Work Stress and Diurnal Cortisol Secretion:

Is There Gender Specificity?

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Abstract

Background: So far equivocal evidence has accumulated on work stress related dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. It remains unclear whether the relation applies to men and women equally. Conflicting evidence on the gender-specific effect of work stress and its relation to health warrants further exploration on the mediating role of the HPA axis. This study aims to assess the gender-specific relation between work stress and diurnal cortisol secretion in a large-scale population cohort, in which potential confounders could be controlled.

Methods: Work stress was assessed by two main theoretical models: the job-demand-control model and the effort-reward-imbalance model using questionnaires. Salivary cortisol samples were collected six times over a normal day at Whitehall II Phase7 (2003-2004). Four parameters were used to model the diurnal cortisol profile: morning cortisol, cortisol awakening response (CAR), diurnal cortisol decline (slope) and evening cortisol. Linear regression was used to analyze the association between work stress and cortisol secretion adjusting for other covariates.

Results: Different components of work stress were associated with cortisol in a gender-specific manner. For women, a reduced CAR was associated with higher demand, lower support and higher job strain. For men, higher effort, effort reward imbalance and over-commitment were related to a flatter slope, elevated evening cortisol and lower morning cortisol.

Conclusions: The gender-specific cortisol response reflects the gender-specific health outcomes addressed by different work stress models. The findings highlight the possibility that interpretation of work stress may vary by gender, and provide evidence that the HPA axis may be an important neuroendocrine pathway connecting the psychosocial environment to health consequences.

1. Background

Work stress has been established as a major risk factor for a body of health impairments, particularly cardiovascular diseases (Kuper and Marmot, 2003, Chandola et al., 2005), the metabolic syndrome (Chandola et al., 2006, Gimeno et al., 2010), Type 2 Diabetes Mellitus (T2DM) (Heraclides et al., 2011, Kumari et al., 2004), mental disorders (Van Vegchel et al., 2005, Stansfeld et al., 1999, Elovainio et al., 2002) and poor health functioning (Elovainio et al., 2009, Stansfeld et al., 2000). Interestingly, a paradox has emerged when using different work stress models to assess T2DM. Effort-reward imbalance appears to be a risk factor for T2DM risk in men only (Kumari et al., 2004), whereas the demand-control model appears more relevant to women, as iso-strain was a risk factor for women but not men (Heraclides et al., 2011, Heraclides et al., 2009). Given variations in exposure to work stress (Bosma et al., 1997) and gender-relevant response to stressors, analyses of psychosocial pathways of health impairments should take gender-specific effects of work stress models into account.

The mechanisms underlying the link between work stress and adverse health outcomes remain unclear. Two central mechanisms have been proposed for the association, the direct neuroendocrine mechanism and the indirect behavioural mechanism (Chandola et al., 2008, Brunner and Marmot, 2006). The hypothalamic pituitary adrenal (HPA) axis, one of the main axes of neuroendocrine stress responses, can be

quantitatively analyzed using psycho-physiological stress biomarkers. However, inconsistent evidence has accumulated on work stress related dysregulation of the HPA axis, likely due to small study sample sizes, different methodologies, non-adherence to cortisol sampling protocol and inadequate adjustments for confounding factors (Hjortskov et al., 2004).

In view of the paradoxical findings outlined above, current evidence provides an opportunity to analyze the mediating role of the HPA axis by addressing the gender-specific effect of two work stress models. As the extent to which HPA axis response to stress reflects the gender-specific work stress—T2DM findings would produce novel evidence concerning the importance of the neuroendocrine pathway. Elucidating this "missing link" might also shed light on the pathophysiological pathway in relations between work stress, increased cardiovascular and metabolic diseases.

1.1. Work stress models

Two validated theoretical models of work stress have been widely employed in studying psychosocial factors: the job demand control (JDC) model (Karasek Jr, 1979), and the effort-reward imbalance (ERI) model (Siegrist, 1996). The JDC model has three basic components, job control, job demands and social support at work. This model postulates a combination of lower control (less skill utilization and lower decision authority) and higher work demand (more quantitative work load and conflicting demands) will trigger job strain, a leading risk factor for various health impairments, in particular cardiovascular diseases (CVD). Moreover, iso-strain, defined as people

experiencing job strain are also socially isolated, can result in even higher risk for diseases.

The ERI model explicitly emphasizes social reciprocity. A sustained unfair trade-off between cost and gain will elicit negative emotions and further lead to adverse long-term health consequences. There are two components of the ERI model: the extrinsic component, addressing the situational factors of work environment; and the intrinsic (personal characteristics) component, where over-commitment is exhibited by people who are highly motivated, have a high need for approval and commit excessively to work. It is hypothesized that over-commitment is an independent predictor of CVD events.

Similarities exist between these two models as both of them tap psychosocial disequilibrium in the work organization (demand versus control, effort versus reward) (Harma et al., 2006). In both models, information regarding risk factors is collected through self-administered questionnaires and corresponding data are analyzed based on standard scoring (Siegrist et al., 2004). Besides, overlapping and highly correlated items are adopted in respective scales (Bosma et al., 1998). For example, demand of the JDC model is correlated with effort, the extrinsic part of the ERI model; social support at work is related with esteem reward.

Nevertheless, distinctive conceptual and methodological differences should be noted. Confined to the structural characteristics of the psychosocial environment, the JDC model place emphasis on the power structure, labour division and workplace

democracy (Elovainio et al., 2009). Thus the JDC model is a more objective measure of stressors, specific to job task characteristics and without intrinsic components (Li et al., 2006). On the other hand, the ERI model takes personal coping strategy into account, including both extrinsic (situational) and intrinsic (personal) characteristics. In the ERI model, reward is weighted against effort and the degree of equivalence defines the level of work stress (Kivimäki et al., 2007), which highlights the cognitive levels of reciprocity, embodied by wage/salary, esteem and job security (Van Vegchel et al., 2005, Siegrist et al., 2004). Therefore compared to JDC, additional macro-economic market conditions are being considered in the ERI model (Bosma et al., 1998).

Moreover, evidence shows the two work stress models may exert differential impacts on men and women (Bildt and Michélsen, 2002, Bond et al., 2004, Matthews et al., 1998, Peter et al., 2002, Heraclides et al., 2011, Kumari et al., 2004, Vermeulen and Mustard, 2000). As the JDC model emphasizes the labour division while the ERI model points to distributive fairness (Siegrist et al., 2004), different theoretical orientations of the two models may capture disparate aspects of the psychosocial environment experienced by men and women (Vermeulen and Mustard, 2000, Artazcoz et al., 2007). On the other hand, gender variation in susceptibility as well as perception of work stress may also result in different explanatory power of work stress models in relation to health outcomes (Li et al., 2006, Roxburgh, 1996).

Considering different aspects of the two work stress models, it is plausible to employ them simultaneously to compare different approaches in quantifying work

stress, to better evaluate adverse work environment and to assess gender-specific health effects. Several studies have shown the two models can independently predict health outcomes, and combining them can help identifying different aspects of the psychosocial work environment (Bosma et al., 1998, Kivimäki et al., 2007, Li et al., 2006, De Jonge et al., 2000).

1.2. HPA axis and salivary cortisol

The HPA axis has long been considered as a crucial linkage between psychosocial environment and various health outcomes (Selye, 1976). It not only maintains normal physiological functions but also regulates other relevant systems, including the immune system, the metabolic system and the central nervous system (Dickerson and Kemeny, 2004, Dowd et al., 2009, Brunner et al., 2002). In stress response, stressor stimulates the HPA axis, causing an increase of peripheral cortisol. As the end product of the hormonal cascade, cortisol modulates main organ systems and generates energy in order to cope with challenge (Fries et al., 2009). In the short term, the mobilization of cortisol and other related glucocorticoid hormones is essential for physiological functioning. However, a prolonged, frequent or extreme activation of the HPA axis can provoke adverse health consequences (Lundberg, 2005). The pathway underlying dysregulation of the HPA and ill-health has been well established by experimental and clinical evidence (Brunner and Marmot, 2006).

Stress induced HPA axis activation is complex and regulated by various factors. The three most studied HPA axis-related endocrine signals are adrenocorticotropic

hormone (ACTH), total cortisol in blood and salivary cortisol. These three parameters depict partially different aspects of the HPA axis functioning profile and, ideally, measuring a combination of theses three analytes would provide the most comprehensive information (Hellhammer et al., 2009). However, the feasibility and acceptability of collecting multiple blood samples is the major barrier to field study. Thus the convenience of sampling salivary cortisol provides an opportunity to obtain non-invasive, stress-free and real-time samples in a naturalistic setting, without medical personnel (Hansen et al., 2008, Koh and Koh, 2007). Those advantages facilitate ambulatory assessments with repeated collections of cortisol data throughout the day. Studies of validity and reliability suggest salivary cortisol is a practical biomarker to assess the neuroendocrine stress response (Hellhammer et al., 2009, Hjortskov et al., 2004, Chida and Steptoe, 2009, Hansen et al., 2008).

Another important feature of salivary cortisol is that it can capture the marked circadian rhythm of the HPA axis (Edwards et al., 2001a). The circadian secretion profile of salivary cortisol is characterized by a low concentration in slow-wave nocturnal sleep, which steadily accumulates over the night and rises to a peak concentration some 30 minutes after awakening. Cortisol concentration then declines sharply until 3 hours post-awakening followed by a more gradual decreasing trend during the remainder of the day to the lowest point in the first half of the night (Koh and Koh, 2007, Edwards et al., 2001a). This diurnal cortisol pattern has been modelled using several parameters, such as cortisol awakening response (CAR), diurnal cortisol slope, area under the daytime cortisol curve (AUC), cortisol at special times (wak-

ing/evening cortisol) and cortisol reactivity to stress. The former three are the most commonly employed, due to higher reliability (Adam and Kumari, 2009).

CAR, the magnitude of the cortisol rise 30-45 minutes post-awakening, is increasingly used as an indicator of the HPA axis activity (Chida and Steptoe, 2009, Adam and Kumari, 2009, Clow et al., 2004). An elevated CAR was related to over-commitment or anticipatory stress (Pruessner et al., 1997, Pruessner et al., 2003, Steptoe et al., 2004b); on the other hand, a flattened CAR was associated with chronic health problems, posttraumatic disorder or burn-out (Pruessner et al., 1997). The reasons why CAR attracts increasing attentions are: first, CAR is a feasible and unique parameter of the HPA axis function (Maina et al., 2009b, Hellhammer et al., 2009); second, as a genuine reaction to wakeup, CAR has high intra-individual stability (Pruessner et al., 1997, Wilhelm et al., 2007, Wustsnm et al., 2000); third, CAR has a regulatory mechanism, independent of the remaining diurnal cycle and unrelated to the mean concentration of cortisol secretion (Edwards et al., 2001b, Wilhelm et al., 2007); fourth, genetic factors appear only to influence CAR but not the rest of diurnal profile, making CAR a distinctive indictor (Kudielka et al., 2009).

Diurnal cortisol decline (slope), measured across the day from awakening to bedtime, ideally indexes the magnitude of cortisol concentration changes throughout the day. Steeper decline typically relates to better health whereas a flattened diurnal cortisol slope appears to indicate chronic stress and increased risk of sub-clinical diseases (Spiegel et al., 2006, Adam and Kumari, 2009), and further predicts higher mortality rates in healthy adults and in women diagnosed with breast cancer (Kumari

et al., 2011, Sephton et al., 2000). As the waking and evening cortisol levels are highly related to cortisol slope (Adam and Gunnar, 2001, Aardal-Eriksson et al., 2001, Cohen et al., 2006), those two along with CAR and cortisol slope were examined in the present study to fully investigate the diurnal cortisol profile.

Table1.1. Frequently used parameters of diurnal cortisol secretion and their interpretation.

	Morning cortisol	CAR	Slope	Evening cortisol
Definition	Level takes as soon as possible after waking	The magnitude of the cortisol rise 30-45 minutes post-awakening	Degree of change in cortisol levels from wakeup to bedtime	Level at bedtime.
Selected Literature	(Kunz-Ebrecht et al., 2004a, Steptoe et al., 2000, Cohen et al., 2006, Kumari et al., 2009a)	(Pruessner et al., 1997) (Federenko et al., 2004, Clow et al., 2004)	(Adam and Gunnar, 2001, Cohen et al., 2006, Adam, 2006)	(Cohen et al., 2006)
Lower /Flatter decline	1.Flatter cortisol slope 2. Higher levels of stress in exhausted individuals might suppress morning cortisol levels.	Burn-out, chronic health problems, posttraumatic stress disorder, chronic fatigue syndrome sleep disorders	HPA-axis dysfunction chronic and acute psychological stress, sub-clinical diseases	Normal diurnal pattern of cortisol secretion.
Higher /Steeper decline	Reflect anticipatory stress	perceived stress over commitment to work high demand plus social stress	A normal rhythm, healthy	1.Flatter cortisol slope 2.Post traumatic syndrome patients reported a higher evening cortisol level

Considering variability, strong diurnal cortisol variation, substantial intra-individual (Dahlgren et al., 2009) and inter-individual variation (Kudielka et al., 2009, Stone et al., 2001) should be estimated and parameterised in statistical models where possible (Hansen et al., 2008). Previous studies using data of Whitehall II found participants who were older, being male, a current smoker (Badrick et al.,

2007), heavy drinker (Badrick et al., 2008), from lower social economic groups (Kumari et al., 2010a), generally or centrally obese (Kumari et al., 2010c), slower walking speed and shorter sleep duration (Kumari et al., 2009b) had a shallower pattern of diurnal cortisol release (Kumari et al., 2010b). Meanwhile, sampling day specific factors, such as wakeup time, time difference between waking and taking first sample should also be used in statistical modelling (Badrick et al., 2008, Adam and Kumari, 2009, Kudielka and Kirschbaum, 2003). Extra cautions should been given to differentiate covariates which may mediate the relation of work stress and cortisol secretion, as over statistical adjustment for those variables would blur possible associations (Hjortskov et al., 2004).

1.3. Previous literature on the relation of work stress and cortisol secretion

There are three reviews on the relation of work stress and the HPA function. Hansen et al. (2009) focused on cortisol change in serum and blood and no consistent relation to work stress was found. In contrast, work stress was consistently and positively associated with CAR in Chida and Steptoe (2009). This finding was partially in concordance with Chandola et al. (2010), though general poor quality of the reviewed studies resulted in a less clear pattern of cortisol response. Different nature of the studies reviewed (the Hansen et al. (2009) included studies using urinary cortisol samples, while salivary samples for the Chida and Steptoe (2009) and the Chandola et al. (2010)) as well as different sampling schedules of cortisol may lead to discrepant findings. Moreover, Chida and Steptoe only reviewed studies on CAR, while Chandola expanded the relation considering the whole diurnal cortisol rhythm.

1.3.1 Cortisol studies utilizing work stress models

Equivocal evidence has accumulated on the relationship between work stress measured by different models and cortisol secretion pattern. In terms of JDC, high job strain has been associated with raised morning cortisol (Alderling et al., 2006, Steptoe et al., 2000, Maina et al., 2009a, Maina et al., 2009b, Chandola et al., 2008), higher evening cortisol (Rystedt et al., 2008, Harris et al., 2007) and increased output throughout the day (Kunz-Ebrecht et al., 2004), whereas inverse or no significant relations have also been reported (Steptoe et al., 1998, Dahlgren et al., 2005, Fujiwara et al., 2004). Moreover, a positive association between high social support and cortisol levels on leisure day has been identified (Fujiwara et al., 2004, Evans and Steptoe, 2001).

Similarly, a mixed picture emerges regarding the ERI model. Most studies reported a blunted cortisol response in relation to high over-commitment and high ERI (Bellingrath and Kudielka, 2008, Bellingrath et al., 2008, Maina et al., 2009a) yet other two studies Harris et al. (2007) and Steptoe et al. (2004) did not observe any significant association between ERI and cortisol levels, even though greater over-commitment was related to increased CAR and elevated cortisol production in Steptoe's study. Only one study found ERI was consistently associated with elevated morning cortisol levels and CAR in both cross-sectional and longitudinal designs (Eller et al., 2006, Eller et al., 2011a).

To date, only three studies have examined both JDC and ERI models simultaneously. Opposing effects on cortisol secretion were observed by Maina and colleagues:

a positive relationship between job strain and higher early cortisol output whereas a negative association of ERI with CAR and diurnal cortisol secretion (Maina et al., 2009a). The authors suggested it may be useful to combine the two complementary models. Eller et al. also examined the two theoretical models in relation to cortisol secretion, focusing on work-family interference. However, the low Cronbach's alpha for the JDC scale rendered the measurements questionable (Eller et al., 2006a). The other study by Harris also employed two work stress models. While none of the work stress components was associated with either morning cortisol or CAR, the study only reported finding on decision authority, which was marginally (p=0.052) related to lower evening cortisol (Harris et al., 2007).

1.3.2. Findings from the Whitehall II study

Several studies have examined the relation between work stress and cortisol secretion using Whitehall II data. Within a sub-sample of 196 healthy volunteers drawn from Whitehall II, Kunz and colleagues found a larger CAR on workday than weekend, and this response was greater among women than men (Kunz-Ebrecht et al., 2004a). However, as a small subset of the Whitehall II data, selection bias may account for the finding. Employing the same small subset, Steptoe assessed the relation in terms of the ERI model. In men both CAR and averaged cortisol output through the day were related to over-commitment, but not to ERI. Association was absent among women. As part of the mechanism analysis on work stress and CVD, Chandola et al. (2008) explored the association between the dysregulated HPA axis and job strain. While little association was found in terms of cumulative work stress, a

cross-sectional correlation showed between work stress and an altered CAR (Chandola et al., 2008). The author argued that a 12-year lag period between earlier phases (1&2) work stress exposures and disturbed cortisol secretion rhythm in phase7 may obscure the neuroendocrine effect.

1.3.3. Gender-specific findings

Work stress models may predict salivary cortisol level in a gender-specific manner. Several studies reported gender-specific analyses: a positive association between job strain and cortisol levels was more pronounced in women, especially during weekdays (Alderling et al., 2006, Maina et al., 2009b, Kunz-Ebrecht et al., 2004); on the other hand, over-commitment and ERI were only related to elevated cortisol among men but not women (Eller et al., 2011a, Steptoe et al., 2004b, Eller et al., 2006b).

According to the definition of the US Institute of Medicine, the term "gender" refers to "A person's self representation as male or female, or how that person is responded to by social institutions…"; while "sex" is a biological term, defined as "the classification of living things generally as either male or female, according to their reproductive organs and functions assigned by the chromosomal complement." (Wizemann and Pardue, 2001).

In present study, we employed the "gender" term as focus is placed on the social constructional disparities between men and women. Different labour market structure, work climate, job responsibility and reward/support from supervisors or colleagues would result in different effects of work stress on men and women

(Artazcoz et al., 2007, Messing et al., 2003, Ursin and Eriksen, 2004, Matthews et al., 1998), which could be embodied by the stress indicator, cortisol, showing gendered disturbances in diurnal cortisol secretion patterns. Therefore, it is important to clarify the association between work stress and cortisol with regard to gender.

1.4. Summary of previous literature and design of current study

In total, we reviewed 18 population-based studies investigating the relation of work stress and diurnal salivary cortisol in recent ten years: 10 studies using the JDC model, 8 studies using the ERI model and 3 studies using both models (Table 1.2). By and large, no clear pattern of the relation can be synthesized from the reviewed studies regarding either model. Literature to date has not systematically explored the gender-specific aspects of work stress in terms of diurnal cortisol profile. Only 5 studies reported gender-specific findings while the majority of the other studies used gender as a confounder. Inappropriate application of multivariate regression may discount the question that whether or not gender could be modelled as a covariate. On the other hand, insufficient adjustments for other potential confounding factors may also obscure the relation by introducing differential bias.

1.4.1. Limitations of existing studies

Several limitations have been cited as potential sources of inconsistent findings. Limitations include lacking of concurrent information on all aspects of work stress, which may lead to overlooking the true association of different work stress factors and cortisol secretion (Eller et al., 2006a); the effect of gender has not been properly addressed; non-adherence to cortisol sampling protocol (particularly the accuracy of

collection time) and inadequate parameters used in modelling cortisol secretion pattern (Kunz-Ebrecht et al., 2004a, Hjortskov et al., 2004); potential confounders are not properly controlled (Kunz-Ebrecht et al., 2004b, Maina et al., 2009b, Hjortskov et al., 2004); and small sample sizes and low response rate have resulted in modest statistical power to detect a relationship should one exist (Chandola et al., 2010).

1.4.2. Gaps in evidence

Mainly due to the limitations listed above, evidence to date can not generate a conclusive association between work stress and diurnal cortisol secretion. It is also unclear, whether the cortisol response to various aspects of work stress applies to men and women equally. Conflicting evidence on gender-specific effect of work stress and its relation to health warrants further exploration on the mediating role of the HPA axis.

1.4.3. Design of current study

The current study examines the cross-sectional association of two complementary work stress models and several parameters of diurnal salivary cortisol secretion using data of Whitehall II Phase7. Particular attention has been given to gender differences, as each association is evaluated gender specifically. With data on socioeconomic status, anthropometry and health status, potential confounders can be better evaluated and controlled.

The large sample size of Whitehall II Phase 7 bolsters strong statistical power. Even in the case of iso-strain, which has the smallest sample size in terms of work stress measures (n=2006), an approximated power of 80.08% can be held at the sig-

nificant level of 90%, mean difference of CAR at level of 0.1 (power calculation was performed using online OE 2.3 calculator). Therefore, compared with previous small scale studies, the biggest sample size of the current study facilitates a comprehensive investigation on the relation of work stress and diurnal cortisol secretion.

Table1.2. Studies on JDC and/or ERI models and cortisol secretion.

First-author +year	Sample size	Occupation	Work-stress Model	Salivary cortisol sampling protocol and parameters	Covariates	Results
(Maina et al., 2009a)	104(28M/78F)	Call centre operators	JDC ERI	2 working days and 1 leisure day 7 times per day CAR, AUC, DC	Gender, age education, marital status, morning awakening time, sleep duration and quality, weekdays, work schedule, adherence to sampling procedure.	1. Job strain was positively associated with cortisol output in the awakening period. 2. ERI imbalance was negatively associated with both cortisol awakening response and lower diurnal secretion. Gender, weekday and adherence to sampling schedule are significant influencing factors.
(Maina et al., 2009b)	36(20w/16m)	Call handlers	Job Strain	collected seven daily salivary samples on two workdays and a weekend CAR/ cortisol output over the day	gender, weekdays and adherence to the sampling schedule	High strain was associated with higher CAR. CAR showed gender-specific and weekday differences.
(Kunz-Ebrecht et al., 2004a)	128 (69m/ 59w)	Civil servants WHII	Stress/ control/happiness Focusing on weekday and weekend difference (no specific work stress model)	First sample (after awakening), CAR (+30mins), on 2 days (one weekday and one weekend).	sleep quality, time of waking, and health behaviour(smoke, alcohol), marital status, BMI,WCR , time of awakening Sleep quality	No gender, socioeconomic or weekend/weekday differences showed in terms of morning cortisol. CAR was greater on work than weekend days. Women showed larger increases than men on weekday, but there were no gender differences on the weekend day.

Table1.2. (continued)

(Chandola et al., 2008)	Phase 7 2810	Civil servants WHII	JDC	Morning rise cortisol	adjusted for age, sex, employment grade total cholesterol hypertension, smoking history and other health behaviors waking up time	Cross-sectional association between work stress and a higher CAR was observed, while little association with cumulative work stress.
(Evans and Steptoe, 2001)	93(40m, 53w)	Nurses accountants	Social support	Cortisol morning and evening 5 days (3 working & 2 leisure)	Psychological distress, age, sex, smoking, and physical activity.	Work social support was related to elevated cortisol on leisure days but not on work day. There were no gender and occupational effects.
(Fujiwara et al., 2004)	16 f	Nurses (health care providers)	Job strain	Salivary cortisol 3 days a rest day + day shift+ night shift	age demographic variables, tobacco, alcohol, and sleep domestic factors, and work related variables	High job strain was associated, but marginally, with a decreased level of cortisol during day shift. Morning cortisol levels were lower in the groups with high job strain, although the difference was non significant.
(Rystedt et al., 2008)	77 (53m/24f) Longitudinal	White-collar	JDC: iso-strain Chronic stress (3.5 years)	Morning Evening cortisol 7 consecutive days	Age Sex (no influence)	Iso-strain affected evening cortisol levels while no effects on morning cortisol secretion.

Table1.2. (continued)

(Alderling et al., 2006)	529(348w/181m)	Population based	JDC (4 categories Active/strain)	Awaking, 30 min later, lunch time and bed-time	Full/part time life events, age, smoking, obesity, depression (all no significant)	Compared with women in high strain or passive/active groups, women had neither high demand nor low control had significantly lower morning cortisol and CAR. No differences found in men.
(Harris et al., 2007)	44(w)	Health care workers (nursing staff)	JDC ERI	Wake-up time CAR slope evening cortisol	Age coffee tobacco Quality of life health complaints	No relation between work stress and morning cortisol and CAR. Decision authority was significantly related to evening cortisol levels
(Steptoe et al., 2000)	105(41m/64w)	School teachers	Job strain	First sample (8:00-8:30) at school, 2-hour intervals till 22:00-22:30 on a working day. Circadian rhythm (variability)	Age gender anger Smoking negative affect	Job strain is positively associated with early cortisol concentrations but not with shallower slope over the working day. A gender difference had also been noticed independent of job strain.
(Steptoe et al., 2004b)	197(105m/92f)	Civil servants WHII	ERI Over-commitment	Waking, 30 min later and then 2 hour interval form 8:00 to 22:00. CAR//Secretion over the day	age, socioeconomic position, smoking, time of waking up, and job demands height waist hip sleep problems	In men, CAR and cortisol averaged from 8 samples over the working day were positively associated with over-commitment

Table1.2. (continued)

(Eller et al., 2006b)	83(28m/55f)	healthy volunteers 2002	JDC ERI	ARC / Excretion throughout the day 6 times during a working day	Age, physical activity, tobacco use and the time of the first saliva sample time pressure	In both women and men, effort and effort reward imbalance were nearly significantly associated with higher levels of cortisol. Over-commitment was only associated with men.
(Eller et al., 2011a)	70 (48w/22m) Longitudinal	Volunteers 2002+2008	JDC ERI	Wakening 30+ 18:00 (Ln cortisol)	2002: waist–hip ratio, systolic blood pressure, alcohol consumption, tobacco, physical activity levels of total-cholesterol and HbA1c	Effort- reward imbalance was associated with high LnCortisol in men
(Eller et al., 2011b)	480(352w/128m)	public sector employees (Approximately 90% were white-collar Workers.)	ERI	Awakening (S0) CAR	time of awakening, perceived stress, quality of sleep, age, waist–hip ratio total-cholesterol HbA1c, alcohol consumption tobacco physical activity	ERI was inversely associated with morning cortisol for women and positively associated with CAR. (Hanson et al., 2000)

Table1.2. (continued)

(Hanson et al., 2000)	77 (43m/34w)	Health professionals and office workers	ERI	8:00am—10:30pm 6 times /10 times a day (2 days)	type of occupation, gender, and smoking	Neither ERI nor demand was associated with cortisol
(Bellingrath and Kudielka, 2008)	53(20m/33w)	School teacher	ERI	Pattern of cortisol	Depressive symptoms	ERI and OC were marginally related to cortisol secretion. In the subgroup of responders (CAR> 2.5 nmol/l) Higher OC was related to lower salivary cortisol responses.
(Bellingrath et al., 2008)	135(40m/95f)	School teachers	ERI	Pattern of cortisol secretion	Gender, age, BMI, WHR, smoking, sleep quality, and awakening time	Basal cortisol activity was not associated with ERI. When dexamethasone was applied, lower reward was related to stronger cortisol suppression.

DC: diurnal cycle; AUC: area under curve; CAR: cortisol awakening response. BMI: body mass index; WHR: waist–hip-ratio.

JDC: Job-demand-control; ERI: effort-reward imbalance; OC: over-commitment.

1.5. Aim, objectives and hypotheses

The study aims to assess the association between work stress, measured by two main work stress models, JDC and ERI, and diurnal cortisol secretion with regards to gender in a large-scale population cohort, in which potential confounders could be controlled.

The *objectives* of the study are:

Firstly, to understand the nature of the relationships between work stress models and indices of cortisol secretion, considering the correlation between dimensions of the two work stress models.

Secondly, to analyze gender-specific cortisol responses according to the two work stress models.

Thirdly, to test the consistency of the relationships by adjusting for potential confounding factors. Particularly, social economic status (SES) and BMI are examined to verify the robustness of the findings.

The following research *hypotheses* are addressed:

1. Adverse psychosocial work conditions, defined by lower control, higher demand, lower social support, higher job strain and iso-strain, higher effort, lower reward, higher ERI and over-commitment are associated with disturbances in diurnal cortisol secretion (CAR, diurnal cortisol slope and morning/evening corti-

sol levels). Specifically, it is hypothesized that higher work stress is associated with an elevated CAR and a flatter diurnal cortisol decline (slope).

2. The JDC and ERI models are associated with diurnal cortisol secretion in a gender-specific manner. It is hypothesized that ERI is positively associated with cortisol levels in men and job strain is associated with higher cortisol secretion in women.

3. In line with theoretical evidence and arguments from earlier studies, it is hypothesized that the relation of work stress and cortisol may be confounded by SES (employment grade) and/or other biological factors (BMI, waist circumference and hypertension).

2. Methods

2.1. Study population

Established in 1985, the Whitehall II study is an on-going cohort with 10,308 participants (66% male , aged 35-55) recruited from 20 London based civil service departments. After the baseline clinical health check-up, further self-administered questionnaires were executed in every follow-up phases while repeated clinical examinations were only carried out in odd phases with five-year interval. Details of the cohort were previously reported (Marmot and Brunner, 2005).

By Phase7 (2003-2004) the number of participants is 6,967 with a response rate of 68%. Compared with those lost to follow-up, participants remained in the cohort were slightly younger, more likely to be male, from higher employment grade and had a lower prevalence of work stress at baseline. However, the differences were small (Kumari et al., 2010a). Out of the 6,967 participants in Phase7, 6,484 (93.4%) had a clinical assessment and 4,967 collected saliva samples. 4,069 (90.1%) participants returned the saliva samples. The present analysis focused on participants who were still working in Phase7, with information on psychological work stress, diurnal cortisol secretion and other covariates included in multivariable analyses. Ethical approval for the Whitehall II study was obtained from the University College London Medical School Committees on the Ethics of Human Research. At each phase informed consents were collected from participants.

2.2. Measurements of work-stress

2.2.1. The JDC model

The self-reported Job Strain Questionnaire was employed to assess the psychological stress at work environment. Job demands were measured by 4 items, decision latitude (job control) by 15 items and social support at work by 6 items (Cronbach's α for each component: demand 0.67, control 0.84, support 0.79). A full list of the 25 questions has been published (Bosma et al., 1997) (Appendix1). A four point scale from ‘‘often’’ to ‘‘never/almost never’’ were used to answer all these items. When applicable, an average score based on other answered items were assigned to no answered item. Responses were combined into summary scales. Scores were converted into a 0 to 100 scale, where higher scores indicate higher control, demand or support. In line with previous Whitehall II studies, work stress was present when participants' responses had high score on demand and low score on control. A continuous scale of job strain was calculated by using demand score minus control score. Further, iso-strain was exhibited by people who simultaneously reported job strain and had the lowest social support at work.

2.2.2. The ERI model

ERI and over-commitment were assessed based on multi-item scales adopted in Whitehall II phase5 (Chandola et al., 2005). The English version of ERI questionnaires were constructed from the validated 23 Likert scaled items (Siegrist et al., 2004) (Appendix1), which contain extrinsic and intrinsic dimensions of the full ERI

model. For the extrinsic part, effort and reward each was rated on a five points scale, 4 items for effort (Cronbach'sα= 0.80) and 8 items for the reward (Cronbach'sα= 0.87). Average scores for each component were computed (range 1-5). A ratio of effort-reward imbalance was calculated by the formula e/r*c, where 'e 'stands for the average score of efforts, 'r' is the average score of rewards and 'c' is a correction factor which weights the different numbers of items in numerator and denominator. In this study, 'c' equals 2 (8/4). Thus a value beyond 1.0 reflects a disproportionate effort, whereas a value from 0 to 1 indicates a favourable balance (relatively low effort vs. high reward). In our analysis, the continuous effort reward ratio was taken the logarithm to distinguish any inverse imbalance within the same distance from the balance point "1" (Pikhart et al., 2004).

Over-commitment, the intrinsic component (measuring the psychological coping pattern), was assessed with 5 items ("As soon as I get up in the morning, I start thinking about work problems", "Work rarely lets me go, it is still on my mind at midnight", "If I postpone something that I was supposed to do today, I will have trouble sleeping at night", "People close to me say I sacrifice myself too much for my job" "When I come home, I can easily switch off", Cronbach'sα=0.82). Respondents rated their answer for each item on a four-point scale: 1 is agree, 2 somewhat agree, 3 somewhat disagree and 4 disagree. In calculation, we recoded the former 4 items to reflect the reversed wording of those items (higher score indexes higher commitment). A summary score of each item was calculated (range 1-4).

2.3. Cortisol collection and analysis

The protocol of saliva sampling used in Whitehall II has been reported previously (Badrick et al., 2007). Salivette (Sarstedt, Leicester, UK) was used to collect participants' saliva samples. Participants were instructed to collect 6 daily samples at awakening, 30 minutes after waking, 2.5 hours after waking, 8 hours after waking, 12 hours after waking and bedtime. Time of sampling should be recoded simultaneously. Participants were required to take samples immediately after awakening (rather than the time got out of bed). Caffeine and acidic drinks in the first 30 minutes, bushing teeth or eating or drinking 15 minutes before a sample collection were not allowed. Other information about the day of sampling (mood, smoking, alcohol consumption, exercise and stressful events) was recoded in a logbook, which posted back along with salivettes. Salivary samples were centrifuged at 3000 rpm for 5 minutes. The clear supernatant was assayed via chemiluminescence detection (CLIA; IBL-Hamburg, Hamburg, Germany) to measure the salivary cortisol levels. The lower concentration limit of this assay was 0.44 nmol/liter; intra- and inter-assay coefficients of variance were less than 8%. Any sample over 50 nmol/l was repeated.

2.4. Assessment of covariates

2.4.1. Demographic and sample collection variables

Data on gender, age, ethnicity and marital status were collected by questionnaires. Waking up time ("Time of being awake for the day and not going back to

sleep") was available from the logbook on the day of sample collection. Time delay between waking and taking first sample was categorized into every 5-minute intervals (<5 min, 5-10 min, 10-15 min, 15-20 min, 20 min+).

2.4.2 Social economic status (SES)

Social economic status was decided by current employment grade if participants were still working as the civil servants or according to the last job grade once participants had left civil service. Three categories (administrative, professional and clerical) were used in this analysis. As education attainment was not associated with cortisol parameters and had missing values, education was not used in final models.

2.4.3. Biological variables

Measured by clinical nurses, height was assessed using a stadiometer with head in the Frankfort plane, and weight was assessed using a portable digital scale (Tanita, Yiewsley, Middlesex, UK). BMI was calculated as weight (in kilograms)/height squared (in square-meters). Given a nonlinear association of BMI with diurnal cortisol decline (slope) (Kumari et al., 2010c), BMI was categorized using the cut-points suggested by that study (less than 21, 21~31 and 31plus).

Waist circumference was measured as participants in the standing position and unclothed, defined as the smallest circumference at or below the costal margin. Different cut-points were used for men and women, low waist (men <90 cm and women <80 cm), medium (men 90-102 cm and women 80-88 cm) and high waist (men >102 cm and women >88 cm).

Hypertension was defined as participants on antihypertensive medicine or ever been told by the GP or with a systolic blood pressure more than 140 mmHg or diastolic blood pressure more than 90 mmHg (Chobanian et al., 2003). Blood pressure was measured twice after a 5-minute rest in a sitting position at the clinical screening, using an Omron HEM 907 (Omron Healthcare, Inc., Bannockburn, IL). The average value of the measurements was used in current study.

2.5. Statistical analysis

2.5.1. Data reduction for cortisol assessment

Approximately 1% of the cortisol values that were three standard deviations above the mean were removed (n=43), which may be influenced by altered pH-values or blood contamination (Kunz-Ebrecht et al., 2004a). Additionally, participants reporting either eating, drinking, exercising or brushing their teeth before the first sample (n=41) as well as those taking steroid medication (n=231) were excluded. Data were analyzed for difference between weekday/weekend collections. Since no statistically significant differences showed, data were combined for further analyses. A strong positive skew still existed even took out the outliers. Thus the cortisol data were transformed by square root to achieve normality.

2.5.2. CAR and slope calculation

The CAR was computed as the difference between first cortisol sample values at waking and second sample values 30 minutes after waking. Conventionally, a de-

layed sample collected over 10 minutes after waking was removed due to a reduced CAR (Kudielka et al., 2004). According to this criterion, in our sample, 14.63% of the individuals with cortisol data were non-compliant. However, recent study found that a 15-minute delay would not influence the response (Dockray et al., 2008). Therefore, instead of excluding the delayed samples completely, time delay was included as a covariate and was recoded into 5-minute intervals. Thus time difference between waking and taking first sample and its influence on CAR can be better examined.

The methodology used to calculate the slope has been previously reported (Kumari et al., 2009a). In short, the slope was derived from regressing cortisol concentration of five samples over the day excluding the second sample. The reason for taking out cortisol level 30 minutes after awakening (second sample) is that CAR and slope might be modulated by different neurobiological systems (Clow et al., 2004). A hierarchical linear model was employed to predict the log cortisol, taking measurement occasion as a level one identifier, person as a level two identifier and sample time as the independent covariate. For each person, the slope was estimated as the overall negative slope plus the level two slope residual. A more rapid cortisol decline over the day was represented by more negative slope value, whereas flatter diurnal rhythms were indicated as slope values close to zero.

2.5.3. Analytic strategy

Analysis part 1: The baseline characteristics, distribution of work stress measures and cortisol profile of the study population were analyzed according to gender. Gender differences were assessed by using unpaired t-test or ANOVA for continuous variables and Chi-square test for categorical variables. The correlations between work stress measures were assessed by the Spearman rank statistic (ρ) gender specifically.

Analysis part 2: Linear regression was employed to assess the association of work stress and cortisol secretion. One at a time, the diurnal cortisol parameters were used as dependent variables and each component of work stress models as independent variable. In all analyses, age, ethnicity, waking time and time difference between waking and taking first sample were used as covariates. Analyses were first carried out in the whole study sample, with gender as a risk factor. Non-linearity tests were conducted for each relation to test the linearity assumption.

Analysis part 3: The interaction between gender and the measures of work stress were then assessed. Gender-specific associations of work stress and cortisol outcomes were reported. As one of the research objectives was to detect the gender-specific effects of work stress models on cortisol secretion, and given the fact in this male-dominated cohort, insufficient female numbers in some categories may result in statistical insignificance (Messing et al., 2003), we retained the gender*work stress interaction effect even when it was not statistically significant. Separate

analyses in men and women were carried out to assess the reliability of the gender-specific analysis.

Analysis part 4: We further tested the robustness of the significant associations (P-value < 0.10) by adjusting for potential confounding factors in men and women separately. All analyses were conducted within the whole population by recoding each gender as baseline group. Additional adjustments for covariates were run by using multivariable adjusted linear regression models step-wisely including the following sets of covariates: SES (employment grade), biological variables (BMI, waist circumference and hypertension) and all variables together.

Results were presented for an increase in standard deviation, since in all analyses continuous variables were used to prevent any information reduction due to artificial categorizing. The data were analyzed using STATA version 11. A P-value below 0.10 was considered significant in the association between work stress and cortisol secretion as well as the gender interaction term. We chose a significant P-value less than 0.10 in order to capture any subtle changes in the HPA axis in reaction to work stress exposure and also given the fact there were fewer working women (n=481) in the study sample which may result in a weak gender*work stress interaction test. As for other tests, a P–value below 0.05 was considered statistically significant.

3. Results

3.1. Descriptive results

In Phase7 only half (49.19%) of the participants were still working (n=3,413), 45.01% were retired and 4.09% were out of work due to sickness. Compared with people who were still working, those retired or not working were more likely to be female, older and generally unhealthier. As regards social economic position, people remained in workplace were more likely to stay in a higher employment grade. Participants included in the current analysis were those who were still working, with any measures of cortisol secretion and work stress components. The final number of participants for this analysis was 2,126 of whom 481 (22.62%) were women. They were more likely to be male (p = 0.001), younger (p < 0.0001) and had higher employment grade (P < 0.001) in comparison with those who were still working in Phase7 but not eligible for this analysis (Table3.1).

TABLE3.1. Participants Characteristics at Whitehall II Phase 7 (2002-2004)

	Participants who attended Phase 7 (n=6,967)	Participants still working in Phase 7 (n=3,413)	Participants included in this analysis(n=2,126)
Male (%)	70.2	75.5	77.4
Mean age (SD)	61.2 (6.0)	57.5 (4.3)	57.1 (4.0)
Ethnic (non-white) (%)	8.2	7.2	6.6
Not married/cohabiting (%)	24.6	21.0	21.6
Lowest employment grade (%)	10.8	8.0	7.0
BMI (SD)	26.8 (4.4)	26.8 (4.3)	26.8 (4.3)
WC (SD)	91.3 (12.4)	91.5 (12.3)	91.5 (12.3)
Hypertension (%)	34.2	30.1	29.4

The basic characteristics of participants were summarized by gender in Table 3.2. There were more men (77.38%) than women (22.62%) in the study sample. Compared with women, men were slightly older ($p = 0.04$), more likely to live with partner ($p < 0.001$), less likely to have an ethnic minority background ($p < 0.001$), worked in a higher employment level ($p < 0.001$) and had a lower prevalence of hypertension ($p < 0.0001$).

TABLE3.2. Participant characteristics for men and women with data available for work stress and cortisol secretion at the Whitehall II Phase 7 (2002-2004)

		Men (N=1,645)		Women (N=481)	
	N	Mean	SD	Mean	SD
Demographic Variables					
age (years)	2,126	57.2	4.0	56.8*	4.0
ethnic (non-white) (%)	2,126	4.6		13.7*	
living without partner (%)	2,123	16.7		38.1*	
Social Economic Position					
lowest employment grade (%)	2,126	3.7		18.3*	
Biological variables					
mean BMI (kg/m^2)	2,121	26.7	3.9	26.9	5.4
mean waist circumference (cm)	2,124	94.0	10.8	83.0*	13.1
hypertension (%)**	2,126	26.6		38.9*	
Work-stress measures					
control score	2,094	72.7	14.9	67.7*	15.5
demand score	2,110	59.0	20.4	57.0	20.6
support score	2,023	75.7	19.2	75.8	19.9
job strain score[a]	2,094	-13.7	23.4	-10.9	21.7
Iso strain (%)[b]	2,006	11.7		9.2	
effort score	2,104	1.91	0.63	1.89	0.71
reward score	2,095	4.43	0.62	4.39	0.69
effort-reward imbalance score	2,090	0.91	0.46	0.94	0.66
over commitment score	2,108	1.95	0.77	1.97	0.82
Cortisol					
morning cortisol (nmol/l)	2,092	16.2	8.4	15.3*	8.2
evening cortisol (nmol/l)	2,067	2.24	2.47	2.31	2.44
cortisol awakening response (nmol/l)	2,063	7.5	11.6	8.3	11.4
slope in cortisol secretion (nmol/l/hr)	1,955	-0.128	0.024	-0.129	0.022

*** Difference between gender is significant ($p<0.05$) at Chi-2 or un-paired t-test.**

**** Hypertension: participants on antihypertensive medicine ever been told by the GP or with a systolic blood pressure >140 or diastolic blood pressure >90; [a] job strain=demand-control; [b] iso-strain lowest support plus job strain.**

In terms of distribution of work stress measures, men had significantly higher control score ($p < 0.0001$) than their female counterparts. Similar demands score resulted in an average higher job strain score in women ($p = 0.02$). Other components of work stress, such as support at work, effort, reward, ERI and over-commitment were all comparable across gender. As regards diurnal cortisol secretion profile, the mean level of morning cortisol was lower in women (15.3±8.2 nmol/l) than men (16.2±8.4 nmol/l) ($p = 0.04$). CAR seemed to be higher in women (8.3±11.4 nmol/l) than men (7.4±11.6 nmol/l), but not statistically significant ($p = 0.18$). There was no significant difference regarding evening cortisol or cortisol decline over the day (slope) in men and women.

3.2. Correlation of work stress measures

Table3.3. Gender specific correlation matrix for the work-stress measures

	control		demand		support		job strain		effort		reward		ERI ratio	
Men														
demand	0.14	*												
support	0.24	*	-0.17	*										
job strain	-0.46	*	0.76	*	-0.31	*								
effort	0.04	**	0.67	*	-0.16	*	0.54	*						
reward	0.31	*	-0.28	*	0.48	*	-0.45	*	-0.37	*				
ERI ratio	-0.05	**	0.65	*	-0.28	*	0.59	*	0.94	*	-0.60	*		
over commitment	0.10	*	0.52	*	-0.22	*	0.39	*	0.56	*	-0.32	*	0.58	*
Women														
demand	0.17	*												
support	0.21	*	-0.19	*										
job strain	-0.47	*	0.72	*	-0.35	*								
effort	0.05	**	0.71	*	-0.25	*	0.54	*						
reward	0.19	*	-0.29	*	0.52	*	-0.42	*	-0.38	*				
ERI ratio	-0.04		0.68	*	-0.38	*	0.57	*	0.95	*	-0.61	*		
over commitment	0.11	*	0.52	*	-0.27	*	0.35	*	0.56	*	-0.41	*	0.59	*

The spearman rank correlation coefficient (P) are reported
*** p<0.0001, ** p<0.05**

Table 3.3 shows the gender-specific matrix of work stress measures. Similar patterns were seen in men and women. Demand and effort, support and reward were highly correlated confirming those measures tapping similar aspects of work stress. Demand seemed to be a stronger influential factor than control in the job strain model. Similarly, the ERI score was highly driven by the effort score. Overall, the directions of those associations confirmed the theoretical assumptions underlying those work stress models.

3.3. Relation between work stress and salivary cortisol indices

The linear regression is presented adjusted for gender (Table 3.4) and gender stratified (Table 3.5). Overall, significant associations were only found in terms of the ERI model (Table 3.4). Lower reward, higher ERI and over-commitment were associated with shallower slopes. Meanwhile, ERI was significantly related to higher evening cortisol. There was a tendency of elevated evening cortisol level in those reporting higher job strain and lower reward ($p = 0.10$). Unexpectedly, in relation with morning cortisol, all dimensions of work stress models tended to show reversed patterns as we hypothesized: higher work stress (higher job strain/ERI) lower morning cortisol, while none of the relations were significant.

Gender effects were analyzed by adding an interaction term between gender and work stress. Gender-specific coefficient and its corresponding p-value were assessed by recoding each gender as baseline group (Table 3.5). The interaction terms were only significant between gender and demand ($p = 0.03$), support ($p = 0.05$) and

job strain (p = 0.03) in relation with CAR, and effort in relation with slope (p = 0.10). To assess the reliability of the gender-specific analysis, we analyzed the data in women and men separately (Appendix2). Similar trends showed when splitting the data, while due to a smaller sample size, the p-values for women were not significant as in the whole study population. In women, a lower CAR was significantly associated with higher demand, lower support and higher job strain. A reversed pattern showed in men while not significant. Job strain was also positively associated with evening cortisol level and iso-strain was associated with higher morning cortisol level. In men, higher effort and over-commitment were negatively related to morning cortisol level. Higher effort and ERI were significantly associated with elevated evening cortisol levels and shallower slopes.

Table 3.4. Measures of work stress and cortisol secretion measures at WHII Phase 7, adjusted for age, gender, e

	Morning Cortiso				Evening Cortiso				CAR				Slope			
	N	Coef.	CI	P	N	Coef.	CI	P	N	Coef.	CI	P	N	Coef.	CI	P
JDC model																
Control	2017	0.001	(-0.002,0.004)	0.72	1993	-0.001	(-0.003,0.001)	0.47	1988	-0.006	(-0.04,0.27)	0.71	1926	1E-05	(-0.00005,0.00008)	0.71
Test for nonlinearity				0.31				0.56				0.67				0.66
Demand	2032	-0.001	(-0.003,0.002)	0.51	2008	0.001	(-0.001,0.002)	0.26	2003	-0.0003	(-0.03,0.03)	0.98	1940	4E-05	(-0.00001,0.0001)	0.14
Test for nonlinearity				0.78				0.65				0.86				0.76
Support	1950	0.001	(-0.002,0.003)	0.71	1926	-0.001	(-0.002,0.001)	0.18	1922	0.007	(-0.02,0.03)	0.61	1863	-1E-05	(-0.0001,0.00004)	0.49
Test for nonlinearity				0.91				0.75				0.41				0.53
Job strain	2017	-0.001	(-0.003,0.001)	0.38	1993	0.001	(-0.004,0.002)	0.17	1988	0.002	(-0.02,0.02)	0.87	1926	2E-05	(-0.00002,0.00007)	0.36
Test for nonlinearity				0.66				0.41				0.91				0.39
ERI model																
Effort	2027	-0.046	(-0.12,0.03)	0.21	2003	0.036	(-0.01,0.08)	0.12	1988	0.17	(-0.63,0.98)	0.67	1934	0.001	(-0.0001,0.003)	0.18
Test for nonlinearity				0.45				0.96				0.71				0.47
Reward	2019	0.023	(-0.05,0.096)	0.54	1995	-0.04	(-0.08,0.001)	0.11	1990	0.40	(-0.41,1.21)	0.33	1927	-0.002	(-0.003,0.00002)	0.05
Test for nonlinearity				0.78				0.59				0.62				0.93
ERI ratio (Log ERI)	2015	-0.05	(-0.17,0.06)	0.36	1991	0.07	(0.005,0.143)	0.04	1986	-0.33	(-1.56,0.90)	0.61	1922	0.002	(-0.0002,0.005)	0.06
Test for nonlinearity				0.71				0.63				0.63				0.54
Over commitment	2031	-0.04	(-0.96,0.02)	0.21	2007	0.028	(-0.009,0.064)	0.13	2002	-0.19	(-0.85,0.46)	0.55	1939	0.001	(-0.0001,0.003)	0.09
Test for nonlinearity				0.91				0.19				0.33				0.13

Table3.5. Gender specific association between measures of work stress and cortisol secretion measures at WHII Phase 7, adjusted for age,ethnicity, time of waking and time since waking.

	Morning Cortisol					Evening Cortisol					CAR					Slope				
	Men		Women		P*	Men		Women		P*	Men		Women		P*	Men		Women		P*
	Coef.	P	Coef.	P		Coef.	P	Coef.	P		Coef.	P	Coef.	P		Coef.	P	Coef.	P	
JDC model																				
Control	0.001	0.68	-0.00003	0.99	0.83	-0.004	0.71	-0.002	0.42	0.61	-0.009	0.64	0.003	0.94	0.77	1E-05	0.78	2E-04	0.77	0.91
Demand	-0.001	0.28	0.001	0.53	0.27	0.001	0.52	0.002	0.21	0.42	0.014	0.35	-0.049	0.06	0.03	3E-05	0.31	7E-04	0.21	0.53
Support	0.001	0.51	-0.001	0.69	0.51	-0.001	0.31	-0.001	0.37	0.77	-0.007	0.63	0.05	0.05	0.05	-2E-05	0.38	9E-06	0.87	0.57
Job strain	-0.001	0.21	0.001	0.58	0.27	0.001	0.49	0.003	0.06	0.18	0.013	0.29	-0.05	0.06	0.03	1E-05	0.56	5E-04	0.34	0.55
Iso strain	0.08	0.32	0.29	0.09	0.28	-0.001	0.99	0.09	0.39	0.43	0.34	0.71	-2.44	0.21	0.19	-0.001	0.47	0.002	0.64	0.46
ERI Model																				
Effort	-0.08	0.05	0.05	0.44	0.09	0.05	0.06	-0.0002	0.99	0.32	0.59	0.21	-1.01	0.19	0.08	0.002	0.04	-0.01	0.49	0.10
Reward	0.03	0.44	-0.01	0.94	0.64	-0.02	0.47	-0.09	0.05	0.19	0.27	0.57	0.78	0.33	0.58	-0.002	0.11	-0.002	0.26	0.88
ERI ratio (log)	-0.09	0.19	0.04	0.72	0.31	0.79	0.05	0.06	0.36	0.78	0.22	0.76	-1.78	0.13	0.14	0.003	0.03	2E-04	0.95	0.27
Overcommitment	-0.06	0.09	0.03	0.66	0.22	0.02	0.32	0.05	0.19	0.53	-0.01	0.97	-0.76	0.25	0.32	0.001	0.23	0.002	0.17	0.55

***:P-value for gender and work stress measurement interaction.**

3.4. Further adjustment for confounders

Table 3.6 and Table 3.7 show further adjustments for confounding factors in women and men respectively. Further adjustments were only conducted in those significant associations ($p < 0.10$) derived from the gender-specific analyses. In women, the association between CAR and two components of the JDC model, demand and job strain, attenuated after controlling for employment grade. But additional adjustment for biological variables provided little influence on these associations. Neither employment grade nor biological factors had substantial effects on the relation of iso-strain and morning cortisol or job strain and evening cortisol. Among women, we also further tested the effects of menopause and hormone replacement treatment (HRT). But none of them (p for menopause 0.99, p for current HRT use 0.95) were associated with CAR. As for the ERI model in men, the coefficients of effort and ERI with slope and their corresponding p-values remained almost unchanged after adjusting for either covariate. Biological factors only played a small role in relation of over-commitment and morning cortisol level. To conclude, controlling for employment grade or biological factors in either gender failed to alter the results to any great extent.

Table 3.6. Women, role of confounders of the association of work-stress (JDC) and cortisol secretion.

	Age, ethnicity, wake time and time between waking and taking first sample (Model 1)		Model 1+ employment grade		Model 1+ BMI+WC+hypertension		Model 1 + all covariates	
	[Regr.Coeff. (CI)]	P	[Regr.Coeff. (CI)]	P	[Regr.Coeff. (CI)]	P	[Regr.Coeff. (CI)]	P
CAR								
demand								
per 1 SD increase	-0.049 (-0.11,0.01)	0.06	-0.044 (-0.097,0.010)	0.11	-0.051 (-0.103,0.001)	0.06	-0.045 (-0.09,0.009)	0.10
support								
per 1 SD increase	0.052 (-0.001,0.11)	0.05	0.052 (-0.0004,0.105)	0.05	0.055 (0.001,0.108)	0.04	0.055 (0.002,0.108)	0.04
job-strain								
per 1 SD increase	-0.046 (-0.095,0.004)	0.06	-0.043 (-0.092,0.007)	0.09	-0.047 (-0.096,0.003)	0.06	-0.044 (-0.093,0.006)	0.08
Morning cortisol								
Iso-strain								
yes	0.289 (-0.05,0.63)	0.09	0.291 (-0.05,0.63)	0.09	0.304 (-0.032,0.641)	0.07	0.305 (-0.031,0.642)	0.08
Evening cortisol								
job-strain								
per 1 SD increase	0.003 (-0.001,0.005)	0.06	0.003 (-0.0001,0.006)	0.06	0.003 (-0.0002,0.005)	0.07	0.003 (-0.0001,0.005)	0.06

Table3.7. Men,role of confounders of the association of work stress (ERI) and cortisol secretion.

	Age, ethnicity, wake time and time between waking and taking first sample (Model 1)			Model 1+ employment grade			Model 1+ BMI+WC+hypertension			Model 1 + all covariates		
	[Regr.Coeff. (CI)]		P	[Regr.Coeff. (CI)]		P	[Regr.Coeff. (CI)]		P	[Regr.Coeff. (CI)]		P
Morning cortisol												
effort												
per 1 SD increase	-0.083	(-0.17,0.001)	0.05	-0.086	(-0.17,-0.001)	0.04	-0.081	(-0.17,0.003)	0.06	-0.084	(-0.17,0.002)	0.05
over commitment												
per 1 SD increase	-0.058	(-0.13,0.01)	0.09	-0.061	(-0.13,0.01)	0.08	-0.053	(-0.12,0.02)	0.13	-0.055	(-0.12,0.01)	0.12
Evening cortisol												
effort												
per 1 SD increase	0.05	(-0.002,0.10)	0.06	0.05	(-0.002,0.10)	0.05	0.05	(-0.003,0.10)	0.07	0.05	(-0.003,0.10)	0.06
Slope												
effort												
per 1 SD increase	0.002	(0.00001,0.004)	0.04	0.002	(0.00004,0.004)	0.04	0.002	(0.00001,0.004)	0.05	0.002	(0.00001,0.004)	0.05
ERI ratio												
per 1 SD increase	0.003	(0.0003,0.006)	0.03	0.003	(0.0003,0.006)	0.03	0.003	(0.0002,0.006)	0.04	0.003	(0.0002,0.006)	0.04

4. Discussion

The present study found different components of work stress were related to cortisol secretion in a gender-specific manner. For women, a reduced CAR was associated with higher demand, lower support and higher job strain. For men, higher effort, ERI and over-commitment were related to a flatter cortisol decline (slope), elevated evening cortisol and lower morning cortisol. Those associations were independent of employment grade and other biological factors (BMI, WC and hypertension).

4.1. The effect magnitude of work stress on cortisol secretion

We only observed moderate to weak correlations of work stress and cortisol secretion with p-values around 0.10. The reasons are twofold. From the stressors side, a body of animal and human research has proven that though psychological stressors are indeed able to activate the HPA axis, the effects are various (Dickerson and Kemeny, 2004). Only those prolonged stressful conditions which involve with uncontrollable, social-evaluative and unpredictable elements can significantly affect the magnitude of cortisol response and time to recovery (Dickerson and Kemeny, 2004, Kudielka and Kirschbaum, 2005). Therefore in normal living conditions, routine work-related stressors may not be severe enough to evoke a detectable disturbance in cortisol secretion considering the breadth of inter-individual differences (Kajantie and Phillips, 2006, Hanson et al., 2000). On the other hand, the majority of cortisol (90-95%) in the blood is bound to protein. Only 5% to 10% of the total is biological active “free” cortisol and only “free” cortisol can appear in saliva

(Kudielka and Kirschbaum, 2005). Given other affecting factors, such as negative feedback loops, adrenal sensitivity and capacity, a perfect dose-effect relation between the perceived stress and salivary cortisol level is not to be expected (Hellhammer et al., 2009).

4.2. Gender-specific effects of work stress and cortisol secretion indices

Our study confirmed the value of using different components of work stress to analyze the diurnal cortisol profile in men and women, as gender-specific effects were observed with CAR and the diurnal cortisol decline (slope).

4.2.1. CAR and job strain

In our sample, CAR was affected by the JDC model but not the ERI model in women. Unexpectedly, a reduced CAR was related to higher job demand and higher job strain but also to lower support. This finding is opposite to our hypothesis and against the majority of the reviewed small-scale studies (Alderling et al., 2006, Steptoe et al., 2000, Chida and Steptoe, 2009, Maina et al., 2009b, Maina et al., 2009a). However, there is prior evidence for a decreased rather than increased cortisol response to high strain (Fujiwara et al., 2004, Evans and Steptoe, 2001, Yang et al., 2001, Steptoe et al., 1998, Sluiter et al., 2000, Theorell et al., 1988). Lower cortisol concentration was found in high job strain as well as lower supervisory support groups in a Japanese female health care providers' study (Fujiwara et al., 2004). Additionally, inverse associations between cortisol levels and job strain (Steptoe et al., 1998, Theorell et al., 1988) or job demand (Sluiter et al., 2000) have also been recorded in western studies.

These conflicting findings may reflect different stages in stress response. A two-stage stress reactivity framework has been proposed by Siegrist (1996): at initial stage, a heightened cortisol response would be expected in response to the perceived stress; however, in the long run, a lower rather than higher response would take place as a result of chronic high work stress. That is why participants reporting work overload, burnout, chronic stress or worrying showed an altered CAR (Schlotz et al., 2004, Kudielka and Kirschbaum, 2003, Wilhelm et al., 2007, Janssens et al., 2011). Though the present analysis was based on work stress status at Phase7, it is possible that people being followed up had been exposed to daily work stress for up to three decades. Repeated work-related neuroendocrine reactivity combining with insufficient recovery may maintain participants in a relative high stress status. Thus a snapshot in phase 7 might give a brief look into participants' cumulative work stress status: after chronic "fatigue debt" (Sluiter et al., 1998), the body may functionally adapt to the consistent strain by developing progressive tolerance, down-regulating regulatory receptors or enlarging negative feedback, and finally resulting in an inactive HPA axis (Siegrist, 1996, Maina et al., 2009a, Fujiwara et al., 2004).

Besides the potential long-term effect of work stress and the genuine inconsistent nature of the association, cortisol measurements and analysis may also lead to the current finding. Intra-individual variation in diurnal cortisol secretion can be quite high, particularly in the time period of awakening (Dowd et al., 2009, Dahlgren et al., 2009). To characterize individual's cortisol awakening response, at least six days of sampling would be necessary (Hellhammer et al., 2007). As we only meas-

ured cortisol secretion in a single day, situational factors (for example, sleep quality and sleep duration etc.) may blur the work stress and CAR association.

Compliance with the protocol is another crucial factor in cortisol measurements (Hansen et al., 2008, Fries et al., 2009). We used self-reported cortisol collection time to measure compliance with protocol. Though indictors showed most participants followed the instruction correctly, we still can not detect non-compliance if people did not recode information correctly. In present analysis, 14.6% of the salivary samples were taken later than 10 minutes after awakening. Compared with people complied with the protocol, those non-adherent participants had a higher morning cortisol level and a smaller CAR. We further analyzed the data of people took first sample within 10 minutes after awakening as well as a sub-sample of participants with cortisol rise (CAR > 0), but the associations were qualitatively similar. Therefore, the negative relation of work stress and CAR is unlikely due to delayed sampling time.

4.2.2. Slope and effort reward imbalance

Our results also show, in men, a flattened slope was associated with higher effort and ERI, comprising an elevated evening cortisol level and a depressed morning cortisol level. Previous Whitehall II studies found depressed morning cortisol levels and shallower slopes in cortisol decline were related to fatigue and can predict onset of fatigue (Kumari et al., 2009a). Flatter slopes and raised evening cortisol levels were also linked to increased risk of all-cause mortality, largely driven by cardiovascular deaths (Kumari et al., 2011). Mirroring similar diurnal cortisol profiles, our

results extend previous findings by contributing potential causes of those flat slopes, depressed morning levels and raised evening levels.

The flatter cortisol secretion patterns with raised levels of evening cortisol may largely be explained by impaired feedback regulation of the HPA axis (Spiegel et al., 2006). Moreover, evening cortisol, as a relatively stable indicator of cortisol secretion, may be more sensitive to long-term stress process than transient stressors (Dahlgren et al., 2005, Rystedt et al., 2008). Therefore, the observed shallower slope in men would result from prolonged stress measured by ERI and over-commitment, corresponding to our finding in relation to CAR and job strain in women.

4.2.3. Chronic work stress and hypoactive HPA axis

Taken together, our results indicate, in this ageing population, a reduced energy mobilization in response to work stress. This trend is in agreement with the pattern concluded in Chandola's review (2010), which found increasing literature supporting the link between chronic work stress and exhausted stress reactivity profile. Thus the disturbed diurnal cortisol secretion in response to stress could be interpreted as an indicator of hypoactive HPA axis, in other words, hypocortisolism. Hypocortisolism is characterized by flat diurnal cortisol decline and blunted cortisol response (Heim et al., 2000). Originally, this pattern was mainly described for individuals with post-traumatic stress disorder (PSTD) or sub-clinical diseases (Yehuda et al., 1996, Kudielka and Kirschbaum, 2003, Wessa et al., 2006). However, growing studies has showed hypocortisolism is frequently observed among healthy population under chronic stress condition or bodily disorders (Heim et al., 2000, Gunnar and Vazquez,

2001, Janssens et al., 2011). Potential mechanisms are reduced hormone biosynthesis at either level of the HPA axis; down-regulation of receptors and cortisol binding globulin (CBG); increased negative feedback and chronic allostatic adjustment (Heim et al., 2000).

Adopting a latent variable mixture modelling approach, previous study of Whitehall II Phase7 found 27% of the participants had a blunted pattern of cortisol decline (Kumari et al., 2010a). This proportion is higher than a 10% level averaged from four different cohorts of young or middle aged participants (Stone et al., 2001). It is plausible to reason older adults are more prone to age-related disorder, depletion of gland and dysfunction of regulation systems (Otte et al., 2005). Given chronic work stress exposures, ageing population are more likely to be worn out, and eventually result in a malfunctioned or hypoactive HPA axis (Gunnar and Vazquez, 2001, Heim et al., 2000). However, as a cross-section study, we can not explicitly verify whether the observed hypoactive HPA axis was due to chronic work stress, or vice verse, an age-related dysfunctional HPA axis incurred more report of work stress. Prospective study should further analyze this association longitudinally.

4.3. Gender-specific work stress response

The current study analyzed the data by gender with the intention to assess the stress indicator cortisol in the context of different psychosocial environments experienced by men and women. The findings confirmed the value of separate analysis on the two work-stress models by gender, since different aspects of work stress affected cortisol response differently in men and women. In our study sample, men's

cortisol levels were largely affected by work stress measured by the ERI model. Regarding Whitehall II study, Steptoe and colleagues found over-commitment but not ERI can predict CAR in men, whereas the association was absent in women (Steptoe et al., 2004b). In a population-based volunteer study in Denmark, both ERI and over-commitment were significantly associated with cortisol secretion in men rather than in women (Eller et al., 2011a, Eller et al., 2006b).

On the other hand, in women, we found work stress measured by the JDC model was more relevant to cortisol response, especially in terms of job demand, support and job strain. Those patterns parallel previous finding in a sub-study of Whitehall II. Kunz-Ebrecht reported the job demand component of JDC model was more relevant to women than to men regarding cortisol output (Kunz-Ebrecht et al., 2004b). The disturbance in cortisol secretion became more pronounced among women in lower SES (Kunz-Ebrecht et al., 2004b) and during weekday, when women may face a double burden from work demand and family responsibility (Kunz-Ebrecht et al., 2004a). In the Swedish PART study, women having neither low control nor high demands (low strain) showed an altered CAR in comparison with women in high strain, passive or active jobs; whereas no similar pattern was found in male participants (Alderling et al., 2006). The gender-specific work stress cortisol response also corresponds with the finding of an Italy call-handlers' cohort, where the higher CAR in women may relate to females' vulnerability to work-family interference (Maina et al., 2009b, Maina et al., 2008).

4.4. Gender-specific effects of work stress and health

Our results mirrored the gender-specific work stress—T2DM associations previously found in Whitehall II (Heraclides et al., 2009, Kumari et al., 2004). Kumari et al. found a positive association between ERI and increased risk of T2DM in men, which remained after adjustment for health behaviours and common CVD risk factors (hypertension etc.). On the other hand, a positive relation of job strain and T2DM was reported by Heraclides, where a further adjustment for obesity and other biological factors attenuated the effect by 20% (Heraclides et al., 2009). Due to a limited cortisol data at Phase 5, the potential mediator role of cortisol was not fully investigated in both studies. As a catabolic hormone, cortisol counteracts the effect of insulin. Through reducing the translocation of glucose transporters and inhibiting the glucose utilization in the periphery, cortisol contributes to insulin resistance, which would lead to hyperglycaemia and T2DM (Piroli et al., 2007). Albeit the role of cortisol linking work stress and adverse health outcomes have been fairly explored in experimental studies (Lundberg, 2005, Brunner and Marmot, 2006), no conclusive evidence has been found to support the direct neuroendocrine pathway in large-scale epidemiological study. Our results largely follow the pattern of the gender-specific work stress T2DM relation, thus partially explain the gender-specific work stress—T2DM association and also provide evidence to bolster the neuroendocrine pathway underlying the psychosocial environment to health consequences.

Whitehall II is not the only cohort that has reported gender-specific effects of work stress models. The gendered associations between work stress and different health outcomes have been demonstrated in several studies (Bildt and Michélsen, 2002, Bond et al., 2004, Matthews et al., 1998, González-Morales et al., 2006, Peter et al., 2002, Li et al., 2006). Mental health has been related to job strain (Bildt and Michélsen, 2002) and reward/support (Li et al., 2006, Bond et al., 2004, González-Morales et al., 2006) in women, whereas in men psychological distress was more relevant to high job demand (Bond et al., 2004). Men's physical health was associated with job control and over-commitment, yet no significant pattern showed in women (Li et al., 2006). As for cardiovascular diseases, the Stockholm Heart Epidemiology (SHEEP) study found extra risk of myocardial infraction can be attributed to extrinsic and intrinsic parts of the ERI model in men and in women, respectively (Peter et al., 2002). Although no consistent pattern can be synthesized from current literature, mainly due to different cohort background (nationality, age, ethnicity, occupation) and incomparable scales of work stress models, those studies supported our findings that different components of work stress may exert different impacts on health in a gender-specific way.

4.5. Potential reasons for gender-specific association

We proposed three potential explanations for the gender-specific association, namely, gendered labour market structure, gender relevant perceptions of work stress and biological difference.

4.5.1. Labour market structure

Working environment and job responsibility may differ fundamentally from men and women even for the same position (Eller et al., 2011a, Messing et al., 2003, Artazcoz et al., 2007, Bond et al., 2004, Bildt and Michélsen, 2002, De Smet et al., 2005). As in our male-dominated civil servants cohort, vertical segregation showed in the form that majority of women occupied lower employment positions compared to their male counterparts. Men gravitated towards the top of the professional hierarchy, where they had more autonomy and higher control. Albeit higher employment grade was also positively associated with higher job demand, in our sample, job demands did not significantly differ from men and women. Driven by a markedly lower control score, more women experienced job strain (23.11%) than men (20.06%). For those women with lower control power, higher demand (job strain) and lower support (iso-strain) might be more detrimental to their health.

4.5.2. Gender relevant perceptions of psychological stressors

Women and men may have different perceptions of stress. Measured by free cortisol response, a laboratory study found achievement challenges were more important to men than women, whereas women were more sensitive to social rejection challenges (Stroud et al., 2002). A review on sex difference in the HPA axis stress response (Kudielka and Kirschbaum, 2005) concludes that perceived challenge or threat is more important to men while interpersonal concern is more important to women. Differences in upbringing, education and socialization may also lead to gender-specific way of perception of risk and coping with stress (Gustafson, 1998,

Messing et al., 2003, González-Morales et al., 2006, Vermeulen and Mustard, 2000). As the JDC model emphasizes the structural aspect of the work environment, situational and interpersonal aspects of psychosocial hazards can be better captured by this model, which appears to be more relevant to women. For men, the perceived threat from work may elicit an exaggerated coping reaction (over-commitment), as successful achievement in work is a major source of self-esteem given the socialized gender roles and social expectation (Steptoe et al., 2004b, Messing et al., 2003).

4.5.3. Biological difference

The observation of gender-specific cortisol response to different work stress models could also be explained by the biological differences in women and men. Sexual dimorphisms in the structure and function of limbic regions of the brain, differences in cognitive processing of stressors and levels of sex steroids and CBG in circulation may all be potential mechanisms underlying the observed cortisol stress responses (Kudielka et al., 2009, Kudielka and Kirschbaum, 2005, Kirschbaum et al., 1999). We further adjusted menopausal status and current HRT use in women as biological correction factors, but this adjustment seemed to be insufficient to explain the gender-specific association. On the other hand, some studies argued psychosocial work environment and gender roles per se might have more explanatory power than biological factors in the gender-specific stress responses (Lundberg, 2005).

4.6. Further adjustment for confounding factors

As an observational study, potential confounding factors need to be properly adjusted to verify the robustness of our finding. Although studies on work stress and

cortisol secretion normally controlled for health behaviors (smoking, drinking and physical activity), in present study, health behaviours were not considered as potential confounders. It could be argued unhealthy behaviours are responses to work stress and control for those factors might result in over statistical adjustments (Hjortskov et al., 2004). In a cross-sectional setting, it is difficult to disentangle the sequence of work stress and unhealthy behaviours. Hence this study did not control for health behaviours.

As regards SES, a review on SES and cortisol secretion (Dowd et al., 2009) found consistent relation between lower SES and blunted slope. Previous Whitehall II studies showed participants in the lowest civil servants grade were more likely to have a shallower slope (Kumari et al., 2010a). Kunz-Ebrecht and colleagues specifically explored the relation between SES, work stress and cortisol, showing a positive association between job demand and CAR was tuned by SES (Kunz-Ebrecht et al., 2004b). We therefore reasoned SES, measured by civil service employment grade, might be a confounding factor in the relation of work stress and cortisol secretion. However, after adjustment for employment grade in women and men separately, a slight attenuation effect of employment grade only showed in women in terms of demand and CAR relation. Other associations between work stress and cortisol secretion persisted after taking employment grade into account. This may be due to participants remained in civil servants had a relatively higher employment grades compared to those dropped-out or retired. In our sample only 7.01% participants were in the lowest clerical grade. Thus the adverse effects of the lowest employment grade or the buffering effects of the highest grade would not be so prominent in cur-

rent analysis. Meanwhile, as participants were at the later stage of their working life, employment grade itself may not be able to capture the whole picture of older peoples' current social economic status (Blane, 1999, McMunn et al., 2006, Theorell, 2000).

BMI was used as a biological variable to further assess the extent to which health states influence the observed associations. A non-linear relation of BMI and diurnal cortisol secretion has been reported (Kumari et al., 2010c) and abdominal obesity was related with higher CAR in men (Therrien et al., 2007). Thus BMI may be considered as an indicator of dysfunctional HPA axis in the obese (Steptoe et al., 2004a, Chida and Steptoe, 2009). On the other hand, evidence from Whitehall II suggested people's initial BMI status largely predicted their weight change in reaction to work stress (Kivimäki et al., 2006) and an increased risk of work stress related T2DM only found among obese women (Heraclides et al., 2011). Therefore we considered obesity, as an important measurement of health state, should be controlled in our analysis. Nonetheless, further adjustments for BMI, waist circumference and hypertensions did not contribute any reductions in the association. Though we can not discount other unmeasured health state effects, we can confidently conclude the observed associations of work stress on cortisol secretion are independent of obesity (measured by BMI and waist circumference) and hypertension.

4.7. Strengths and limitations

The accurate measures of the main variables strengthened the confidence of our findings. The data on work stress are detailed and comprehensive since the White-

hall II study was set up to value the associations of psychosocial work environment and adverse health consequences. Diurnal cortisol data were collected repeatedly throughout the day on a large-scale population cohort, and additional information on sampling day was recoded on a logbook. Besides a high response rate, indicators also showed that participants correctly followed the instructions and took salivary samples accordingly.

The weaknesses of the current analysis are, firstly, cross-sectional design makes it hard to discern the direction of the relation and rules out other alternative explanations to the results. Previous work stress exposure may not be accurately measured as only one phase assessment was used. However, we still carried out a cross sectional analysis for following concerns. In light of previous Whitehall II study by Chandola (2008), a cross-sectional association between work stress and dysregulated HPA axis was found while the association was absent longitudinally. The changing status of work stress over the follow-up time (Theorell, 2000) as well as different questionnaires used to tapping psychosocial factors made it difficult to generate conclusive chronic work stress scores from early phases of Whitehall II. As our main objectives are to understand the nature of the association as well as to test the gender specificity, a cross-sectional design may be a more straightforward first attempt.

Secondly, the main exposure (work stress) is measured by self-reported questionnaires. Reporting bias may rise as sensitive people would report a higher work stress score (Hintsanen et al., 2011). Nevertheless, the subjective work stress data were still highly reliable and important in assessing interaction between individual

cognitions and psychosocial environment, inasmuch as only self-reported questionnaires can capture both descriptive and evaluative data of the anticipatory psychosocial environment. Besides other techniques fail to obtain information on both personal coping strategy and distant work conditions (Siegrist et al., 2004).

Thirdly, the reduced sample size of current analysis is another weakness. At Phase7 49.19% participants were retired. Those who retired or dropped-out were more likely to come from lower employment grade, resulting in an underestimation of the social gradient. In particular, as a male-dominated civil servants' cohort, female was under-presented in Whitehall II. Insufficient number of women may make the potential gender difference less likely to be detected and lead to a weak interaction test. Last but not least, salivary cortisol samples were only collected on a single day, the intra-individual variation can not be fully captured and may obscure the situational association (Dowd et al., 2009, Hellhammer et al., 2007).

4.8. Implications and further research

Elucidating the relation of work stress and cortisol secretion has several implications for further research.

This study reveals a hypoactive HPA axis in relation to work stress in older population. This finding once confirmed can be quite relevant to the public health agenda especially in terms of population ageing. However, due to the cross-sectional design, we can not identify whether the down-regulated HPA axis is resulted from chronic work stress or age-related dysfunction. It would be interesting to further verify the association longitudinally and by age group. Meanwhile, the implication of

this pattern for disease vulnerability is still unclear. Whether it is an allostatic adaptation showing more resilient, or will it indicate other pathophysiology of stress-related bodily disorders (such as immunosuppressive actions) needs further elaboration.

Another implication of our finding is the differences and similarities of alternative work stress models and their gender relevant effects. The two work stress models have different conceptions and methodologies, thus can capture specific aspects of the psychosocial environment. Men and women may have different interpretation and coping manners for anticipatory work stress, which are contingent on one's occupational position, perception of stress and biological structure. Therefore, the gender role needs to be properly addressed in the future research. Identifying gender-specific aspects of the adverse psychosocial environment would also help implementing well targeted interventional studies and prevention programmes.

The gender-specific associations between work stress and cortisol secretion provide an explanation for the paradoxical relations: in men between over-commitment and T2DM; in women between job strain and T2DM. Additionally, we also proved work stress is an important factor for a flatter diurnal cortisol decline (slope), which has been related to future fatigue, cardiovascular death and total mortality rate. Hence, our results innovatively illustrate the direct neuroendocrine pathway underlying work stress and various health outcomes. This work contributes evidence to further understanding the importance of the HPA axis in mediating the pathophysiological pathway from adverse psychosocial environment to

health consequences. Future research may carry on exploring this "missing link" by finding the predictive properties of cortisol secretion for health outcomes.

4.9. Conclusion

This study analyzed the association between two theoretical work stress models and the diurnal cortisol secretion profile by gender in a sample of British civil servants. Though the cross-sectional design limited causal interpretation between work stress and cortisol secretion, the results go towards explaining different components of work stress models and their associations with the quantification parameters of salivary cortisol with regards to gender. Women's vulnerability in work situations was evident in the JDC model, presenting as depressed CAR related to higher demand, lower support and higher job strain. Men were more sensitive to the dimensions of the ERI model, exhibiting a flatter cortisol decline (slope), elevated evening cortisol and depressed morning cortisol. Those associations were independent of employment grade and other biological factors. Taken together, our results suggest a low active HPA axis may be characteristic of work stress response in the older population. More importantly, given the links between work stress, disturbed diurnal cortisol secretion and T2DM, the gender-specific cortisol response reflects the gender-specific T2DM associations addressed by the two work stress models. The findings not only highlight the possibility that interpretation of work stress may vary by gender, but also provide evidence that the HPA axis may be a vital neuroendocrine pathway connecting the psychosocial environment to health consequences. Prospective studies are needed to confirm our findings and further elaborate the role of cortisol in predicting the development of diseases.

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Appendix

Appendix1. Scales for JDC and ERI models

1) Job-demand-control model

Self reports of the work environment

Three characteristics of the work environment—job control, job demands, and social support—were assessed by means of 25 items. Response categories ranged from 1 (often) to 4 (never).

Job control— Nine of the 15 items for job control covered decision authority and six covered skill discretion; these subscales were equally weighted. Cronbach's α= 0.84 (measure of internal consistency). The nine items for decision authority were Do you have a choice in deciding how you do your job? Do you have a choice in deciding what you do at work? Others take decisions concerning my work; I have a good deal of say in decisions about work; I have a say in my own work speed; my working time can be flexible; I can decide when to take a break; I have a say in choosing with whom I work; and I have a great deal of say in planning my work environment. The six items for skill discretion were Do you have to do the same thing over and over again? Does your job provide you with a variety of interesting things? Is your job boring? Do you have the possibility of learning new things through your work? Does

your work demand a high level of skill or expertise? Does your job require you to take the initiative?

Job demands—Cronbach's α= 0.67 for job demands, which had four items: Do you have to work very fast? Do you have to work very intensively? Do you have enough time to do everything? Do different groups at work demand things from you that you think are hard to combine?

Social support—Cronbach's α= 0.79 for social support, which had six items: How often do you get help and support from your colleagues? How often are your colleagues willing to listen to your work related problems? How often do you get help and support from your immediate superior? How often is your immediate superior willing to listen to your problems? Do you get sufficient information from line management (your superiors)? Do you get consistent information from line management (your superiors)?

2) Effort-reward-imbalance model

Effort

ERI1 I have constant time pressure due to a heavy work load.

ERI2 I have many interruptions and disturbances in my job.

ERI3 I have a lot of responsibility in my job.

ERI4 I am often pressured to work overtime.

ERI6 Over the past few years, my jobhas become more and more demanding.

Reward

Component esteem

ERI7 I receive the respect I deserve from my superiors.

ERI8 I receive the respect I deserve from my colleagues.

ERI9 I experience adequate support in difficult situations.

ERI10 I am treated unfairly at work.

ERI15 Considering all my efforts and achievements, I receive the respect and prestige I deserve at work.

Component job promotion

ERI11 My job promotion prospects are poor.

ERI14 My current occupational position adequately reflects my education and training.

ERI16 Considering all my efforts and achievements, my work prospects are adequate.

ERI17 Considering all my efforts and achievements, my salary/income is adequate.

Component job security

ERI12 I have experienced or I expect to experience an undesirable change in my work situation.

ERI13 My job security is poor.

Over-commitment

OC1 I get easily overwhelmed by time pressures at work.

OC2 As soon as I get up in the morning I start thinking about work problems.

OC3 When I get home, I can easily relax and 'switch off' work.

OC4 People close to me say I sacrifice too much for my job.

OC5 Work rarely lets me go, it is still on my mind when I go to bed.

OC6 If I postpone something that I was supposed to do today I'll have trouble sleeping at night.

Appendix2. Gender specific cortisol and work stress association in men and women.

	MEN			WOMEN			
	N	Coef.	SE	P-value	**N**	Coef.	SE	P-value
CAR								
Demand	1,558	0.01	0.02	0.48	445	-0.04	0.03	0.18
Support	1,489	-0.01	0.02	0.69	433	0.05	0.03	0.09
Job strain	1,546	0.01	0.01	0.40	442	-0.03	0.03	0.19
Iso-strain	1,478	0.21	0.91	0.82	427	-2.38	1.91	0.21
Effort	1,555	0.52	0.48	0.28	443	-0.76	0.78	0.33
ERI ratio	1,546	0.07	0.74	0.93	440	-1.37	1.17	0.25
Morning cortisol								
Job strain	1,567	-0.002	0.001	0.20	450	0.001	0.002	0.68
Iso-strain	1,498	0.09	0.08	0.31	435	0.31	0.17	0.08
Effort	1,576	-0.09	0.04	0.04	451	0.05	0.07	0.48
ERI ratio	1,567	-0.10	0.07	0.16	448	0.03	0.11	0.81
Over commitment	1,578	-0.06	0.04	0.08	453	0.03	0.06	0.61
Evening cortisol								
Job strain	1,552	0.006	0.001	0.43	441	0.002	0.002	0.11
Effort	1,560	0.05	0.03	0.05	443	-0.02	0.04	0.71
Reward	1,554	-0.02	0.03	0.47	441	-0.08	0.04	0.05
Slope								
Effort	1,505	0.002	0.001	0.04	429	-0.002	0.002	0.33
ERI ratio	1,496	0.003	0.002	0.03	426	-0.002	0.002	0.93