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Psychophysiological biomarkers of workplace stressors

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Abstract

Workplace stressors are associated with greater coronary heart disease risk, although there is debate over the psychophysiological consequences of work stress. This study builds on recent reviews and examines the literature linking work stress with sympatho-adrenal biomarkers (plasma catecholamines and heart rate variability) and HPA axis biomarkers- the post-morning profile of cortisol.

Methods—Relevant studies using appropriate search terms were searched using the bibliographic databases *PubMed*, *Embase*, *Biosys* and *Toxline*. Four studies on plasma catecholamines, ten studies on heart rate variability, and sixteen studies on post-morning cortisol were reviewed.

Results—In the majority of studies that examined the association of HRV and work stress, greater reports of work stress is associated with lower heart rate variability. The findings for plasma catecholamines and cortisol secretion are less clear cut and suffer from poorer quality of studies in general.

Conclusion—There is evidence that work stress is related to elevated stress responses in terms of sympatho-adrenal and HPA axis biomarkers.

Keywords

work stress; catecholamines; HPA axis; neuro-endocrine; cortisol

Psychophysiological biomarkers of workplace stressors and health

Exposure to workplace stressors (or “work stress”) increases the risk of heart disease. A recent systematic review concluded that there was moderate evidence that adverse psychosocial working conditions are a risk factor for ischaemic heart disease among men. (Eller *et al.* 2009) A meta-analysis estimated that there was an average 50% excess risk for CHD among employees with work stress. (Kivimaki *et al.* 2006) The mechanisms leading from exposure to workplace stressors to CHD are hypothesised to be indirect effects through unhealthy behaviours (such as smoking, unhealthy dietary patterns, lack of exercise), as well as direct effects on neuro-endocrine stress responses. (Chandola *et al.* 2008) Activation of these pathways can be quantified using psychophysiological stress biomarkers. However, there is some debate on whether such daily life stressors are associated with elevated

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neuroendocrine stress responses,(Gersten, 2008) especially as many studies report no significant associations and a few report a decreased stress response with work stress.

Neuroendocrine pathways linking stress to disease

Stressful stimuli serve to activate neural, neuroendocrine and endocrine pathways. Short term biological responses to stressful stimuli can be adaptive; for example, an increase in the capacity of the blood to clot under stress can serve to reduce blood loss in case of injury. However extreme, frequent or chronic activations of such mechanisms may be detrimental to health. These include changes in the function of two main axes of the stress response: (i) the sympatho-adrenal axis, which includes activation of the sympathetic nervous system leading to changes in peripheral adrenaline and noradrenaline levels; and (ii) the hypothalamic-pituitary function, leading to changes in a wide variety of endocrine factors including cortisol and prolactin.

Sympatho-adrenal biomarkers

Activation of the sympathetic nervous system can be assessed by measurement of peripheral adrenaline or noradrenaline levels (catecholamines), however these are short acting and short lived molecules and researchers have tended to examine these using integrated methods for example in urine collections, or examine change in these factors in response to an acute stress. Researchers have also examined factors that may reflect the autonomic system function more generally and assess sympathetic or parasympathetic activity. These include measures such as heart rate or heart rate variability, which reflect the balance between sympathetic and parasympathetic activity. Heart rate variability is a measure widely used as a marker of autonomic influences on the heart. This is assessed by power spectral analysis and typical measures include total and low frequency power (relative sympathetic predominance) as well as high frequency power (vagal tone).

Hypothalamic Pituitary Adrenal axis biomarkers

A primary axis activated upon stress is the Hypothalamic-Pituitary-Adrenal (HPA) axis. Stressful stimuli serve to activate HPA function to cause an increase in peripheral cortisol. Cortisol can effect physiological changes that encompass most of the main organ systems, and help to provide the energetic resources needed to face acute stressors, Cortisol also helps to modulate and contain other components of the physiological stress response.(Sapolsky, 2000) Increasingly, HPA-axis researchers are focusing on the marked diurnal rhythm in the release of cortisol, with various elements of this rhythm viewed as essential indicators of HPA axis functioning. The diurnal cortisol rhythm is typically characterised by high levels upon waking, a substantial (50–60%) increase in cortisol concentration following awakening, peaking at about 30–45 minutes after awakening (called the Cortisol Awakening Response or CAR), and a subsequent decline over the remainder of the day, reaching a low point or nadir around midnight.(Kirschbaum and Hellhammer, 1989) Healthy HPA-axis function is thought to require the presence of strong diurnal patterning. It has been suggested that deviations from the typical diurnal cycle of cortisol may provide valuable information regarding environmental influences on the HPA axis and the role of the HPA axis in disease processes.(Carney *et al.* 2001)

Additional less well considered neuroendocrine pathways that are altered upon stress include increases in prolactin and decreases in testosterone. Additionally, activation of the HPA axis leads to decreases in activity in the hypothalamic-pituitary-growth hormone pathway and in the reproductive pathways leading to changes in reproductive hormones in men and women.

Defining workplace stressors (“work stress”)

There are three main validated models of work stress. The demands/control/support model (Karasek and Theorell, 1990) measures three factors: psychological job demands, decision latitude (or job control) and social support at work. Job strain, a measure of workplace stress, can be derived from the demands/control/support model and posits that people working in jobs that are simultaneously characterized by high demands and low control are at risk of stress-related ill health and disease. Iso-strain, a related measure of workplace stress, hypothesizes that people experiencing job strain and who are simultaneously socially isolated (experience low work social support) carry even higher risk for disease.

The theoretical approach of the Effort-Reward Imbalance (ERI) model is focused on the notion of social reciprocity where efforts are equalized by respective rewards (Siegrist, 1998). Failed reciprocity resulting from a violation of this norm elicits strong negative emotions and sustained stress. Related to effort-reward imbalance, overcommitment at work is an additional workplace stressor, which may lead to conditions of high effort/low reward.

Organisational justice refers to the extent to which employees perceive workplace procedures, interactions and outcomes to be fair in nature (Elovainio *et al.* 2002). There are two main components. Relational justice refers to the extent supervisors consider their employees' viewpoint, are able to suppress personal biases, and take steps to deal with subordinates in a fair and truthful manner. Procedural justice involves the fairness of formal decision-making procedures.

Recent reviews linking workplace stressors to neuroendocrine responses

There have been two recent reviews on workplace stressors and neuroendocrine responses. One focussed on physiological changes in blood and urine (Hansen *et al.* 2009) while another focussed on the cortisol awakening response (Chida and Steptoe, 2009). The Hansen *et al.* review found 11 studies that linked adverse psychosocial working conditions with urinary catecholamines, while a further four studies showed no association (Hansen *et al.* 2009). The review did not find any evidence for an association between work stress and lower levels catecholamines. This review also did not report any studies on work stress and plasma catecholamines.

The Hansen *et al.* review also concluded that there are no consistent associations between cortisol in serum or urine and the psychosocial working environment. In contrast, the Chida & Steptoe (Chida and Steptoe, 2009) review concluded there is a positive association between work stress and the cortisol awakening response. The reasons for this discrepancy may partly lie in the nature of the studies reviewed (predominantly urinary cortisol samples for the Hansen *et al.* review, while the Chida & Steptoe review included saliva samples), and also in the inclusion of differing sampling schedules of cortisol reviewed in the Hansen *et al.* paper. On the other hand, the Chida & Steptoe review explicitly took the diurnal profile of cortisol into account, and only looked the cortisol awakening response (CAR). In relation to cortisol and the importance of the diurnal patterning outlined above, this is probably the stronger study and so their conclusion that work stress is related to CAR is more robust.

Despite these two recent reviews on work stress and neuroendocrine responses, there are a few areas not covered in relation to plasma catecholamines, heart rate variability and the diurnal (post-morning) profile of cortisol. These psychophysiological biomarkers will be the subject of review in this paper.

Methods

We searched for relevant studies using the bibliographic databases PubMed, Embase, Biosys and Toxline for the period until August 2009. We also scrutinised reference lists from relevant reviews and articles. The search terms used for the sympatho-adrenal biomarkers included: *catecholamines*, *adrenaline*, *epinephrine*, *noradrenaline* *norepinephrine*, and *heart-rate-variability*, *HRV*, *vagal-tone*. The search terms for workplace stressors included *job-stress*, *work-stress*, *job-strain*, *job-control*, *job-demands*, *work-social-support*, *effort-reward-imbalance*, *overcommitment*, *organisational-justice*, *organizational-justice*.

The inclusion criteria were papers written in English, with measures of work stress. The exclusion criteria were studies not using validated work stress measures (job demands/control/support/job strain/iso-strain, effort-reward imbalance, organisational justice and some specific professional stress scales). In addition, specific exclusion criteria were used for the catecholamines results (excluding studies with urinary samples) and for the cortisol analysis (excluding CAR only analyses and morning only samples).

The search strategy returned four studies on plasma catecholamines, ten studies on heart rate variability and sixteen studies on post-morning cortisol. A quantitative assessment of these studies was not carried out as the measurement protocols of the psychophysiological biomarkers of stress and the work stress exposure vary considerably from study to study. The studies were reviewed in terms of study population, sample size, exposure measurement, study design (whether work stress was measured cross-sectionally or longitudinally) and association. The associations were labelled as “positive” (work stressors were associated with higher levels of the biomarkers), “negative” (work stressors were associated with lower levels of the biomarkers) and “non-significant” (the significance level for the statistical test of association was <0.05).

Results (Table 1)

Sympatho-adrenal biomarkers

Plasma catecholamines—Two out of four studies report a negative association between work stress and plasma catecholamines, (Kawaguchi *et al.* 2007; Wirtz *et al.* 2008). Two studies report a non-significant association, (Nomura *et al.* 2005; vonKanel *et al.* 2009) although one of them (vonKanel *et al.* 2009) reports a marginally positive association ($p=0.06$) between overcommitment and noradrenaline.

Kawaguchi *et al.* (Kawaguchi *et al.* 2007) assessed work stress (Hurrell, Jr. and McLaney, 1988) among nurses, and reported greater job control is correlated with higher levels of noradrenaline. Workload (job demands) was not associated with catecholamines. Wirtz *et al.* (Wirtz *et al.* 2008) showed overcommitment among male volunteers is associated with lower baseline levels of noradrenaline and lower stress reactivity to a stress test. These findings are congruent with previous results showing reduced responsiveness to stress among those with chronic effort-reward imbalance (Siegrist *et al.* 1997). The authors (Wirtz *et al.* 2008) suggest that overcommitment may lead to an initially heightened stress response, but over time this leads to vital exhaustion (Appels, 1997) and compensatory down-regulation of stress hormone production. However the study (Wirtz *et al.* 2008) is cross sectional and cannot evaluate if overcommitment does represent an overtaking of biological stress responses.

The collection of urine samples is very intensive, invasive and not conducive for large sample sizes so it may be expected that plasma biomarkers are more readily measured in large scale studies. However the plasma catecholamine studies reviewed had small sample

sizes. In addition, three studies recruit from single occupational groups such as teachers(vonKanel *et al.* 2009) and nurses.(Kawaguchi *et al.* 2007) Two of the studies measured workplace stressors using the Effort-Reward Imbalance/Overcommitment model(vonKanel *et al.* 2009; Wirtz *et al.* 2008), one used the job strain model.(Nomura *et al.* 2005) Most of the studies were cross-sectional, and only one study(vonKanel *et al.* 2009) measured changes in work stress (over a 13–27 month period).

This review found no clear association between work stress and plasma levels of catecholamines. The small sample sizes and restricted sample populations makes it hard to generalise to other working populations.

Heart rate variability

Seven of the ten studies reviewed found a negative association between workplace stressors and heart rate variability which suggests work stress reduces vagal activity. Some used the Job Demands/Control/Support model to report an association with job strain(Collins *et al.* 2005; Kang *et al.* 2004), iso-strain(Chandola *et al.* 2008) or low job control(Collins *et al.* 2005; Hemingway *et al.* 2005). Other studies have found an association with effort-reward imbalance(Hanson *et al.* 2001; Hintsanen *et al.* 2007; Vrijkotte *et al.* 2000). Only one study (vanAmelsvoort *et al.* 2000) reported a positive association job strain and higher heart rate variability. Two studies found no significant associations(Elovainio *et al.* 2006; Riese *et al.* 2004) although both reported negative associations between work stress and heart rate variability. Riese *et al.*(Riese *et al.* 2004) suggest that the effect of job strain on (lower) heart rate variability is less apparent for women compared to men, however this is contradicted by other studies in Table 2 with women workers showing positive associations between work stress and (lower) heart rate variability. Elovainio *et al.* (Elovainio *et al.* 2006) reported low perceived justice was also related to an 80% excess risk of reduced high frequency heart rate variability compared to high perceived justice, but this association was not statistically significant.

Unlike the majority of studies on the association between work stress and plasma catecholamines, most of the studies analysing the effect of work stress on heart rate variability do not sample a single occupational group. Furthermore, the sample sizes of these studies tend to be larger, with the Whitehall II civil servants study comprising the largest single study. Three of the studies used longitudinal measures of work stress to ascertain chronic work stress(Chandola *et al.* 2008; Collins *et al.* 2005; Riese *et al.* 2004)

The review of studies largely finds a negative association between work stressors and the heart rate variability components. This suggests that workplace stress leads to vagal withdrawal and sympathetic saturation, indicating a prevalence of sympathetic mechanisms leading to cardiac electrical instability.(Malik and Camm, 1993)

HPA axis biomarker: Post-morning cortisol levels

There is no clear pattern of association in Table 3. Six studies report positive associations, four studies report negative associations and nine studies report no significant associations.

Reduced cortisol reactivity (negative associations)—In a study of school teachers, (Bellingrath *et al.* 2008; Bellingrath and Kudielka, 2008) highly overcommitted teachers as well as those reporting lower rewards at work showed lower cortisol responses after an acute stress challenge compared to teachers with lower levels of overcommitment and greater rewards. Siegrist *et al.*(Siegrist *et al.* 1997) also observed reduced increased cortisol responses in stressed middle managers in terms of ERI, after a stress test. The results from these studies are similar to those from Wirtz(Wirtz *et al.* 2008) which found

overcommitment was associated with reduced stress reactivity. In a study of nurses and accountants (Evans and Steptoe, 2001), work social support was not related to cortisol on work days, but on leisure days, cortisol was lower among individuals reporting low social support. In contrast to the studies cited above (Bellingrath *et al.* 2008; Bellingrath and Kudielka, 2008; Siegrist *et al.* 1997; Wirtz *et al.* 2008),

Evans *et al.* (Evans and Steptoe, 2001) suggest that cortisol measured during the daytime and evening, and especially during non-work days is not a good marker of psychobiological responses to work. Differences in cortisol output early in the day may be much more sensitive to work and chronic strain. (Pruessner *et al.* 1997)

Increased cortisol reactivity (positive associations)—Six studies found positive associations between work stress and cortisol levels measured in the afternoon or evening. In a longitudinal study of white collar workers, (Rystedt *et al.* 2008) chronic work stress (iso-strain) was associated with higher evening cortisol levels. The authors suggest morning cortisol may be more affected by current levels of job strain, while evening levels of cortisol are influenced by chronic psychosocial stressors. This result is in concordance with the findings by Dahlgren *et al.*, (Dahlgren *et al.* 2005) in which evening cortisol was shown to be affected by self reported “stress” levels during working days. In a study of women care workers, (Harris *et al.* 2007) those with lower levels of work stress (having greater job control) had lower cortisol levels in the evening. In a study of healthy volunteers (Eller *et al.* 2006), men who were overcommitted and reported greater effort-reward imbalance had higher evening levels of cortisol than men reporting less work stress. Two studies from the Whitehall II civil servants study report greater overcommitment (Steptoe *et al.* 2004) and low job control (Kunz-Ebrecht *et al.* 2004) among men are associated with elevated cortisol production throughout the day. Three studies reported gender specific analyses: work stressors were associated with higher levels of cortisol during the day among men but not women in these studies. However, other studies with women participants report positive associations between work stressors and cortisol. Hence there is no consistent evidence to suggest that the association of work stress with cortisol reactivity is stronger among men.

It is clear that there are studies that find greater levels of work stress are associated with both lower cortisol reactivity and higher levels of cortisol production throughout the day. It has been speculated that reduced cortisol responses in individuals reporting work stress might be the consequence of a chronic state of stress. However, only three studies in this review actually used longitudinal data to measure chronic work stress and among them only one study (Rystedt *et al.* 2008) found chronic work stress was associated with higher evening cortisol levels. There was no evidence that work stress measured longitudinally (“chronic work stress”) was associated with lower cortisol reactivity.

Overall, most of the studies reviewed suffered from the same limitations as the review for plasma catecholamines- most were cross-sectional, with small sample sizes and restricted sample populations making it hard to generalise to other working populations. The lack of a clear pattern in the results may arise primarily from these limitations.

Workplace stress and other biomarkers

The review by Hansen (Hansen *et al.* 2009) also examined associations between work stressors and testosterone and prolactin. It found 8 studies showing negative associations between work stressors and testosterone, while a further three found non-significant associations. Out of 17 studies on work stressors and prolactin, nine studies reported positive associations, four studies reported negative associations and a further four studies reported no significant associations.

Oxidative DNA damage, measured through urinary concentrations of 8-hydroxy-2'-deoxyguanosine (8-OHdG), has been associated with organisational injustice among men and job strain among women.(Inoue *et al.* 2009) In an experiment, the group that received no (vs. some) rewards (effort-reward imbalance) had hyperactivations in the medial prefrontal, anterior cingulate and dorsolateral prefrontal cortex measured through fMRI scans.(Siegrist *et al.* 2005) This indicates a compromised ability of adapting brain activation among those suffering from chronic social reward frustration.

Discussion

In this review, we find evidence that work stressors are associated with increased levels of catecholamines (particularly from urinary samples), lower levels of heart rate variability, a greater cortisol awakening response, higher levels of prolactin and lower levels of testosterone (see Figure 1). Thus there is evidence that work stressors are related to elevated stress responses in terms of sympatho-adrenal and HPA axis biomarkers.

Our review of the studies available suggests that measurement of biomarkers of work stress tends to be limited to small focussed studies rather than large scale epidemiological cohorts. Studies are also largely cross sectional, with few studies on longitudinal measurements of work based stress and autonomic or neuroendocrine function. Despite measuring work stress only cross-sectionally, a number of studies discuss how chronic work stress leads to blunted stress reactivity profiles. This had led to the interpretation of reduced levels of stress biomarkers with work stress as evidence of the effect of chronic work stress on physiological stress responses. However, only longitudinal studies would be able to examine the suggested bi-modal response of these outcomes to work based stressors; whether work stress leads to an initial activation followed by exhaustion of the pathways.(Appels, 1997) Furthermore, even longitudinal assessment of work stressors may not necessarily reveal exhaustion if the assessment periods of work stress has not been long enough.

We did not conduct a formal meta-analysis of the literature because of the wide heterogeneity in the measurement of the work stress exposure and stress response. For example, although heart rate variability had the most consistent associations in the literature, the methodology varied considerably between studies. For example, Chandola *et al.* (Chandola *et al.* 2008) measured heart rate variability for 15 minutes during a clinical visit and found a positive association between job strain and lower HRV while Riese *et al.*, (Riese *et al.* 2004) measured heart rate variability for 24 hours on two occasions and failed to find an association. Measurement decisions are based on many factors including participant burden, size of study, but harmonisation of methodologies across a number of studies may serve to reduce imprecision in findings.

We were careful to distinguish the association of the stressor, in this case work based stress from the stress response in our review. This review did not consider burnout, anxiety(Kawachi *et al.* 1995) and panic disorder(Yeragani *et al.* 1993) as within the remit as these measures do not distinguish the stress generating working conditions from the psychological stress response. We also did not consider inflammatory markers as within the remit of this review even though they may be important mediators between stressors and health. This is because we aimed to examine 'upstream' markers that may mediate the stressor-health relationship. In the allostatic load paradigm, these may be considered 'primary mediators' in the cascade. (McEwen and Seeman, 1999) Inflammatory markers represent secondary mediators in the cascade. Additionally, inflammatory marker levels are substantially influenced by adiposity as adipocytes release inflammatory markers(Mohamed-Ali *et al.* 1997) contributing up to one third of circulating levels.

Most of the studies reviewed used either the job strain or the effort-reward imbalance models to measure work place stressors. Although these models differ in their theoretical basis, they also measure overlapping concepts (especially in relation to job demands and efforts at work). The review did not find any systematic association of either model with specific biomarkers, suggesting that physiological stress reactions to work stress are basically the same irrespective of the source of stressors.

Our review suggests that work based stress measures are consistently associated with alterations in the autonomic nervous system such that there is an apparent alteration in sympathetic-parasympathetic balance. These changes in autonomic function have been associated with adverse health outcomes. Delayed heart rate recovery and lower cardiac autonomic reactivity (heart rate, pre-ejection period, and heart rate variability) were prospectively associated with higher carotid atherosclerosis over a 2-year period.(Heponiemi *et al.* 2007) In 1999 participants of the Whitehall II study, measures of autonomic function are associated with some measures of work based stress and in prospective analyses with measures of health, in particular with obesity, blood pressure and cholesterol.(Britton *et al.* 2007) This adds to the plausibility that work stress leads to coronary heart disease partly through activation of the physiological stress responses reviewed in this study.

The association of cortisol secretion with health outcomes is currently unclear with no consistent evidence from large scale prospective surveys of an independent association with health outcomes. Currently there is poor empirical evidence that the cortisol awakening response is associated with clinical end points while there is evidence that slope in diurnal cortisol secretion is predictive of increased mortality in patient populations.(Sapton *et al.* 2000)

Limitations

This review has several limitations. A limitation inherent in most reviews is that they are restricted to the evaluation of results in published articles. Authors are more likely to submit and editors more likely to accept papers with positive rather than null or negative findings, which may lead to a positive publication bias. Another limitation is the inconsistent use of psychophysiological biomarkers between studies, leading to over-representation of some biomarkers (eg. cortisol) and very limited use of others (eg. DHEA). Also, the cortisol response patterns vary as a function of stressor, and therefore there is no single method for assigning reactivity and recovery to all studies of cortisol in response to acute stress. (Dickerson and Kemeny, 2004). The variety in exposure and outcomes limits the ability to formal statistical examination of the literature. Due to these limitations, as well as the small number of studies identified for some biomarkers, the findings for specific biomarkers should be interpreted with caution.

Conclusion

In this review, we find that in the majority of studies that have examined the association of HRV and work based stress, greater reports of work stress is associated with lower heart rate variability. The findings for plasma catecholamines and cortisol secretion are less clear cut and suffer from poorer quality of studies in general. Taken in conjunction with recent reviews,(Chida and Steptoe, 2009; Hansen *et al.* 2009) there is evidence that work stressors are related to elevated stress responses in terms of sympatho-adrenal and HPA axis biomarkers.

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Figure 1.

Summary figure of the association between work stressors and neuroendocrine biomarkers

Table 1

Studies on Workplace Stressors and Plasma Catecholamines

Plasma Catecholamines

1st author	Year	Sample	Occupation	Exposure	Study design	Association
Nomura	2005	396m	information technology	job strain	C	-
Kawaguchi	2007	128f	nurses	(low) job control	C	↑
Wirtz	2008	58m	non-smoking middle aged men	OC	C	↑
von Kanel	2009	19m/33f	teachers	ERI/OC	L	-

Heart Rate Variability

1st author	Year	Sample	Occupation	Exposure	Study design	Association
van Amelsvoort	2000	113m/22f	industrial/hospital workers	job strain	C	↑
Vrijotte	2000	109m	white collar workers	ERI	C	↑
Hanson	2001	39m/31f	white collar workers	OC	C	↑
Kang	2004	169m	industrial shipyard workers	job strain	C	↑
Riese	2004	159f	nurses	job strain	L	-
Collins	2005	36m	population based sample	(low) job control	L	↑
Hemingway	2005	2197m	white collar workers	(low) job control	C	↑
Elovainio	2006	57f	care workers	org justice	C	-
Hintsanen	2007	406m/457f	population based sample	ERI	C	-m/↑f
Chandola	2008	2373m/919f	white collar workers	iso strain	L	↑

Post-Morning Cortisol

1st author	Year	Sample	Occupation	Exposure	Study design	Association
Brantley	1988	18m	medical residents/lab technicians	Daily Stress Inventory*	C	↑
Siegrist	1997	68	middle managers	ERI	C	↑
Hanson	2000	43m/34f	health professionals & office workers	ERI	L	-
Steptoe	2000	41m/64f	school teachers	job strain	C	-
Evans	2001	40m/53f	nurses and accountants	(low) work social support	C	↑
Fujiwara	2004	16f	nurses	job strain	C	-
Kunz-Ebrecht	2004	97m/84f	civil servants	(low) job control	C	↑m/-f

Plasma Catecholamines

1st author	Year	Sample	Occupation	Exposure	Study design	Association
Steptoe	2004	105m/92f	civil servants	OC	C	↑m/-f
Alderling	2006	181m/384f	population	job strain	L	-
Eller	2006	28m/55f	volunteers	ERI	C	↑m/-f
Harris	2007	44f	care workers	(low) job control	C	↑
Bellingrath	2008	20m/33w	school teachers	ERI/OC	C	↓
Bellingrath	2008	40m/95f	school teachers	ERI	C	↓
Maina	2008	16m/89f	call centre workers	job strain	C	-
Rystedt	2008	53m/24f	white-collar workers	iso-strain	L	↑
Maina	2009	16m/20f	call centre workers	job strain	C	-

m: males

f: females

OC: Overcommitment

ERI: Effort-Reward Imbalance

C; Cross-Sectional measure of work stress

L: Longitudinal measure of work stress

↑: Positive association (greater work stress with higher levels of biomarker)

↓: Negative association (greater work stress with lower levels of biomarker)

-: non statistically significant association (at 5% level)

* measured from the NIOSH job stress inventory(Hurrell, Jr. and McLaney, 1988)