# Emotional demands at work, physiological mechanisms, and mental health

**Marianne Agergaard Vammen**

**PhD Thesis**

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*The Faculty of Health and medical Sciences, University of Copenhagen*

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Marianne Agergaard Vammen

Faculty of Health and Medical Sciences

University of Copenhagen

Department of Occupational and Environmental Medicine

Bispebjerg University Hospital

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**Author:** *Marianne Agergaard Vammen, Cand.scient.san.publ.*
Department of Occupational and Environmental Medicine,
Bispebjerg University Hospital, Copenhagen, Denmark

**Assessment Committee:** *Naja Hulvej Rod, PhD, Associate Professor*
Department of Public Health, University of Copenhagen, Denmark

*Ingibjörg Jonsdottir, Professor*
Institutet för stressmedicin, Sweden

*Jussi Vahtera, Professor,*
University of Turku, Finland

**Academic advisors:** *Jane Frølund Thomsen, MD, PhD*
Department of Occupational and Environmental Medicine,
Bispebjerg University Hospital, Copenhagen, Denmark

*Sigurd Mikkelsen, MD, DMSc.*
Department of Occupational and Environmental Medicine,
Bispebjerg University Hospital, Copenhagen, Denmark

*Åse Marie Hansen, Professor*
Department of Public Health, University of Copenhagen
and National Research Centre for the Working Environment,
Copenhagen, Denmark

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Department of Occupational and Environmental Medicine
Bispebjerg University Hospital
DK-2400 Copenhagen NV
Denmark
Telephone: +45 35 31 60 60
Email: arbejdsmedicin@bbh.regionh.dk Denmark

## PREFACE AND ACKNOWLEDGEMENTS

In the very beginning of my Ph.D. journey I had the opportunity to visit hospital departments of hematology, oncology, and psychiatric for short but inspiring experiences. As a candidate in public health, I have only been on few short visits to hospitals. Consequently, I though handling severely ill patient must be burdensome and contain a great deal of emotional demands.

During my stay, I saw a young doctor telling his patient and her husband that she was going to die. I observed a severely ill patient at the psychiatric department being maintained by a large team of employees due to behavior that otherwise would have harmed him or others. One of the things that touched me was the calmness and patience shown towards the patients by the employees, in spite of the severity attached to the situations and the always present workload.

Later on my journey I had the opportunity to talk to school teacher around the country about their demands at work. Professionally they felt well trained, but they had a difficult time and experienced a lack of tools handling young people with personal problems. These types of demands were increasing, according to them, and it was challenging in an unpleasant way. Thus, a teacher defined emotionally demanding work as the emotional issues that one could not let go off when the workday ends.

This is qualitative observations and in this thesis, emotional demands at work have been examined using an epidemiological approach including data from the Danish project on “Psychological RISk factors in the work environment and biological MEchanisms in the development of stress, burnout and depression” (PRISME).

My work was carried out at the Department of Occupational and Environmental Medicine, Bispebjerg University Hospital. It was funded by the Danish Work environment Research Fund and Lundbeck A/S and supervised by Jane Frølund Thomsen, Sigurd Mikkelsen, and Åse Marie Hansen. I like to thank my supervisors for their skilled guidance and support through the years. I have learned a lot from your thoroughness and great expertise.

I would also like to thank my co-authors from the PRISME research group for their comments on the papers and contribution with knowledge from the occupational field. Specially, I like to thank Matias B Grynderup for always having the time to discuss process and findings.

My journey also included a stay at the Department of Public Health, University of Copenhagen and the National Research Center for the Working Environment. Thank you Kirsten Nabe-Nielsen and Ida E H Madsen for your assistance in the arrangements and to all fellow researchers that made me feel welcome both places.

To all my current and former colleagues at Bispebjerg, thank you for an excellent and inspiring research environment, and most of all for you friendships, that I have appreciated so much.

Finally, I would like to thank my mom, dad, family, and friends for love and support. I could not have done this without you. Special thanks goes do my dearest husband Mikkel, your support and encouragement are endless and your love is invaluable, together we have made great things come through in these years most importantly our daughter and son. Clara and Gustav, thank you for constantly reminding me what is important in life.

*Marianne Agergaard Vammen*

*Allerød, June 2016*

## LIST OF PAPERS

This thesis is based on the following original papers that will be referred to by their roman numerals:

**Paper I**

Emotional demands at work and the risk of clinical depression - a longitudinal study in the Danish public sector. Vammen MA, Mikkelsen S, Hansen AM, Bonde JP, Grynderup MB, Kolstad H, Kærlev L, Mors O, Rugulies R, Thomsen JF.

Accepted with minor revisions in *Journal of Occupational and Environmental Medicine* 2016.

**Paper II**

Emotional demands and exhaustion – cross-sectional and longitudinal associations in a cohort of Danish public sector employees. Vammen MA, Mikkelsen S, Forman JL, Hansen AM, Bonde JP, Grynderup MB, Kolstad H, Kærlev L, Rugulies R, Thomsen JF.

*Draft*

**Paper III**

Salivary cortisol and depression in public sector employees: Cross-sectional and short term follow-up findings. Vammen MA, Mikkelsen S, Hansen AM, Grynderup MB, Andersen JH, Bonde JP, Butterschøn HN, Kærlev L, Mors O, Rugulies R, Thomsen JF.

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**ABBREVIATIONS**

| | |
|---|---|
| CATS | Cognitive Activation Theory of Stress |
| CI | Confidence Interval |
| COPSOQ | Copenhagen Psychosocial Questionnaire |
| CMDQ | Common Mental Disorder Questionnaire |
| DHEA | Didehydroepiandrosterone |
| DISC | Demand-Induced Strain Compensation Questionnaire |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| ED | Exhaustion Disorder |
| ICD | International Classification of Diseases |
| MBI | Maslach Burnout Inventory |
| MDI | Major Depression Inventory |
| OR | Odds ratio |
| PRISME | Psychological RISk factors in the work environment and biological MEchanisms in the development of stress, burnout and depression |
| QEAW | Questionnaire on the experience and assessment of work |
| SCAN | Schedules for Clinical Assessment in Neuropsychiatry |
| SIMPH | Short Inventory to Monitor Psychological Hazards |

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## SUMMARY


### ENGLISH SUMMARY

#### BACKGROUND

A large proportion of the working population is employed in service professions where the work involves human contact. This type of work has previously been shown to be related to an increased risk of mental health problems and studies have further indicated that this may partly be due to emotional demands at work. In previous studies, items on emotional demands concerning how the work environment is perceived by the individual have been mixed with items reflecting the specific content of the work. Furthermore, mental health in the sense of exhaustion and depression has been measured with non-work-independent items and proxies for disease making interpretation of associations difficult.

Cortisol levels have been suggested to play a role in the physiological mechanism behind the development of depression, and as such be a potential hormone linking work stress to depression. Associations have been shown in some studies but not consistently. The timing of an association is uncertain, and long-term follow-up studies may miss associations in narrower time windows.

This thesis aimed to analyze if high emotional demands at work increase the risk of depression and exhaustion and if this risk is modified by other work characteristics. Furthermore, the role of cortisol was examined to see if an altered cortisol profile and the development of depression was associated.

#### METHODS

In 2007, 4,489 (response rate: 45%) Danish public service employees participated in the PRISME study by completing postal questionnaires on personal characteristics, the psychosocial work environment, and health, 3,224 (response rate: 72%) participated in the follow-up in 2009. Emotional demands scales measured: perceived (personal experience), content-related (specific exposures), and patient-care (patient related exposures) emotional demands. Exhaustion was measured with the scale of general exhaustion from the Copenhagen Burnout Inventory (CBI). Participants with high baseline scores of self-reported depressive symptoms, exhaustion, and perceived stress were invited to a standardized interview (SCAN) to identify cases of clinical depression. Morning (30 min after awakening) and evening (2000 h) salivary samples were collected at baseline and follow-up. In a subsample, on average 3.6 months later, participants collected three morning saliva samples (at awakening, 20 min and 40 min after awakening) plus an evening sample (2000 h). Data were analysed in three studies.

In *study I*, 62 cases of clinical depression were diagnosed. Emotional demands were examined as perceived, content-related, and patient-care emotional demands, individually reported and work-unit-based, crude and adjusted for effects of potential confounders. Further, the effect of doing patient work was investigated. Emotional enrichment, meaningful work, support from supervisor and colleagues were considered as potential effect modifiers.

In *study II*, for content-related emotional demands, the cross-sectional and longitudinal associations with exhaustion were analysed in the same model and adjusted for effects of potential confounders. Effect modifications were examined separately for self-reported emotional enrichment, meaningful work, job control, support from supervisor and colleagues as well as quantitative demands.

In *study III*, four cross-sectional and two short-term follow-up analyses were conducted and odds ratios of depressive symptoms and of clinical depression were estimated for morning, evening, mean and the difference between morning and evening cortisol (slope). For the subsample, awakening response (CAR) and area under the curve (AUC) cortisol measures were calculated. The models were adjusted stepwise for potential confounders.

**RESULTS**

*Study I*: Individually reported perceived emotional demands predicted depression. The work-unit-based odds ratio was in the same direction, though not significant. Content-related and patient-care emotional demands did not predict depression. In this population, doing patients work was associated with a lower risk of depression. The risk was only high for very high exposures to perceived emotional demands, contrary to the rest of the population. Support, meaningful work and enrichment did not modify the results.

*Study II*: Exhaustion increased with increasing content-related emotional demands, both cross-sectionally and longitudinally. However, the effect was small. Three of the six potentially modifying work characteristics were statistically significant; the effect of emotional demands on exhaustion was significantly lower for participants with high levels of emotional enrichment (cross-sectionally and longitudinally), high levels of meaningful work (longitudinally), and higher for high levels of quantitative demands (cross-sectionally).

*Study III*: None of the measures of salivary cortisol were associated with self-reported depressive symptoms or clinical depression, except from the morning cortisol in 2009. Because of the large number of statistical non-significant results, we considered the one exception to be due to chance.

**CONCLUSIONS**

Overall, the studies indicated that the effect of emotional demands at work depended on the personal perception with regards to the effect on depression. Specific content-related emotional demands at work had

no or small effect on depression and exhaustion, respectively. Findings supported the modifying effects of emotional enrichment, meaningful work, and quantitative demands between content-related emotional demands and exhaustion. Cortisol was not found to play a role in the physiological mechanism behind the development of depression.

**PERSPECTIVE**

Effects of emotional demands were small but could possibly be relevant at the population level. Prevention at the workplace could focus on reducing specific emotionally demanding factors and improving other psychosocial workplace factors. The present thesis has added to the current knowledge by emphasizing the need of instruments to characterize types of emotional demands at work that may be suitable for prevention. Future studies may refine this knowledge.

## DANSK RESUMÉ

### BAGGRUND

En stor del af den erhvervsaktive befolkning er beskæftiget i serviceerhverv, hvor arbejdet indebærer menneskelig kontakt. Denne type arbejde har tidligere vist sig at være relateret til en øget risiko for mentale helbreds problemer og undersøgelser har vist, at dette til dels skyldes følelsesmæssige krav i arbejdet. I tidligere undersøgelser, har spørgsmål vedrørende individets egen opfattelse af følelsesmæssige krav i arbejdet været målt blandet med elementer, der afspejler specifikke følelsesmæssige karakteristika ved arbejdet, som for eksempel at håndtere patienters lidelse og død. Endvidere er udmattelse i eksisterende studier ikke målt uafhængigt af arbejdet og depression er diagnosticeret ved brug af standardiserede kliniske interviews. Kortisol er blevet foreslået som fysiologisk mekanisme og årsag til udviklingen af depression, og som en forklarende mekanisme i relationen mellem stress og depression. Relationen er vist i nogle undersøgelser men ikke konsekvent. Få longitudinelle studier har undersøgt sammenhængen mellem kortisol og depression i en stor arbejdende population.

Denne afhandling har til formål at analysere, om høje følelsesmæssige krav i arbejdet øger risikoen for depression og udmattelse, og samtidigt om en sådan risiko er modificeret af andre psykosociale karakteristika ved arbejdet. Endvidere blev det undersøgt om klinisk depression var forbundet med en ændret kortisolprofil.

### METODER

I 2007, besvarede 4489 (svarprocent: 45%) offentlig ansatte spørgeskemaer om personlige forhold, psykosocialt arbejdsmiljø og sundhed. Ved opfølgning i 2009 deltog 3224 (svarprocent: 72%) ansatte. Følelsesmæssige krav i arbejdet blev målt med tre skalaer vedrørende: 1) den ansattes subjektive følelse af belastning (generelle), 2) det følelsesmæssige indhold i arbejdet (specifikke), og 3) patient relaterede følelsesmæssige krav. Udmattelse blev målt med spørgsmål fra Copenhagen Burnout Inventory (CBI). Deltagere med høje selvrapporterede depressive symptomer, udmattelse, og stress ved baseline blev inviteret til et standardiseret klinisk interview for at identificere tilfælde af klinisk depression. Spytprøver blev indsamlet morgen (30 min efter opvågning) og aften (klokken otte om aftenen) ved baseline og opfølgning. Nogle af deltagerne blev, efter i gennemsnit 3,6 måneder, bedt om at indsamlet yderligere tre morgen spytprøver (ved opvågning, 20 min og 40 min efter opvågning) plus en aften prøve (klokken otte om aftenen). På baggrund af data blev der gennemført tre studier.

I **studie I** blev 62 tilfælde af klinisk depression diagnosticeret. Generelle, specifikke og patient relaterede følelsesmæssige krav blev undersøgt, både individuelt rapporteret og baseret på gennemsnit for arbejdesenheder, samt med kontrol for effekten af potentielle konfoundere. Den modificerende effekt af

følelsesmæssig berigelse, oplevelsen af arbejdet som meningsfuldt samt støtte fra vejleder og/eller kolleger blev undersøgt samt effekten af at have patientarbejde blev undersøgt i forhold til depression.
I **studie II**, blev tværsnits og longitudinelle sammenhængene mellem specifikke følelsesmæssige krav og udmattelse undersøgt. I den samme model indgik både tværsnits- og longitudinelle associationer estimeret justeret for effekten af potentielle konfoundere. Den modificerende effekt af følelsesmæssig berigelse, meningsfuldt arbejde, job kontrol, støtte fra vejleder og/eller kolleger samt kvantitative krav blev undersøgt.
I **studie III** blev fire tværsnits- og to korte longitudinelle undersøgelser gennemført. Odds ratioen for depressive symptomer og klinisk depression i forhold til 1) morgen, 2) aften, 3) gennemsnits- og 4) forskellen mellem morgen og aften kortisol blev estimeret. For deltagere med ekstra kortisol prøver blev associationer for opvågnings respons (CAR) og arealet under kurven (AUC) estimeret. Modellerne blev justeret trinvist for potentielle konfoundere.

**RESULTATER**

**Studie I**: Individuelt rapporteret generelle følelsesmæssige krav var forbundet med udvikling af klinisk depression. Arbejdesenhed-baserede resultater pegede i samme retning, men var ikke statistisk signifikant. Specifikke og patient-relaterede følelsesmæssige krav var ikke forbundet med depression. Inddragelse af support, meningsfuldt arbejde og emotionel berigelse ændrede ikke på resultaterne for følelsesmæssige krav og depression. I denne population, viste patientarbejde sig relateret til en lavere risiko for depression.
**Studie II**: Følelsesmæssige krav i arbejdet var forbundet med en stigning i udmattelse, både i tværsnit og i longitudinelle undersøgelser, effekten var lille. Effekten af følelsesmæssige krav var statistisk signifikant lavere for deltagere med høje niveauer af følelsesmæssig berigelse, høje niveauer af meningsfyldt arbejde, og signifikant højere for høje niveauer af kvantitative krav i arbejdet (arbejdspres).
**Studie III**: Ingen af målene for kortisol var forbundet med selvrapporterede depressive symptomer eller klinisk depression, bortset fra morgen kortisol i 2009. På grund af det store antal af statistiske ikke-signifikante resultater, betragtes det ene fund som et udslag af tilfældighed.

**KONKLUSION**

Samlet set viste undersøgelserne, at effekten af følelsesmæssige krav i arbejdet afhænger af den personlige opfattelse af emotionelle belastninger i arbejdet i forhold til udvikling af depression. Specifikke indholdsrelaterede følelsesmæssige krav i arbejdet havde henholdsvis ingen og lille effekt på depression og udmattelse. Følelsesmæssig berigelse og meningsfyldt arbejde minskede risikoen for udmattelse som følge af emotionelle krav, mens kvantitative krav i arbejdet øgede risikoen. Kortisol var ikke forbundet med depression i denne population, og ser derfor ikke ud til at være en fysiologisk mekanisme bag udviklingen af depression.

**PERSPEKTIV**

Effekter af følelsesmæssige krav i arbejdet var små, men kan være relevante på populationsniveau. Forebyggelse af udmattelse og depression på arbejdspladsen bør fokusere på at reducere de følelsesmæssigt krævende forhold i arbejdet og samtidigt forbedre andre psykosociale forhold på arbejdspladsen. Denne afhandling har biddraget til den aktuelle viden ved at vise behovet for at skelne mellem forskellige måder at måle følelsesmæssige krav i arbejdet, for dermed at opnå en større viden om hvordan følelsesmæssige krav kan forebygges.

## 1.0 INTRODUCTION

Psychosocial factors have gained increasing attention over the last decades as important contributors to a healthy working environment. In order to achieve the best conditions and health for working people, a wide range of demands at work and their consequences have historically been studied, with a focus on quantitative demands, such as work load and work pace (1-4). However, as modern work is increasingly person-related, the work is also characterized by different levels of emotional demands (1). Former research has raised the question of whether emotional demands may predict emotional exhaustion and depression, and some evidence points to emotional demands as being as important and sometimes more important than quantitative demands (physical and task demands)(5-8). At the same time, person-related work may also contribute to positive and meaningful experiences and thus contains both potentially stressful as well as protective characteristics (9-12). This thesis examines the relationship between emotional demands at work and the occurrence of exhaustion and depression, including the possible modifying effects of positive work characteristics.

A physiological mechanism behind this relationship could be the stress-hormone cortisol. The hypothalamic-pituitary-adrenal axis constitutes a major part of physiological response to stress, and the activity can be measured by cortisol in saliva (13, 14). This thesis further covers the relationship between cortisol as a physiological mechanism and depression.

Several methodological concerns regarding former research on psychosocial work environment and mental health have been raised, such as independence between exposure and outcome, reporting bias and residual confounding, thus any conclusion regarding causality between psychosocial factors and mental health is vulnerable to these sources of bias (3, 4, 15). Thus, there is a need for longitudinal studies dealing with exposure measures that are less affected by the individual's perception of the work and with sufficient sample sizes to include relevant confounders. This thesis will address these issues. A subsequent increased understanding of emotional demands at work, mechanisms, and health outcomes could contribute to preventions in the workplace and at the individual level.

Data from the cohort on Psychological RISk factors in the work environment and biological MEchanisms in the development of stress, burnout and depression (the PRISME cohort) form the basis of the studies in this thesis.

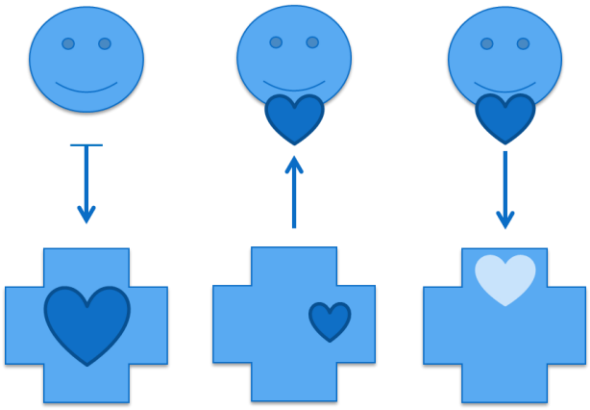
## 2.0 BACKGROUND

### 2.1 EMOTIONAL DEMANDS AT WORK

Previous researchers have argued that emotional demands as part of person-related work are a particularly important aspect of health outcomes (6, 8, 16). The characteristics and effects of these demands have traditionally been examined within two specific fields related to various research traditions, though there has not always been a clear distinction between these two; emotional labour, as presented by sociologists (11, 17, 18) and the epidemiological approach of emotional demands at work (6, 9, 19).

The emotional labour approach focuses on emotional regulation processes at work (11, 18). Emotional demands at work has been operationalised in many ways; but the exact meaning of this concept is seldom explained (5). This thesis elaborates on the concept of emotional demands and proposes a subdivision by separating questions on the emotional content from those on the emotional perception of the work. Accordingly, distinctions will be made among the expressions, experiences, and exposures of emotions at work. The approaches are illustrated in FIGURE 1 where the face illustrates the employee, and the cross and heart exemplify work and feelings, respectively. In the first case, an employee handles others people's emotions at work and, as part of the work, disregards his or her own emotions (content-related). In the second case, the employees are affected by the work they are doing. A reporting of emotional demands depends, in this case, on the personal (perceived) experience of the demands. And finally, in the third situation, the employees must regulate (hide or change) feelings as part of the job (emotional regulation or emotional labour). Of course in the actual work, all tree situations are at play at the same time to different degrees.

**FIGURE 1: Illustration of content-related and perceived emotional demands at work as well as emotional labour.**
***The figure shows the described interactions between the employee, the employee's work and the employee's feelings.***



The focus here will be the content-related exposure to as well as the perception and experience of emotional demands at work, whereas the expression and regulation perspective primarily will be included in the presentation of the concept of emotional demands at work in the following section. Furthermore, the work's possible positive emotional effects, will be taken into account (emotional enrichment at work).

### 2.1.1 THE HISTORY AND CONCEPT OF EMOTIONAL DEMANDS AT WORK

The sociologist Arlie Russell Hochschild was the first to study the role and handling of feelings as part of work (18, 20). She began in the early 1980s, and her work forms the basis for numerous subsequent studies of emotions at work (21). In her book *The Managed Heart – Commercialization of Human Feeling* (18), she introduced the concept of emotional labour through examples: flight attendants had to hide their true feelings in order to deliver an optimal service and put the passengers first, and bill collectors were alienated from their feelings when collecting bills.

Hochschild (1983) defined emotional labour as a form of emotional regulation, or, in her words: "The management of feeling to create a publicly observable facial and bodily display". The employee was, according to her, required "to induce or suppress feelings in order to sustain the outward countenance that produces the proper state of mind in others" (18). She further characterised emotional labour by face-to-face or voice-to-voice contact with the public, an employer's allowance of the employee having some degree of control, and the requirement that the employee produce certain emotional states in another person (18). Hochschild (1983) suggested two ways of regulating emotions: surface acting and deep acting (18). Surface acting involves an

employee's hiding his or her true feelings and possibly pretending to feel something different from what she or he is actually feeling (change of expressions), whereas deep acting is the process where the employee adapts and eventually changes internal feelings to align with the required emotions (change of feelings)(18). Because of the unpleasantness and the effort it takes to manage emotions at work, Hochschild proposed that emotional labour causes burnout and job stress and therefore was potentially damaging to employees' mental health (18, 22).

In 2000, Grandey integrated three existing perspectives on emotional labour (11). Grandey explained that emotional labour are generally characterised by emotions that "are being managed at work in order to meet the display rules stated by the organisation" (11). James, in a broader definition, described emotional labour "…as the labour involved in dealing with other peoples´ feelings, a core component of which is the regulation of emotions" (17). This definition prioritises to a lesser extent the direct role of the management or the organisation and covers situations where employees deal with other people's emotions as part of their work (James 1989). Accordingly, two dimensions of emotional labour exist, one of which is a subset of the other. The first dimension is about handling other people's feelings as a part of the work (client, patient, student etc.), and the second dimension relates to the regulating of one's feelings (one's own, one's clients', or others' feelings).

The perspective that the employees as part of work may have to handle feelings in a broad sense is the occupational epidemiological literature's main interest. The concept has been termed emotionally demanding work and may include the concept of emotional labour and regulations, as described previously.

Historically, the most widely used occupational stress model - the demand control (DC) model - was developed by Karasek and Theorell in the late 1970s (23-25) and describes workers' health as the result of the interaction of high demands (work load and time pressure) and low control (perceived control of work and utilisation of skills). The model reflects the fact that it was developed from an analysis of industrial work. In 1996, Söderfeldt et al. raised a criticism of the model. According to Söderfeldt et al. (1996), the prominent demands in human service work[1] are not accounted for in the DC model (1, 26). They mention the emotional demands as a missing dimension. In accordance with Hochschild (1983), Söderfeldt et al. (1996) noted that demands and control in

[1] Human service work is the work carried out in human service organisations, and is defined by Hasenfeld (1974) as " ... that set of organizations whose principal function is to protect, maintain, or enhance the personal well-being of individuals by defining, shaping, or altering their personal attributes".

human service work do not interact in the same way as they do for industrial workers, as human service workers have some kind of control over the object that they are working with, i.e. humans are the "raw material"(1). Emotional demands at work are suggested to occur when the employee has some degree of control in relation to the person that the employee is responsible for serving (1). To address problems with the DC model in relation to human service work, Söderfelt et al. (1996) suggested focusing on other specific stressors at work. In this context, they mention emotional demands as the type of demands that are especially pronounced in person-related work, saying, "There are also special emotional demands, due to the nature of the work. Workers in human service organisations are confronted with poverty, disease, criminality and many other facets of human problems and suffering, together with gnawing feelings of own inadequacy". Söderfeldt et al.'s (1996) articulation of demands in human service organisations described work as being demanding when it includes the witnessing of others' problems and suffering (1).

Subsequently, numerus studies of psychosocial work environment have addressed the issue of emotional demands at work as well as the health consequences (6, 8, 19, 27-32). And some research has suggested that emotional demands can predict mental health problems and may be as important or more important as quantitative demands at work (5, 7, 33). However, the definition of emotional demanding work is rarely expressed, maybe because emotional demands seldom are the main focus of past studies (5).

Van Vegchel et al. (2004) suggested the following definition of emotional demands at work: "…those aspects of the job that require sustained emotional effort because of interactional contact with clients" (6). This definition includes both James (1989) and Söderfeldt at al.'s (1989) previous definitions as well as the face-to-face and voice-to-voice criteria Hochschild (1983) proposed (1, 17, 18). It has, however, been criticized as it restricts emotional demands to occur in the work with clients (8). Other jobs than client-related jobs may involve handling other people's feelings (17) or the confrontations with others' suffering and feelings of inadequacy (1). Furthermore, this restriction that only person-related work includes emotional demands, makes it impossible to examine emotional demands among employees doing non-person-related work, and thus to test if the premise is true (34). In the work by Madsen (2009), she suggested a reformulation as "those aspects of the job that require sustained emotional effort" (p. 16)(34).

### 2.1.2 HOW TO MEASURE EMOTIONAL DEMANDS?

In this section, I will present the most commonly used questionnaires applied to measure emotional demands in epidemiological studies, all of which are covered under the latter presented definition; however, different dimensions of emotional demands will be identified.

Emotional demands at work have been measured with several different sets of items. In 1994, Veldhoven and Meijmann formulated items concerning emotional demands at work in the Questionnaire on the Experience and Assessment of Work (QEAW) (35). The most widely used questions on emotional demands are perhaps the questions from the Copenhagen Psychosocial Questionnaire (COPSOQ) (36), where questions on emotional demands first appeared in 2005 (37). Today there is free access on the internet to emotional demands questions in the QEAW (35), Demand-Induced Strain Compensation Questionnaire (DISC) (38, 39), and the COPSOQ (40). The Table 1 displays the most used items on content-related and perceived emotional demands. In the table, items are colored in relation to the emotional dimension (perceived, content-related, or emotional labour), due to items impurrity the categorisation is debateable.

**Table 1: Summary of the most commonly used scales on emotional demands, year of publication and reference.**
***The items are coloured based on what the emotional dimension assessed: content-related items are blue, items concerning the perception of demands are green, and emotional labour items are orange. The table focuses on scales presenting content-related, and perceived emotional demands items, alone or in combinations.***

| **Year of publication (Reference)** | **Title** | **Questions** | **Response categories** |
|---|---|---|---|
| Van Veldhoven and Meijman (1994)<br><br>http:// www.marcvanveldhoven.com /ques.html | Questionnaire on the experience and assessment of work (QEAW) | • Does your work demand a lot from you emotionally?<br>• Are you confronted with things that affect you personally in your work?<br>• Do others call on you personally in your work?<br>• Do you feel personally attacked or threatened in your work?<br>• Do you have contact with difficult clients or patients in your work?<br>• In your work, do you have to be able to convince or persuade people?<br>• Does your work put you in emotionally upsetting situations? | Response categories:<br>Always, Often, Sometimes, never |
| Ohlson, Söderfeldt, Söderfeldt, Jones, and Theorell (2001) (41) | Developed specifically for the study (Target group: Human service organization) | • Do you think that your work tasks are emotionally demanding, entailing a strong commitment to the clients?<br>• Are you bothered by not being able to switch off thoughts about work during your free time?<br>• Do you think that too much responsibility rests on you? | 5-point scale ranging from 'never' to 'always' |
| Kristensen, Hannerz, Høgh, and Borg (2005) (42) | The Copenhagen Psychosocial Questionnaire (COPSOQ) | • Does your work put you in emotionally disturbing situations? (A)<br>• Is your work emotionally demanding? (B)<br>• Do you get emotionally involved in your work? (B) | A. Always, Often, Sometimes, Seldom, Never/hardly ever.<br>B. To a very large extent, To a large extent, Somewhat, To a small extent, To a very small extent. |
| Muntaner, Li, Xue, Thompson, Chung, and O'Campo (2006) (43) | Inspired by Söderfeldt et al. (44) | **In the past six months…**<br>My consumer(s)<br>• Hits me or becomes violent<br>• Has a lot of physical pain<br>• Has difficulty communicating with me<br>• Is very sick<br>• Is overly dependent on me<br>• Refused needed medical care | The response format is a 5 point LIKERT scale. |

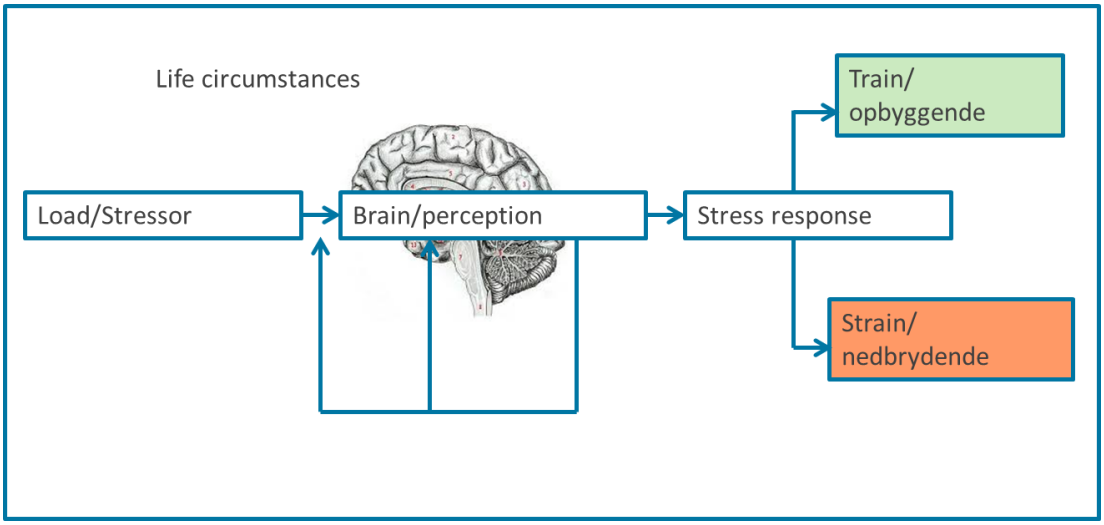
| | | | |
|---|---|---|---|
| | | • I don't have time to talk to my consumer<br>• I cannot provide my consumer with things that they need such as food, soap, towels, clothing<br>• I don't have enough time to comfort the consumer emotionally | |
| Notelaers, De Witte, Van Veldhoven, Vermunt (2007) (45) | Short Inventory to Monitor Psychological Hazards (SIMPH) | • Is your work load heavy from an emotional point of view?<br>• Are you confronted in your work with elements which affect you personally?<br>• Does your work put you in emotional situations? | Response categories:<br>Always, often, sometimes, and never |
| Van Veldenhoven, Meijman, Broersen, Fortuin (2007) (7) | Applied by Taris and Schreurs (7) | • Are you in your work confronted with things that really upset you emotionally?<br>• Is your work emotionally demanding?<br>• In your work, do you feel personally threatened by clients?<br>• Does your work require you to deal with emotionally laden situations? | Scale: 1='never' – 5='always' |
| Kolstad, Thomsen, Hansen, and Kærkaard (2007) (46) | PRISME (37, 47-50) | **A. Person-related emotional demands (perceived)**<br>a. Is your work emotionally demanding?<br>b. Do you get emotionally involved in your work?<br>**B. Content-related emotional demands**<br>a. Do you have to care for the emotional needs of others?<br>b. Do you have to deal with others' grieves and worries?<br>c. Do you have to cope with the suffering or death of others?<br>d. Do you have to deal with "difficult" patients, clients, students etc.?<br>e. Are you at risk of making mistakes that may hurt other people?<br>**C. Patient-care emotional demands**<br>a. On average, how many times daily are you involved in procedures that are painful for the patient?<br>b. In the last month, how many consultations have you had with patients or relatives about a poor condition of the patient?<br>c. In the last month, how many patients that you have been in direct contact with have died?<br>d. In the last month, how many times have you participated in surgery that did not work out as planned or had a high risk? | A, B and D) Scored: 1='to a very large extent', 2='to a large extent', 3='to some extent', 4='to a small extent' and 5='to a very small extent'<br>C) Scored: 1='none, 2='one', 3='two-three, 4='four-five', 5='six-ten' and 6='more than ten'. |

| | | | |
|---|---|---|---|
| | | **D. Emotional enrichment**<br>a. Do you feel that your work with patients, clients, students etc. is emotionally enriching and satisfying? | |
| De Jonge, Dormann, Van Vegchel, Von Nordheim, Dollard, Cotton and Van den Tooren (2009)(38) | The DISC Questionnaire English Version 2.1 | **After having had one year of experience in a job similar to mine...**<br>• Employee X will have to deal with people (e.g. clients, colleagues or supervisors) who have unrealistic expectations.<br>• Employee X will have to control his/her emotions to complete tasks within a limited time frame.<br>• Employee X will have to deal with people (e.g. clients, colleagues or supervisors) whose problems touch him/her emotionally.<br>• Employee X will have to deal with people (e.g. clients, colleagues or supervisors) who get easily angered towards him/her.<br>• Employee X will have to do a lot of emotionally draining work.<br>• Employee X will have to display emotions (e.g. towards clients, colleagues or supervisors) that are inconsistent with his/her current feelings. | Never or very rarely, rarely, occasionally, often, very often or always. |
| Pejtersen, Kristensen, Borg, and Bjorner (2010) (36) | The Copenhagen Psychosocial Questionnaire (COPSOQ-II) | • A) Does your work put you in emotionally disturbing situations?<br>• A) Do you have to relate to other people's personal problems as part of your work?<br>• B) Is your work emotionally demanding?<br>• B) Do you get emotionally involved in your work? | A) Always, Often, Sometimes, Seldom, Never/hardly ever<br>B) Always; Often; Sometimes; Seldom; Never/hardly ever; Not relevant |

The items relating to emotional demands are distributed within the following areas: unmet care needs, threats and violence, demands for hiding emotions (emotional labour), risk of making mistakes, witnessing severe physical or psychological malaise, poor communication or contact with clients, and the personal perception of emotional demands at work. In relation to home-care work, demands such as unfair treatment and clients' family abuse have been studied (12). Whether all types of items are included as part of the emotional demands scale varies. Few scales are designed to measure the content-related specific demands at work separate from the employee's experience or perception of demands (
Table 1)(43, 46). For example the item "Do you have to relate to other people's personal problems as part of your work?" questions the specific content of the work, whereas the item "Is your work emotionally demanding?" questions how the worker perceives the work. These items both originate from one scale in the COPSOQ-II (see Table 1). Different employees will perceive the same work content differently, a division of the items on content-related and perceived demands allows an insight into these matters.

The stress model Ursin and Eriksen (2004) proposed, entitled the Cognitive Activation Theory of Stress (CATS)(51), differentiates between exposure to and perception of a stressor. The model shows how a stressor affects the brain and results in a stress response. The main component in CATS is the feedback to the brain from the outcome of the response, which alters both the employee's exposure to the stressor and his or her perception of the stressor Figure 2. According to this model, an employee may consider a stressor to be exciting or threatening depending on previous experiences and expectations of the outcome. The brain's processing explains why people react differently to different stressors (51). If we incorporate the concept of emotional demands into this model, the content-related emotional demands can be equated with the stressor, whereas perceived emotional demands may result from the employee's processing of the stress in the brain.

**Figure 2: Illustration of the cognitive activation theory (Ursin and Eriksen 2004)(51)**




In practice, what does this differentiation mean? Being able to distinguish between the specific content of the work and the person's perception of the work is important if an association is found empirically and interventions are planned accordingly. Very different intervention approaches may be required, depending on whether the risk arises from the nature and content of the work or the individual's perception of the work. Appling content-related demands could also be assumed to be less effected by reporting bias due to e.g. the individual workers' interpretation of his or her psychological working conditions, low mood, or personal characteristics (52).

Emotional demands at work were first presented as something that negatively affected an employee's health and well-being (18). In accordance with the CATS model, however, emotional demands do not necessarily have a negative impact on the employees; such also depend on the personal perception of the situation. Ashforth et al. (1993) suggested that the feelings in relation to work may be genuine or that the management of feelings eventually may become routine and effortless and therefore not a source of stress (53). Furthermore, the work content could impose a positive experience e.g. if a client shows gratitude, or simply when a patient's health is improving. The possible positive effects of doing person-related work have been mentioned previously when discussing consequences of emotional demands (10, 12, 22).

In the present study, separate effects of perceived emotional demands and content-related emotional demands will be examined.

## 2.2 MENTAL HEALTH

Emotional demands have been associated with various mental health conditions (32, 54-56). Here, the focus is on symptoms of exhaustion, depressive symptoms, and clinical depression. The conditions will be examined in the following section, and each section ends with a summary of the existing knowledge related to emotional demands at work. This information is also summarized in Tables 2, 4, and 5.

### 2.2.1 DEPRESSION

Depression is an affective disorder characterised by depressed mood, loss of interest or pleasure, and decreased energy accompanied by symptoms such as feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration (57). Depression is regarded by the World Health Organisation as the leading cause of disability in the world (58). The lifetime prevalence is estimated to be about 15% in a general population and with a point-prevalence of about 5% (59). In Denmark, the corresponding prevalence is estimated to be between 17 to 18% and 3 to 4 %, respectively (60). Additionally, the intake of antidepressants has increased in recent decades (59). In 2011, over 460,000 Danes were prescribed an antidepressant (8.3% of the population) (59). Because of lost productivity, the estimated costs of depression per year is DKK 3,110 million (60).

Depression can be long-lasting, is often recurrent, and can be chronic (61). The duration of a single episode is, in most cases, less than six months. However, one study found that 20% had not recovered within 24 months (61). Consequences of depression affect all aspects of life and health (57, 58). The cost of depression is thus substantial for the individual, the family and society as a whole (60, 62, 63).

#### *2.2.1.1 Ethology*

A complex of social, psychological, biological and genetic factors and, especially, frequency of and interaction among these factors may cause depression. The ethology, however, has not been clearly established (64). Family history and previous episodes of depression predispose one to the disease. Stressful life events with a particular importance of events in early life (65), changes in hormone levels, personality and a variety of psychosocial factors are believed to be causes of depression (66). Depression has also been associated with life circumstances such as socioeconomic status (low), education (low), age (high), alcohol consumption and smoking. The disease occurs twice as often in women as in men (67).

Changes in the brain have been observed among depressed patients, such as increase of white matter lesions, atrophy of cerebral structures, and decreased blood flow (68-70). Neurotransmitter disturbances have been found for subgroups of depressed patients such as in the degradation of serotonin, noradrenaline and dopamine (64). The medical treatment targeting these transmitter systems improves the condition for some depressed patients. Genes expressed in receptors or otherwise in connection with transmitter systems have been particularly studied (especially 5-HTT-gene). The risk of depression is higher among people with a specific genetic structure (71). This gene structure is, however, not regarded as a sufficient cause of the disease (71).

Hypercortisolemia and abnormal dexamethasone-suppressions tests have been found among half of depressed patients (72). These abnormalities can lead to increased blood pressure, blood sugar, and lipids and are over time unhealthy to the body. It is, however, unknown whether the cortisol changes are involved directly in the pathogenesis of depression (72). This has been suspected due to observed clinical relevant depression among 50 to 70% of patients with Cushing's syndrome (72). The causes and mechanisms underlying what can be diagnosed as depression may thus vary from patient to patient.

*2.2.1.2 Measurements*

Most people will, as a part of life, experience episodes with depressed moods. Symptoms may be few and short-termed, or, at the other end of the scale, extremely debilitating and long-lasting. To distinguish mood changes from mental disorders, different approaches can be employed.

In Denmark, depression is diagnosed by an examination that, according to national recommendations, is based on the International Classification of Diseases (ICD-10) diagnostic criteria (73). The ICD-10 classification defines depression as a state with several simultaneous symptoms that have been present for two weeks or more. The depressed state should be significantly different from what is habitual for the patient and without an organic cause. The number of existent core-symptoms (depressed mood, loss of interest and pleasure, and reduced energy) and accompanying symptoms (reduced self-confidence and self-esteem, guilt and self-blame, suicidal thoughts or acts, poor concentration and attention, agitation or slowing of movements, disturbed sleep, change in appetite or weight) determines the severity. Depressive episodes can be divided into mild, moderate, and severe (73). Another system by which depression can be clinically diagnosed is the Diagnostic and

Statistical Manual of Mental Disorders (DSM) most used by mental health professionals in the United States (73).

In epidemiological studies, self-administrated questionnaires can be used to measure symptoms of depression, e.g. the Major Depression Inventory (74), the Hospital Anxiety and Depression Scale (75), the Center for Epidemiological Studies – Depression Scale (76), the Beck Depression Inventory (77), the Common Mental Disorder Questionnaire (78), or the Symptom Check list (79).

The golden standard for a research diagnosis of depression is the structural clinical interview conducted by trained interviewers and relying on the diagnostic criteria for depressive episodes, i.e. either the DSM or the ICD. Manuals for clinical interviews based on the diagnostic criteria are the Composite International Diagnostic Interview (CIDI) or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (80). Other proxy measures for diagnosis used are prescription antidepressant medicine in register studies or hospital admissions due to depression (19, 54).

The advantage of self-reported questions and registers is lower expenses, and the ability to determine the degree of depression and changes in the degree more regularly. Advantages of the structural clinical interviews are, however, the possibility of more precise, systematic, validated, and generalizable assessments, which are less dependent on the individual's own appraisal.

### 2.2.2 EMOTIONAL DEMANDS AT WORK AND DEPRESSION

A number of studies document the relationship between emotional demands and depression (8, 12, 19, 29, 54, 56). In a Danish context, a register study by Wieclaw et al. (2006) found that depression was most common among specific occupational groups doing human service work, with health and social services being particularly at risk, as opposed to education professionals and social workers (16). The possibility that this result could be due to emotional demands at work was suggested (16). Cross-sectional studies are not sufficient when aiming at estimating causal relationships. Longitudinal studies of content-related and/or perceived emotional demands at work and depression are reviewed in Table 2 and summarized below.

Prospective Scandinavian register-based studies have been conducted among employees (8, 29, 54)

Table 2). Two studies with data from The Danish Work Environment Cohort Study demonstrate consistent, statistically significant associations between perceived emotional demands at the baseline and during subsequent use of antidepressants (8, 29), as do a study with data from the same cohort supplemented with data from the Swedish Longitudinal Occupational Survey of Health (54). The follow-up periods in these studies vary from one to five years. One Danish register-based study by Thielen et al. (2011) show a tendency toward an elevated risk among women, although not statistically significant (30). This study differs from the other register-based studies by including only working men and women aged 40 to 50 years (30).

Longitudinal studies using multiple measures of emotional demands and with depressive symptoms as outcome generally confirm the positive findings (12, 43, 56), although not statistically significant when controlled for anxiety score, as in the study by Andrea et al. (2004). Kim et al. (2013) measured emotional demands by specific content-related emotional demands scales assessing the home care workers ability to meet the need of the clients (unmet care needs), dealing with violent clients (client-provider interactions), witnessing sickness (client health), unfair treatment by a client or family members (unfair treatment), and verbally or physically abuse by client's family (client's family absue) (12). Among the 1062 employees only unmet care needs was related to depressive symptoms after half a year (12).

Emotional demands have also been associated with hospitalization for depression in a case-control study based on Wieclaw et al.'s (2008) job-exposure matrix of work-related psychosocial exposures, although only for women (19). Applying the job-exposure-matrix, the researchers estimated exposures by job group, thus, exposure was not measured on the individual level (19).

Overall, studies have documented an increased risk of depression in relation to emotional demands. An important strength of previous research is the existence of several longitudinal studies, increasing the reliability of an actual causal relationship between emotional demands as exposure and subsequent depression. However, the existing research suffers from some limitations, because of uncertainties related to the measurement both of exposure and of outcomes.

One methodological characteristic of the previous studies is that the exposure is self-reported, with the exception of Wieclaw et al.'s, which applied a job-exposure-matrix. The studies may thus be subject to a reporting bias, because a pre-clinical state of depression or personality traits may affect the individual's

perception and thus his or her reporting of the work environment. This could also be relevant in longitudinal studies of depression, since depression may exist at a pre-clinical stage. As mentioned earlier, reporting bias may be particularly pronounced for items concerning perceived emotional demands compared to the content-related items.

Regarding the outcome measures in existing studies, only proxy-measures of depression have been applied. Anti-depressants are used to treat disorders other than depression (e.g. anxiety, sleep disorders, bulimia, etc.) (8, 81). Thus, there is a lack of longitudinal studies conducted in a larger general working population with the use of a differentiated exposure measure and a valid clinical outcome.

**Table 2: Longitudinal studies investigating the association between emotional demands and depressive symptoms/depression**

| Longitudinal studies on emotional demands and depression | | | | | |
|---|---|---|---|---|---|
| **Longitudinal studies of emotional demands and antidepressant medicine** | | | | | |
| **Reference (Year)(ref)** | **Design** | **Confounders/ Effect modifiers** | **Emotional demands** | **Depression** | **Conclusion** |
| Madsen et al. (2014)(29) | Population: The Danish Work Environment Cohort Study (n = 6,096) and the Swedish Longitudinal Occupational Survey of Health (n = 3,411). Age 20-59 years.<br><br>Excluded: Individuals with poor self-reported baseline mental health or antidepressant purchases within 8.7 months before baseline.<br><br>Follow-up: 2 years and 6 month<br><br>Statistical analysis: Cox-regression (HR) | Sex, age, marital status, education, income, and employment status | COPSOQ | National registers on antidepressants | HR: Emotional demands (high vs. low) = 1.73 (95% CI: 1.41–2.13)<br>If quality of leadership was poor HR = 1.84 (95 % CI: 1.32–2.57) or good HR = 1.70 (95 % CI: 1.25–2.31) |
| Magnusson Hanson et al. (2013)(54) | Population: The Danish Work Environment Cohort Study (n = 6,418) and the Swedish Longitudinal Occupational Survey of Health (n = 3,661)<br>Age: 20-59 years.<br>Excluded: Individuals with poor self-reported baseline mental health or antidepressant use before baseline.<br><br>Follow-up: 1 year<br><br>Statistical analysis: Cox-regression (HR) | Model 1: Sex, age, cohabitation, education, income, and employment status<br>Model 2: Model 1 + depressive symptoms, sickness absence, and self-rated health. | COPSOQ | National registers on antidepressants | Model 1:<br>HR: Emotional demands (high vs. low) = 1.74 (95% CI: 1.54–1.95)<br>Model 2:<br>HR: Emotional demands (high vs. low) = 1.45 (95% CI: 1.24–1.66)<br>(stronger associations were found for drug use >179 ddd/year) |

| | | | | | |
|---|---|---|---|---|---|
| Thielen et al. (2011)(30) | Population: The Danish Longitudinal study on work, unemployment and health (n = 4661).<br>Age: 40 and 50 years.<br>Excluded: Unemployed, current and past users of antidepressants, had major depression (within 2 weeks).<br><br>Sex stratified<br>Follow-up: 3.5 years<br><br>Statistical analysis: Logistic regression (OR) | Model 1: Lifestyle, social relationships, co-morbidity, socio-demographic factors<br>End-model: Model 1 + other work characteristics and major depression inventory score (baseline) | COPSOQ | National registers on antidepressant | Model 1:<br>Women, OR=1.36 (95% CI: 0.83–2.22)<br>Men, OR=1.04 (95% CI: 0.53–2.03)<br>End-model:<br>Women, OR=1.10 (95% CI: 0.65–1.85)<br>Men, OR=0.88 (95% CI: 0.43–1.77) |
| Madsen et al. (2010)(8) | Population: The Danish Work Environment Cohort Study (n = 4,958)<br>Excluded: Individuals with poor self-reported baseline mental health or antidepressant before baseline.<br><br>Follow-up: 5 years<br><br>Statistical analysis: Logistic regression (OR) | Sex, age, cohabitation, parental status, and socioeconomic position | COPSOQ | National register on antidepressant | Model 1:<br>Emotional demands (high vs. low) OR=1.51 (95% CI: 1.18–1.94)<br><br>(Type of work: healthcare OR=5.63, educational=5.76, social OR=9.91, and customer service OR=0.84 compared to non-person-related work) |
| **Longitudinal studies of emotional demands and depressive symptoms** | | | | | |
| **Reference (Year) (ref)** | **Design** | **Confounders** | **Emotional demands** | **Depression (symptoms)** | **Conclusion** |
| Kim et al. (2012)(12) | Population: Homecare workers (n = 1062) from Los Angeles<br>Data collected by telephone interviews<br><br>Follow-up: ½ year (June 2003-September 2003 and December 2003-February 2004). | Sex, age, marital status, education, ethnicity, and life events | Scales:<br>a) Unfair treatment<br>b) Client's family abuse<br>c) Unmet care needs<br>d) Client health<br>e) Emotional suppression | The Center for Epidemiologic Studies Depression Scale | Adjusted model: Unmet care needs; OR=1.19 (95% CI: 1.01–1.41)<br>(The other emotional demands scales are not statistically significant in the follow-up) |

| | | | | | |
|---|---|---|---|---|---|
| Muntaner et al. (2006)(43) | Population: Nursing assistants (n = 241)<br><br>Follow-up: 2 years | Age, race, marital status organisations, and country-level | 6 items<br>Ref.: Ohlson et al 1997 and Söderfeldt et al. 1997 (44, 82) | The Center for Epidemiologic Studies Depression Scale | Regression coefficient (standard errors and p-value) =0.32 (0.14; p<0.05) |
| Andrea et al. (2004)(56) | Population: The Maastricht Cohort study on fatigue at work (n = 7,472)<br><br>Follow-up: 2 years and 8 month | Sex stratified<br>Age, education, living alone, and chronic condition | QEAW + self-formulated items. | Hospital Anxiety and depression scale (HAD-scale) | Women, emotional demands (high vs. no) OR=2.32 (95% CI: 1.22–4.42)<br>Men, emotional demands (high vs. low) OR=4.21 (95% CI: 3.07–5.78)<br>(Furthermore, a final model is adjusted for anxiety score: women, OR=1.29 (95% CI: 0.57–2.96) and men, OR=1.60 (95% CI: 1.11–2.31)) |
| **Studies of emotional demands and depressive diagnose (patient)** | | | | | |
| **Reference (Year) (ref)** | **Design** | **Confounders** | **Emotional demands** | **Depression** | **Conclusion** |
| Wieclaw et al. (2008)(19) | Population: The Danish Psychiatric Central Research Register (psychiatric patients with depression or anxiety) (n=14,166) and controls (n=58,060) from Statistics Denmark's Integrated Database for Labour Market Research. Age: 18-69 years.<br><br>Design: Job Exposure Matrix was applied to assess psychosocial working conditions in a population-based nested case-control study. | Marital status, having children, income, education, level of unemployment, residence, nationality<br><br>Sex stratified | Exposures were estimated by job group applying the job-exposure-matrix | Patient register | Women, Emotional demands (high vs. low) IRR=1.39 (95% cl: 1.22–1.58)<br>Men, Emotional demands (high vs. low) IRR=1.12 (95% CI: 0.96–1.30)<br>(Working with people were associated with depression in men and women) |

### 2.2.3 EXHAUSTION

Exhaustion is not recognized as a medical condition, but represents a set of symptoms that constitute a syndrome (83). Hereafter we will see that different approaches seem to characterise exhaustion as a condition of chronic tiredness that develop over a prolonged period of time. In this section, I will review the history and development of the concept of exhaustion. Finally, I will look in to the causes, correlations, and consequences of exhaustion using existing epidemiological findings.

#### *2.2.3.1 The history and measurement of exhaustion*

Emotional exhaustion has been described as the core symptom of burnout (9, 84, 85). Burnout was originally a grassroots term for prolonged occupational stress among human service workers, as described by Herbert Freudenberg and Christina Maslach independently in the 1970s (86, 87). Maslach and Jackson developed the most widely used questionnaire to measure burnout; the Maslach Burnout Inventory (MBI) (84-86), which included the measurement of three psycho-social dimensions: emotional exhaustion (to be overworked and drained of emotional resources), depersonalization (a negative attitude towards the recipient of care) and reduced personal accomplishment (a feeling of reduced competence and success in work) (84, 86). However, research has shown that the MBI factors are separate concepts and a coherent cluster of factors pointing to one underlying syndrome has not been found (88, 89).

Based on the desire to generalize the questionnaire to non-health professionals, Maslach et al. developed the MBI-General Survey to be applicable to all employees in the workforce (84, 89). And later, Pines and Aronson developed another widely used questionnaire, the Burnout Measure (84). This instrument was even broader in its approach as it was applicable to all persons, within and without the workforce. It measured physical, emotional and mental exhaustion (90). Pines and Aronson thus referred to exhaustion as the core of the phenomenon in accordance with subsequent research (9, 84, 91), which also indicate that this subscale is the most robust and reliable (84).

Kristensen and colleagues (2005) developed a way to integrate the former approaches and retained the focus on exhaustion (89). They developed the Copenhagen Burnout Inventory (CBI) that measured fatigue and exhaustion in three domains: 1) personal or generic burnout–to be answered by all human beings 2) work-related burnout–to be answered by individuals having a paid job, and 3) the client-related burnout–to be answered by individuals doing person-related work (89). It was especially important to the authors that the

questions included in the CBI were generalizable, especially across professions (89). The preliminary validity testing was satisfactory. Today, the CBI is publicly available (

Table 3). Other scales used to measure exhaustion are the Oldenburg Burnout Inventory and the Shirom-Melamed Burnout Measure. The first scale assesses the dimensions of exhaustion and disengagement, and the last assesses the dimensions of physical fatigue and cognitive weariness (92).

Recently, the Swedish Board of Health and Welfare have provided tentative diagnostic criteria for chronic stress, termed Exhaustion Disorder (ED) (83, 93) and self-rating scales have been developed in order to measure ED, that is the Karolinska Exhaustion Scale, the Karolinskea Exhaustion Disorder Scale and the Stress-Related Exhaustion Disorder Scale (83, 93, 94). According to research so far, it is questionable whether ED is synonymous with burnout (94). The reliability of the ED scale is shown to be satisfactory in terms of being different from depression and anxiety (83). Further validating studies are in progress.

In order to separate causes and effect in measurement of exhaustion, the personal burnout dimension from the CBI questionnaire (six items) was used in the present study (Table 3). This dimension is characterized by a state of prolonged physical and psychological exhaustion (89). It does not explicitly include the work perspective, and thus allows for a separate estimation of work environment characteristics and symptoms of exhaustion. In occupational epidemiology, the MBI scale is the most widely used. The referenced literature in the following thus primarily refers to the exhaustion dimension of the MBI (emotional exhaustion).

Table 3: Exhaustion items originating from the Personal Burnout Scale in the Copenhagen Burnout Inventory.

| Questionnaire | Questions | Response category |
|---|---|---|
| **Personal Burnout from the CBI (=a state of prolonged physical and psychological exhaustion)** | • How often do you feel tired?<br>• How often are you physically exhausted?<br>• How often are you emotionally exhausted?<br>• How often do you think: ”I can’t take it anymore”?<br>• How often do you feel worn out?<br>• How often do you feel weak and susceptible to illness? | Response categories: Always, Often, Sometimes, Seldom, Never/Almost never.<br>. |

*2.2.3.2 Causes, correlates, and consequences*

Several work-related factors have epidemiologically been related to the development of exhaustion. Alarcon et al. (2011), using samples from all types of occupations, found in a review that job demands played a significant role in the development of exhaustion, and thus were not restricted to person-related professions (95). The review further proposed that role conflict, workload, and role ambiguity were important predictors of exhaustion (95). A recent review of the literature showed that quantitative demands, lack of support from supervisors and lack of support from the workplace in general contribute to exhaustion, while work-control was protective against exhaustion (96).

Reasons for exhaustion outside the labour market have been less studied, and the causal relationship is unclear; however, younger age, sex (women), being unmarried, and lifestyle have been factors related to exhaustion (84, 97). A review by Grossi et al. (2015) showed a strong association between disturbed sleep and ED and, to a lesser degree, the association between ED and impaired working memory (93). Individual differences or personal characteristics that are relatively stable over situation and time (personality traits) may play a role in the development of exhaustion (92). Hardiness as a personality trait is protective against exhaustion, whereas type-A behaviour, neuroticism, emotional stability, and having a passive coping style have been associated with increased risks of exhaustion (84, 98). However, it cannot be ruled out that the observed

relationships between personality traits and exhaustion are due to an artefact resulting from overlap in concepts and included items as well as a negative affectivity bias (84).

Research has identified a persistent relationship between exhaustion and physical and mental health outcomes (84, 92). With regard to physical health, exhaustion is shown to predicted insomnia (99), type-2-diabetes (100), gastroenteritis, the common cold (101, 102), coronary heart disease, headaches and musculoskeletal disorders (101, 103). Some studies show an increase in saliva cortisol (104, 105) whereas others show a decrease (106, 107) or normal (108). Furthermore, exhaustion is found to predict sickness-related absence (84, 109) and reduced job performance (110).

Research has also shown that exhaustion leads to poor mental health. A large body of research documents the relationship between exhaustion and depression or depressive symptoms (111-116). However, the overlap and temporal delimitations between exhaustion and depression have been widely debated (111, 116). States of prolonged exhaustion, like burnout and ED, have been suggested to be included among the affective disorders of depression and anxiety (83). Åsberg et al. (2014) stated that ED is distinct from depression since low mood is not a prerequisite for ED (83). Furthermore, they mention that anti-depressive drugs do not have an effect on people with ED (83). Generally, it is agreed that exhaustion and depression have a significant overlap of symptoms and but at the same time completely redundant (112).

### 2.2.4 EMOTIONAL DEMANDS AT WORK AND EXHAUSTION

Studies of exhaustion have mostly been done among health care workers (Table 4), which may be a consequence of the history of the concept as described. Conceptually, a relationship between emotional demands at work and exhaustion can be expected, and this specific relationship has also been the subject of great research interest. Compared with depression, for example, a similar body of literature found through a search in PubMed revealed four times as many studies that include emotional demands at work and burnout than emotional demands at work and depression[2].

[2] Date: 28.05.2016: Search, Query, Items found: #1"Search ((emotional demand*[Title/Abstract]) AND work [Title/Abstract]) AND burnout [Title]",12.#2"Search (((emotional demand*[Title/Abstract]) AND work [Title/Abstract]) AND depression[Title])",3.

A number of studies, mostly cross-sectional, have documented an increased risk of exhaustion in relation to emotional demands at work. Longitudinal studies have been conducted, including a few larger studies. Table 4 summarize studies of work-related emotional demands and exhaustion, divided into cross-sectional and longitudinal studies. Furthermore, Table 4 indicates whether the scales regarding emotional demands represent perceived, content-related, or combined emotional demand items.

In the very large cross-sectional study among 11,361 female Dutch home care employees, Taris et al. (2008) found an association between emotional demands assessed by a mixed scale of perceived and content-related questions and exhaustion (MBI) (7). Similarly, positive associations were found cross-sectionally in larger studies that included human service employees (n=2,391)(117) nurses (n=1,561)(118) and higher education employees (n=1,012)(119). However, emotional demands and exhaustion were measured differently in the three studies (Table 4) which compromised the comparison. In another Dutch cross-sectional study among health care workers (9), questions regarding perceived emotional demands and content-related emotional demands were divided into scales concerning “general emotionally demanding work” (i.e. perceived emotional demands), “confrontation with death, dying, illness and suffering” (i.e. content-related emotional demands), perceived emotional demands were associated with exhaustion (MBI) whereas content-related demands were not (9).

Longitudinal studies have also reported mainly positive relationships between emotional demands and exhaustion (6, 31, 117, 120-122). Borritz et al. (117) measured exhaustion in a similar way to the present study among human service workers. The positive association between baseline emotional demands and exhaustion three years later were not statistically significant in the final adjusted model, including adjustment for baseline exposure and other psychosocial factors; however, the effect was statistically significant when controlled only for the baseline sociodemographic variables. All other longitudinal studies had shorter follow-up periods, typically of one year. Van Vegchel et al. (2004) found an association between emotional demands (e.g. “handling troublesome clients”) and exhaustion (emotional exhaustion from MBI) among social insurance employees. And Van de Ven et al. (2013) showed similarly an association among employees in the technology sector (31), thus an association has been found not only among health care professionals.

In the study by Sundin et al. (2011) the longitudinal association between content-related emotional demands and exhaustion was examined, other longitudinal studies used perceived emotional demands scales or mixed

scales (content-related and perceived demands) (Table 4). The experience of "pain and death" in patients, "Patient and relative needs", and "professional worries for making mistakes" were examined among nurses (120). In order to explore changes in exposures over time and the association with exhaustion, Sundin et al. constructed four categories of participants, namely: continually low, decreasing, increasing, or continually high (120). They identified professional worries of making mistakes as a risk factor for exhaustion (OR = 2.56, 95%CI = 1.34-4.82). When professional worries were analysed according to the exposure categories, only the results for the continually highly exposed group were statistically significant (OR = 3.52, 95%CI = 1.68-7.36)(120). The grouping resulted in a small number of participants, which may explain the non-significant results, and will, together with the dichotomised exposures, result in loss of information. Also, this study did not control for a baseline level of exhaustion and changes in status from baseline till follow-up in potential confounders.

The differences in previous studies and methodological limitations with regard to measurement of exposure and outcome make comparison of results difficult. Only a limited number of the studies have included an adjustment for a baseline exhaustion level (6, 117, 121), and none have accounted for cross-sectional associations at baseline and at follow-up. In the longitudinal studies, the follow-up periods were generally short (Table 4), populations were specific (e.g. nurses, insurance people), and few potential confounders were included. Thus, studies including a general population, longer follow-up periods, and a larger number of potential confounders could be beneficial to the field. One study have examined isolated content-related emotional demands in a longitudinal design (120). Overall, there is a need for studies including a specific content-related measure of emotional demands and a general measure of exhaustion in order to test the earlier longitudinal findings.

**Table 4: Studies investigating cross-sectional and longitudinal associations between emotional demands (perceived (1), content-related (2) or combined (3)) and exhaustion.**

| Cross-sectional studies of emotional demands and exhaustion | | | | | |
|---|---|---|---|---|---|
| **Reference (Year) (ref)** | **Population** | **Confounders** | **Emotional demands**<br>**1) Perceived**<br>**2) Content-related**<br>**3) Combined scale** | **Exhaustion** | **Results** |
| Freimann et al. (2015)(123) | 404 Nurses | None | 1 | Exhaustion (CBI) | Positive association |
| Tuxford et al. (2014)(5) | 556 Primary school teachers | Employment classification Deep acting, Surface acting, Emotion work, Social support Teaching self-efficacy | 3 | Exhaustion (MBI) | Positive association |
| Zis et al. (2014)(124) | 263 Medical residents | Age, sex, marital status, specialty, supervisor support, workload, etc. | 3 | Exhaustion (MBI) | No association |
| Cho et al. (2013)(125) | 746 Nurses | Age, sex, marital status, academic degree, years in profession specialty (general, oncology, ICUs) | 1 | Exhaustion (CBI) | Positive association |
| Kozak et al. (2013)(126) | 409 Human service personal (for intellectual disabled) | Age, sex, professional experience, alternating shifts, and stressed by aggression | 1 | Exhaustion (CBI) | Positive association |
| Peng et al. (2010)(127) | 418 Insurance salespersons | Sex, education, tenure. | 3 | Exhaustion (MBI) | Positive association |
| Taris et al. (2009)(7) | 11,361 Home care workers (female) | Quantitative demands, control, support, and age | 3 | Exhaustion (MBI) | Positive association |

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|---|---|---|---|---|---|
| De Jonge et al. (2008)(9) | 826 Health care workers (elder care) | Age, sex, education, working hours per week | 1 and 2<br><br>2a) illness and death<br>2b) patient-related | Exhaustion (MBI) | For perceived emotional demands (1): Positive association<br>For content-related emotional demands (2a): No association<br>For content-related emotional demands (2b): No association |
| Sundin et al. (2007)(118) | 1,561 Nurses | Age, sex, marital status, profession, on sick leave, work outside work, job demands, support, and more | 2 | Exhaustion (MBI) | Positive association |
| Borritz et al. (2005)(117) | 1,772 human service workers | Age, sex, cohabitant status, number of children, education, job function, socio-economic status, health-related life style. | 1 | Exhaustion (CBI) | Positive association |
| Bakker et al. (2005)(119) | 1,012 Higher education employees | Separate analyses for work characteristics | 3 | Exhaustion (MBI) | Positive association |
| De Jonge et al. (1999)(128) | 212 health care workers | Age, sex | 2 | Exhaustion (MBI) | No association |
| **Longitudinal studies of emotional demands and exhaustion** | | | | | |
| **Reference (Year)** | **Population (Follow-up period)** | **Confounders** | **Emotional demands**<br>**1) Perceived**<br>**2) Content-related**<br>**3) Combined scale** | **Exhaustion** | **Results (Interaction and statistical significance - S/NS)** |
| Idris et al. (2014)(121) | 117 employees from 27 Malaysian private sector organizations (3-month follow-up) | Psychosocial safety climate and exhaustion (T1) | 1 | Exhaustion (MBI) | Effect (SE): 0.17 (0.08), $p<0.05$ |
| Huynh et al. (2013)(122) | 126 volunteer fire-fighters (1 year follow-up) | None | 3 | Exhaustion (MBI) | Cronbach's alpha: 0.31, $p<0.001$ |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | (NS for ”family/friends-support) |
| Van de Ven et al. (2013)(31) | 711 employees in the technology sector<br>(1-year follow-up) | None | 3 | Exhaustion (a subscale of MBI) | Pearson correlation: 0.29, p<0.05<br><br>(NS for job resources, S for emotional support seeking) |
| Sundin et al. (2011)(120) | 555 nurses<br>(1 year follow-up) | Age, sex, marital status, number of years in profession, no. of years at current workplace. | 2<br><br>Scales:<br>- “Pain and Death”<br>- “Patient and relative needs”<br>- ”Professional worries” | Exhaustion (MBI) | Univariate:<br>“Pain and Death”<br>OR:=1.53 (0.83, 2.82)<br>“Patient and relative needs”<br>OR=1.80 (0.97, 3.34)<br>”Professional worries”<br>OR=2.68 (1.44, 5.00)<br><br>Adjusted:<br>”Professional worries”<br>OR=2.56 (1.34, 4.82) |
| Lorente Prieto et al. (2008)(129) | 274 school teachers<br>(8 month) | Age, sex, work characteristics, personal resources<br>(Results not specified when adjusted for exhaustion at baseline) | 3 | Exhaustion (MBI) | Beta: 0.16, p<0.05 |
| Borritz et al. (2005)(117) | 952 from human service sector<br>(3 years of follow up) | Model 1: Age, sex, cohabitant status, children<7 years, education, job function, socio-economic status, health related life style.<br><br>Model 2: Model 1 + psychosocial work characteristics and exhaustion at baseline. | 1 | Exhaustion (CBI) | Model 1:<br>Estimate for one standard deviation (SE): 3.528 (0.566), p<0.0001<br><br>Model 2:<br>Estimate for one standard deviation (SE): 3.303 (0.543), p<0.577 |
| Van Vegchel et al. (2004)(6) | 2,255 employees from the Social Insurance Organization<br>(1-year follow-up) | Sex, age, education, exhaustion at baseline. | 3 | Exhaustion (MBI) | Beta: 0.09, p<0.001<br><br>(S for control, NS support from supervisor and colleagues) |
| Van der Ploeg et al. (2003) | 123 Ambulance service workers | (Results of the multiple regression analysis for | 3 | Exhaustion (MBI) | Pearson correlation:<br>High vs. low emotional |

| | | | | | |
|---|---|---|---|---|---|
| | (1-year follow-up) | emotional demands are not shown) | | | demands: 0.27, p<0.01 |

### 2.2.5 OTHER PSYCHOSOCIAL WORK CHARACTERISTICS AND POTENTIAL MODIFIERS

The health consequences of psychosocial work factors have been studied widely (3, 15, 92), and the most frequently used work environment model applied has been the demand-control model (24, 25). According to this model, a combination of high demands and low control puts strain on the workers. This has been suggested to have a negative impact on health. Social support has later been incorporated in the model; thus if the employee, in addition to high strain, experiences low support, then the job is considered to be particularly harmful (24). The stress induced by high strain in the job can concurrently be prevented or coped with by increasing the control and support. Another work stress model is the effort-reward-imbalance model proposed by Siegrist et al. (130, 131). The model addressed the balance between efforts spent and rewards received at work. Violations of expected reciprocity and adequate exchange predispose one to ill health (130, 132). Again, negative health outcomes can be prevented by rewards such as money (salary), esteem (e.g. respect and support), and other career conditions (e.g. promotion and job security)(130).

The newer Job Demands-Resources (JD-R ) model suggests that the work load results from the balance between job demands and job resources (133, 134). The model is, however, not restricted to single demands or resources. The model assumes that the job may affect employee health as long as demands and resources under investigation are relevant aspects of the particular job (134); an occupation may have its own specific risk factors associated with job stress. According to this model, job resources may buffer the impact of job demands on job strain. All three occupational stress models hypothesize that some kind of resource may prevent negative health outcomes. The JD-R model is interesting as it leaves room for the concept of emotional demands as both stressors and as enriching factors. Furthermore, it implies that matching resources may modify the effect of the demands, whereby the model also incorporates the possibility of things such as emotional enrichment as a relevant work characteristic with respect to emotional demands at work.

Some studies suggest that high job control and social support may reduce the effect of emotional demands on health (6, 9, 31, 119, 122). Limited longitudinal evidence exists exploring the modifying effect of work environmental characteristics and the associations between emotional demands and depression or exhaustion (6, 31, 122). Jobs that include emotional demands are suggested to be not only demanding but also enriching and meaningful (12, 22), this may be a resource that in line with the JD-R model may counteract negative effects of work. Furthermore, any effects of emotional demands on mental health could possibly be aggravated

if other demands in work were high. The existence of modifying effects positive or negative will provide opportunities for preventive interventions.

## 2.3 CORTISOL

The steroid hormone cortisol is involved in physiological stress response and can be used as a measurement thereof. The hormone has multiple functions, with its main roles being involvement in the regulation of the metabolic system and anti-inflammatory pathways that are important for the body's adaptation to increased energy demands during times of stress (135, 136). An increase in cortisol levels stimulates the degradation of proteins and fats and contributes to an increased supply of energy and oxygen, which translates to a temporary increase in blood pressure, blood glucose levels and free fatty acids. The anti-inflammatory property of cortisol consists of reducing the inflow of white blood cells to a required destination (13). Other implications of cortisol are bone metabolism, gene-expression modulations, increase of blood sugar, promotion of gastric acid secretion, effects on cognitive functions, etc. (135, 137-142).

Cortisol is released into the blood as a response to the experience of stressors (the experience of a situation that is potentially threatening or demanding to such a degree that personal resources are perceived as insufficient (143)). The experience of stressors triggers the activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading to a secretion of the corticotrophin releasing hormone (CRF) from the hypothalamus, with impact on the adrenocorticotropic hormone (ACTH) from the anterior pituitary, which in turn stimulates the production and secretion of glucocorticoids (e.g. cortisol) from the adrenal cortex. The elevated cortisol concentration then inhibits the CRH and ACTH via a negative feedback. The secretion of cortisol is slower than other stress hormones (e.g. adrenaline and noradrenaline), peaking typically after 20 to 30 minutes, and acts on the intracellular nuclear receptors found in most cell types, regulating the transcription of target genes (144).

In plasma, 10% of cortisol is unbound and biologically active(145); otherwise it is bounded to proteins. The free hormones diffuse from the blood stream into the tissue fluid, bind to the receptors of the target cell and trigger a biological response. It is the free fraction of cortisol that reflects any glucocorticoid hyper- or hypofunction, with Cushing’s and Addison’s diseases as the clinical entities (146).

The normal diurnal variation in cortisol levels presents a peak approximately 30 to 45 minutes after awakening and declining throughout the day, with the lowest levels at midnight (147, 148). The peak values in the morning may be 10-fold higher or more than are the levels at night. Cortisol exhibits both diurnal but also day-to-day and seasonal variations (13, 147).

In epidemiologic studies, the measurement types most commonly used are saliva samples of single-time-point measures at fixed times, typically in the morning and/or in the evening, when more than one measurement is taken. Means, deviations and slopes can be estimated. The cortisol awakening response (CAR) is usually measured as the deviation in the level of cortisol from awakening till the peak 30 minutes after (137), and the slope is measured as the difference between the morning peak and the evening sample. With more than two measurement points, an area under the curve can be calculated (AUC). The various cortisol measurements contribute to a description of the HPA axis's reactivity.

In the short course, a cortisol response of the HPA axis is a normal and appropriate physiological reaction. According to the principle of allostasis (internal stability of an organism), a prolonged period of heightened HPA-axis activity (allostatic load) can lead to pathophysiology (149). Cortisol is thus a possible mediating factor in the relationship between emotionally demanding work and mental health, and it is also a risk marker for psychosocial stressors and negative health outcomes. In the following section, I will briefly describe the epidemiological knowledge of the associations between the imbalance in the HPA axis measured by the cortisol concentration and mental health in terms of depressive symptoms and clinical depression.

### 2.3.1 PSYCHOSOCIAL WORK CHARACTERISTICS AND CORTISOL

Acute experience of stress has been found to be associated with increased levels of cortisol (150-152). One can thus expect that stress resulting from psychosocial working conditions (e.g. high demands and low social support) will be associated with cortisol. A review of psychosocial work stressors identified 27 studies, including 185 analyses resulting from different cortisol measures (morning, evening, mean and slope etc.). Of these analyses, 77% showed no association, 13% showed negative associations and 29%, positive. Among the findings, no patterns were found regarding time of sampling and associations found (153). According to the authors, an explanation for the non-significant results may be due to low exposure contrast between groups (153).

One cross-sectional study specifically on emotional demands among 103 human service workers showed that levels of blood cortisol increased slightly with higher emotional demands (41). The association between emotional demands and cortisol has been relatively unexplored.

### 2.3.2 CORTISOL AND DEPRESSION

Findings of hypercortisolemia among patients as well as elevated risk of depression among patient treated with corticosteroids has led to a widely accepted hypothesis that increased cortisol levels and depression are associated (14, 154). This may be true when examining the acute relationship (151); however, epidemiological findings have not always confirmed this (155).

In patient studies, depression has been related to elevated levels of cortisol (156-158) but it has also been related to decreased levels or no change in level (14, 159-161). Reviews shows a tendency towards elevated morning and evening cortisol levels among patients, and a decreased morning-to-evening slope compared with healthy controls (14, 155).

A great number of cross-sectional small-scale studies (n<100) exists (for reviews see Jonsdottir et al. (155)and Stetler et al. (14)). The larger cross-sectional studies show mixed results. In a Swedish working age population, Sjögren et al. (2006) showed lower levels of morning measures of cortisol as well as a flatter morning-to-evening slope (162). Similar negative findings were found for morning cortisol levels among U.S. army veterans (163) and slope cortisol levels for middle-aged women (164) in relation to depression and symptoms of depression. Muhtz et al. (2009) found elevated cortisol among women with depressive symptoms (165), whereas Bremmer et al. (2007) found a U-shaped association for plasma cortisol in an older-aged population (166).

Longitudinal studies have shown mixed results (Table 5) (167-174). Most of these studies were conducted among adolescents (167-171, 173). One included adult women who were especially likely to develop depression (172) and one include a working adult population (174). All studies but one study (174)found one or more positive longitudinal associations between cortisol and depression but for different measures of cortisol (morning, evening, slope, etc.) and not in a consistent pattern. The most consistent finding was higher morning cortisol levels as a risk factor for depression (168-170, 172). Vrshek-Schallhorn et al. (2012) and Adam et al. (2010) found increased responses for cortisol levels upon awakening (167, 173). Vrshek-Schallhorn et al. (2012) followed an adolescent cohort with one year intervals over a period of four years and showed that increased cortisol levels upon awakening were prospectively linked to depression up until two and a half years after the baseline measurement, while no associations were found for morning, evening, mean, and slope measures of saliva cortisol (173). Grynderup et al. (2013) found that the risk of clinical depression decreased after two years

by increasing the daily mean cortisol level and increasing the differences between morning and evening concentrations at the baseline (174). At the single-time-point measures, morning and evening cortisol levels were not associated with depression.

Among studies of cortisol and depression, pronounced inconsistencies between studies have been seen. However, the studies differ extensively with regards to e.g. number of and sampling times for cortisol measurements, included study populations, follow-up periods, and confounder adjustment. Among the longitudinal studies, none were found with follow-up periods of less than one year. Furthermore, few studies have investigated the relationship between cortisol and depression in representative samples of the general working population. Consequently, the associations found are not entirely consistent and well-replicated and the role of cortisol in the interaction between stressful conditions and mental health, particularly among the working population, remains undecided (153, 155).

**Table 5: Studies investigating longitudinal associations between cortisol and depression.**
***Results are shown for: Morning, evening, mean, morning-evening slope, CAR, and AUC. The association for statistical significant elevated cortisol (+), no association (0), and/or decreased levels are indicated (-).***

| Longitudinal studies of cortisol and depression | | | | | |
|---|---|---|---|---|---|
| **Reference (Year)** | **Population (Follow-up period)** | **Confounders** | **Cortisol (Time of sampling)** | **Depression** | **Results**<br>**+ : Elevated level of cortisol**<br>**0 : No association**<br>**- : Decreased levels of cortisol** |
| Grynderup et al. (2013) (174) | 2920 public sector employees, mean age 45.5 years<br>(2 years) | Sex, age, previous depression, family history of depression, income, education, alcohol intake, smoking, and body mass. | Awakening, +30 min and +20h | Clinical depression (ICD-10) | Morning: 0<br>Evening: 0<br>Mean: -<br>Slope: - |
| Vrshek-Schallhorn (2012) (173) | 270 High school students, mean age 17.06 years, with high neuroticism score<br>(4 years) | Sex, life events, race, neuroticism, previous depression, socioeconomic status, time of awakening, hours of sleep, hormonal contraceptive use. | Awakening, +40min, +3h, +8h, + 12h, and at bedtime (collected on three consecutive weekdays) | Clinical depression (DSM-IV) | Morning: 0<br>Evening: 0<br>Mean: 0<br>Slope: 0<br>CAR: + |
| Ellenbogen (2011) (168) | 28 offspring of parents with bipolar disorder and 31 offspring of parents with no affective disorder, mean age 17.5 years<br>(1-6 years) | Age, sex, baseline mental disorder, parental bipolar disorder | Awakening, +30min, +60min, +15h, +20h, and at bedtime | Clinical depression (DSM-IV) | Morning: +<br>Evening: +<br>Mean: + |
| Goodyer (2010) (169) | School children, mean age 13.6 years<br>(1 year) | Age, sex, life events, baseline depressive symptoms, psychosocial risk profile, BDNF, 5-HTTLPR. | 08h (four consecutive schooldays) | Depression (DSM-IV) | Morning: + |
| Adam | 230 high school students, | Age, sex, neuroticism, | Awakening, +40 min, +3h, | Clinical depression | |

| | | | | | |
|---|---|---|---|---|---|
| (2010) (167) | mean age 17.0 years, with high neuroticism score<br>(1 year) | psychotropic medicine, smoking, asthma, hours of sleep, time of awakening. | +8h, +12h, and at bedtime<br>(collected on four consecutive weekdays) | (DSM-IV) | Morning: 0<br>Evening: 0<br>Mean: 0<br>Slope: 0<br>CAR: + |
| Halligan<br>(2007) (171) | 83 offspring of mothers with postnatal depression, mean age 13 years<br>(3 years) | Sex, life events, depressive symptoms at baseline pubertal development, body mass, family conflict, maternal postnatal depression | 8h and 20h<br>(collected on 10 consecutive weekdays) | Depressive symptoms<br>(self-reported) | Morning: +<br>Evening: 0 |
| Harris<br>(2000)(172) | 116 women recruited from general practice, mean age 38.5 years<br>(13 months) | Age, life events, smoking, social support, negative self-evaluations, saliva DHEA. | 8h and 20h | Clinical depression<br>(ICD-10) | Morning: +<br>Evening: 0 |
| Goodyer<br>(2000) (170) | 180 adolescents, mean age 13.5 years<br>(1 year) | Age, sex, life events, baseline depressive symptoms, saliva DHEA | 8h and 20h<br>(four consecutive days) | Depression<br>(DSM-IV) | Morning: +<br>Evening: 0 |

## 3.0 AIM AND HYPOTHESES

The aim of this thesis was to explore the relationship between emotional demands at work and the risk of developing depressive symptoms, clinical depression or exhaustion. A further aim was to contribute to the mapping of the possible biological pathway between these factors.

The main hypotheses were (pathways A-D):

- High emotional demands at work increase the risk of depression and exhaustion (A and B)
- This risk is modified by other work characteristics, i.e. reduced or increased in the presence of enriching or aggravating work characteristics (C)
- An altered cortisol profile is related to the development of depression (D)

These hypotheses were tested in the following three studies (I-III):

Study I — Title: Emotional demands at work and the risk of clinical depression: A longitudinal study in the Danish public sector (A and C, Study I).

The specific aim of the study was to examine the effect on depression of different dimensions of emotional demands, i.e. individual and group-based, perceived and content-related demands, with a separate focus on patient work. Furthermore, the aim was to study the moderating effects of enriching work factors.

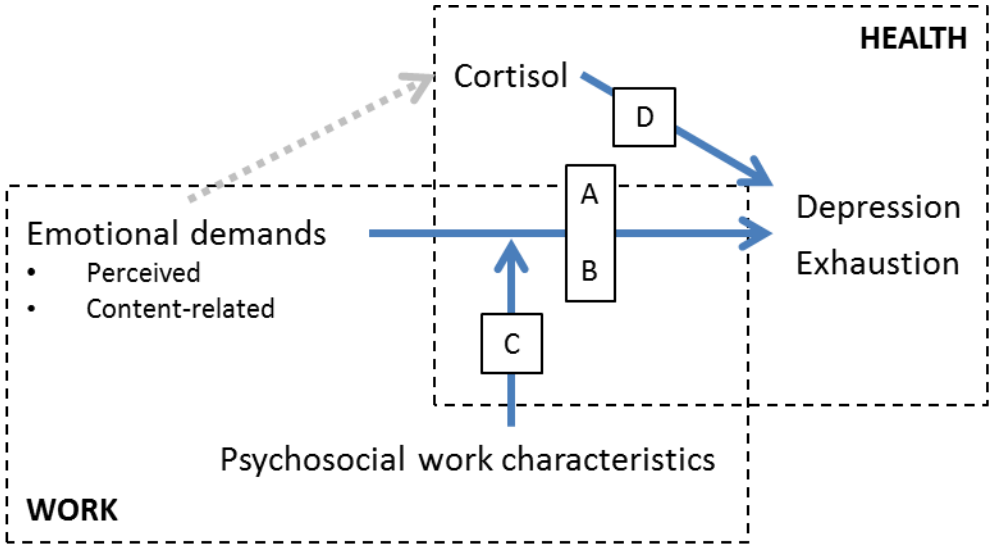
Study II — Title: Emotional demands and exhaustion: Cross-sectional and longitudinal associations in a cohort of Danish public sector employees (B and C, Study II).

With the use of questions concerning content-related emotional demands, the specific aim was to examine the effect of these on self-reported exhaustion symptoms, separating the possibly biased longitudinal from the cross-sectional associations and also exploring the moderating effect of work characteristics.

Study III — Title: Salivary cortisol and depression in public sector employees: Cross-sectional and short term follow-up findings (D, Study III).

The study examined the associations between different saliva cortisol measures as exposures and the outcomes depressive symptoms and clinical depression diagnosed with the use of standardised clinical interviews.

**Figure 3: Pathways investigated between types of emotional demands at work, cortisol and poor mental health outcomes (depressive symptoms, clinical depression and symptoms of exhaustion).**
***The blue arrows show the relationships being investigated in this thesis.***



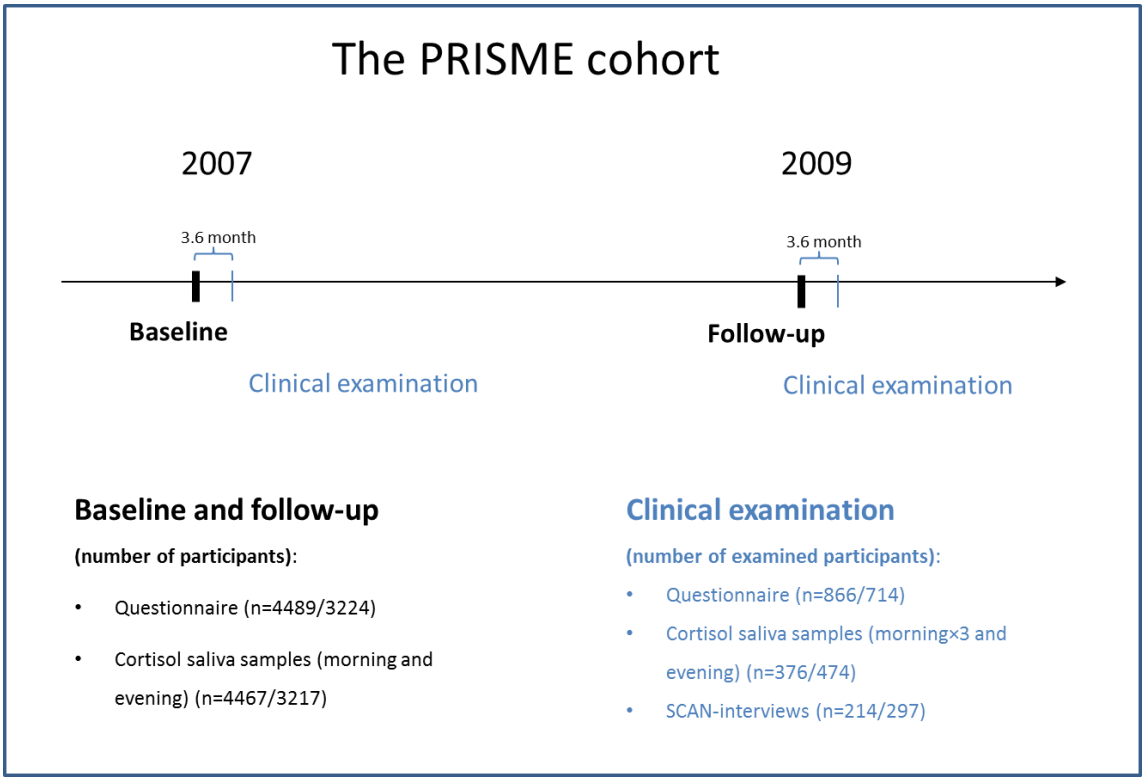
## 4.0 MATERIALS AND METHODS

The results of the studies included in the thesis are based on data from the PRISME cohort. Design, population, measures of potential modifiers, and other work characteristics, as well as assessments of exposures and outcomes are presented below, followed by a description of the applied statistical methods.

### 4.1 DESIGN

The Danish PRISME cohort was established with the overall purpose of investigating psychological risk factors in the work environment and biological mechanisms in the development of stress, burnout and depression. The cohort was established in January 2007 and the questionnaire responders were invited to participate in a re-examination in January 2009 (52, 174-176). At the baseline and at the follow-up, data was collected by means of several data sources: the employee register files, self-administered questionnaires, and saliva samples from self-administered test tubes. Clinical examinations included additional saliva samples and standardized clinical interviews (described in Section 4.6). The clinical interviews were carried out among a selected group of participants from March to July at both rounds (Figure 4). The project was undertaken in cooperation between the hospitals' departments of occupational medicine in Herning, Aarhus, and Bispebjerg as well as in the National Research Centre for the Working Environments and the Centre for Psychiatric Research, Aarhus University Hospital.

Figure 4: The PRISME study design




## 4.2 POPULATION

At baseline, 10,036 employees from 502 work units were recruited within public service workplaces in the county and municipality of Aarhus, Denmark. A work unit was defined by the employee's immediate supervisor.

A total of 4,489 employees (44.7%) from 474 work units participated by filling in a postal questionnaire concerning work, life style, personal circumstances and health. Participants from the baseline were invited to participate at follow-up, and 3,224 (72%) filled in a similar questionnaire.

The workplaces included hospitals, schools, day-care centres, and from social, technical and environmental services and administrations. The most common professions were nurses, social workers, counselling professionals, teachers, managers, medical doctors, nursing aids, office clerks and preschool teachers (52).

## 4.3 WORK CHARACTERISTICS

### 4.3.1 SELF-REPORTED AND WORK-UNIT BASED EMOTIONAL DEMANDS AT WORK

Emotional demands were measured with the self-administrated questionnaires at the baseline and at follow-up. The PRISME items are presented in Table 1FIGURE 1 together with response options and item scores. The questionnaire included measures of perceived emotional demands (two items), content-related emotional demands (five items) and patient-care emotional demands (four items). Each of the three measures was scored as the mean of the item scores. If more than half of the items were missing, the score was marked "missing".

Work-unit-based measures of emotional demands were assessed by the means of emotional demands scores for each work unit. Thus, the same mean value was allocated to all employees in a particular work unit.

### 4.3.2 POTENTIAL EFFECT MODIFIERS

The COPSOQ was used to construct scales measuring quantitative demands (4 items), decision authority (4 items), skill discretion (4 items), social support from supervisors (1 item), social support from colleagues (1 item) and meaningful work (3 items) (36, 37). All items were scored from 1 to 5. Scales were constructed as the mean of the item scores. High scores indicated a high level of the work characteristic (e.g. high demands, high control etc.). If more than half of the items were missing, the score was marked "missing". A scale of job control was constructed as the mean of decision authority and skill discretion. Emotional enrichment was measured by a single item designed for this study (Table 1).

## 4.4 OTHER COVARIATES

Covariates were selected based on literature review and due to their associations with depression (177-181). Socioeconomic status was assessed based on personal annual income in Danish crowns (continuous), and professional education beyond primary or high school (none or short training (< 3 years), medium and higher (3-4 years) and long and higher (>4 years) education). Lifestyle was assessed by leisure time physical activity frequency (rarely vs. often), weekly alcohol consumption (continuous), body mass index (BMI= self-reported weight (kg)/ self-reported height$^2$ ($m^2$)), and smoking (never and former vs. present smoker). Other personal aspects and circumstances assessed from the questionnaire items were the following: living in a permanent relationship (good, problematic or no relationship), impact of traumatic life events during the last six months (no-impact, impact, high-impact) (182), physician-diagnosed diseases (none, one, two, more than two), family

history of depression (yes vs. no), loneliness (yes vs. no), cohabitation (yes vs. no), sleep quality (poor, good, very good), and neurotic personality traits (neuroticism) measured by the Eysenck Personality Questionnaire Revised-Abbreviated version (continuous) (183). Sex and age (continuous) were extracted from employee files. The covariates were included in various combinations in the studies that were specified in the statistical analyses section. Neuroticism, depressive symptoms (see below), and items on previous or present physician-diagnosed depression were included in sensitivity analysis, which will also be specified later (SEE statistical analyses).

### 4.5 SYMPTOMS DEPRESSION, STRESS, AND EXHAUSTION

Depressive symptoms were assessed by the Common Mental Disorder Questionnaire subscale for depression (six items) (78), stress symptoms by the Perceived Stress Scale (4 items)(184), and exhaustion by the CBI (personal burnout, 6 items) (37). All questions concerned the last four weeks and responses were given on 5-point ordinal scales. Items regarding depressive symptoms were dichotomized (0=item score <3, 1=item score ≥3), and summed to a depression symptom scale with scores from 0 to 6. The scores of exhaustion and perceived stress were calculated as the mean of item scores (range 1 to 5). Higher scale scores indicate higher levels of symptoms. If responses to more than half of the items of a scale were missing, the scale score was marked “missing”.

### 4.6 CLINICAL EXAMINATION AND DIAGNOSIS OF DEPRESSION

Clinical cases of depression were diagnosed by the psychiatric diagnostic Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (Version 2.1, Part I, Sections 6, 7, 8 and 10) according to the International Classification of Diseases (Tenth Revision: diagnostic criteria for research; ICD-10-DCR)(80). The interviews referred to symptoms from the previous three months (185). Participants fulfilling the criteria for a mild, moderate or severe ICD-10-DCR depression were categorised as clinically depressed. Students of medicine or psychology conducted the interviews (n=10). They were trained on a one-week course by a WHO-certified trainer (inter-rater reliability was 0.71 in 2007 and 0.77 in 2009).

Participants invited for clinical examination in 2007 represented participants reporting high scores on measures of depressive symptoms (score ≥3) and/or exhaustion (score ≥4 ), perceived stress (score ≥2.5)(n=470), high psychosocial exposures (n=522), as well as a random sample (n=434) of the 4,489 participants who had

returned questionnaires. This selection procedure aimed at identifying participants who could have clinical depression and to collect supplementary data from high-exposed participants. A total of 1,162 participants were invited, and 866 showed up. Of these, 590 went through the SCAN-interview, and 100 were diagnosed with depression.

In 2009, the screening procedure was slightly changed to improve the sensitivity. Thus, the participants who were invited for clinical examination in 2009 were those who reported a high level of depressive symptoms (score ≥2), exhaustion (score ≥2.5) and perceived stress (score ≥2.5) in the 2009 questionnaire (n=599), a random sample of the total population from 2007 (n=201) and additional participants with clinical depression or high psychosocial exposures in 2007 (n=238). In 2009, 1,039 participants were invited, 752 showed up, and 562 participated in the SCAN-interview. In total, 62 cases of depression were identified.

## 4.7 SALIVA CORTISOL

### 4.7.1 CORTISOL SAMPLES AT BASELINE AND FOLLOW-UP

All participants were asked to collect saliva samples, preferably on a workday or on a day off work, and to fill in a questionnaire on sampling circumstances (time of awakening, sleep quality and duration, work and work hours, etc.). Saliva samples were to be collected 30 minutes after awakening and in the evening at approximately 8:00 p.m., and stored in a refrigerator until they were returned by mail. The returned samples were stored at -20 °C and analysed within six months. Samples were collected at the same time of the year in 2007 and in 2009. The determination of the cortisol concentration was carried out with competitive radioimmunoassay. For a morning sample to be valid, we required that it was taken within 2 hours from awakening and before 12:00 p.m., and for evening values, we required that the sample was taken between 5:00 p.m. and 04:00 a.m.

First, the level of morning and evening cortisol was measured. Then, the mean cortisol level (average of the morning and evening cortisol levels) and the slope of the cortisol level (decrease in the cortisol level per hour) were calculated.

Of the 10,036 employees invited, 4,467 returned saliva samples in 2007. Participants with missing or invalid cortisol concentrations or invalid sample times (n=817), pregnant women (n=138), and participants with

missing questionnaire data (n=44) were excluded. A total of 3,536 participants were included in the analysis at the baseline.

In 2009, the participants from 2007 were approached again. Participants with missing or invalid cortisol concentrations or invalid sample times (n=671), pregnant women (n=63), and participants with a missing main questionnaire (n=76) were excluded, and a total of 2,408 participants were included in the analysis at the follow-up.

*4.7.1.1 Clinical examination and cortisol samples*

Participants invited for clinical examination (Figure 4) were asked to collect additional saliva samples. Samples were to be collected preferably on a workday or on a day off work, and four times a day: at awakening, 20 and 40 minutes after awakening, and in the evening at approximately 8:00 p.m.

At baseline, 376 participants collected four saliva samples and of these, 214 participated in the psychiatric diagnostic SCAN-interview. At follow-up, 474 collected four saliva samples, and of these, 297 participated in the SCAN-interview.

The cortisol mean value across the day was calculated as the average of the morning maximum value and the evening value, and the slope value as the decrease from the maximum morning value to the evening value per hour. Furthermore, CAR was assessed as the maximum cortisol increase from awakening to the second or third saliva sample in the morning. AUC was defined by the three morning concentrations subtracted by the area below the awakening curve.

## 4.8 STATISTICAL ANALYSES

This section summarizes the statistical analyses applied in the three studies referring to the figure of the investigated pathways.

### 4.8.1 STUDY I: EMOTIONAL DEMANDS AND DEPRESSION

The association between emotional demands at baseline and clinical depression at follow-up was assessed by logistical regression. The three measures of emotional demands were included separately as exposures. The

analyses were further performed separately for the individual-based and work-unit-based measures of emotional demands, and in all analyses, both continuous-scale exposure information and exposure divided into tertiles were used.

The following covariates were included as potential confounders in three steps: step one included sociodemographic variables (sex, age, education beyond primary or high school, personal annual income in Danish crowns); step two included factors related to mental health and social life (family history of depression, previous episodes of depression, traumatic life events during the last six months, cohabitation, and loneliness); and step three included lifestyle factors (alcohol consumption, smoking, physical activity, and body mass index). All potential confounders were determined at baseline with the exception of traumatic life events within the last six months being assessed at follow-up. Potential confounders were excluded at each step if their effect was not statistically significant at $p<0.25$ and at the same time did not alter the effect estimate of emotional demands by more than 10%. The final selected models were further tested by including neuroticism and depressive symptoms.
The linearity of effects of all continuous covariates were examined in crude analyses by including quadratic and cubic terms. These terms had no statistically significant effects.

The effect of work-unit clustering was analysed by inclusion of a work-unit-random-effect term using mixed logistic regression models. This term had no statistically significant effects in any of the models.

*4.8.1.1 Additional analyses: Potential modifiers and patient-work*

Positive work environment factors (supervisor support, colleague support, meaningful work, and emotional enrichment) were considered as potential modifiers by including a multiplicative interaction term between these factors and emotional demands in the models.

The effect of having patient work or not (patient work: yes vs. no) was examined in logistic regression models with patient work as exposure and clinical depression as an outcome. Also the association between patient work and perceived or content-related emotional demands were analysed. Thereafter the combined effects of patient work and (perceived or content-related) emotional demands on clinical depression were examined. An interaction term between patient-work and emotional demands was included.

### 4.8.2 STUDY II: EMOTIONAL DEMANDS AND EXHAUSTION

The cross-sectional and longitudinal effects of emotional demands on exhaustion as the dependent variable were analysed in a linear, mixed model, controlling for potential confounders, examination round (fixed effects), and for repeated measurements. Analyses were performed on a continuous scale and with tertile categorization. Finally, the effect of neuroticism was tested in the models.

The method proposed by Fitzmaurice et al. (186) estimates cross-sectional and longitudinal effects, concurrently (mutual adjustment), whereby potential cross-sectional effects are estimated separately from the longitudinal effects, and direct longitudinal effects are estimated. The cross-sectional effect (between-person effect) was estimated as the effect of the average emotional demands score across the two examination rounds on the exhaustion score, and the longitudinal effect (within-person effect) as the effect of the change in emotional demands from 2007 to 2009 on changes in exhaustion from 2007 to 2009. This model assumes that the association between exposure and outcome is the same at the two measurement points. This was tested and confirmed.

#### *4.8.2.1 Additional analyses: Potential modifiers and Hausman test*

The work environment characteristics quantitative demands, job control, supervisor support, colleague support, meaningful work and emotional enrichment were considered to be potential modifiers by including a multiplicative interaction term between these factors and emotional demands in the models, separately for each factor.

All models were tested for differences in cross-sectional and longitudinal effects (the Hausman test). Differences in effects may indicate a bias in the cross-sectional effect due to uncontrolled confounding from time-invariant factors (186).

### 4.8.3 STUDY III: CORTISOL, DEPRESSIVE SYMPTOMS AND CLINICAL DEPRESSION

Odds ratios of depressive symptoms and clinical depression were assessed by ordinal and binary logistic regression analyses with cortisol as the explanatory factor. The assumption of proportional odds in the ordinal logistic regression analyses of depressive symptoms was accepted.

Cortisol (nmol/l saliva) was logarithm-transformed to normalize the cortisol distribution and to reduce skewness and variances. Each of the cortisol measures was examined separately. Analyses were performed on a continuous-scale and with tertile categorisation. The effects of each of the cortisol measures were examined by linear and quadratic terms to test for linearity.

We made four cross-sectional (at baseline, at follow-up, and at both clinical examinations rounds) and two short-term follow-up analyses (at the baseline of the clinical examination and at follow-up of the clinical examination) (Figure 4). The cross-sectional analyses were performed for depressive symptoms and clinical depression in both 2007 and 2009.

The short-term follow-ups were performed for depressive symptoms and clinical depression both years, excluding participants with depressive symptoms (sum-score≥2) at baseline. The follow-up analyses were adjusted for number of days from baseline (the saliva test at baseline) to filling in a questionnaire on depressive symptoms at the clinical examination. The follow-up time was on average 3.6 months (Figure 4).

The adjustment for potential confounders measured at baseline was done in two steps. The first step included sex, age, education, income and family history of depression, and the next step included traumatic life events, sleep quality, alcohol consumption, smoking, physical activity and BMI. However, the relationship between cortisol and clinical depression could only be analysed in crude models because of the small number of incident cases (2007/2009: n=10/n=16).

*4.8.3.1 Additional Analyses: Examination of Changes and Sensitivity Analyses*

Additionally, we analysed the data to see if changes in cortisol from baseline to follow-up were associated with changes in the symptom score in the same period. The cortisol level at baseline was included as a covariate in these analyses.

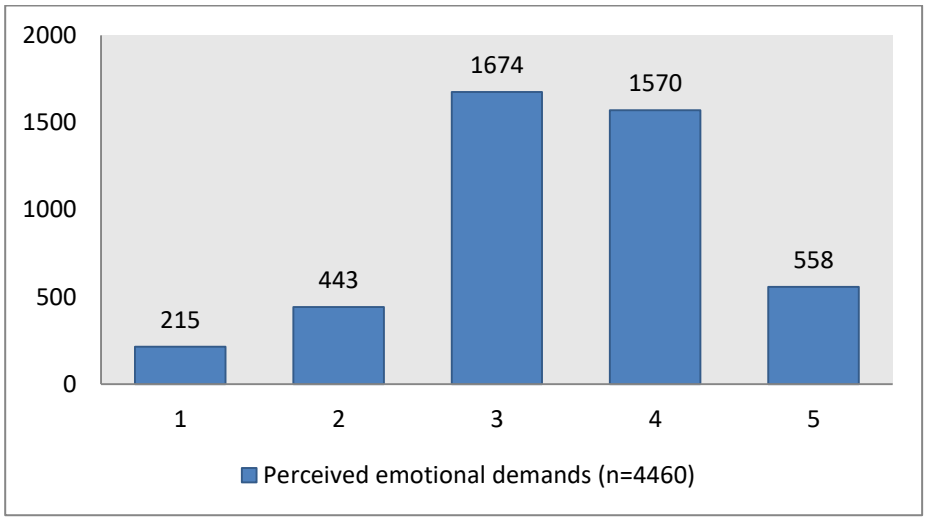
Analyses validating the cross-sectional results with respect to sampling times were performed by including only 90%, 80% and 50% of the populations that collected their saliva samples closest to the intended time of sampling. Analyses were performed for morning, evening, mean and slope in relation to depressive symptoms in both 2007 and 2009.

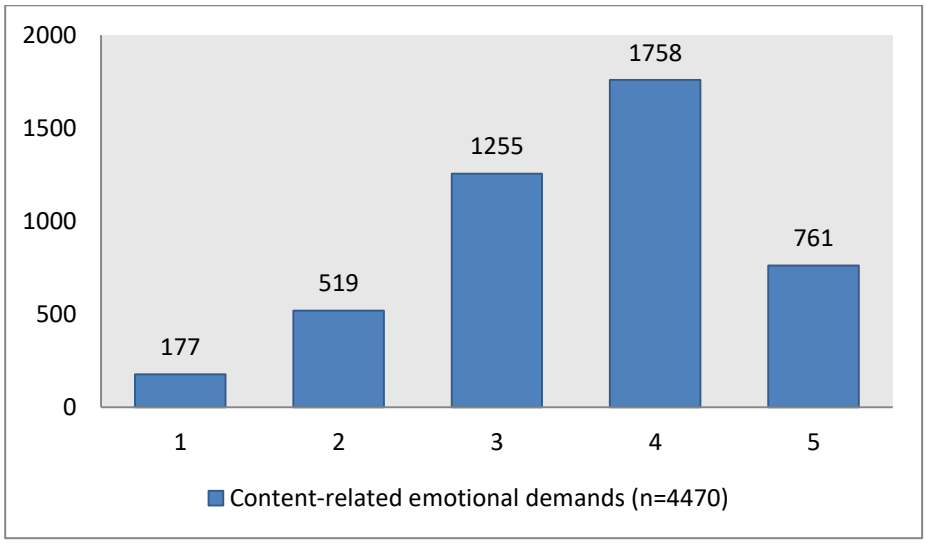
To test for potential sex-specific effects of cortisol, crude analyses of interaction effects between sex and morning and evening cortisol were performed. Furthermore, neuroticism and previous or present depression diagnosed by a physician were controlled for in-sensitivity analyses.

## 5.0 RESULTS

In this section, a summary of the results from the three studies will be presented. Initially, the descriptive distributions are shown for perceived and content-related emotional demands at baseline among the 4489 participants.

**Figure 5: The distribution of perceived and content-related emotional demands of the employees (n = 4489; 29 and 19 are non-respondents, respectively)**



## **5.1 STUDY I:** EMOTIONAL DEMANDS AND DEPRESSION

Individually reported perceived emotional demands predicted clinical depression with an adjusted odds ratio of 1.40 per unit increase in perceived emotional demands (95% CI:1.02-1.92). The corresponding work-unit-based odds ratio for perceived emotional demands was in the same direction though not statistically significant (odds ratio: 1.24; 95% CI: 0.75-2.07). Content-related emotional demands did not predict depression.

The main results changed only marginally when the main models were further adjusted for neuroticism and depressive symptoms.

Meaningful work, support from supervisor or colleges, and enrichment did not modify the associations between emotional demands and clinical depression. However, for patient-care emotional demands, an interaction with meaningful work ($p=0.012$) and with supervisor support ($p=0.019$) became statistically significant for individually reported data. At low levels of patient-care, emotional demands and higher levels of meaningful work reduced the risk of depression, and at high levels of patient care, emotional demands and higher levels of meaningful work increased the risk. A similar pattern was found for the interaction between patient-care emotional demands and supervisor support. Meaningful work and supervisor support at baseline were independent predictors of a reduced risk of depression in all tested models.

### 5.1.1 PATIENT WORK

Sub-analyses showed that participants working with patients reported statistically significantly higher levels of perceived emotional demands and content-related emotional demands than other participants ($p<0.01$). However, participants dealing with patients had a lower risk of depression (adjusted odds ratio: 0.50 (95% CI: 0.27-0.94)).

The interaction term for perceived emotional demands and patient work was statistically significant. The incidence rate of depression was lower for participants with patient work than for those without, except for the highest levels of perceived emotional demands (emotional demands > 2.5). The risk of depression increased steeply with perceived emotional demands for employees doing patient work.

## **5.2 STUDY II:** EMOTIONAL DEMANDS AND EXHAUSTION

The model assumption of equal associations between cross-sectional effects in 2007 and 2009 was accepted for content-related emotional demands. However, perceived emotional demands had a more negative effect with regards to exhaustion in 2007 than in 2009, and these could not be investigated by means of the method suggested by Firtzmarice (2012)(186).

Increasing content-related emotional demands were associated with increasing levels of exhaustion, longitudinally and cross-sectionally. Exhaustion increased 0.037 units (95% CI: 0.019-0.055) by a one unit increase in emotional demands cross-sectionally, and 0.034 units (95% CI: 0.006-0.061) longitudinally.

Modifications of effects were observed for emotional enrichment, meaningful work, and quantitative demands. Exhaustion increased at a steeper rate by increasing emotional demands when emotional enrichment was low than when it was high, cross-sectionally as well as longitudinally. A similar modification effect was seen longitudinally for meaningful work. Exhaustion increased at a steeper rate by increasing emotional demands when quantitative demands were high than when they were low. Job control, support from supervisor and support from colleagues had an independent protective effect on exhaustion but had no modifying effect.

The inclusion of neuroticism in the adjusted main model resulted in a stronger cross-sectional association, whereas the longitudinal association between emotional demands and exhaustion as well as the modification effect from quantitative demands was no longer statistically significant.
The cross-sectional associations between emotional demands and exhaustion were compared for participants who only participated in the first round (n=1,280) with those who participated in both rounds (n=3,224). Exhaustion increased with 0.065 (95% CI: 0.03-0.10) units by a one unit increase in emotional demands among only first round participants compared with 0.062 (95% CI: 0.04-0.08) for both round participants, adjusted for participants' sex and age.

## **5.3 STUDY III:** CORTISOL, DEPRESSIVE SYMPTOMS AND CLINICAL DEPRESSION

The levels of the different cortisol measurements were not associated with depressive symptoms or clinical depression in the four cross-sectional and two short-term follow-up analyses; e.g. in 2007, the adjusted odds ratios of depressive symptoms by a one unit increase in morning and evening cortisol levels (ln(nmol/liter

saliva)) were 1.01 (95% CI: 0.88-1.17) and 1.05 (0.93-1.18), respectively. One statistically significant exception was that morning cortisol levels were lower in clinically depressed participants than in non-depressed participants in the 2009 cross-sectional analysis (odds ratio 0.40 (95%CI: 0.16 -0.97)).

Additional analyses of changes in cortisol levels from baseline to follow-up showed no statistical significant associations with changes in depressive symptom scores.

Initial analyses did not indicate any sex-specific effects of cortisol on depression. Neuroticism was associated with depression (Pearsons correlation = 0.56). However, including neuroticism in cross-sectional analyses did not change the results. The sensitivity analyses testing the temporally more accurate sampling did not change the results, as no statistically significant associations were found.

## 6.0 DISCUSSION

In this section, the findings of the three studies are summarized and discussed in relation to methodological shortcomings and limitations. Furthermore, the results are related to previous studies in the field leading to the final conclusion of the thesis.

## 6.1 MAIN RESULTS

Overall, this thesis found that emotional demands at work depended on the personal perception with regards to the effect on depression. Specific content-related emotional demands at work had no or only a small effect on depression and exhaustion, respectively. Findings supported the modifying effects of some work environment characteristics between emotional demands and exhaustion. It was not supported that cortisol plays a role in the physiological mechanism behind the development of depression.

Below, the main results of the three studies are summarized, referring to the pathways modelled in

Figure 3.

A) The specific content-related emotionally demanding work tasks did not predict the onset of depression, whereas the personal perception of emotional demands in work did. The association was attenuated (and no longer statistically significant) when grouping exposure by work units. Participants having patient work had an overall lower risk of developing depression when compared to the rest of the included population.

B) Specific content-related, emotionally demanding work tasks were associated with a small increase in the level of exhaustion both cross-sectionally and longitudinally.

C) Positive work characteristics did not modify the effect of (any) emotional demands on depression. The longitudinal association of specific emotional demands at work on exhaustion was reduced if the work was experienced as emotionally enriching and meaningful, and aggravated by increasing quantitative demands.

D) Repeated cross-sectional and short-term follow-up analyses did not show associations between different measures of cortisol and depressive symptoms or clinical depression. One exception was a cross-sectional finding of lower morning cortisol levels among the clinically depressed than among the non-depressed participants, but considering the number of tests this could be a chance finding.

## 6.2 METHODOLOGICAL CONSIDERATIONS

The strengths of this work on emotional demands, physiological mechanisms, and mental health compared with previous literature are the examination of perceived and content-related emotional demands separately as well as saliva cortisol in a large working population, addressing outcomes by a clinical measure of depression and exhaustion by non-work related items.

The methodological advantages were the longitudinal design and the possibility of including a large number of confounders, moreover, depending on the study, the application of work-unit based exposure assessments or estimating mutually adjusted cross-sectional and longitudinal effects. There are, however, several methodological points to consider with regard to the three studies conducted. In the following limitations of the studies will be examined.

### 6.2.1 EXPOSURE ASSESSMENTS

#### *6.2.1.1 Reporting bias and misclassification*

To avoid misclassification as a result of recall bias and common method variance we applied content-related items on emotional demands (study I and II) and work-unit-based estimates of exposure (study I). Overall, we see this approach as an important strength of the studies compared to previous studies (52) although the possibility of bias may not be completely circumvent (187).

A prime concern with regards to the epidemiological assessment of psychosocial work environment and related consequences is bias due to self-reported measurements (15, 52). Self-reports may affect results in the direction of positive findings, when e.g. the same personal or situational factor cause individuals to report

negatively on both work demands and mental health outcomes. This type of bias has been termed “common method variance”(30, 188). Several studies of good quality have avoided this bias through the use of the registers, where outcome is determined independently of the individual’s own reports (8, 29, 30, 54). However, also register studies involve some shortcomings, as will be discussed later (section: 6.2.3).

The risk of common method variance may especially be considered with regard to the study of emotional demands and exhaustion (study II) as both measures of exposure and outcome were based on self-reports. Content-related emotional demands questions were applied as we assumed they were less prone to reporting bias and less dependent on the individual’s interpretation of the working conditions compared with perceived emotional demands. The results from study I may support this assumption where we found an association with depression for perceived demands and not for content-related demands. But even with this measure, the results may be biased with the risk of an overestimation of the association (189).

Reporting bias was not relevant in relation to saliva cortisol (study III). The method used is precise and validated (190, 191) and misclassification is unlikely, if any, it would be expected to be non-differential.

Irrespective of the character of outcome (register or clinical depression) reporting of exposure may still be affected by early or preclinical stages of the condition or disease outcome. To solve potential reporting-related problems and avoid overrated associations in the study of depression we excluded cases of depression at baseline and applied aggregated group based exposure measures (192).

*6.2.1.2 Grouping of exposures*

A difference in results between self-reported and work-unit based results was observed for perceived emotional demands and not for the content-related emotional demands (study I). A possible explanation, besides reporting bias, for the difference could be non-differential misclassification. The working conditions may vary widely between employees in a unit and aggregating the exposure may not capture this variance. However, the estimated risks obtained by grouping of exposure are not expected to be attenuated because grouping accounts for random misclassification and leads mainly to Berkson type error in exposure assessments (193). Still, the grouping approach may increase uncertainty (the size of the confidence intervals) of the estimated results (193). This would, however, be most pronounced in smaller studies. Accordingly,

confidence intervals were wider in our work-unit-based analyses. A point of further consideration when conducting aggregated analysis is the identification of the organizational level at which individuals are aggregated (187). We have used the work-unit level assuming that emotional demands would be relatively homogeneous within these units.

Another way to circumvent reporting bias can be to estimate demands at work with a more objective approach (194). An observation and counting of e.g. how many times an employee is confronted with other people's grief and worries may be a way to measure one type of specific emotional demands.

### 6.2.2 CORTISOL SAMPLING

For practical and economic reasons only one morning and one evening saliva sample were taken at baseline and follow-up among the total population. More measurements, especially in the morning, could help to estimate CAR and show fluctuations during the day, also measurements of cortisol over several days could provide more reliable estimates of the participants' cortisol levels. In support of our findings, the results based on data from participants taking four cortisol samples per day showed similar results. Cortisol has a substantial diurnal variation and varies between days (13), many different measurement strategies have been applied (148, 195), it can thus not be rule out that a more complex association exists which would require a more complex measurement strategy.

The saliva samples were not collected at the exact sampling time, according to the instruction manual, by many participants. To estimate the effect of imprecise sampling on the association between cortisol and depression we did restricted analyses, including selected groups of participants with more precise sampling times. This approach resulted in loss of power, and a better way to adjust for sampling times may have been to include sampling times as covariates in the analyses. The results of the restricted analyses were, however, possible due to the size of the study and results were in line with the main analyses. Including the exact sampling times was not likely to alter the results.

### 6.2.3 OUTCOME ASSESSMENTS

At baseline we identified 100 cases of depression from the population of 4489 responding to the baseline questionnaire. Compared to a point prevalence of about 3-4% in the Danish population (60), we would have

expected nearly twice the number of cases. The PRISME population is, however, a selected population as it only includes actively working persons. Furthermore, a large part of the participants worked in the hospital sector with patients. This part of the PRISME population had a low prevalence of depression. The low number of cases may also be due to the selection process, where participants with a high symptom score (and a small random sample) were invited for diagnostic interviews and in this process we may have missed cases of depression (CMDQ og SCAN). Incomplete assessments of depression may not be related to exposure and cause bias, but could reduce the statistical power of the study.

A clinical assessment of depression may be superior to e.g. register studies with regard to specificity, as register information of depression, will to some extent be contaminated by false positive registrations (196) and it is well known that not all people with depression receive treatment (197, 198). Any measure of depression are, however, based on the person's own statements and thus based on the individual's own perception of the symptoms and thus eventually also a diagnose of depression can be affected by personal characteristics.

### 6.2.4 CONFOUNDERS

The size of the study enabled the inclusion of a large number of confounders. Therefore, we do not expect our estimates to be subject to major confounding, but we cannot preclude that there might be residual confounding. This could especially be the case in the sub-analyses of cortisol and clinical depression (study III) where we were not able to control for the full set of confounders because of too low power. Similarly, in the analysis of emotional demands and clinical depression (study I) we had to do a stepwise selection of confounders as we excluded potential confounders if their effect was not statistically significant at $p<0.25$ unless the exclusion caused the effect estimate of emotional demands to change by more than 10%. In study II, the Hausman-test for unmeasured confounders indicates a relevant confounder selection as it was insignificant. Also, the adjusted cross-sectional association were comparable with follow-up estimate.

The temporal relationship between a potential confounder, exposure, and outcome may be clear e.g. when measuring sex and age. We also adjusted for many potential confounding factors for which the causal relation with emotional demands and mental health is not clear e.g. lifestyle and traumatic life event. E.g a high BMI may be caused by depression or play a causal role in the development of depression, therefore various potential confounders were included stepwise in study I and III.

To avoid confounding of longitudinal effects with cross-sectional association in study II we chose an analytical model where the cross-sectional effects were controlled for. This is important as a major concern in this type of studies, as already mentioned, is the risk of reporting bias when exposure and outcome are reported simultaneously (186). The model may also indicate if adjustment for unmeasured time-invariant factors is inadequate by the Hausman-test (186).

Neuroticism was included in the PRISME study as a trait measure of personality. However, this measure is correlated with depression and not very stable over time. We chose not to include this variable in the main analyses but tested the effect in sensitivity analyses. Including neuroticism and depressive symptoms in sensitivity analyses did not change the main results in any of the analyses.

### 6.2.5 STUDY DESIGN

#### *6.2.5.1 Participation*

The participation rate at baseline and follow-up could result in biased estimates if associated with both exposure and outcome. Non-participation at baseline was associated with younger age, being male, increased sick leave and prescription of antidepressant medication. However, risk estimates for sick leave and prescription of antidepressant medication during follow-up did not differ between baseline participants and non-participants with respect to age, sex, civic status, social status and work-unit level of psychosocial work characteristics (job demands, decision latitude, job strain, effort-reward imbalance, and organizational justice variables) (176). We cannot be certain that these results can be extrapolated to results of emotional demands. However, the associations at baseline between content-related emotional demands and exhaustion for participants responding twice (baseline + follow-up) and once (baseline only) were almost identical, further the level of emotional demands at baseline did not predict participation at follow-up indicating that the drop-out rate did not bias the results. We did not expect the association between cortisol and depression to be biased due to loss to follow-up. Depression was associated with participation. However, cortisol levels are not assumed to be associated with participation.

The baseline response rate was 45 % and selection bias may be possible. A selection into the working population may have occurred, as unhealthy workers are less likely to be at the labour market, but also a

selection into the study may be possible. Thus, the low number of cases identified can be due to a healthy worker effect and the population do not represent the general Danish adult population. The estimated effects on the mental health in all three studies may be biased towards the null or the power could be too low to show any real effect.

*6.2.5.2 Follow-up design*

Regarding the assessment of causality, longitudinal studies are superior to cross-sectional studies. They are however, not without limitations. Issues remain e.g. with regard to the duration of follow-up and frequency of measurements as will be addressed in the following.

Measures of exposure, covariates, and outcomes were assessed only at baseline and follow-up and fluctuations in between were unknown. Thus, with regard to depression, we could not identify transient cases the two year in-between. Most depressive episodes have durations of three till twelve months, and 20% last longer and may be chronic conditions (61). A two years follow-up study may therefore oversample the chronic cases of depressions. Suppose a difference exists between short term and long term depression, this would bias the results and associations relevant to short term depressions may not be revealed. Register studies, with continuous case finding during follow-up, support our findings regarding perceived emotional demands and depression (8, 54).

Register-based studies of exhaustion have not been conducted, but studies with different follow-up times have shown positive associations (Table 4). However, we are not aware of studies examining content-related emotional demands with follow-up periods of more than one year, thus to generalise our findings regarding a longitudinal association with exhaustion more studies are needed.

With regard to the relationship between cortisol and depression, the studies are few and difficult to compare (Table 5) complicating an overall conclusion on the temporal correlation. Prospective adolescent studies indicate that high baseline cortisol awakening response are associated with incident depression at follow-up to two and a half years after the baseline measurement, although decaying over time (173). Whether this predictive stability can be generalized to an adult population is uncertain. This was not supported in another study using PRISME data with two year follow-up (174). That study found associations for low mean and slope

cortisol levels contradicting the initial hypothesized positive association. To further clarify causal relationships between e.g. cortisol in relation to mental health it could be interesting to see the parallel fluctuations of cortisol and the outcome measure over time, which will require more measurements with shorter follow-up periods.

In the study of emotional demands and exhaustion (study II) we applied a statistical approach that estimated cross-sectional and longitudinal effects simultaneously in the same model. Cross-sectional associations may be expected to be stronger compared with longitudinal associations and present at baseline and follow-up, whereby the cross-sectional associations bias the longitudinal association estimated. The applied method has advantages in respect to adjustment for cross-sectional effects, and allowing measures of covariates from baseline and follow-up to be implemented in the same model.

## 6.3 INTERPRETATIONS OF FINDINGS

### 6.3.1 PERCEIVED VS. CONTENT-RELATED EMOTIONAL DEMANDS

As described, perceived emotional demands and content-related emotional demands can be distinguished as work either can be experienced as demanding by the employee or include emotional situations that the employee has to handle. However, in most studies on mental health only perceived emotional demands or mixed items have been examined (5, 7, 8, 31, 56, 117, 119, 125), and only a few are based on content-related items separated from perceived emotional demands (9, 12, 120). Positive associations between emotional demands and mental health have mainly been found in studies using items on perceived emotional demands (7, 117, 125) while studies using content-related items have found mixed results (9, 12, 120). In one other study on health care workers and risk of exhaustion both the content-related and perceived emotional demands were examined cross-sectionally (9), and only perceived emotional demands increased the risk of exhaustion. In accordance we found that the associations for perceived and content-related demands differed in relation to depression. We would also expect perceive emotional demands to show an association with exhaustion in the current study, although not investigated, due to the associations found with depression (study I), former research on exhaustion in Danish context (117), and the elevated risk of reporting bias leading to possible overestimated effect. The differences in results for perceived and content-related demands with regards to depression may to some degree reflect reporting bias as discussed, but it also specify that the risk of depression associated with emotional demands at work has a stronger relation to personal perception of work than to specific emotionally demanding work tasks.

In the studies by Kim et al. (2012) and Sundin et al. (2011) several content-related scales were presented e.g. “pain and death” (e.g. caring for dying patients) and “professional worries” (e.g. worries for making mistakes) and “unmet care needs” (12, 120). These scales are even more specific compared to the more general content-related scale implemented in the present study including risk of making mistakes, caring for difficult or dying others etc. In study I, we also included a scale with more specific items concerning patient-care work. The content-related and patient-care related scales showed similar effects. The advantage of a more general scale is that it can be applied more broadly, and that the results consequently are more likely to be generalized across populations allowing comparison of exposure between professions. However, a more specific measure may allow a more precise estimation of situations in work associated with an elevated risk and may allow more effective intervention subsequently.

### 6.3.2 EMOTIONAL DEMANDS AND CLINICAL DEPRESSION

Several Scandinavian studies have addressed the longitudinal association between emotional demands at baseline and antidepressant use assessed by registers (Table 2) and generally found that higher levels of demands related to a higher risk of depression. All these studies used questions on perceived emotional demands. Other studies using mixed scales for measuring emotional demands and depression, tend to support this finding (43, 56). The present results support the conclusions of previous studies of perceived emotional demands, but add to the field by addressing content-related emotional demands at work separately. One other study addressed content-related emotional demands and depression with specific content-related scales and found a small association but only for unmet care needs (12). In the present study, both individual and average responses with individuals grouped by work-units were conducted and assessment of outcome was uniquely done by standardized clinical interviews. When applying these approaches, no association could be found between emotional demands at work and depression. This may indicate that personal factors and coping with emotional demands are more important as risk factors for depression than the emotional content of the work.

Person-related work has been assumed to involve high emotional demands (8, 16). This was also the case in the present study, where high levels of emotional demands were reported by employees working with patients. However, patient work was associated with a lower risk of depression, contradicting earlier studies showing higher risk of depression among human service workers (8, 16). The suggested selection of healthy participants into the present study may to some extent explain this discrepancy. Other explanations may be that the earlier Danish studies differed from our study by determine health-care work by profession and not according to their own assessment of whether they do patient work or not. Earlier studies further assessed depression by medication intake and not clinically.

### 6.3.3 EMOTIONAL DEMANDS AND EXHAUSTION

As reviewed in section (Table 4), no former studies exist analyzing the association between specific content-related emotional demands and exhaustion assessed by items that are independent of exposure (e.g. the CBI items) and few studies examine the longitudinal relationship. Perceived emotional demands and mixed items scales show manly positive associations. In order to show if the results from these studies could be reproduced

with the use of a content-related scale, we used a content-related scale in our study. Although only small effects were found, our presumably less biased results supported the previous longitudinal findings.

### 6.3.4 MODIFICATION OF WORK CHARACTERISTICS

In accordance with the JD-R model, work characteristics were hypothesized to moderate the association between demands at work and health outcomes. The moderating effect of work characteristics on the association between emotional demands and exhaustion or depression has been investigated, primarily in cross-sectional studies with exhaustion as outcome (9, 119), showing some support for the hypothesis. Few longitudinal studies have been conducted (6, 31, 122). Job control but not support has been found to modify the association between emotional demands and exhaustion in one longitudinal study (6, 31). The results of the present thesis did not support the hypothesis of a moderating effect of the included positive work characteristics with regards to depression, neither for the content- or perceived emotional demands. However, several characteristics moderated the association between content-related demands and exhaustion in the expected directions. These findings may have positive implications in a prevention perspective.

### 6.3.5 SALIVA CORTISOL AND DEPRESSION

Previous studies including working populations comparable or similar to the present found negative associations between cortisol levels and depression (162, 174) contradicting findings from patient studies and other longitudinal studies (Table 5) (14, 155). Sjøgren et al. (2006) measured cortisol three consecutive work days in a Swedish population and found that depressive symptoms were negatively correlated to single time points measures in the morning (awakening and to +30 minute cortisol), though not to the cortisol awakening response or the evening cortisol. PRISME data used in the study by Grynderup et al. (2013) showed that depression were also associated with a smaller difference between morning-evening measures of cortisol (slope)(174). This two year study further reported a negative association for the mean cortisol level and depression. The present study did not support previous findings of positive or negative associations; the overall finding was that there were no associations. Several methodological differences between studies may cause inconsistence in results, as studies differ in terms of included populations, follow-up time, and measures of exposure and outcome. This large study with repeated measurements, comprehensive confounder adjustment, and several measures of cortisol during the day showed that cortisol and depression were not associated in this

working population. Thus, the hypothesis that cortisol is a mechanism in the development of depression was not supported.

## 7.0 CONCLUSION

High perceived emotional demands were associated with an increased risk of depression diagnosed by standardised clinical interviews. For perceived emotional demands based on work-units, the association was in the same direction but lower and statistically non-significant. Depression was not associated with content-related measures of emotional demands (pathway A).

Increasing content-related emotional demands was associated with increasing levels of exhaustion, both cross-sectionally and longitudinally. Participants doing patient work had lower risk of developing depression compared to the rest of the included population (pathway B).

The effect of content-related emotional demands on exhaustion was found to be modified by work characteristics; the effect was reduced if the work was experienced as emotionally enriching and meaningful and aggravated by increasing quantitative demands (pathway C).

Cortisol was not associated with depressive symptoms of depression in repeated cross-sectional and in short-term follow-up analyses in this study including a large population of working public sector employees. This study does not indicate that cortisol is a mechanism linking work stress and depression (pathway D).

## 8.0 PERSPECTIVE

### 8.1 PRACTICAL IMPLICATIONS

Exhaustion at work is common and together with depression they form major problems for the health status of the population and the employee workability. We observed that reducing the employee's experience of emotional demands and the content of emotional demands at work could reduce depression and exhaustion, respectively. However, the emotional content of human service work is an integrated part when e.g. working with severely ill patients; experiencing grief and worries comes with the job. Thus, an interesting finding is that these demands may be eased by work characteristics such as emotional enrichment, support, and meaningfulness, or worsened by high workload and work pace with regards to exhaustion. We found only small effects of emotional demands at work that may be relevant at the population level. Together with the modifying effects of work characteristics this suggest that prevention at the workplace could focus on reducing specific emotionally demanding factors and support initiatives to improve psychosocial workplace factors.

### 8.2 PERSPECTIVES FOR FUTURE RESEARCH

The present thesis has added to the current knowledge by emphasizing the need of instruments to characterize types of emotional demands that may be relevant to prevention and intervention in the work place. Future studies may refine this knowledge, e.g. by the use of qualitative research methods.

To further understand why and when emotional demands becomes detrimental to health, qualitative research may examine, if we are measuring the right and most relevant emotional demands for specific populations. Also emotional demands outside the health care system may be relevant to explore further.

Longitudinal studies on saliva cortisol and depression in a general working population are few. Future studies on the temporal relation between work stressors, cortisol and mental health problems may benefit form including shorter and repeated follow-up times and ensure that cases of severe depression are contained.

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## 10.0 APPENDIXES

**Paper I** Emotional demands at work and the risk of clinical depression - a longitudinal study in the Danish public sector.
Vammen MA, Mikkelsen S, Hansen AM, Bonde JP, Grynderup MB, Kolstad H, Kærlev L, Mors O, Rugulies R, Thomsen JF.

**Paper II** Emotional demands and exhaustion – cross-sectional and longitudinal associations in a cohort of Danish public sector employees
Vammen MA, Mikkelsen S, Forman JL, Hansen AM, Bonde JP, Grynderup MB, Kolstad H, Kærlev L, Rugulies R, Thomsen JF.

**Paper III** Salivary cortisol and depression in public sector employees: Cross-sectional and short term follow-up findings.
Vammen MA, Mikkelsen S, Hansen AM, Grynderup MB, Andersen JH, Bonde JP, Butterschøn HN, Kærlev L, Mors O, Rugulies R, Thomsen JF.

**Paper I**

# Emotional demands at work and the risk of clinical depression

# – a longitudinal study in the Danish public sector


**AUTHORS**

Marianne Agergaard Vammen (Cand.scient.san.publ.) [1] , Sigurd Mikkelsen (MD)[1], Åse Marie Hansen (Professor)[2,3], Jens Peter Bonde(Professor)[1] , Matias B Grynderup (PhD)[2], Henrik Kolstad(Professor)[4] , Linda Kærlev (PhD) [5,6], Ole Mors (Professor)[7], Reiner Rugulies(Professor) [2,3,8], Jane Frølund Thomsen(PhD)[1]

**AFFILIATIONS**

[1]Department of Occupational and Environmental Medicine, Copenhagen, Bispebjerg University Hospital, Bispebjerg Bakke

[2]Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[3]National Research Centre for the Working Environment, Copenhagen, Denmark

[4] Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Denmark

[5]Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

[6]Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

[7]Research Department P, Aarhus University Hospital, Risskov, Denmark

[8]Department of Psychology, University of Copenhagen, Denmark



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**ABSTRACT**

**Objective:** This study is a two-year follow-up study of different dimensions of work-related emotional demands as predictor for clinical depression.

**Methods:** In a two wave study, 3,224 (72%) public employees from 474 work-units participated twice by filling in questionnaires. Sixty-two cases of clinical depression were diagnosed. Emotional demands were examined as perceived and content-related emotional demands, individually reported and work-unit-based. Support, meaningful work and enrichment were considered as potential effect modifiers.

**Results:** Individually reported perceived emotional demands predicted depression (odds ratio: 1.40; 95% confidence intervals: 1.02-1.92). The work-unit-based odds ratio was in the same direction, though not significant. Content-related emotional demands did not predict depression. Support, meaningful work and enrichment did not modify the results.

**Conclusions:** The personal perception of emotional demands was a risk factor for clinical depression but specific emotionally demanding work tasks were not.

## INTRODUCTION

Depression constitutes a major burden of disease in middle- and high-income countries assessed by disability-adjusted life years and a large health problem in the working-age population (1-3). The point prevalence of depression is estimated to 3.5-5 % in the Nordic countries and may be increasing (4).

Person-related work, especially within health care, education and social work, has repeatedly been identified as a risk factor for depression, other mental disorders and use of anti-depressive medication (5-8).

Emotional demands at work are a characteristic of person-related work (9) and may be an explanatory factor with respect to developing depression. In three prospective register-based studies of working populations emotional demands at baseline predicted the subsequent use of antidepressants (5, 10, 11), however, not significantly so in one of them (11). In two prospective questionnaire-based population studies, emotional demands predicted a high level of depressive symptoms (12, 13). Emotional demands was also associated with hospitalization for clinical depression in a case-control study based on a job-exposure-matrix of work-related psychosocial exposures, although only for women (14).

Emotional demands have been measured by different sets of items (15-19). Some have relied on perceived emotional demands without considering the content (e.g.: Is your work emotionally demanding?)(15) and others on assessment of content related emotional demands without considering how it is perceived (e.g. Do you have contact with difficult clients or patients in your work?)(16). Some scales of emotional demands include both types of items (19). It could be assumed that questions concerning content-related emotional demands would result in a less individual-dependent assessment of exposure than perceived emotional demands.

Measures of work-related psychosocial exposures less dependent on individual assessment may also be achieved by averaging individual self-reported exposures by occupations or work-units assumed to have homogeneous exposures (20). One study used a job-exposure-matrix in the analyses of the relation between emotional demands and depression (14) all other studies were based on individual exposure assessments of emotional demands (5, 10-12, 21).

There may be significant differences in estimated associations between work environment risk factors and depression, depending on whether the exposure is assessed by individual self-reports or aggregated work-units reports (20). Individual exposure assessment is a special problem when depression is the outcome, because depression or subclinical depression may influence the perception of the exposure, resulting in inflated exposure-response associations. Individual perceptions may be affected by life circumstances outside the workplace also affecting the person's mood and potentially bias the estimates.

Depression has been defined and measured in different ways in studies of emotional demands. In some studies, self-reported depressive symptoms have been the outcome measure (13, 21) whereas in other studies psychiatric patient records or, as a proxy for disease, prescription registers have been used (5, 11, 14). Self-reported symptoms and the use of prescription registers may lead to misclassification of cases (5, 13). Psychiatric patient-records may include severely ill individuals who may not be comparable to individuals in the working population (14, 22).

Any adverse effects of emotional demands could potentially be buffered by positive work factors. Emotionally demanding work may be emotionally enriching or rewarding (23). Emotional demanding work may also be felt as very meaningful. Social support by colleagues and superiors is generally considered to counteract negative effects of negative work environment factors. Meaningful work and social support at work has been associated with lower risk of depression (11, 12, 21).

This study is a two-year follow-up study of different dimensions of work related emotional demands at baseline as predictor for clinical depression at follow-up. Emotional demands were examined as individually reported measures of perceived and of content-related emotional demands, respectively, and of the same measures aggregated by work-units. Content-related emotional demands were included as a generic measure and as a measure for a subgroup of health care professionals. Clinical depression was assessed by a standardised interview of participants with high levels of questionnaire-reported mental symptoms. We further examined if the relation between emotional demands and depression was modified by positive work factors in terms of meaningful work, social support and emotional enrichment.

## MATERIALS AND METHODS

### Design

The design is a two-year follow-up study on emotional demands at work, measured at baseline, as a predictor for depression at follow up. Cases with clinical depression were diagnosed by a standardized psychiatric interview of participants with high levels of mental symptoms, at baseline and at follow-up. The study is based on the Danish PRISME cohort study with data collection in 2007 and 2009 (20, 24, 25).

### Population

In January 2007, we invited 10,036 public employees from 502 work-units in Aarhus, Denmark, to participate in the PRISME study. A work unit was defined by the employee's immediate supervisor. The workplaces included hospitals, schools, day care centers, social, technical and environmental services and administration. The most common professions were nurses, social workers and counseling professionals, teachers, managers, medical doctors, nursing aids, office clerks and preschool teachers (20).

A total of 4,489 employees (44.7%) from 474 work-units participated by filling in a postal questionnaire on work, health, life style and personal circumstances. Participants from 2007 were invited to participate in January 2009 and 3,287 (72%) filled in the follow-up questionnaire.

### Emotional demands

We used three measures of emotional demands: perceived emotional demands, content-related emotional demands and patient-care emotional demands. The items, response options and item scores are shown in figure 1. Each of the measures was scored as the mean of item-scores. If more than half of the items were missing the score was set to missing.

**Figure 1: Measures of emotional demands**

| | Questions |
|---|---|
| **Perceived emotional demands*** | |
| | • Is your work emotionally demanding?<br>• Do you get emotionally involved in your work? |
| **Content-related emotional demands*** | |
| | • Do you have to care for the emotional needs of others?<br>• Do you have to deal with others' grieves and worries?<br>• Do you have to cope with the suffering or death of others?<br>• Do you have to deal with "difficult" patients, clients, students etc?<br>• Are you at risk of making mistakes that may hurt other people? |
| **Patient-care emotional demands**** | |
| | • On average, how many times daily are you involved in procedures that are painful for the patient?<br>• In the last month, how many consultations have you had with patients or relatives about a poor condition of the patient?<br>• In the last month, how many patients that you have been in direct contact with have died?<br>• In the last month, how many times have you participated in surgery that did not work out as planned or had a high risk? |

* Introduction text: Please answer the following questions about your work. Scored: 1='to a very large extent', 2='to a large extent', 3='to some extent', 4='to a small extent' and 5='to a very small extent'.

** Introduction text: The following questions are answered only if you have to do with patients in your daily work. Scored on six-level: 1='none, 2='one', 3='two-three, 4='four-five', 5='six-ten' and 6='more than ten'.

Perceived emotional demands items were derived from the emotional demands scale of the Copenhagen Psychosocial Questionnaire (15, 19). Content-related emotional demands items were collected from

multiple existing questionnaires (26-29). Patient-care emotional demands items were designed specifically for this study.

**Mental symptoms**

We assessed depressive symptoms by the Common Mental Disorder Questionnaire subscale for depression (six items) (30), stress symptoms by the Perceived Stress Scale (four items)(31), and burn-out by the Copenhagen Burn-Out Inventory (six items) (15). All questions concerned the last four weeks and responses were given on 5-point ordinal scales (scores 1-5). Depression items were dichotomized (0=item score <3, 1=item score ≥3), and summed to a depression symptom scale with scores from 0 to 6. Burn-out and perceived stress scale scores were calculated as the mean of item scores (range 1 to 5). Higher scale scores indicate higher levels of depression, burn-out and perceived stress, respectively. If responses to more than half of the items of a scale were missing the scale score was set to missing.

**Screening for clinical depression**

Participants with high levels of mental symptoms were invited to participate in standardized psychiatric interview. At baseline we invited participants with a depression symptom score ≥3, a burn-out score ≥4 or a perceived stress score ≥2.5. We further invited a random sample of questionnaire responders. Analyses of these baseline data showed that the screening for cases with clinical depression would be more efficient with slightly changed selection criteria. At follow-up we invited participants with a high symptom level on at least two of the three mental symptom scales. High symptom levels were defined as a score ≥2 on the depression symptom scale, ≥2.5 on the burn-out scale, and ≥2.5 on the perceived stress scale.

**Diagnosis of clinical depression**

Clinical depression was diagnosed by a psychiatric SCAN-interview (Schedule for Clinical Assessment in Neuropsychiatry, version 2.1, part I, section 6, 7, and 8 and 10) according to the International Classification of Diseases, Tenth Revision: diagnostic criteria for research (ICD-10-DCR)(32). The interviews referred to symptoms the previous three months (33). Participants fulfilling the criteria for a mild, moderate and severe ICD-10-DCR depression were categorised as depressed.

**Positive work characteristics**

We hypothesized that any adverse effects of emotional demands would be modified by social support from colleagues and superiors, by experiencing the work as meaningful and important, and as emotionally enriching. These aspects of work were measured from questionnaire data in 2007. Social support from supervisors and colleagues were measured separately by 5-level items on supervisors and colleagues support (9) and meaningful work were assessed by the mean score of three 5-level items (e.g. “Is your work meaningful? “, “Do you feel that the work you do is important?”)(15). Emotional enrichment was measured by one question designed for this study: “Do you feel that your work with patients, clients, students etc. is emotionally enriching and satisfying?” scored on a 5-level scale from 1 “to a very small extent” to 5 “to a very large extent”.

**Potential confounders**

We included the following socio-demographic variables as potential confounders: sex, age (continuous), education beyond primary or high school (none or short training (< 3 years), medium higher (3-4 years) and long higher (>4 years) education), personal annual income in Danish crowns (continuous). As factors related to mental health and social life, we used: family history of depression (yes/no), previous episodes of depression (yes/no), traumatic life events during the last six months (continuous), cohabitation (yes/no),

and loneliness (yes/no). Participants' lifestyle was assessed by alcohol consumption (continuous), smoking (never and former/present smoker), physical activity, and body mass index (BMI, continuous).

Age and sex were recorded from the employee register files. The other information was recorded from the questionnaires. BMI was calculated from self-reported weight and height (BMI=weight (kg)/height$^2$($m^2$)). Traumatic life events within the last six months were measured in 2009 with nine questions on e.g. death of or serious illness among relatives or friends, marital problems or financial problems (34). Items were scored as 0='no' or 'yes, it was not bad', 1= 'yes, it felt bad', 2='yes, it felt very bad'. For the analyses we used the maximum score of the 9 items.

Neurotic personality trait (neuroticism) was measured with Eysenck Personality Questionnaire Revised-Abbreviated version (continuous, scale 0-1) (35).

**STATISTICAL ANALYSIS**

We pursued less individual-dependent assessments of emotional demands by calculating the means of the three emotional demands variables for each work-unit. The mean values were then assigned to all employees in a particular work-unit. Positive work characteristics and potential confounders were analysed at the individual level.

The association between emotional demands at baseline and the risk of clinical depression at follow-up was examined by logistic regression, separately for each of the three individual-based emotional demands variables, and for the three work-unit-based emotional demands variables. Analyses were performed using both continuous-scale exposure information and exposure divided into tertiles forming a low-, medium-, and high-exposure group.

Potential confounders were included in three steps; step one included sociodemographic variables, step two included factors related to mental health and social life and finally lifestyle factors were included. At each step we excluded potential confounders if their effect was not statistically significant at $p<0.25$ unless the exclusion caused the effect estimate of emotional demands to change by more than 10%. The final multivariate logistic regression models of perceived emotional demands and content-related emotional demands (individual-based and work-unit-based) included the covariates: personal income, previous episodes of depression, traumatic life events during the last six months (at follow-up), loneliness, and smoking. The final models of patient-care emotional demands (individual-based and work-unit-based) included previous episodes of depression, traumatic life events during the last six months (at follow-up) and smoking.

We also examined if work-unit clustering had any effects by inclusion of a work-unit random effect term using mixed logistic regression models, but this term had no statistically significant effects and was omitted from the final models.

Linearity of effects of all continuous covariates were examined in preliminary crude analyses by including quadratic and cubic terms, but none of these terms had statistically significant effects.

Finally, neurotic personality trait and depressive symptoms were included as covariates in the final models in sensitivity analyses.

**Patient-care work**

The association of patient-care work (yes/no) with depression, perceived emotional demands and content-related emotional demands was examined in supplemental analyses. The association with depression was examined in logistic regression models with the dichotomous patient-care variable and potential confounders from the final models of the previous analyses. To these analyses we added perceived emotional demands or content-related emotional demands as covariates and their interaction term with the dichotomous patient-care variable to examine, if the emotional demands variables had a different effect on depression for participants with and participants without patient-care.

**Interactions with positive work characteristics**

We tested for effect modification from supervisors' support, colleagues' support, meaningful work and emotional enrichment (all continuous) by including an interaction terms with emotional demands in the final logistic regression models.

For all analysis, we used the software SAS 9.3 (proc glimmix; SAS Institute, Cary, NC).

**RESULTS**

A total of 3,209 answered the questionnaire both at baseline and follow-up. We identified 70 participants with depression at baseline. After excluding clinically depressed at baseline and participants not answering questions on perceived emotional demands or content-related emotional demands our final study population comprised 3,125 workers from 455 work-units. Of those, 62 were clinically depressed at follow-up.

The baseline characteristics of the population with corresponding crude odds ratios (OR) of depression are shown in table 1. The majority of participants were women (78%), the mean age was 45 years (range 20-66 years). Smoking, low income, previous depression and loneliness at baseline and traumatic life events in the previous six months were associated with a higher frequency of incident depression at follow-up. Meaningful work and social support from colleagues and social support from supervisor were associated with a lower frequency of depression (table 1).

**Table 1: Baseline characteristics (2007) of total population and participants with or without a diagnosis of depression at follow-up (2009)**

| Characteristic | Total population (n=4389) | | Participants (n=3125) | | | | |
|---|---|---|---|---|---|---|---|
| | n | % | Non-depressed at follow-up (n=3063) | % | Depressed at follow-up (n=62) | % | OR (95% CI)[a] |
| **Sociodemographic** | | | | | | | |
| **Gender** | | | | | | | |
| Male | 951 | 21.7 | 667 | 21.8 | 10 | 16.1 | 1 |
| Female | 3438 | 78.3 | 2396 | 78.2 | 52 | 83.9 | 1.45 (0.73-2.86) |
| **Age**[b] | | | | | | | 1.00 (0.97-1.03) |
| <35 years | 964 | 22.0 | 602 | 19.7 | 14 | 22.6 | |
| 35-44 years | 1073 | 24.5 | 733 | 23.9 | 13 | 21.0 | |
| 45-54 years | 1528 | 34.8 | 1111 | 36.3 | 24 | 38.7 | |
| ≥55 years | 824 | 18.8 | 617 | 20.1 | 11 | 17.7 | |
| **Personal income (DDK)**[b] | | | | | | | 0.57 (0.35-0.93)[c] |
| ≤299 999 | 2148 | 51.8 | 1435 | 49.1 | 36 | 63.2 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 300 000 - 499 999 | 1750 | 42.2 | 1309 | 44.8 | 20 | 35.1 | |
| ≥500 000 | 247 | 6.0 | 179 | 6.1 | 1 | 1.8 | |
| **Professional education beyond primary or high school** | | | | | | | |
| <3 years | 866 | 19.8 | 531 | 17.4 | 12 | 19.4 | 1 |
| 3-4 years | 3008 | 68.8 | 2148 | 70.3 | 45 | 72.6 | 0.93 (0.49-1.76) |
| >4 years | 500 | 11.4 | 375 | 12.3 | 5 | 8.1 | 0.59 (0.21-1.69) |
| **Mental health and social life** | | | | | | | |
| **Cohabitation** | | | | | | | |
| Yes | 3544 | 80.9 | 2489 | 81.4 | 52 | 83.9 | 1 |
| No | 836 | 19.1 | 570 | 18.6 | 10 | 16.1 | 0.84 (0.42-1.66) |
| **Family history of depression** | | | | | | | |
| No | 2810 | 70.8 | 1986 | 71.1 | 33 | 60.0 | 1 |
| Yes | 1161 | 29.2 | 808 | 28.9 | 22 | 40.0 | 1.64 (0.95-2.83) |
| **Previous depression** | | | | | | | |
| No | 3692 | 86.5 | 2619 | 87.8 | 32 | 54.2 | 1 |
| Yes | 574 | 13.5 | 364 | 12.2 | 27 | 45.8 | 6.07 (3.60-10.25)[c] |
| **Traumatic life event** | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | No events | 2802 | 64.0 | 1990 | 65.1 | 26 | 41.9 | 1 |
| | Yes, felt bad | 942 | 21.5 | 657 | 21.5 | 21 | 33.9 | 2.45 (1.37-4.38)[c] |
| | Yes, felt very bad | 634 | 14.5 | 411 | 13.4 | 15 | 24.2 | 2.79 (1.47-5.32)[c] |
| **Loneliness** | | | | | | | | |
| | No | 4200 | 96.2 | 2940 | 96.4 | 55 | 88.7 | 1 |
| | Yes | 168 | 3.9 | 110 | 3.6 | 7 | 11.3 | 3.70 (1.52-7.64)[c] |
| **Lifestyle** | | | | | | | | |
| **Physical activity** | | | | | | | | |
| | Rarely | 2308 | 52.9 | 1589 | 52.1 | 34 | 54.8 | 1 |
| | Often | 2058 | 47.1 | 1459 | 47.9 | 28 | 45.2 | 0.90 (0.54-1.49) |
| **Alcohol consumption**[b] | | | | | | | | 0.88 (0.71-1.10) |
| | Low | 3336 | 76.9 | 2298 | 75.8 | 48 | 77.4 | |
| | High | 1002 | 23.1 | 735 | 24.2 | 14 | 22.6 | |
| **BMI**[b] | | | | | | | | 1.03 (0.97-1.09) |
| | Low | 2828 | 65.2 | 1983 | 65.4 | 38 | 62.3 | |
| | High | 1509 | 34.8 | 1052 | 34.6 | 23 | 37.7 | |
| **Smoking** | | | | | | | | |
| | No/former | 3577 | 82.0 | 2585 | 85.0 | 39 | 62.9 | 1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Smoker | 784 | 18.0 | 458 | 15.1 | 23 | 37.1 | 3.30 (1.95-5.58)[c] |
| **Positive work characteristics** [b] | | | | | | | |
| **Meaning of work (1-5)** | | | | | | | 0.54 (0.36-0.79)[c] |
| Low (1- <4) | 941 | 21.6 | 607 | 19.9 | 21 | 33.9 | |
| High (4-5) | 3424 | 78.4 | 2447 | 80.1 | 41 | 66.1 | |
| **Social support (1-5)** | | | | | | | |
| **Colleagues support** | | | | | | | 0.71 (0.56-0.91)[c] |
| Low (1- <4) | 1172 | 27.0 | 777 | 25.5 | 24 | 38.7 | |
| High (4-5) | 3180 | 73.1 | 2268 | 74.5 | 38 | 61.3 | |
| **Supervisor support** | | | | | | | 0.65 (0.53-0.79)[c] |
| Low (1- <4) | 1988 | 45.7 | 1358 | 44.7 | 42 | 67.7 | |
| High (4-5) | 2358 | 54.3 | 1682 | 55.3 | 20 | 32.3 | |
| **Emotional enrichment (1-5)** | | | | | | | 0.80 (0.61-1.01) |
| Low (1- <4) | 1536 | 35.6 | 1050 | 34.7 | 29 | 47.5 | |
| High (4-5) | 2777 | 64.4 | 1975 | 65.3 | 32 | 52.5 | |
| **Sensitivity** | | | | | | | |
| **Neuroticism (0-1)**[b] | | | | | | | 37.2 (15.4-89.7)[c] |
| No (0) | 1944 | 44.5 | 1418 | 46.4 | 2 | 3.3 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| yes (>0) | 2423 | 55.5 | 1636 | 53.6 | 59 | 96.7 | |
| **Depressive symptoms (0-6)** | | | | | | | 1.74 (1.5-2.02)[c] |
| Low (0-2) | 4140 | 94.8 | 2915 | 97.2 | 53 | 56.5 | |
| High (3-6) | 229 | 5.2 | 140 | 2.8 | 9 | 43.6 | |
| **Job change** | | | | | | | 0.83 (0.42-1.66) |
| No | 2337 | 79.4 | 2268 | 79.3 | 46 | 82.1 | |
| yes | 602 | 20.7 | 592 | 20.7 | 10 | 18.0 | |
| **Emotional demands** | | | | | | | |
| **Perceived emotional demands** | | | | | | | 1.51 (1.13-2.02)[c] |
| Low (1- <4) | 2332 | 52.3 | 1620 | 53.0 | 27 | 43.6 | |
| High (4-5) | 2128 | 48.0 | 1434 | 47.0 | 35 | 56.5 | |
| **Content-related emotional demands** | | | | | | | |
| Low (1- <4) | 1337 | 30.0 | 909 | 29.7 | 21 | 33.9 | 1.18 (0.93-1.48) |
| High (4-5) | 3133 | 70.0 | 2153 | 70.3 | 41 | 66.1 | |
| **Patient-care emotional demands** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Low (1- <4) | 1610 | 86.1 | 1143 | 86.3 | 12 | 75.0 | 1.04 (0.58-1.85) |
| High (4-5.5) | 256 | 13.9 | 182 | 13.7 | 4 | 25.0 | |

[a] Calculated by logistic regression, [b] Continuous variable in the analysis, [c] $p<0.01$.

Perceived emotional demands was statistically significantly associated with depression in analyses based on individual data ($OR_{adj}$ = 1.40 per unit increase in perceived emotional demands (95%CI 1.02-1.92), p=0.04) but not in analyses based on work-unit data, although the association was in the same direction (table 2). The ORs of the associations of the other measures of emotional demands with depression were close to unity and statistically not significant in all analyses (table 2). These results changed only marginally when the adjusted main models were further adjusted for neurotic personality trait and depressive symptoms (results not shown).

**Table 2: Odds ratios of clinical depression by increasing level of emotional demands**

| | Individual-based | | | | Work-unit-based | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **OR** | **95% CI** | **OR[a]** | **95% CI** | **Tertiles** | **OR** | **95% CI** | **OR[a]** | **95% CI** |
| **Perceived emotional demands (continuous, 1-5)** | 1.51 | 1.13-2.02 | 1.40 | 1.02-1.92 | | 1.31 | 0.82-2.10 | 1.24 | 0.75-2.07 |
| **Perceived emotional demands (tertiles)** | | | | | | | | | |
| **Low (1-3)** | 1 | | 1 | | **Low (1-3.14)** | 1 | | 1 | |
| **Medium (>3 - 3.5)** | 1.28 | 0.63-2.61 | 1.43 | 0.67-3.04 | **Medium (>3.14-3.48)** | 1.54 | 0.81-2.94 | 1.72 | 0.88-3.39 |
| **High(>3.5-5)** | 1.93 | 0.94-3.94 | 1.77 | 0.82-3.82 | **High (>3.48-5)** | 1.36 | 0.71-2.59 | 1.21 | 0.61-2.41 |
| **Content-related emotional demands (continuous)** | 0.99 | 0.76-1.28 | 0.93 | 0.70-1.24 | | 0.90 | 0.64-1.27 | 0.92 | 0.62-1.35 |
| **Content-related emotional demands (tertiles)** | | | | | | | | | |
| **Low (1-3.2)** | 1 | | 1 | | **Low (1-3.39)** | 1 | | 1 | |
| **Medium (>3.2-4)** | 0.98 | 0.54-1.76 | 1.06 | 0.57-1.98 | **Medium (>3.39-3.9)** | 1.20 | 0.66-2.20 | 1.21 | 0.64-2.30 |
| **High(>4-5)** | 0.82 | 0.44-1.54 | 0.77 | 0.39-1.49 | **High (>3.9-5)** | 0.94 | 0.50-1.76 | 0.93 | 0.47-1.81 |
| **Patient-care emotional demands (continuous)** | 1.03 | 0.58-1.85 | 1.14 | 0.62-2.09 | | 0.72 | 0.28-1.81 | 1.01 | 0.39-2.68 |
| **Patient-care emotional demands (tertiles)** | | | | | | | | | |
| **Low (1-1.75)** | 1 | | 1 | | **Low (1-2.08)** | 1 | | 1 | |
| **Medium (> 1.75-2.5)** | 0.94 | 0.29-3.10 | 0.79 | 0.21-2.90 | **Medium (>2.08-2.36)** | 0.75 | 0.24-2.39 | 0.86 | 0.23-3.19 |
| **High(>2.5-5.5)** | 1.21 | 0.37-4.00 | 1.24 | 0.33-4.66 | **High (>2.36-5.5)** | 0.59 | 0.17-2.04 | 1.00 | 0.27-3.80 |

[a] Analyses of perceived and content-related emotional demands are in the final model adjusted for personal income, previous episodes of depression, traumatic life events, loneliness and smoking. Analyses of patient-care emotional demands are adjusted for all the same variables with the exception of personal income and loneliness.

**Patient-care work**

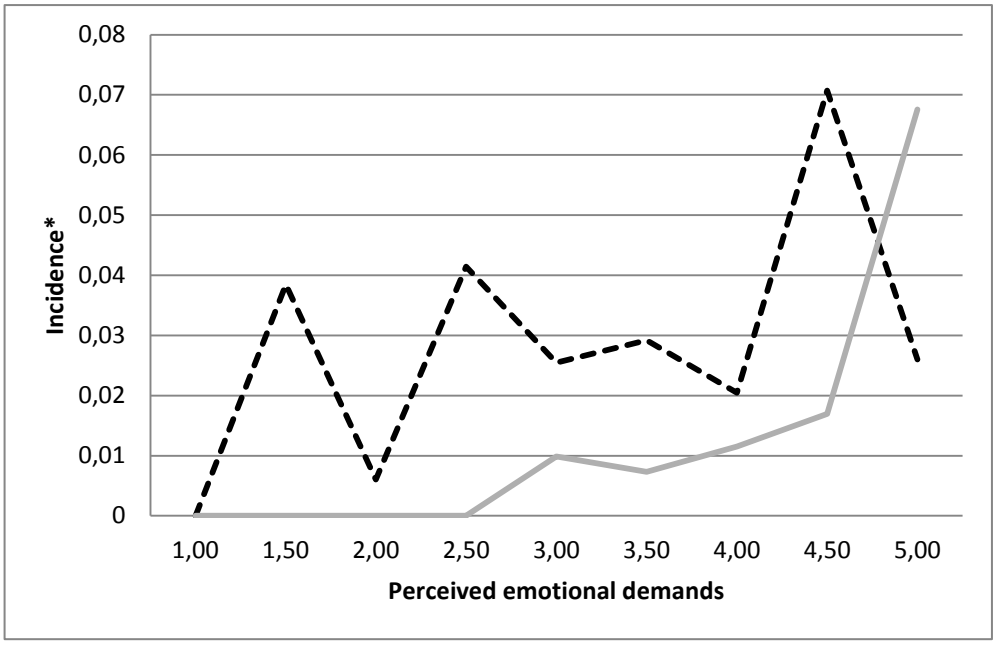
Participants dealing with patients (n=1366 (44%)) reported statistically significantly higher levels of perceived emotional demands and content-related emotional demands than other participants ($p<0.01$, crude and adjusted for covariates in the final model). Participants dealing with patients, however, had a lower risk of depression crude and adjusted for covariates in the final model (OR=0.50 (95% CI: 0.27-0.94), p=0.003).

This finding was unexpected, and we therefore examined if individual-based perceived emotional demands and content-related emotional demands had different effects among participants dealing with patients than among those who did not. The patient-care variable was included in the main analyses models for perceived emotional demands and content-related emotional demands together with an interaction term between the patient-care variable and the emotional demands variables.

The interaction term for perceived emotional demands and patient-care was significant in the final model (p=0.045) but the interaction term for content-related emotional demands and patient-care was not. Among patient-care participants a one unit increase in perceived emotional demands was associated with an OR of depression of 2.92 (95% CI: 1.41-6.04). The corresponding OR among participants without patient-care was 1.25 (95% CI: 0.89-1.75).

Over the entire range of individually perceived emotional demands, except for the highest level, the incidence rate of depression was lower for participants with patient-care than for those without. The risk of depression increased steeply with perceived emotional demands above 2.5 for patient-care workers. For participants without patient-care the risk of depression was irregular with only a modest average increase with increasing perceived emotional demands.

**Figure 2: Proportion with depression at follow-up by categories of individually perceived emotional demands for participants with patient-care work (gray) and without patient-care work (dotted).**




*Incidence: Calculated as the number of cases divided by the total number of participants within the groups of participants with and without patients, respectively.

We also examined the patient-care factor work-unit based. The same pattern was seen, however, no interactions were observed.

**Positive work characteristics**

Meaningful work and supervisor support at baseline predicted a reduced risk of depression at follow-up when added as covariates in the main analyses models. Analyses of colleague support and emotional enrichment showed results in the same direction but did not reach statistical significance. The effect sizes in the adjusted analyses were similar to those of the crude analyses (shown in table 1). The associations between the emotional demands variables and depression changed less than 15% by adding positive work

characteristics to the other adjustment variables and did not change any significant results of emotional demands.

Interaction terms between the emotional demands variables and positive work characteristics had no statistically significant effects, except for patient-care emotional demands with meaningful work (p=0.012) and with supervisor support (p=0.019), and only for individual-based data. At low levels of patient-care emotional demands, higher levels of meaningful work reduced the risk of depression, and at high levels of patient-care emotional demands, higher levels of meaningful work increased the risk. The same pattern was found for the interaction between supervisor support and patient-care emotional demands (data not shown).

**DISCUSSION**

Like several previous studies this study found an increased risk of depression for those who reported high levels of emotional demands when this was measured as responses to generally formulated questions about the individual's perception of the extent of emotional demands at work. When work-unit measures were used, the OR was in the same direction but lower and not statistically significant. These findings could, however, not be reproduced in the individual and group-based analyses of content-related emotional demands. Thus, questions relating directly to the emotional dimensions of work situations, like e.g. having to deal with other people's grieves or suffering did not show any relationship with the development of depression. We had expected that positive factors such as meaningful work, social support and enrichment would moderate the effect of the perceived emotional demands but this was not the case. Meaningful work and supervisor support were both strong independent predictors of a reduced risk of depression.

The results regarding the subjective experience of perceived emotional demands generally corroborate previous findings on the relationship between emotional demands and depression. Wieclaw et al observed an elevated risk of depression among women only (IRR 1.39 95%CI 1.22-58) in a Danish population-based case-control study with a job exposure matrix used to asses psychosocial working exposures and with cases from psychiatric patients records (14.166 cases) (14). Madsen et al reported an elevated use of antidepressant medicine among employees with high emotional demands (OR: 1.51 (95% CI 1.18-1.94)) in a follow-up study on a representative sample of working Danes (5). A recent study with data from the same cohort, supplemented with data from a Swedish cohort, showed similar results (HR: 1.45 95%CI 1.24-1.66)(10). Another Danish study showed associations in the same direction although not statistically significant between emotional demands and use of antidepressant in a working population among employees aged 40 and 50 years (11). All four studies were longitudinal and used the emotional demands

questions from COPSOQ, similar to the perceived emotional demands scale in this study with register-based outcomes. Few other longitudinal studies have also dealt with emotional demands at work. In these studies, emotional demands were determined using tools other than COPSOQ and both exposure and outcomes were self-assessed. The findings were in general consistent and showed an association. Thus, Andrea et al. observed an association between emotional demands and depression symptoms in a study with one year follow-up among men (n = 7,472 employees men/women) (21). In a later study with two years of follow-up time and a population including a subset of the former, they reported an association between emotional demands and depression symptoms in both genders, although not statistically significant when controlled for other psychosocial work factors (12). In a six-month follow-up study among homecare workers Kim et al. reported a relationship between a dimension of emotional demands referred to as "unmet care needs" – involving elements of content-related emotional demands - and depression symptoms (13). Finally, a small American multilevel follow-up study among nursing assistants (n=241) also demonstrated an association between self-reported emotional demands and depression symptoms (36). Overall, a possible association between emotional demands and depression may exist although reporting bias and misclassification may explain the findings.

The present study contributes to the earlier studies in particular by the use of a separate content-related dimension of emotional demands and work-unit-based estimates of the exposures. The content-related approach asks specifically for emotionally demanding situations at work assuming that responses would be less influenced by e.g. the mood of the participant. Furthermore, in the work-unit-based analyses, measures of exposure represented the average worker and were thus less dependent on the individual worker's interpretation of his/her psychosocial working environment. Overall, these measures of exposure may have the ability to avoid false associations because of "common method bias", occurring when both exposure and mental health problems are self-reported (11, 20, 37). Still, if only the exposure and not the

outcome are self-reported, as seen in other Danish studies in this area (5, 11), personal affectivity may disturb the individual's reporting on the degree of exposure, and compromise the ability to estimate the actual exposure effect (20). The results of the less individual-dependent exposure analyses (based on content-related emotional demands and work-unit-based measures) in the present study did, however, not show a relationship between emotional demands and depression and thus did not support the existing general understanding of a relationship between high emotional demands and the development of depression. Thus, the association found here and in previous studies may be explained by personal perception and not the content of specific emotionally demanding work tasks.

A limitation of the group-based approach is reduced contrasts between groups compared to individual-based analyses, resulting in a possible extension of the confidence intervals but not necessarily an attenuation of the risk estimates (38). Results of both the individual-based content-related emotional demands and work-unit-based measures were all statistically non-significant. However, both individual and group-based measures showed positive risk estimates for the dimension of emotional demands concerned with the individual's perception of emotional demands (perceived emotional demands) in work and clinical depression.

Participants working with patients had higher perceived emotional demands and content-related emotional demands than other participants. However, their risk of depression was only half of the risk of other participants. This finding was unexpected since previous findings have indicated that health care workers have a higher risk of hospitalization for depression (8, 14) and of purchasing antidepressant medication (5). However, both of these outcomes could be inflated by earlier and easier access to treatment as opposed to our outcome which was independent of access to treatment. Another explanation could be selection into the health care professions of persons who are robust to adverse effects of the specific emotional demands

in these professions, and selection out of the professions of persons who find themselves uneasy with these demands. Such a selection could possibly also explain why the effect of perceived stress on depression was different for participants with and without patient-care, and why only higher levels of perceived emotional demands was associated with depression among patient-care participants in our study. The risk of depression seemed particularly high at the highest level of perceived emotional demands. However, this level included only four patient-care depression cases, and the result is therefore considered as unstable.

We hypothesized that higher levels of positive work characteristics would buffer any adverse effects of high emotional demands on depression. However, the analyses did not support this hypothesis. In twelve analyses of interaction effects we observed two significant effects, both of them for patient-care emotional demands, i.e. meaningful work and supervisor support. However, the risk of depression for combinations of levels of patient-care emotional demands and the two other work characteristics had no meaningful interpretation. Among participants caring for patients there were only few cases with depression (n=16) and a few changes in emotional demands scores among these cases could have changed the results. Although formally statistically significant we consider these findings as probably due to chance.

The analyses, however, demonstrated that meaningful work and supervisor support were two strong independent protectors of depression. This is supported by previous studies in the field (11, 12). The experience of the work as emotionally rewarding tended to reduce the risk of depression, but the results were not statistically significant. These analyses were performed at the individual level. In order to achieve less individual-dependent results, it would be appropriate in future analyses to examine these associations at the work-unit level. Our purpose was here primarily to illustrate possible interaction effects. The

individual-level will in this context be most sensitive, since we observed no significant interactions at this level, we have not analysed it further.

**Methodological considerations**

Depression was assessed by guided interviews using a WHO validated instrument and interviewers had received a week's training beforehand. However, we selected the participants to participate in the SCAN-interviews based on their questionnaire responses. In this process we could have missed depressed people. Furthermore, this method does not allow for continuous identification of cases, as for example register studies do, and therefore participants may be in remission at the time of follow-up. Overall, this could lead to a possible loss of power and bias a true effect towards the null.

To achieve the best possible confounder control despite a limited number of cases, we made a careful confounder selection. Thus, it has been possible to include multiple possible confounding factors. Only in sensitivity analyses we took into account variables regarding personality and depressive symptoms, as we wanted the population to the best extent possible to be comparable to a normal Danish working population. However, these factors did not change the main results.

Participation rate at baseline was only 45%. In previous analyses, however, we found no indications that the low baseline participation distorted the estimates of the associations between other psychological work environment demands and the use of antidepressants at follow-up (25). At follow-up, participation rate was higher (72%), but drop-outs may still bias the results. However, emotional demands did not predict participation at follow-up (results not shown) indicating that the drop-out rate did not bias the results.

If selection into and out of the healthcare profession is taking place, job change may be a factor affecting the relationship between emotional demands and depression. The possibility of making a job change could

be a protective factor in relation to the development of a depression when a person experiences high demands at work. We had the opportunity to account for 'job change within the last year' measured at follow-up. The variable was not significant in any of the final models, neither when included as a potential confounder nor as an interaction term (data not shown). However, it is important to realise that the choice of profession and selection into and out of a job are complex processes that are not covered by this time-limited question alone.

## CONCLUSION

In conclusion, individually reported perceived emotional demands were associated with an increased risk of depression diagnosed by standardised clinical interviews. For perceived emotional demands based on work-unit, the OR was in the same direction but lower and statistically non-significant. Depression was not associated with content-related measures of emotional demands. The study may indicate that personal factors and coping with emotional demands are more important as risk factors for depression than emotional demands as such.

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**Paper II**

# Emotional demands and exhaustion

## – cross-sectional and longitudinal associations in a cohort of Danish public sector employees


**AUTHORS**

Vammen MA[1], Mikkelsen S[1], Forman JL[2], Hansen AM[2], Bonde JP[1], Grynderup MB[2], Kolstad H[4], Kærlev L[5,6], Rugulies R[2,3,7], Thomsen JF[1].

**AFFILIATIONS**

[1]Department of Occupational and Environmental Medicine, Copenhagen, Bispebjerg University Hospital, Bispebjerg Bakke

[2]Department of Public Health, University of Copenhagen, Copenhagen, Denmark

[3]National Research Centre for the Working Environment, Copenhagen, Denmark

[4] Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Denmark

[5]Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

[6]Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark

[7]Department of Psychology, University of Copenhagen, Denmark


*DRAFT*

**Objective:** To examine cross-sectional and longitudinal associations between emotional demands at work and exhaustion, and to investigate if these associations were modified by other psychosocial work characteristics.

**Methods:** In 2007, 4,489 Danish public service employees participated in the PRISME study by completing postal questionnaires, and 3,224 participated in the follow-up in 2009. Emotional demands were measured by a scale (scored 1 to 5) based on five work-content-related items, and exhaustion was measured with the scale of general exhaustion from the Copenhagen Burnout Inventory (CBI) (scored 1 to 5). The cross-sectional and longitudinal associations with exhaustion were analysed in the same model and adjusted for effects of potential confounders. Effect modifications were examined separately for self-reported emotional enrichment, meaningful work, job control, social support at work and quantitative demands.

**Results:** Exhaustion increased with increasing emotional demands, both cross-sectionally and longitudinally. However, although statistically significant, the effect was small. In the longitudinal analysis a one unit increase in emotional demands was associated with a 0.034 unit (95% CI: 0.006-0.061) increase in exhaustion. We found a statistically significant effect modification for three of the six potentially modifying work characteristics. The effect of emotional demands on exhaustion was significantly lower for participants with high levels of emotional enrichment (cross-sectionally and longitudinally), high levels of meaningful work (longitudinally), and higher for high levels of quantitative demands (cross-sectionally).

**Conclusions:** This study showed that increasing emotional demands was associated with increasing levels of exhaustion, cross-sectionally and longitudinally. This effect was reduced if the work was experienced as emotionally enriching and meaningful, and aggravated by increasing quantitative demands.

## INTRODUCTION

Exhaustion resulting from emotional demands at work has attracted much attention, scientifically and in the public, since Freudenberger and Maslach in the mid 1970's described a state of prolonged occupational stress and energy deficit among human service workers (1-3). The condition was labelled "burnout" and defined as a syndrome including three psychosocial dimensions: high emotional exhaustion reduced personal accomplishment and depersonalisation, caused by human service work. The Maslach Burnout Inventory (MBI) (2, 4) was developed as a research tool to measure these dimensions.

Subsequent research, however, has shown that the three-dimensional burnout syndrome is psychometrically questionable since negative correlations between the three dimensions may occur (5). Furthermore, high burnout scores may be found in other work than human service work. These findings have redirected research towards emotional exhaustion, assumed to be the core-dimension in burnout (6-10), and to distinguish between exhaustion as such, and if persons attribute this exhaustion to their work. These considerations were the background for the development of the Copenhagen Burnout Inventory (CBI) (11). This instrument includes two scales of exhaustion attributed to work in general and to human service work, and one scale of exhaustion with no attribution aspects. The instrument was developed in the context of burnout research and the scale of exhaustion with no attribution aspects was therefore labelled as "personal burnout". However, leaving connotations to the burnout literature behind, the scale is better and simpler labelled as a scale of exhaustion.

Exhaustion has been associated with sleep problems, common infections, sickness absence, depression, and poor quality of life with negative consequences for workplaces and society at large (12-15). If work-related exposures can be identified as causes of exhaustion these effects could possibly be prevented by targeted intervention programs at the work place.

Emotional demands at work have been associated with exhaustion in many studies. Most of these are cross-sectional (9, 16-24), but positive associations between emotional demands at baseline and exhaustion at follow-up have also been found in a few longitudinal studies (25-29).

Emotional demands have almost exclusively been measured by questionnaires or interviews (30, 31). Items and scales of emotional demands may reflect subjective perceptions of emotional demands at work (perceived emotional demands) or the specific job content which the researchers assume will involve emotional demands (content-related emotional demands). Most studies on emotional demands and exhaustion are based on measures of perceived emotional demands (20, 23, 29), some studies are based on a mixture of perceived and content-related items (16, 19, 27), and a few are based on content-related items separated from perceived emotional demands (9, 18, 32). The positive association between

emotional demands and exhaustion has mainly been found in studies using items on perceived emotional demands (20, 23, 29) while studies using content-related items have found mixed results (9, 18, 32).

Another important aspect of the relation between emotional demands and exhaustion is the extent to which this relation may be modified by other psychosocial work characteristics. Some studies suggest that high job control and social support may reduce the effect of emotional demands on exhaustion (9, 19, 26-28). Emotional demands at work may arise from working with people in difficult situations, which at the same time may be felt as rewarding and enriching (30, 33). If so, any effects of emotional demands on exhaustion could possibly be reduced. A similar argument may hold if work is perceived as very meaningful. And contrary, any effects of emotional demands on exhaustion could increase if other demands were high (e.g. quantitative demands). If such modifying effects exist preventive interventions could also be targeted at changing these factors.

Perceived emotional demands may be influenced by personal factors such as personality, present emotional state and a tendency to attribute negative feelings to external causes (34) . Content-related factual information is assumed to be less influenced by such personal factors, and specific work-place factors are more readily accessible for intervention changes at the workplace than personal perception factors.

This study examines the associations between content-related emotional demands and exhaustion in a two-year follow-up study of a large population of public sector employees. We hypothesized 1) that the level of exhaustion increases with increasing emotional demands, and 2) that this association decreases by increasing levels of emotional enrichment, meaningful work, job control, and social support at work, and increases by increasing quantitative demands.

## MATERIALS AND METHODS

### Study population and design

In January 2007 we invited 10.036 public sector employees in Aarhus, Denmark to participate in a study on psychological risk factors in the work environment and mental health disorders (the PRISME-cohort study) (34). They were asked to fill in a questionnaire on psychosocial working conditions, health and other personal factors. A total of 4.489 (45%) returned the questionnaire in 2007. In January 2009, participants from 2007 were asked to participate in a follow-up study. A total of 3.224 (72%) employees participated at follow-up. The workplaces included hospitals, schools, day care centres, social, technical and environmental services and administration. The most common professions among participants were nurses, social workers and counselling professionals, teachers, managers, medical doctors, nursing aids, office clerks and preschool teachers (34).

### Emotional demands

We measured emotional demands by five items about specific work characteristics assumed to be emotionally demanding: "Do you have to care for the emotional needs of others?", "Do you have to deal with others' grieves and worries?", "Do you have to cope with the suffering or death of others?", "Do you have to deal with "difficult" patients, clients, students etc.?" and "Are you at risk of making mistakes that may hurt other people?" Items were scored: 1='to a very small extent', 2='to a small extent', 3='to some extent', 4='to a large extent', and 5='to a very large extent'. A scale of emotional demands was calculated as the mean of item-scores. If more than half of the items were missing the score was set to missing.

### Exhaustion

Exhaustion was measured with the complete scale of personal burnout from the CBI (4): "How often do you feel tired? ", "How often are you physically exhausted? ", "How often are you emotionally exhausted? ", "How often do you think: 'I can't take it anymore'? ", "How often do you feel worn out? ", and "How often do you feel weak and susceptible to illness? ". Items were scored: 1='never', 2= 'rarely', 3= 'sometimes', 4= 'often', and 5= 'always' and calculated as the mean of the item-scores. If more than half of the items were missing the score was set to missing.

### Other psychosocial work characteristics

We used items from the Copenhagen Psychosocial Questionnaire (COPSOQ) (31, 35) to construct scales measuring quantitative demands regarding work load and time pressure (4 items), decision authority

(4 items) skill discretion (4 items), social support from supervisors (1 item), social support from colleagues (1 item) and meaningful work (3 items). All items were scored 1 to 5. Scales were constructed as the mean of item scores. High scores indicate a high level of the variable content (e.g. high demands, high control etc.). If more than half of the items were missing the score was set to missing. A scale of job control was constructed as the mean of decision authority and skill discretion. Emotional enrichment was measured by a single item designed for this study: "Do you feel that your work with patients, clients, students etc. is emotionally enriching and satisfying?" scored: 1='to a very small extent', 2='to a small extent', 3='to some extent', 4='to a large extent', and 5='to a very large extent'

**Potential confounders**

Gender and age (continuous) were extracted from employee files. Other information was extracted from baseline and follow-up questionnaires. Socioeconomic status was assessed from personal annual income in Danish crowns (continuous), and professional education beyond primary or high school (none or short training (< 3 years), medium higher (3-4 years) and long higher (>4 years) education).

Lifestyle was assessed by leisure time physical activity (low vs. high), weekly alcohol consumption (continuous), body mass index (BMI= self-reported weight (kg) divided by self-reported height squared ($m^2$), continuous), and smoking (never and former vs. present smoker).

Personal aspects and circumstances were assessed from questionnaire items about living in a permanent relationship (good, problematic or no relationship); impact of traumatic life-events during the last six month was measured with nine items about experienced events (e.g. death of or serious illness among relatives or friends, divorce or financial problems) and their impact (scored 0= no event or the event felt not too bad, 1= yes, the event felt bad, 2=yes, the event felt very bad) (36); number of previous or present physician diagnosed disorders (list of sixteen specified disorders, e.g. depression, ischemic heart disease, diabetes, cancer) scored as none, one, two, and more than two; and neurotic personality trait (neuroticism) measured by the Eysenck Personality Questionnaire Revised-Abbreviated version (continuous) (37).

**Statistical analysis**

We analysed exhaustion as the dependent variable with emotional demands as the explaining variable, adjusting for potential confounders, except for neuroticism which was only included in a sensitivity analysis. The associations between emotional demands and exhaustion were analysed both linearly and by tertile categories of emotional demands to investigate potential non-linear associations.

A preliminary analysis showed that there was no statistically significant difference between the cross-sectional associations between emotional demands and exhaustion in 2007 and 2009. For this analysis we used a linear mixed model controlling for repeated measurements and potential confounders.

We then compared the cross-sectional and longitudinal associations of emotional demands on exhaustion using a linear mixed model controlling for examination round and potential confounders (fixed effects) and for repeated measurements (random effect of individual). The cross-sectional association was estimated as the effect of the average emotional demands score across the two examination rounds on the exhaustion score, and the longitudinal effect as the effect of the change in emotional demands from 2007 to 2009 on changes in exhaustion from 2007 to 2009 as described by Fitzmaurice et al. (38). We tested the differences in estimated cross-sectional and longitudinal associations using the so-called *Hausman test* for unmeasured confounders. A difference between the longitudinal and cross-sectional effects may indicate a bias in the cross-sectional effect due to uncontrolled confounding from time-invariant factors (38).

We further examined if the association of emotional demands with exhaustion was modified by emotional enrichment, meaningful work, job control, supervisor support, colleague support, and quantitative demands by including a multiplicative interaction term between these factors and emotional demands in the regression models. In these analyses, emotional demands and other psychosocial factors were included as continuous covariates and analyses were made separately for each factor.

As sensitivity analyses we included neuroticism in the adjusted main model and in the models that examined for effect modification. Furthermore, we examined if the relation between emotional demands and exhaustion was different for participants who only participated in the first round and those who participated in both rounds.

We analysed the data with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA). Mixed models were analysed with the HPMIXED procedure.

**RESULTS**

*Descriptive Statistics*

Characteristics of the baseline and follow-up population are shown in table 1. Compared to the baseline population, participants at follow-up reported a higher income and education, consisted of fewer smokers and had fewer traumatic life events during the last six months. The level of emotional demands and exhaustion decreased from baseline to follow-up.

In the follow-up population, lower levels of emotional demands and exhaustion were associated with increasing age and alcohol consumption. Higher means for emotional demands and exhaustion were found for smokers, living in a problematic relationship, and neuroticism (Table 1).

Furthermore, emotional demands increased with increasing income and higher scores for emotional demands were found for participants with 3-4 years of education.

Exhaustion decreased with increasing income. The exhaustion score was higher for participants that were rarely physically active, experienced a traumatic life event, and had two or more physician diagnosed diseases. Same trends were seen in the baseline population.

**Table 1: Population characteristics at baseline (2007) and at follow-up (2009) with corresponding distribution characteristics of emotional demands (scale 1-5) and exhaustion (scale 1-5)(mean and standard deviation (SD)) .**

| Characteristics | Baseline | | | | Follow-up | | | |
|---|---|---|---|---|---|---|---|---|
| | Participants | | Emotional demands | Exhaustion | Participants | | Emotional demands | Exhaustion |
| | n | % | Mean (SD) | Mean(SD) | n | % | Mean (SD) | Mean (SD) |
| **TOTAL** | **4489** | **100** | **3.52 (0.97)** | **2.61 (0.62)** | **3224** | **100** | **3.41 (0.98)** | **2.43 (0.54)** |
| **Sociodemographic** | | | | | | | | |
| **Gender** | | | | | | | | |
| Men | 968 | 21.6 | 3.17 (1.03) | 2.45 (0.62) | 692 | 21.5 | 3.09 (1.06) | 2.31 (0.55) |
| Women | 3521 | 78.4 | 3.62 (0.92) | 2.66 (0.61) | 2532 | 78.5 | 3.49 (0.95) | 2.47 (0.54) |
| **Age** | | | | | | | | |
| <35 years | 982 | 21.9 | 3.80 (0.92) | 2.63 (0.62) | 481 | 14.9 | 3.75 (0.95) | 2.47 (0.53) |
| 35-44 years | 1105 | 24.6 | 3.52 (0.95) | 2.63 (0.63) | 756 | 23.5 | 3.41 (0.99) | 2.45 (0.55) |
| 45-54 years | 1559 | 34.7 | 3.53 (0.93) | 2.62 (0.61) | 1121 | 34.8 | 3.42 (0.98) | 2.45 (0.55) |
| ≥55 years | 843 | 18.8 | 3.17 (0.98) | 2.57 (0.62) | 866 | 26.9 | 3.18 (0.96) | 2.39 (0.56) |
| **Personal income (DDK)[a]** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ≤299 999 | 2201 | 51.9 | 3.51 (0.97) | 2.68 (0.62) | 1106 | 36.5 | 3.38 (0.99) | 2.51 (0.55) |
| 300 000 - 499 999 | 1790 | 42.2 | 3.50 (0.95) | 2.55 (0.59) | 1662 | 54.8 | 3.39 (0.97) | 2.41 (0.54) |
| ≥500 000 | 247 | 5.8 | 3.75 (0.92) | 2.41 (0.59) | 264 | 8.7 | 3.47 (1.05) | 2.27 (0.56) |
| **Professional education** | | | | | | | | |
| **- beyond primary or high school** | | | | | | | | |
| <3 years | 888 | 19.9 | 2.86 (1.06) | 2.66 (0.67) | 513 | 16.3 | 2.72 (1.14) | 2.46 (0.56) |
| 3-4 years | 3081 | 68.9 | 3.73 (0.81) | 2.62 (0.60) | 2241 | 71.2 | 3.59 (0.83) | 2.44 (0.55) |
| >4 years | 505 | 11.3 | 3.46 (1.12) | 2.47 (0.60) | 392 | 12.5 | 3.27 (1.17) | 2.37 (0.54) |
| **Lifestyle** | | | | | | | | |
| **Leisure time physical activity** | | | | | | | | |
| Low | 2373 | 53.1 | 3.47 (0.99) | 2.69 (0.62) | 1604 | 50.2 | 3.37 (1.00) | 2.52 (0.55) |
| High | 2093 | 46.9 | 3.58 (0.92) | 2.53 (0.60) | 1592 | 49.8 | 3.44 (0.98) | 2.36 (0.54) |
| **Alcohol consumption** [b] | | | | | | | | |
| Low | 3410 | 76.8 | 3.47 (0.99) | 2.63 (0.62) | 2408 | 75.6 | 3.43 (0.99) | 2.45 (0.55) |
| High | 1028 | 23.2 | 3.58 (0.92) | 2.56 (0.61) | 776 | 24.4 | 3.33 (0.97) | 2.39 (0.56) |
| **BMI** | | | | | | | | |
| Low | 2892 | 65.2 | 3.56 (0.94) | 2.60 (0.61) | 2028 | 63.4 | 3.41 (0.99) | 2.41 (0.54) |
| High | 1542 | 34.8 | 3.46 (1.01) | 2.64 (0.62) | 1169 | 36.6 | 3.39 (0.99) | 2.48 (0.56) |
| **Smoking** | | | | | | | | |
| Never or former smoker | 3651 | 81.8 | 3.55 (0.96) | 2.59 (0.61) | 2751 | 86.2 | 3.41 (0.98) | 2.42 (0.54) |
| Present smoker | 810 | 18.16 | 3.42 (1.00) | 2.73 (0.65) | 440 | 13.8 | 3.39 (1.02) | 2.53 (0.61) |
| **Private life and personal characteristics** | | | | | | | | |
| **Permanent relationship** | | | | | | | | |
| Good | 3124 | 69.8 | 3.52 (0.94) | 2.68 (0.64) | 2273 | 70.9 | 3.41 (0.96) | 2.49 (0.56) |
| Problematic | 571 | 12.8 | 3.66 (0.91) | 2.84 (0.61) | 397 | 12.4 | 3.52 (0.97) | 2.67 (0.55) |
| No relationship | 781 | 17.5 | 3.50 (0.98) | 2.56 (0.61) | 535 | 16.7 | 3.38 (1.00) | 2.38 (0.54) |
| **Traumatic life events** | | | | | | | | |
| No events/or very little | 2852 | 63.7 | 3.49 (0.97) | 2.55 (0.61) | 2109 | 65.8 | 3.37 (1.02) | 2.37 (0.53) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Yes, little Impact | 963 | 21.5 | 3.54 (0.94) | 2.67 (0.59) | 698 | 21.8 | 3.49 (0.92) | 2.53 (0.56) |
| Yes high-impact | 663 | 14.8 | 3.64 (0.96) | 2.82 (0.66) | 398 | 12.4 | 3.44 (0.95) | 2.60 (0.59) |
| **Physician diagnosed disease** | | | | | | | | |
| None | 1567 | 35.1 | 3.53 (0.96) | 2.45 (0.57) | 1097 | 34.1 | 3.42 (1.02) | 2.32 (0.50) |
| One | 1389 | 31.1 | 3.52 (0.98) | 2.55 (0.57) | 989 | 30.8 | 3.38 (0.97) | 2.37 (0.52) |
| Two | 814 | 18.2 | 3.48 (0.97) | 2.72 (0.60) | 645 | 20.1 | 3.39 (0.97) | 2.53 (0.55) |
| More | 701 | 15.7 | 3.54 (0.93) | 2.97 (0.66) | 482 | 15.0 | 3.41 (0.99) | 2.60 (0.60) |
| **Neuroticism (scale 0-1)** | | | | | | | | |
| No (0) | 1950 | 43.7 | 3.47 (0.97) | 2.30 (0.51) | 1548 | 48.4 | 3.38 (1.00) | 2.20 (0.46) |
| yes (>0) | 2517 | 56.4 | 3.56 (0.96) | 2.85 (0.59) | 1652 | 51.6 | 3.42 (0.98) | 2.65 (0.54) |

[a] One Euro is equivalent to 7.5 DKK. [b] Low alcohol consumption = less than 168 gram pure alcohol per week.

Means and standard deviations as well as the correlations between emotional demands, other work characteristics, and exhaustion are presented in table 2. Baseline and follow-up means and standard deviations were similar, and the table therefore presents the results for the average of baseline and follow-up scores. The highest correlations was seen for supervisor support and colleagues support (r=0.57), emotional demands and emotional enrichment (r=0.53), meaning in work and emotional enrichment (r=0.43) as well as meaning in work and job control (r=0.45), all others were below +/- 0.35. The correlations of neuroticism with exhaustion and emotional demands were 0.53 and 0.01, respectively, and the correlation of neuroticism at baseline with neuroticism at follow-up was 0.67.

**Table 2: Distribution of emotional demands, other psychosocial work characteristics and exhaustion (means and standard deviations (SD))* and their correlation among participants at baseline and follow-up (n=3224).**

| | | | Pearson correlation coefficients | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** |
| **1. Emotional demands** | 3.46 | 0.92 | 1.00 | .. | .. | .. | .. | .. | .. | |
| **2. Quantitative Demands** | 2.85 | 0.83 | 0.12 | 1.00 | .. | .. | .. | .. | .. | |
| **3. Job control** | 3.51 | 0.50 | 0.10 | -0.04 | 1.00 | .. | .. | .. | .. | |
| **4. Meaningful work** | 4.22 | 0.58 | 0.24 | -0.07 | 0.45 | 1.00 | .. | .. | .. | |
| **5. Colleague support** | 4.00 | 0.98 | 0.05 | -0.23 | 0.27 | 0.29 | 1.00 | .. | .. | |
| **6. Supervisor support** | 3.54 | 1.04 | -0.08 | -0.23 | 0.32 | 0.25 | 0.57 | 1.00 | .. | |
| **7. Emotional enrichment** | 3.71 | 0.94 | 0.53 | -0.06 | 0.32 | 0.43 | 0.23 | 0.14 | 1.00 | |
| **8. Exhaustion** | 2.51 | 0.52 | 0.09 | 0.33 | -0.24 | -0.23 | -0.28 | -0.28 | -0.17 | 1.00 |

*All scales run from 1 till 5. A high score refers to a high level of the variable (e.g. high score= high demands, high control, etc.).

*Cross-sectional and longitudinal associations between emotional demands and exhaustion*

Higher emotional demands were associated with higher levels of exhaustion, both cross-sectionally and longitudinally (Table 3). These results were statistically significant when emotional demands were analysed as a linear variable. For example, a one unit increase in emotional demands predicted a 0.034 units (95% CI: 0.006-0.061) increase in exhaustion in the longitudinal analysis. Thus, a change in emotional demands from lowest to highest possible exposure category corresponds to approximately 3.5 % increase in exhaustion (equivalent to 0.14 (95% CI: 0.02-0.24) on the exhaustion scale). Results for the categorised emotional demands (tertiles) were consistent with the continuous linear effects.

**Table 3. Cross-sectional and longitudinal associations between emotional demands and exhaustion.**

| | | | Crude model [b] | | | Adjusted Model 1 [c] | | |
|---|---|---|---|---|---|---|---|---|
| | **Emotional demands** | Number of obs. | Effect estimate [a] | 95% CI | p | Effect estimate [a] | 95% CI | p |
| **Continuous** | | | | | | | | |
| | **Cross-sectional** | 7449 | 0.052 | 0.035-0.069 | <0.001 | 0.037 | 0.019-0.055 | <0.001 |
| | **Longitudinal** | 5922 | 0.033 | 0.007-0.060 | 0.013 | 0.034 | 0.006-0.061 | 0.018 |
| | Hausman test [e] | | | | 0.248 | | | 0.822 |
| **Categorical** [d] | | | | | | | | |
| | **Cross-sectional** | 7449 | | | | | | |
| | Low | | 1 | | | 1 | 1 | |
| | Medium | | 0.065 | 0.021-0.108 | 0.003 | 0.045 | 0.002-0.088 | 0.038 |
| | High | | 0.124 | 0.080-0.169 | <0.001 | 0.086 | 0.041-0.131 | <0.001 |
| | **Longitudinal** | 5922 | | | | | | |
| | Low | | 1 | | | 1 | 1 | |
| | Medium | | 0.025 | -0.019-0.068 | 0.263 | 0.029 | -0.017-0.075 | 0.215 |
| | High | | 0.041 | -0.015-0.096 | 0.150 | 0.034 | -0.025-0.092 | 0.257 |
| | Hausman test [e] | | | | 0.066 | | | 0.341 |

[a] Number of units of change in the exhaustion score by a one unit increase in emotional demands (continuous models) or by a higher category of emotional demands compared to the lowest category (categorical models).

[b] Mutually adjusted cross-sectional and longitudinal effects, no other adjustments.

[c] Crude model with adjustment for age, gender, education, income, smoking, alcohol, physical activity, body mass index, type of relationship, traumatic life events, severe disease, and for repeated measurements.

[d] Emotional demands categorised by tertiles: low 0.0-<3.2 medium 3.2-<4.2 high 4.2-5.0

[e] p-value of no difference between cross-sectional and longitudinal effects (Hausman test).

*Modifying effects of other psychosocial work characteristics*

We examined if the cross-sectional or longitudinal linear associations between emotional demands and exhaustion were modified by six other psychosocial work factors: emotional enrichment, meaningful work, job control, supervisor support, colleague support, and quantitative demands. We found a statistically significant effect modification in four of these twelve analyses (table 4 and Figure 1). Exhaustion increased at a steeper rate by increasing emotional demands when emotional enrichment was low compared to when it was high. This was found both for the cross-sectional (Figure 1a) and the longitudinal (Figure 1b) association. A similar effect modification was seen for meaningful work, but the interaction term was only statistically significant for longitudinal results (Figure 1c). Exhaustion increased at a steeper rate by increasing emotional demands when quantitative demands were high than when they were low (Figure 1d). Job control, support from supervisor and support from colleagues had an independent protective effect on exhaustion but had no moderating effect.

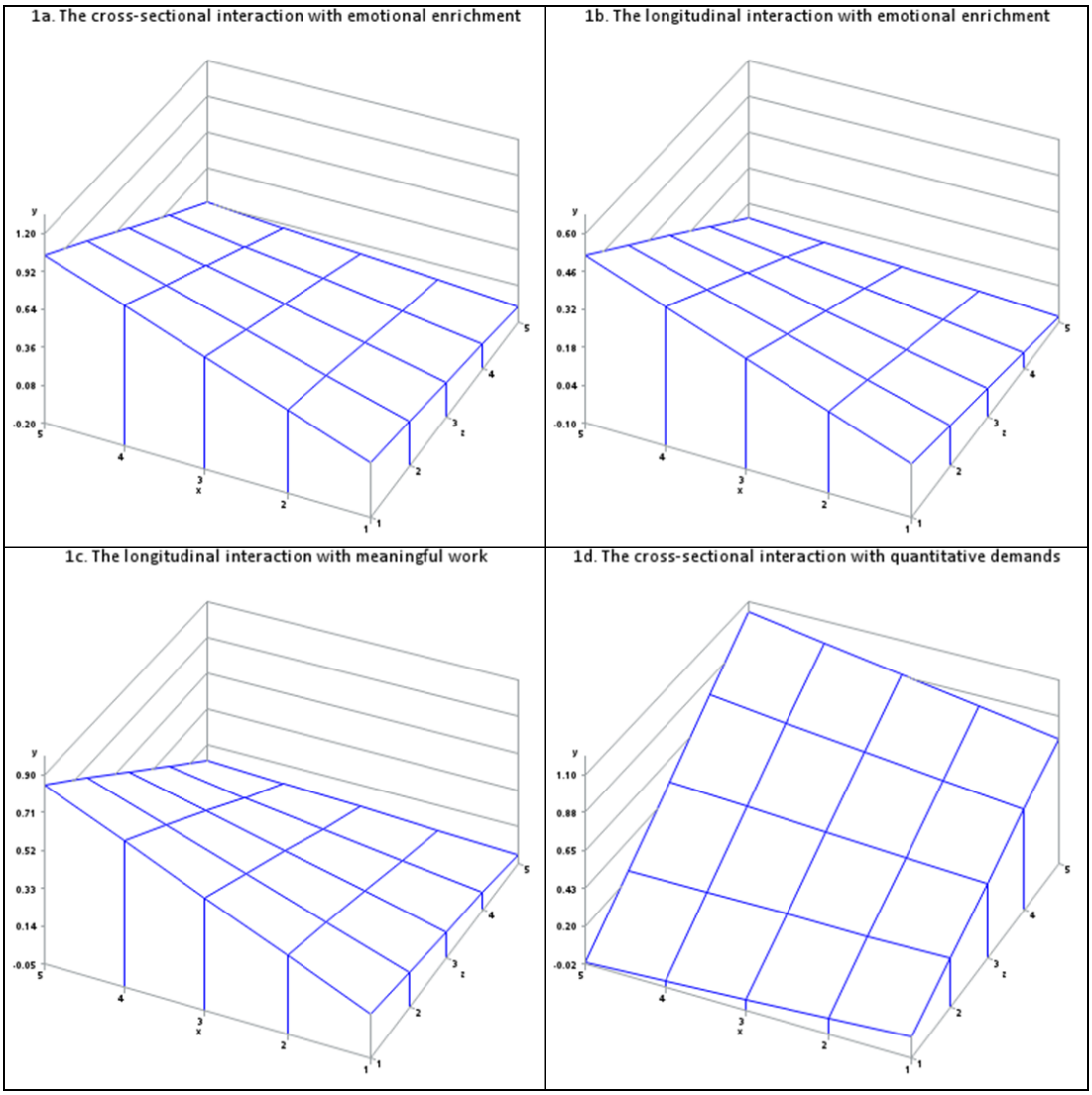
**Table 4: Effects of emotional demands and other psychosocial work characteristics on exhaustion. Main effects and interaction effects[a].**

| Step [a] | Variables [b] | Effect estimate cross-sectional [c] (95% CI) | Effect estimate follow-up [c] (95% CI) | Hausman-test (p) |
|---|---|---|---|---|
| 1 | Emotional demands | 0.017 (<0.001,0.034)* | 0.013 (-0.015, 0.040) | |
| | Quantitative demands | 0.220 (0.201, 0.240)*** | 0.166 (0.142, 0.190)** | 0.782 |
| 2 | Emotional demands | -0.055 (-0.111, 0.001) | 0.041 (-0.023, 0.106) | |
| | Quantitative demands | 0.133 (0.066,0.200)*** | 0.202(0.124,0.280)*** | |
| | **Emotional demands*quantitative demands** | **0.026 (0.007, 0.044)**** | -0.010 (-0.032, 0.011) | 0.012 |
| 1 | Emotional demands | 0.074 (0.056, 0.091) *** | 0.048 (0.020-0.075)*** | |
| | Meaningful work | -0.260 (-0.288, -0.231)*** | -0.137 (-0.170, -0.104)*** | 0.125 |
| 2 | Emotional demands | 0.085 (-0.028, 0.198) | 0.210 (0.088, 0.332)** | |
| | Meaningful work | -0.251(-0.345, -0.157)*** | -0.004 (-0.107, 0.099) | |
| | **Emotional demands*Meaningful work** | -0.003 (-0.029, 0.024) | **-0.039 (-0.067, -0.010)**** | 0.063 |
| 1 | Emotional demands | 0.105 (0.086, 0.125) *** | 0.051 (0.022, 0.081)*** | |
| | Emotional enrichment | -0.156 (-0.1766, -0.136)*** | -0.049 (-0.070, -0.027)*** | 0.003 |
| 2 | Emotional demands | 0.256 (0.201, 0.311)*** | 0.131(0.069, 0.193)*** | |
| | Emotional enrichment | -0.024 (-0.073, 0.025) | -0.019 (-0.033, 0.071) | |
| | **Emotional demands*emotional enrichment** | **-0.043 (-0.058, -0.028)***** | **-0.023 (-0.038, -0.007)**** | 0.060 |
| 1 | Emotional demands | 0.045(0.027, 0.063)*** | 0.036 (0.008, 0.063)* | |
| | **Job control** | **-0.212 (-0.242,-0.183)***** | **-0.116 (-0.154, -0.078)***** | 0.581 |
| 1 | Emotional demands | 0.045 (0.027, 0.062)*** | 0.038 (0.009, 0.066)** | |
| | **Social support from colleagues** | **-0.156 (-0.173, -0.140) ***** | **-0.048 (-0.066, -0.029) ***** | 0.675 |
| 1 | Emotional demands | 0.030 (0.012, 0.047)** | 0.029 (0.012, 0.057)* | |
| | **Social support from supervisor** | **-0.119 (-0.132, -0.105) ***** | **-0.048 (-0.063, -0.034) ***** | 0.974 |

[a] **Step 1** is results for the main effects without interactions. **Step 2** is the results for main and interaction effects in the case of statistically significant interactions. If interactions were not statistically significant, results for step 2 are not shown.
[b] Emotional demands are continuous and all steps are adjusted for potential confounders (age, gender, education, income, smoking, alcohol, physical activity, body mass index, type of relationship, traumatic life events, severe disease)
[c] Regression coefficient and confidence limits.

*p<0.05, **p<0.01, ***p<0.001

**Figure 1: Modification of emotional demands (x) on exhaustion (y) by psychosocial work characteristics (z);**
**1a**. Cross-sectional effect, z=emotional enrichment. Regression equation: **y=0.256*x - 0.024*z - 0.043*x*z**
**1b**. Longitudinal effect, z=emotional enrichment. Regression equation: **y=0.131*x - 0.019*z - 0.023*x*z**
**1c**. Longitudinal effect, z=meaningful work. Regression equation: **y=0.210*x - 0.004*z - 0.039*x*z**
**1d**. Cross-sectional effect, z=quantitative demands. Regression equation: **y=-0.055*x + 0.133*z + 0.026*x*z**



*Sensitivity analyses*

When neuroticism was included in the main model the relations between emotional demands and exhaustion became stronger for cross-sectional and weaker for longitudinal associations but significant findings remained significant (data not shown). When neuroticism was included in the final steps in the effect modification analyses, the statistically significant interaction of emotional demands with meaningful work and with emotional enrichment remained significant, but the interaction with quantitative demands was no longer statistically significant (data not shown).

In the analyses addressing a possible selection bias we compared the cross-sectional relation between emotional demands and exhaustion among participants who only participated in the first round (n=1280), and those who participated in both rounds (n=3224). Among the first round only participants exhaustion increased 0.065 (95% CI: 0.03-0.10) units by a one unit increase in emotional demands. For both round participants, the corresponding increase at baseline was 0.062 (95% CI: 0.04-0.08).

**DISCUSSION**

We found that increasing emotional demands were associated with increasing levels of exhaustion, both cross-sectionally and longitudinally. Quantitative demands, meaningful work and emotional enrichment moderated the association in the expected directions. However, the effect size was small.

The study has some methodological limitations. The response rate obtained at baseline was only 45%. In a previous study we have found that non-participation at baseline was associated with younger age, male gender, increased sick leave and prescription of antidepressant medication. Thus, data was not missing at random. However, risk estimates for sick leave and prescription of antidepressant medication during follow-up differed only marginally between baseline participants and non-participants with respect to age, gender, civic status, social status and work-unit level of psychosocial work environment factors (job demands, decision latitude, job strain, effort-reward imbalance, and organizational justice variables) (39). These findings are comforting but may not be extrapolated to the present study of the relation between emotional demands and exhaustion. However, the association between emotional demands and exhaustion at baseline was very similar for participants who only participated at baseline and those who also participated at follow-up.

We focused strictly on content-related emotional demands to reduce the influence of personal factors such as mood, perceptions and personality on the reporting of emotional demands. Even so, the results may still be influenced by reporting bias, since exposure and outcome were both self-reported (34). More objective or person-independent measures of emotional demands at work could be aggregated group based exposure measures (40) or objective recordings of emotionally demanding events at work.

Emotional demands and exhaustion were measured twice two years apart. However, the within-person levels of both variables may fluctuate during the observation period. Some of this fluctuation may be due to unknown factors or to random variation, and could influence our effect estimates, most likely towards the null. However, at the group level the distributions of emotional demands and exhaustion were quite similar across examination rounds, and the cross-sectional and longitudinal effects were similar in the adjusted analyses.

The Hausman-tests were not statistically significant indicating that the results were not biased by unmeasured time-invariant factors.We adjusted for more potential confounders than most related studies, but cannot exclude residual confounding.

We included neuroticism in sensitivity analyses to adjust for personality aspects. However, neuroticism was not as time-constant across the two examination rounds as one would expect from a personality variable since the correlation across the two examination rounds was only 0.67. State-changes in neuroticism may be related to depression (ref: study I) and some of the variation in neuroticism could even be caused by

emotional demands. We therefore consider the results from these sensitivity analyses as difficult to interpret. In this study we were limited to examining the importance of personality through the neuroticism variable. However, the role of personality may be important for the relation between emotional demands and exhaustion and future studies could probably benefit from including more comprehensive and time-constant measures of personality.

Comparison of our results with results from previous studies of the relation between emotional demands and exhaustion is complicated by the diversity of measures of emotional demands in different studies. Furthermore, the specific items used to construct a scale of emotional demands, are not always specified, and it may therefore be difficult to accurately assess the extent to which the scale is based on purely perceived emotional demand items (e.g. “Do you feel that your work is emotionally demanding?”, on items which only queries about factual events as in our study, or on items mix scales.

We are aware of only four studies which are based on scales of emotional demands which only include items of content-related demands at work (9, 18, 32, 41). Three of these were cross-sectional studies of health care workers. De Jonge et al. examined 826 health care workers and found no association between MBI exhaustion and participant reports of confrontation with death and dying, illness, and suffering (9), These results were similar to those of a previous cross-sectional study by the same first author (41). Sundin et al. examined 1,561 nurses and found a statistically significant positive association between MBI exhaustion and reports of having to face and carry much of the patients worries/burdens/destinies of life (18). One longitudinal study of 555 nurses included content-related items concerning “Pain and Death”, “Patient and relative needs”, and ”Professional worries”. In this study professional worries for making mistakes were associated with exhaustion one year later (odds ratio: 2.56 and 95% CI: 1.34, 4.82)(32).

Other longitudinal studies including scales with mixed items on emotional demands have indicated that high emotional demands are associated with exhaustion (25-29, 32). Some of the studies are characterized by few participants (25, 26, 42), single occupations (26, 32, 42, 43), and adjustment for only few potential confounders (25-27). The largest longitudinal surveys also adjusted for baseline exposure level of exhaustion (27-29). In a study by Van Vegchel et al. with one year of follow-up the estimated effect of emotional demands on exhaustion among 2,255 social insurance employees are comparable with results from the present study. Another one year follow-up study by Van de Ven et al. showed positive results measuring emotional demands among 711 employees in the technology sector (27). The only longitudinal study measuring exhaustion independent of work found a positive association between emotional demands and exhaustion among 952 human service workers when controlled only for the baseline sociodemographic variables but not in the final adjusted model including adjustment for baseline exposure and other psychosocial variables.

In this study we have combined content-related items of exposure with work independent measure of outcome. We found a small statistically significant association between emotional demands and exhaustion. Longitudinally, exhaustion increased with 3.5 % if emotional demands changed from lowest till highest score. We do not know if this effect of emotional demands has practical implications, but could possibly be relevant at the population level.

The Job-Demand-Resource model suggests that resources available to the employee counteracts harmful effects of job demands on health and well-being (44). Longitudinal studies investigating modifying effects of other factors on the association between emotional demands and exhaustion have mostly considered social support. In line with the present study these studies found no modifying effect of social support (26-28). Job control has been found to moderate the effect longitudinally (28). This was not confirmed by the present study. Our results showed statistically significant interactions between emotional demands and three out of six work characteristics. The effect of emotional demands on exhaustion was reduced if the work was experienced as emotionally enriching and meaningful, and aggravated by increasing quantitative demands. These findings are new and they are particularly interesting as emotional demands at work often are an integral part of the work and therefore cannot be removed. However, if the work environment can be improved by making the work more enriching and meaningful and reducing quantitative demands, negative effects of emotional demands on health could possibly be prevented.

To avoid confounding of longitudinal effects with cross-sectional effects we chose an analytical model which includes separate parameters that represent cross-sectional and longitudinal effects and thus allows for simultaneous estimation of both types of effects (38). The model may also indicate if adjustment for unmeasured time-invariant factors is inadequate (38). Previous longitudinal studies have only adjusted for potential confounders measured at baseline, presuming that these characteristics are stable over time. The analytical model used in our study accounts for changes over time for all variables. Overall, the strengths of the study is the longitudinal design with the use of a large mixed population, inclusion of the content-related items, outcome measured assessed independently of work, and the cross-sectional adjustment of the longitudinal results.

## CONCLUSION

This study showed that increasing content-related emotional demands was associated with increasing levels of exhaustion, both cross-sectionally and longitudinally. This effect was reduced if the work was experienced as emotionally enriching and meaningful and aggravated by increasing quantitative demands.

These findings suggest that prevention at the workplace could focus on reducing specific emotionally demanding factors and improving other psychosocial workplace factors. The effects size was small but could possibly be relevant at the population level.

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# Salivary cortisol and depression in public sector employees: Cross-sectional and short term follow-up findings

Marianne Agergaard Vammen [a,*], Sigurd Mikkelsen [a], Åse Marie Hansen [b], Matias Brødsgaard Grynderup [c], Johan Hviid Andersen [d], Jens Peter Bonde [a], Henriette Nørmølle Buttenschøn [e], Henrik Albert Kolstad [c], Anette Kærgaard [d], Linda Kærlev [f], Ole Mors [g], Reiner Rugulies [h], Jane Frølund Thomsen [a]

[a] *Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, Copenhagen, Denmark*
[b] *Department of Public Health, University of Copenhagen, Copenhagen, Denmark and National Research Centre for the Working Environment, Copenhagen, Denmark*
[c] *Danish Ramazzini Centre, Department of Occupational Medicine, Aarhus University Hospital, Aarhus, Denmark*
[d] *Danish Ramazzini Centre, Department of Occupational Medicine, Regional Hospital Herning, Herning, Denmark*
[e] *Centre for Psychiatric Research, Aarhus University Hospital, Risskov, Denmark*
[f] *Center for Clinical Epidemiology, Odense University Hospital, Odense, Denmark*
[g] *Research Department P, Aarhus University Hospital, Risskov, Denmark*
[h] *National Research Centre for the Working Environment, Copenhagen, Denmark*

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**Summary**
*Introduction:* Increased cortisol levels have been suggested to play a role in the development of depression. An association has been shown in some studies but not consistently. The timing of an association is uncertain, and long-term follow-up studies may miss associations in narrower time windows. In the present study, we examined the association of several cortisol measures and depression in a repeated cross-sectional and short-term follow-up design. Depression was assessed by both self-reported symptoms of depression and clinical interviews.

* Corresponding author at: Department of Occupational and Environmental Medicine, Copenhagen, Bispebjerg University Hospital, Bispebjerg Bakke, DK2400 Copenhagen NV, Denmark. Tel.: +45 3531 3772; fax: +45 35316060; mobile: +45 25565793.
*E-mail addresses:* marianne.agergaard@regionh.dk, maagergaard@gmail.com (M.A. Vammen).

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*Method:* In 2007, 10,036 public sector employees received a questionnaire along with salivary cortisol test tubes for home administration. Morning (30 min after awakening) and evening (2000 h) salivary samples were collected. Questionnaires and valid saliva samples were returned from 3536 employees. Approximately 3.6 months later a subsample of the participants collected three morning saliva samples (at awakening, 20 min and 40 min after awakening) plus an evening sample (2000 h); participants with high baseline scores of self-reported depressive symptoms, burnout and perceived stress were invited to a standardized interview (SCAN) to detect clinical depression; and the symptom questionnaire was repeated for subsample participants. The study was repeated in 2009 with questionnaires and salivary test tubes ($n = 2408$). In four cross-sectional and two short-term follow-up analyses odds ratios of depressive symptoms and of clinical depression were estimated by logistic regression for morning, evening, mean and the difference between morning and evening cortisol (slope). For the subsample, awakening response (CAR) and area under the curve (AUC) cortisol measures were calculated. We adjusted for sex, age, income, education, family history of depression, physical activity and alcohol consumption.
*Results:* None except one of the measures of salivary cortisol were associated with self-reported depressive symptoms or clinical depression, neither in the four cross-sectional analyses nor in the two short term follow-up analyses. E.g. in 2007, the adjusted odds ratios (OR) of depressive symptoms by a one unit increase in morning and evening cortisol (ln(nmol/litre saliva)) were 1.01 (95% CI: 0.88—1.17) and 1.05 (0.93—1.18), respectively. The one exception was significant at $p = 0.04$ and was considered as due to chance.
*Conclusion:* In this large study, salivary cortisol was not associated with self-reported symptoms of depression or with clinical depression.
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## 1. Introduction

Depression is a leading cause of disability and a major contributor to the global burden of disease (Burcusa and Iacono, 2007). Reduced quality of life, increased somatic illness, long-term sick leave and increased mortality are associated with depression (Brown et al., 2004; Hammen, 2005; Sinokki et al., 2009; Chang et al., 2010). Serious life events or other stressors may play an important role in the development of depression (Brugha et al., 1985) and it is discussed, whether a possible mechanism in the development of depression involves changes in hypothalamic-pituitary-adrenal (HPA) activity and cortisol levels (Hellhammer et al., 2009; Kristenson et al., 2012). We know that acute stressors create an immediate strong increase in the cortisol level (van Eck et al., 1996; Kudielka et al., 2004). However, it is still uncertain whether continuous stress leads to persistent changes in cortisol homeostasis and if these changes lead to a higher risk of depression (Kristenson et al., 2012).

Studies of patients with depression have formed the basis for the hypothesis that elevated cortisol levels is associated with an increased incidence of depression (Holsboer et al., 1995; Bhagwagar et al., 2003; Pariante and Lightman, 2008). Patients with Cushings syndrome (hypercortisolaemia) have an elevated prevalence of depression (Brown et al., 2004) supporting the hypothesis. However, evidence of no association or even lower cortisol among depressed patients has also been found (Young et al., 2002; Peeters et al., 2003; Ahrens et al., 2008; Stetler and Miller, 2011).

Studies of the relation between cortisol and depression in population studies or outpatient populations have shown diverging results. Phillips et al. found in a large population of 4256 US army veterans lower levels of serum cortisol among those who were depressed. Pointing in the same direction, a flat diurnal cortisol profile was associated with depression in two studies of randomly selected men and women (Sjogren et al., 2006; Power et al., 2011). This was contrasted by a study of outpatients recruited from general practise with current major depression, a history of depression, and controls. Here, cortisol levels (awakening response and 1000 h) were higher in the depressed groups (Vreeburg et al., 2009). Other studies have suggested a U-shaped curve (Bremmer et al., 2007) as well as no associations (Burke et al., 2005). Thus, these studies show mixed picture of associations in cross-sectional settings.

There have only been published few follow-up studies on adult populations. In one study, high morning cortisol predicted onset of major depression 13 months later (Harris et al., 2000). In another study, a low cortisol awakening response predicted depression after two years (Vreeburg et al., 2013).

We have recently published 2-year follow-up results from a large study of public sector employees showing that a low mean saliva cortisol level and a flat morning-to-evening cortisol slope at baseline predicted clinical depression (Grynderup et al., 2013). Morning and evening cortisol levels did not predict depression. However, considering the course of a depression, two years may be a too long follow-up period as half of those affected with major depressive episodes recover within three months (Spijker et al., 2002).

The aim of the present study was to test if cortisol levels are associated with depression. We had the opportunity to test the associations in the same study of public sector employees using both repeated cross-sectional and short-term follow-up data including a range of cortisol measures as well as depressive symptoms and clinical depression.

## 2. Methods and materials

### 2.1. Design

The purpose of the Danish PRISME (Psychological RISk factors in the work environment and biological MEchanisms in the development of stress, burnout and depression) study was to examine job-related psychosocial determinants of mental health, including depression. A cohort of public sector employees was established in 2007 and re-examined in 2009 (Kaerlev et al., 2011; Kolstad et al., 2011; Hansen et al., 2012; Grynderup et al., 2013).

### 2.2. Population

#### 2.2.1. Total population 2007 and 2009

In January 2007, 10,036 employees were recruited within public service workplaces in the county and municipality of Aarhus, Denmark. The workplaces included hospitals, schools, day care centres, social, technical and environmental services and administration.

A total of 4533 employees (45%) returned a completed main questionnaire ($n = 4489$) and/or saliva samples ($n = 4467$). Participants with missing or invalid cortisol concentrations or invalid sample times ($n = 817$), pregnant women ($n = 138$) and participants with a missing main questionnaire ($N = 44$) were excluded, leaving 3536 participants for analysis (population-07) (Fig. 1).

In 2009, participants from 2007 were approached again with a similar main questionnaire and 3287 (72%) participated. Leaving out participants with missing or invalid cortisol concentrations or invalid sample times ($n = 671$), pregnant women ($n = 63$) and participants with a missing main questionnaire ($n = 76$), a total of 2408 participants were included in the analysis (population-09) (Fig. 1).

#### 2.2.2. Subsample 2007 and 2009

A subsample invited for clinical examination in 2007 consisted of participants reporting high scores on validated measures of depressive symptoms, burnout and perceived stress ($n = 470$), high psychosocial exposures ($n = 522$) and a random sample ($n = 434$) of the 4489 participants who had returned the main questionnaire. There was a considerable overlap between the groups. This selection procedure aimed primarily at identifying participants who could have clinical depression but the purpose was also to collect supplementary data from high-exposed participants and from a random sample (not reported here). The clinical examinations included a subsample questionnaire, the psychiatric diagnostic Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview, described below, and supplementary saliva samples. A total of 1162 participants were invited and 866 showed up. The participants completed the subsample questionnaire, including the same items on depression symptoms as in the main questionnaire. 590 of the 866 went through the SCAN-interview. Furthermore, 376 of the 866 participants collected four saliva samples (subsample-07) and of these 214 participated in the psychiatric diagnostic SCAN-interview (Fig. 1). The clinical examinations took place 1.5—5.7 months (median 3.6 months) after filling in the main questionnaire.

In 2009, the screening procedure was slightly changed in order to improve the number of depression cases identified based on calculations from responses in 2007. Thus, participants invited for clinical examination in 2009 were participants reporting a high level of mental symptoms in the 2009 main questionnaire ($n = 599$), a random sample of the total population from 2007 ($n = 201$) and additionally participants with clinical depression or high psychosocial exposures in 2007 ($n = 238$). Again, there was an overlap between groups. In 2009, 1039 participants were invited. Of these, 714 completed the subsample questionnaire and 562 participated in the SCAN-interview, 474 collected four saliva samples (subsample-09) and of these 297 participated in the SCAN-interview. The clinical examinations took place 1.4—5.8 months (median 3.6 months) after filling in the main questionnaire.

### 2.3. Cortisol

Saliva test tubes were sent along with the main questionnaire. The participants were asked to collect saliva samples, preferably on a workday or else on a day off work. Furthermore, they were asked to fill in a small questionnaire on sampling circumstances (time of awakening, sleep quality and duration, work and work hours etc.). Saliva samples were to be collected in Salivette® cotton tubes two times a day: 30 min after awakening and in the evening at approx. 2000 h, and stored in a refrigerator until they were returned by mail. The returned samples were stored at −20 °C and analyzed within six months. Samples were collected at the same time of year in 2007 and 2009.

Saliva from the subsample populations (subsample-07 and -09) was to be collected four times a day: at awakening, +20 min and +40 min after awakening and in the evening at approx. 2000 h.

The determination of saliva cortisol was carried out with a competitive radioimmunoassay (RIA) designed for quantitative in vitro measurement of cortisol in serum, plasma, urine and saliva, the Spectria Cortisol Coated Tube RIA, purchased from Orion Diagnostica, Espoo, Finland, according to the manufacturer's specifications as described by Hansen et al. (2012). The sample volume was 150 ml, the range of the standard solutions prepared was 1.0—100.0 nmol/l and the incubation time was 30 min at 37 °C. The specifications given by the manufacturer were a sensitivity of twice the standard deviation of the zero binding value in saliva (0.8 nmol/l), a bias of 10% (3—15%), an intra-assay variation of 5.4% and an inter-assay variation of 7.3%. Cross-reactivity to cortisone was <0.2%. A 1470 Wizard Gamma Counter (Wallac, Turku, Finland) was used for measurement of radioactivity. A method evaluation of certified reference material in water performed by our laboratory showed no bias of the method and recovery being 97% (95% CI: 94.0—100.9). The limit of detection (LOD) was 1.59 nmol/l. Between-run coefficients of variation (CVs) were 19% at 11.5 nmol/l and 16% at 49.2 nmol/l (Hansen et al., 2003). Concentrations below the LOD were assigned a random value between 0 and LOD extracted from a uniform distribution. Concentrations above 100 nmol/l were considered outliers and deleted from the sample (Hansen et al., 2012).

To show equivalence between different runs, natural saliva samples (5.9 nmol/l and 18.5 nmol/l) were used as control materials and analyzed together with the samples.

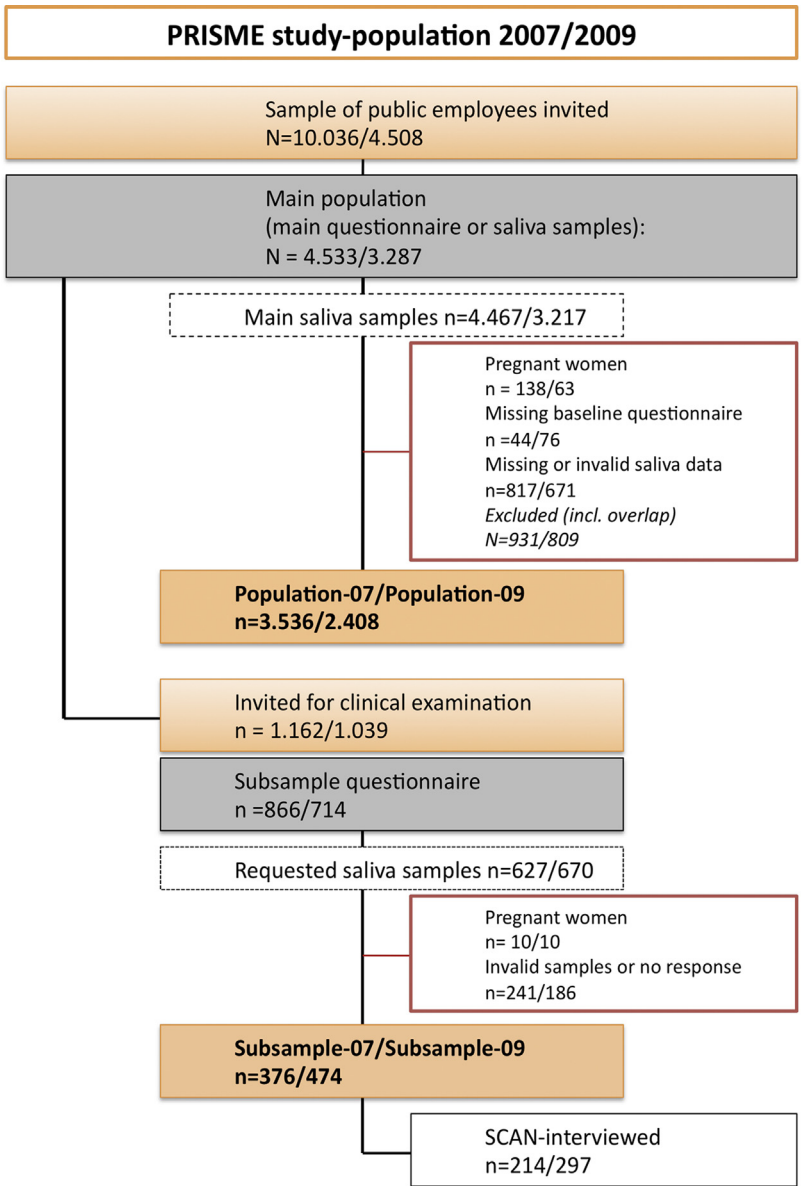


**Figure 1** Flow diagram of public sector employees included in 2007 and 2009. The subsample included in the clinical studies filled in a supplementary questionnaire, collected saliva samples and participated in SCAN-interviews.

Westgard control charts were used to document the analytical methods and secure that the trueness and the precision of the analytical methods remained stable (Westgard et al., 1981). The performance of the methods has been further validated by participation in interlaboratory comparison schemes (Garde et al., 2003; Hansen et al., 2012).

Different measures of cortisol were calculated. The cortisol measures used among the population-07 and population-09 were: (1) morning cortisol, (2) evening cortisol, (3) mean cortisol (average of morning and evening cortisol) and (4) slope of cortisol (decrease in cortisol per hour from morning to evening sample). For the subsample-07 and subsample-09, with four cortisol values per day, the following cortisol measures were used in the analyses: (1) morning cortisol (maximum of the three morning cortisol measurements), (2) evening cortisol, (3) mean cortisol (average of maximum morning and evening cortisol) (4) slope of cortisol (decrease in cortisol per hour from maximum morning to evening sample), (5) CAR (the maximum cortisol increase from the awakening to the second or third saliva sample in the morning) and (6) $AUC_i$ (the area under the curve) defined by the three morning concentrations subtracted by the area below the awakening concentration; also known as AUC with respect to increase, with the first cortisol value used as reference (Kristenson et al., 2012). In all, we had 10 cortisol measures.

## 3. Depression

### 3.1. Depressive symptoms

Depressive symptoms were measured with the six-item subscale SCL-DEP6 for depression in the Mental Disorder Questionnaire (CMDQ) (Christensen et al., 2005).

The CMDQ depression symptoms were included in the main questionnaires and in the subsample questionnaires at both examination rounds. The questions referred to the last 4 weeks and were measured on a 5-point response scale from ''not at all'' to ''extremely'' (scored 1–5). Questions were phrased e.g. as: ''During the last four weeks how much were you bothered by feelings of worthlessness.'' In the analyses, each of the six responses was dichotomised ($\leq$2 equal to 0 and if $\geq$3 equal to 1) and added to a sum-score ranging from zero to six. Since there were few observations with high scores, categories 4, 5 and 6 were collapsed.

Participants with a sum-score $\geq$3 were defined as cases of depressive symptoms and were all invited to participate in the SCAN-interview. With this cut-point, CMDQ has shown a high external validity compared to the SCAN-interview (Christensen et al., 2005).

### 3.2. Clinical depression

Clinical depression was determined by SCAN interview (version 2.1, part I, sections 6, 7, 8 and 10). Clinical depression was assessed in the interview according to International Classification of Diseases, Tenth Revision: diagnostic criteria for research (ICD-10-DCR) (Wing et al., 1990). The interviews referred to symptoms the previous three months.

Ten students of medicine or psychology conducted the interviews. They were trained on a one week course by a WHO certified trainer (inter-rater reliability was $K = 0.71$ in 2007; $K = 0.77$ in 2009).

Participants fulfilling the criteria for a mild, moderate and severe ICD-10-DCR depression were categorized as depressed.

### 3.3. Covariates

The covariates selected for the analysis were known to be associated with cortisol and/or depression according to reviews of the literature (Burcusa and Iacono, 2007; Kessler, 1997; Andersen et al., 2009). The following covariates (categories in parenthesis) were considered: sex (male, female), age (continuous), education beyond primary or high school (none or short training, vocational, short higher (2–3 years), medium higher (3–4 years) and long higher (>4 years) education), personal annual income in Danish crowns (approx.: 0–40300/40300–67200/ > = 67200 Euro), family history of depression (yes/no), traumatic life events (see below) during the last six months (continuous), loneliness (''Does it ever happen that you are alone, even if you would rather be with others'' (yes/no)), neuroticism (continuous, scale 1–6) (Eysenck and Eysenck, 1975), sleep quality (poor/good/very good), alcohol consumption (<=14 g per week/>14 g per week), smoking (never/former/present smoker), physical activity in leisure time (rare, often) and body mass index (BMI) (<18.5, 18.5–25, >25 kg/m$^2$).

Age and sex were recorded from the employee register files. The other information was recorded from the main questionnaires. BMI was calculated from self-reported weight and height (BMI = weight (kg)/height$^2$ (m)). Traumatic life events were recorded by nine events occurring within the last six months: serious illness, serious injury, death of or serious illness among relatives or friends, marital problems, or problems with close friends or relatives, serious injury or assault of a close relative, financial problems or conflict with the law (Brugha et al., 1985). Items were scored as 0 = 'no' or 'yes, it was not bad', 1 = 'yes, it felt bad', 2 = 'yes, it felt very bad'. For the analyses we used the maximum score of the 9 items.

An item of previous episodes of depression was formulated as follows: Has a physician ever told you that you have or have had depression? This item includes present and past depression and we therefore did not include the item in the main analyses.

### 3.4. Statistics

Depressive symptoms (ordinal, five categories 0–4) and clinical depression (yes/no) were analyzed as outcomes by ordinal and binary logistic regression analyses, respectively. The proportional odds assumption in the analyses of depressive symptoms was accepted. Cortisol measures were log-transformed to reduce skewness and variances. Each of the cortisol measures was examined separately and included in the models with a linear and a quadratic term to account for a non-linear relation with depression. The quadratic term was excluded if its effect was not significant. The effects of each of the cortisol measures were also examined by categories based on tertiles. *P*-values of less than 0.05 were considered statistically significant.

The crude associations between depression and cortisol were adjusted in two steps. One model included sex, age, education, income and family history of depression (basic model), and one model also included traumatic life events, loneliness, sleep quality, alcohol consumption, smoking, physical activity and BMI (full model). In the basic model all included covariates were expected to precede depression whereas in the full model the temporal relationship between the additionally included covariates and depression may go either way.

To validate the results with respect to sampling times all analyses were performed for 90%, 80% and 50% of the populations by excluding, respectively, 5, 10 and 25% of the participants who collected their morning and/or evening samples earliest and latest. Analyses were performed for morning, evening, mean and slope in relation to depressive symptoms in both 2007 and 2009.

The follow-up analyses were performed for participants in the population-07 and population-09 who filled in the subsample questionnaire in 2007 and in 2009 on average 3.6 months after baseline, respectively. Morning and evening cortisol were measured at baseline and mean and slope were calculated, as described. In the analyses, the log-transformed baseline cortisol measures were tested as predictors for onset of depressive symptoms or clinical depression. Cases of depressive symptoms at baseline were excluded (sum-score $\geq$2). The same set of covariates as in the cross-sectional analyses was included in the analyses of depressive symptoms. Further, we included the number of days from the saliva sample at baseline to filling in the subsample questionnaire as a covariate. The association between cortisol and clinical depression could only be analyzed in the crude model because of few incident cases (2007/2009: $n = 10$/$n = 16$).

Additionally, we analyzed if changes in cortisol from baseline to follow-up was associated with changes in symptom score in the same period. The cortisol level at baseline was included as a covariate in these analyses.

All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

### 3.5. Ethical considerations

The study protocol was approved by the local ethics committee (RRS 2006-1028) and the Danish Data Protection Agency (2009-41-3215).

## 4. Results

The study population from 2007 consisted of 3536 public sector employees with a majority of women (78%). The mean age was 44 years (range 19–66 years) (Table 1).

In 2009 the study population consisted of 2408 public sector employees with a mean age of 46 (range 22–68 years).

Table 2 shows the distribution of depressive symptoms and clinical depression among participants in 2007 and 2009.

In the population-07 the median level of cortisol was 12.5 nmol/l in the morning and 2.1 nmol/l in the evening. In the population-09 the median level of cortisol in the

**Table 1** Characteristics of the baseline sample of 3536 public employees and odds ratios for the unadjusted association with depression symptoms in 2007.[a]

| Characteristic | *N* | % | OR | 95% CL |
|---|---|---|---|---|
| Sex | | | | |
| Woman | 2750 | 77.8 | **1.37** | **1.11–1.68** |
| Age | | | | |
| 19–29 | 289 | 8.2 | 1 | |
| 30–39 | 833 | 23.6 | 1.00 | 0.73–1.39 |
| 40–49 | 1074 | 30.4 | 1.11 | 0.81–1.51 |
| 50–59 | 1179 | 33.3 | 0.88 | 0.64–1.21 |
| 60–66 | 161 | 4.6 | **0.40** | **0.22–0.72** |
| Professional education beyond primary or high school | | | | |
| None or short training | 101 | 2.9 | 1 | |
| Vocational | 298 | 8.5 | 0.94 | 0.54–1.65 |
| Short higher (2–3 years) | 302 | 8.6 | 0.93 | 0.53–1.62 |
| Medium higher (3–4 years) | 2421 | 68.6 | 1.09 | 0.66–1.77 |
| Long higher (>4 years) | 406 | 11.5 | 0.70 | 0.40–1.21 |
| Personal income (DDK) | | | | |
| ≤299,999 | 1724 | 51.5 | 1 | |
| 300,000–499,999 | 1440 | 43.0 | **0.79** | **0.67–0.94** |
| ≥500,000 | 185 | 5.5 | **0.38** | **0.23–0.62** |
| Family history of depression | 954 | 29.8 | **2.16** | **1.80–2.58** |
| Traumatic life event | | | | |
| No events/felt not bad | 2241 | 63.5 | 1 | |
| Felt bad | 755 | 21.4 | **1.32** | **1.07–1.61** |
| Felt very bad | 531 | 15.1 | **2.71** | **2.21–3.32** |
| Loneliness | 146 | 4.1 | **7.45** | **5.47–10.1** |
| Physical activity | | | | |
| Rarely | 1888 | 53.7 | 1 | |
| Often | 1630 | 46.3 | **0.75** | **0.64–0.89** |
| BMI | | | | |
| Under weight (<18.5) | 66 | 1.9 | 1 | |
| Normal weight (18.5–24.9) | 2228 | 63.7 | 0.70 | 0.41–1.22 |
| Over weight (25–29.9) | 941 | 26.9 | 0.71 | 0.41–1.24 |
| Obese (>=30) | 262 | 7.5 | 1.05 | 0.57–1.92 |
| Alcohol consumption above 14 grams/week | 289 | 10.0 | 1.23 | 0.93–1.63 |
| Smoking | | | | |
| No never | 1655 | 47.1 | 1 | |
| Former smoker | 1239 | 35.3 | **1.23** | **1.03–1.50** |
| Smoker | 618 | 17.6 | **1.65** | **1.33–2.05** |
| Sleep quality | | | | |
| Poor | 872 | 24.9 | 1 | |
| Good | 1411 | 40.3 | **0.30** | **0.25–0.36** |
| Very good | 1223 | 34.9 | **0.13** | **0.10–0.16** |

[a] Significant results with *p*-values of less than 0.05 are marked in bold.

**Table 2** Depressive symptoms and clinical depression among participants with valid cortisol measurements in 2007 and 2009.

| Depression | 2007 | | 2009 | |
|---|---|---|---|---|
| | *n* | % | *n* | % |
| Depressive symptoms[a] | | | | |
| None | 2789 | 79.2 | 2057 | 85.8 |
| Low | 345 | 9.8 | 158 | 6.6 |
| Medium | 257 | 7.3 | 127 | 5.3 |
| High | 130 | 3.7 | 55 | 2.3 |
| Total | 3521[b] | 100 | 2397[b] | 100 |
| Clinical depression | | | | |
| No | 166 | 77.6 | 249 | 83.8 |
| Yes | 48 | 22.4 | 48 | 16.2 |
| Total | 214 | 100 | 297 | 100 |

[a] Categorisation of depressive symptoms score: none = 0; low = 1; medium = 2—3 and high = 4—6.
[b] Missing due to non-response in 2007 (*n* = 15) and 2009 (*n* = 11).

morning and the evening was 14.8 and 2.4 nmol/l, respectively. Time of sampling and cortisol concentrations in 2007 and 2009 are shown in Table 3.

There were no significant differences between the population-07 and the subsample-07 regarding sex, income and education. As intended by the subsample selection procedure, the population and subsample differed with respect to depression symptoms. The prevalence of symptom score $\geq 3$ was 6.7% and 28.2% in the population-07 and subsample-07, respectively. The corresponding figures in 2009 were 4.2% and 13.5%, respectively.

In 2009, the population-09 had a lower depression score and a higher personal income compared to the population-07 ($p < 0.01$). This was partly due to selection and partly due to changes from 2007 to 2009. However, differences in participation rates in relation to depression and income were not related to cortisol concentrations (data not shown). No differences were seen for sex and education.

### 4.1. Cross-sectional analyses

Table 4 presents ORs for having depressive symptoms and clinical depression by a one unit increase of the log-transformed cortisol measures among the participants in 2007 and 2009. Estimates from the crude, basic and full model are shown in the table. None of the cortisol measures were associated with self-reported symptoms of depression. In the analysis of CAR and AUC the model was reduced because of small strata.

Cortisol measures were not associated with clinical depression in any of the two cross-sectional analyses from 2007 and 2009 except for morning cortisol in 2009 (Table 4). Morning cortisol in 2009 was lower among clinically depressed compared to non-depressed (OR: 0.40 95% CI: 0.16 −0.97). For depressive symptoms and clinical depression, we observed no systematic or significant differences between the basic model and the fully adjusted model.

Questions regarding neuroticism showed high correlation with depression (Pearson's corr. = 0.56) and the two concepts were measured by partly overlapping items. We therefore only included this variable in the final model in a separate step. This did not change the results.

Similarly, we only introduced the item on previous or present depression diagnosed by physician in a last separate step. This did not change the results.

## 5. Follow-up analyses

The crude analyses showed that the risk of developing depressive symptoms did not change with baseline cortisol levels (morning, evening, mean, and slope). These results were confirmed in the basic and fully adjusted models for depressive symptoms as shown in Table 5. Analyses were repeated with different categorisations of symptoms with no changes in the results.

The number of cases of depression after exclusion of baseline symptom cases was low and allowed only crude analyses. These analyses did not indicate a higher baseline level of cortisol among participants with depression diagnosed at short-term follow-up in any of the examination rounds (data not shown).

Changes in cortisol levels from baseline to follow-up were not associated with corresponding changes in depressive symptom scores, neither in the crude, basic nor fully adjusted models (data not shown).

**Table 3** Concentration of cortisol in saliva and sample time among baseline and subsample populations in 2007 and 2009.

| | 2007 | | 2009 | |
|---|---|---|---|---|
| | 50% (5 and 95% percentiles) | | 50% (5 and 95% percentiles) | |
| | Time of sampling (h) | Cortisol (nmol/l saliva) | Time of sampling (h) | Cortisol (nmol/l saliva) |
| Total population | (*N* = 3536) | | (*N* = 2408) | |
| Morning | 7:00 (5:45, 9:00) | 12.5 (3.10, 25.2) | 7:07 (5:45, 9:10) | 14.8 (4.10, 29.4) |
| Evening | 20:37 (19:30, 23:00) | 2.08 (0.40, 5.40) | 20:51 (19:30, 23:30) | 2.14 (0.40, 5.70) |
| Subsample | (*n* = 376)[a] | | (*n* = 474)[a] | |
| At awakening | 6:25 (5:15, 8:40) | 7.80 (2.90, 18.6) | 6:25 (5:15, 8:45) | 9.40 (3.20, 21.0) |
| +20 min | 6:47 (6:40, 9:05) | 12.3 (4.80, 25.3) | 6:45 (5:35, 9:05) | 14.6 (6.30, 30.4) |
| +40 min | 7:10 (6:00, 9:30) | 13.6 (4.80, 26.3) | 7:10 (6:00, 9:30) | 15.9 (6.00, 33.6) |
| Evening | 20:00 (19:45, 22:30) | 1.50 (0.50, 5.00) | 20:20 (19:45, 23:00) | 1.70 (0.50, 5.10) |

[a] Subgroup of participants returning both additional questionnaire and saliva samples.

**Table 4** Results from cross-sectional analyses in 2007 and 2009. Odds ratios of depressive symptoms and clinical depression by increasing cortisol measures.[a]

| Cortisol measure | Crude model | | Basic model[b] | | Full model[c] | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **Depressive symptoms** | | | | | | |
| Population-07 ($n$ = 3536) | | | | | | |
| Morning | 0.98 | 0.87—1.10 | 0.95 | 0.83—1.09 | 1.01 | 0.88—1.17 |
| Evening | 1.02 | 0.92—1.13 | 1.02 | 0.91—1.14 | 1.05 | 0.93—1.18 |
| Mean | 1.00 | 0.86—1.15 | 0.95 | 0.81—1.11 | 1.02 | 0.86—1.21 |
| Slope | 1.02 | 0.92—1.14 | 0.98 | 0.87—1.08 | 1.03 | 0.91—1.17 |
| Population-09 ($n$ = 2408) | | | | | | |
| Morning | 0.94 | 0.79—1.12 | 0.89 | 0.73—1.07 | 0.93 | 0.76—1.14 |
| Evening | 0.93 | 0.81—1.08 | 0.94 | 0.80—1.10 | 0.99 | 0.83—1.18 |
| Mean | 0.90 | 0.73—1.11 | 0.86 | 0.68—1.08 | 0.92 | 0.77—1.10 |
| Slope | 0.92 | 0.80—1.07 | 0.88 | 0.74—1.04 | 0.95 | 0.74—1.21 |
| Subsample-07 ($n$ = 376) | | | | | | |
| Morning | 0.85 | 0.57—1.26 | 0.79 | 0.49—1.28 | 1.11 | 0.66—1.87 |
| Evening | 0.83 | 0.63—1.10 | 0.87 | 0.64—1.23 | 0.83 | 0.58—1.17 |
| Mean | 0.72 | 0.66—1.11 | 0.73 | 0.43—1.22 | 0.82 | 0.47—1.42 |
| Slope | 1.08 | 0.83—1.39 | 1.00 | 0.75—1.34 | 1.17 | 0.85—1.60 |
| CAR | 0.96 | 0.67—1.37 | 0.78 | 0.52—1.18 | 0.81[d] | 0.52—1.26 |
| AUC | 1.18 | 0.74—1.90 | 1.04 | 0.59—1.83 | 1.23[d] | 0.69—2.21 |
| Subsample-09 ($n$ = 474) | | | | | | |
| Morning | 0.84 | 0.59—1.20 | 0.78 | 0.53—1.18 | 0.97 | 0.60—1.54 |
| Evening | 1.03 | 0.80—1.32 | 1.18 | 0.87—1.60 | 1.22 | 0.87—1.69 |
| Mean | 0.97 | 0.67—1.43 | 1.11 | 0.70—1.77 | 1.37 | 0.81—2.30 |
| Slope | 0.91 | 0.72—1.15 | 0.80 | 0.60—1.05 | 0.87 | 0.65—1.18 |
| CAR | 0.84 | 0.59—1.20 | 0.78 | 0.51—1.19 | 0.80 | 0.51—1.23 |
| AUC | 1.18 | 0.81—1.72 | 0.91 | 0.56—1.48 | 0.96 | 0.56—1.64 |
| **Clinical depression** | | | | | | |
| Subsample-07 ($n$ = 214) | | | | | | |
| Morning | 0.81 | 0.42—1.54 | 0.92 | 0.39—2.20 | 1.33 | 0.48—3.70 |
| Evening | 0.69 | 0.43—1.12 | 0.77 | 0.44—1.38 | 0.72 | 0.34—1.54 |
| Mean | 0.56 | 0.27—1.18 | 0.67 | 0.26—1.76 | 0.83 | 0.26—2.66 |
| Slope | 1.14 | 0.75—1.72 | 1.09 | 0.66—1.79 | 1.25 | 0.65—2.40 |
| CAR | 0.69 | 0.43—1.12 | 0.78 | 0.44—1.38 | [e] | – |
| AUC | 0.70 | 0.31—1.73 | 0.66 | 0.22—1.94 | [e] | – |
| Subsample-09 ($n$ = 297) | | | | | | |
| Morning | 0.55 | 0.29—1.03 | 0.48 | 0.23—1.01 | 0.40[f] | 0.16—0.97 |
| Evening | 1.09 | 0.70—1.70 | 1.16 | 0.66—2.02 | 1.32 | 0.70—2.52 |
| Mean | 0.82 | 0.40—1.66 | 0.82 | 0.34—2.00 | 0.84 | 0.20—2.37 |
| Slope | 0.75 | 0.50—1.11 | 0.70 | 0.44—1.14 | 0.61 | 0.35—1.06 |
| CAR | 1.06 | 0.58—1.93 | 0.97 | 0.46—2.07 | 0.80 | 0.34—1.89 |
| AUC | 0.46 | 0.18—1.17 | 0.67 | 0.21—2.11 | [e] | – |

[a] Odds ratios estimate the effects of a one unit increase in the log-transformed cortisol measures (see text for definitions).
[b] Adjusted for sex, age, education, income and family history of depression.
[c] Adjusted for sex, age, education, income, family history of depression, traumatic life event, loneliness, physical activity, BMI, alcohol consumption, smoking and sleep quality.
[d] Adjusted as the full model except BMI (excluded due to small strata), and income variable was dichotomized.
[e] It was not possible to run the full model due to small strata.
[f] $p$ = 0.04.

### 5.1.1. Interactions and sensitivity analyses

Initial analyses of interaction effects between sex and morning and evening cortisol did not indicate any sex specific effects cortisol on depression, and separate analyses for men and women were therefore not implemented.

Furthermore models with categorized cortisol measures and quadratic terms as covariates were not significant.

In the sensitivity analyses of 90%, 80% and 50% of the population that collected their saliva samples closest to the intended time of sampling we observed no significant results and no systematic patterns, e.g. OR for morning cortisol was

**Table 5** Results from follow-up analyses in 2007 and 2009. Odds ratios of depressive symptoms by increasing cortisol measures[a]

| Cortisol measure | Crude model | | Basic model[b] | | Full model[c] | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Follow-up-07 ($n$ = 2789)[d] | | | | | | |
| Morning | 0.84 | 0.51–1.38 | 0.86 | 0.51–1.43 | 1.05 | 0.56–1.97 |
| Evening | 1.21 | 0.79–1.87 | 1.31 | 0.81–2.12 | 1.35 | 0.79–2.30 |
| Mean | 0.78 | 0.40–1.51 | 0.82 | 0.41–1.63 | 1.09 | 0.48–2.49 |
| Slope | 0.75 | 0.48–1.17 | 0.65 | 0.40–1.06 | 0.73 | 0.38–1.38 |
| Follow-up-09 ($n$ = 2253)[d] | | | | | | |
| Morning | 0.85 | 0.51–1.41 | 0.77 | 0.45–1.34 | 0.78 | 0.43–1.41 |
| Evening | 1.31 | 0.86–2.00 | 1.25 | 0.77–2.04 | 1.39 | 0.79–2.45 |
| Mean | 0.73 | 0.37–1.44 | 0.65 | 0.31–1.38 | 0.70 | 0.30–1.62 |
| Slope | 0.81 | 0.51–1.29 | 0.75 | 0.43–1.29 | 0.79 | 0.42–1.47 |

[a] Odds ratios estimate the effects of a one unit increase in the log-transformed cortisol measures (see text for definitions).
[b] Adjusted for sex, age, education, income (dichotomized), family history of depression and days from the saliva sample to filling in the subsample questionnaire.
[c] Adjusted for sex, age, education income (dichotomized), family history of depression, traumatic life event, loneliness, physical activity, BMI, alcohol consumption, smoking, sleep quality and days from the saliva sample to filling in the subsample questionnaire.
[d] Depressive symptoms analyzed by binary logistic regression (depressive symptoms (CMDQ): no = 0, 1 and yes = 2, 3, 4). Analyses included participants without depressive symptoms at baseline.

between 0.92 and 1.01 in 2007 and between 0.96 and 1.12 in 2009.

## 6. Discussion

Neither repeated cross-sectional or short term follow-up analysis could show that measures of cortisol levels were associated with depressive symptoms or clinical depression in this study of public sector employees. We examined the effects of several saliva cortisol measures: morning, evening, mean of morning and evening, the decline over the day (slope) and the awakening response represented by the CAR and AUC measures and found no association in all but one of the analyses. Thus, we could not confirm our previous 2-years follow-up results where a low mean saliva cortisol level and a flat morning-to-evening slope predicted clinical depression (Grynderup et al., 2013).

The one exception was that morning cortisol was lower in clinical depressed participants compared to non-depressed participants in 2009. This association was found in one out of thirty-two full cross-sectional models, it was not replicated in the crude or the partially adjusted analysis or in the corresponding analysis of 2007 data. We therefore consider this finding to be due to chance. Although the findings from 2007 and 2009 are not completely independent we consider that the consistency of the findings adds to the robustness of our results.

Our results are not in accordance with the commonly held view that depression is associated with increased levels of cortisol (Stetler and Miller, 2011; Herbert, 2012). The background for this hypothesis is evidence of hypercortisolism and disturbed hypothalamic-pituitary-adrenal (HPA) axis function in studies of patients with major depression (Heuser et al., 1998; Michael et al., 2000; Cowen, 2002). Furthermore, patients with Cushings's syndrome and patients treated with corticosteroids have an increased risk of depression (Brown et al., 2004). However, the evidence of disturbed HPA axis function or hypercortisolism among depressed patients is not consistent across studies. One recent systematic review and metaanalysis (Stetler and Miller, 2011) concluded that HPA hyperactivity can vary considerably across patient groups and seems strongest among older hospitalized patients who display melancholic or psychotic features of depression. Another systematic review and meta-analysis concluded that there is no firm evidence of a difference of salivary cortisol in depressed patients and control persons (Knorr et al., 2010).

It is possible that the increased levels of cortisol commonly observed in patient populations could be attributed to the hospitalization. Stetler et al. found that being hospitalized due to depression was associated with an increase in cortisol independent of symptom severity (Stetler and Miller, 2011). The discrepancies in results between studies may also relate to the intensity of depression (depressive symptoms versus major depression) and reduced capacity for confounder control in small-scale studies.

The relation between saliva cortisol and depression has also been studied in population-based studies, both cross-sectional (Burke et al., 2005; Sjogren et al., 2006; Bremmer et al., 2007; Phillips et al., 2011) and follow-up studies (Harris et al., 2000; Goodyer et al., 2000; Halligan et al., 2007; Adam et al., 2010; Goodyer et al., 2010; Power et al., 2011; Ellenbogen et al., 2011; Vrshek-Schallhorn et al., 2012). However, only one of these studies is based on a general adult population (Sjogren et al., 2006) comparable to our study. The other studies examined populations selected by criteria which make sensible comparisons with our results difficult: age over 65 (Bremmer et al., 2007), poverty and material hardship (Burke et al., 2005), Vietnam veterans (Phillips et al., 2011), adolescents (Goodyer et al., 2000; Halligan et al., 2007; Adam et al., 2010; Goodyer et al., 2010; Ellenbogen et al., 2011; Vrshek-Schallhorn et al., 2012), the use of a combined outcome (anxiety and depression) (Power et al., 2011) and vulnerability to depression (Harris et al., 2000). These studies found mixed results. Overall, the findings in cross-sectional studies mostly found reduced cortisol responses to depression, while the prospective studies found evidence of an increased risk of incident depression with high morning cortisol levels at baseline.

However, the findings differed somewhat by different cortisol measures (morning, evening, CAR, AUC, slope, reactivity to acute stress) and cortisol sampling differed by sampling schemes.

The comparable study by Sjogren et al. (2006) consisted of 257 participants, 30–64 years old, randomly selected from the general population in two consecutive steps with a combined response rate of approximately 40%. Depression symptoms were measured by the Major Depression Inventory scale. Saliva samples were taken at awakening, 30 min later and before going to bed. The mean cortisol concentrations of samples from three consecutive work days were used in the analyses. Depressive symptoms were negatively correlated to awakening and to +30 min cortisol ($0.01 < p < 0.05$) but not to the cortisol awakening response or the evening cortisol. Depressive symptoms were also associated with a flatter morning–evening slope ($p < 0.01$). Our results did not confirm a negative association between +30 min cortisol or a flattened diurnal relation with depressive symptoms in neither the cross-sectional nor in the short-term follow-up analyses.

In cross-sectional data the temporal relation between depression and cortisol is lost. However, if cortisol hypo- or hypersecretion is a predictor of depression or secondary to depression, we would expect cross-sectional population studies and short-term follow-up studies to demonstrate an association between depression and levels of cortisol. This expectation presumes that cortisol effects on or response to depression goes in the same direction for participants with depression. It has been suggested in accordance with the concept of allostasis (McEwen, 2007) that cortisol is elevated when temporally close to depression onset and becomes reduced in the long run after depression or other lifetime psychological ill-health (Miller et al., 2007; Power et al., 2011; Kristenson et al., 2012). In our cross-sectional data we cannot distinguish between depression or depressive symptoms of recent or distant onset. However, in our follow-up subsamples of recent onset outcomes we did not find that cortisol was elevated. Consequently, if the second part of the theory is true, we should expect to find a negative relation between cortisol and depression in our cross-sectional data, if the group of depressed participants included a substantial number of longstanding or previous depressions with reduced cortisol. We did not find such a negative relation. Furthermore, adjustment for previous depression did not change the results. Thus, our data do not support the concept of allostasis with respect to cortisol and depression.

### 6.1.1. Strengths and limitations

Our study is large compared to most other studies, many of which include less than 250 participants (Harris et al., 2000; Bhagwagar et al., 2003; Vrshek-Schallhorn et al., 2012). The size of the study also allowed us to include a larger number of potential confounders than in many smaller studies. These potential confounders, age, family history of depression, experiences of traumatic life events, loneliness and poor sleep quality showed the expected relations to depression (significantly associated: $p < 0.001$) (Kessler, 1997; Burcusa and Iacono, 2007) indicating a basic validity of these data. We cannot exclude confounding due to lifetime psychological ill-health (Power et al., 2011) but we adjusted for experienced life-events and previous depression.

We also consider the parallel use of self-reported symptoms and a standardized clinical outcome as strengths of the study. Furthermore, the consistency of the results in repeated cross-sectional analyses with a two-year time interval added to the robustness of the results.

It is a limitation that we only had one morning and one evening saliva sample in the larger 2007 and 2009 populations. However, results based on the subsamples with four cortisol samples per day showed similar results. Furthermore, the results seemed unaffected by the fact that a fairly large proportion of the participants took their saliva samples at times that deviated somewhat from the recommended times.

Another limitation was the low participation (45% in 2007). Participation could be differentially related to depression. Registry information showed that participants in 2007 were prescribed antidepressant medicine less often than non-participants and were less frequently on sick leave (Kaerlev et al., 2011). Participation was higher in 2009 (72% of the baseline population), but could still be influenced by different participation rates related to depression. The proportion of participants with a high score ($\geq$3) on the depression scale was 6.7% among those who only participated in 2007 and 4.2% among those who participated in both 2007 and 2009. Thus, depression status seems to have influenced participation to some degree in 2007 and in 2009 as well. It seems plausible that especially more severe cases of depression would be on sick leave or felt unable to participate in the study. However, the different participation rates by depression scores was not related to cortisol concentrations and will therefore not confound the associations between depression and cortisol.

Nevertheless, participation of the more severe degrees or types of depression in population-based studies remains a crucial issue. A low participation of these cases may decrease the power of a study to demonstrate a true association between cortisol and depression, especially if the association is much more pronounced or exclusively present in severe versus mild depression as indicated in the psychiatric literature (Stetler and Miller, 2011).

Another crucial issue is the time intervals of examination in longitudinal studies and how the results from longitudinal analyses are related to the cross-sectional results from each of the examination rounds. Since the median duration of episodes of major depression seems to vary between 3 and 12 months with only 10–30% lasting longer than two years (Spijker et al., 2002) a two year follow-up period is too long to catch all new or recurrent cases prospectively during this period. Furthermore, a cortisol concentration which in many cases has been measured a long time before the onset of a recorded period of depression may not be the proper cortisol concentration to associate with this episode. The same considerations apply to mood changes and cortisol measured at different points in time. This potential misclassification could bias the results towards the null-hypothesis of no association in follow-up studies with a long time period between examination rounds and does not explain the discrepant findings in our cross-sectional and longitudinal analyses. We conducted the short-term follow-up analyses in order to address the potential misclassification due to too long follow-up time

but could not confirm the long-term follow-up results. Prospective adolescent studies indicate that high baseline cortisol awakening response are associated with incident depression at follow-up after one year (Adam et al., 2010) and even up to two and half years after the baseline measurement, although decaying over time (Vrshek-Schallhorn et al., 2012). Whether this predictive stability can be generalized to an adult population is uncertain, but was not supported in our 2-year follow-up study (Grynderup et al., 2013).

However, considering the results of our cross-sectional and short-term follow-up analyses we cannot exclude that the findings in our previous 2-year follow-up study (Grynderup et al., 2013) could be due to chance. The two significant associations in the 2-year follow-up were for interrelated cortisol measures (mean of morning and evening cortisol and morning to evening slope), and may therefore be considered as a single finding, and the upper confidence limits were close to unity.

## 7. Conclusion

In conclusion, cortisol was not associated with depressive symptoms or clinical depression in repeated cross-sectional and in short-term follow-up analyses in this study of a large population of working public sector employees. This study does not indicate that cortisol is a mediating factor between stress and depression.

Future studies on the temporal relation between stressors, cortisol and the development of depression should focus on the feasibility of shorter and repeated follow-up times and methods to ensure that severe cases of depression are included in the study.

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## Conflict of interest

There is no conflict of interest. Marianne A. Vammen was funded by the Lundbeck Foundation. The Lundbeck Foundation was not involved in any parts of the study or the preparation of the article.

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