Psychosocial working conditions, physiological stress, and the risk of depression

PhD dissertation

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

I Grynderup MB, Mors O, Hansen AM, Andersen JH, Bonde JP, Kaergaard A, Kaelev L, Mikkelsen S, Rugulies R, Thomsen JF, Kolstad HA. A two-year follow-up study of risk of depression according to work-unit measures of psychological demands and decision latitude. *Scand J Work Environ Health* 2012; 38(6):527-536.

II Grynderup MB, Mors O, Hansen AM, Andersen JH, Bonde JP, Kaergaard A, Kaelev L, Mikkelsen S, Rugulies R, Thomsen JF, Kolstad HA. Work-unit measures of organisational justice and risk of depression - a 2-year cohort study. *Occup Environ Med* 2013; 70: 380-385.

III Grynderup MB, Kolstad HA, Mikkelsen S, Andersen JH, Bonde JP, Buttenschøn HN, Kaergaard A, Kaelev L, Mikkelsen S, Rugulies R, Thomsen JF, Vammen MA, Mors O, Hansen AM. A two-year follow-up study of salivary cortisol concentration and the risk of depression. *Psychoneuroendocrinology* 2013.

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List of abbreviations:

ACTH	Adrenocorticotropic hormone
BDI	Beck Depression Inventory
CES-D	Center for Epidemiological Studies – Depression Scale
CI	Confidence Interval
CIDI	Composite International Diagnostic Interview
CRH	Corticotrophin-releasing hormone
DIS	National Institute of Mental Health Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
GHQ	General Health Questionnaire
HAD-D	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-Pituitary-Adrenal
ICD	International Classification of Diseases
ICD-DCR	International Classification of Diseases – Diagnostic Criteria for Research
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Age Children
MDI	Major Depression Inventory
MFQ	Mood and Feelings Questionnaire
OR	Odds ratio
PHQ	Patient Health Questionnaire for Depression
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM-IV
SCL	Symptom Check List
SDS	Patient Health Questionnaire for Depression
SF36	36-item Short-Form Health Survey

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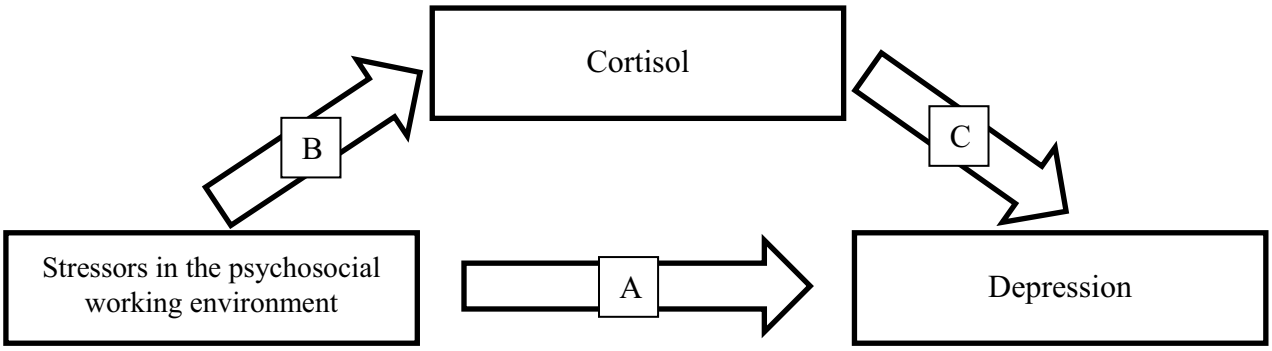
1. Introduction

Stress is a complicated word with many meanings that may designate 1) exposure to stressors, 2) a physiological stress response, and 3) a health outcome (distress). These have all been suggested to be related to depression [1-7]. The physiological stress response has been suggested as a biological pathway linking psychosocial stressors to subsequent depression [8-11].

There are many alternative ways to define and measure stressors and many aspects of life can act as a stressor, such as interpersonal relationships, demanding working conditions, threatening situations, traumatic events, and all kinds of daily hassles [1]. In this thesis, the only stressors to be examined are stressors in the psychosocial working environment. Likewise, the physiological stress response can be measured in different ways. Concentrations of corticotrophin-releasing hormone, adrenocorticotropic hormone, and cortisol have often been used to evaluate hypothalamic-pituitary-adrenal activity, and thereby measure the physiological stress response [4;12]. In this thesis, the only parameter of the physiological stress response that will be studied is salivary cortisol concentration.

This thesis covers the relations between the psychosocial working environment, cortisol, and depression (Figure 1). The objectives are 1) to examine stressors in the psychosocial working environment and the risk of subsequent depression (A) and 2) to examine cortisol concentration and subsequent depression (C). The association between stressors in the psychosocial working environment and cortisol (B) will not be studied, but will be briefly discussed.

Figure 1. Stressors in the psychosocial working environment, cortisol and depression.



1.1.1 Depression

Depression is a mental disorder with a lifetime prevalence of approximately 13% in the European population [13]. Depression has a harmful effect on both quality of life and workplace functioning [14]. Depression is characterized by depressed mood, loss of interest, and decreased energy accompanied by other symptoms such as loss of self-esteem, decrease in activity, reduced capacity for enjoyment and concentration, tiredness after minimal effort, disturbed sleep, feelings of guilt, changes in appetite, loss of libido, and psychomotor retardation [15]. Depression is currently the leading burden of disease assessed by disability-adjusted life years in middle and high-income countries [16].

The etiology of depression is not clearly established, but many studies indicate that biological, psychological, social, and genetic factors are involved [17;18]. Women are more likely to develop depression than men, and high age, low socioeconomic status, low educational level, alcohol consumption, smoking, family history of depression, personality traits, previous depression, and stressful life events have been related to the occurrence of depression [17;19-24]. Depression has a high co-morbidity with other mental disorders [25], and even though a depressive episode rarely last more than half a year [25;26] the disorder is highly recurrent and thus has a high lifetime effect [22].

Many epidemiological studies of depression have relied on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM) [27] or the highly similar diagnostic criteria for depressive episodes in the International Classification of Diseases (ICD) [15]. Studies using the DSM or ICD diagnostic criteria for depression often used standardized clinical interviews such as the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [28] or the Composite International Diagnostic Interview (CIDI) [29]. Other studies measure depressive symptoms using questionnaires such as the Major Depression Inventory (MDI) [30], the Center for Epidemiological Studies – Depression Scale (CES-D) [31], the Beck Depression Inventory (BDI) [32], or the Symptom Check List (SCL) [33]. Though these questionnaires are not as detailed as the standardized clinical interviews they often show high diagnostic accuracy and external validity [34]. Some population studies use other measures of depression such as prescription of antidepressant medication [35],

health insurance claims due to depression [36], sick leave due to depression [37], or hospital referral due to depression [38].

1.1.2 Psychosocial working conditions

The word psychosocial has many definitions, but one useful definition from the Oxford English Dictionary is the influence of social factors on an individual's mind or behavior [39]. Based on this definition, the study of psychosocial working conditions pertains to the social working conditions that have an influence on an individual's mind or behavior. The mental health consequences of psychosocial working conditions have been examined in numerous studies for more than three decades [40]. The psychosocial working conditions vary considerably between different jobs and work places and many models of different psychosocial stressors have been used in different studies. The most frequently used model has been the job strain model by Karasek and Theorell [2;41] that describes mental strain as the result of the interaction of high psychological demands (role conflicts, work load, and time pressure) and low decision latitude (control over work activities and ability to utilize specific skills at work) [42].

The effort-reward imbalance model [43] and the organizational justice model [44;45] have been used with increasing frequency in recent years. The effort-reward imbalance model addresses the violation of expected reciprocity and adequate exchange caused by an imbalance between high effort spent and low reward received at work [46]. The organizational justice model describes the effect of varying levels of procedural justice (the extent to which decision-making procedures include input from affected parties, are consistently applied, suppress bias, and are accurate, correctable, and ethical) and relational justice (polite, considerate, and fair treatment of individuals) [47].

These three models are, however, far from the only ways that psychosocial working conditions have been measured. Other measures are for example hospital ward overcrowding [48], workplace social capital [49], job insecurity [50], bullying [51], working hours [52], work climate satisfaction [53], or emotional demands [54]. Some models of psychosocial working conditions are complementary and measure different aspects of the working environment [55;56] while others are redundant and measure similar factors

using different notions. Distributive justice and effort-reward imbalance [57;58] are examples of the latter.

Most studies have used self-administered questionnaires to measure the psychosocial working conditions, such as the job content questionnaire for measuring the different components of Karasek and Theorell's job strain model [59] or the effort-reward imbalance questionnaire [60]. The job content questionnaire contains statements such as: "Your job was very hectic?", "Your job required that you do things over and over?", and "Your job allowed you freedom to decide how you did your job?" The effort-reward imbalance questionnaire contains statements such as: "Over the past few years, my job has become more and more demanding?", "My current occupational position adequately reflects my education and training?", and "Considering all my efforts and achievements, I receive the respect and prestige I deserve at work?" Some studies have used comprehensive questionnaires that cover a large variety of psychosocial working conditions, for example the Copenhagen psychosocial questionnaire [61] or the General Nordic Questionnaire for Psychological and Social Factors at Work [62], while other studies only use a single question to measure a chosen aspect of the participants working conditions, such as "On an average weekday, approximately how many hours do you spend on the following activities (if applicable): Work (daytime and work brought home)?" [63].

Self-administered questionnaires are a straightforward and cost-effective way to gather information about the perceived frequency and severity of different psychosocial working conditions. The main disadvantage is that the way the working environment is perceived may not only be influenced by the psychosocial working conditions, but also by personality traits, health, and other unintended factors, and thus cause misclassification and reporting bias [64]. Some studies use interviews to obtain information about the psychosocial working conditions [65;66]. An interview makes it possible to collect thorough information about the working environment, but still relies on the participants' self-reported exposure information.

Averaging of exposure information across work units [35], work places [49;53], and occupations [38;67] has been used to obtain information less affected by reporting bias.

Registry information [48;68;69] or expert assessment [36;70] have been used to obtain exposure information independent of the perception of the participants.

1.1.3 Cortisol

Cortisol is a steroid hormone produced in the adrenal cortex and regulates the metabolic system and anti-inflammatory pathways [71]. The release of cortisol is mediated by the Hypothalamic-Pituitary-Adrenal (HPA) axis through corticotrophin-releasing hormone (CRH) produced in the hypothalamus and adrenocorticotropic hormone (ACTH) produced in the pituitary gland [71]. Cortisol has implications for the immune system, bone metabolism, the formation and retrieval of memories, the secretion of gastric acid, the expression of genes, and numerous other functions [72-75]. In this thesis, the main interest in cortisol is due to its role as a measure of physiological stress and HPA-axis activity.

When experiencing demanding and threatening situations (stressors) CRH is secreted from the hypothalamus, which causes an increased secretion of ACTH from the pituitary gland, and the ACTH increases the secretion of cortisol from the adrenal cortex [76;77]. The elevated cortisol concentration then inhibits the secretion of CRH and ACTH via a negative feedback mechanism [78;79]. This interaction between the hypothalamus, pituitary gland, and adrenal gland is a key feature of the HPA axis. Cognitive abilities and metabolic and psychiatric disorders may affect HPA-axis activity [80]. The entire HPA system allows organisms to adapt to physical and psychosocial changes in their environments [81].

The responsiveness and stability of the HPA axis in a changing environment is essential. McEwen introduced the term allostasis to describe the process of adapting and responding to challenges and different conditions, such as sleep, hunger, danger, infection, and coping with unpleasant situations [82]. When exposed to a challenge, the secretion of CRH, ACTH, and cortisol increases, and when the situation is no longer challenging the concentration of the hormones return to baseline levels through a negative feedback mechanism. According to this hypothesis a prolonged period of heightened load on the allostatic process can lead to pathophysiology. This may happen when exposed to a challenging situation for a long time, or when the negative

feedback system does not sufficiently turn off the response when no longer needed [83]. According to McEwen, a failure to activate the physiological stress response in a demanding or threatening situation will constitute an extra burden on health as the physiological imbalance will be maintained. There is a risk of cascade effects when other physiological systems need to compensate for the failure, and of inadequate responsiveness of the physiological stress system [82].

Cortisol exhibits both a diurnal and seasonal variation [84]. Cortisol concentration begins to rise steeply after awakening and peaks approximately 30-45 minutes after awakening. At this time the cortisol concentration is typically higher than the rest of the day. The concentration declines slowly during the day and is usually lowest late at night, where the concentration often is 5-10 times lower than the morning peak [85].

The distinct diurnal cortisol pattern offers several challenges when selecting a sampling strategy. The simplest method is to measure cortisol at a fixed point in time, most frequently in the morning, when the cortisol concentration is at its highest, or in the evening, when cortisol concentration is lower. It is also possible to combine information from several samples to measure a mean cortisol concentration during a given period of time. Finally, the deviation between two cortisol concentrations measured at different times gives an indication of the cortisol reactivity to stressors in the intervening period or the ability to recover after an increased cortisol secretion[86]. The cortisol awakening response is one such measure that describes the morning peak cortisol concentration at two or more points, typically within one hour after awakening. The difference between morning and evening cortisol concentration, called the slope or diurnal variation, indicate the daily capacity for recovery [77].

Cortisol concentration is affected by several physiological and demographic factors, such as age, ethnicity, socioeconomic status, and body mass index are associated with cortisol concentration [87;88]. Low morning cortisol concentration, high evening cortisol concentration, and a small difference between morning and evening cortisol concentration (low slope) have been associated with somatic diseases, such as cardiovascular disease, breast cancer, and rheumatoid arthritis [89].

1.1.4 Psychosocial working conditions and cortisol

Acute psychological stressors, such as the Trier Social Stress Test[90], have been shown to increase the cortisol levels [91;92]. Similar increases in cortisol concentration during work have been shown among professional dancers during competition [93], air traffic controllers [94], rescue service personnel [95], critical care nurses and physicians [96]. Long-term exposure to demanding psychosocial working conditions have been suggested to be related to cortisol level, but a recent review show no consistent association [6]. The review identified 27 studies of the psychosocial working environment and cortisol level. These 27 studies includes in total 185 analyses of cortisol measures, such as morning cortisol concentration, evening cortisol concentration, mean cortisol concentration, and morning-to-evening slope. Of these 185 analyses, 29 (16%) showed an association between the psychosocial working environment stressors and high cortisol levels, 13 (7%) showed an association with low cortisol levels, and 143 (77%) showed no association. It is possible that the majority of non-significant results are due to methodological limitations, such as an insufficient exposure contrast [6].

It has been hypothesized that chronic stress may result in hypocortisolism after a prolonged period of hypercortisolism [97]. A meta-analysis found a negative association between months since onset of a long-term stressor and both morning concentration and daily mean concentration of cortisol. Initially cortisol concentration increased, but eventually the concentration was reduced to below normal levels [98]. No such pattern was observed for evening cortisol concentration. A pattern of increased cortisol levels followed by decreased cortisol levels may also explain the inconsistent findings from studies of psychosocial working conditions and cortisol. It is, however, also likely that there are simply no effect of psychosocial working conditions on cortisol.

1.1.5 Cortisol and depression

Hyperactivity of the HPA axis has been called one of the most consistent biological findings in depression psychiatry [4;12], and HPA hyperactivity has been put forth as an important mechanism explaining the pathophysiology of depression [4]. However, the association may not be entirely consistent and well-replicated [5]. The most recent reviews of the association between HPA axis activity, cortisol, and depression indicate that morning and evening cortisol concentration is increased in patients with

depression, and that their morning-to-evening slope is flatter than that of healthy controls. The increased cortisol levels were most pronounced in older in-patients with either melancholic or psychotic depression [4;5]. Furthermore, HPA hyperactivity has been shown in patients who have recovered from a depression [99], in non-depressed people with a parental history of depression [100;101], and people at increased risk of depression due to a personality characterized by neuroticism [102]. On the other hand, HPA hypoactivity has been implicated in atypical, seasonal, and climacteric depression, fibromyalgia, post-traumatic stress disorder, chronic fatigue syndrome, and following periods of chronic stress [71]. Likewise, depression is frequent among those afflicted with Cushing's syndrome which is characterized by hypercortisolism, but also among those afflicted with Addison's disease which is characterized by hypocortisolism [103].

The vast majority of studies examining the association between cortisol and depression are cross-sectional studies of differences between patients with depression and healthy controls. Very few studies of the longitudinal association between cortisol concentration and the risk of depression have been published. To identify these studies a review of the literature was needed.

1.1.6 Psychosocial working conditions and depression

The interest in the association between working conditions and depression are growing and many studies, examining this important question, have been carried out in the last two decades [64;104]. The majority of these studies have, however, been published during the last 5 years, and were not included in the latest systematic reviews of psychosocial working conditions and the risk of depression [2;41;43]. Thus, an updated review of the literature was needed.

1.2 Literature review – materials and methods

1.2.1 Literature search of psychosocial working conditions and depression

The literature search used the databases EMBASE (1980-), PsychINFO (1967-), and PubMed (1960-) on the 26th of July 2012. Search terms were selected based on search strategies, titles, and keywords from three recent reviews on this field [2;41;43]. The search strategy reflected the following inclusion criteria:

1. The study must be longitudinal.
2. The study must include psychosocial working conditions as exposure.
3. The study must include depression or depressive symptoms as outcome.

The full electronic search strategies for all databases are presented in appendix 1. A total of 4,199 papers were identified (1,691 in EMBASE, 842 in PsychINFO, and 1,666 in PubMed), while 26 longitudinal studies of psychosocial working conditions and depression were identified through other sources, such as reference lists from papers and reviews on this topic. 1050 of these records were duplicates, leaving a total of 3175 unique papers. The screening process excluded 2933 records based on their title and additionally 132 papers based on their abstract. 110 full-text articles were assessed for eligibility and 44 of those were excluded (31 were not longitudinal studies, 7 did not use depression or depressive symptoms as an outcome, 5 did not use psychosocial working conditions as an exposure, 1 were **study I** of this thesis, which were excluded to enable comparison between all previous studies and **study I-III** of this thesis). The 66 longitudinal studies of psychosocial working conditions and the risk of depression are presented in table 1.

Figure 2. Four-phase flow diagram[105] of information from review of longitudinal studies of psychosocial working conditions and depression.

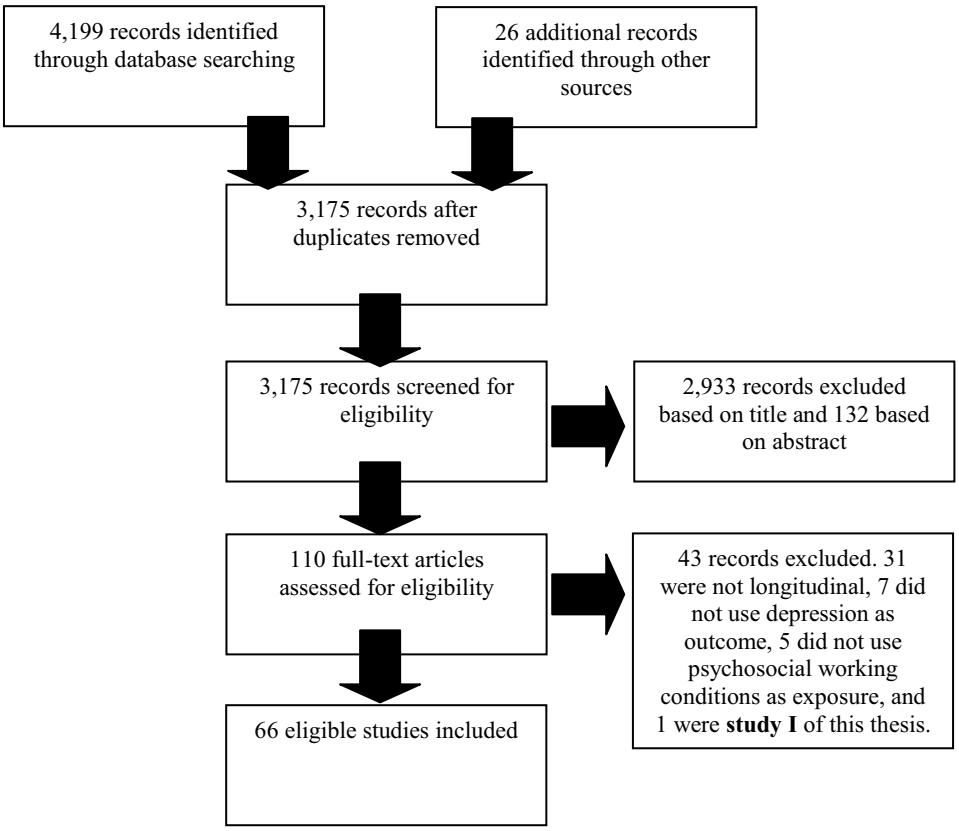


Table 1. Characteristics of 66 longitudinal studies of the psychosocial working environment and the risk of depression, 1990-2012.

Study, publication year, country	Follow-up period	Population (no. of males/females)	Exposure	Source of exposure information	Source of outcome information *	Confounders considered
Kawakami [106] 1990, Japan	3 years	Industrial workers (3045, 0)	Work load, forced pacing, job unsuitability, poor human relationships	Questionnaire	Clinical interview	Shift work, education, depressive symptoms, type A behavior, inadequate income, health status, family satisfaction, number of close friends, parents death before age 17
Kawakami [107] 1992, Japan	1 year	Industrial workers (468, 0)	Work load, decision latitude, job unsuitability, poor human relationships	Questionnaire	SDS	Age, marital status, education, type A behavior, initial medical treatment
Niedhammer[108] 1998, France	5 years	Industrial workers (8422, 3130)	Psychological demands, decision authority, social support, stressful events	Questionnaire	CES-D	Gender-stratified. Age, marital status, number of children, educational level, occupation, previous absenteeism for mental disorders, stressful personal and occupational events
Shields[109] 1999, Canada	2 years	Working population (2,181, 1,649)	Job strain, job insecurity, supervisor support, working hours	Questionnaire	CIDI as questionnaire	Gender-stratified. Age, marital status, educational attainment, household income and the presence of children younger than 12 in the household, occupation, self-employment, shift work, multiple jobs, high job strain, high job insecurity, low supervisor support
Mausner-Dorsch[110] 2000, USA	12 years	Working population (403, 502)	Job strain	Questionnaire	DIS	Gender-stratified. Age, race, marital status, education, occupation
Schonfeld[111] 2001, USA	12 years	Teachers (0, 184)	Episodic stressors (threats, confrontations)	Questionnaire	CES-D	Age, socioeconomics, race, marital status
de Lange[112] 2002, Netherlands	4 years	Working population (247, 577)	Job strain	Questionnaire	CES-D	Age, gender, education
Griffin[113] 2002, England	5 years	Public employees (5091, 2179)	Decision latitude	Questionnaire	GHQ	Gender-stratified. Age, employment grade, number of children, marital status, caregiver status, home control
Patermiti[114] 2002, France	3 years	Industrial workers (7729, 2790)	Psychological demands, decision latitude, social support	Questionnaire	CES-D	Gender-stratified. Age, education, income, marital status, stressful events, chronic disease, personality, occupation, working hours, physical workload factors
Kivimaki[115] 2003, Finland	2 years	Hospital employees (601, 4831)	Bullying	Questionnaire	Self-reported doctor diagnosed depression	Age, gender, income
Michelsen[116] 2003, Sweden	24 years	Working population (177, 190)	Mental load, monotonous work, hectic work, social support	Interview	Clinical interview	Gender-stratified. Age, education, living alone, children at home (and 18 others).
Tokuyama[117] 2003, Japan	5 years	Insurance company workers (647, 718)	Workload, difficult job, inadequate evaluation of contribution, problem with co-workers, stressful events, working hours, social support	Questionnaire	SDS	Age, gender, major trauma before age 18, parental rearing style, neuroticism, extraversion, family problems, close friend problems, health problems, poor economic status, lack of support, life events
de Lange[118] 2004, Netherlands	4 years	Working population (461, 207)	Psychological demands, decision latitude, supervisor support	Questionnaire	CES-D	Age, gender

Moore[119] 2004, USA	2 years	Manufacturing company workers (970, 274)	Layoffs	Questionnaire	CES-D	Age, gender, education
Ferrie[120] 2005, England	12 years	Public employees (3276, 1171)	Job insecurity	Questionnaire	GHQ	Gender-stratified. Age, socioeconomic position, self-reported health, negative affect
Godin[121] 2005, Belgium	1 year	Working population (1066, 920)	Effort reward imbalance, overcommitment	Questionnaire	SCL	Age, education, job dissatisfaction, workplace instability
Ylipaavalniemi [122] 2005, Finland	2 years	Hospital employees (537, 4278)	Psychological demands, decision latitude, job strain, work climate, procedural justice, relational justice	Questionnaire	Self-reported doctor diagnosed depression	Age, gender, income, alcohol consumption, smoking, sedentary lifestyle, obesity,
Wang[123] 2005, Canada	2 years	Working population (6633 total)	Work stress (sum of psychological demands, skill discretion, decision authority, job insecurity, physical demands, and social support)	Interview	CIDI	Age, gender, marital status, family income, education, race, number of long term medical illnesses, child and adulthood traumatic events, recent life events, baseline and subsequent mental health service use.
Muntaner[124] 2006, USA	2 years	Nursing assistants (7, 234)	Emotional demands	Questionnaire	CES-D	Age, marital status, race, ownership type, gini-index, proportion of African Americans
Rugulies[125] 2006, Denmark	5 years	Working population (2129, 2004)	Psychological demands, decision authority, supervisor support, co-worker support, skill discretion, job insecurity	Interview	SF36	Gender-stratified. Age, family status, education, employment status, baseline depression, smoking, alcohol consumption, physical activity, socioeconomic status
Shields[126] 2006, Canada	2-8 years	Working population (6125, 5886)	Job strain, day-to-day stress, co-worker support, supervisor support	Interview	CIDI as questionnaire	Gender-stratified: occupation, working hours, shift work, self-employment, age, marital status, the presence of children in the household, education, personal income, heavy monthly drinking and low emotional support
Wieclaw[67] 2006, Denmark	1 year	Human service professionals (49483, 75768)	Occupation	Registry linkage	Hospital records	Stratified on age, gender, time. Controlled for marital status, having children, education, income, unemployment, residence, nationality.
Ahola [127] 2007, Finland	3 years	Dentists (664, 1891)	Job strain	Questionnaire	BDI	Age, gender, marital status.
Clays[128] 2007, Belgium	6.6 years	Working population (1950, 871)	Job strain, isostrain, psychological demands, decision latitude, social support	Questionnaire	CES-D	Gender-stratified. Age, educational level, social network, satisfaction with private life, baseline depressive symptoms, and locus of control.
Kivimaki[56] 2007, Finland	2-4 years	Public employees (3975, 14091) and hospital employees (532, 4301)	Effort-reward imbalance, procedural justice, relational justice	Questionnaire	Self-reported doctor diagnosed depression	Age, gender, occupational status
Melchior[65] 2007, New Zealand	32 years	Birth cohort (485, 406)	Psychological demands, decision latitude, social support, physical demands	Interview	DIS	Gender-stratified. Socioeconomic status, negative affectivity, juvenile psychiatric disorders

Plaisier[129] 2007, Netherlands	2 years	Working population. (1529, 1117)	Psychological demands, decision latitude, job insecurity, social support	Interview	CIDI	Age, gender, education, health
Virtanen[130] 2007, Finland	3 years	Working population (1662, 1704)	Job strain, psychological demands, decision latitude	Interview	Prescription of antidepressant medication	Gender-stratified. Age, marital status, occupational grade, household income, lifetime and baseline mental disorders
Buddeberg-Fischer[131] 2008, Switzerland	4 years	Medical doctors (233, 200)	Effort-reward imbalance, overcommitment	Questionnaire	HAD-D	Gender, physical health, mental health, measurements at baseline
Kouvonen[49] 2008, Finland	2-5 years	Public employees (6623, 26954)	Workplace social capital	Questionnaire and work place average	Purchase of antidepressant medication and self-reported doctor diagnosed depression	Age, gender, marital status, socioeconomic position, place of work, smoking, alcohol use, physical activity, body mass index, psychological distress
Virtanen[68] 2008, Finland	2.5 years	Hospital employees (587, 6753)	Work load	Registry linkage	Prescription of antidepressant medication	Age, gender, occupation, type and length of employment contract, hospital district, specialty, and calendar year.
Waldenström[70] 2008, Sweden	3 years	Working population (241, 431)	Cognitive requirements, possibility of influence and required conformance to schedule, time pressure and hindrances concerning goals, resources and instrumental support	Expert assessment	SCAN	Age, gender, mental illness at baseline, self-reported, financial difficulties, living alone and negative life events
Wieclaw[38] 2008, Denmark	1 year	General population (27446, 44780)	Psychological demands, decision latitude, job strain, emotional demands, working with people	Job exposure matrix	Hospital records	Gender-stratified. Marital status, children, education, income, unemployment, residence, nationality.
Andrea[132] 2009, Netherlands	2 years	Working population (2811, 965)	Psychological demands, decision latitude, social support, emotional demands, co-worker support, supervisor support, job insecurity, working hours	Questionnaire	HAD-D	Age, gender, education, living alone, smoking, (psycho)somatic conditions, shocking events outside work
Bonde[35] 2009, Denmark	12 years	Public employees (6886, 14243)	Psychological demands, decision latitude, job strain, isostrain, skill discretion, decision authority, social support, work climate, management, work load, professionalism, cooperation	Work unit average	Prescription of antidepressant medication	Age, gender, marital status, children under age of 15, socio-economic status

Burgard[133] 2009, USA	10 years	General population (652, 564)	Job insecurity	Questionnaire and interview	CES-D	Age, gender, health shock, mental health at age 16, neuroticism (and 12 others).
Clumeck[134] 2009, Belgium	3 years	Working population (2447, 6103)	Psychological demands, decision latitude, social support	Questionnaire	Sick leave due to depression.	Gender-stratified. Age, living situation, baseline depression, occupational level
Godin[37] 2009, Belgium	1-5 years	Working population (6671, 2725)	Psychological demands, decision latitude, co-worker support, supervisor support, work centrality, work dissatisfaction	Questionnaire	Sick leave due to depression.	Gender-stratified. Age, educational level, job strain, social support from colleagues, social support from supervisor, work centrality, work satisfaction, private life satisfaction, private life social support, baseline depressive symptoms
Magnusson[135] 2009, Sweden	2 years	Working population (2720, 3265)	Psychological demands, decision authority, social support, conflicts at work	Questionnaire	SCL	Gender-stratified. depressive symptoms at baseline, age, marital status, birth country, labor market sector, income at baseline and employment status at follow-up
Sinokki[136] 2009, Finland	3 years	General population (1663, 1684)	Work climate	Questionnaire	Prescription of antidepressant medication and CIDI	Age, gender, marital status, occupational grade, lifetime mental disorders, baseline DSM-IV disorders, job tenure, job demands, job control
Sinokki[137] 2009, Finland	3 years	General population (1695, 1734)	Co-worker support, supervisor support, private life support	Questionnaire	Prescription of antidepressant medication and CIDI	Age, gender, marital status, occupational grade, lifetime mental disorders, baseline CIDI diagnoses
Wang[138] 2009, Canada	6 years	General population (2633, 2233)	Job strain	Interview	CIDI	Age, gender, education, status of major depression 2 years before and after follow up, perceived health status, childhood traumatic events
Iennaco[36] 2010, USA	4.7 years	Industrial workers (7115, 451)	Psychological demands, decision latitude	Expert assessment	Insurance information.	Age, gender, race, education, tenure, smoking, body mass index, cholesterol, job grade
Inoue[139] 2010, Japan	5.1 years	Industrial workers (15256, 0)	Psychological demands, decision latitude, job strain, supervisor support, co-worker support, job insecurity, role ambiguity, role conflict	Questionnaire	Sick leave due to depression.	Age, education, marital status, occupation, chronic physical conditions, baseline depressive symptoms, neuroticism
Jensen[53] 2010, Denmark	6.3 years	Public employees (2869, 10554)	Work climate	Work unit average	Hospital records.	Age, gender, marital status, children less than 15 years of age, occupational grade, size of work unit
Joensuu[140] 2010, Finland	15 years	Forest industry employees (10620, 3248)	Skill discretion, decision authority, supervisor support, co-worker support	Questionnaire	Hospital records.	Age, gender, occupational status, physical health, physical work environment
Kalil[141] 2010, USA	1 year	General population (91, 99)	Job insecurity	Questionnaire	CES-D	Gender-stratified. Age, race, marital status, education, income, employment status, baseline depressive symptoms
Kivimaki[48] 2010, Finland	1 year	Nurses (0, 2784)	Psychological demands, work load	Registry linkage	Sick leave due to depression.	Age, length of employment, permanent contract, hospital district, speciality field, smoking, physical activity, alcohol consumption, body mass index
Madsen[54] 2010, Denmark	5 years	Working population (2553, 2405)	Emotional demands, demands for hiding emotions, threats, violence	Questionnaire	Incident use of antidepressants	Age, gender, cohabitation, parental status, socioeconomic position

Munir[142] 2010. Denmark	1.5 years	Elderly care staff (78, 110)	Transformational leadership	Questionnaire	MDI	Age, gender, cohabitation, number of dependents, occupational status, tenure
Netterstrøm[143] 2010, Denmark	2 years	Public employees (183, 502)	Merger, job change	Questionnaire	MDI	Age, gender, occupation, department, supervisor function
Rugulies[50] 2010, Denmark	3.5 years	General population (2435, 2707)	Job insecurity	Questionnaire	Prescription of antidepressant medication	Age, gender, cohabitation, socioeconomic position, alcohol consumption, depressive symptoms at baseline
Virtanen[69] 2010, Finland	2 years	Hospital employees (363, 4803)	Work load	Registry linkage	Sick leave due to depression.	Age, gender, occupation, employment contract, hospital district, specialty
Ybema[144] 2010, Netherlands	3 years	Working population (866, 653)	Distributive justice, procedural justice	Questionnaire	CES-D	Age, gender, education.
D'Errico[145] 2011, Italy	5-6 years	Union workers (1569, 477)	Psychological demands, decision latitude, job strain, working hours	Questionnaire	Prescription of antidepressant medication	Age, gender, shift work, overtime, loud noise, psychological violence
Horton[146] 2011, USA	2-4 years	Industrial workers (0, 223)	Job strain, social support, isometric load, physical demands, job insecurity, work dissatisfaction, hazardous work	Questionnaire	CES-D	Age, marital status, education level (and 12 others).
Lang[147] 2011, USA	3-6 months	Soldiers (1244, 65)	Distributive justice, interpersonal justice, informational justice, procedural justice	Questionnaire	CES-D / PHQ	None
Strazdins[148] 2011, Australia	4 years	Mid-aged cohort (995, 980)	Psychological demands, decision latitude, job insecurity	Questionnaire	Questionnaire	Gender, education, relationship status, part-time employment, behavioral inhibition system, anxiety prone personality, life events, work conditions
Thielen[149] 2011, Denmark	3.5 years	General population (2439, 2222)	Quantitative demands, work pace, emotional demands, co-worker support, supervisor support, sense of community, meaning of work, physical demands, opportunity for development, variation of work	Questionnaire	Prescription of antidepressant medication	Gender-stratified. Age, family status, SEP, alcohol consumption, smoking, physical activity, obesity, private life conflicts, private social support, co-morbidity, work characteristics, baseline depressive symptoms
Virtanen[52] 2011, England	5 years	Public employees (2248, 712)	Working hours	Questionnaire	GHQ	Age, gender, occupational grade, marital status, chronic illness, smoking, alcohol consumption, employment status at follow up
Wang[66] 2011, Canada	6 years	General population (3196, 2812)	Job strain	Interview	CIDI	Age, gender, marital status, education, employment status, self-rated health, long-term medical conditions, life events, chronic stress, childhood traumatic events
Innstrand[150] 2012, Norway	2 years	Working population (3475 total)	Work engagement	Questionnaire	SCL	None
Rugulies[51] 2012, Denmark	2 years	Elderly care staff (0, 5701)	Bullying	Questionnaire	MDI	Age, cohabitation, type of job, seniority, length of follow-up, depression at baseline

Smith[151] 2012, Canada	2 years	General population (2030, 1705)	Job strain, psychological demands, decision latitude, social support	Questionnaire	CIDI	Age, gender, marital status, presence of children, occupation change, level of education, baseline exposure levels, presence of chronic health conditions, subclinical depression at baseline, family history of depression, previous depression
Virtanen[63] 2012, England	5.8 years	Public employees (1626, 497)	Working hours	Questionnaire	CIDI	Age, gender, occupational grade, marital status, chronic physical disease, smoking, alcohol consumption, job strain, social support
Wang[152] 2012, Canada	1 year	Working population (1547, 1205)	Job strain, effort-reward imbalance, supervisor support, co-worker support, job insecurity, working hours, family to work conflict	Interview	CIDI	Gender-stratified. Age, marital status, job type, job grade, comorbid anxiety disorder, education, income

* BDI (Beck Depression Inventory), CES-D (Center for Epidemiological Studies–Depression Scale), CIDI (Composite International Diagnostic Interview), DIS (The National Institute of Mental Health Diagnostic Interview Schedule), GHQ (General Health Questionnaire), HAD-D (Hospital Anxiety and Depression Scale), MDI (Major Depression Inventory), PHQ (Patient Health Questionnaire for Depression), SCAN (Schedules for Clinical Assessment in Neuropsychiatry), SCL (The Symptom Checklist), SDS (Zung Self-Rating Depression Scale), SF36 (the 36-item Short-Form Health Survey)

1.2.2 Litterature search of cortisol and depression

The literature search was carried out by using the databases EMBASE (1980-), PsychINFO (1967-), and PubMed (1960-) on the 21th of August 2012. Search words were selected based on search strategies, titles, and keywords from recent reviews on this field [4;5;12;153]. The search strategy reflected the following inclusion criteria:

1. The study must be longitudinal.
2. The study must examine the association between a measure of cortisol concentration at baseline and the risk of depression or depressive symptoms at follow-up.

The full electronic search strategies for all databases are presented in appendix 1. The search strategy identified 1,076 papers (149 in EMBASE, 279 in PsychINFO, and 656 in PubMed). A total of 7 longitudinal studies of cortisol concentration and depression were identified through other sources such as reference lists from papers and reviews on this topic. 500 of these records were duplicates, leaving a total of 583 unique papers. The screening process excluded 442 records based on their title and additionally 123 papers based on their abstract. 18 full-text articles were assessed for eligibility and 11 of those were excluded (4 were not longitudinal studies, 5 did not analyse depression as an outcome, 2 did not use cortisol concentration as a determinant of depression). The 7 longitudinal studies of cortisol concentration and the risk of depression are presented in table 2.

Figure 3. Four-phase flow diagram[105] of information from review of longitudinal studies of cortisol and depression.

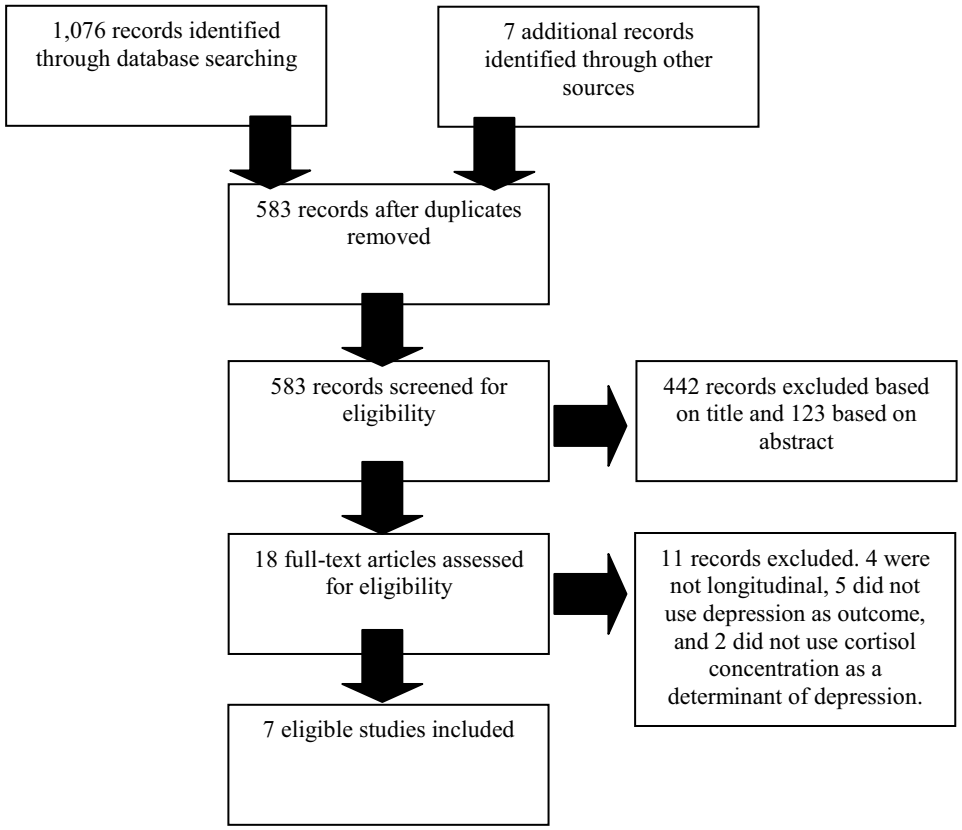


Table 2. Characteristics of 7 longitudinal studies of cortisol and the risk of depression, 2000-2012.

Study, publication year, country	Follow-up period	Population (no. of males/females), average age	Selection	Cortisol measurements	Outcome information *	Confounders considered
Goodyer[154] 2000, England	1 year	School students (73, 107), 13.5 years.	High risk for depression.	Salivary cortisol collected on 4 consecutive days at 08.00 h and 20.00 h.	K-SADS (DSM-IV)	Age, gender, life events, baseline depressive symptoms, salivary dehydroepiandrosterone
Harris[155] 2000, England	13 months	Women recruited from general practices (0, 116). 38.5 years.	High risk for depression	Salivary cortisol collected on 4 consecutive days at 08.00 h and 20.00 h.	SCAN (DSM-IV)	Age, life events, smoking, social support, negative self-evaluation, salivary dehydroepiandrosterone
Halligan[156] 2007, England	3 years	Offspring of mothers with and without postnatal depression (43, 44), 13.0 years.	48 offspring of mothers with postnatal depression.	Salivary cortisol collected on 10 consecutive schooldays at 08.00 h and 20.00 h. Derivative values: maximum concentration and variability,	MFQ (Depressive symptoms)	Gender, life events, baseline depressive symptoms, pubertal development, body mass index, family conflict, maternal postnatal depression
Adam[157] 2010, USA	1 year	High school students (57, 173), 17.0 years.	High neuroticism scores.	Salivary cortisol collected on 3 consecutive weekdays at awakening, 40 min, 3h, 8h,12h post awakening and bedtime. Derivative values: cortisol awakening response, slope and average across the day.	SCID (DSM-IV)	Age, gender, smoking, neuroticism, psychotropic medication, asthma, hours of sleep, time of awakening.
Goodyer[158] 2010, England	1 year	School students (192, 173), 13.6 years.	High risk for depression.	Salivary cortisol collected on 4 consecutive schooldays at 08.00 h.	K-SADS (DSM-IV)	Age, gender, life events, baseline depressive symptoms, psychosocial risk profile, BDNF, 5-HTTLPR.
Ellenbogen[159] 2011, Canada	1-6 years (mean 2.5)	Offspring of parents with and without bipolar disorder (28, 31), 17.5 years.	28 offspring of parents with bipolar disorder	Salivary cortisol collected at awakening, 30 and 60 min post-awakening, 15.00 h, 20.00 h, and at bedtime. Derivative values: average across the day.	SCID (DSM-IV)	Age, gender, baseline mental disorder, parental bipolar disorder
Vrshek-Schallhorn[160] 2012, USA	4 years	High school students (75, 195), 17.1 years.	High neuroticism scores.	Salivary cortisol collected on 3 consecutive weekdays at awakening, 40 min, 3h, 8h,12h post awakening and bedtime. Derivative values: cortisol awakening response, slope and average across the day.	SCID (DSM-IV)	Gender, life events, race, neuroticism, previous depression, socioeconomic status, time of waking, hours of sleep, hormonal contraceptive use, interaction between cortisol awakening response and time.

* K-SADS (Schedule for Affective Disorders and Schizophrenia for School-Age Children), MFQ (Mood and Feelings Questionnaire), SCAN (Schedules for Clinical Assessment in Neuropsychiatry), SCID (Structured Clinical Interview for DSM-IV)

1.2.3 Meta-analysis of psychosocial working conditions and depression

To describe, contrast, and combine the evidence from all studies of psychosocial working conditions and depression a meta-analysis was performed using the random effects model. In order to compare results from the 66 studies the following procedure was used:

1. Only studies reporting an odds ratio, relative risks, hazard ratio or comparable effect measure with confidence intervals were included. Some studies only reported results from linear regression or structural equation modeling, and were reported separately.
2. Only studies reporting results independent of statistical significance were included. Including studies reporting only significant results would falsely inflate the association between exposure and outcome.
3. Only exposure measures analysed in 3 or more studies were included, except for procedural and relational justice, which were included to allow for comparison with **study II**.

Odds ratios, relative risks, hazard ratios and comparable results were pooled and will subsequently all be referred to as odds ratios. To investigate the influence of the different study methods and designs the studies were separated into subgroups based on the following characteristics: gender, duration between assessment of exposure and outcome, baseline adjustment of depressive symptoms, source of exposure information, and source of outcome information (Table 3).

For each exposure measures a summary estimate was calculated based on all studies. Summary estimates were also reported for each of the 13 subgroups in table 3 if one or more studies reported a relevant odds ratio. Additionally, overall summary estimates were calculates based on the pooled results of all exposure measures included in the meta-analysis. To assess publication bias, a funnel plot, based on odds ratios and standard errors, was generated for each exposure measure (Appendix 2).

Table 3. Subgroup analyses.

Characteristic	Subgroup of studies
Gender	Men
	Women
	Both genders
Duration of follow-up	0 – 2 years
	2.1 – 5 years
	>5 years
Baseline adjustment of depressive symptoms	Adjustment
	No adjustment
Self-reported exposure	Not self-reported
	Self-reported
Outcome measure	Questionnaire
	Clinical interview
	Other methods

All analyses were conducted with the STATA 12 statistical software (StataCorp LP, College Station, Texas, USA) using the metan command to perform a random effects meta-analysis using the method of DerSimonian & Laird, with the estimate of heterogeneity being taken from the from the Mantel-Haenszel model [161] and the metafunnel command to create funnel plots that display a measure of study size on the vertical axis against a the association between exposure and outcome on the horizontal axis [162].

1.3 Results:

1.3.1 Psychosocial working conditions and depression, study characteristics

The literature search of psychosocial working conditions and depression identified 66 longitudinal studies (Table 1).

1.3.1.1 Measures of psychosocial working conditions

The 66 eligible studies present 73 different measures of psychosocial working conditions (Table 1). Some measures are used by several studies, especially the components of Karasek and Theorell's job strain model [42], but most measures are only used in a few studies. The 16 measures of psychosocial working conditions used in 3 or more studies are, in order of frequency: Decision latitude (n=21), psychological demands (n=20), job strain (n=17), social support (n=13), job insecurity (n=13), supervisor support (n=11), co-worker support (n=9), work load (n=7), working hours (n=6), decision authority (n=5), skill discretion (n=4), effort-reward imbalance (n=4), work climate (n=4), emotional demands (n=4), procedural justice (n=4), and physical demands (n=3). Some are conceptually close (hectic job, conformance to schedule, time pressure, and forced pacing). There is, however, no evidence supporting that these exposure measures are in fact identical and can be treated as such. Thus, each aspect of the psychosocial working conditions needs to be studies individually.

Not only did the studies differ with respect to measures of the psychosocial working conditions. They also differ in the methods used to collect the information. The vast majority used self-reports by the individual participants (self-administered questionnaire [37;49-52;54;56;63;106-115;117-122;124;127;128;131-137;139-151] or interview[65;66;116;123;125;126;129;130;133;138;152]). Few studies used non-self-reported exposure information. These studies used registry linkage [48;67-69], expert assessment [36;70], averaging of work units or work places [35;49;53], or a job exposure matrix [38] to assess the psychosocial working conditions of the participants.

1.3.1.2 Measures of depression

The most frequent method to assess depression was self-administered questionnaires (Table1), especially the Center for Epidemiological Studies – Depression Scale (CES-D) [31] has been used often [108;111;112;114;118;119;124;128;133;141;144;146;147]. These questionnaires does typically not measure depression according to diagnostic criteria, but identify the presence and severity of depressive symptoms. Some studies use a standardized clinical interview to diagnose depression according to the ICD of DSM diagnostic criteria. Some studies use other methods to diagnose depression, such as registry information about prescription and redemption of antidepressant medication [35;49;50;54;68;130;136;137;145;149], sick-leave due to depression [37;48;69;134;139], hospital records [38;53;67;140], self-reported doctor-diagnosed depression [49;56;115;122], or insurance information [36]. The different methods of assessment of depression and depressive symptoms in the available studies reduce the comparability of the results [43]. There are several advantages of using standardized clinical interviews to diagnose depression. If we want to study the association between psychosocial working conditions and depression, a diagnosis of depression is a better measure than the presence of depressive symptoms or redemption of antidepressant medication [2;41;43]. Depression as a disorder is well defined in the both ICD-10 [15] and DSM-IV [27], and though there is differences between the two set of diagnostic criteria, they are highly similar [22]. Most of the self-administered questionnaires and rating scales are validated and precise tools [30-34], but they do not give adequate information to diagnose depression.

1.3.1.3 Study design

The included studies were most frequently been performed on Finnish (n=12), Danish (n=11), or American (n=9) populations. The only studies performed outside Europe and North America were from Japan [106;107;117;139], Australia [148], or New Zealand [65]. Most studies include a study population comprised of workers from a heterogeneous selection of occupations or work-places (n=21) or from the general population (n=10). Other studies include a more homogenous study population, such as a population comprised entirely of industrial workers (n=7), public employees (n=9), or hospital employees (n=5).

The duration of follow-up varied significantly between the studies. The shortest duration is 3-6 months[147] and the longest 32 years[65]. Most studies have a follow-up period of 1-2 years (n=27) or 2.1-5 years (n=25). Some studies have a follow-up period of more than 5 years (n=14), and a single study of less than 1 year[147]. Most of the studies examine their study population twice, once at baseline and again at follow-up, with no access to information on case status in the intermediate time period. Some studies have access to this information, such as through registries [35;49;50;54;68;130;136;137;145;149] or by repeated examinations of the study population [65;112;118;144].

Most of the included studies adjust for age, gender, socioeconomic factors, and other well-known risk factors of depression (table 1). Most studies exclude depressed participants at baseline and some adjusts for baseline depressive symptoms, neuroticism, or negative affectivity (n=16).

1.3.2 Psychosocial working conditions and depression, selection procedure for the meta-analysis

Of the 66 studies identified in the literature search 17 studies were excluded because they did not report an odds ratio or comparable effect measure [48;111;114;118-120;124;131;133;135;141;142;144;146-148;150], two were excluded because they measured change in exposure levels instead of baseline exposure levels [112;151], two were excluded because they did not report odds ratios and confidence intervals of insignificant results [106;116], and seven were excluded because they did not examine at least one frequently examined type of exposure [49;51;67;70;115;123;143]. The following exposure measures were analyzed in three or more of the remaining studies: Job strain, psychological demands, decision latitude, decision authority, skill discretion, social support, co-worker support, supervisor support, effort-reward imbalance, emotional demands, job insecurity, work climate, work load, and working hours. Additionally, the two studies examining procedural and relational justice were also included to allow for comparison with **study II**. The selection procedure for the meta-analysis resulted in the inclusion of 38 studies [35-38;50;52-54;56;63;65;66;68;69;107-110;113;117;121;122;125-130;132;134;136-140;145;149;152].

1.3.3 Psychosocial working conditions and depression, results of the meta-analysis

Results of the meta-analyses are reported in figure 4. The summary estimates for job strain (OR: 1.23; 95% CI: 1.12-1.35), psychological demands (1.21; 1.12-1.35) decision latitude (1.17; 1.06-1.29), social support (1.33; 1.16-1.49), co-worker support (1.42; 1.16-1.69), supervisor support (1.34; 1.14-1.55), effort-reward imbalance (1.70; 1.42-1.97), procedural justice (1.48; 1.23-1.72), relational justice (1.57; 1.31-1.83), and emotional demands (1.28; 1.10-1.47) were associated with subsequent depression. No such associations were found for decision authority (0.88; 0.48-1.28), skill discretion (1.09; 0.87-1.31), job insecurity (1.23; 0.93-1.53), work climate (1.47; 0.98-1.95), work load (1.33; 0.99-1.66), and working hours (1.20; 0.87-1.53). The overall meta-estimate showed a small to moderate association between adverse psychosocial working conditions and depression (1.27; 1.21-1.33), when including all studies regardless of differences in methods and design.

1.3.4 Psychosocial working conditions and depression, results of the subgroup analyses

The results of the subgroup analyses are presented in figure 5-21.

1.3.4.1 Gender

There was no clear indication that gender modifies the association between psychosocial working conditions and depression (Figure 5-21). The few exposure measures indicating a substantial gender effect are limited by few studies and consequently wide confidence intervals (Figure 7, 20, and 21).

1.3.4.2 Duration of follow-up

The subgroup analyses of duration from baseline to follow up gave no clear indication of a general pattern. There may be some indication that work climate, decision latitude, and job strain show a stronger association to depression 5 or more years after exposure characterization at baseline, while work climate, co-worker support, supervisor support and job insecurity show stronger associations during the initial 2 years of follow-up. Overall there is an indication of stronger effects at shorter follow-up times (Figure 5).

Figure 4: Odds ratios of depression for low levels of 16 different exposures. The results are based on the highest available exposure group from each study with the lowest exposure group as reference (job strain, psychological demands, effort-reward imbalance, emotional demands, job insecurity, work load, working hours) or the lowest available exposure group from each study with the highest exposure group as reference (decision latitude, decision authority, skill discretion, social support, co-worker support, supervisor support, procedural justice, relational justice, work climate). The overall estimate is based on all 16 exposures. 38 studies included [35-38;50;52-54;56;63;65;66;68;69;107-110;113;117;121;122;125-130;132;134;136-140;145;149;152].

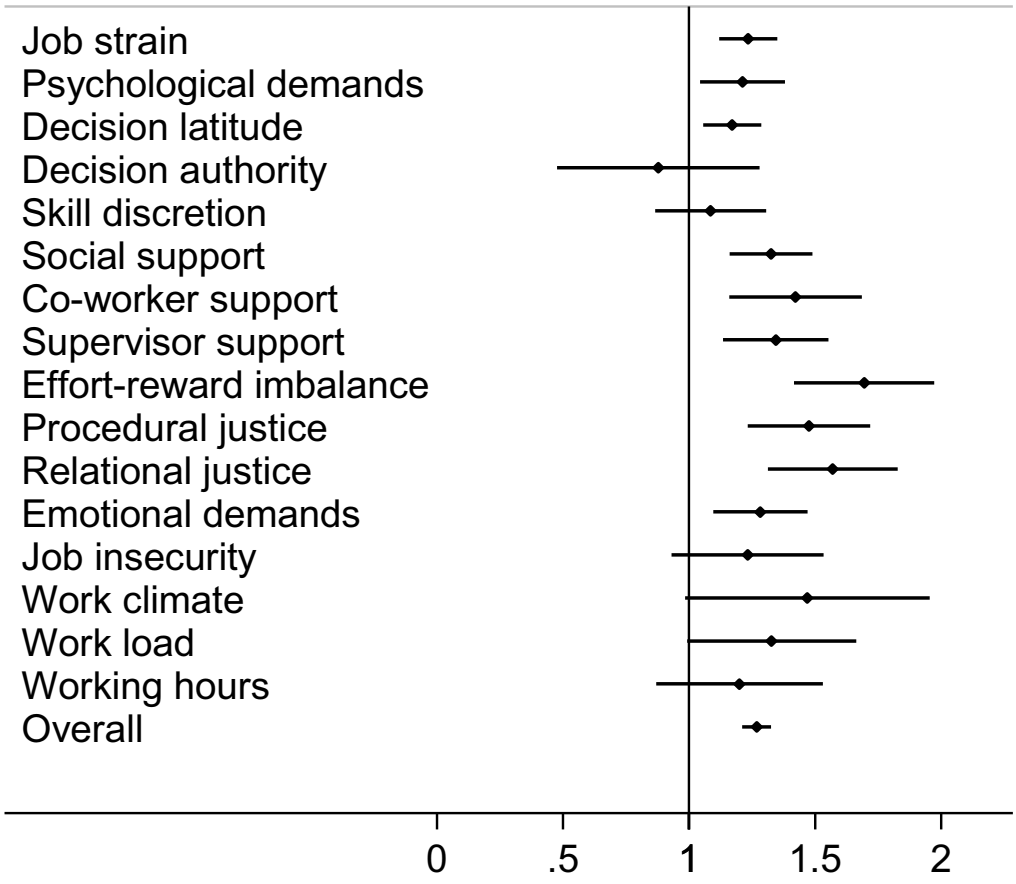


Figure 5: Odds ratios of depression for **all measures of the psychosocial working environment**. Only suitable studies are included in the estimates from the sub-group analyses. 38 studies included [35-38;50;52-54;56;63;65;66;68;69;107-110;113;117;121;122;125-130;132;134;136-140;145;149;152].

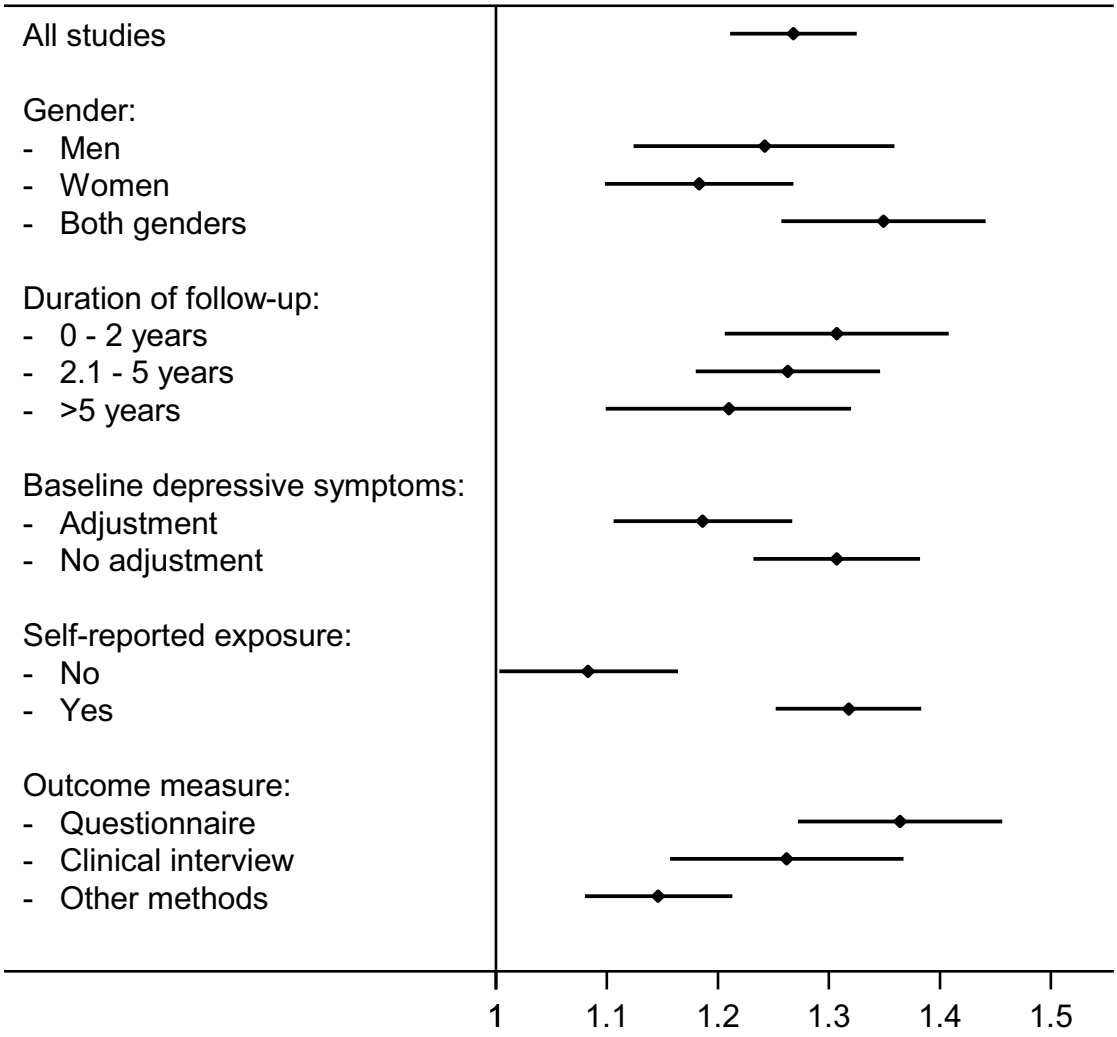


Figure 6: Odds ratios of depression for low levels of **co-worker support**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 9 studies included [37;125;126;132;137;139;140;149;152].

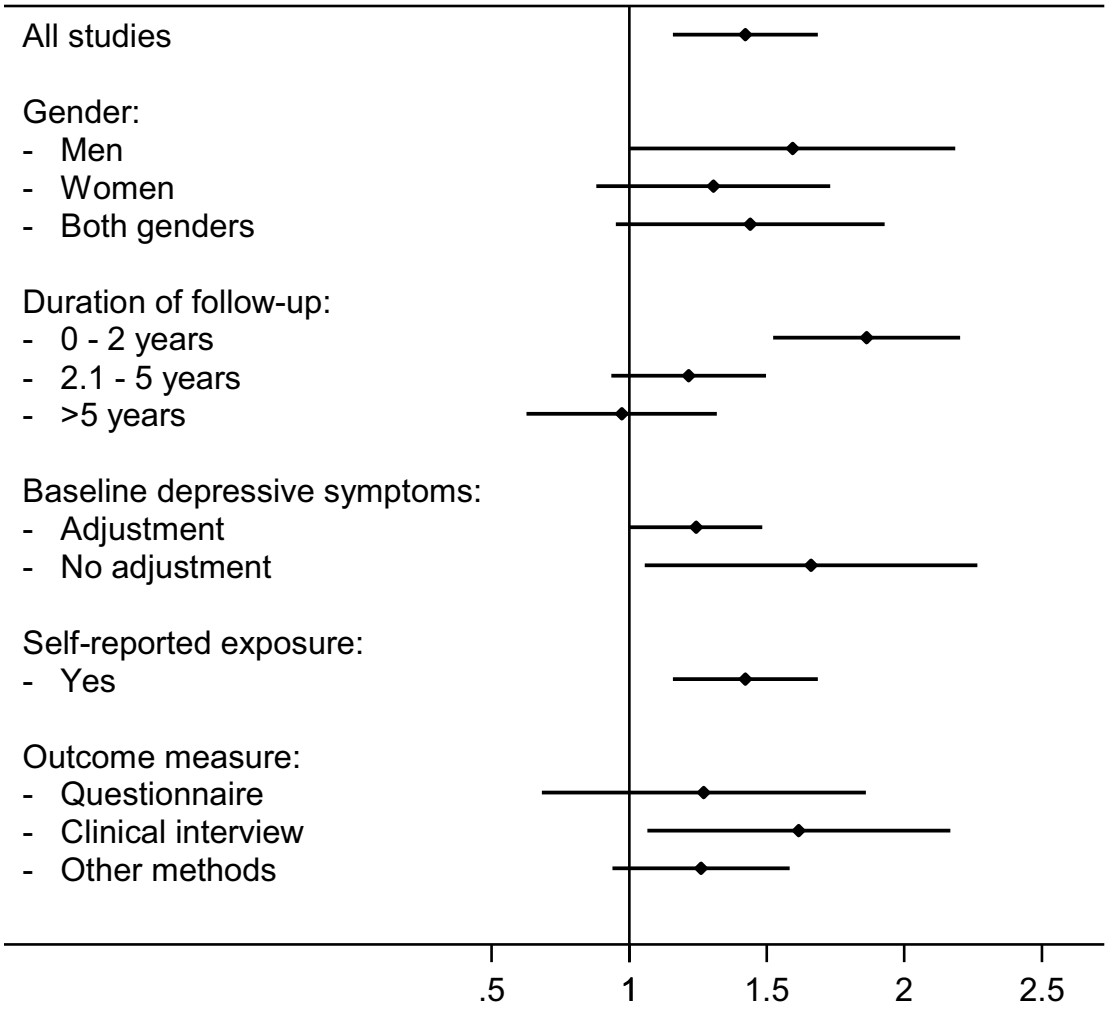


Figure 7: Odds ratios of depression for low levels of **decision authority**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 3 studies included [35;125;140].

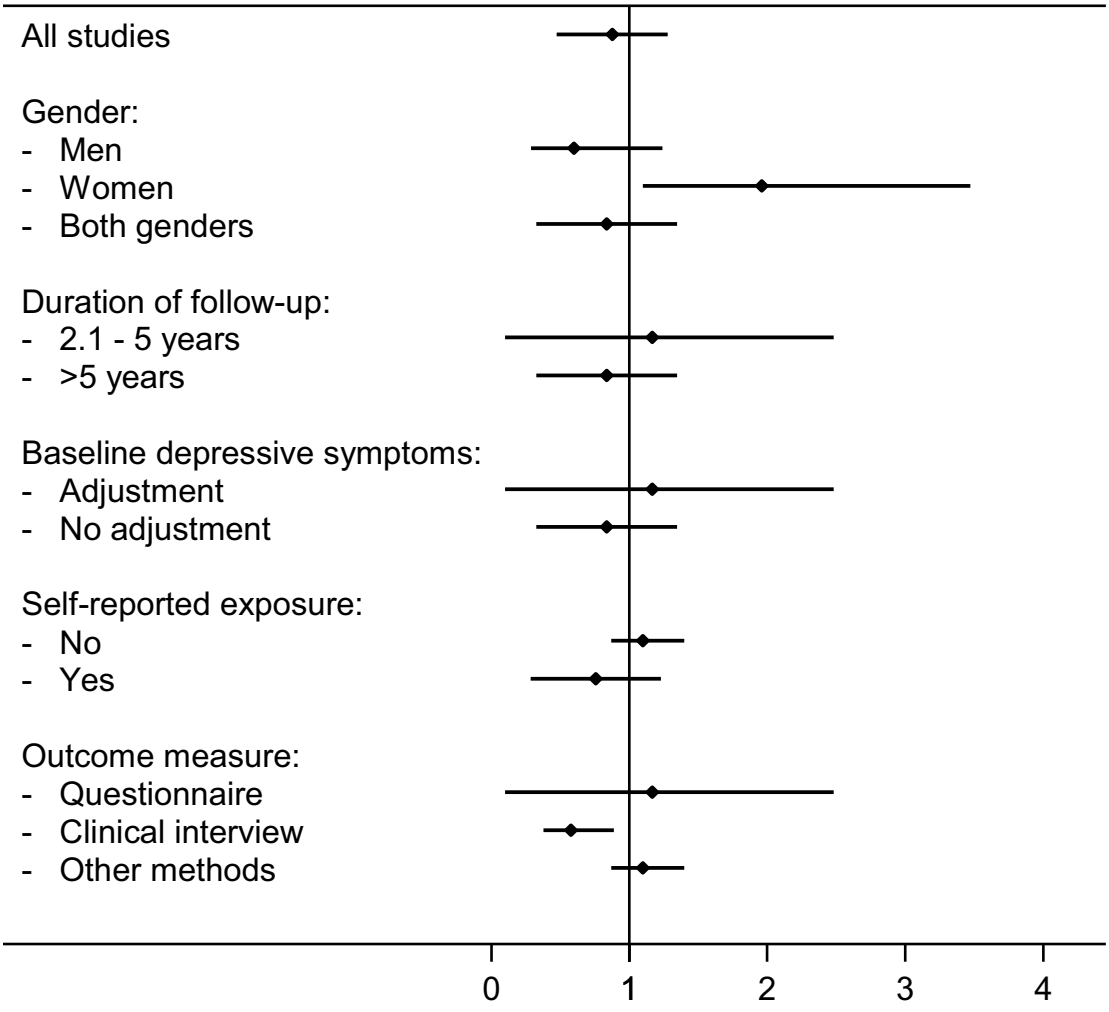


Figure 8: Odds ratios of depression for low levels of **decision latitude**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 15 studies included [35;36;38;65;107;108;113;122;128-130;132;134;139;145].

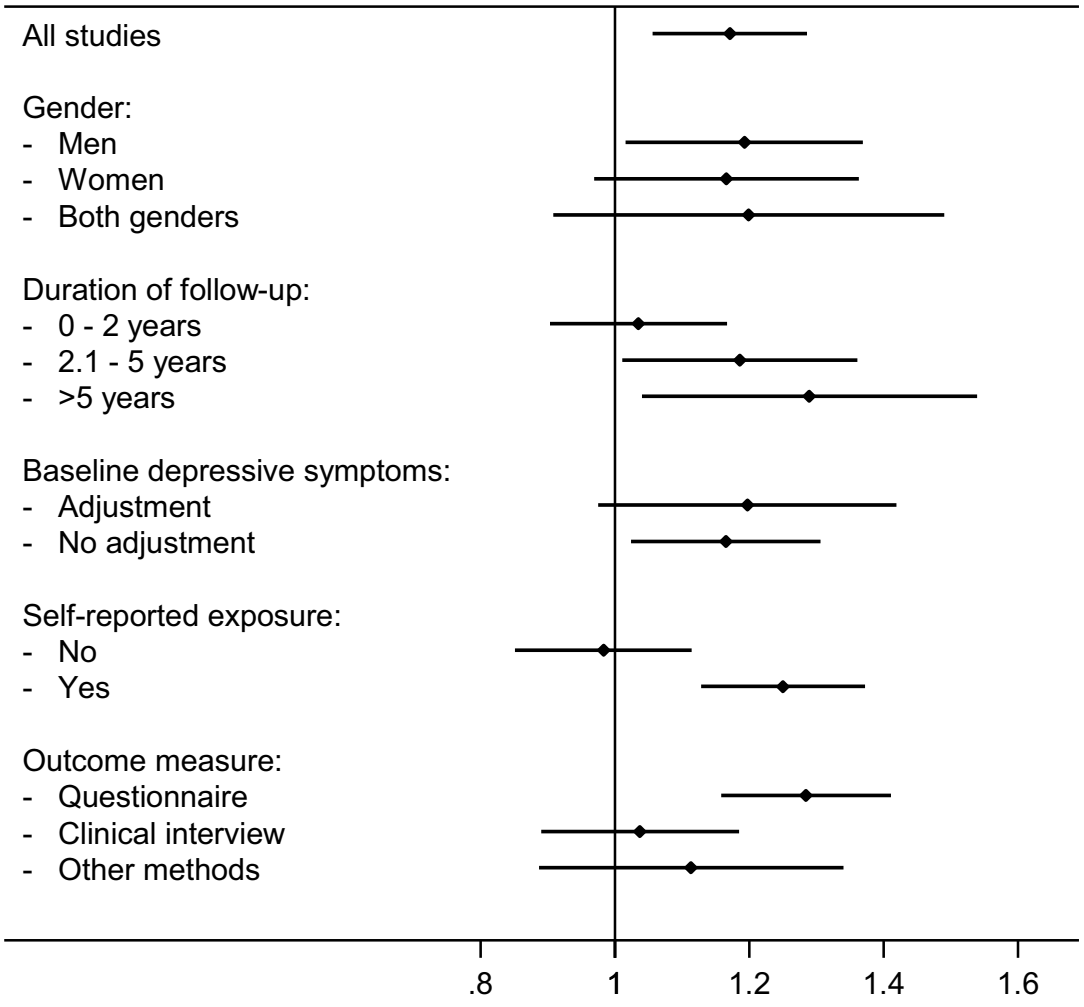


Figure 9: Odds ratios of depression for high levels of **effort-reward imbalance**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 3 studies included [56;121;152].

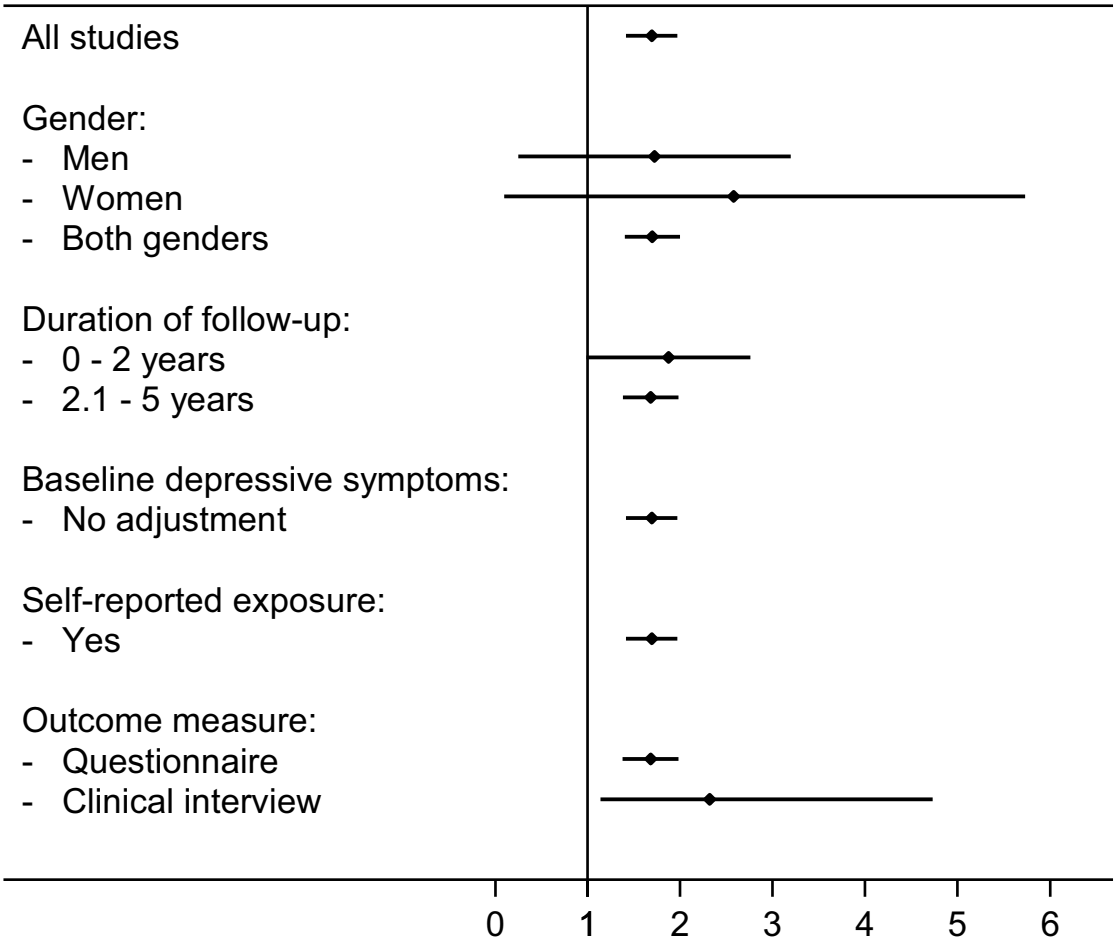


Figure 10: Odds ratios of depression for high levels of **emotional demands**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 4 studies included [38;54;132;149].

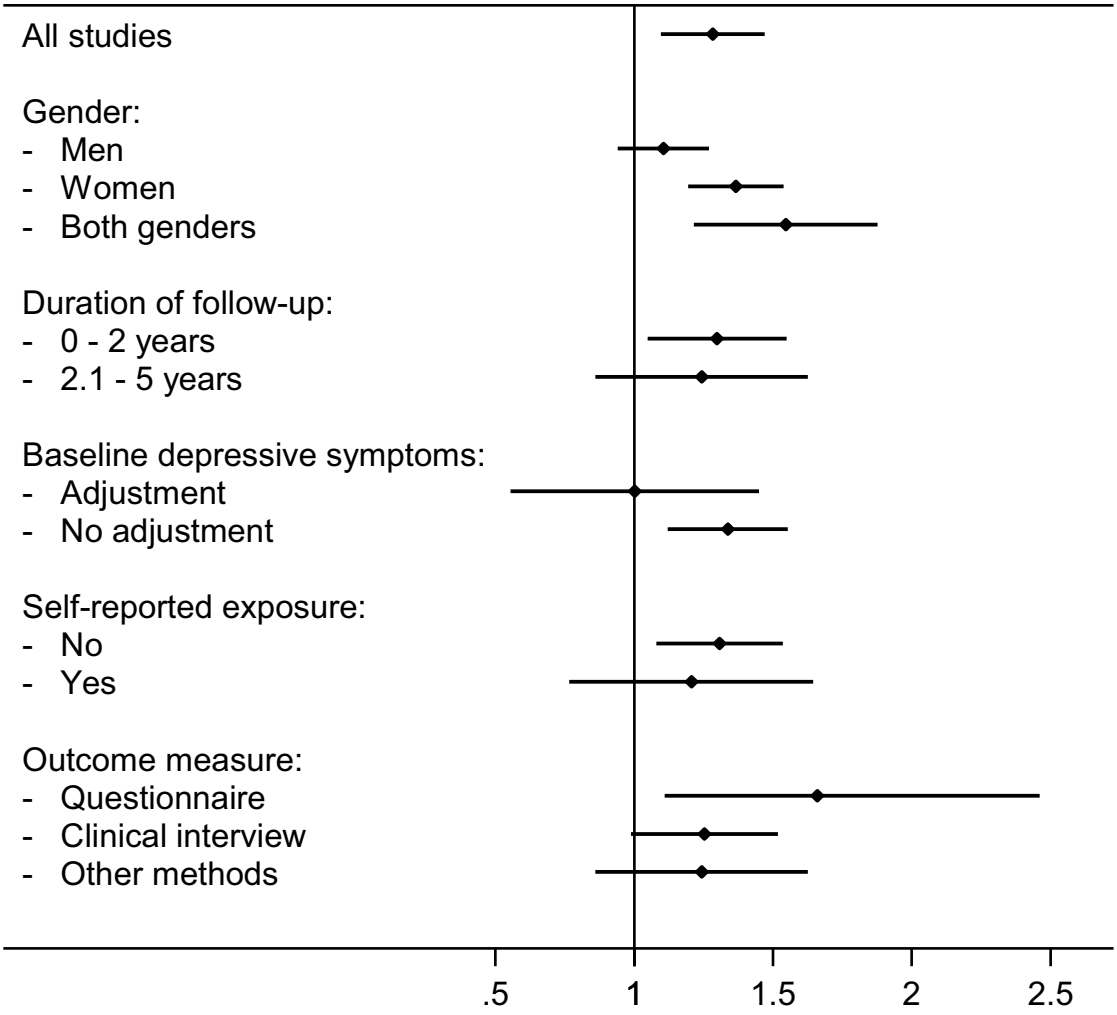


Figure 11: Odds ratios of depression for high levels of **job insecurity**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 7 studies included [50;109;125;129;132;139;152].

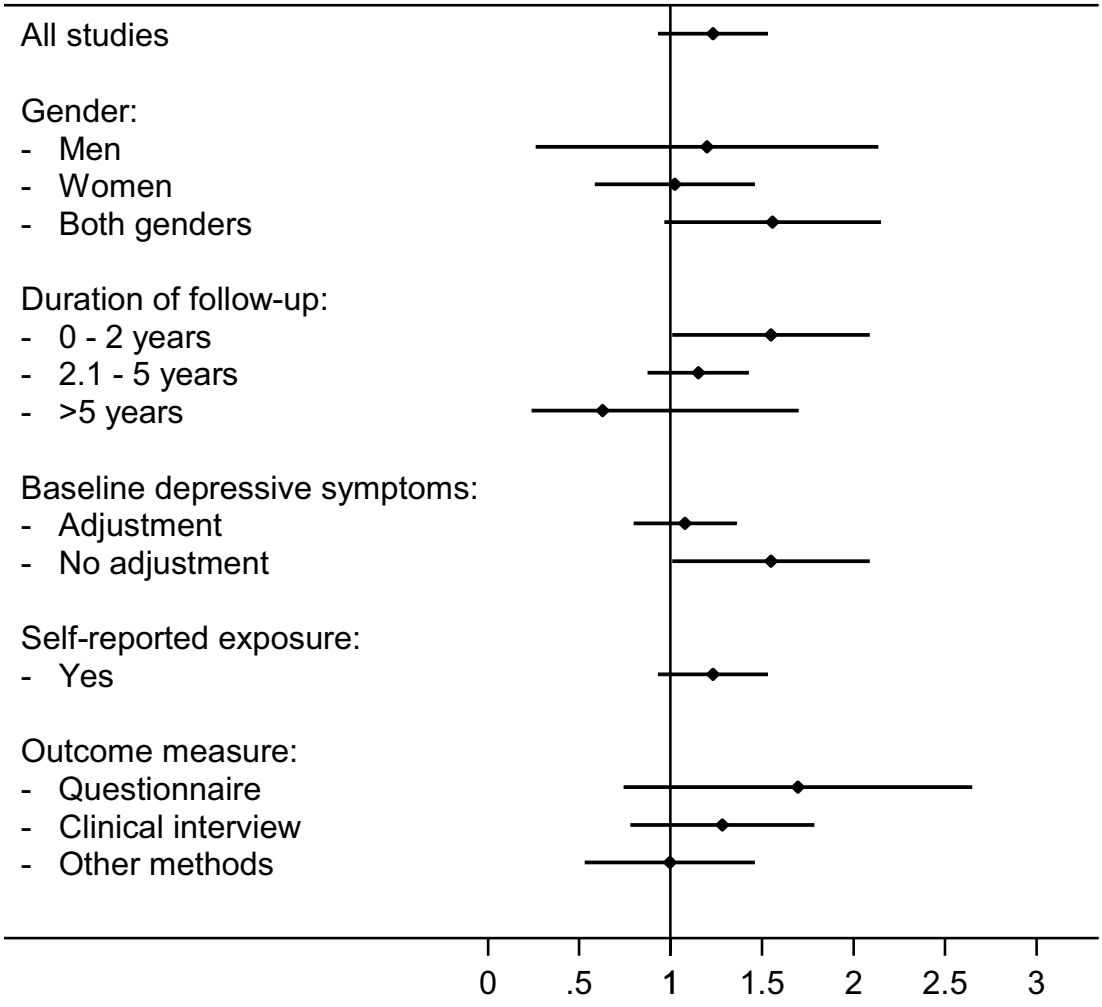


Figure 12: Odds ratios of depression for high levels of **job strain**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 15 studies included [35;37;38;66;109;110;122;126-128;130;138;139;145;152].

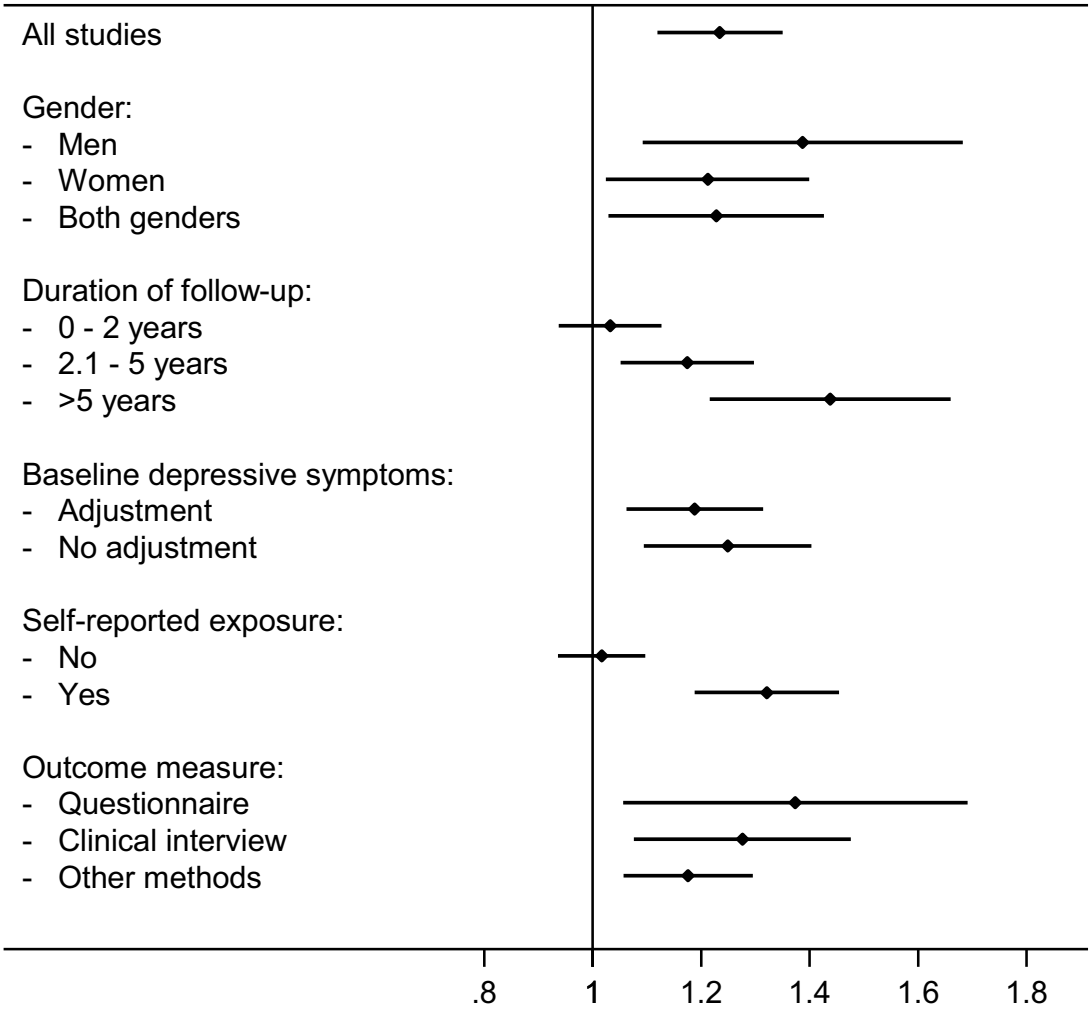


Figure 13: Odds ratios of depression for low levels of **procedural justice**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 2 studies included [56;122].

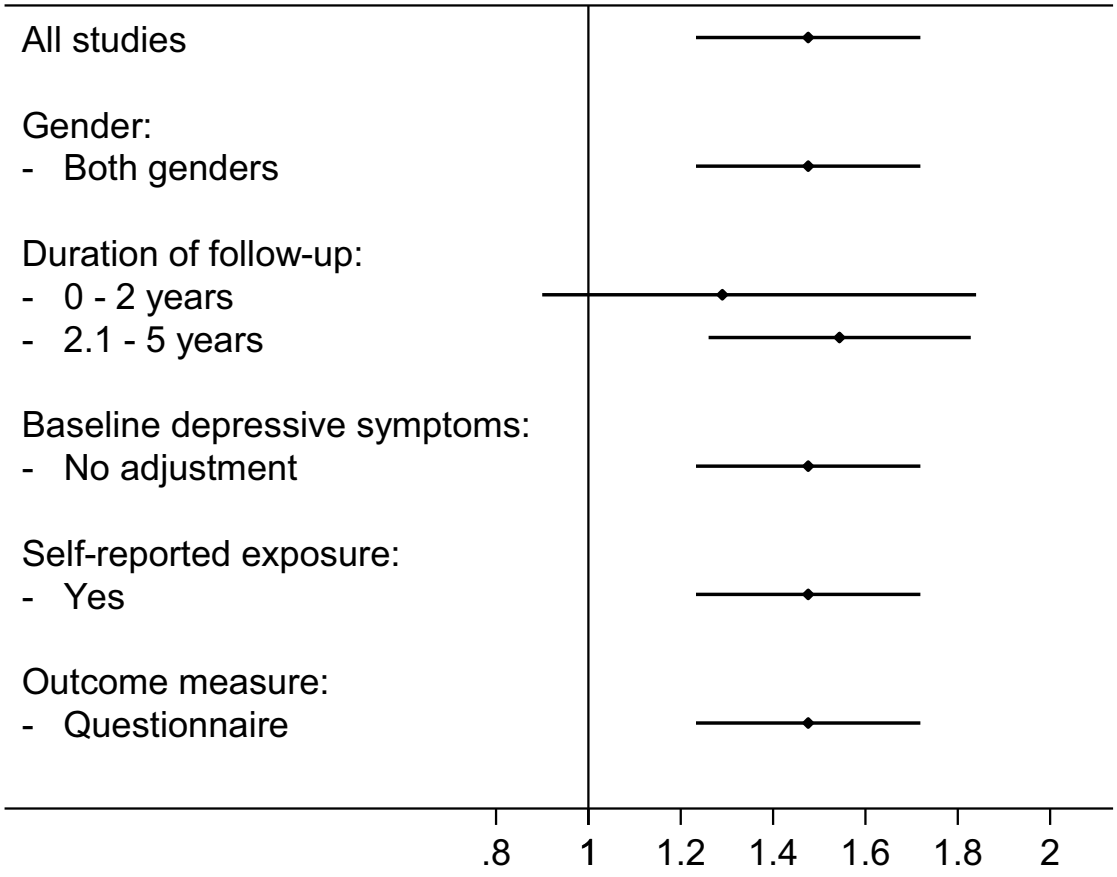


Figure 14: Odds ratios of depression for high levels of **psychological demands**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 14 studies included [35;36;38;65;108;122;125;128-130;132;134;139;145].

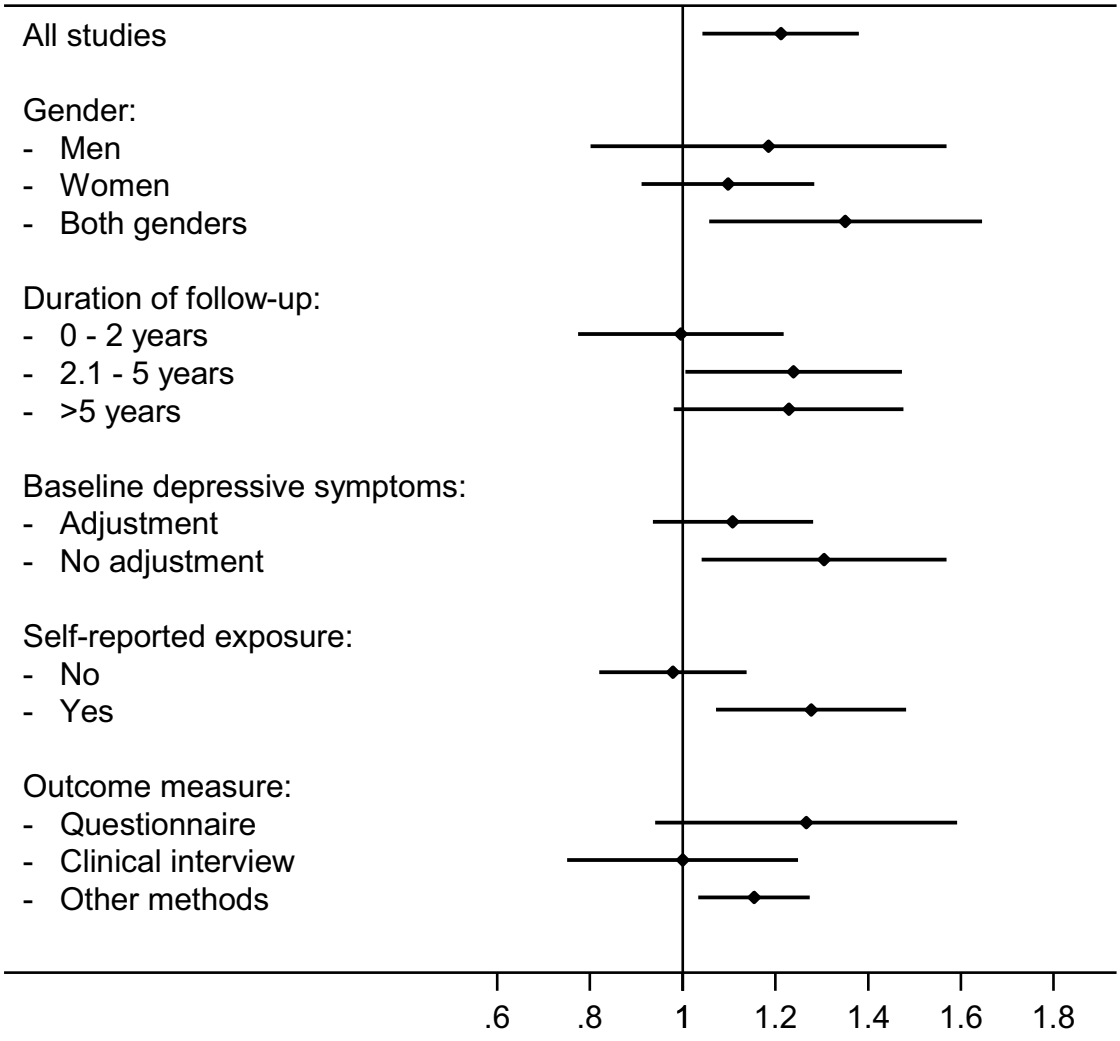


Figure 15: Odds ratios of depression for low levels of **relational justice**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 2 studies included [56;122].

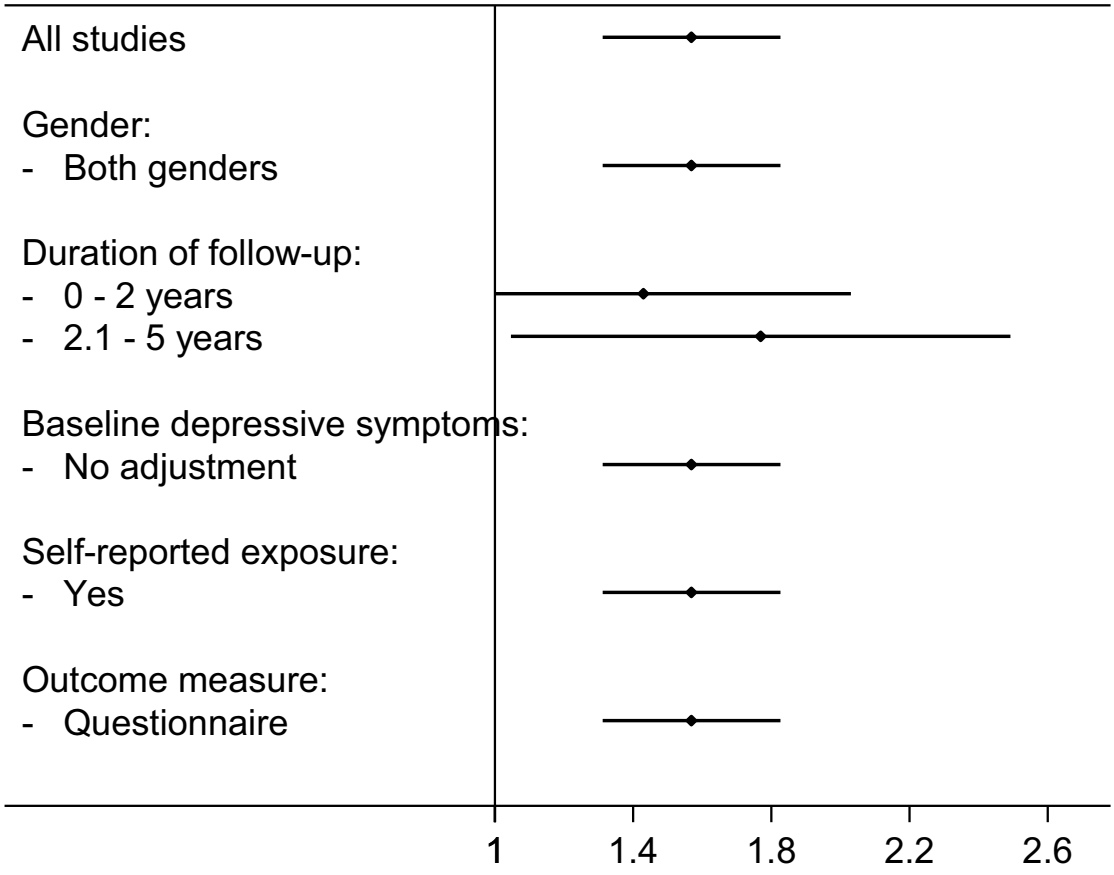


Figure 16: Odds ratios of depression for low levels of **skill discretion**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 3 studies included [35;125;140].

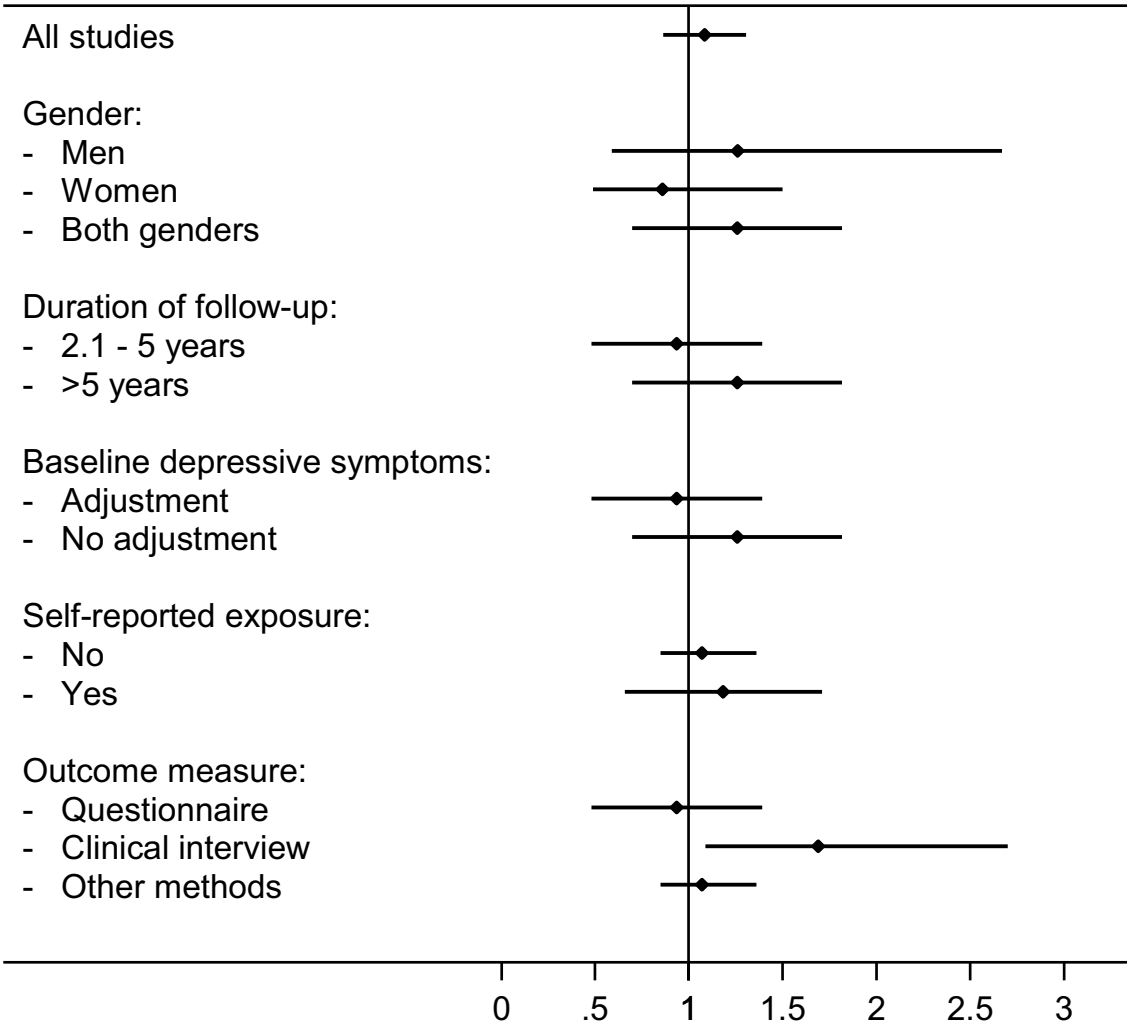


Figure 17: Odds ratios of depression for low levels of **social support**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 8 studies included [35;65;108;117;128;129;132;134].

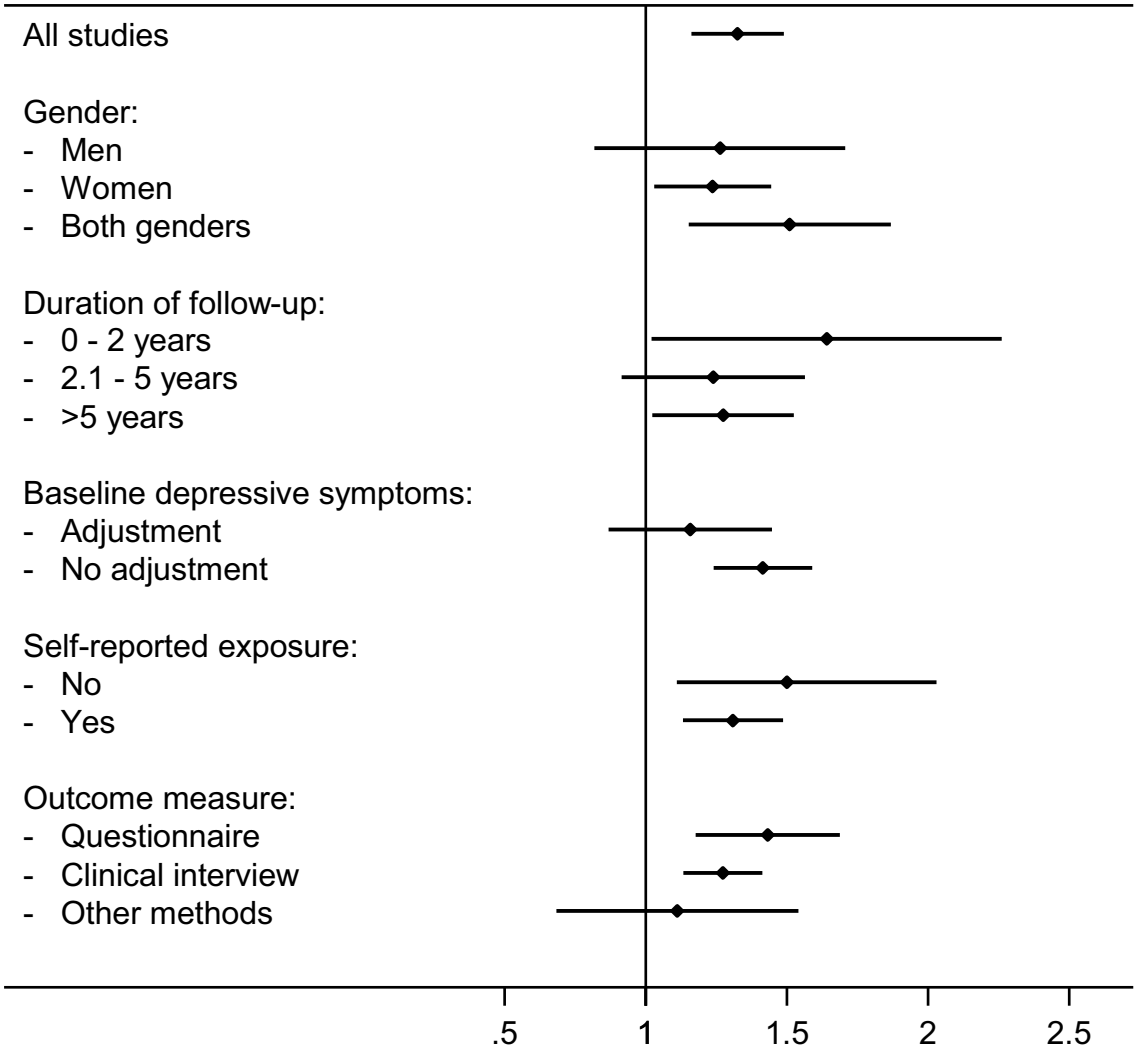


Figure 18: Odds ratios of depression for low levels of **supervisor support**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 10 studies included [37;109;125;126;132;137;139;140;149;152].

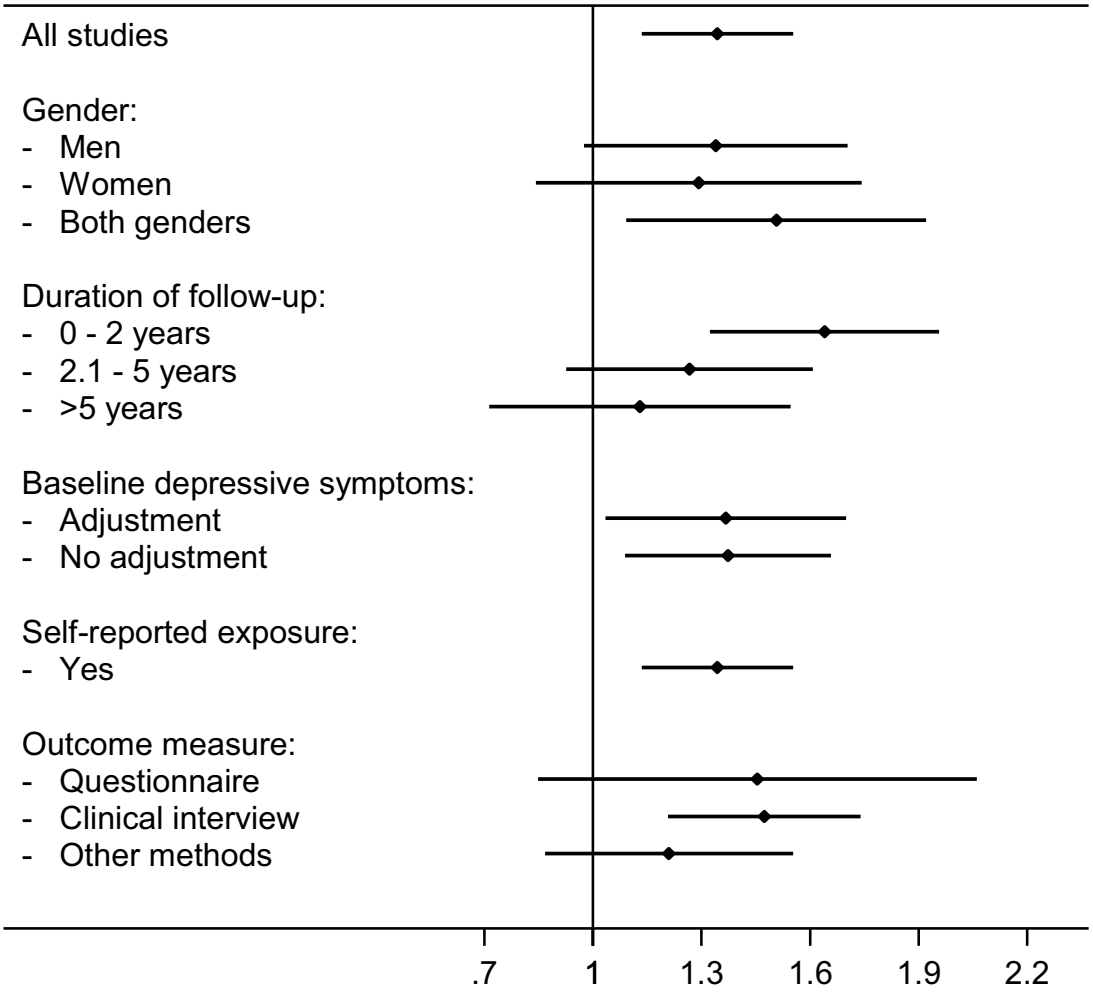


Figure 19: Odds ratios of depression for low levels of **work climate**. The results are based on the lowest available exposure group from each study with the highest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 4 studies included [35;53;122;136].

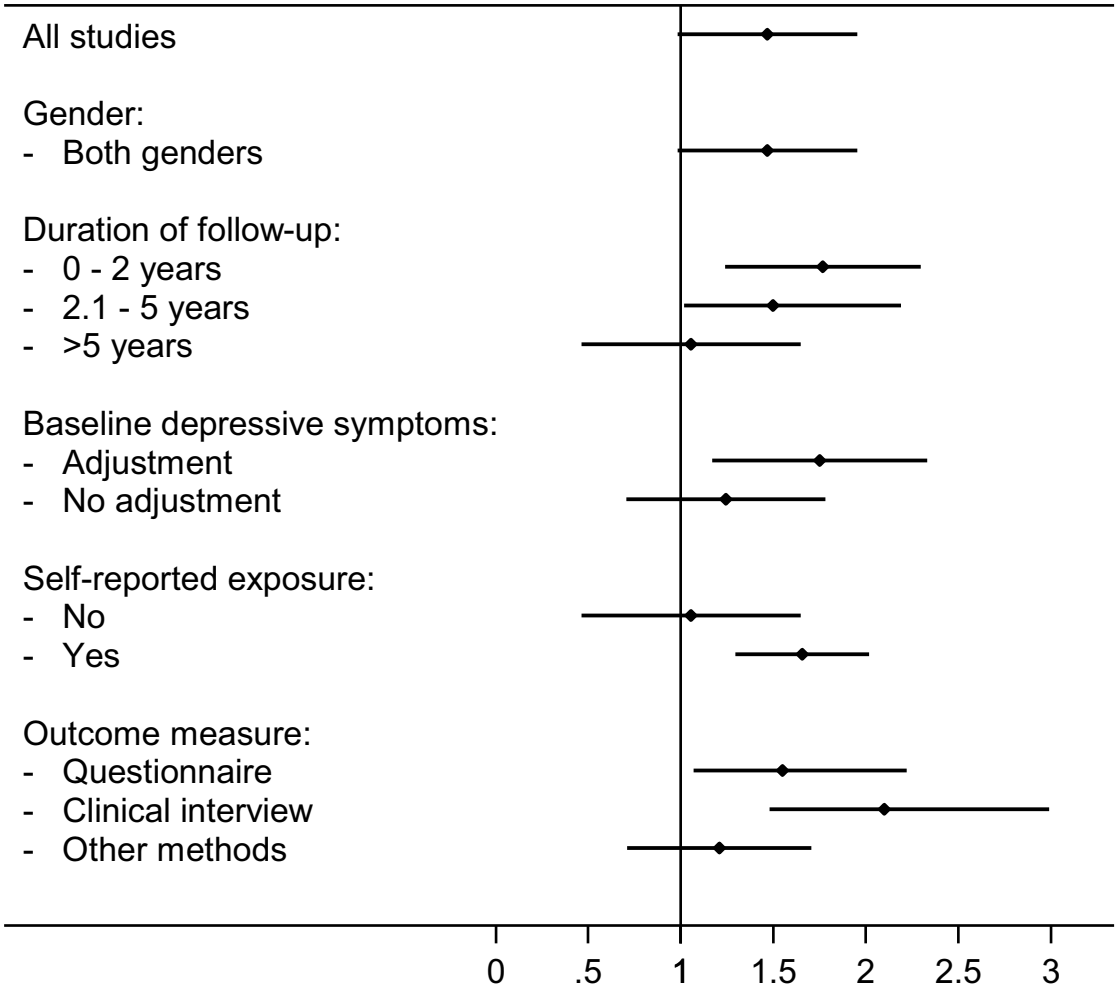


Figure 20: Odds ratios of depression for high levels of **work load**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 6 studies included [35;68;69;107;117;149].

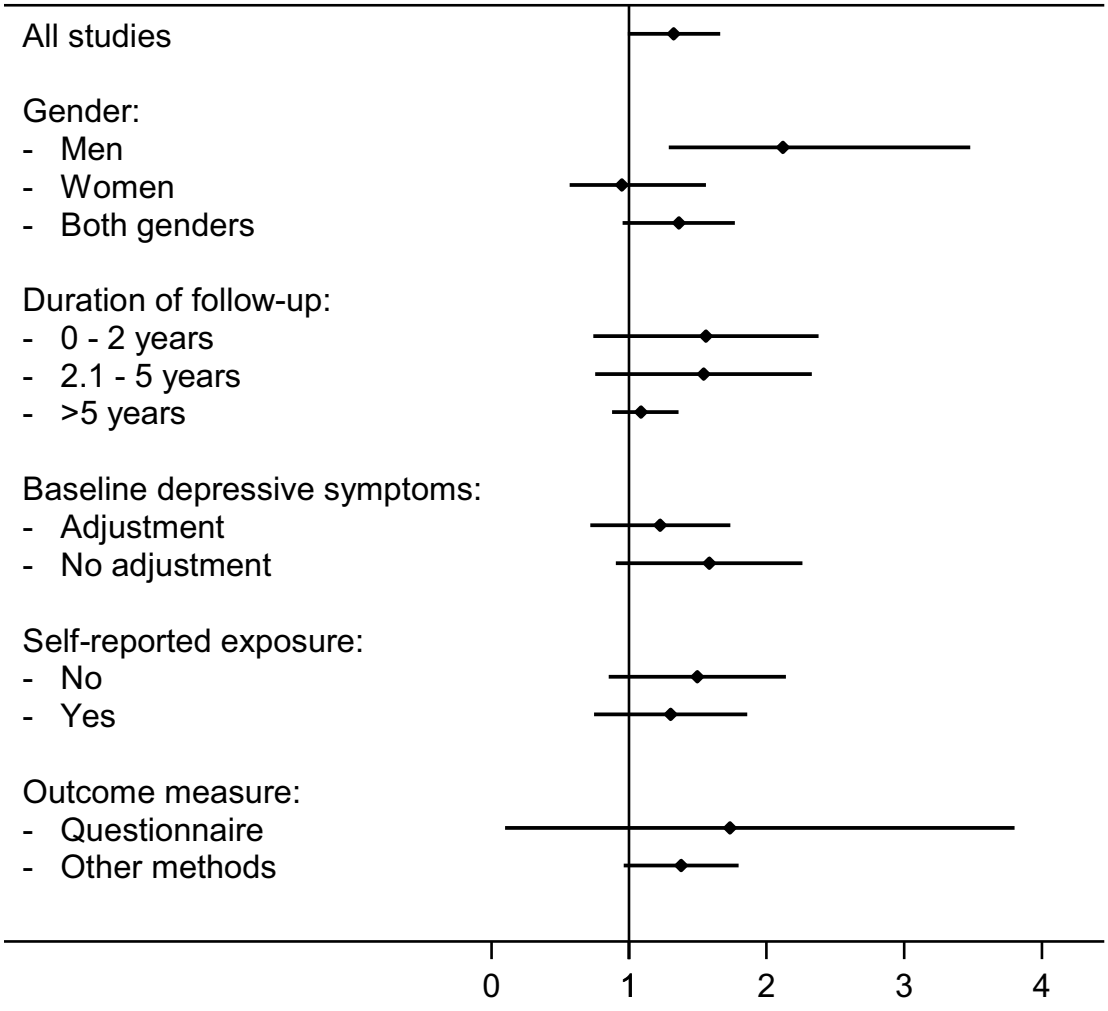
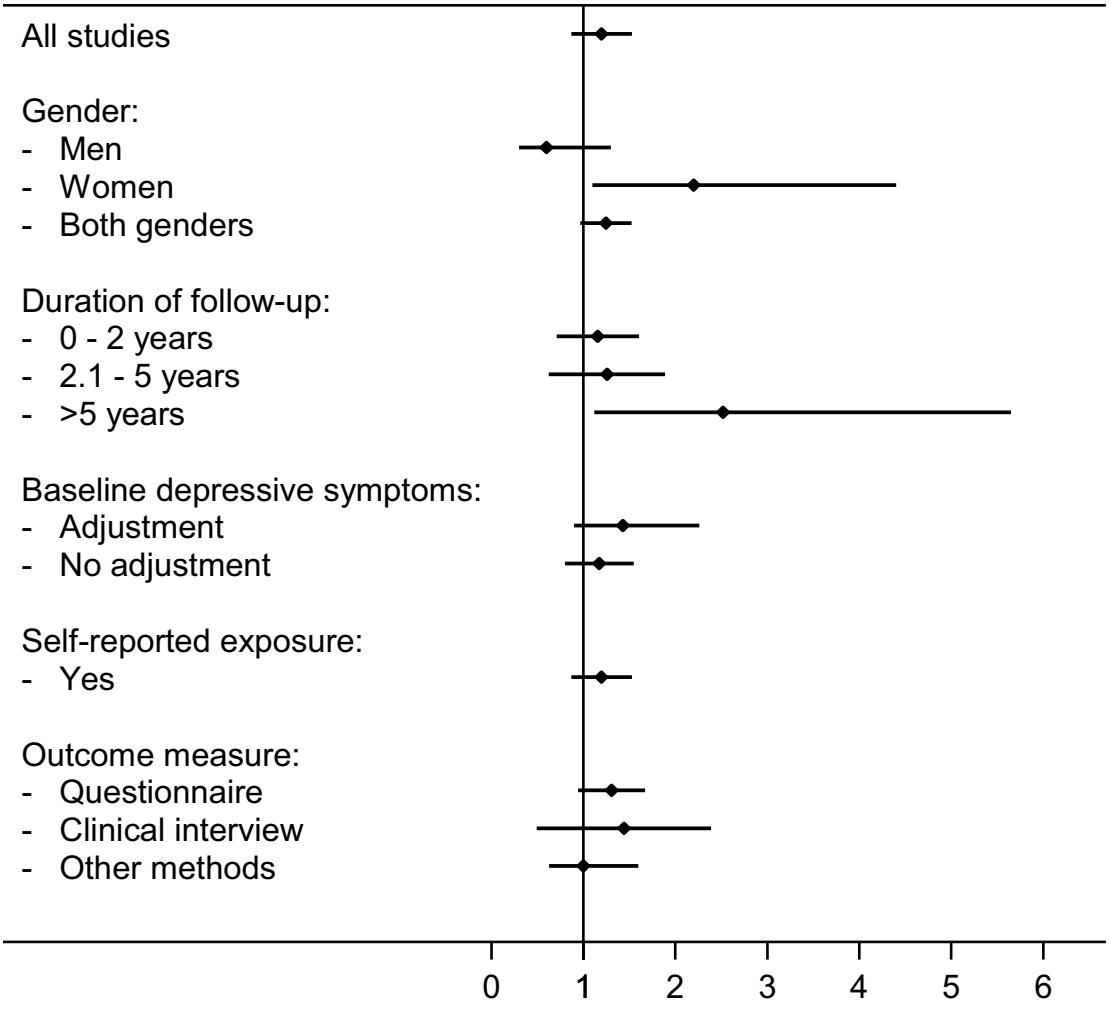


Figure 21: Odds ratios of depression for high levels of **working hours**. The results are based on the highest available exposure group from each study with the lowest exposure group as reference. Only suitable studies are included in the estimates from the sub-group analyses. 7 studies included [52;63;109;117;132;145;152].



1.3.4.3 Baseline adjustment of depressive symptoms

There was no strong indication of a different association between psychosocial working conditions and depression depending on whether analyses are adjusted for baseline depressive symptoms or not. Overall there is an indication of stronger effects when not adjusting for baseline depressive symptoms (Figure 5), and while this is a general tendency among the exposure specific analyses the differences between studies with and without adjustment for baseline depressive symptoms are small (Figure 6-21).

1.3.4.4 Self-reported exposure

When comparing the results of studies relying on self-reported exposure with studies using non-self-reported information results differed substantially (Figure 5). Generally, self-reported measures of exposure showed moderate to strong associations with depression (co-worker support, job strain, psychological demands, decision latitude, decision authority, work climate, effort-reward imbalance, emotional demands, procedural justice, relational justice, social support, supervisor support), while non-self-reported exposure measures show weak (social support) or no associations with depression (decision latitude, psychological demands, job strain, work load, work climate, skill discretion, emotional demands, procedural justice, relational justice, and decision authority).

1.3.4.5 Outcome measure

The subgroup analyses based on different outcome measures of depression showed a pattern. Overall there was an indication of stronger effects when relying on questionnaire diagnosed depression, and weaker effects when using neither questionnaires nor clinical interviews to diagnose depression (Figure 5). While there was some indication of this pattern in the analyses of specific exposures, the pattern was not entirely consistent and the differences between the strength of the associations were rarely substantial (Figure 6-21).

1.3.5 Psychosocial working conditions and depression, qualitative synthesis

The 66 longitudinal studies presented 73 different measures of psychosocial working conditions, but only 38 studies and 16 exposure measures were included in the meta-analysis. Six of the 28 studies not included in the meta-analysis examined psychological demands, and five showed a significant association between high psychological demands and depression [48;114;118;148;151], while one study showed an association only for men [135]. Two additional studies showed an association between decision latitude and depression [118;148], one showed no association [151], and one showed an association only for men [114]. One of the 28 studies showed an association between job strain and depression [112], two showed no association [146;151]. One study showed no association between co-worker support [111], and one study showed an association only for women [135]. One study showed no association between supervisor support [111], and one study showed an association only for men [135]. Two studies showed an association between social support and depression [114;118], and three showed no association [116;146;151]. Two studies showed an association between job insecurity and depression [120;148], two showed no association [133;146], and one showed an association only for women [141]. One study showed an association between procedural justice and depression [144], and one showed no association [147]. One study showed an association between work load and depression [48], and one showed no association [106]. One study showed an association between decision authority [135] and emotional demands [124].

The remaining 57 measures of psychosocial working conditions are only examined in few studies. The following exposure measures were associated with depression (n=17): bullying [51;115], conflict with supervisor [135], control over workplace [107], day-to-day stress [126], demands for hiding emotions [54], episodic stressors [111], family-to-work conflict [152], hindrance: support from colleagues and supervisors [70], job unsuitability [106;107], layoffs [119], over-commitment [121;131], occupation: human service professional [67], role ambiguity [139], stressful events [108;117], transformational leadership [142], work engagement [150], and work stress (sum of psychological demands, skill discretion, decision authority, job insecurity, physical demands, and social support)[123].

The following exposure measures were not related to depression (n=34): cognitive requirements [70], cooperation [70], forced pacing [106], hazardous work [146], hectic work [116], job difficulty [117], hindrance: goals and resources [70], inadequate evaluation of contribution [117], influence on what to do [70], influence on how to do it [70], informational justice [147], interpersonal justice [147], isometric load [146], job change [143], management [35], meaning of work [149], mental load [116], mergers [143], monotonous work [116], opportunities for development [149], physical demands [65;146;149], private life support [137], professionalism [35], required conformance to schedule [70], role conflict [139], sense of community [149], threats [54], time pressure [70], variation of work [149], violence [54], work centrality [37], work dissatisfaction [37;146], work pace [149], and workplace social capital [49].

The following exposure measures showed conflicting results (n=6): conflict with co-workers [117;135], distributive justice [144;147], isostrain [35;128], poor human relations [106;107], quantitative demands [149], and working with people [38].

1.3.6 Publication bias

The funnel plots based on the different exposure measures (Appendix 2) were used to assess publication bias. There was a clear indication of substantial publication bias in studies of decision latitude (Figure 24 – Appedix 2) and job strain (Figure 28 – Appendix 2), and some publication bias in studies of psychological demands (Figure 30 – Appendix 2). The publication bias in these studies is likely to have inflated the summary estimates of the meta-analysis. Since the studies of psychological demands, decision latitude, and job strain are numerous, the overall estimate also indicated some publication bias (Figure 38 – Appendix 2). Many of the exposure measures have been examined in too few studies to allow assessment of publication bias, such as procedural and relational justice that has only been included as exposures in 3 of the eligible studies.

1.3.7 Cortisol and depression, study characteristics

All 7 studies measured only salivary cortisol. All included morning cortisol concentration [154-160], and most studies measure evening cortisol concentration [154-157;159;160]. Some studies included morning-to-evening slope [157;160], cortisol awakening

response [157;160], daily mean cortisol concentration [157;159;160], maximum cortisol concentration [156], and variability in cortisol concentration [156].

Some studies measured morning cortisol concentration at 08.00 hours [154-156;158], while the others measured morning cortisol concentration with two or more samples and relative to time of awakening [157;159;160]. Evening cortisol concentrations were measured either at 20.00 hours [154-156], at bedtime [157;160], or both [159].

Most studies used clinical interviews to identify cases of depression. These were the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [154;158], the Structured Clinical Interview for DSM-IV (SCID) [157;159;160], and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [155]. A single study did not use a standardized clinical interview to diagnose depression, but instead used the self-administered Mood and Feelings Questionnaire (MFQ) to measure the presence of depressive symptoms [156]. Compared to the very diverse methods used to measure cortisol, the studies used a very similar method for diagnosing depression. The MFQ is a validated rating scale and the clinical interviews are considered the gold standard for diagnosing depression [156].

Three studies examined children with a mean age at baseline of 13.0, 13.5, and 13.6 years, respectively [154;156;158]. Three studies examined adolescents with a mean age at baseline of 17.0, 17.1, and 17.5 years, respectively [157;159;160]. Only one study examined an adult population with a mean age at baseline of 38.5 years [155]. The majority of studies included participants with a high risk of developing depression due to personality traits or familial disposition [155-157;159;160]. Finally the number of participants in the studies ranged from 59 to 365.

Duration from cortisol level was determined until cases of depression were identified varied between 1 year [154;155;157;158] and 2.5 to 4 years [156;159;160].

1.3.8 Cortisol and depression, overall findings

There were too few studies of the association between cortisol and the risk of depression to perform a meta-analysis. Instead the results of the studies are presented in table 4. The 7 studies performed in total 22 analyses of cortisol and depression and

in 11 (50%) of these cortisol level were significantly associated to subsequent depression. In all 11 cases a high cortisol concentration, high cortisol awakening response, or high cortisol variability were associated with a high risk of depression. No studies showed that a low cortisol concentration, awakening response, or variability was related to a high risk of depression.

Table 4. Associations between salivary cortisol level and the occurrence of depression in 7 longitudinal studies, 2000-2012. + indicates that a high concentration, cortisol awakening response or variability were associated with a high risk of depression. 0 indicates no significant association between cortisol and depression.

Study	Morning cortisol	Evening cortisol	Daily mean cortisol	Morning-to-evening slope	Cortisol awakening response	Maximum cortisol	Variability of cortisol
Goodyer, 2000 [154]	+	0					
Harris, 2000 [155]	+	0					
Halligan, 2007 [156]	+	0				+	+
Adam, 2010 [157]	0	0	0	0	+		
Goodyer, 2010 [158]	+						
Ellenbogen, 2011 [159]	+	+	+				
Vrshek-Schallhorn, 2012 [160]	0	0	0	0	+		

A total of five studies showed that a high morning cortisol concentration was associated with a high risk of depression [154-156;158;159]. All studies that measure morning cortisol concentration at 08.00 hours showed an association [154-156;158], while of the three studies that measure morning cortisol concentration relative to time of awakening [157;159;160] only one showed an association [159]. Only one study showed an association between evening cortisol, daily mean cortisol, and depression [159], or between maximum cortisol, variability of cortisol, and depression [156]. No studies showed an association between morning-to-evening slope and depression [157;160], and two studies showed an association between cortisol awakening response and depression [157;160].

1.4 Discussion

1.4.1 Main results

Overall the studies of psychosocial working conditions and depression showed a small to moderate increased risk of depression for high levels of job strain, psychological demands, effort-reward imbalance, and emotional demands, and for low levels of decision latitude, social support, co-worker support, supervisor support, procedural justice, and relational justice. No such associations were found for decision authority, skill discretion, job insecurity, work climate, work load, and working hours. However, the sub-analyses showed that studies not using questionnaire diagnosed depression or self-reported exposure information overall showed no association between psychosocial working conditions and depression.

Overall the studies of cortisol and depression may indicate that a high morning cortisol concentration is a risk factor for depression, but possibly only when measured at 08.00 hours and not when measured relative to time of awakening. However, no clear conclusion can presently be drawn on the association between cortisol level and risk of depression due to the few studies, different methods for measuring cortisol, and somewhat inconsistent results.

1.4.2 Measures of exposure

The studies of psychosocial working conditions and depression measured a plethora of different aspects of the working environment. These different measures of psychosocial working conditions are independent constructs, and though many are quite similar, have to be studied independently of each other's.

Most studies used self-reported exposure information, which may be a cause of misclassification and reporting bias [2;64;163]. This is especially important when studying depression. Decreased energy and activity, reduced capacity for concentration, disturbed sleep, psychomotor retardation, and loss of self-esteem are likely to affect how the depressed perceives and report their working conditions, since depression is strongly associated with negative thinking [164]. Biased reporting of exposure inflates

the association between high psychological demands and low decision latitude at work and the occurrence of depression, if studies rely on individual self-reports [163], and it is likely that this reporting bias also is a problem when studying other aspects of the working environment.

The studies that did not rely on self-reported exposure information, but instead on methods such as registry linkage, expert assessment, averaging across work units or work places, or job exposure matrices, were less likely to be affected by reporting bias due to sub-clinical depression. These studies also had the advantage of circumventing other non-work related factors that could influence the reporting of psychosocial working conditions [64;163], such as personality traits, gender, age, and socioeconomic status, which may all affect the risk of depression [20;23]. Furthermore, risk estimates obtained from grouped exposures are not expected to be attenuated because grouping accounts for random misclassification and leads to predominance of Berkson-type error in exposure assessment [165]. There were, however, only few studies that relied on non-self-reported measures of psychosocial working conditions and the results, both positive and negative, have to be interpreted with caution.

In the studies of cortisol and depression the exposure measure was well defined and was not subject to reporting bias. However, due to the diurnal cortisol variation, the exact time of cortisol sampling was important. The inconsistent results of these studies may be caused by different sampling times. All studies measuring morning cortisol concentration at a fixed time point (08.00 hours) found an association between high cortisol concentration and risk of depression, while most studies that measured cortisol concentration relative to time of awakening found no such association. The daily peak of cortisol concentration is expected to occur about 30 minutes after awakening, and thus, morning cortisol concentration is affected more by the time of awakening than by the time of the day [166;167]. Furthermore, depression may be associated with a blunted cortisol response when exposed to an acute stressor and a subsequent impaired recovery [86]. Thus, it is possible that the samples collected at the fixed time point do not reflect the morning cortisol peak, but the capacity for recovery following the morning peak, which could explain why these studies showed an association between cortisol concentration and depression, since the participants had a high risk of developing depression and may also have had a blunted cortisol response.

1.4.3 Measures of depression

The majority of studies of cortisol relied on a clinical interview to identify cases of depression, but the studies of psychosocial working conditions used numerous methods. The different methods used to identify the cases of depression may have reduced comparability between studies and some measures of depression may have caused misclassification.

While most questionnaire based diagnoses of depression are both effective and validated the clinical interview is, however, the gold standard of diagnosing depression [34], and the studies that used clinical interviews would be less likely to have misclassified depression than studies that used questionnaires or other methods of diagnosing depression.

Most studies that used questionnaires to measure psychosocial working conditions also used questionnaires to diagnose depression. When both data on exposure and outcome were collected by the same method, such as self-administered questionnaires, the results could be affected by common method bias [41], and the risk of circular reasoning and trivial results was increased [163]. Thus, it is likely that the stronger associations between psychosocial working conditions and depression shown in studies using questionnaire diagnosed depression were, at least in part, caused by common-method bias.

1.4.4 Study population

The populations in the studies of psychosocial working conditions differed in composition by gender, occupations, nationality, socioeconomic status, age, and many other characteristics, but were predominantly healthy, adult working populations. Depression is twice as frequent [13], has an earlier onset, higher rate of recurrence, longer duration, and lower rate of spontaneous remission in women than in men [168]. The substantial gender differences in depression were reflected in the fact that all studies included only participants of a single gender, adjusted for gender in their analysis, or performed analyses separately for both genders.

The studies that examined the association between cortisol and the risk of depression were performed on more similar study populations. The majority of these studies were performed on small groups of teenagers at high risk for developing depression.

The age of the study population is important when studying cortisol. Compared to non-depressed peers, young adults currently suffering from depression have a higher morning cortisol concentration, daily mean cortisol concentrations, and cortisol awakening response. However, no such difference between the depressed and non-depressed was found for older adults [169]. Thus the results may not be comparable between the age groups, and results based on teenagers in high risk of depression may not be generalized to a healthy adult population.

The studies of cortisol were mainly performed on participants in high risk of developing depression due to personality traits or familial disposition. The relatively small numbers of participants in these studies explain the need to select participants with a high risk for developing depression in order to obtain sufficient cases for a statistical analysis. However, the association between cortisol and depression in a high risk group may not be comparable to the association in the entire population. There was some indication that high morning cortisol concentration is a risk factor for depression among children and adolescents The association between cortisol concentration and subsequent depression among adults has so far only been examined in a single study of a high risk population that showed an association between high morning cortisol concentration and risk of depression, but no association between evening cortisol concentration and depression. No studies have included a large, healthy, adult working population.

1.4.5 Duration of follow-up

Only one study has a follow-up time shorter than 1 year [147]. The relatively long duration of follow-up may be a problem, since a depressive episode rarely last more than half a year [25;26]. Most studies only measured depression at follow-up and were unable to identify transient depression. Furthermore, they were unable to show any immediate effect of the psychosocial working environment or cortisol concentration since a quickly developed depression would likely have run its course by the time of

the follow-up examination. Thus, the studies with a long duration of follow-up would be more likely to identify cases of chronic or long-term depression than cases of short-term depression. This will be a problem if the risk factors in the working environment are different for long-term and short-term depression.

Shortly after a stressful life-event the risk of depression increases steeply and declines during the following months [170]. However, long-term contextual threats also increase the risk of depression, but not nearly as immediately as stressful life events [171]. The intensity of the psychosocial working conditions measured varies from intense exposures such as hazardous working condition, threats, and violent assaults to less intense exposures such as monotonous working conditions and lack of opportunities for development. It is unknown if the temporal relation between these different exposures differ. One may speculate that the more intense and immediate exposures may be more similar to stressful life events, while the less intense but persistent exposures may be similar to long-term contextual threat. Thus, the associations between the different exposures and depression may vary according to the duration of follow-up used in the studies. Overall the strongest effects were seen in studies with a short duration of follow-up (Figure 5).

The association between cortisol and subsequent depression may decrease over time and thus the strongest associations may be expected in studies with a short duration of follow-up [160]. This was, however, a limitation of all the studies, and is thus unlikely to explain any inconsistent results.

1.4.6 Confounder adjustment

Many studies excluded depressed participants at baseline [2;41]. This method can be used to avoid bias due to reverse causation, but may not be sufficient when studying depression. Depression is an insidious disorder that may have a long preclinical course with sub-clinical depressive symptoms. This sub-clinical depression can also be a cause of bias and inflate the reporting of psychosocial working conditions [163]. One way to prevent such bias is, as previously mentioned, to avoid using self-reported exposure information. Another way is to adjust for sub-clinical depressive symptoms measured at baseline. This will not prevent other non-work related factors from

affecting the results, but will circumvent any bias caused by sub-clinical depression if adequately adjusted for. There were, however, only small differences between the estimates from studies with and without adjustment for baseline depressive symptoms.

The majority of studies included many well-known risk factors for depression in their statistical analyses (age, gender, socioeconomic factors), and generally performed adequate confounder adjustment. Few studies did only perform limited confounder adjustment (Table 1). These studies often had a very homogenous study population [115;119;127] or performed structural equation modeling [147;150]. Thus, the results from the meta-analysis were unlikely to be biased by insufficient adjustment for confounders.

1.4.7 Qualitative synthesis

The results from the studies that were not included in the meta-analysis can still be compared to those that were included if they examined the same exposures. There were 17 such studies [48;106;111;112;114;116;118;120;124;133;135;141;144;146-148;151]. Overall, they showed conflicting results with almost as many studies showing no association between the measures exposures as studies showing a significant association. Specifically, the only measure of exposure examined by more than one study that did not show contradictory results was psychological demands that was related to depression in all six examining studies [48;114;118;135;148;151], though only for men in one of the studies [135]. However, there was an indication of publication bias in the studies of psychological demands that have been included in the meta-analysis (Appendix 2, figure 30), which could also have affected these studies and further inflated the association between psychological demands and depression. Only one study was not based on self-reported exposure [48], and showed a significant association with psychological demands and work load. This did not support that reporting bias had inflated the associations. The few studies that did not rely on questionnaire based diagnoses of depression primarily showed no associations [106;116;151], except for the one study using non-self-reported exposure measures [48]. This supports the pattern from the meta-analysis where questionnaire diagnosed depression seemed to have inflated results. However, based on only one study not relying on self-reported exposure measures and four studies not relying on questionnaire diagnosed depression the evidence is sparse.

The remaining 57 exposure measures not included in the meta-analysis were too numerous and each based on too few studies to merit a detailed description. Overall, the majority of the exposure measures were not related to depression (n=34), some were related to depression (n=17), and few showed conflicting results (n=6). Some studies not relying on self-reported measures of exposure showed no association between any of the 57 types of exposure and depression [35;49], one study showed a significant association [67], one study showed an associations for one type of exposure, but not for six others [70], and one study showed an association only for women [38]. Five studies not relying on questionnaire diagnosed depression showed no association between any of the 57 types of exposure and depression [35;37;49;65;116;137], three showed only significant associations [67;123;152], and five showed both exposures that were related to depression and exposures that were not related to depression [38;54;106;139;149]. This did not provide any clear indication that studies using self-reported exposure measures or questionnaire diagnosed depression were less prone to find significant associations between the psychosocial working conditions and depression, as the number of studies in each category reflects that there were only half as many exposures related to depression (n=17) as not related to depression (n=34) based on the studies presented in table 1.

1.5 Conclusions leading to the present studies

Results from previous studies were in line with a moderately increased risk of depression following adverse psychosocial working conditions. This association often diminished or disappeared if a diagnosis of depression was based on clinical interviews and especially in studies not relying on self-reported exposure. There were limited evidence supporting an association between psychosocial working conditions and depression that did not rely on self-reported exposure information and questionnaire diagnosed depression. More studies are needed to determine if the association shown in previous studies is a product of bias caused by self-reported exposure measures and questionnaire diagnosed depression.

The results for cortisol have primarily been based on cross-sectional studies and the few longitudinal studies were limited by different measures of cortisol. Only a single

longitudinal study examined an adult population. The cross-sectional studies showed a somewhat consistent pattern of an increased cortisol concentration among the depressed. The longitudinal studies indicated the same association, but the results were far from consistent. More studies are needed to examine if increased cortisol concentration is a risk factor for depression in an adult population.

2 Aims of the thesis

The thesis presents the results of the PhD study with the following objectives:

- To examine if high psychological demands or low decision latitude in a work-unit increase the risk of depression (**Study I**).

- To examine if low procedural or relational justice in a work-unit increase the risk of depression (**Study II**).

- To examine if high cortisol concentration or low difference between morning and evening cortisol concentration is a risk factor of depression (**Study III**).

3 Materials and methods

3.1 Design

The studies in this thesis are based on the Danish PRISME cohort established in 2007 [163] and re-examined in 2009. All three studies have a longitudinal design with baseline in 2007 and follow-up in 2009. In 2007 we measured psychosocial working conditions and salivary cortisol. Cases of depression were identified in both 2007 and 2009 by a two-step procedure: First, participants reporting mental symptoms (symptoms of depression, stress, or burn-out) were identified. Second, participants were invited to take part in a standardized psychiatric interview to clinically diagnose depression. **Study I** examines the association between psychological demands and decision latitude at baseline and depression at follow-up. **Study II** examines the association between procedural justice and relational justice at baseline and depression at follow-up. **Study III** examines the association between salivary cortisol concentration at baseline and depression at follow-up.

3.2 Population

Study I+II: 10,036 public employees from 502 work units were recruited and 4,489 employees from 474 work units participated by filling in a postal questionnaire concerning working conditions and health. Participants with depression at baseline (n=100), with no identifiable work-unit leader (n=5), and members of work-units with less than three responders who were non-depressed at both baseline and follow-up (n=147) were excluded. A total of 4,237 participants from 378 work units were eligible for follow up, and 3,046 employees from 376 work units participated, comprising the final study population for **study I**. In **study II** the final study population were 3,047 participants. The difference in participants was due to a different number of missing questionnaire answers in the exposure measures of the two studies.

Study III: 10,036 public employees were recruited and 4,467 employees participated by collecting saliva samples and filling in a postal questionnaire. Participants with a depression at baseline (n=98) and pregnant women (n=138) were excluded. A total of

4,231 participants were eligible for follow up, and 3,031 participated. Of these 2,920 provided at least one valid saliva sample and comprised the final study population for **study III**.

3.3 Measures of psychosocial working conditions (Study I+II)

To avoid any reporting bias caused by depression, mean values of the psychosocial working conditions were calculated for each of the 376 work units after the exclusion of participants with depression at baseline or at follow-up. The mean values were assigned to all employees in a particular work unit.

Psychosocial working conditions were measured according to Karasek's and Theorell's job strain model [42] in **study I**, and according to the Moormans organisational justice model [172] in **study II**.

In **study I**, psychological demands, decision authority, and skill discretion were each measured by four items on a scale from "always" (1) to "never" (5). For each scale, a mean value of the four items was calculated. Decision latitude was computed as the mean value of decision authority and skill discretion. In **study II**, procedural and relational justice were also measured as the mean of four items rated on a five-point scale from "strongly disagree" (1) to "strongly agree" (5).

3.4 Measures of salivary cortisol concentration (Study III)

All participants were instructed to collect saliva samples 30 minutes after awakening, and at 8 PM, using a cotton swap. Determination of the cortisol concentration was carried out with a competitive radioimmunoassay. The samples were considered valid if morning samples were collected within two hours of awakening, and evening samples were collected between 5 PM and 4 AM. There were a total of 2,615 valid morning samples, 2,856 valid evening samples, and 2,533 participants collected both valid morning and evening samples. Only valid samples were included in the analyses.

Morning and evening cortisol concentration were measured directly, and daily mean cortisol concentration and morning-to-evening slope were derived from the morning and evening values. The daily mean cortisol concentration was calculated as the mean of morning and evening cortisol concentration. Morning-to-evening slope was calculated as the difference between morning and evening cortisol concentration divided by the number of hours between the collections of the two samples. Only participants with both valid morning and evening samples, where the evening sample were collected at least nine hours after the morning sample, were included in analyses of daily mean and morning-to-evening slope.

3.5 Measures of mental symptoms (Study I-III)

Due to limited resources it was not possible to invite all participants to take part in a standardized psychiatric interview to clinically diagnose cases with depression. The presence and severity of mental symptoms related to depression was used as a screening tool to select participants for the psychiatric interview. Depressive symptoms was assessed by the Common Mental Disorder Questionnaire subscale for depression (six items) [34], stress by the Perceived Stress Scale (four items) [173], and burn-out by the Copenhagen Burn-Out Inventory (six items) [174]. All questions concerned the last four weeks and responses were given on five-point scales (scores 1 to 5).

At baseline, participants were selected for the psychiatric interview if their point score was 3.0 or higher on three or more of the six items on the depression scale, the mean score was 2.5 or more on the stress scale, or the mean score was 4.0 or more on the burn-out scale.

At follow-up participants with high scores in at least two of the three mental symptom scales (depressive scores of 3.0 or higher on two or more of the six items, average stress and burn-out scores of 2.5 or higher) were selected for the psychiatric interview.

3.6 Diagnosis of depression (Study I-III)

Diagnoses of depression were obtained by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (version 2.1 part I, section six, seven, eight, and ten) [28] according to the ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research (ICD-10-DCR). All questions referred to the previous three months. Diagnosis of depression was categorized as a dichotomous variable including mild, moderate, and severe cases of depression.

3.7 Cases of depression (Study I-III)

In **study I+II**, a total of 100 participants were diagnosed with depression and excluded from the study at baseline. The ICD-10-DCR diagnostic criteria for a mild, moderate, and severe depressive episode were fulfilled for 40, 43 and 17 participants, respectively. At follow-up, a total of 58 participants were diagnosed with depression. The ICD-10-DCR diagnostic criteria for a mild, moderate, and severe depressive episode were fulfilled for 15, 32 and 11 participants, respectively.

In **study III**, a total of 98 participants were diagnosed with depression, since two of the depressed participants from **study I** and **II** did not collect saliva samples. At follow-up, a total of 63 participants were diagnosed with depression. The ICD-10-DCR diagnostic criteria for a mild, moderate, and severe depressive episode were fulfilled for 19, 32 and 12 participants, respectively.

3.8 Statistical analyses (Study I-III)

In **study I**, odds ratios of depression were analysed by logistic regression with robust clusters based on the work unit of the participants [175]. Analyses were performed on a continuous-scale and with tertile categorization. In **study I**, the following potential confounders were included and measured based at baseline: gender, age, previous episodes of depression, family history of depression, income, years of education beyond primary or high school, full-time work, alcohol consumption, living alone, neuroticism, baseline depressive symptoms, body mass index, and smoking. Traumatic life events [176] during the last six months were included measured at follow-

up. A second model included only previous depression, traumatic life events, depressive symptoms, and neuroticism as covariates. These covariates were determined by likelihood-ratio testing and stepwise exclusion of non-significant terms. The data were examined for an interaction between the two exposure variables as both continuous data and dichotomous data split on the median level. Linearity of the relation between the exposure variables and depression was examined by logistic regression models including quadratic and cubic terms and by locally weighted scatterplot smoothing [177]. The associations were further explored using regression analysis with restricted cubic splines due to the non-linear relation between the two.

In **study II**, odds ratios of depression were analysed by logistic regression with robust clusters based on the work unit of the participants [175]. Analyses were performed on a continuous-scale and with tertile categorization. The homogeneity of self-reported procedural and relational justice within the work units were assessed by within-group interrater agreement indices [178]. In **study II**, the following potential confounders were included and measured based at baseline: gender, age, previous episodes of depression, family history of depression, income, years of education beyond primary or high school, alcohol consumption, living alone, neuroticism, baseline depressive symptoms, body mass index, and smoking. Traumatic life events [176] during the last six months were included measured at follow-up. A second model included only gender, previous depression, traumatic life events, living alone, baseline depressive symptoms, and neuroticism as covariates. These covariates were determined by likelihood-ratio testing and stepwise exclusion of non-significant terms. Linearity of the relation between the continuous exposure measures and depression were tested using likelihood-ratio tests comparing linear models to models including quadratic transformations, cubic transformations, and restricted cubic spline regression analysis

In **study III**, odds ratios of depression were analysed by logistic regression. Logarithm transformation was used to normalize the cortisol distribution. Analyses were performed on a continuous-scale and with tertile categorization. Linearity of the relation between the continuous cortisol measures and depression were tested using likelihood-ratio tests comparing linear models to models including both linear and quadratic terms as covariates. In **study III**, the following potential confounders were included and measured at baseline: gender, age, previous episodes of depression,

family history of depression, income, and years of education beyond primary or high school, alcohol consumption, body mass index, and smoking. A second model did not include lifestyle factors (alcohol consumption, body mass index, and smoking). Linearity of the relation between the continuous cortisol measures and depression were tested using likelihood-ratio tests comparing linear models to models including quadratic transformations. The effect of measuring time was examined in sub-analyses where only the 90%, 80% and 70% of the population that collected their saliva samples closest to the intended time of sampling were included.

4 Results

Study I: A two-year follow-up study of risk of depressing according to work-unit measures of psychological demands and decision latitude

Main findings

Psychological demands and decision latitude were not significantly associated with depression. The adjusted odds ratio of the highest and the medium tertiles of psychological demands compared to the lowest tertile were 0.80 (95% CI: 0.38, 1.69) and 0.72 (95% CI: 0.33, 1.57), respectively. For low decision latitude, we found an adjusted odds ratio of 1.85 (95% CI: 0.55, 6.26) for a one point decrease on the five-point scale. In analyses of the decision latitude sub-scales, we found adjusted odds ratios of depression of 1.58 (95% CI: 0.71, 3.53) for decision authority and 1.23 (95% CI: 0.32, 4.67) for skill discretion for a one point decrease on the five-point scales.

Additional analyses

By likelihood-ratio testing, we found no significant differences between the two models with different covariates for neither psychological demands nor decision latitude. We observed no interaction between psychological demands and decision latitude as dichotomous exposure variables or continuous exposure variables. The relation between the level of psychological demands and depression was not accepted as linear, but we found a linear relation between the level of decision latitude and depression using both locally weighted scatterplot smoothing and likelihood-ratio testing.

Study II: Justice at work and the risk of depression: a prospective two-year cohort study

Main findings

Members of work units with low levels of procedural or relational justice had a substantially increased risk of developing depression over a two-year period. The adjusted odds ratios for a one-point decrease on the five-point justice scales were 2.96 (95% CI: 1.19, 7.34) and 4.84 (95% CI: 2.15, 10.90) for procedural and relational justice, respectively.

Additional analyses

We found an average interrater agreement of 0.75 for procedural justice and 0.77 for relational justice, indicating a strong homogeneity within work units. By likelihood-ratio testing, we found no significant differences between the two models with different covariates for neither procedural nor relational justice, but we did find similar results in both models. Neither quadratic, nor cubic, nor spline models fitted the data significantly better than the linear models of exposure. We found no interaction between gender and procedural justice ($p=0.84$) or gender and relational justice ($p=0.85$), and found very similar results when examining only female participants. One depressed participant would not have been included among the depressed cases if we had applied the same screening criteria for being invited to the psychiatric interviews at baseline as at follow-up. Excluding this single participant did not change our results.

Study III: A two-year follow-up study of salivary cortisol concentration and the risk of depression

Main findings

Participants with a high daily mean concentration of cortisol or a steep morning-to-evening slope had a decreased risk of depression two years later. Morning cortisol concentration and evening cortisol concentration were not significantly associated with depression. The adjusted odds ratio for 1.0 nmol/l increase on the logarithmic scale in morning, evening, and daily mean cortisol concentration were 0.69 (95% CI: 0.45, 1.05), 0.87 (95% CI: 0.59, 1.28), and 0.53 (95% CI: 0.32, 0.90), respectively. The adjusted odds ratio for a 1.0 nmol/l increase in slope on the logarithmic scale was 0.64 (95% CI: 0.45, 0.90).

Additional analyses

We did find similar results in the model including lifestyle factors as covariates and the model not including lifestyle factors. Models with quadratic terms of cortisol concentration included as covariates did not perform significantly better than the simple linear models. The sub-analyses including only the 70-90% of the population that collected their saliva samples closest to the intended time of sampling showed even stronger inverse relations between saliva cortisol level and odds ratio of depression than the analyses including the whole study population.

5 Discussion

5.1 Main results

Being part of a work-unit with high psychological demands or low decision latitude did not predict onset of depression. Low procedural justice and low relational justice predicted onset of depression. There was no indication that increased cortisol level is a risk factor for depression, but the opposite was indicated. The risk of depression decreased by increasing daily mean cortisol concentration and by increasing difference between morning and evening concentrations. There was no association between morning or evening cortisol concentrations and depression.

5.2 Measures of exposure

5.2.1 Reporting bias and misclassification of exposure

One of the methodological characteristics of the previous studies of psychosocial working conditions and depression (Table 1) that most consistently affected the association between exposure and depression was whether the exposure measure was based on self-reported information or not. A likely explanation is that the studies that have relied on self-reported exposure information were subject to reporting bias, because depressed mood may affect the individual's perception and reporting of the work environment. This is relevant even in follow-up studies, because depression often has a long insidious preclinical stage [2;163;179].

To circumvent the problem of biased self-reporting of psychosocial working conditions we excluded participants who were diagnosed with depression at baseline or follow up from the calculation of the work-unit mean exposure scores. By including only participants who were non-depressed throughout the study we avoided reporting bias related to current depression or preclinical depressive symptoms which could influence the assessment of working conditions. Other individual factors that may cause reporting bias, such as personality traits and health, were circumvented as well [64].

Another possible explanation of the differences between the studies relying on self-reported exposure information and those that do not, is that the methods used to obtain the non-self-reported information are prone to non-differential misclassification of exposure [180]. Working conditions may vary significantly between workers within a work unit, and one may argue that this variance was not captured by our work-unit average exposure measure. It is also possible that the work-unit-level was not the level that is most suitable for aggregation. Aggregation at the workplace-level or based on job titles are other possibilities that might be more suitable and cause less misclassification of exposure in some cases [64]. Even though we explicitly identified units of workers that shared leadership, colleagues, and work content it is unlikely that every member of a specific work unit were exposed to identical levels of psychological demands, decision latitude, and justice. We did, however, find a strong homogeneity within work units (average interrater agreement of 0.75 for procedural justice and 0.77 for relational justice), which justified aggregation in a multilevel analysis [178]. Furthermore, risk estimates obtained from grouped exposures are not expected to be attenuated because grouping accounts for random misclassification and leads to predominance of Berkson type error in exposure assessment [165].

Reporting bias was not an issue when measuring salivary cortisol concentration, and misclassification of exposure was unlikely since the method used to determine the cortisol concentration is precise and validated [181;182].

5.2.2 Correlation of exposure measures

Many different measures of the psychosocial working environment are somewhat similar. This is also the case for procedural justice, relational justice, and decision latitude, which all, to some degree, measure the workers influence over their working environment [42;47]. Decision latitude was moderately correlated to procedural justice (r=0.44) and relational justice (r=0.41). Procedural justice was highly correlated to relational justice (r=0.60), but psychological demands were not significantly correlated to decision latitude, procedural justice, or relational justice. Further studies are needed to determine if procedural and relational justice are both risk factors for

depression if they are included in the same statistical models or if the association between depression and one type of justice is mediated by the other type.

Slope, morning, and mean cortisol concentration were highly correlated ($r>0.9$). Evening cortisol was correlated to mean cortisol concentration ($r=0.4$) but not to slope or morning cortisol concentration. The four cortisol measures did not reflect four independent factors. This was no surprise since slope and mean cortisol concentration were derived from the morning and evening cortisol levels.

5.2.3 Time of cortisol sampling

Due to the diurnal cortisol variation and differences in cortisol awakening response among depressed and non-depressed participants, we had to take sampling time into account, since the same may be the case for those who develop depression from baseline to follow-up. The morning cortisol concentration peaks about 30 minutes after awakening [166;167], which is the time we instructed the participants to collect their morning saliva samples. Many participants did, however, not collect the sample at this exact time. Similarly, many participants did not collect their evening sample at the instructed time. The imprecise cortisol sampling may be a source of misclassification or may have biased results if sampling time is related to subclinical depression or other correlates that predict later depression. To examine the effect of the imprecise sampling times we performed a sensitivity analysis based only on the sub-group of participants who collected their samples closest to the instructed time. This analysis showed even lower odds ratios of depression for this sub-group compared to the original results. This indicates that the imprecise sampling times have biased our results and that we can expect even smaller odds ratios of depression for higher levels of morning cortisol concentration, evening cortisol concentration, daily mean cortisol concentration, and morning-to-evening slope.

5.3 Measures of depression

5.3.1 Change in screening procedures

We identified participants reporting symptoms of depression, stress, or burn-out in the baseline and follow-up questionnaire, and invited them to take part in the standardized psychiatric interviews to clinically diagnose cases with depression. However, the selection criteria for the interviews changed from baseline to follow-up and this may have affected our results. The different threshold at follow-up could result in problems with identifying whether the new cases of depression were actually also depressed at baseline and not really incident cases of depression. However, only a single depressed participant would not have been selected for the psychiatric interview at follow-up, and subsequently diagnosed with depression, if we had applied the baseline selection criteria for follow-up as well. As expected, a sensitivity analysis showed that excluding this participant did not change the results in the study of justice and depression. Substantial changes due to the exclusion of this one participant are unlikely in the other studies.

5.3.2 Low number of depressed participants

The prevalence of clinical depression in Denmark is approximately 4% [183]. With a source population of 10,036 people, we would expect about 400 cases of prevalent depression at baseline if our study population was representative of the general population. Even with the low baseline participation rate (45%) we would have expected nearly twice the number of cases in a representative population compared to the 100 cases we identified. The low number may in part be due to a healthy worker effect into the occupational groups studied as well as participation into the study population. The latter was corroborated by our finding that non-participants at baseline were more often prescribed antidepressant medication than those who participated [184]. Some participants with depression would also not have been identified by our screening procedure. The true number of unidentified cases of depression is unknown, but we expect that few depressed participants have been missed. The primary reason for the low number of depressed participants is thus likely

to be that our study population is a working population and not representative of the general population in Denmark.

5.3.3 Time dependent sampling of cases with depression

There are two primary challenges when selecting duration of follow-up for a study that only identify cases of depression at baseline and follow-up, and are not able to identify transient cases of depression in the intervening time. One is the identification of both short-term and long-term cases of depression. The other is selection of an appropriately long duration in which the psychosocial working conditions have enough time to cause new cases of depression, if there is a causal relation.

We only identified cases of depression at baseline and follow-up. Thus, we were not able to identify and include transient cases of depression occurring during the two-year period in-between baseline and follow-up. Thus, it is possible that several participants in our study have developed and recovered from depression during the two year period. Depressive episodes typically have durations between 3 months and a year, and only 20% of the episodes last for longer than 2 years [26]. The inability to identify transient cases may have caused us to oversample cases of prolonged or chronic depression. Most previous studies have used a similar procedure for case identification, and only examine participants at baseline and follow-up, but the duration between baseline and follow-up varies from study to study. This may reduce the comparability across different studies since there may be differences between those participants who are not depressed at baseline, but who are depressed 1 year later, those who are depressed 2 years later, and those who develop depression later than that. This will especially be a problem if there are different risk factors for long-term and short-term depression.

The temporal relations between psychosocial working conditions, cortisol, and depression are uncertain. Following a traumatic life-event the risk of depression increases steeply and then declines during the subsequent months [170], while long-term contextual threats have also been shown to increase risk of depression significantly [171]. If the psychological demands, decision latitude, justice, and high cortisol levels are immediate risk factors of depression, as is the case for traumatic life-events, our

follow-up period may have been sub-optimal and our effects underestimated. However, there is no indication of the effect estimate depending on the duration of follow-up in the studies of psychosocial working conditions and depression. Additionally, we performed a sensitivity analysis of questionnaire-reported physician-diagnosed cases of depression from baseline to follow-up, where transient cases of depression may have been identified. The results from this sensitivity analysis were based on the association between psychological demands, decision latitude, and depression, and were comparable to the results of the primary analysis. Thus, there was no indication that the undiagnosed cases of depression between baseline and follow-up affected the odds ratio estimates.

5.4 Study population and design

5.4.1 Participation at baseline

The baseline participation rate was low (45%), which could have biased results, if participation was associated with exposure as well as depression. We investigated this by extrapolating the work unit estimates of psychological demands, decision latitude, and justice to the non-responding members of work units with responding colleagues, and by accessing registry information on redeemed antidepressant medication for the entire source population that has been published elsewhere [184]. We found no indication that the low baseline participation distorted the estimates of the association between psychological demands, decision latitude, justice, and depression, since none of the associations between these exposure measures and antidepressant use were different for participants and non-participants at baseline. We had no way to assess cortisol concentration for non-participants at baseline, but we would not expect cortisol concentration to be related to participation. If cortisol concentration were related to participation status, our results may have been biased due to differential participation, since participation status was associated to depression.

5.4.2 Participation at follow-up

The participation rate at follow-up was higher (72%) than at baseline, but there is still a risk that our results could be affected by selection bias. We did, however, find no

difference in baseline levels of psychological demands between participants and non-participants at follow-up. We found only small differences in decision latitude, procedural justice, relational justice, morning cortisol concentration, and evening cortisol concentration between participants and non-participants at follow-up. These small differences may indicate some selection bias, but baseline exposure and depressive symptoms did not significantly predict participation at follow-up and we found that the relation between cortisol concentration and depressive symptoms at baseline did not differ between participants and non-participants at follow-up. Thus, strong bias due to selective loss to follow-up is unlikely.

5.4.3 Limited statistical power

The studies included only 63 cases of depression, and 5 of those were excluded in the studies of psychosocial working conditions since they were not part of a work-unit with three or more non-depressed participants, leaving 58 cases of depression. This limits the statistical power of the study and the ability to adjust for all potential confounders. The crude and adjusted results were, however, very similar in the analyses of psychological demands, decision latitude, morning cortisol concentration, evening cortisol concentration, daily mean cortisol concentration, and morning-to-evening slope. The adjusted association between procedural justice, relational justice, and depression were stronger than the crude associations. This increase was primarily because female gender, low income, and frequent previous depression were negatively related to work-unit levels of justice and positively related to depression. Adjusting for them, thus, increased the association between justice and depression.

Due to the limited statistical power we would be unable to show any low to moderate associations between the exposure measures and depression. Results from most previous studies have shown a moderate association between psychosocial working conditions and depression. This association was even smaller in studies that do not use self-reported exposure and outcome information. The combination of low statistical power and a low to moderate expected association between exposure and outcome increased the risk of a false negative result. Thus, it is possible that the non-significant findings for psychological demands, decision latitude, morning cortisol concentration, and evening cortisol concentration are false negatives due to

insufficient statistical power. This was more likely in the cases of decision latitude and morning cortisol concentration, where the results were borderline-significant. The most appropriate conclusion, however, is that there are no associations between psychological demands, decision latitude, morning cortisol concentration, evening cortisol concentration, and depression.

5.4.4 Confounding

The selection of potential confounders was based on a review of the literature and includes many known risk factors for depression [19;20;22-24]. Some potential confounders are well defined and easily measured, such as age and gender, while others are more challenging, such as personality, lifestyle, and socioeconomic status. Working conditions are likely to be related to social class and thereby to lifestyle factors [185]. We adjusted for income, educational level, alcohol consumption, body mass index and smoking in all studies, and any effects of confounding from non-controlled socioeconomic and lifestyle factors therefore seem small. Some personality traits may influence the perception of ones working conditions and may be risk factors of depression [22;164;186]. Thus, in the studies of psychosocial working conditions and depression, we included neuroticism as a possible confounder, but did not take other personality traits into account. Neuroticism is the personality trait that is the strongest risk factor of depression [22]. Trait anxiety and hostility have also been suggested to be related to depression, but did not have strong confounding effects on the relation between perceived justice and depression in a recent study [186]. This makes confounding due to these personality traits unlikely in our study.

The limited statistical power and accompanying limited ability to adjust for all potential confounders may have biased our results. We did not adjust for alternative psychosocial working conditions, and were thus unable to determine whether the shown associations are mediated by other factors in the work environment. Many other psychosocial working conditions have been suggested as possible causes of depression, such as social support, effort-reward imbalance, work climate, or management style [2;41;43], and could confound our results when not adjusted for. On the other hand, many factors in the work environment are highly correlated, such as procedural justice, relational justice, and effort-reward imbalance [56] and one such

factor may be a part of the causal chain connecting another factor to depression. One such example is that management style can affect justice at the workplace [187]. Thus, it could bias the association of justice and depression to adjust for management style.

5.5 Possible biological mechanisms

Physiological stress has been suggested to be the mechanism linking psychological stressors in a social context to somatic diseases [81;82]. More specifically, increased activation of the HPA-axis has been suggested as a biological pathway linking psychosocial stressors to depression [8-11]. While the studies included in this thesis do not directly examine this hypothesis and were not designed to do so, we would still expect the results to reflect the above hypothesis if it is true. Thus, we would expect **study I and II** to show that a high level of psychological demands and low levels of decision latitude, procedural justice and relational justice were associated with a high risk of depression. Likewise, we would expect **study III** to show that a high cortisol concentration was associated with a high risk of depression.

This was not the case. While **study II** did show that procedural and relational justice were related to subsequent depression, **study I** showed no association between psychological demands, decision latitude and depression, and **study III** showed that high cortisol levels were not a risk factor of depression, but that low cortisol levels may be associated with depression. Our results, while not in line with the above hypothesis, were in line with the homeostasis [188] and allostasis [82] models, which suggest that hyperactivity, as well as hypoactivity, of the physiological stress system can be harmful. The HPA-axis responds to demanding and threatening situations in daily life and allows organisms to adapt to physical and psychosocial changes in their environments [76]. Elevations in cortisol levels typically inhibit the HPA system via negative feedback mechanisms in the hippocampus [78;79]. A failure to activate the physiological stress response in a demanding or threatening situation can cause cascade effects when other physiological stress systems need to compensate for the failure and will trigger compensatory increases in other physiological systems due to lacking counterregulation, which will put too much of a burden on the HPA-axis [82]. Chronic physiological stress or an inability to turn of the physiological stress response when it is no longer needed also puts an unhealthy burden on the body [83].

It has been hypothesized that chronic or traumatic stress may result in hypocortisolism after a prolonged period of hypercortisolism [97], and several studies show that after long-term exposure to stressors, the HPA axis will eventually become dishabituated, resulting in a disruption of the regulatory systems and a subsequent decrease of cortisol secretion [189]. Initially psychosocial stressors may increase cortisol concentration, but eventually the concentration could be reduced to below normal levels [98]. This pattern could also explain the inconsistent results from studies of psychosocial working conditions and cortisol [6].

With only a single baseline measure of cortisol, we are not able to determine if our study population followed this suggested pattern of initial hypercortisolism and subsequent hypocortisolism. It was also not clear from the analyses performed in study I-III if psychosocial working conditions were related to cortisol levels. While our results were not in line with the hypothesis that increased HPA-axis activity is the mechanism linking psychosocial working conditions to depression, it may be in line with the hypothesis that a dishabituated or exhausted HPA-axis is a mechanism linking psychosocial working conditions to depression, if working conditions are related to cortisol in our population. Further analyses are needed to answer that question.

5.6 Comparison with previous findings

5.6.1 Psychological demands, decision latitude, and depression

Psychological demands and decision latitude have frequently showed an increased risk of depression [36;65;107;108;128-130;132;134;139;145], and the overall estimates from the meta-analysis of all eligible longitudinal studies of psychological demands (OR: 1.21; 95% CI: 1.12-1.35) and decision latitude (OR: 1.17; 95% CI: 1.06-1.29) showed associations to depression (Figure 4). However, there was an indication of strong publication bias in the studies of psychological demands and decision latitude (Appendix 2 – Figure 24 and 30). Additionally, most studies not relying on self-reported exposure [35;36;38], studies using a clinical interview to diagnose depression

[38;65;129], and studies with a follow-up duration of two years of shorter [38;107;122;129;132] found no association between psychological demands, decision latitude and depression, and had a design similar to **study I**. The overall estimates from these subgroup meta-analyses showed no association. Only three studies have examined the decision latitude sub-scales, decision authority and skill discretion, and showed no overall association between these exposures and depression [35;125;140]. We found no significant association between psychological demands, decision latitude, decision authority, skill discretion, and depression. Since our study did not rely on self-reported exposure information, used clinical interviews to diagnose depression, and had a two year follow-up period, the results were comparable to the previous studies with similar characteristics.

5.6.2 Procedural justice, relational justice, and depression

There are only four previous studies of procedural justice [56;122;144;147] and two studies of relational justice and the risk of depression [56;122]. Two of the studies showed an association between procedural justice and depression [56;144] and between relational justice and depression [56;122], while a single study showed no effect of either type of justice [147]. All these studies relied on self-reported exposure information and questionnaire diagnosed depression. Two studies analysed the association between justice and depression by structural equation modelling and, thus, were not eligible for inclusion in the meta-analysis [144;147]. The meta-analysis showed a moderate association between procedural justice, relational justice, and depression (Figure 13 and 15). We found an association between procedural justice, relational justice, and the risk of depression. The result of our study is comparable to most other studies examining the relation between justice and depression, and is comparable to the overall estimate from the meta-analysis of the few eligible studies on this topic (Figure 13 and 15).

5.6.3 Cortisol concentration and depression

There are only few longitudinal studies of cortisol and the risk of depression [154-160]. Most studies found an association between high morning cortisol concentration and subsequent depression [154-156;158;159], but no association between evening cortisol concentration and depression [154-157;160]. Only few studies examined daily mean

cortisol concentration [157;159;160] or morning-to-evening slope [157;160] and neither was related to depression in the majority of studies. All studies that found an association between cortisol concentration and depression showed that a high cortisol concentration increased the risk of depression. We found no association between morning cortisol concentration, evening cortisol concentration, and depression, but found that a low daily mean cortisol concentration and a low morning-to-evening slope increased the risk of depression. This is in conflict with the results from many of the previous studies, since no previous study found that low levels of cortisol increased the risk of depression. The only result from our study that was comparable to the majority of previous studies is that there was no association between evening cortisol concentration and depression. The conflicting results are likely caused by differences in study populations and methods for measuring morning cortisol concentration. No other study examined a healthy, adult, working population, and six of the seven previous studies examined children and adolescents [154;156-160]. The one study that examined adults selects participants in high risk of developing depression [155].

6 Conclusion

According to prevailing theories and thinking, a demanding work environment as well as an increased physiological stress response, are risk factors of depression. However, these hypotheses could not be corroborated by this thesis. This thesis, on the other hand, indicates that low daily mean salivary cortisol concentration, a small difference between morning and evening cortisol concentration, and a work environment characterized by low levels of justice were risk factors for depression. Low levels of morning cortisol and a work environment characterized by low decision latitude may be risk factors of depression, but no statistically significant associations were seen. Evening cortisol concentration and a work environment characterized by high levels of psychological demands were not risk factors of depression.

7 Perspectives

7.1 Practical implications

We observed that the social interaction in the work place, contrary to workload and work pace, is a risk factor of depression. The results of this thesis indicate that a consistent work environment where all employees are allowed to voice their concerns and challenge the decisions of the management, where supervisors treat their employees with kindness, consideration, and truthfulness, and where employees have a certain degree of co-determination and are allowed to utilize and develop their work specific skills could be an important step in the prevention of depression. These are important findings that may guide employers, employees, and regulatory authorities in the design of healthy workplaces.

7.2 Perspectives for future studies

There is a clear and consistent association between the individual's perception of high psychological demands or of low decision latitude and the risk of depression. However, the evidence linking any type of psychosocial working conditions and depression is much scarcer when not relying on self-reported exposure information. In future studies more focus needs to be placed on the source of exposure and outcome information to avoid bias. Other theoretical models of the psychosocial working conditions than psychological demands and decision latitude, such as organizational justice, may provide novel information and needs to be considered. The longitudinal studies of cortisol and depression are sparse and have primarily been performed on similar study populations comprised of few participants. Studies conducted on healthy adults are needed in order to verify or reject the association between low cortisol levels and subsequent depression in this population. Further studies examining psychosocial stressors, physiological stress, and depression are needed in order to understand if physiological stress is the biological pathway linking the psychological stressor to poor health.

8 English summary

BACKGROUND: Depression is a frequent mental disorder with harmful effects on life quality and workplace functioning. The physiological stress response and psychosocial stressors at work have been suggested to be causally related to depression. The physiological stress response has furthermore been suggested as the mechanism linking psychosocial stressors to depression.

Results from the majority of previous longitudinal studies show a moderate association between depression and psychosocial stressors at work, such as high psychological demands, low decision latitude, or low justice. This association, however, is weak or non-existing for studies using clinical interviews to diagnose depression or studies not relying on self-reported exposure. Thus, it is unclear if this association is a result of bias due to self-reported exposure measures and questionnaire diagnosed depression.

Increased cortisol secretion is a marker of the physiological stress response and high cortisol levels have repeatedly been reported in cross-sectional studies of patients diagnosed with depression. There are only few longitudinal studies examining this association, and the results are equivocal, but do overall indicate that high cortisol levels may be a risk factor of depression. None of the previous studies examined a large, healthy working population.

We aimed to analyse if aggregated workplace measures of psychological demands, decision latitude, and justice at work that are robust to reporting bias by the depressed are risk factors of subsequent depression. We also aimed to determine if a high level of salivary cortisol is a risk factor of depression.

METHODS: In 2007, we enrolled 4,389 non-depressed Danish public employees within 474 different work units. Mean levels of psychological demands, decision latitude, procedural justice, and relational justice were computed for each work unit by averaging the ratings of workers who were non-depressed at both baseline and follow-up. The averages were assigned to all workers of each specific work unit.

Morning and evening salivary cortisol concentration were collected for each participant. Two years later in 2009, 3,154 participated at follow-up. Those reporting high levels of depressive, burnout or stress symptoms were assigned to a psychiatric diagnostic interview and 63 cases of new onset depression were identified. For the analyses of psychosocial stressors at work, we excluded members of work-units with less than three valid ratings. Thus, 3,046 participants were included in the analyses of psychological demands and decision latitude, and 3,047 participants in the analyses of procedural and relational justice. For the analyses of cortisol, we included 2,920 participants who had provided at least one valid saliva sample at baseline. Depression odds ratios were estimated by multivariable logistic regression accounting for established risk factors for depression.

RESULTS: Being part of a work-unit with high psychological demands or low decision latitude did not predict the onset of depression, but low procedural justice and low relational justice predicted onset of depression. The risk of depression decreased by increasing daily mean cortisol concentration and by increasing difference between morning and evening concentrations. The association between morning or evening cortisol concentrations and depression were not statistically significant.

CONCLUSION: Our results did not indicate that an increased cortisol level or a work environment characterized by high psychological demands and low decision latitude are risk factors of depression. However, a low daily mean salivary cortisol concentration, a small difference between morning and evening cortisol concentration, and a work environment characterized by low levels of justice were risk factors for depression.

PERSPECTIVES: According to prevailing theories and thinking, a demanding and hectic work environment as well as an increased physiological stress response, are risk factors of depression. However, these hypotheses could not be corroborated by this thesis. Thus, less focus should be put on workload and work pace and more focus on social interaction in the work place, such as organizational justice. These are important findings that may guide employers, employees, and regulatory authorities in the design of healthy workplaces.

9 Danish summary – Dansk resumé

BAGGRUND: Depression er en hyppig psykisk lidelse med skadelige effekter på livskvalitet og arbejdsevne. Det er blevet antaget, at den fysiologiske stressreaktion og psykosociale stressfaktorer på arbejdspladsen skulle have en kausal sammenhæng med depression. Den fysiologiske stressreaktion har desuden været antaget som værende den biologiske mekanisme, der forbinder psykosociale stressfaktorer med depression.

Resultater fra størstedelen af tidligere longitudinelle undersøgelser viser en moderat sammenhæng mellem depression og psykosociale stressfaktorer på arbejdspladsen, såsom høje krav, lav kontrol, eller lav retfærdighed. Denne sammenhæng er imidlertid svagere eller ikke-eksisterende i undersøgelser baseret på klinisk diagnosticeret depression, og i undersøgelser, der ikke er afhængige af selvrapporterede eksponeringsoplysninger. Derfor er det uklart, om denne sammenhæng er et resultat af bias som følge af selvrapporterede eksponeringsoplysninger eller spørgeskema-diagnosticeret depression. Forøget kortisolsekretion er en biomarkør for den fysiologiske stressreaktion, og høje kortisolniveauer er gentagne gange, i tværsnits-undersøgelser, blevet rapporteret hos patienter diagnosticeret med depression. Der er kun få longitudinelle studier, der undersøger denne mulige sammenhæng, og selvom resultaterne ikke er entydige, tyder det overordnet på, at høje kortisolniveauer kan være en risikofaktor for depression. Ingen af disse tidligere studier er udført på en stor, rask og erhvervsaktiv studiepopulation.

Vi ønskede at analysere, om målinger på arbejdsenhedsniveau af krav, kontrol og retfærdighed på arbejdspladsen, som ikke var påvirket af reporting bias fra deprimerede deltagere, er risikofaktorer for depression. Vi ønskede også at undersøge, om et højt niveau af spytkortisol er en risikofaktor for depression.

METODER: I 2007 rekrutterede vi 4.389 ikke-deprimerede danske offentligt ansatte fra 474 forskellige arbejdsenheder. De gennemsnitlige niveauer af krav, kontrol, processuel retfærdighed og relationel retfærdighed blev målt i hver arbejdsenhed på baggrund af vurderinger fra ansatte, der ikke var deprimerede ved undersøgelsens start eller senere ved dens opfølgning. Disse gennemsnitlige niveauer blev tildelt alle

ansatte i en given arbejdsenhed. Morgen- og aftenkortisol-koncentration blev indsamlet individuelt for hver enkelt deltager. To år senere i 2009, deltog 3.154 i studiets opfølgning. De, som rapporterede høje niveauer af depressions-, udbrændtheds- eller stresssymptomer blev indkaldt til et diagnostisk interview, hvor 63 tilfælde af depression blev identificeret blandt de, som ikke var deprimerede ved undersøgelsens start. Ved analyserne af psykosociale stressfaktorer på arbejdspladsen ekskluderede vi ansatte fra arbejdsenheder med færre end tre deltagere. Samlet deltog 3.046 i analyserne af krav og kontrol og 3.047 deltagere i analyserne af processuel og relationel retfærdighed. Ved analyserne af kortisol deltog 2.920, som havde afleveret mindst én valid spytprøve ved undersøgelsens start. Odds ratio for depression blev udregnet med multivariabel logistisk regression og justeret for velkendte risikofaktorer for depression.

RESULTATER: At være ansat i en arbejdsenhed med høje psykologiske krav eller lav kontrol var ikke en risikofaktor for depression, men at være ansat i en arbejdsenhed med lav processuel eller relationel retfærdighed var en risikofaktor for depression. En lav gennemsnitsværdi for morgen- og aftenkortisol-koncentration og en lav forskel på morgen- og aftenkortisol-koncentration var begge risikofaktorer for depression. Vi fandt ingen signifikant sammenhæng mellem morgen- og aftenkortisol-koncentration og depression.

KONKLUSION: Vores resultater tyder ikke på, at et højt kortisol niveau eller et arbejdsmiljø præget af høje krav og lav kontrol er risikofaktorer for depression. Resultaterne tyder på, at et lavt gennemsnitligt kortisolniveau, en lille forskel mellem morgen- og aftenkortisol-niveau og et arbejdsmiljø præget af lave niveauer af retfærdighed er risikofaktorer for depression.

PERSPEKTIVER: Ifølge fremherskende teorier og tænkning er en krævende og hektisk arbejdsdag, samt et højt niveau af fysiologisk stress, begge risikofaktorer for depression. Disse hypoteser kan ikke bekræftes af denne afhandling. Derfor bør man fokusere mindre på arbejdsbyrde og arbejdstempo og mere på den sociale interaktion, som finder sted på arbejdspladsen, f.eks. i form af organisatorisk retfærdighed. Dette er vigtige overvejelser, som kan vejlede arbejdsgivere, medarbejdere og myndigheder i udformningen af et sundt arbejdsliv.

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Appendix 1 – Search strategies

Pubmed: Psychosocial working conditions and depression

("psychosocial stress*" OR "occupational stress*" OR "job stress*" OR "work stress*" OR "workload" OR "work conditions" OR "job conditions" OR "working hours" OR "working time" OR "psychosocial work*" OR "psychosocial job*" OR "psychosocial factor*" OR "effort reward" OR "emotional demands" OR "job strain" OR "job security" OR "job insecurity" OR "psychological demands" OR "job control" OR "justice" OR "injustice" OR "demand control" OR "work event*" OR "bullying" OR "mobbing") AND ("depression" OR "depressive" OR "mood disorder*" OR "affective disorder*") AND "english"[Language] AND "journal article"[Publication Type] AND (Humans[MeSH])

Pubmed: cortisol and depression

(cortisol* OR HPA* OR hypothalamic* OR hydrocortison* OR corticosteroid* OR cortison*) AND (prospective* OR longitudinal* OR "follow up" OR follow-up) AND ("depression" OR "depressive" OR "mood disorder*" OR "affective disorder*") AND "english"[Language] AND "journal article"[Publication Type] AND (Humans[MeSH])

PsychINFO: Psychosocial working conditions and depression

("psychosocial stress*" OR "occupational stress*" OR "job stress*" OR "work stress*" OR "workload" OR "work conditions" OR "job conditions" OR "working hours" OR "working time" OR "psychosocial work*" OR "psychosocial job*" OR "psychosocial factor*" OR "effort reward" OR "emotional demands" OR "job strain" OR "job security" OR "job insecurity" OR "psychological demands" OR "job control" OR "justice" OR "injustice" OR "demand control" OR "work event*" OR "bullying" OR "mobbing") AND ("depression" OR "depressive" OR "mood disorder*" OR "affective disorder*")

Scholarly journals, human subjects, English language, longitudinal studies

PsychINFO: Cortisol and depression

(cortisol* OR HPA* OR hypothalamic* OR hydrocortison* OR corticosteroid* OR cortison*) AND (prospective* OR longitudinal* OR "follow up" OR follow-up) AND ("depression" OR "depressive" OR "mood disorder*" OR "affective disorder*")

Scholarly journals, human subjects, English language, longitudinal studies

Embase: Psychosocial working conditions and depression

("psychosocial stress" OR "psychosocial stressor" OR "occupational stress" OR "occupational stressor" OR "job stress" OR "job stressor" OR "work stress" OR "work stressor" OR "workload" OR "work conditions" OR "job conditions" OR "working hours" OR "working time" OR "psychosocial work environment" OR "psychosocial job" OR "psychosocial factors" OR "effort reward" OR "emotional demands" OR "job strain" OR "job security" OR "job insecurity" OR "psychological demands" OR "job control" OR "justice" OR "injustice" OR "demand control" OR "work events" OR "bullying" OR "mobbing") AND ("depression" OR "depressive" OR "mood disorders" OR "affective disorders")

Map to preferred terminology (with spell check)
Include sub-terms/derivatives (explosion search)
Search terms must be of major focus in articles found
Embase + Medline
Humans
With abstract
Article
English

Embase: Cortisol and depression

(cortisol OR HPA OR hypothalamic OR hydrocortison OR corticosteroid OR cortison) AND (prospective OR longitudinal OR "follow up" OR follow-up) AND ("depression" OR "depressive" OR "mood disorders" OR "affective disorders")

Map to preferred terminology (with spell check)
Include sub-terms/derivatives (explosion search)
Search terms must be of major focus in articles found
Embase + Medline
Humans
With abstract
Article
English

Appendix 2 – Funnel plots

Figure 22: Funnel plot of all studies of **co-worker support**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 9 studies included [37;125;126;132;137;139;140;149;152].

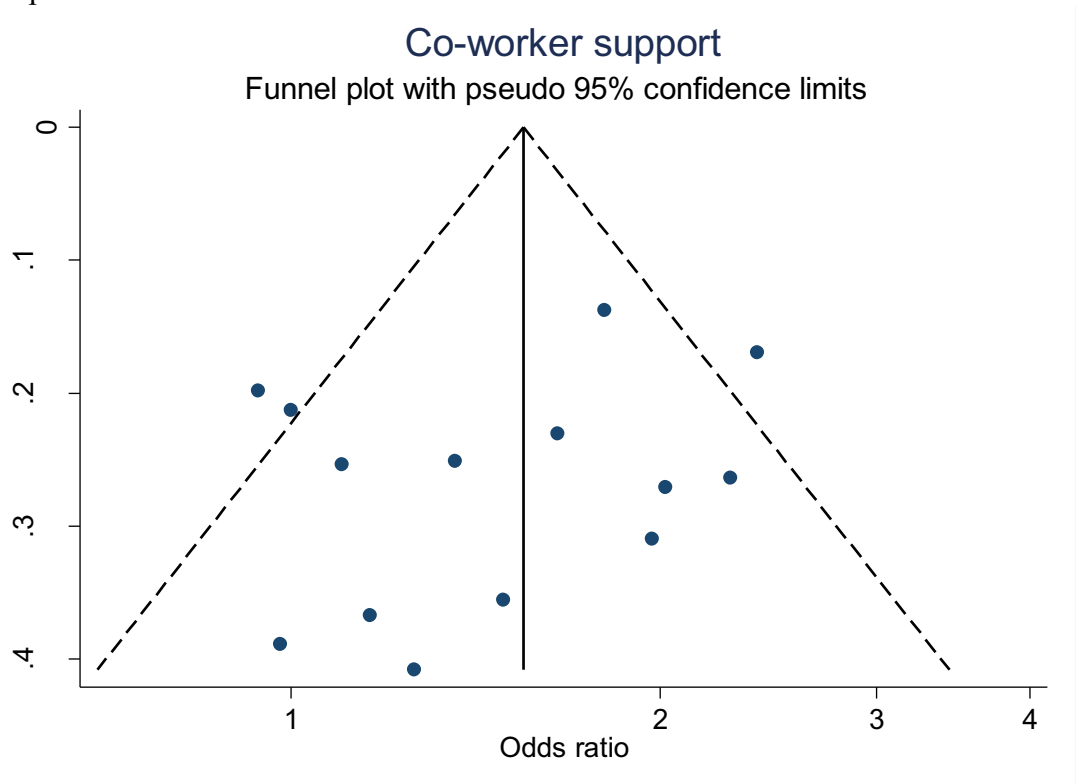


Figure 23: Funnel plot of all studies of **decision authority**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 3 studies included [35;125;140].

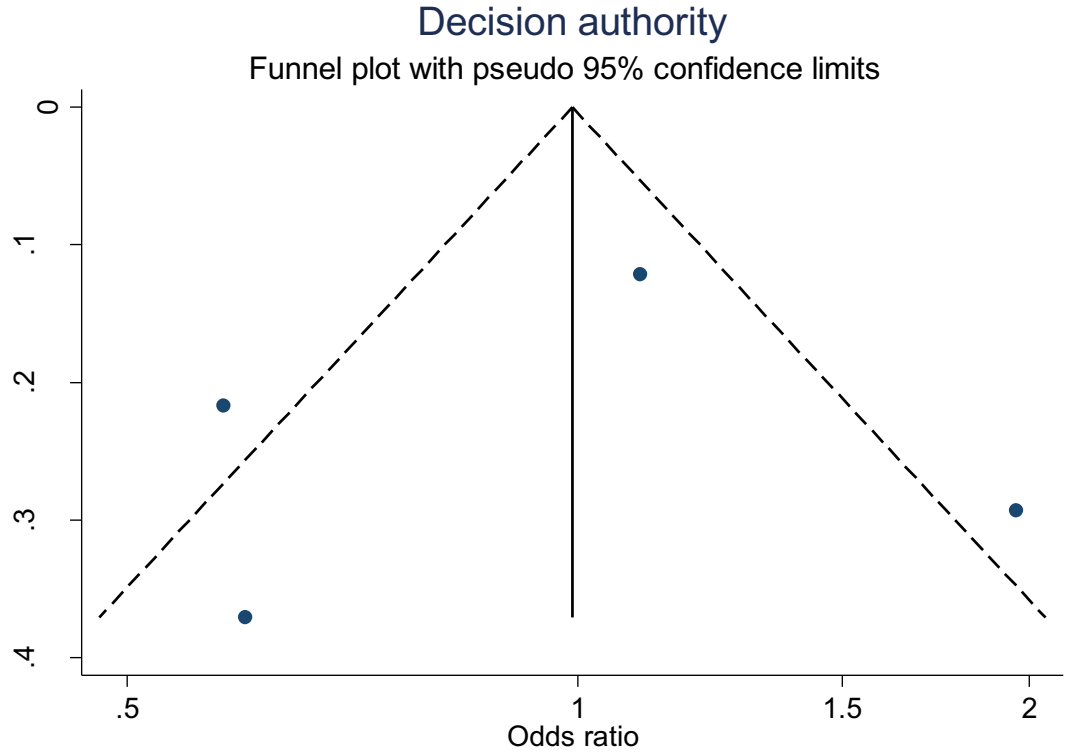


Figure 24: Funnel plot of all studies of **decision latitude**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 15 studies included [35;36;38;65;107;108;113;122;128-130;132;134;139;145].

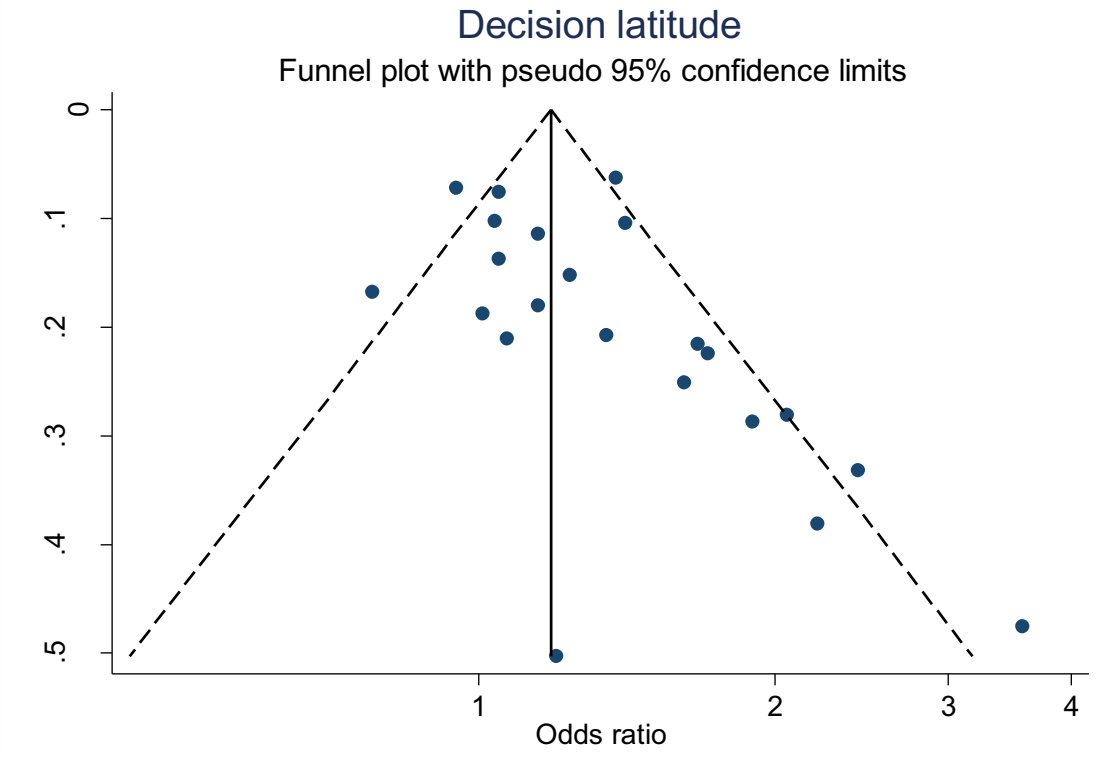


Figure 25: Funnel plot of all studies of **effort-reward imbalance**. The odds ratios are based on the highest available exposure group from each study with the lowest exposure group as reference. 3 studies included [56;121;152].

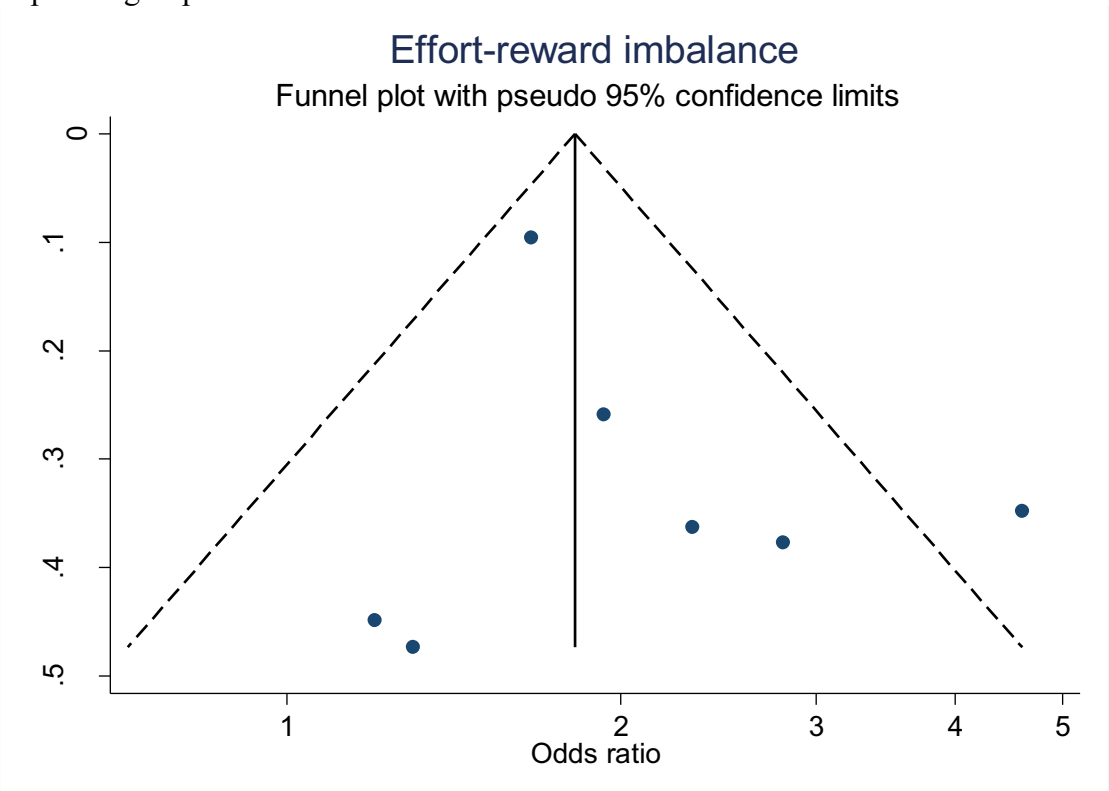


Figure 26: Funnel plot of all studies of **emotional demands**. The odds ratios are based on the available highest exposure group from each study with the lowest exposure group as reference. 4 studies included [38;54;132;149].

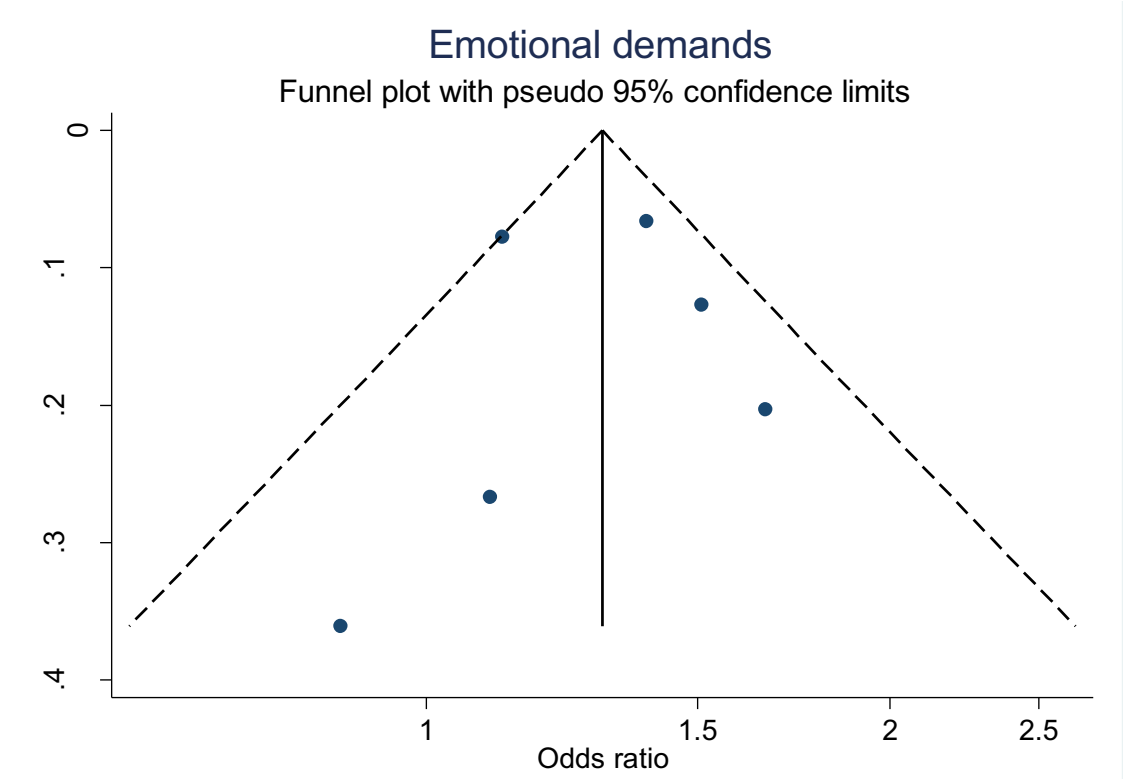


Figure 27: Funnel plot of all studies of **job insecurity**. The odds ratios are based on the highest available exposure group from each study with the lowest exposure group as reference. 7 studies included [50;109;125;129;132;139;152].

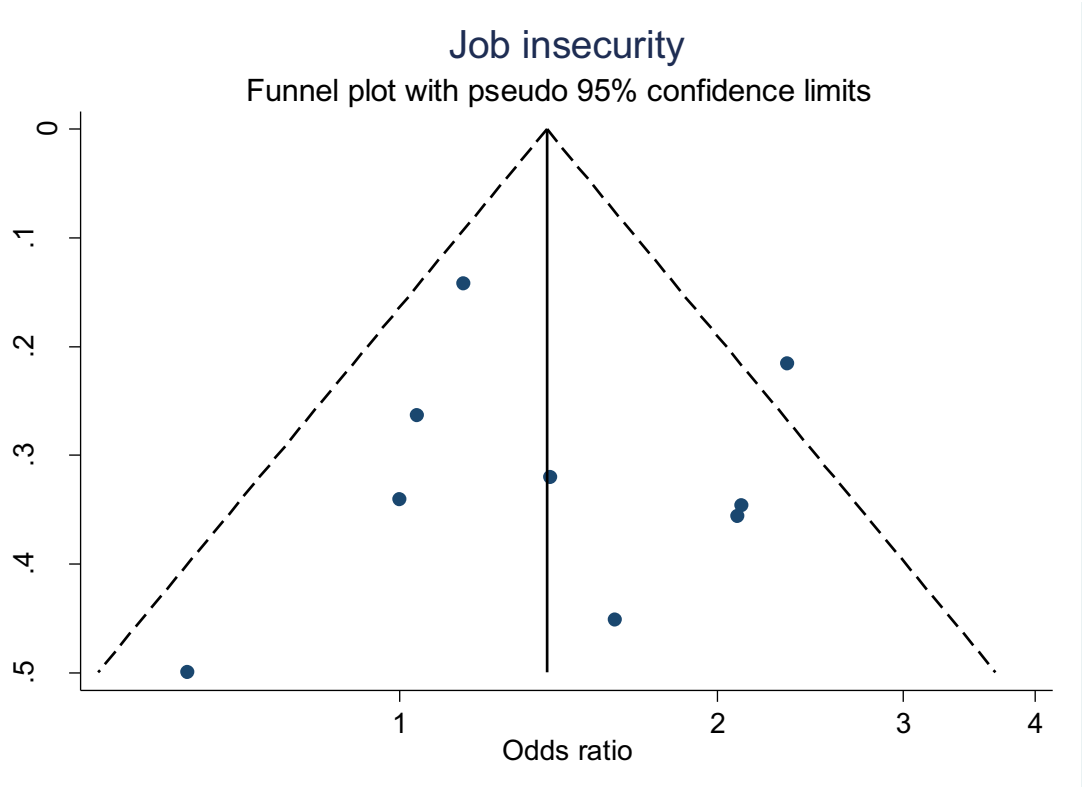


Figure 28: Funnel plot of all studies of **job strain**. The odds ratios are based on the highest available exposure group from each study with the lowest exposure group as reference. 15 studies included [35;37;38;66;109;110;122;126-128;130;138;139;145;152].

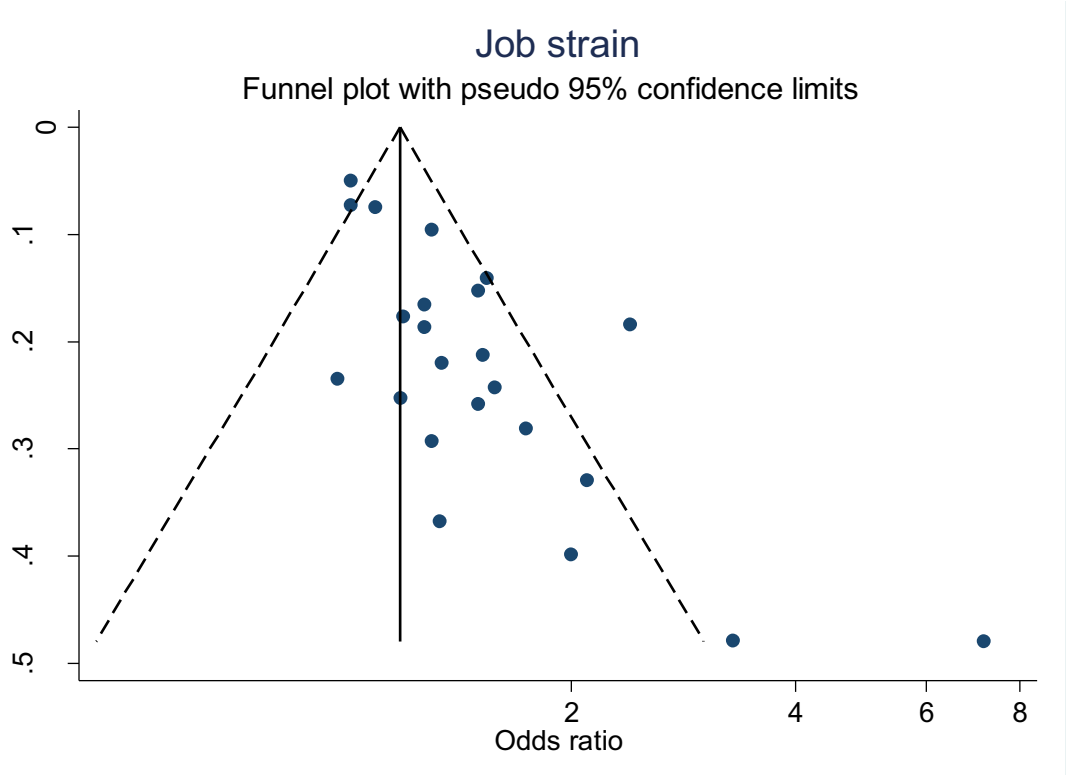


Figure 29: Funnel plot of all studies of **procedural justice**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 2 studies included [56;122].

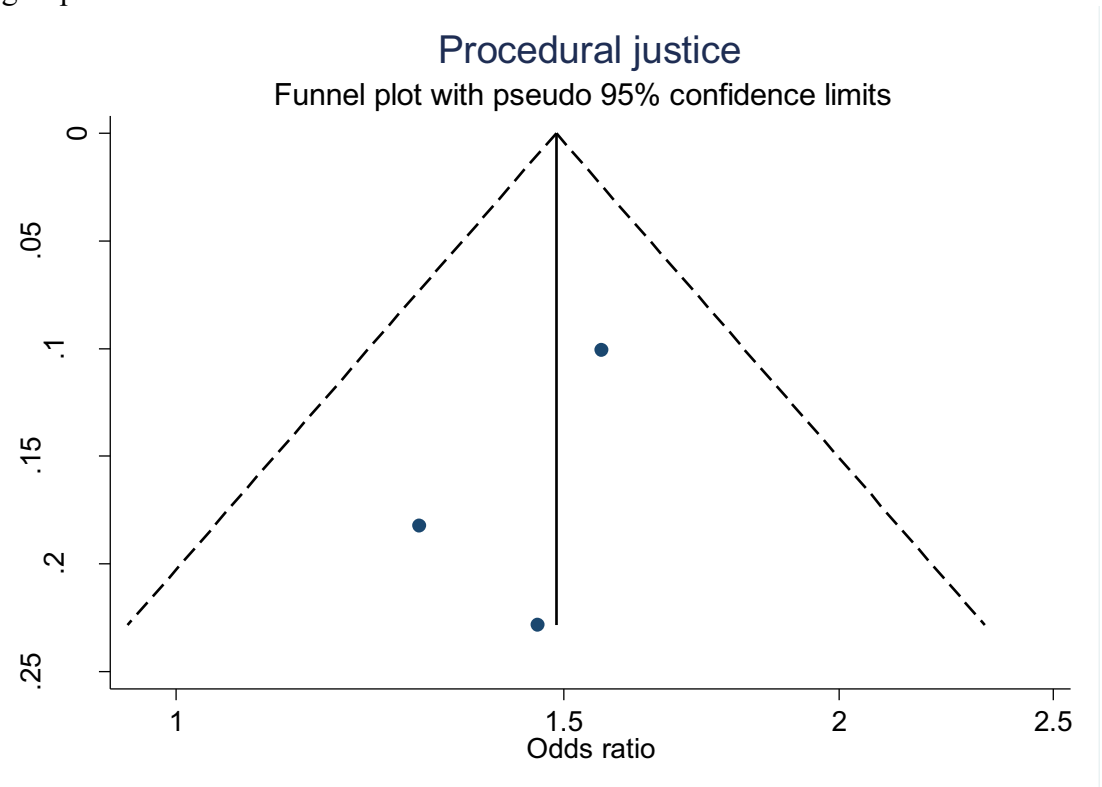


Figure 30: Funnel plot of all studies of **psychological demands**. The odds ratios are based on the highest available exposure group from each study with the lowest exposure group as reference. 14 studies included [35;36;38;65;108;122;125;128-130;132;134;139;145].

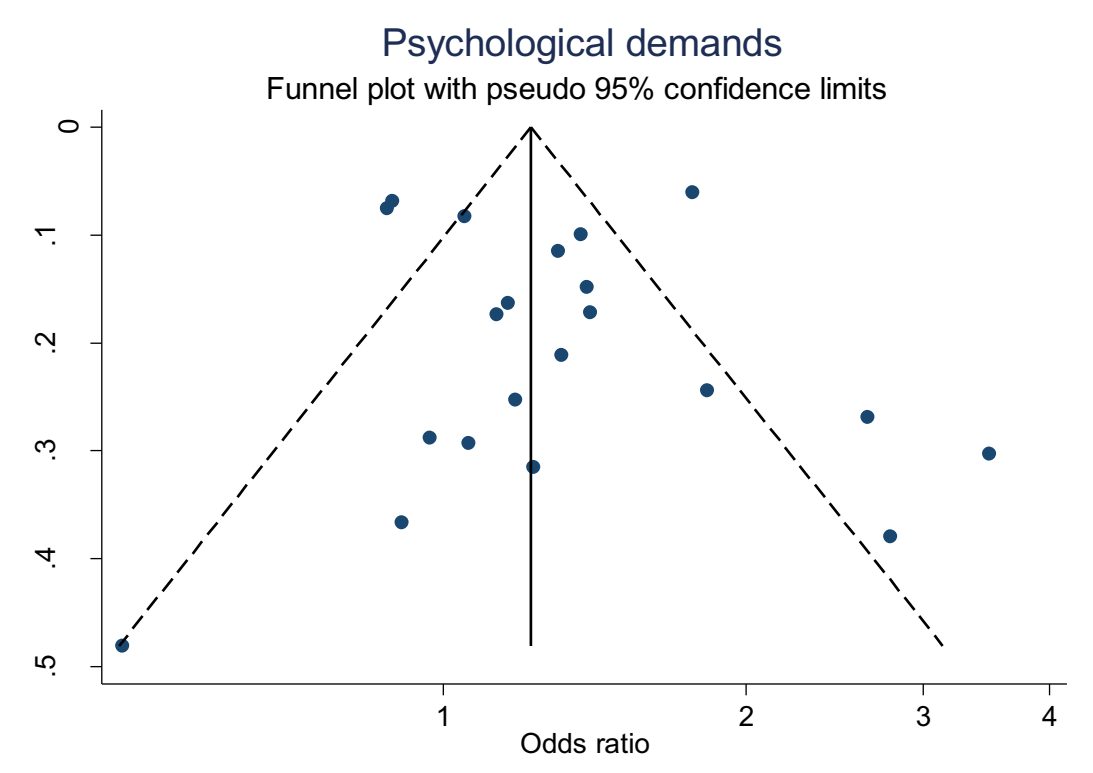


Figure 31: Funnel plot of all studies of **relational justice**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 2 studies included [56;122].

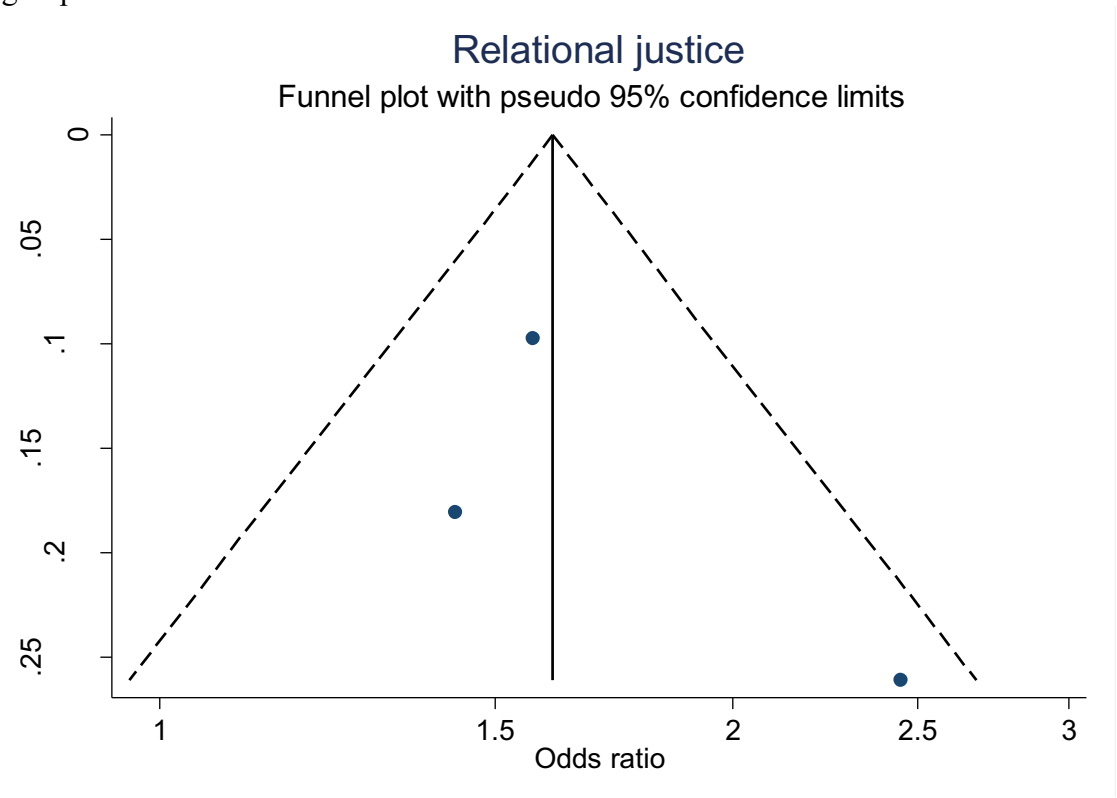


Figure 32: Funnel plot of all studies of **skill discretion**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 3 studies included [35;125;140].

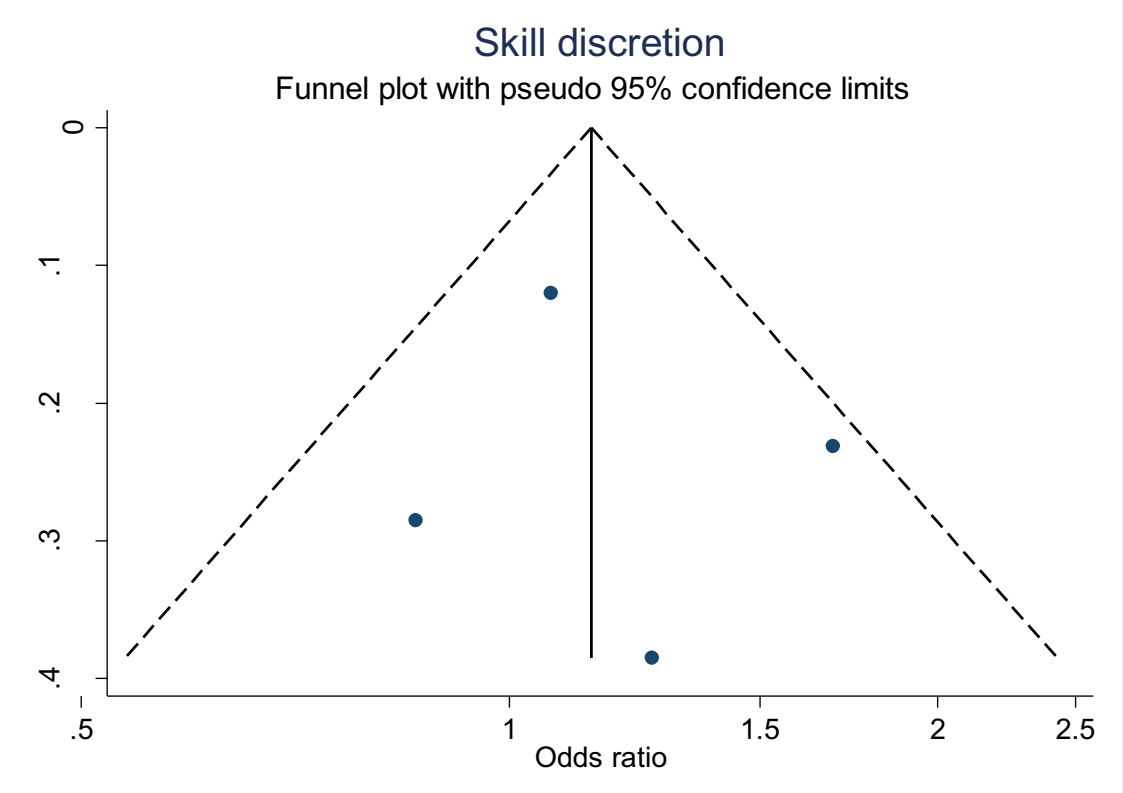


Figure 33: Funnel plot of all studies of **social support**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 8 studies included [35;65;108;117;128;129;132;134].

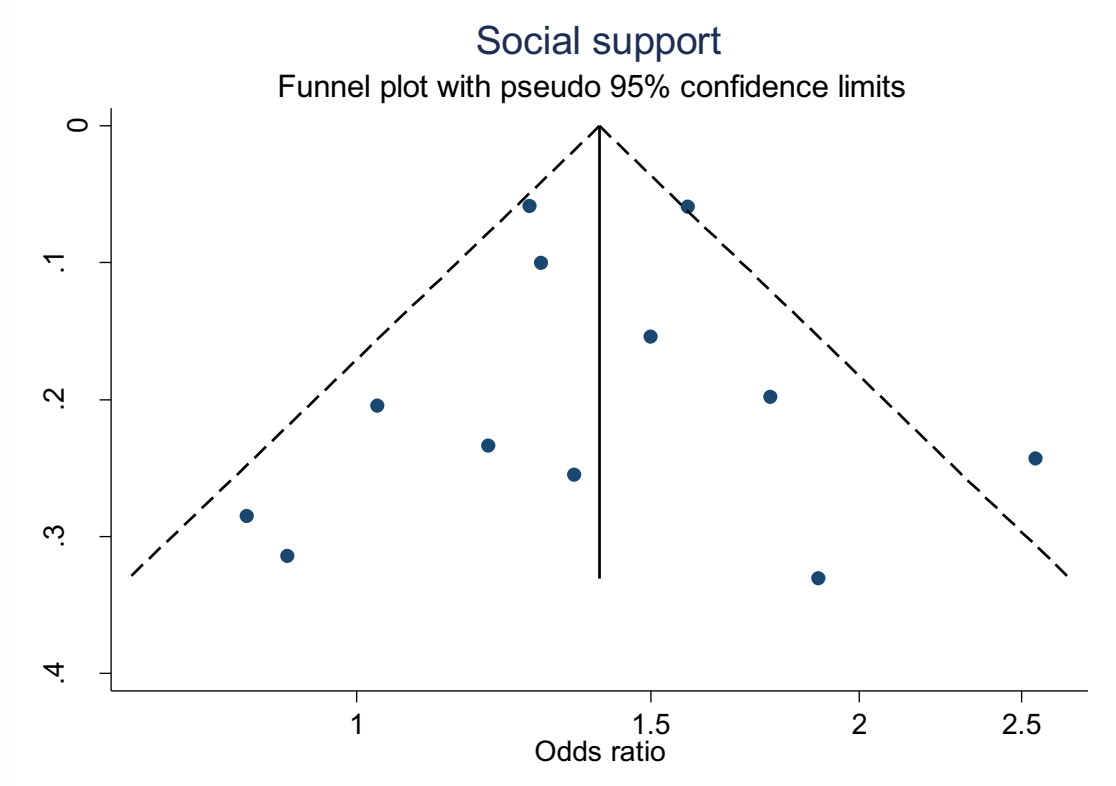


Figure 34: Funnel plot of all studies of **supervisor support**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 10 studies included [37;109;125;126;132;137;139;140;149;152].

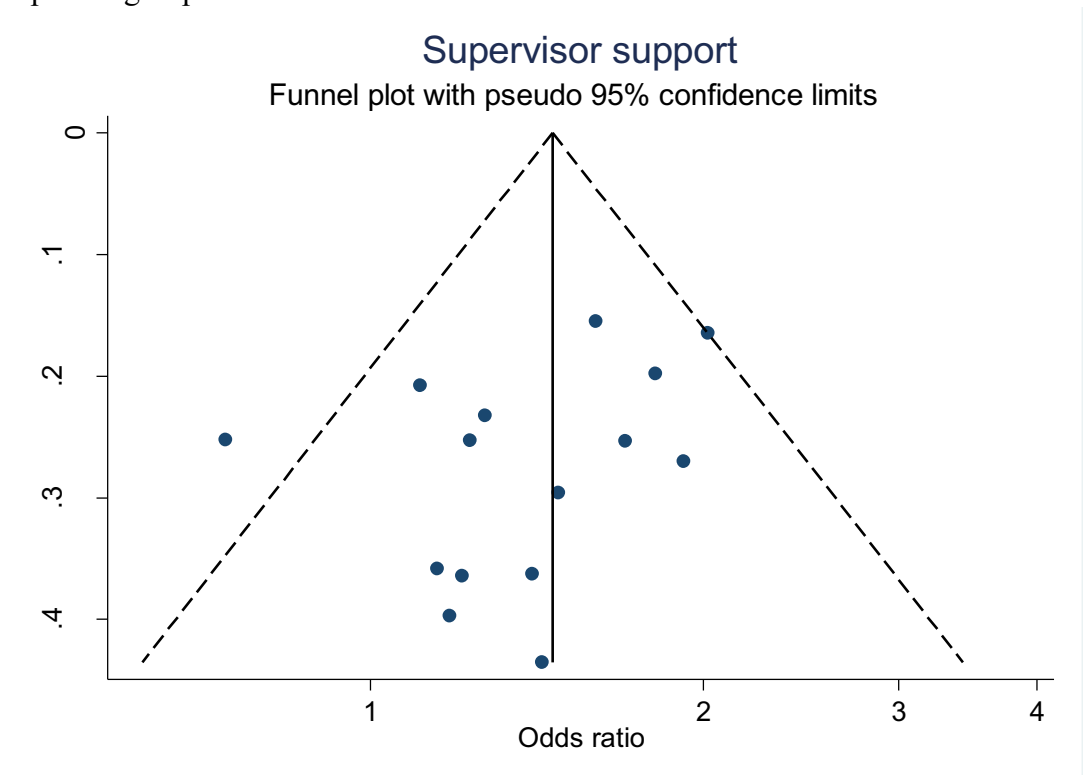


Figure 35: Funnel plot of all studies of **work climate**. The odds ratios are based on the lowest available exposure group from each study with the highest exposure group as reference. 4 studies included [35;53;122;136].

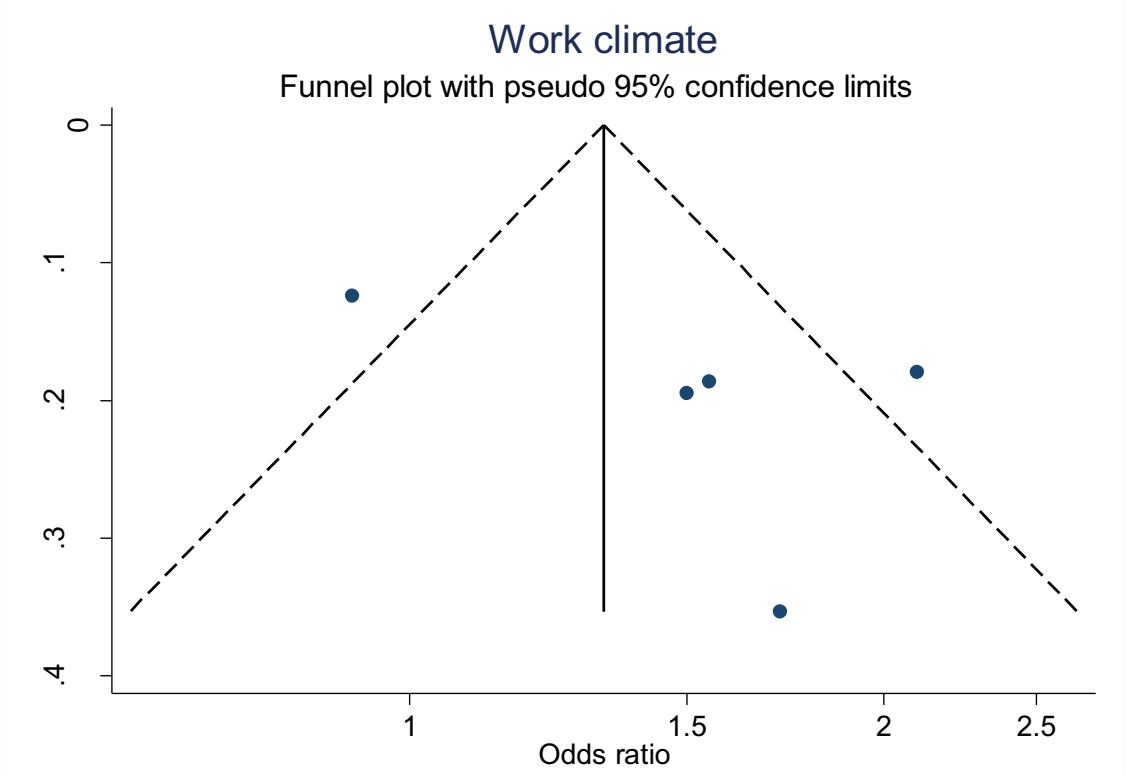


Figure 36: Funnel plot of all studies of **work load**. The odds ratios are based on the highest available exposure group from each study with the lowest exposure group as reference. 6 studies included [35;68;69;107;117;149].

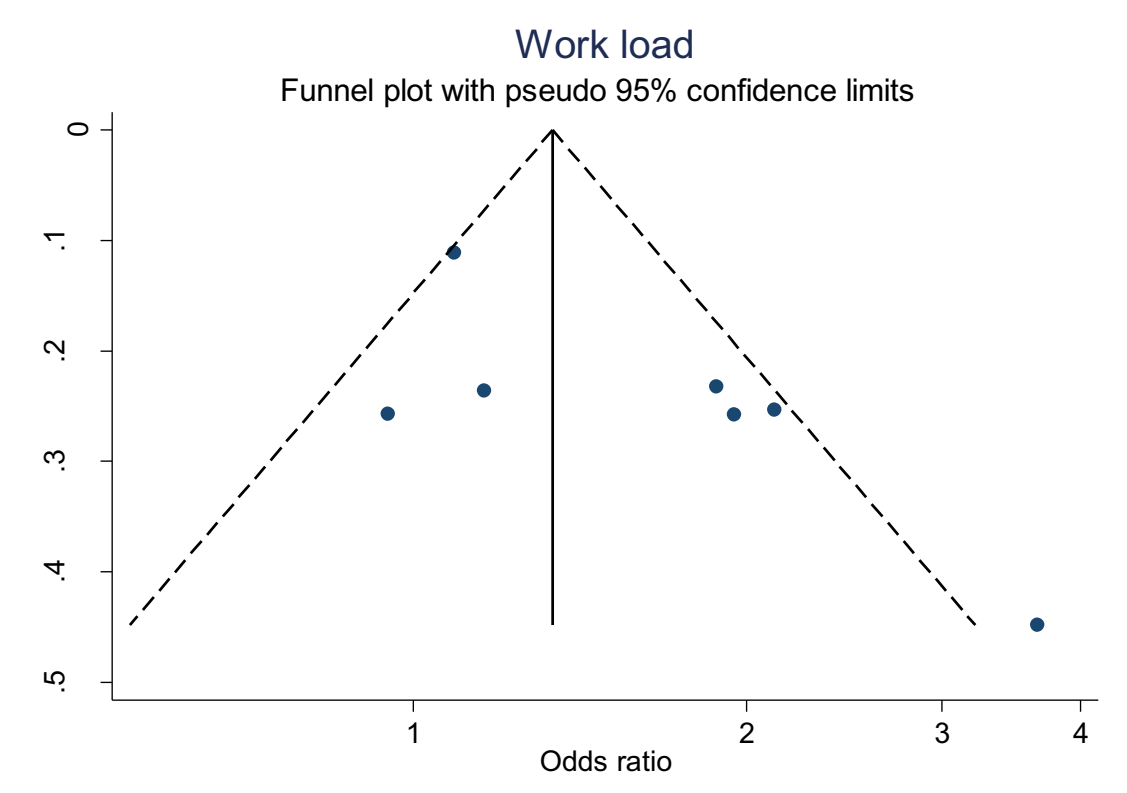


Figure 37: Funnel plot of all studies of **working hours**. The odds ratios are based on the highest available exposure group from each study with the lowest exposure group as reference. 7 studies included [52;63;109;117;132;145;152].

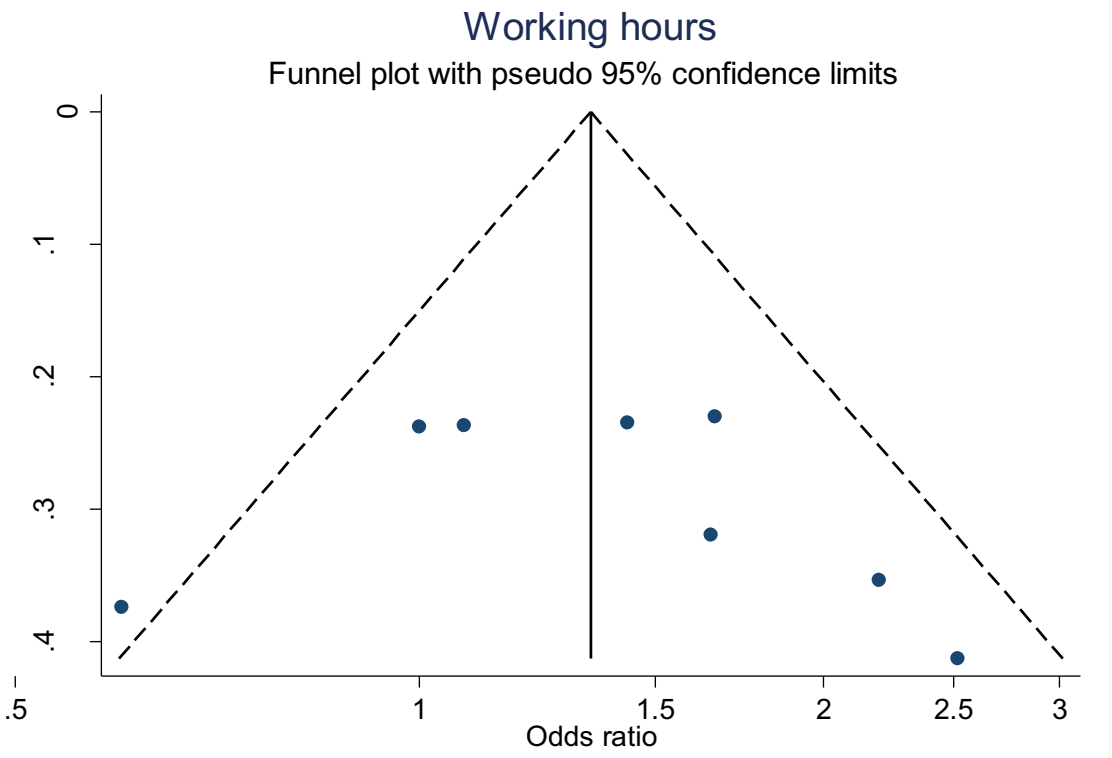
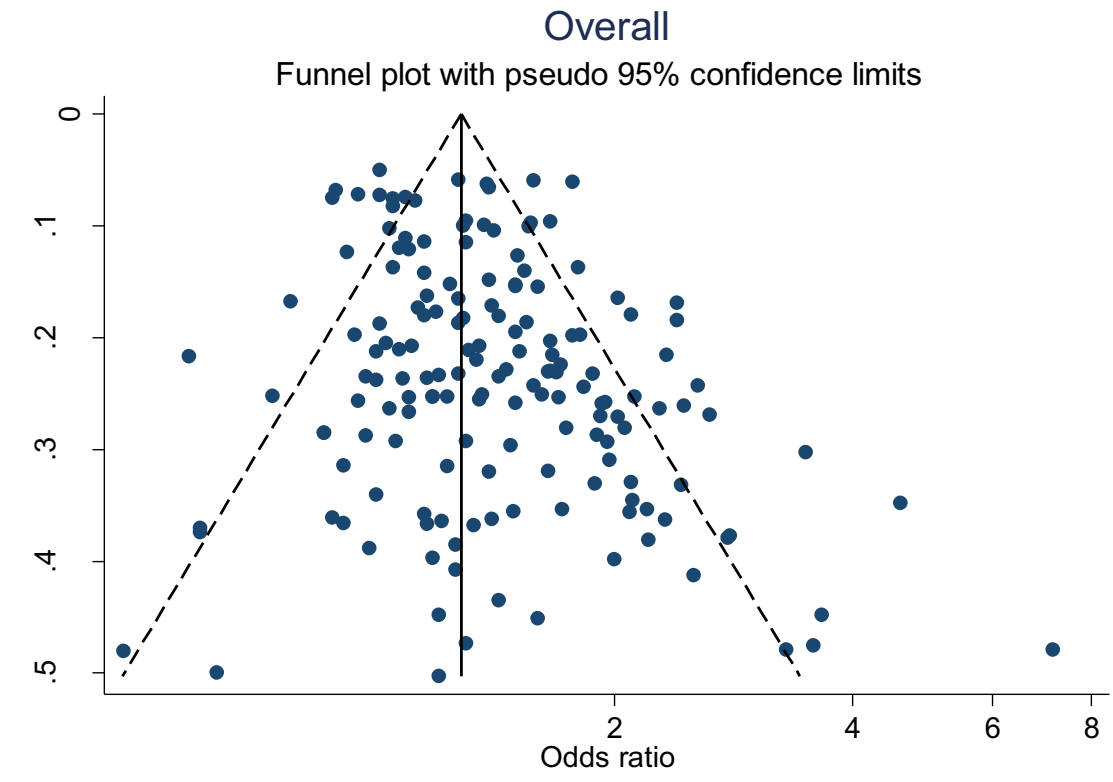


Figure 38: Funnel plot of **all studies** of the psychosocial working environment. 38 studies included [35-38;50;52-54;56;63;65;66;68;69;107-110;113;117;121;122;125-130;132;134;136-140;145;149;152].



Original article

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A two-year follow-up study of risk of depression according to work-unit measures of psychological demands and decision latitude

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Objectives The aim of this study was to examine if high psychological demands and low decision latitude at work increase the risk of depression.

Methods In 2007, 4237 non-depressed Danish public employees within 378 different work units were enrolled in the study. Mean levels of psychological demands and decision latitude were computed for each work unit to obtain exposure measures that were robust to reporting bias. In 2009, 3046 (72%) participated at follow-up, and those reporting high levels of depressive, burnout or stress symptoms went through a psychiatric interview by which 58 cases of new onset depression were diagnosed. Odds ratios (OR) of depression for different levels of work unit mean psychological demands and decision latitude were estimated by logistic regression taking established risk factors into account.

Results The OR for depression according to psychological demands was 1.07 [95% confidence interval (95% CI) 0.42–2.49] for every unit of change on a 5-point scale. The corresponding OR for decision latitude was 1.85 (95% CI 0.55–6.26). No interactive effects of psychological demands and decision latitude were observed.

Conclusion These findings suggest that low decision latitude may predict depression, but confidence intervals are wide and findings are also compatible with no increased risk.

Key terms epidemiology; mental health; occupational health; stress; work environment.

Depression is a mental disorder characterized by depressed mood, loss of interest, and decreased energy accompanied by other symptoms such as loss of self-esteem (1) and is currently the leading burden of disease assessed by disability-adjusted life years in middle and high-income countries (2).

Several prospective studies have indicated that the risk of depression is influenced by psychosocial working conditions, most frequently characterized by Karasek & Theorell's job strain model based upon perceived psychological demands and decision latitude (3–5). Psychological demands cover role conflicts, workload, and time pressure, whereas decision latitude covers the degree of the employee's work activity control and the ability to utilize specific skills at work. The model predicts that mental strain is the result of the interaction of high psychological demands and low decision latitude (6).

Most previous studies have depended on self-reported exposure information and are thus subject to reporting bias, because depressed mood may affect the individual's perception and reporting of the work environment. This is relevant even in follow-up studies, because depression often has a long insidious preclinical

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stage (4, 7, 8). Personality, temperament, and attitude to work may also be important causes of reporting bias. The majority of the previous studies have focused on the individual's perception of the psychosocial working environment (3–5). Such experiences are expected to be important elements of the causal pathway between job strain and depression (4, 9) but may not provide an unbiased description of the work environment (10).

Non-self-reported measures of psychosocial working conditions are probably the only option to circumvent the serious problem of reporting bias (7, 8, 11). Measures such as registry information on hospital overcrowding, reorganization, and workload (12–14), expert assessment (10, 15), employer assessment (16), job title (17), and averaging across work units (8, 18, 19) or workplaces (20) are different approaches to this problem.

To identify preventable, environmental, and psychosocial risk factors affecting the majority of the workforce, measures of agreed-upon exposure are needed (21). This may be obtained by aggregated measures among workers with similar psychosocial working conditions (8).

Work-unit aggregated measures of psychosocial work characteristics have several advantages. First, the inherent and uncontrollable ties between individual self reports of exposure and outcome are broken and reporting bias is circumvented (7, 8, 11). Second, these measures are independent of a specific, individual workers' appraisal of his or her working conditions but reflects an average workers' psychological processing that is not accounted for by registry information on organizational conditions or external assessment of work tasks (22). Third, such estimates of exposure can be provided also for non-respondents from measured work units (23). A disadvantage is that work-unit aggregation will reduce exposure contrast as well as statistical power (24). The method has also been discussed controversially (25).

In the present study, we used work unit mean scores of self-reported demands and decision latitude to avoid reporting bias as a potential explanation of a positive association with depression. Participants in the work unit who were diagnosed with depression at baseline were excluded from the calculation of the mean scores as this could influence their assessment of the psychosocial work environment. We also excluded participants diagnosed with depression at follow-up because they could have preclinical depressive symptoms that could influence their assessment of working conditions. By including only non-depressed participants throughout the study, we avoid any reporting bias caused by depression.

The objective of this follow-up study was to examine if high psychological demands and low decision latitude increase the risk of depression.

Methods

Design

This follow-up study is based on the Danish PRISME cohort established in 2007 and re-examined in 2009 (8). The main purpose of the PRISME study is to examine to what extent psychological work factors affect the risk of depression, burnout and stress symptoms. The study examines the relation between decision latitude and psychological demands measured in 2007 and depression during follow-up from 2007–2009. Cases of depression were identified by a two-step procedure: Firstly, we identified participants reporting mental symptoms (depressive, stress, or burn-out symptoms) in a questionnaire. Secondly, these participants were invited to participate in a standardized psychiatric interview identifying cases of depression based on criteria from the ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research (ICD-10-DCR).

Population

In 2007, the Danish PRISME cohort of 10 036 public employees from 502 small work units in Aarhus, Denmark, was recruited for the baseline study, and 4489 employees (44.7%) from 474 work units participated by filling in a postal questionnaire concerning working conditions and health. At baseline, we identified 100 participants with depression (as defined later). In 2009, all participants from 2007 were approached again, and a total of 3224 completed the questionnaire. We identified 78 cases of depression, of which 63 were non-depressed at baseline.

Participants with mild, moderate, and severe depression present at baseline (N=100) were excluded from the study. We also excluded five participants from five work units, for which we could not identify the work unit leader as well as participants from work units with less than three responders who were non-depressed at both baseline and follow-up (147 workers from 90 work units) to avoid very unstable work unit measures of exposure. The average participation rate in the included work units was 71% ranging from 17–100%. A total of 4237 participants from 378 work units were eligible for follow-up. In 2009, 3046 of these workers from 376 work units participated and thus comprised our final study population. Further details of design and baseline population have recently been reported in more detail (8).

Measures of psychosocial working conditions

Psychosocial working conditions were measured in 2007 according to Karasek' & Theorell's job strain model (6) with scales from the Copenhagen Psychosocial

Questionnaire (26). Psychological demands, decision authority, and skill discretion were each measured by four items on a scale from "always" (1) to "never" (5). For each scale, a mean value of the four items was calculated. Decision latitude was computed as the mean value of decision authority and skill discretion. The items are listed in figure 1.

Mean values of decision latitude and psychological demands were calculated for each of the 376 work units after the exclusion of participants with depression at baseline or at follow-up. The mean values were assigned to all employees in a particular work unit.

Measures of mental symptoms

Depressive symptoms were measured with the Common Mental Disorder Questionnaire (CMDQ), which is a brief case-finding instrument (27). The questionnaire has shown a high external validity when using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) standardized psychiatric interview as the gold standard (27). We used the six-question subscale for depression from the CMDQ. The questions referred to the last 4 weeks and were measured on a 5-point response scale from "not at all" to "extremely". Questions were phrased eg, as: "During the last four weeks how much were you bothered by feelings of worthlessness." Stress symptoms were measured with four questions from the short version of the Perceived Stress Scale (28). Burn-out scores were measured with six questions from the Copenhagen Burn-Out Inventory (29). All symptom questions concerned the last four weeks and were measured on point scales from "not at all" or "never" (1) to "extremely", "very often", or "always" (5).

At baseline, we selected participants with (i) a score ≥3 on ≥3 of the 6 depressive symptom questions, (ii) the highest average score (≥2.5) on the perceived stress questions, and (iii) the highest burn-out score (≥4) for the standardized psychiatric interview.

At follow-up, we chose selection criteria for the standardized psychiatric interviews based on tabulation of the frequency of ICD-10-DCR depression by different cut-off levels of depressive, stress, and burn-out scores in the 2007 data to identify the largest possible number of depressive cases with the lowest number of interviews (a high positive predictive value). We selected participants with a high symptom score on ≥2 of the 3 mental symptom scales at follow-up (depression, stress, or burn-out). A high score on the depression scale was defined as a score of ≥3.0 on ≥2 items; a high stress score was defined as a mean score of ≥2.5; and a high burn-out score was defined as a mean score of ≥2.5.

Diagnosis of depression

Diagnoses of depression were obtained by the SCAN interview (version 2.1 part I) (30) according to the ICD-10-DCR criteria for research. The sections regarding depressive (6, 7, and 8) and bipolar (10) disorders were used. The interviews referred to the previous three months. The interviews were conducted by ten students of medicine or psychology trained at a one-week course conducted by a WHO certified trainer (OM). Inter-rater reliability on item level was found to be satisfactory (κ=0.71).

Participants diagnosed with depression

In 2007, we invited 715 workers to participate in the SCAN interview; 552 participated and 100 (2.2% of all participants at baseline) were diagnosed with depression. In 2009, we invited 671 workers to participate in the SCAN interview; 426 participated and a total of 78 were diagnosed with depression (2.4% of all participants at follow-up). Of these, 15 participants were excluded because they were also diagnosed with depression at baseline. Furthermore, five participants were excluded because they were employed in a work unit with <3 non-depressed employees or had no identifiable leader as described previously. These exclusions left 58 cases of depression for the analyses. In 2007, 40, 43, and 17 participants fulfilled the ICD-10-DCR diagnostic criteria for a mild, moderate, and severe depressive episode,

Psychological demands
- Is your workload unevenly distributed so it piles up?
- How often do you not have time to complete all your work tasks?
- Do you get behind in your work?
- Do you have enough time for your work tasks?

Decision latitude (decision authority)
- Do you have a large degree of influence concerning your work?
- Do you have a say in choosing with whom you work?
- Can you influence the amount of work assigned to you?
- Do you have any influence on what you do at work?

Decision latitude (skill discretion)
- Does your work require you to take the initiative?
- Do you have the possibility of learning new things through your work?
- Can you use your skills or expertise in your work?
- Does your work give you the opportunity to develop your skills?

Figure 1. Items measuring the level of psychological demands and decision latitude.

respectively, and 15, 32, and 11 fulfilled the criteria in 2009. No participants fulfilled the criteria for bipolar disorder in either 2007 or 2009.

Measures of potential confounders

The following potential confounders were measured based on data from the baseline questionnaire: gender, age (≤34, 35–44, 45–54, ≥55 years), previous episodes of depression (yes, no), family history of depression (yes, no), income (continuous), education beyond primary or high school (<3, 3–4, >4 years), full-time work (<30, ≥30 hours per week), alcohol consumption (≤14, >14 grams per week), living alone (yes, no), neuroticism (0–2, 3–6 on the neuroticism scale of the Eysenck Personality Questionnaire Revised-Abbreviated version) (31), depressive symptoms (rating of ≥3 on <2, ≥2 questions from the CMDQ) (27), body mass index (<18.5, 18.5–25, >25 kg/m^2), and smoking (never, <20 years, ≥20 years). Traumatic life events (32) during the last six months were measured at follow-up. A traumatic life event was defined as serious illness, serious injury, being assaulted, death of a relative or friend, marital problems, or serious illness, serious injury or assault of a close relative. The selection of these potential confounders was based upon a review of the literature (33–37).

Participation

Responders and non-responders at baseline were compared in a previous study (23). Work-unit average levels of psychological demands and decision latitude were assigned to responders and non-responders of every work unit. Outcome data on prescription of antidepressant medication were available through linkage to national registers. Non-participants (4.1%) were more often prescribed antidepressant medication than participants (3.4%). We found no clear indications that the low baseline participation had distorted our estimates of the associations between psychological demands, decision latitude and depression. The relative hazard ratios for use of antidepressant medication in the high psychological demands groups were 1.17 [95% confidence interval (95% CI) 0.90–1.53] for the participant population compared to the source population. The relative hazard ratios were 1.36 (95% CI 0.89–2.08) for decision latitude.

Participation at follow up was associated with older age, educational, income, alcohol consumption, and work-unit average decision latitude (table 1).

Statistical analysis

Odds ratios (OR) of depression were analyzed by logistic regression with robust clusters based on the work unit of the participants which included all the selected potential confounders (38). Analyses were performed using both continuous-scale exposure information and exposure divided into tertiles forming a low-, medium-, and high-exposure group. The data were analyzed for interaction between psychological demands and decision latitude. The interaction term was calculated based on both continuous and dichotomous data. The cut-off level for the dichotomization was the median level (psycho-

Table 1. Baseline characteristics at follow-up. [BMI=body mass index; CMDQ=common mental disorder questionnaire; OR=odds ratio; 95% CI=95% confidence interval]

Characteristic	Participant at follow-up (N=3046)	%	Non-participant at follow-up (N=1232)	%	OR	95% CI
Psychological demands						
Low	1010	33.2	410	33.3	1	
Medium	1002	32.9	383	31.1	1.06	0.90–1.25
High	1034	34.0	439	35.6	0.96	0.81–1.12
Decision latitude						
High	1045	34.3	369	30.0	1	
Medium	957	31.4	421	34.2	0.80	0.68–0.95
Low	1044	34.3	442	35.9	0.83	0.71–0.98
Women	2392	78.9	959	79.6	0.96	0.81–1.13
Age						
<35 years	602	19.9	336	27.9	1	
35–44 years	728	24.0	316	26.2	1.29	1.07–1.55
45–54 years	1096	36.2	369	30.6	1.66	1.39–1.98
≥55 years	605	20.0	184	15.3	1.84	1.48–2.27
Previous depression	382	13.0	177	15.1	1.20	0.99–1.45
Family history of depression	806	27.0	312	26.4	1.00	0.86–1.17
Education beyond primary or high school						
<3 years	509	16.9	308	25.7	1	
3–4 years	2147	71.1	782	65.2	1.66	1.41–1.96
>4 years	365	12.1	110	9.2	2.01	1.55–2.59
Household income >500 000 DKr	1482	50.9	499	43.5	1.35	1.17–1.54
Alcohol consumption >14 grams/week	725	24.2	237	20.0	1.28	1.08–1.51
Living alone	564	18.6	239	19.9	0.92	0.78–1.09
Full-time work	2581	91.8	1011	91.7	1.00	0.78–1.29
Neuroticism personality trait [a]	450	14.9	204	16.9	0.86	0.71–1.03
CMDQ depressive symptoms [b]	272	9.0	118	9.9	0.90	0.72–1.13
Smoking						
Never smoked	1446	52.6	524	49.0	1	
0–19 years	633	23.0	270	25.2	0.85	0.71–1.01
≥20 years	672	24.4	276	25.8	0.88	0.74–1.05
BMI (kg/m^2)						
<18.5	53	1.8	21	184	0.99	0.59–1.65
18.5–25	1918	63.9	751	63.4	1	
>25	1030	34.3	413	34.9	0.98	0.85–1.13

[a] Dichotomized score based on neuroticism scale from Eysenck Personality Questionnaire Revised (31).

[b] A screening instrument designed for case finding (27).

logical demands, 2.8, and decision latitude, 2.5). Linearity of the relation between the exposure variables and depression was examined by logistic regression models including quadratic and cubic terms and by locally weighted scatter plot smoothing (39). The associations were further explored using regression analysis with restricted cubic splines due to the non-linear relation between the two. We used four knots defined by the percentiles 5, 35, 65, and 95. The spline analyses were adjusted for previous depression, traumatic life events, depressive symptoms, and neuroticism. We determined these covariates by log likelihood testing and stepwise exclusion of non-significant terms (P>0.05), starting with the least significant potential confounder. All analyses were conducted using the STATA 11 statistical software (StataCorp LP, College Station, TX, USA).

Results

Nurses (30%), social workers (18%), teachers (11%), managers (7%), and medical doctors (6%) were the most prevalent professions among the participants. Members of work units with high psychological demands had less frequently a family history of depression, were more educated, and had more depressive symptoms at baseline than members of work units with low psychological demands. Members of work units with low decision latitude were more often women, had less frequently a family history of depression, were less educated, had smaller household incomes, consumed less alcohol, and reported neuroticism and depressive symptoms more frequently at baseline than members of work units with high decision latitude

Table 2. Baseline characteristics of public employees with low, medium or high levels of psychological demands and decision latitude. [BMI=body mass index; CMDQ=common mental disorder questionnaire]

Characteristic	Psychological demands						Decision latitude					
	Low 1.70–2.66		Medium 2.67–2.99		High 3.00–4.06		High 1.73–2.37		Medium 2.38–2.62		Low 2.63–3.72	
	N	%	N	%	N	%	N	%	N	%	N	%
Women	789	78.8	786	78.8	871	79.2	681	72.8	849	80.3	862	83.0
Age												
<35 years	163	16.3	230	23.1	209	20.3	151	16.1	213	20.2	238	22.9
35–44 years	249	24.9	247	24.8	232	22.5	223	23.8	271	25.6	234	22.5
45–54 years	380	38.0	340	34.1	376	36.4	356	38.0	370	35.0	370	35.7
≥55 years	209	20.9	181	18.1	215	20.8	206	22.0	203	19.2	196	18.9
Previous depression	132	13.5	120	12.4	130	13.0	116	12.8	132	12.8	134	13.3
Family history of depression	281	28.6	267	27.1	258	25.4	267	29.0	280	26.9	259	25.4
Professional education beyond primary or high school												
<3 years	192	19.2	138	13.9	179	17.4	118	12.7	160	15.2	231	22.3
3–4 years	755	75.6	731	73.5	661	64.4	664	71.2	742	70.4	741	71.6
>4 years	52	5.2	126	12.7	187	18.2	150	16.1	152	14.4	63	6.1
Household income >500 000 DKr	460	48.3	502	52.2	520	52.2	533	58.9	536	53.1	413	41.5
Alcohol consumption >14 grams/week	247	25.0	234	23.8	244	23.8	271	29.2	236	22.7	218	21.2
Traumatic life event during last six months [a]	347	34.4	308	30.7	327	31.6	317	33.7	324	30.5	341	32.7
Living alone	179	17.9	186	18.6	199	19.3	170	18.2	204	19.3	190	18.3
Full-time work	833	90.1	852	92.3	896	92.9	769	89.9	902	92.4	910	92.7
Neuroticism personality trait [b]	152	15.2	129	12.9	169	16.4	105	11.2	161	15.2	184	17.7
CMDQ depressive symptoms [c]	82	8.2	91	9.2	99	9.6	70	7.5	107	10.2	95	9.2
Smoking												
Never smoked	446	49.7	515	55.9	485	52.0	459	54.1	512	52.7	475	51.0
0–19 years	203	22.6	214	23.2	216	23.2	179	21.1	230	23.7	224	24.0
≥20 years	248	27.7	193	20.9	231	24.8	210	24.8	229	23.6	233	25.0
BMI (kg/m^2)												
<18.5	18	1.8	19	1.9	16	1.6	15	1.6	16	1.5	22	2.1
18.5–25	634	64.0	630	63.9	654	63.8	589	63.5	692	66.3	637	61.9
>25	338	34.1	337	34.2	355	34.6	324	34.9	336	32.2	370	36.0

[a] Serious illness, serious injury, being assaulted, death of a relative or friend, marital problems, or the serious illness, serious injury or assault of a close relative. Measured at follow-up.

[b] Dichotomized score based on neuroticism scale from Eysenck Personality Questionnaire Revised (31).

[c] A screening instrument designed for case finding (27).

(table 2). Previous depression, a family history of depression, neuroticism, smoking, and depressive symptoms reported at baseline, and traumatic life events reported at follow-up, were significantly associated with a diagnosis of depression at follow-up (table 3).

We observed no interaction between psychological demands and decision latitude (P=0.36 for dichotomous exposure variables and P=0.49 for continuous exposure variables). We analyzed psychological demands and decision latitude in separate models. We found a linear relation between the level of decision latitude and depression using both locally weighted scatter plot smoothing and log likelihood testing to exclude quadratic and cubic effects, and analyzed decision latitude as a continuous variable. The relation between the level of psychological demands and depression was not accepted as linear. The results are presented in table 4.

By log likelihood testing, we found no significant differences between the models used in the logistic regression (adjusted for age, gender, previous episodes of depression, family history of depression, educational level, income, alcohol consumption, traumatic life-events, living alone, depressive symptoms, smoking, body mass index, and neuroticism), and the partially adjusted models used in the spline analyses (adjusted for previous episodes of depression, traumatic life-events, depressive symptoms, smoking, and neuroticism) for neither psychological demands (P=0.96) nor decision latitude (P=0.96).

Psychological demands were not significantly associated with depression. The adjusted OR of the highest and the medium tertiles of psychological demands compared to the lowest tertile were 0.80 (95% CI 0.38–1.69) and 0.72 (95% CI 0.33–1.57), respectively.

For low decision latitude, we found an adjusted OR of 1.85 (95% CI 0.55–6.26) for a one point decrease on the five-point scale.

In separate analyses of the decision latitude subscales, decision authority and skill discretion, we found adjusted OR of depression of 1.58 (95% CI 0.71–3.53) and 1.23 (95% CI 0.32–4.67), respectively for a 1-point decrease on the 5-point scale (see table 5 on http://www.sjweh.fi/data_repository.php).

Figure 2 shows the results of the restricted cubic spline regression of the relation between increasing psychological demands and the OR of depression as well as the linear effect based on logistic regression on exposure measure. The figure shows no consistent trend in the depression OR by level of psychological demands.

Figure 3 shows the results of the restricted cubic spline and linear logistic regression analyses of the relation between increasing decision latitude and depression. The two analyses show a similar monotonous, but non-significant, increase in the depression OR by decreasing levels of decision latitude.

Table 3. Baseline characteristics of 3046 public employees with or without a diagnosis of depression at follow-up. [BMI=body mass index; CMDQ=common mental disorder questionnaire; OR=odds ratio; 95% CI=96% confidence interval]

Characteristic	No depression at follow-up (N=2988)	%	Depression at follow-up (N=58)	%	OR	95% CI
Women	2343	78.8	49	86.0	1.65	0.78–3.50
Age						
<35 years	590	19.8	12	21.1	1	
35–44 years	716	24.1	12	21.1	0.82	0.37–1.85
45–54 years	1073	36.1	23	40.3	1.05	0.52–2.13
≥55 years	595	20.0	10	17.5	0.83	0.35–1.93
Previous depression	358	12.4	24	44.4	5.67	3.28–9.80
Family history of depression	784	26.8	22	38.6	1.93	1.10–3.40
Education beyond primary or high school						
<3 years	499	16.8	10	17.5	1	
3–4 years	2104	71.0	43	75.4	1.02	0.51–2.04
>4 years	361	12.2	4	7.0	0.55	0.17–1.78
Household income >500 000 DKr	1462	51.2	20	37.7	0.58	0.33–1.01
Alcohol consumption >14 grams/week	712	24.2	13	22.8	0.93	0.50–1.73
Traumatic life event during last six months [a]	947	3178	35	60.3	3.28	1.93–5.58
Living alone	556	18.7	8	14.0	0.71	0.33–1.50
Full-time work	2533	91.8	48	88.9	0.71	0.30–1.69
Neuroticism personality trait [b]	427	14.4	23	40.4	4.04	2.35–6.92
CMDQ depressive symptoms [c]	253	8.5	19	33.3	5.36	3.04–9.44
Smoking						
Never smoked	1423	52.7	23	44.2	1	
0–19 years	624	23.1	9	17.3	0.89	0.41–1.94
≥20 years	652	24.2	20	38.5	1.90	1.03–3.48
BMI (kg/m^2)						
<18.5	51	1.7	2	3.6	2.17	0.51–9.29
18.5–25	1884	64.0	34	60.7	1	
>25	1010	34.3	20	35.7	1.10	0.63–1.92

[a] Serious illness, serious injury, being assaulted, death of a relative or friend, marital problems, or the serious illness, serious injury or assault of a close relative. Measured at follow-up.

[b] Dichotomized score based on neuroticism scale from Eysenck Personality Questionnaire Revised (31).

[c] A screening instrument designed for case finding (27).

As a sensitivity check, we analyzed incident cases (N=103) of questionnaire-reported physician-diagnosed depression occurring between baseline and follow up. We found an adjusted OR of depression of 0.75 (95% CI 0.41–1.36) for a 1-point increase on the psychological demands scale and an adjusted OR of 1.43 (95% CI 0.60–3.39) for a 1-point decrease on the decision latitude scale.

Table 4. Odds ratios (OR) of depression by increasing levels of psychological demands and decreasing levels of decision latitude. [95% CI=95% confidence interval; OR_{adj}=adjusted OR.]

Exposure	Depression (N=58)	No depression (N=2988)	OR	95% CI	OR_{adj} [a]	95% CI	OR_{adj} [b]	95% CI
Psychological demands								
Low (1.70–2.66)	26	984	1		1		1	
Medium (2.67–2.99)	15	987	0.58	0.30–1.09	0.72	0.33–1.57	0.76	0.36–1.61
High (3.00–4.06)	17	1017	0.63	0.34–1.17	0.80	0.38–1.69	0.78	0.37–1.62
Continuous [c]	58	2988	0.82	0.42–1.61	1.07	0.46–2.49	1.00	0.44–2.24
Decision latitude								
High (1.73–2.37)	14	926	1		1		1	
Medium (2.38–2.62)	22	1040	1.40	0.71–2.75	1.30	0.56–3.02	1.26	0.55–2.88
Low (2.63–3.72)	22	1022	1.42	0.72–2.80	1.65	0.72–3.74	1.71	0.77–3.79
Continuous [c]	58	2988	1.48	0.55–4.01	1.85	0.55–6.26	1.81	0.57–5.76

[a] Adjusted for age, gender, previous episodes of depression, family history of depression, educational level, income, alcohol consumption, traumatic life-events, living alone, depressive symptoms, smoking, body mass index, full-time work, and neuroticism.
[b] Adjusted for previous episodes of depression, traumatic life-events, depressive symptoms, and neuroticism.
[c] Increase in OR by 1 on the 5-point scale.

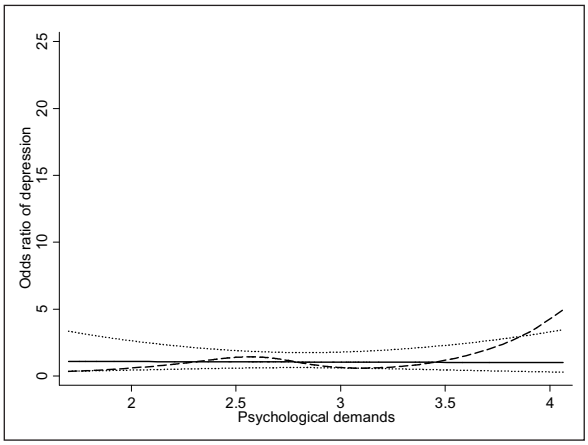

Figure 2. Psychological demands and adjusted odds ratio of depression. Results of a restricted cubic spline analysis (dashed line) and of logistic regression (solid line) with 95% confidence intervals (dotted lines) adjusted for previous depression, traumatic life events, baseline depressive symptoms, and neuroticism.

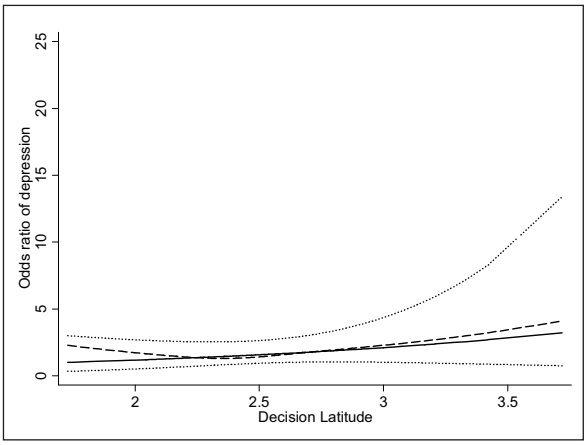

Figure 3. Decision latitude and adjusted odds ratio of depression. Results of a restricted cubic spline analysis (dashed line) and of logistic regression (solid line) with 95% confidence intervals (dotted lines) adjusted for previous depression, traumatic life events, baseline depressive symptoms, and neuroticism.

Discussion

We did not find any statistically significant relation between either work unit average levels of decision latitude or psychological demands and depression. We did, however, find a statistically non-significant relation between low levels of decision latitude and depression. This is an important finding because these measures of exposure were independent of the individual workers' interpretation of his or her psychological working conditions but represented a hypothetical average worker. Therefore, this study circumvented the serious problem of reporting bias due to low mood of depressed participants. Other individual factors that may bias findings due to self-reported measures of the working environment, such as personality and temperament, were circumvented as well.

Only few studies have been conducted in this field using independent measures of psychosocial working conditions. Some studies based on non-self reported measures have shown a relation between psychological demands and depression (10, 12, 14), and some have shown a relation between other measures of psychosocial working conditions and depression (15, 17, 40, 41). The few studies investigating non-self-reported measures of decision latitude have found no statistically significant results (10, 16, 18). It is unclear, whether these conflicting results are caused by differences in the methods of obtaining exposure information or other factors.

Participants with sub-clinical depression would not be diagnosed with depression in the SCAN examination and thus not excluded at baseline. In order to avoid confounding by sub-clinical depression, the analyses of this study are adjusted for depressive symptoms at baseline.

The study included only 58 cases of depression which limits the statistical power as illustrated by the wide confidence intervals of most risk estimates, and this may explain our negative findings. Based on previously reported prevalence and recurrence rates of depression we had expected twice the number of cases (35, 42). Our lower-than-expected number of cases may in part be due to a healthy worker effect, as non-participants at baseline were more often prescribed antidepressant medication (23), and in part due to the low baseline participation rate.

The low number of cases, furthermore, limits the ability to adjust thoroughly for potential confounders. However, we found no significant differences between the fully adjusted models used in the logistic regression and the partially adjusted models used in the spline analyses. The confidence intervals for dichotomous and continuous interaction between psychological demands and decision latitude were very wide indicating that the power of the study was not sufficient to determine any possible interaction.

At baseline, only 45% of the invited workers participated and this could have affected the external validity due to differential participation, but we found no clear indications that the low baseline participation distorted the estimates of the associations between psychological demands or decision latitude and use of antidepressants at follow-up (23).

During follow-up, the participation rate (72%) was higher than at baseline, but selection may still have biased our findings. However, we found only a small difference between participants' and non-participants' levels of decision latitude at baseline and no difference between psychological demands and depressive symptoms (table 1).

Traditionally, the combined effects of high psychological demands and low decision latitude (job strain) have been described as a quadrant term with median splits of psychological demands and decision latitude. We examined their combined effects in regression analyses with demands and decision latitude included as independent covariates and further included their multiplicative interaction term. We examined the effects with continuous variables and dichotomized at the median. In our opinion, this method of analyses gives more information than the traditional quadrant median split model (43). We found no interaction effects, and the mutually adjusted linear effects of demands and decision latitude were very similar to the separate effects of the two factors. We have therefore only reported the separate effects.

The level of psychological demands ranged from 1.7–4.1 [mean 2.84, standard deviation (SD) 0.39], and the level of decision latitude ranged from 1.7–3.7 (mean 2.52, SD 0.26). It is thus not possible to determine the effect of very low or high levels of exposure based on this population. Studies with higher exposure contrast are needed to determine the risk of more extreme levels of exposure. The limited variation between work units may also be a problem due to the low statistical power of the study. We previously reported that the contrasts in mean exposure levels between work units were 15.3% for psychological demands and 19.5% for decision latitude, which is comparable to those found for other work-unit-based grouping strategies for psychosocial factors at work (8). The exposure homogeneity within work units was higher than that seen for grouping strategies for gaseous and other chemical exposures. Fifty percent of the work units had ratios of the 97.5th and the 2.5th percentiles below 2.95 for psychological demands and below 2.17 for decision latitude.

Decision latitude is related to social class, and it has been argued that the associations between low decision latitude and poor health are confounded by material disadvantage (44). Work unit mean levels of decision latitude and income are associated in our population ($P<0.001$), and our results might have been confounded by socioeconomic factors. However, we adjusted our results for income, educational level, alcohol consumption, and smoking, and any effects of residual confounding from non-controlled socioeconomic factors therefore seem small.

The period from baseline measurement of exposure until case classification at follow-up lasted two years and new, transient cases occurring during this period were not included. From studies of traumatic life-events, we know that the risk of depression increases steeply shortly after the event and then declines during the next months (45). On the other hand, long-term contextual threat has been shown to play an important etiological role in depression and to increase the subsequent risk of depression significantly (46). Thus, the temporal relation between psychosocial exposure and depression is uncertain, our follow-up period might have been sub-optimal and our effects underestimated. Cross-sectional analyses may capture some of the short-term effects of job strain on the risk of depression.

The results of the sensitivity analysis of questionnaire-reported physician-diagnosed depression are comparable with the results of the primary analysis and do not indicate that the undiagnosed cases of depression between baseline and follow-up affect the OR estimates.

The analyses were adjusted for confounders measured on the individual level. It is, however, possible that the results have been confounded by risk factors of depression shared by members of the different work units. Many other aspects of the work environment, such as unjust working conditions or an imbalance between effort and reward, have been suggested as possible causes of depression (3–5) and could bias the results.

Likewise, factors such as management style and group culture in the work unit may also be possible confounders. It is important to consider the lack of adjustment for possible confounders on the group level in this study.

In conclusion, this study suggests that low decision latitude may predict depression, but overall no statistically significant associations between high psychological demands or low decision latitude and depression were seen.

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ORIGINAL ARTICLE

Work-unit measures of organisational justice and risk of depression—a 2-year cohort study

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ABSTRACT

Objectives The aim of this study is to analyse if low justice at work, analysed as aggregated workplace means, increases the risk of depression.

Methods A total of 4237 non-depressed Danish public employees within 378 different work units were enrolled in 2007. Mean levels of procedural and relational justice were computed for each work unit to obtain exposure measures that were robust to reporting bias related to depression. Two years later in 2009, 3047 (72%) participated at follow-up. Those reporting high levels of depressive, burn-out or stress symptoms were assigned to a psychiatric diagnostic interview. In the interview 58 cases of new onset depression were identified. Depression ORs by work unit level of procedural and relational justice were estimated by multivariable logistic regression accounting for established risk factors for depression.

Results Working in a work unit with low procedural justice (adjusted ORs of 2.50, 95% CI 1.06 to 5.88) and low relational justice (3.14, 95% CI 1.37 to 7.19) predicted onset of depression.

Conclusions Our results indicate that a work environment characterised by low levels of justice is a risk factor for depression.

Depression is the leading burden of disease assessed by disability-adjusted life years in middle-income and high-income countries.[1] Strong evidence links bereavement and other emotionally painful life events causally with depression.[2] Less distressing but long-lasting strenuous psychosocial working conditions may also be a risk factor for depression.[3 4] However, most studies of this relation may have been hampered by biased self reports of working conditions related to individual characteristics such as personality traits or subclinical depressive symptoms.[5 6] Measures of psychosocial working conditions that are obtained independently of the depressed participants may be the only option to circumvent the serious problem of reporting bias.[3 6] This is relevant even in follow-up studies, because depression often has a long insidious preclinical stage.[3 5 6] Averaging across work units[6 7] or workplaces,[8] assessment by experts[9] or employers,[10] or information on hospital overcrowding, reorganisation, work load or job titles[11] are different approaches to obtain exposure information less affected by reporting bias.

Organisational justice at work is a relatively novel approach to an understanding of how psychological working conditions may affect health, wellbeing and productivity.[12] Organisational justice is composed of two separate elements. Procedural justice describes the consistency of the decision-making procedures in a workplace, the accuracy of information collected to make decisions and the degree in which all involved are allowed to voice their concern and challenge any decisions. Relational justice describes the degree to which supervisors consider employees' viewpoints, suppresses personal bias and treats the employees with kindness, consideration and truthfulness.[12] Low levels of justice at work may increase the risk of depression[13–15] and impact on other aspects of workers' health, such as self-rated health,[12 16] sickness absence,[12 16] psychological distress,[17] coronary heart disease[18] and cardiovascular death.[19] Prolonged stress has been suggested as a causal link between organisational justice and health problems.[20] A work environment characterised by organisational justice may help employees cope with uncertainty and mistrust. Justice may also affect employees' behaviours, feelings, beliefs, self-esteem and social identity.[21] Increased inflammation, cardiac dysregulation, poor sleep quality and impaired cognitive function have also been suggested but are still hypothetical.[20]

In the present study we used mean scores of self-reported justice obtained in small work units with homogeneous working conditions. Participants in the work unit who were diagnosed with depression at baseline were excluded from the calculation of the mean scores because their depression could have influenced their assessment of the psychosocial work environment. We also excluded participants who were diagnosed with depression at follow-up from the calculation of the mean scores because they could have had preclinical depressive symptoms which could have influenced their assessment of their working conditions. By including only participants who were non-depressed throughout the study we should have avoided any reporting bias caused by depression.

The aim of this article is to investigate if low levels of justice at work, aggregated at the work unit level, increase the risk of depression in a prospective cohort study of Danish employees.

MATERIALS AND METHODS

Design

We measured relational and procedural justice in 2007 and analysed if lower levels predicted new-onset depression present at follow-up in 2009. Cases of depression were identified in 2007 and 2009 by a two-step procedure: First, we identified participants reporting mental symptoms (symptoms of depression, stress or burn-out) in a questionnaire. Second, these participants were invited to take part in a standardised psychiatric interview to clinically diagnose cases with depression.

Population

In 2007, the Danish PRISME (Psychological risk factors in the work environment and biological mechanism for the development of stress, burnout and depression) cohort of 10 036 public employees from 502 work units in Aarhus, Denmark, was recruited for the baseline study, and 4489 employees (44.7%) from 474 work units participated by filling in a postal questionnaire concerning working conditions and health. Participants with depression at baseline (as defined below) were excluded (n=100). We also excluded five participants from five work units for which we could not identify the work unit leader and participants from work units with less than three responders who were non-depressed at baseline and follow-up (147 workers from 90 work units) to avoid unstable work unit measures of exposure. A total of 4237 participants from 378 work units were eligible for follow-up. In 2009, all participants from 2007 were approached again, and 3047 (72%) participated, comprising our final study population. Further details of the study have been reported in more detail elsewhere.[6 22]

Measures of psychosocial working conditions

Procedural and relational justice were measured with a Danish version of the organisational justice questionnaire originally developed by Moorman[23] and modified by Kivimäki *et al*.[16] The questionnaire contained four items about procedural justice and four items about relational justice (figure 1). All items were rated on a 5-point scale from 1 ('strongly disagree') to 5 ('strongly agree'). Mean values of all items on both justice scales were calculated for each work unit after exclusion of participants with depression at baseline or follow-up. The mean values of each work unit were assigned to all employees working in the particular work unit.

Measures of mental symptoms

We assessed depressive symptoms by the Common Mental Disorder Questionnaire subscale for depression (six items),[24] stress by the Perceived Stress Scale (four items),[25] and burn-out by the Copenhagen Burn-Out Inventory (six items).[26] All questions concerned the last 4 weeks, and responses were given on 5-point scales.

At baseline in 2007, participants were selected for the psychiatric interview if a) their point score was 3 or higher on three or more of the six depressive symptoms items, b) the mean score was 2.5 or more on the perceived stress scale or c) the mean score was 4 or more on the Copenhagen Burn-Out Inventory. The selection criteria for depressive symptoms were chosen to obtain optimal validity.[24] We expected that participants with depression would also have high perceived stress and burn-out levels and therefore included participants based on these mental symptom scales.

At follow-up in 2009, we redefined the selection criteria for the psychiatric interviews based on tabulation of the frequency of a depression diagnosis by different cut-off levels of depressive, stress and burn-out scores in the 2007 data. We did this to identify the largest number of depression cases with the lowest number of interviews. We selected participants with high scores on at least two of the three mental symptom scales (depressive scores of 3 or higher on two or more of the six questions, average stress and burn-out scores of 2.5 or higher).

Diagnosis of depression

Diagnoses of depression were obtained by the Schedules for Clinical Assessment in Neuropsychiatry interview (V.2.1 part I, sections 6, 7, 8 and 10)[27] according to the International Classification of Disease, 10th revision, Diagnostic Criteria for Research (ICD-10-DCR). All questions referred to the previous 3 months. The interviews were conducted by 10 students of medicine or psychology who had been trained at a 1 week course by a WHO certified trainer (OM). Inter-rater reliability on item level was satisfactory (κ=0.71).

Procedural justice

Procedures are designed to hear the concerns of all those affected by the decision.

Procedures are designed to collect accurate information necessary for making decisions.

Procedures are designed to provide opportunities to appeal or challenge the decision.

Procedures are designed to generate standards so that decisions can be made with consistency.

Relational justice

Your supervisor considers your viewpoint.

Your supervisor is able to suppress personal biases.

Your supervisor treats you with kindness and consideration.

Your supervisor takes steps to deal with you in a truthful manner.

Figure 1 Items measuring the level of procedural and relational justice. From Kivimäki *et al*.[16]

Cases of depression

In 2007, a total of 100 participants were diagnosed with depression and excluded from the study. The ICD-10-DCR diagnostic criteria for a mild, moderate and severe depressive episode were fulfilled for 40, 43 and 17 participants, respectively. In 2009, a total of 58 of 3047 participants were diagnosed with a new onset of depression. The ICD-10-DCR diagnostic criteria for a mild, moderate and severe depressive episode were fulfilled for 15, 32 and 11 participants, respectively.

Statistical analyses

ORs of depression were calculated by logistic regression analyses with robust clusters based on the work unit of the participants.[28] As the data were cluster-sampled the analyses must account for this. Since the main focus of the analyses were not to provide an apportionment of the variance into between and within clusters, but to report risk estimates on a population level, we used robust variance estimation. Analyses were performed with continuous-scale exposure information (linear, quadratic and cubic transformations) and tertile categorisation. Associations were further explored with restricted cubic spline regression analysis (four knots on percentiles 5, 35, 65 and 95). Linearity of the relation between exposure variables and depression was tested with likelihood-ratio testing.

We included the following potential confounders as measured at the individual level at baseline in all models: gender, age (continuous), previous episodes of depression (yes, no), family history of depression (yes, no), income (continuous), years of education beyond primary or high school (<3, 3–4, >4), alcohol consumption (continuous), living alone (yes, no), neuroticism (continuous with quadratic term; from the neuroticism scale of the Eysenck Personality Questionnaire Revised-Abbreviated version[29]), depressive symptoms (continuous with quadratic term; from the Common Mental Disorder Questionnaire), body mass index (continuous), years of smoking (continuous). Traumatic life events defined as serious illness or injury, assault, death of a relative or friend, marital problems, or serious illness or assault of a close relative[30] during the last 6 months were also included and measured at follow-up. The selection of these potential confounders was based upon a review of the literature.[31–35] We examined all continuous covariates for linearity by likelihood-ratio testing. Linearity was not accepted for neuroticism and baseline depressive symptoms, so these potential confounders were included as linear and quadratic terms. We tested for interaction between gender and procedural and relational justice, respectively, and performed subanalyses for female participants only.

We used likelihood-ratio testing to identify the strongest potential confounders of new-onset depression, and performed similar analyses on a model only including these variables. The homogeneity of self-reported procedural and relational justice within the work units were assessed by intraclass correlation and within-group inter-rater agreement indices.[36] Since our screening criteria for being invited to the psychiatric interviews changed slightly from baseline to follow-up we checked if exclusion of cases of depression that would not have been identified by the baseline criteria changed our findings. All analyses were conducted with the STATA 11 statistical software (StataCorp LP, College Station, Texas, USA).

RESULTS

Nurses (30%), social workers (18%), teachers (11%), managers (7%) and medical doctors (6%) were the most prevalent professions among the participants. Previous depression, a family history of depression, traumatic life events, neuroticism and subclinical depressive symptoms at baseline predicted depression at follow-up (table 1). There were only small differences between responders and non-responders at follow-up. Responders had a mean level of procedural justice of 2.82 and a mean level of relational justice of 2.20 compared with non-responders with 2.82 and 2.23. Responders had a mean age of 43 years, 80% were women and 83% had 3 or more years of education. Non-responders had a mean age of 45 years, 79% were women, and 74% had 3 or more years of education. The 100 depressed participants who were excluded at baseline had a mean level of procedural justice of 2.88, a mean level of relational justice of 2.30, a mean age of 44.5 years, 83% were women and 78% had 3 or more years of education.

The risk of depression increased monotonously by lower levels of procedural and relational justice. The adjusted ORs for a 1-point decrease on the 5-point justice scales were 2.96 (1.19 to 7.34) and 4.84 (2.15 to 10.90) for procedural and relational justice, respectively (table 2). Neither quadratic, nor cubic, nor spline models fitted the data significantly better than the linear models of exposure. The adjusted ORs for the lowest tertile compared with the highest tertile were 2.50 (1.06 to 5.88) for procedural justice and 3.14 (1.37 to 7.19) for relational justice (table 2).

In a model only including the strongest potential confounders (gender, previous depression, traumatic life events, living alone, depressive symptoms at baseline and neuroticism) we observed similar results as those obtained by the fully adjusted model (data not shown). We found a medium to large intraclass correlation of 0.16 and 0.15 for procedural and relational justice, respectively. We found an average inter-rater agreement of 0.75 for procedural justice and 0.77 for relational justice, indicating a strong homogeneity within work units.

We found no interaction between gender and procedural justice ($p=0.84$) and gender and relational justice ($p=0.85$). We found very similar results when only examining female participants (data not shown). One depressed participant would not have been included among the cases if we had applied the same screening criteria for being invited to the psychiatric interviews at baseline as at follow-up. Excluding this single participant did not change the results (data not shown).

DISCUSSION

Members of work units with low levels of procedural or relational justice had a substantially increased risk of developing depression over a 2-year period. The results showed an exposure-response relationship.

The baseline participation rate was low (45%), which could have biased results, if participation was associated with level of justice as well as depression. We investigated this by extrapolating the work unit justice estimates to the non-responding members of the work units and by accessing registry information on redeemed antidepressant medication for the entire source population that has been published elsewhere.[37] We found relative ORs of antidepressant use of 1.01 (0.75 to 1.37) for low procedural justice and 1.01 (0.74 to 1.38) for low relational justice when comparing responders with the entire source population. This indicates that the low baseline participation did not distort the estimates of the associations between justice and depression, since the relation between justice and antidepressant use are almost identical for participants and non-participants.

Based on previously reported prevalence and recurrence rates of depression we had expected twice the number of cases.[33 38]

Table 1 Baseline characteristics of participants with or without depression at follow-up

Characteristic	No depression at follow-up (n=2989)	%	Depression at follow-up (n=58)	%	OR	95% CI
Women	2344	78.8	50	86.2	1.65	0.78 to 3.50
Age						
<35 years	590	19.8	13	22.4	1	
35–44 years	717	24.1	12	20.7	0.82	0.37 to 1.85
45–54 years	1073	36.1	23	39.7	1.05	0.52 to 2.13
≥55 years	595	20.0	10	17.2	0.83	0.35 to 1.93
Previous depression	358	12.4	24	44.4	5.67	3.28 to 9.81
Family history of depression	786	26.8	22	38.6	1.93	1.10 to 3.40
Professional education beyond primary or high school						
<3 years	499	16.8	10	17.5	1	
3–4 years	2105	71.0	43	75.4	1.02	0.51 to 2.04
>4 years	361	12.2	4	7.0	0.55	0.17 to 1.78
Income >300000 DKr	1463	51.2	20	37.7	0.58	0.33 to 1.01
Alcohol consumption above 14 grams/week	712	24.2	13	22.8	0.93	0.50 to 1.73
Traumatic life event during last 6 months*	947	31.7	35	60.3	3.28	1.93 to 5.58
Living alone	557	18.8	8	14.0	0.71	0.33 to 1.50
Neuroticism personality trait†	427	14.4	23	40.4	4.04	2.35 to 6.92
CMDQ depressive symptoms‡	253	8.5	19	33.3	5.36	3.05 to 9.44
Smoking						
Never smoked	1423	52.7	23	44.2	1	
0–19 years of smoking	624	23.1	9	17.3	0.89	0.41 to 1.94
20 or more years of smoking	653	24.2	20	38.5	1.89	1.03 to 3.47
Body mass index (kg/m^2)						
<18.5	51	1.7	2	3.6	2.17	0.51 to 9.30
18.5–25	1885	64.0	34	60.7	1	
>25	1010	34.3	20	35.7	1.10	0.63 to 1.92

*Serious illness or injury, assault, death of a relative or friend, marital problems, or serious illness or assault of a close relative. Measured at follow-up.
†Dichotomised score based on neuroticism scale from Eysenck Personality Questionnaire Revised.
‡Common Mental Disorder Questionnaire. A screening instrument designed for case finding.
CMDQ, Common Mental Disorder Questionnaire.

Our lower than expected number of cases may in part be due to a healthy worker effect. It may also in part be due to a lower participation rate of depressive employees as non-participants at baseline were more often prescribed antidepressant medication,[37] and in part due to the low baseline participation rate. Additionally, some participants with depression may have not been identified by our screening procedure for the psychiatric interview. However, even if we had indeed missed participants with depression, this can hardly explain the strong associations between organisational justice and depression that we observed.

At follow-up, the participation rate was higher (72%) than at baseline, but selection may still have biased our findings. However, we found only a small difference between responders' and non-responders' levels of justice and depressive symptoms at baseline. Thus, baseline justice and depressive symptoms did not predict participation at follow-up, indicating that bias due to selective loss to follow-up is unlikely.

Table 2 ORs of depression at follow-up by lower levels of justice

Exposure	Exposure mean (range)	Depression (n=58)	No depression (n=2989)	Crude OR	95% CI	Adjusted* OR	95% CI
Continuous exposure†							
Procedural justice	3.18 (1.58–4.75)	58	2989	2.58	1.26 to 5.30	2.96	1.19 to 7.34
Relational justice	3.78 (2.17–4–75)	58	2989	2.83	1.49 to 5.35	4.84	2.15 to 10.90
Categorised exposure							
High procedural justice	3.59 (3.32–4.75)	10	991	1	-	1	–
Medium procedural justice	3.18 (3.02–3.31)	22	1004	2.17	1.00 to 4.72	1.28	0.52 to 3.15
Low procedural justice	2.79 (1.58–3.01)	26	989	2.61	1.22 to 5.55	2.50	1.06 to 5.88
High relational justice	4.13 (3.95–4.75)	12	1003	1	–	1	–
Medium relational justice	3.81 (3.66–3.94)	19	996	1.59	0.77 to 3.31	1.74	0.71 to 4.27
Low relational justice	3.41 (2.17–3.65)	27	990	2.28	1.12 to 4.62	3.14	1.37 to 7.19

*Adjusted for age, gender, previous episodes of depression, family history of depression, educational level, income, alcohol consumption, traumatic life-events, living alone, depressive mood, smoking, body mass index and neuroticism.
†ORs for a 1-point decrease on the 5-point justice scales.

Participants who were diagnosed with depression at baseline were excluded from the calculation of the mean scores since their depression could influence their assessment of the psychosocial work environment. We also excluded participants that were diagnosed with depression at follow-up because they could have preclinical depressive symptoms which could influence their assessment of their working conditions. By including only participants who are non-depressed throughout the study we circumvent the serious problem of biased self-reporting of working conditions which may have hampered most previous studies of psychosocial factors and the risk of depression.[3 6]

Justice at work is likely to be related to social class and thereby to lifestyle factors and the associations between justice and depression may thus be confounded. We therefore adjusted for income, educational level, alcohol consumption, body mass index and smoking, and any effects of confounding from non-controlled socioeconomic and lifestyle factors therefore seem small.

Likewise, personality factors may be related to perceived justice at work as well as to depression.[33 39] We adjusted for neuroticism that is a risk factor of depression,[33] but did not take other personality traits into account. However, hostility and trait anxiety, did not have strong confounding effects on the relation between perceived justice and depression in a recent study.[39] This makes confounding due to these personality traits unlikely in our study.

We did not adjust for other psychosocial work factors, and it is possible that the association between justice and depression was, at least partly, mediated by other work factors, but we did not find any association between psychological demands, decision latitude and depression in a recent analysis of this population.[22]

The adjusted association between relational justice and depression was stronger than the crude association, though the difference was not statistically significant. This increase was primarily because women and participants with previous depression and low income were more prevalent in work units with higher levels of relational justice. These factors were all related to depression and adjusting for them increased the association between relational justice and depression. A similar pattern was also found for procedural justice, although to a smaller degree.

Working conditions may vary significantly between workers within a work unit, and one may argue that this variance was not captured by our work-unit average exposure measure. Therefore, we explicitly identified units of workers that shared leadership, colleagues and work content and thus were expected to experience similar levels of justice. We found a strong homogeneity within work units, which may justify aggregation in a multilevel analysis.[36] Furthermore, risk estimates obtained from grouped exposures are not expected to be attenuated because grouping accounts for random misclassification and leads to predominance of Berkson-type error in exposure assessment.[40]

So far, only few studies linking organisational justice with depression have been published, but earlier results are in line with our findings.[13–15] Low justice at work has also been related to minor psychiatric morbidity, doctor-diagnosed psychiatric disorder, coronary heart disease, cardiovascular death, sickness absence and other health effects.[20 41]

This study provides evidence that a work environment characterised by low procedural and relational justice is a risk factor for depression. This is an important finding that may open new possibilities for prevention of depression because unfair working conditions are amendable to change.

A management style characterised by a clearly articulated concern for being fair reinforced through use of accurate and transparent procedures has been suggested to increase justice at work.[42] Further studies are needed for investigating the exact factors that contribute to an unjust workplace.

What this paper adds

- It has been suggested that low levels of justice at work increase the risk of depression.
- However, studies may have been hampered by biased self-reports of working conditions. Thus, measures of justice at work, analysed independently of the perceptions of the depressed participants, are needed.
- We classified employees of 378 small work units with similar working conditions by the average levels of procedural and relational justice obtained among the non-depressed workers and examined the risk of depression 3 years later. This design should be robust to reporting bias related to depression status.
- We observed that low levels of procedural and relational justice were associated with increased risk of depression. This is an important finding that may open new possibilities for prevention of depression because unfair working conditions are amendable to change.

Contributors MBG: performed the statistical analysis for the present paper, interpreted the analyses and drafted the manuscript. All coauthors have helped with interpretation of the analyses and with revising the manuscript critically. HAK, ÅMH, AK, JFT, LK, SM and MBG: coordinated the data collection, enrolment of participants, data acquisition and quality assurance. OM: designed and assured the quality of the psychiatric interviews. All authors participated in the design and coordination of the PRISME study, development of the questionnaire and have made substantial contributions to interpretation of data; and read and approved the final manuscript.

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A two-year follow-up study of salivary cortisol concentration and the risk of depression

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Summary Stress is a suspected cause of depression. High cortisol concentration, a biomarker of an activated stress response, has been found in depressed patients. The aim of this study was to determine if a high level of salivary cortisol is a risk factor of depression. In 2007, we enrolled 4467 public employees. Morning and evening salivary cortisol concentration were measured for each participant. Participants reporting high levels of depressive, burnout, or stress symptoms, assessed by questionnaires were assigned to a psychiatric interview. In this interview 98 participants were diagnosed with depression and subsequently excluded. Two years later in 2009, 2920 participants who had provided at least one valid saliva cortisol measurement at baseline participated at follow up. The psychiatric interviews were repeated and 62 cases of newly onset depression were diagnosed. Odds ratios of depression were estimated for every 1.0 nmol/l increase in morning, evening, and daily mean cortisol concentration, as well as for the difference between morning and evening cortisol concentration. The risk of depression decreased by increasing daily mean cortisol concentration and by increasing difference between morning and evening concentrations, while morning and evening cortisol concentrations were not significantly associated with depression. The adjusted odds ratios for 1.0 nmol/l increase in morning, evening, and daily mean cortisol concentration were 0.69 (95% CI: 0.45, 1.05), 0.87 (95% CI: 0.59, 1.28), and 0.53 (95% CI: 0.32, 0.90), respectively. The adjusted odds ratio for 1.0 nmol/l

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increase in difference between morning and evening concentration were 0.64 (95% CI: 0.45, 0.90). This study did not support the hypothesis that high salivary cortisol concentration is a risk factor of depression, but indicate that low mean salivary cortisol concentration and a small difference between morning and evening cortisol concentration may be risk factors of depression.

1. Introduction

Stress and stressful life events are often implicated in the causation of depression and numerous other diseases (Maddock and Pariante, 2001; Risch et al., 2009), although there are unresolved questions about the causal mechanisms (Hammen, 2005). Sudden and intense stressors cause an acute increase in cortisol secretion, while it has been suggested that long-term and less intense stressors may cause a low-level increase as well as a lowered cortisol secretion after several years (Yehuda et al., 1996; Rosmond and Bjorntorp, 2000). Abnormalities in the HPA axis have therefore been speculated to play a key role in the development and recurrence of depression (Hammen, 2005).

Increased cortisol level and thus hyperactivity of the HPA axis has repeatedly been reported in cross-sectional studies of patients diagnosed with depression (Brown et al., 2004; Pariante and Lightman, 2008; Knorr et al., 2010; Stetler and Miller, 2011; Jonsdottir et al., 2012). However, it is unclear whether this reflects a causal mechanism leading to depression or mechanisms that are secondary to the inception of the disease. The few longitudinal studies conducted so far show that different measures of increased cortisol level at baseline predict depression at follow up 1 to 6 years later (Goodyer et al., 2000; Harris et al., 2000; Halligan et al., 2007; Adam et al., 2010; Goodyer et al., 2010; Ellenbogen et al., 2011; Vrshek-Schallhorn et al., 2012). Harris et al. (2000) examined 116 adult women screened to have a high risk of depression and observed that a high morning cortisol concentration was associated with depression during 13 months of follow up, but did not find any association with evening cortisol concentration. Goodyer et al. (2000) and Halligan et al. (2007) found similar results during 1 year and 3 years of follow up that included 180 and 57 adolescents, respectively. Goodyer et al. (2010) in a later study examined 401 adolescents and found high concentrations of morning cortisol to be associated with depression 3 years later. Ellenbogen et al. (2011) showed that a high mean concentration of cortisol across the day among 59 adolescents predicted depression during 1–6 years of follow up. Adam et al. (2010) observed no association between morning-to-evening slope or mean cortisol concentration across the day and depression in 230 adolescents during 1 year of follow up. But the cortisol awakening response was a significant predictor of depression. Vrshek-Schallhorn et al. (2012) examined 270 adolescents and showed that the cortisol awakening response predicted depression up to 2½ year after baseline, but not thereafter. They observed no relation between morning-to-evening slope or mean cortisol concentration across the day and depression.

Thus, results from longitudinal studies are equivocal and based on relatively few observations. Studies are mainly conducted among adolescents and include no healthy adult populations. We recruited a large, healthy working population and measured the HPA activity by saliva cortisol concentration and analysed the risk of new onset depression two years later. We hypothesised that a high level of cortisol increases the risk of depression.

2. Methods

2.1. Design

This follow-up study is based on the Danish PRISME cohort established in 2007 and re-examined in 2009 (Kolstad et al., 2011; Grynderup et al., 2012). The purpose of the PRISME study is to examine to what extent psychological work factors and increased HPA axis activity are risk factors of depression, burnout, or stress symptoms. We measured salivary cortisol in all participants in 2007 and analyzed if morning concentration, evening concentration, mean of morning and evening concentration, or the morning-to-evening slope (difference between morning and evening concentration) predicted new-onset of depression at follow up in 2009. Cases of depression were identified in 2007 and 2009 by a two-step procedure: First, we identified participants reporting mental symptoms (symptoms of depression, perceived stress, or burn-out) in a questionnaire. Second, these participants were invited to a standardized psychiatric interview to identify cases with depression.

2.2. Population

In 2007, we approached 10,036 public employees from the municipal and hospital sector in Aarhus, Denmark for participation in the Danish PRISME cohort. Of these 4467 employees (45%) participated by collecting saliva samples and filling in a short questionnaire on sleep, medication, and alcohol intake the day of sampling. Participants with a clinical diagnosis of depression at baseline according to ICD-10 (n = 98) and pregnant women (n = 138) were excluded leaving 4231 participants for follow up. In 2009, all participants from 2007 were approached, and a total of 3031 participated. A total of 2920 of these participants provided a valid salivary cortisol measurement, as described later, and thus comprised the final study population.

2.3. Collection of saliva samples

All participants received Salivette® cotton swabs that they were instructed to keep in the mouth until thoroughly saturated. The saturated swabs were kept in a tube and stored in a refrigerator until they were returned by mail. The average time from date of sampling to date of receiving the samples at the National Research Centre for the Working Environment were 5 days (SD = 3 days). The samples were then stored at −20 °C and analyzed within 6 months. Participants sampled

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saliva during a workday (90.0%) or during a day off work (10.0%), and were instructed to collect the samples 30 min after awakening, and at 8 PM. Morning samples were considered valid if they were collected within 2 h of awakening, and evening samples if they were collected between 5 PM and 4 AM. In this paper we only included valid saliva samples.

The choices of sampling times were based on several factors. For the morning sample, the aim was to detect the morning cortisol peak that is expected to occur about 30 min after awakening (Pruessner et al., 1997; Edwards et al., 2001). Because cortisol concentration is stable during the evening (Ranjit et al., 2005; Kudielka et al., 2007) sampling time is less important and we decided on a fixed time for feasibility reasons. Our funding only allowed two samples per participant and furthermore we expected that more samples would decrease compliance in a field study like this.

2.4. Measurement of cortisol in saliva

Determination of cortisol in saliva 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 (Orion Diagnostica, Espoo, Finland) according to the manufacturer's specifications. The sample volume was 150 μl, 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, with recovery being 97% [95% CI: 94.0—100.9]. Limit of detection was 1.59 nmol/l. Between-run coefficients of variation were 19% at 11.5 nmol/l and 16% at 49.2 nmol/l (Hansen et al., 2003).

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. Westgard control charts were used to document 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., 2003).

2.5. Measures of mental symptoms

We assessed depressive symptoms by the Common Mental Disorder Questionnaire subscale for depression (six items) (Christensen et al., 2005), stress symptoms by the Perceived Stress Scale (four items) (Cohen et al., 1983), and burn-out by the Copenhagen Burn-Out Inventory (six items) (Kristensen et al., 2005). All questions concerned the last four weeks and responses were given on 5-point scales (scores 1—5).

At baseline, participants were selected for the psychiatric interview if their point score was 3 or higher on three or more of the six items on the subscale for depression, the mean score was 2.5 or more on the Perceived Stress Scale, or the mean score was 4 or more on the Copenhagen Burn-Out Inventory.

At follow-up in 2009 we redefined the selection criteria for the psychiatric interviews based on tabulation of the frequency of diagnosed depression by different cut-off levels of depressive, stress, and burn-out scores in the baseline data. We did this in order to identify the largest number of depression cases. We selected participants with high scores in at least two of the three mental symptom scales (depressive scores of 3 or higher on two or more of the six questions, average stress and burn-out scores of 2.5 or higher).

In 2007, we invited 715 workers to participate in the psychiatric interviews and 552 participated (77%). In 2009, 671 workers were invited and 426 participated (63%).

2.6. Diagnosis of depression

Diagnoses of depression were obtained by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (version 2.1 part I, sections 6, 7, 8, and 10) (Wing et al., 1990) according to the ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research (ICD-10-DCR) and referred to the previous three months. The interviews were conducted by 10 students of medicine or psychology, who were trained during a one week course given by a WHO certified trainer (OM). Inter-rater reliability on item level was satisfactory (κ = 0.71).

In 2007, a total of 100 participants were diagnosed with depression and excluded from the study. The ICD-10-DCR diagnostic criteria for a mild, moderate, and severe depressive episode were fulfilled for 40, 43 and 17 participants, respectively. Of these, 98 depressed participants had collected baseline saliva samples. In 2009, a total of 62 among the 2920 participants were diagnosed with depression. The ICD-10-DCR diagnostic criteria for a mild, moderate, and severe depressive episode were fulfilled for 19, 31 and 12 participants, respectively.

2.7. Statistical analyses

Odds ratios of depression were analysed by logistic regression. Diagnosis of depression was categorized as a dichotomous variable including mild, moderate, and severe cases of depression. Logarithmic transformation was used to normalize the cortisol distribution. The morning-to-evening slope was calculated as the difference between morning and evening cortisol concentration in valid saliva samples divided by the number of hours between the collections of the two samples, and was also analyzed on a logarithmic scale. The daily mean concentration of cortisol was calculated as the mean of morning and evening cortisol concentration of valid saliva samples. In the analyses of daily mean cortisol concentration and morning-to-evening slope, we only included participants with both valid morning and evening sample times, and where the evening sample were collected at least 9 h after the morning sample. Analyses of morning, evening, and daily mean cortisol concentrations as well as the morning-to-evening slope were performed on a continuous-scale and with tertile categorization. Linearity of the

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relation between the continuous cortisol measures and depression were tested using likelihood-ratio tests comparing linear models to models including both linear and quadratic terms as covariates.

We included the following potential confounders as measured at baseline in all models: gender (male, female), age (≤34, 35–44, 45–54, ≥55), previous episodes of depression (yes, no), family history of depression (yes, no), income (continuous), and years of education beyond primary or high school (<3, 3–4, >4). We included the following lifestyle factors as potential confounders in some models: alcohol consumption (≤14, >14 g/week), body mass index (continuous), and smoking (never, up to 20 years, 20 or more years). The selection of these potential confounders was based upon a review of the literature (Kessler, 1997; Hasin et al., 2005; Burcusa and Iacono, 2007; Andersen et al., 2009; Boden et al., 2010).

Few participants collected the saliva samples exactly at 8 PM and 30 min after awakening. We therefore performed sub-analyses to examine the effect of sampling time. We excluded the 10% of the participants who collected their morning sample earliest (5%) and latest (5%) during the day and calculated the odds ratio of depression by cortisol level for the remaining 90% of the population. We did the same for 80% and 70% of the population after we had excluded the 10% and 15%, respectively, who collected their samples earliest and latest. Similar sub-analyses were performed for evening and daily mean cortisol concentration and morning-to-evening slope. All analyses were conducted using the STATA 11 statistical software (StataCorp LP, College Station, Texas).

3. Results

Nurses (30%), social workers (18%), teachers (11%), managers (7%), and medical doctors (6%) were the most prevalent professions among the participants. The mean age of the participants were 45.5 years, 78% were women, 82% had 3 or more years of professional education beyond primary or high school, and 13% reported a history of depression before enrolment in the study.

The mean morning cortisol concentration was 12.7 nmol/l based on 2615 valid samples, the mean evening cortisol concentration was 2.1 nmol/l based on 2856 valid samples, the mean daily mean cortisol concentration was 7.44 nmol/l hour based on 2517 valid morning and evening samples, and the mean morning-to-evening slope was 0.79 nmol/l decrease for every hour based on 2517 valid morning and evening samples. Previous depression, income, and smoking at baseline all predicted depression at follow-up (Table 1). Non-depressed participants at follow up, at baseline collected the morning sample on average 43.2 min after awakening on average at 7.04 AM and the evening sample on average at 8.37 PM. These participants had geometric mean morning and evening cortisol concentrations of 10.61 (95% CI: 10.35, 10.88) and 1.44 (95% CI: 1.40, 1.48), respectively. The depressed participants at follow up, at baseline collected the morning sample on average 46.8 min after awakening on average at 7.20 AM and the evening sample at 8.49 PM. These participants had geometric mean morning and evening cortisol concentrations of 9.28 (95% CI: 7.62, 11.31) and 1.36 (95% CI: 1.09, 1.71), respectively (Fig. 1).

Table 1 Baseline characteristics of 2920 public employees with or without a diagnosis of depression at follow-up.

Characteristic	Non-depressed (n = 2858)	%	Depressed (n = 62)	%	OR	95% CI
Women	2220	77.7	52	83.9	1.49	0.76, 2.94
Age						
<35 years	515	18.0	14	22.6	1	
35–44 years	682	23.9	13	21.0	0.70	0.33, 1.50
45–54 years	1076	37.7	24	38.7	0.82	0.42, 1.60
≥55 years	585	20.5	11	17.7	0.69	0.31, 1.54
Previous depression	339	12.3	27	46.6	6.24	3.68, 10.58
Family history of depression	752	26.9	21	34.4	1.56	0.89, 2.71
Professional education beyond primary or high school						
<3 years	505	17.8	11	18.0	1	
3–4 years	1979	69.7	45	73.8	1.04	0.54, 2.03
>4 years	355	12.5	5	8.2	0.65	0.22, 1.88
Income > 300,000 DKr	1401	51.2	21	36.8	0.56	0.32, 0.96
Alcohol consumption above 14 g/week	701	24.9	14	23.0	0.90	0.49, 1.65
Smoking						
Never smoked	1350	52.2	23	41.8	1	
0–19 years of smoking	599	23.2	10	18.2	0.98	0.46, 2.07
20 or more years of smoking	637	24.6	22	40.0	2.03	1.12, 3.66
Body mass index (kg/m^2)						
<18.5	48	1.7	2	3.3	2.09	0.49, 8.93
18.5–25	1805	64.0	36	60.0	1	
>25	967	34.3	22	36.7	1.14	0.67, 1.95

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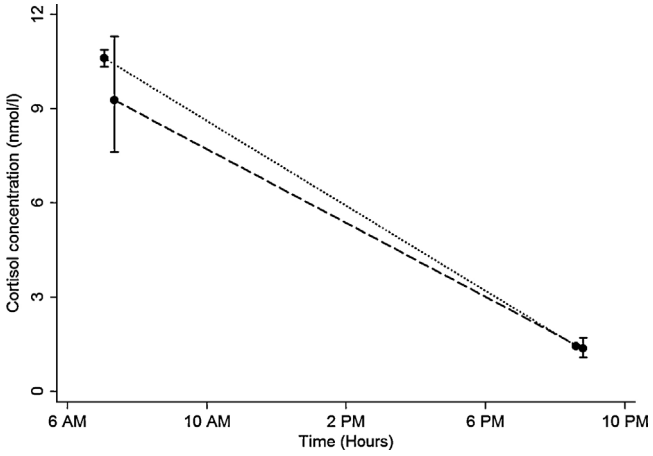

Figure 1 Baseline geometric mean cortisol concentration by average sampling times of the morning and evening samples for participants diagnosed with depression at follow up (dashed line) and participants with no diagnosis of depression at follow up (dotted line).

The risk of depression decreased by increasing daily mean cortisol concentration and by increasing morning-to-evening slope (Table 2). The fully adjusted odds ratio for 1.0 nmol/l increase on the logarithmic scale in morning, evening, and daily mean cortisol concentration were 0.69 (95% CI: 0.45, 1.05), 0.87 (95% CI: 0.59, 1.28), and 0.53 (95% CI: 0.32, 0.90), respectively. The fully adjusted odds ratios for the highest tertile compared with the lowest tertile were 0.48 (95% CI: 0.22, 1.04) for morning cortisol concentration, 1.29 (95% CI: 0.60, 2.76) for evening cortisol concentration, and 0.48 (95% CI: 0.22, 1.05) for daily mean cortisol concentration. The adjusted odds ratio for a 1.0 nmol/l increase in morning-to-evening slope on the logarithmic scale was 0.64 (95% CI: 0.45, 0.90) and the adjusted odds ratio of the highest tertile compared with the lowest tertile was 0.50 (95% CI: 0.22, 1.12) (Table 2). Models with quadratic terms of cortisol concentration included as covariates did not perform significantly better than the simple linear models of morning, evening, or daily mean cortisol; or morning-to-evening slope.

The effect of measuring time was examined in sub-analyses where only the 90%, 80% and 70% of the population that collected their saliva samples closest to the intended time of sampling were included (Fig. 2). These analyses showed even stronger inverse relations between saliva cortisol level and odds ratio of depression. 90% of the participants collected their morning samples between 9 and 102 min after awakening, 80% between 19 and 73 min after awakening, and 70% between 26 and 59 min after awakening. 90% of the participants collected their evening samples between 7.25 PM and 10.56 PM, 80% between 7.48 PM and 10.18 PM, and 70% between 7.58 PM and 9.59 PM.

4. Discussion

We found that participants with a high daily mean concentration of cortisol or a steep morning-to-evening slope had a decreased risk of depression two years later. From our hypothesis we had expected that a high concentration of salivary cortisol showed an increased risk of depression. However, we found the opposite pattern. Thus the hypothesis

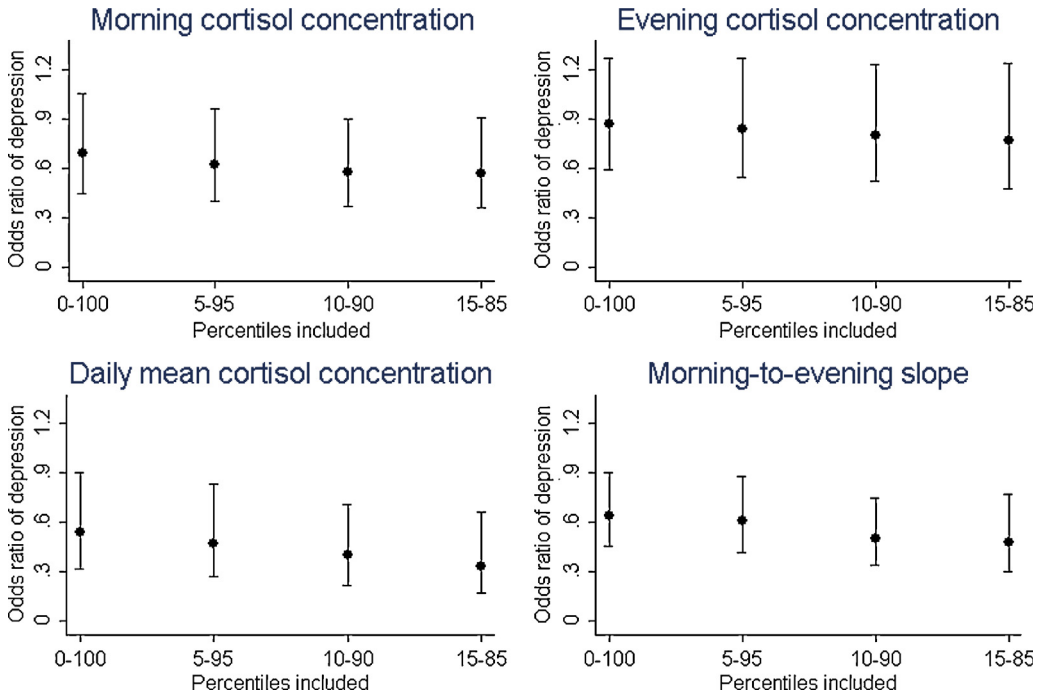

Figure 2 Adjusted odds ratios of depression by a 1.0 nmol/l increase in morning cortisol concentration, evening cortisol concentration, daily mean cortisol concentration, and morning-to-evening cortisol slope for the 100 (the complete population), 90, 80 and 70% who collected their saliva samples closest to the intended sampling hour. The subpopulations were defined by the 0—100, 5—95, 10—90 and 15—85 percentiles.

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Table 2 Odds ratios of depression by increasing concentration of morning-to-evening slope and daily mean, morning, and evening cortisol concentration.

Exposure	Mean (range) nmol/l	Depressed	Non-depressed	Crude OR	95% CI	Adjusted[a] OR	95% CI	Adjusted[b] OR	95% CI
Continuous									
Morning cortisol[c]	12.7 (0.2–99.6)	53	2562	0.75	0.52: 1.10	0.73	0.49: 1.09	0.69	0.45: 1.05
Evening cortisol[c]	2.1 (0.1–83.7)	61	2795	0.91	0.66: 1.26	0.92	0.65: 1.32	0.87	0.59: 1.28
Daily mean cortisol[c]	7.4 (0.25–52.6)	52	2465	0.61	0.38: 0.97	0.58	0.36: 0.96	0.53	0.32: 0.90
Slope[d]	0.8 (−4.28–7.53)	52	2465	0.65	0.48: 0.89	0.65	0.47: 0.90	0.64	0.45: 0.90
Categorical									
Low morning cortisol	6.0 (0.2–8.9)	24	830	1	–	1	–	1	–
Medium morning cortisol	11.6 (9–14.4)	15	864	0.60	0.31: 1.15	0.54	0.27: 1.09	0.45	0.21: 0.96
High morning cortisol	22.0 (14.5–99.6)	14	868	0.56	0.29: 1.09	0.57	0.28: 1.17	0.48	0.22: 1.04
Low evening cortisol	0.7 (0.1–1.0)	17	885	1	–	1	–	1	–
Medium evening cortisol	1.4 (1.1–1.8)	21	958	1.14	0.60: 2.18	1.35	0.66: 2.77	1.20	0.56: 2.57
High evening cortisol	5.6 (1.9–83.7)	23	952	1.26	0.67: 2.37	1.37	0.67: 2.80	1.29	0.60: 2.76
Low mean cortisol	3.8 (0.25–5.34)	24	796	1	–	1	–	1	–
Medium mean cortisol	6.8 (5.35–8.25)	13	840	0.51	0.26: 1.02	0.44	0.21: 0.92	0.40	0.18: 0.86
High mean cortisol	13.3 (8.3–52.6)	15	829	0.60	0.31: 1.15	0.62	0.30: 1.25	0.48	0.22: 1.05
Low slope	0.1 (−4.28–0.54)	24	815	1	–	1	–	1	–
Medium slope	0.7 (0.55–0.94)	15	824	0.62	0.32: 1.19	0.59	0.29: 1.19	0.60	0.29: 1.25
High slope	1.5 (0.95–7.53)	13	826	0.53	0.27: 1.06	0.55	0.26: 1.15	0.50	0.22: 1.12

[a] Adjusted for age, gender, income, educational level, previous episodes of depression, and family history of depression.
[b] Adjusted for age, gender, income, educational level, previous episodes of depression, family history of depression, body-mass index, smoking, and alcohol consumption.
[c] Increase in odds ratio for every increase of 1.0 nmol/l cortisol on the logarithmic scale.
[d] Increase in odds ratio for every 1.0 nmol/l per hour increase in morning-to-evening slope on the logarithmic scale.

that high cortisol concentration is a risk factor of depression was rejected.

Consequently, the results of this study were not in line with results from the few other longitudinal studies of cortisol concentration and the risk of depression (Goodyer et al., 2000, 2010; Harris et al., 2000; Halligan et al., 2007; Adam et al., 2010; Ellenbogen et al., 2011; Vrshek-Schallhorn et al., 2012). The populations investigated in Adam et al. (2010), Ellenbogen et al. (2011), Goodyer et al. (2000), Goodyer et al. (2010), Halligan et al. (2007) and Vrshek-Schallhorn et al. (2012) were much younger than in our study (average age 17.0, 17.5, 13.5, 13.6, 13.0 and 17.1 years, respectively). Increased morning and daily mean cortisol concentrations and a high cortisol awakening response have been shown among young adults with depression compared to young non-depressed adults. Among older adults there were no such difference in cortisol measurements between the depressed and non-depressed (Heaney et al., 2010). This may explain the different results in these studies compared to ours, since the association between depression and diurnal cortisol vary with age, and these studies examined children and adolescents, while our study examine adults. Compared to the participants in the study by Harris et al. (2000), which also examine adults, the participants in our study were older, more educated, were all employed, had a far less frequent history of depression, and were not selected because they were likely to develop depression.

Adam et al. (2010), Ellenbogen et al. (2011), Harris et al. (2000), Halligan et al. (2007) and Vrshek-Schallhorn et al. (2012) selected study populations that had higher risk of developing depression due to personality traits or a familial disposition compared to the population in average. This may also affect the comparability between these studies and ours, since we examined a healthy working population. Less severe depression has shown weaker association with cortisol levels than more severe cases (Stetler and Miller, 2011), and cases of depression are likely to be less severe in our healthy working population.

The 2 years of follow-up in our study were not comparable to Goodyer et al. (2000, 2010) and Harris et al. (2000) with 1 year of follow-up, or Adam et al. (2010) with 13 months of follow-up. Halligan et al. (2007) and Vrshek-Schallhorn et al. (2012) had 3 and 4 years of follow-up, respectively. Ellenbogen et al. (2011) had a follow-up period of 1—6 years (average of 2.5 years). There may be differences between those participants who are not depressed at baseline, but who are depressed 1 year later, those who are depressed 2 years later, and those who develop depression later than that. The duration of a depressive episode has been found to vary widely, with median durations between 3 and 12 months, and around 20% of depressive episodes last longer than 2 years (Spijker et al., 2002). It is possible that several participants in our study have developed and recovered from depression during the 2-year period. It is a limitation of our study that we were not able to identify those participants and we may have oversampled cases of prolonged or chronic depression. However, chronicity does not seem to affect cortisol concentration of the depressed beyond the effect of symptom severity and hospitalization (Stetler and Miller, 2011).

Cortisol concentration exhibits diurnal variation and due to differences in cortisol awakening response among depressed and non-depressed participants the exact time of sampling could be important. We measured morning cortisol concentration 30 min after awakening, which is not comparable to the measurements at 8 AM by Harris et al. (2000), Goodyer et al. (2000), Goodyer et al. (2010), and Halligan et al. (2007), or the measurements 1 h after awakening by Ellenbogen et al. (2011). Adam et al. (2010) and Vrshek-Schallhorn et al. (2012) collected saliva samples 40 min after awakening, and did not find any significant association between morning cortisol concentration and subsequent depression. Morning cortisol concentration is affected more by the time of awakening than by the time of the day (Pruessner et al., 1997; Edwards et al., 2001). Thus, it is possible that the 8 AM samples do not reflect the morning cortisol peak, but the capacity for recovery following the morning peak.

Depression is associated with a blunted cortisol response when exposed to an acute stressor and an impaired recovery (Burke et al., 2005). If a similar pattern is present at the causal path leading to depression this could explain the low morning cortisol among the depressed participants of our study as well as the high 8 AM cortisol concentration among the depressed in the studies by Harris et al. (2000), Goodyer et al. (2000, 2010), and Halligan et al. (2007). We do, however, find no indication of a higher evening cortisol concentration, as would be expected due to the impaired recovery among the depressed.

To account for the fact that all participants did not collect the saliva samples at the exact time they were instructed to; we performed sub-analyses based on sub-groups of participants who collected their samples closest to the instructed time. This sub-analyses showed lower odds ratio of depression by increasing cortisol concentration compared to the entire study population, and indicate that our results are biased towards the null and even stronger inverse association between cortisol level and depression.

The study included only 62 cases of depression. This limits the statistical power. Furthermore, the low number of cases limits the ability to adjust thoroughly for all potential confounders. The similarity between the crude and the two differently adjusted results does however indicate no strong confounding.

The baseline participation rate was low (45%), which could have biased results, if participation was associated with cortisol concentration as well as depression. To assess selective participation we obtained registry information on both responders and non-responders at baseline (Kaerlev et al., 2011). Compared to non-responders, participants were more often women, were older, had higher social class, were less frequently on sick leave, and were less often prescribed antidepressant medication. We did, however, have no way to assess cortisol levels of non-responders, but we would not expect participation to be related to cortisol levels that hardly were known by the candidates for the study. The prevalence of depression in this study population was lower than in the general Danish population. Based on previously reported prevalence and recurrence rates of depression we had expected twice the number of cases (Olsen et al., 2004; Burcusa and Iacono, 2007). Our lower-than-expected number of cases may be due to a healthy worker effect.

During follow up the participation rate was higher (72%) but selection may still have biased our findings. However,

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selection bias is unlikely because cortisol level has no strong perceivable correlates in a healthy, employed population that may have influenced participation. Furthermore, we found that the relation between cortisol concentration and depressive symptoms at baseline did not differ between participants and non-participants at follow up and thus does not indicate strong selection bias. Participants had mean morning and evening cortisol concentrations of 12.7 nmol/l and 2.1 nmol/l, respectively compared to non-participants with mean morning and evening concentrations of 12.2 nmol/l and 2.3 nmol/l, respectively.

The odds ratios of depression for morning-to-evening slope, morning, and daily mean cortisol concentration are strongly correlated ($r > 0.9$). Evening cortisol are correlated to mean cortisol concentration ($r = 0.4$) but are not significantly correlated to morning-to-evening slope. The four cortisol measures do not reflect four independent factors but are strongly related, especially morning-to-evening slope, mean, and morning concentration.

To conclude, this study did not support our hypothesis that high salivary cortisol concentration is a risk factor for depression, but indicate that a low mean salivary cortisol concentration and a flat morning-to-evening curve may be risk factors of depression.

Role of the funding source

The funding sources had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Conflict of interest

All authors declare no conflicts of interest.

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