI the self-labelled method was used to measure workplace bullying, whereas in Paper V, the operational method based on exposures to negative acts at work was used. It is also likely, that responding to items on workplace bullying is influenced by personality (157), e.g. bullied persons with high scores on neuroticism might interpret acts that they are exposed to as negative and ego threatening. If this is the case, then the bullied person's anxiety laden personality and negative attitude might constitute a barrier for attempts that aim to neutralize the bullying process, by altering the tone in the social interaction (157).

It has been recommended to use different methods to measure the stressor-strain relationship (96). We included more various methods and follow-up times to investigate the associations between

workplace bullying and stress reactions (i.e. salivary cortisol (Papers III, IV, and V) and sleep problems (Papers VIII, IX and XI) and register based LTSA (Papers X and XI). Personality may influence responding to items on sleep problems, which may result in unmeasured confounding. In Papers VIII and IX on workplace bullying and sleep problems we adjusted for baseline sleep problems. In the Paper IX where LPTA was tested for moderating the association between workplace bullying and sleep, respondents with sleep problems and depression at baseline were excluded. In Papers X and XI we used of register-based LTSA ( $\geq 30$  consecutive days), which added to the validity of the results, because the outcome measure was not affected by participants' potentially biased recalls. We used register-based LTSA, which reduces the risk of loss-to-follow-up. In Paper X and XI we also excluded data from participants, which were registered as a case during the preceding two years, but we did not exclude participants with shorter spells of sickness absence despite the fact that such participants could be considered as "early stage cases". Moreover, if we suspect shorter periods of sickness absence to increase the risk of being bullied or labelling one-self as being bullied (and similarly regarding unwanted sexual attention), the present study may overestimate the true association between bullying and LTSA (Paper XI).

### *Unmeasured Confounding*

The limitation of Paper I was that time of awakening was not recorded. Time of awakening has been shown in the literature to influence the concentration of salivary cortisol (Paper II/ (101)). In 1999 /2000, when the data was collected, we were not aware of awakening time being a large covariate. This may have affected the reference intervals, but not the method evaluation. Paper I points to the importance of estimating precision and accuracy in measurements. Paper II rather covers interpretation of results, to understand which sources of variability exert systematic influence on sampling, and that variability can be of both biological and methodological origin. Failure to identify sources of variability may induce erroneous interpretations in terms of Type I and Type II errors (Paper II). In the future studies, WBH and PRISME cohorts, we included the time of awakening and adjusted for time of awakening (Papers VI, V and VI).

Bullying and negative behaviour may thrive in poor psychosocial working environments (118). Hence, it is a serious limitation that workplace bullying and sleep problems were self-reported, which may render results vulnerable to common method variance (89, 197). We did not to adjust for other psychosocial work factors in Papers X and XI. It has been debated to which extent the association between psychosocial work factors and sickness absence should be adjusted for (all) other psychosocial work factors (Paper XI). In three recent large-scale studies (n between 29,000 and 46,000), the association between bullying/sexual harassment and sickness absence was studied with and without adjustment for other psychosocial risk factors, without changing the association between workplace bullying and sickness absence significantly (114, 139, 179). Due to unknown causal relationship between different psychosocial work factors and the overlap between them may affect the confounder structure, and therefore also to select an appropriate set of covariates (167).

In the association between workplace bullying and salivary cortisol we observed more women among the frequently bullied compared to the occasionally bullied and the reference group, which raises suspicion of a possible gender bias (Paper IV). Previous studies have shown that normal healthy women tend to have higher cortisol concentrations than normal healthy men (Paper I). Thus, the gender imbalance is not likely to account for the lower concentrations of salivary cortisol that is observed among the frequently bullied. On the contrary, it seems more likely that a potential gender

bias will serve to minimize the differences, which will lead to an underestimation of the effect. We adjusted for gender all analyses (Papers III, IV and V).

When participants are asked to collect saliva samples there will be risk of not providing enough saliva for the analyses of cortisol. In the PRISME cohort we had 15% dry samples due to very little saliva (Paper VI). The dry samples were randomly distributed over the total samples, and thereby considered to be missing at random (Paper VI) and giving less robust results

### ***Causation and reverse causation***

Papers III, IV, and V are cross-sectional studies. The definitions of workplace bullying or negative acts imply that the acts should have taken place for at least 6 months. Hence, at the time of sampling saliva for cortisol the exposure to workplace bullying may be regarded as a chronic stressor and thereby the cortisol response should be interpreted in that way.

Papers VIII and IX showed that workplace bullying was associated with both concurrent and subsequent sleep problems, and that the association was statistically significant after adjustment for the psychosocial work factors described by Karasek (job demands, decision latitude and social support), although the magnitude of the association was somewhat reduced. We also tested for reverse causation and found that sleep difficulties predicted occasionally bullying and witnessing bullying at follow-up (Paper VIII). The reverse association cannot exclude the effects of workplace bullying on sleep, since workplace bullying is a phenomenon of lower prevalence than sleep difficulties. Moreover, sleep is a multi-factorial phenomenon that has a wide range of explanatory variables (82). Hence, we do not expect that one single factor (here workplace bullying) would explain a large part of the variation in sleep problems. It is possible that a vicious circle will be created, i.e. poor psychosocial working environment where bullying and negative behaviour may thrive, may create a vicious circle where sleep difficulties lead to decreased productivity and avoidance of day-time activities which in turn lead to more stress (118).

In the two last studies (Papers X and XI) LTSA were collected the Danish Register of Sickness absence compensation and Social transfer payments two years after being exposed to workplace bullying. We excluded respondents they had LTSA one year prior to the survey to avoid LTSA to lead to workplace bullying. The prospective collection of outcome information contributed to the validity of the results in Papers X and XI. We also used self-reported exposure to workplace bullying and mediators (i.e. measures of poor sleep and perceived stress) collected in each survey year. Paper X showed that workplace bullying in 2007 was a strong predictor of perceived stress in 2009. We also found a statistically non-significant indication that perceived stress in 2007 may be a risk factor for workplace bullying in 2009 (Paper X). These results indicated that some, but not all of the association between bullying and perceived stress may be due to reverse causality. Ideally, measures of the mediators should be collected after the exposure measurements (Paper X). We did not have the opportunity to temporarily separate the measures of exposures and mediators. There was a large drop-out of exposed participants across the surveys (e.g. 19-57% of the employees that reported workplace bullying in one of the surveys did not provide information about difficulties awakening at the subsequent follow-up) (Paper XI). Further it would be problematic to separate the measures of workplace bullying and sleep by two years, due to the effects of bullying on sleep, as a sub-acute stress response, are likely to occur relatively soon after the exposure is initiated (Paper XI). Further, Paper VIII indicated that there could be reverse causation between bullying and poor

sleep, which points to a possible overestimation of the role of poor sleep as mediator (Paper XI). In Paper X, we found that workplace bullying at baseline did not predict sickness absence 3-4 years later when accounting for history of sickness absence. Hence, including perceived stress measured two years after the bullying episode could be a potential effect of LTSA caused by workplace bullying, thus introducing potential reverse causation between the outcome and the mediator (Paper X).

### **Public health implications and future research**

This thesis underlines that workplace bullying is associated with psychological illnesses and LTSA. Although individual responses vary from person to person, people who are bullied at work may experience stress, anxiety, depression, and trouble sleeping. Indeed, most companies have a zero tolerance against bullying in the workplace. Workplace bullying may thrive better at workplace with a poor psychosocial working environment. Prevention of workplace bullying from an organizational level is crucial. However, if companies experience workplace bullying the symptoms of the bullied individual also calls for rehabilitation at individual level. Workplace bullying is detrimental for the individual, but also the workplaces are affected by workplace bullying. When one person is exposed to workplace bullying approximately twice as many report witnessing bullying. Hence, the entire workplace will be affected if workplace bullying occurs. Some tools have been developed to address conflict handling as an antecedent of workplace bullying.

At individual level it is also important to use stress rehabilitation to make the individual return to the workplace. This thesis sheds light on some of the individual effects of workplace bullying measured as physiological stress, psychological stress, sleep, and LTSA. The studies show that there may be a 'dose - response' effect of the bullying - the more exposure to bullying the more severe the effects. This thesis also finds the association between workplace bullying and LTSA to be partly mediated by psychological stress and sleep. We showed that bullied persons are more likely to have sleep difficulties. Sleep problems interfere significantly with daytime functioning and overall well-being, and may have serious clinical consequences. Sleep deprivation may be regarded as a neurobiological and physiological stressor. Sleep has important homeostatic functions, and sleep deprivation is a stressor that may have consequences for the brain, for instance memory and cognitive functions as well as regulation of neuroendocrine systems. The findings that the association between workplace bullying and LTSA were mediated partly by poor sleep and psychological stress are important for the understanding of the pathological processes behind the bullied person's poorer health. Both workplace bullying and high perceived stress levels are risk factors of LTSA.

Stress related effects of workplace bullying call for more research on stress related health effects, such as risk of cardiovascular diseases and diabetes mellitus II (DMII) when exposed to workplace bullying. To date, only one study has looked into workplace bullying and cardiovascular diseases and no studies have investigated an association to DMII. It may also be relevant to study physiological stress as a pathway to chronic disease.

We also need more knowledge on to what extent exposure to workplace bullying may result in early retirement and possible mechanisms for the association between workplace bullying and early retirement.

## **Conclusion**

This thesis summarizes new knowledge on workplace bullying and stress responses, measured by salivary cortisol (Papers I and II) and poor sleep. Moreover, new knowledge is provided on leisure time physical activity as a protective factor in the relationship between workplace bullying and poor sleep. The thesis also provides knowledge on mechanisms (sleep and psychological stress) for how exposure to workplace bullying workplace can lead to LTSA. Until the first study investigating the relationship between workplace bullying and cortisol in saliva (Paper III) was published in 2006, only one short communication presented study did examination of workplace bullying and salivary cortisol. This thesis also adds knowledge to the research workplace bullying as a risk factor of sleep problems. Only five studies have so far examined the relationship between workplace bullying and sleep problems and of these, only one study was a follow-up study. To date, no studies have investigated whether physical activity during leisure time could be a protective factor between workplace bullying and sleep problems. Further, no studies have examined whether the relationship between workplace bullying and LTSA is mediated by psychological stress and poor sleep. The thesis outlines a possible pathway between workplace bullying and health effects. Paper III finds that workplace bullying is associated with low salivary cortisol. Papers IV and V underlined this finding but add to the finding that only among frequently bullied, salivary cortisol was lower. Paper V measured workplace bullying by NAQ and finds that the association to salivary cortisol is in a dose dependant matter. Paper VIII showed that workplace bullied employees had poor sleep. Investigating possible mechanisms makes Paper VI relevant since we find that poor sleep is associated with low cortisol and that this is the case also three months later. Paper VII is also relevant with respect to possible mechanisms as we in this study find that physically active employees perceive more energy, and for men also lower perceived stress, indicating a beneficial stress-energy response. Physical activity during leisure time also affected the association between salivary cortisol and perceived stress and energy, so that respondents being physically active during leisure time and perceiving higher energy showed higher evening saliva cortisol. Paper IX does not find support for leisure time physical activity to be a moderator between workplace bullying and sleep problems, which may indicate that workplace bullying is such a severe stressor that healthy life style cannot diminish the effects of. Papers X and XI show an association between workplace bullying and LTSA and that poor sleep and perceived stress partially mediate the association, and thereby indicating that sleep and perceived stress may be part of the pathways between workplace bullying and LTSA.



## Summary

This thesis consists of a summarizing synopsis on workplace bullying, stress responses and LTSA and 11 papers. The thesis focuses on 1) methodological issues with respect to design, compliance with sampling and analytical measurement validity when using salivary cortisol as a stress response in epidemiological studies, 2) investigate the associations between workplace bullying and the stress response, measured by perceived stress, salivary cortisol, and poor sleep, 3) explore if LTPA moderated in the association between workplace bullying and sleep, 4) finally, to explore possible pathways between workplace bullying and LTSA.

The thesis is based on data from 6 cohort studies 1) the atherosclerosis and work – study that included 130 employees in 1998, 2) The Swedish study, a study in five companies, where 437 participates 3) the Workplace bullying and harassment study, a Danish workplace study, where 3363 participated in 2006 and followed up in 2008 4) the PRISME study, where 4489 participated in 2007 and were followed up in 2009, 5) The health promotion study, where 549 public employed participated, and 6) the Workplace bullying, depression and negative behaviour study (MODENA), a combination of the WBH and PRISME studies, where all respondents from WBH and PRISME cohorts were invited and 5000 responded.

There are several main findings. The thesis address the methodological and design problems related to including physiological measures, such as salivary cortisol as stress response. That is the importance of having knowledge on normal biological variation (e.g., diurnal variation, within-subject variation, and between-subject variation) as well as methodological variation (laboratory techniques, material specifications etc.). The two first Papers (I and II) provide empirical knowledge of biological variation in salivary cortisol and identifying sources of variability, such as time of sampling and time of awakening that may lead to changes erroneously interpreted as effects or as absence of effects.

Paper I provides a method evaluation for the method used to measure salivary cortisol in Papers III, IV, V, VI, and VII. Paper I also estimated reference intervals for morning and evening samples in 130 people at work. Paper II further provides an overview of knowledge and recommendations on different topics that may influence collecting saliva samples in field studies by addressing the impact of biological variation that is theoretically independent of individual choices (i.e. diurnal salivary cortisol profiles, within and between subject variation, seasonal variation, and effects on age and gender), biological variation in relation to behaviour (i.e. life style choices, diet, medication, smoking, alcohol, and physical activity), methodological variation relating to sampling and storage procedures (i.e. cotton versus polyester tampons and freezing of samples in different temperatures) and methodological variation relating to applied laboratory techniques (i.e. analytical method, analytical precision of the measurement, and long-term stability of measurements).

Papers III, IV and V showed that workplace bullying was, across cohorts, consistently associated with physiological responses in terms of lower salivary cortisol. They supplemented each other by using three different ways of measuring workplace bullying in different cohorts. Paper III is the first full study combining workplace bullying (yes/ no), health outcomes and physiological stress response in terms of salivary cortisol. Paper IV adds knowledge by using frequency of workplace bullying (now and then to daily) and salivary cortisol. Paper V is the first study using the

operational methods to assess workplace bullying, i.e. measuring negative acts at the workplace and salivary cortisol as the outcome.

Paper VI found, that low morning cortisol was associated with increased sleep problems during a four-week period prior to sampling and that the respondents. At follow-up three months later, those with sleep problems had a flattened cortisol profile. Paper VI studied the association between physical activity during leisure time and perceived energy stress. If respondents were physically active in leisure time and perceived high energy they also had higher evening saliva cortisol. We showed in Paper VIII that workplace bullying was associated with sleep problems at baseline and two-years later. Paper IX studied whether leisure time physical activity moderated the association between workplace bullying and sleep problems. We found no indication that LTPA at baseline moderated these associations. Thus, our hypothesis that high LTPA would reduce the hazardous effect of workplace bullying on sleep was not supported.

Papers X and XI studied psychological stress and sleep as mediators between workplace bullying and LTSA. Paper X showed that workplace bullying was associated with high levels of perceived stress and with an increased risk of LTSA during a two-year follow-up period. We also found that perceived stress partially mediated the association between workplace bullying and LTSA. Paper XI showed that the association between workplace bullying and LTSA was partly mediated by poor sleep.

Workplace bullying is detrimental for the individual, but also the workplaces are affected by workplace bullying as bullied employees are at risk of LTSA. This thesis underlines, that workplace bullying was related to stress reactions in terms of sleep problems and low salivary cortisol as well as LTSA. The thesis also provides knowledge on mechanisms (sleep and psychological stress) for how exposure to workplace bullying workplace can lead to LTSA. Moreover, the thesis provided on LPTA not being a protective factor in the relationship between workplace bullying and poor sleep.

## Dansk resume

Denne afhandling sammenfatter min forskning om mobning, stress reaktioner og langtidssygefravær (LTSA). Afhandlingen fokuserer på 1) metodiske problemstillinger i forbindelse med at designe, prøvetagning, og måle metodens analytiske validitet når kortisol i spyt bruges til estimere stress reaktionen i felt studier, 2) undersøge sammenhængen mellem mobning på arbejdspladsen og stress reaktionen, målt ved selvrapporeret stress, kortisol i spyt og dårlig søvn, 3) undersøge, om fysisk aktivitet i fritiden (LTPA) modererer sammenhængen mellem mobning og søvn, og 4) undersøge mulige mekanismer for sammenhængen mellem mobning og LTSA.

Afhandlingen er baseret på data fra 6 kohorte studier 1) aterosklerose og arbejde studiet, som inkluderede 130 personer i arbejde i 1998, 2) et svensk studie af fem virksomheder i Sydsverige, som inkluderede 437 personer i 2001, 3) et dansk studie 'Samarbejde og arbejdsklima – forebyggelse af mobning på arbejdspladsen' (WBH), som inkluderede 3363 ansatte i 2006 og fulgt op i 2008, 4) et dansk studie af Psykiske risikofaktorer i arbejdsmiljøet og biologisk mekanisme for udvikling af stress, udbrændthed og depression, hvor 4489 offentlige ansatte valgte at deltage i 2007 og fulgt op igen i 2009, 5) et studie af sundhedsfremme på arbejdspladsen, der inkluderede 549 offentlige ansatte i 2006, og 6) studie om Risiko for psykisk lidelse ved udsættelse for negative handlinger i arbejdslivet (MODENA), som er en opfølgning af WHB og PRISME studierne i 2001. Alle der havde deltaget mindst en gang i de tidligere runder blev inviteret, og i alt valgte 5000 at deltage.

Der er flere hovedfund. Denne afhandling inddrager metodologiske og design problemer relateret til at anvende fysiologiske målinger, såsom kortisol i spyt, i feltstudier. Der handler om nødvendigheden at have viden om normal biologisk variation (fx døgnvariation, inden for individet variation og mellem-emne variation) samt metodisk variation (laboratorieteknikker, materielle detaljer osv.). I de to første studier I og II beskrives biologisk variation i kortisol i spyt hos mennesker på arbejde og hvilke parametre, der har stor betydning for variation i spytkortisol, så som tidspunkt for prøvetagning og opvågning, der kan føre til fejlagtig fortolkning af effekter eller mangel på effekter. Studie I beskriver en metodeevaluering af den anvendte laboratoriemetode til at måle kortisol i spyt. Studie I beskriver også biologisk variation over en dag samt referenceinterval for 130 deltagere ved prøver taget ved opvågning, 20 og 40 min efter opvågning og kl. 20.00.

Studie II diskuterer forskellige faktorer, der kan påvirke indsamling af spytprøver i feltstudier ved at inkludere biologisk variation, der teoretisk er uafhængig af individuelle valg (dvs. døgnprofil i spytkortisol, variation mellem og inden for den enkelte person, sæsonvariation samt indflydelse af alder og køn), biologisk variation relateret til adfærd (dvs. livstil, kost, medicin, rygning, alkohol og fysisk aktivitet), metodiske variationer vedrørende prøvetagning (bomulds- versus polyestertamponer) og opbevaring af prøverne før analyse (kan prøverne holde sig ved frysning i forskellige temperaturer?) og metodevariation henhørende til anvendte laboratoriemetoder (dvs. analysemetode, analytisk præcision af målinger og langsigtet stabilitet af målinger).

Studierne III, IV og V anvendte tre forskellige metoder til at måle mobning på arbejdspladsen og undersøger sammenhængen til kortisol i spyt. Studie III var i 2006 det første felt studie af arbejdstagere der undersøgte mobning på arbejdspladsen og det fysiologiske stress response, målt med kortisol i spyt. Dette studie målte mobning på arbejdspladsen med ja/nej besvarelser. I studie

IV undersøges sammenhængen mellem mobning på arbejdspladsen og spytkortisol med et spørgsmål, hvor deltagerne forud for spørgsmålet blev præsenteret for en definition af mobning og med 5 svarkategorier fra aldrig til dagligt. Dette studie viste en sammenhæng mellem hyppig mobning (daglig og ugentlig) og lav kortisol. I studie V brugte vi 23 spørgsmål om forskellig negativ adfærd til at måle mobning, også kaldet den operationelle metode. I dette studie fandt vi også en sammenhæng med kortisol i snyt: at det at være hyppigt udsat for negative handlinger (dagligt og ugentligt) er associeret til lav kortisol.

I studie VI fandt vi, at lav morgen kortisol var forbundet med dårligere søvn de seneste fire uger blandt 4.066 danske offentligt ansatte. Ved opfølgning tre måneder senere havde deltagere med søvnproblemer en flad kortisol profil. Deltagere med opvågningsproblemer havde generelt lavt spytkortisol.

I studie VII studeres sammenhængen mellem fysisk aktivitet i fritiden og oplevet energi og stress. Fysisk aktivitet i fritiden påvirker sammenhængen mellem spytkortisol og oplevet stress og energi. Deltagere, der er fysisk aktive i fritiden, oplever at have mere energi og havde højere aften spytkortisol.

Studie VIII fandt, at mobning på arbejdspladsen var relateret til søvnproblemer ved baseline og ved opfølgning to år senere. I studie IX undersøges om fysisk aktivitet i fritiden modererer sammenhængen mellem mobning på arbejdspladsen og søvnproblemer. Vi fandt ingen tegn på, at fysisk aktivitet i fritiden målt ved baseline modererer denne sammenhæng. Vores hypotese blev derfor ikke understøttet.

Studierne X og XI undersøger om psykologisk stresssymptomer og søvn er mekanismer for en mulig sammenhæng mellem mobning på arbejdspladsen og langtidssygefravær (LTSA). Studie X viser, at mobning på arbejdspladsen var relateret til øget risiko for LTSA to år efter. Vi fandt også, at sammenhængen mellem mobning og LTSA delvist kunne forklare af høj psykologiske stresssymptomer. Studie XI viser, at sammenhængen mellem mobning og LTSA delvist kunne forklare af dårlig søvn.

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Doctoral Dissertation

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