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Associations among work-related stress, cortisol, inflammation, and metabolic syndrome

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Abstract

This cross-sectional study examined the relationship between work-related stress, cortisol, and C-reactive protein (CRP) in predicting metabolic syndrome (MtS). Self-reported work stress measured by the effort reward imbalance ratio (ERI), anthropometric data, CRP, and saliva cortisol were collected from 204 healthy Jordanian male workers. ERI and cortisol were significantly associated with the presence of MtS (*OR* = 4.74, 95% CI: 2.13–10.55; *OR* = 3.03, 95% CI: 2.08–4.40; *OR* = 11.50, 95% CI: 2.16–59.14, respectively). The odds of MtS in men with high ERI and high cortisol were significantly higher than that of men with low ERI and low cortisol (*OR* = 11.50, 95% CI: 2.16–59.14). CRP was significantly associated with MtS (*OR* = 2.51, 95% CI: 1.50–4.20). The odds of MtS were significantly higher in centrally obese men with both high ERI and CRP level. Thus, high ERI along with high cortisol or high CRP increases the risk for MtS, especially among centrally obese men.

Descriptors: Psychopathological, Biochemical

Work-related stress may adversely affect physical health (Leka & Jain, 2010). Psychological stress in the workplace has mainly been investigated through two theoretical models, the demand-control (DC) model (Karasek, 1979; Karasek & Theorell, 1990) and the effort-reward imbalance (ERI) model (Siegrist, 1996). The DC model emphasizes task-level control, whereas the ERI model emphasizes employee perception of effort-reward imbalance (Tsutsumi & Kawakami, 2004). Effort-reward imbalance is a serious form of psychological work-related stress, since workers may feel undercompensated for their efforts. The ERI model has advantages over the DC model in that ERI focuses on stressors such as adequate payment, job security, job changes, and job promotion prospects (Griep et al., 2009). A high level of ERI is associated with components of metabolic syndrome (MtS), namely, hypertension (Peter et al., 1998), high body mass index (BMI) (Kivimaki et al., 2002), increased triglyceride level (Fan et al., 2009), and high fasting glucose (Kumari, Head, & Marmot, 2004).

Stress activates two fundamental axes, the hypothalamus-pituitary-adrenal (HPA) axis and the sympathomedullo-adrenal (SMA) axis (Figure 1). Altered activity of both the HPA and SMA axes predisposes an individual to increased risk of developing MtS (Bjorntorp & Rosmond, 2000). However, these two axes act through separate pathways, one through hypercortisolemia, and the other through cytokines and inflammatory reactions (Bellingrath, Weigl, & Kudielka, 2009; Black, 2003; Sternberg, Chrousos, Wilder, & Gold, 1992; Yudkin, Stehouwer, Emeis, & Coppack, 1999).

The first pathway through hypercortisolemia involves increases in cortisol levels. Elevated cortisol levels increase glucose production within liver cells resulting in hyperglycemia. In addition, increased cortisol levels inhibit insulin secretion from pancreatic β-cells, as well as inhibit muscle glucose uptake. These effects lead to impaired glucose tolerance and insulin resistance (Amatruda, Livingston, & Lockwood, 1985). Cortisol also stimulates the breakdown of stored triglycerides in the adipose tissue, resulting in an increase in free fatty acids in the plasma. A higher level of free fatty acids prevents the release of insulin, further worsening glucose intolerance and insulin resistance. Density of cortisol receptors is higher in intra-abdominal (visceral) fat than in other fat deposits, and the activity of cortisol in fat accumulation is accentuated in visceral adipose tissue (Bjorntorp & Rosmond, 2000; Salehi, Ferenczi, & Zumoff, 2005), suggesting a mechanism by which excessive cortisol causes further abdominal obesity (Qi & Rodrigues, 2007).

The second pathway involves cytokines that induce acute phase proteins, such as C-reactive protein (CRP) (Gabay & Kushner, 1999). CRP, one of the best characterized systemic inflammatory biomarkers, may interfere with insulin signaling and downregulate corticosteroid-binding globulin, resulting in increased free cortisol levels and consequently insulin resistance as well as other manifestations of MtS (Hotamisligil et al., 1996).

Furthermore, proinflammatory cytokines inhibit lipoprotein lipase activity and increase the concentration of nonesterified fatty acids, contributing to dyslipidemia and insulin resistance (Perry, Sattar, & Petrie, 2001). Central obesity amplifies the release of

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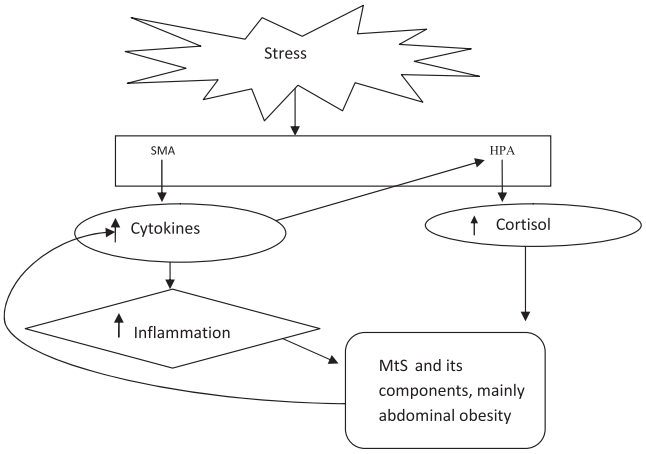

Figure 1. Stress and MtS pathways.

proinflammatory cytokines (Kern, Ranganathan, Li, Wood, & Ranganathan, 2001). Notably, the relationship between stress and inflammation markers (such as CRP) is observed mostly among subjects with central obesity (Almadi, Cathers, Hamdan Mansour, & Chow, 2012b; Shen, Farrell, Penedo, Schneiderman, & Orth-Gomer, 2010).

High stress levels as measured by the ERI (Bellingrath et al., 2009) and mood disturbance (Lutgendorf et al., 1999) induce low-grade inflammatory responses with increased production of proinflammatory cytokines (Black, 2002). Subsequently, these cytokines induce an increase in CRP production (Gabay & Kushner, 1999). This increase in CRP is thought to contribute to the pathogenesis of MtS (Laaksonen et al., 2004). Therefore, in this study, we sought to explore the links between chronic work stress as measured by ERI and the MtS through the stress marker cortisol and the inflammatory marker CRP. These links are explored specifically in obese subjects. The current study sought to answer the following questions: (a) Does ERI predict an increased likelihood of MtS and its components? (b) Does ERI that is associated with a high level of cortisol predict a greater likelihood of MtS and its components? (c) Does ERI that is associated with a high level of CRP predict an increased likelihood of MtS and its components? (d) Does the high CRP in central obesity predict a greater likelihood of MtS compared to noncentral obesity?

Method

Participants

Healthy Jordanian male workers ($N = 264$) were recruited from the veterinary, agricultural, textile, and poultry industries. Screening questionnaires were used to exclude all men with conditions known to influence cortisol secretion and increase CRP plasma levels. Excluded conditions included physical and endocrine abnormality, depression or other mental and psychiatric conditions, substance abuse, inflammatory diseases, CVD, previous stroke, rheumatic disease, diabetes mellitus, liver disease, viral or recent infection, connective tissue disease, peripheral blood disease, tumor, neurological and endocrine disease, and recent injury or surgical operation. We also excluded all male workers on steroid-based medications, hormone or hormone-related therapy, cholesterol-lowering agents, antidepressants, psychotropic medications, or on any medications or drugs that can affect cortisol or lipid levels. Finally, subjects were also excluded if they were taking medications that affected inflammatory response, reductase inhibitors (statins), nonsteroidal antiinflammatory drugs (NSAIDs), analgesic medications, antidepressants, sedatives, antipsychotic medications, or if they had acute illness or were employed in night shifts (Elgharib, Chi, Younis, Wehbe, & Krishnaswamy, 2003; Gabay & Kushner, 1999; Liu, Bravata, Cabaccan, Raff, & Ryzen, 2005; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1997; Ridker, Rifai, Pfeffer, Sacks, & Braunwald, 1999). All subjects gave informed consent for this study, which was approved by the Human Research Ethics Committee of The University of Sydney and Jordan University.

Materials and Procedures

Information was collected on age, race, work characteristics (full-time/part-time), smoking status (current smoker, nonsmoker), and alcohol intake. Four self-reported questionnaires in Arabic were administered: the Effort-Reward Imbalance (ERI) questionnaire (Siegrist, 1996); the Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983); the International Physical Activity Questionnaire (IPAQ; Craig et al., 2003); and the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

The Arabic version of the ERI questionnaire (Almadi, Cathers, & Chow, 2012a) has a Cronbach's alpha coefficient of 0.82. It contains 17 items, 6 are related to "effort" and 11 items are related to "reward." The items of effort and reward include five responses and are answered in two steps. In the first step, the respondents are asked whether the item content describes a typical experience in their workplace. If the participants agree, they are asked about the level of distress by choosing one item of a 4-point Likert scale, ranging from 1 (*I am not at all distressed*) to 4 (*I am very distressed*). The ERI ratio was calculated as Effort/Reward × Correction Factor (correcting for the difference in the numbers of items of the two scales: effort and reward). A ratio of 1 represents a balance of effort and reward, whereas a ratio greater than 1 reflects disproportionate effort. Individuals with an ERI ratio ≥ 1 were classified as the stressed group, and the remainder with a ratio < 1 were in the nonstressed group. Participants were also asked to respond to six additional questions on work "overcommitment," which was scored on a 4-point Likert scale, ranging from 1 (*full disagreement with the statement*) to 4 (*full agreement*). Higher overcommitment scores indicate high-risk conditions for physical or mental disorders (Van Vegchel, de Jonge, Bosma, & Schaufeli, 2005).

Perceived stress was assessed by the Arabic version of the PSS (Almadi, Cathers, Hamdan Mansour, & Chow, 2012a) with a Cronbach's alpha coefficient of 0.68. The scale measures the level of perceived stress experienced over the previous month, and consists of 14 items with a 5-point Likert scale, ranging from 0 (*never*) to 4 (*very often*). A high score represents a high level of perceived stress (Cohen et al., 1983).

Participants were asked to answer questions regarding their amount of physical activity using the Arabic version of the IPAQ (Al-Hazza, 2006). The IPAQ has undergone extensive validation and reliability assessment, and it contains items pertaining to physical activity patterns over the previous week in four areas: work, home, leisure, and travel (Craig et al., 2003).

Sleep quality was measured by the Arabic translated version of the PSQI (Almadi, Cathers, & Chow, 2012b), with Cronbach's alpha coefficient of 0.66. The PSQI is a 19-item questionnaire about sleep quality in the previous month. The total scores of all

items are computed to generate seven component scores with subscale scores of 0 to 3 for the seven components: sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. The sum of responses of all seven components yields a global score of sleep quality. A subject with a global PSQI score greater than 5 is considered to be a poor sleeper, and a subject with a value of ≤ 5 is considered to be a good sleeper (Buysse et al., 1989).

In addition to the self-reported measures, male subjects also provided biologic and physiologic data. Subjects were seated for at least 5 min in a private room before blood pressure was measured with a standard commercial sphygmomanometer (Accoson, UK). Subject height and weight were recorded, and the waist circumference was obtained by measuring at the narrowest point between the lower costal (tenth rib) and the iliac crest. BMI was calculated as weight (kg) divided by height squared (m^2). Venous fasting blood samples were collected in plain tubes and centrifuged at 3,000 rpm for 10 min at room temperature, and serum samples were frozen at −20°C until assayed. Fasting blood glucose (FBG) and blood lipid profile (total cholesterol, high-density lipoprotein, triglycerides, and low-density lipoprotein) were determined (Accent 200 automated chemistry analyzer, Poland) using an enzymatic method kit. High-sensitivity CRP was determined (Automated Roche Diagnostics modular analyzer, Roche, Switzerland) using a particle-enhanced immunoturbidimetry method with a measuring range of 0.085–1,600 mg/L.

Subjects also provided self-sampling of saliva for cortisol assessment. Cortisol assessment through saliva sampling has the advantage of easy and noninvasive sample collection in ambulatory settings. Subjects were given clear written instructions with graphic illustrations in addition to verbal instructions. Instructions provided the method of saliva collection, with emphasis on the importance of timing of saliva collection, and all necessary precautions associated with the collection. Samples were collected using cotton dental rolls that were chewed by subjects for 1 min. Cotton rolls were then stored in Salivette tubes (Sarstedt Pty Ltd., Australia). Participants were instructed to give three saliva samples in a working day. The first sample was collected immediately after early morning awakening, while they were in bed (sitting up). Subsequent samples were taken at 10 and 20 min after awakening, but before brushing their teeth, eating, drinking, smoking, doing physical activity, having a shower, or exposing their eyes to direct room artificial light or sunlight (Clow, Thorn, Evans, & Hucklebridge, 2004). Participants were asked to time their saliva collection accurately and write the time of awakening and the time of collection of each sample. Salivette tubes were bagged and stored in their home freezer until they came for their morning blood collection appointment.

Saliva samples were centrifuged for 15 min at 3,000 rpm, and salivary cortisol was measured immediately once the laboratory received the samples. Salivary cortisol levels were measured on an automated immunoassay analyzer (Elecsys, Roche, Germany).

The area under the curve (AUC) was calculated using the measurements of cortisol concentration over the three time points of 0, 10, and 20 min (Pruessner, Hellhammer, Pruessner, & Lupien, 2003). The AUC for cortisol level after awakening was used as the index of HPA axis activity (Clow et al., 2004; Pruessner et al., 1997; Steptoe, Cropley, Griffith, & Kirschbaum, 2000). This index shows a high degree of intraindividual stability when measured over several days or weeks (Pruessner et al., 1997).

For cortisol analysis, there were 204 subjects, 60 were excluded due to insufficient or missing cortisol samples, or missing data for one or more of the main parameters. CRP analysis was performed for 225 subjects of the study sample. Subjects with CRP levels of 10 mg/L or more were excluded ($n = 25$) from further analysis because they are likely to be related to acute infections or other acute inflammatory conditions (Ford et al., 2003; Jialal, Devaraj, & Venugopal, 2004). Participants ($n = 54$) with missing data for one or more of the study's main parameters were excluded. Thus, data from 146 subjects were used in the final analysis.

MtS was defined according to the International Diabetes Federation (IDF, 2005) criteria of central obesity (waist circumference of ≥ 94 cm for men), plus any two of the following four factors: triglyceride (TG) level of ≥ 150 mg/dL, HDL cholesterol of < 40 mg/dL, blood pressure (systolic blood pressure [SBP] level of ≥ 130 or diastolic blood pressure [DBP] level of ≥ 85 mm Hg), or fasting plasma glucose of ≥ 100 mg/dL.

Statistical Analyses

Baseline characteristics were compared across stress groups (ERI ≥ 1 and ERI < 1), and two-tailed p values were calculated using independent sample t tests. We compared the MtS across work stress and saliva cortisol (AUC) tertiles or CRP tertiles using chi-square and Fisher's exact tests. The distributions of CRP, physical activity score, and triglycerides were skewed and were therefore log-transformed before analysis.

The independent associations of ERI ratio, cortisol (AUC), and CRP with MtS were calculated, adjusting for potential confounders: age (Hildrum, Mykletun, Hole, Midthjell, & Dahl, 2007; Wener, Daum, & McQuillan, 2000), smoking (Kasapis & Thompson, 2005; McDade, Hawkley, & Cacioppo, 2006; Oh et al., 2005), physical activity (Lakka & Laaksonen, 2007), perceived stress (Yoo, Eisenmann, & Franke, 2009), sleep (Jennings, Muldoon, Hall, Buysse, & Manuck, 2007; Okun, Coussons-Read, & Hall, 2009), awakening time (Clow et al., 2004), work type (Sanchez-Chaparro et al., 2008), and work overcommitment (Steptoe, Siegrist, Kirschbaum, Marmot, 2004). Independent variables including the ERI ratio, cortisol (AUC), CRP, awakening time, age, type of work, physical activity, and overcommitment scores that were at 25% level of significance during univariate logistic regression were carried forward to multivariable binary logistic regression for adjustment (Hosmer & Lemeshow, 2000). PSS score, PSQI, smoking status, and education level with a significance level $> 25\%$ were excluded from further analysis. We used multivariable binary logistic regression analysis to adjust for the confounding factors. In addition, we included an interaction term in the multivariable logistic regression model to assess the possible interaction between the ERI ratio and cortisol or CRP. We also conducted separate analyses for the stress groups and for central obesity groups. Multivariable linear regression analysis was also carried out to evaluate the association between ERI ratio and cortisol (AUC), as well as between ERI ratio and CRP with each of the five components of MtS. For linear regression analysis, each component, as dependent variable, was taken on a continuous scale. A two-tailed p value of $\leq 5\%$ was considered significant during multivariable regression analysis. All statistical analyses were performed in SPSS (version 19, IBM).

Results

Participant Characteristics

The majority of Jordanian workers who participated in this study (74%) were aged 26–45 years. In terms of type of work, 74% were

engaged in manual work, 88% worked for private companies, and 99% were full-time workers. Table 1 displays the means and standard deviations for all of the study variables.

Using the World Health Organization's definition of obesity (BMI ≥ 30 < 40 kg/m^2) (WHO, 2004), 25% of the sample was classified as obese. Based on the International Diabetes Federation criteria of MtS (IDF, 2005), 54% of the sample had a waist circumference of ≥ 94 cm, 42% had high triglycerides (≥ 150 mg/dL), 25% had high glucose levels (≥ 100 mg/dL), 48% had low HDL cholesterol levels (< 40 mg/dL), and 18% had high blood pressure. Therefore, 32% fit the criteria of having MtS. A large proportion of the sample (62%) was not very physically activity (< 600 MET-min/week), 54% were active smokers, but none reported consuming alcohol. We found that 51% were poor sleepers (PSQI > 5). High work-related stress, based on an ERI ratio ≥ 1, was prevalent in 65% of the subjects.

Comparison of the Stressed and Nonstressed Groups

Table 1 shows the comparison of stressed (ERI ratio ≥ 1) and nonstressed subjects (ERI ratio < 1). We found that stressed subjects had significantly higher waist circumference, BMI, systolic blood pressure, cortisol levels at 10 min, cortisol levels at 20 min, and cortisol (AUC). In addition, the stressed group had significantly more cases of MtS ($n = 51$) than the nonstressed subjects ($n = 14$, $p < .05$).

ERI and MtS

ERI and MtS through the cortisol pathway. Multiple regression analysis (Table 2) shows that the ERI ratio was significantly associated with MtS, even after adjusting for age, type of work, physical activity, awakening time, and work overcommitment. However, adding cortisol expressed in AUC to the model considerably attenuated the association between the ERI ratio and MtS. In addition, the interaction between cortisol (AUC) and ERI was significantly associated with MtS.

The prevalence of MtS differed significantly across work-stressed (ERI) groups and saliva cortisol (AUC) tertiles ($p \leq .001$; Figure 2). The majority of MtS cases was present in the highest cortisol (AUC) tertile and stressed group. After adjustment for age, type of work, physical activity, awakening time, and work overcommitment, the highest cortisol (AUC) tertile significantly predicted MtS ($OR = 11.50$, 95% CI: 2.16–59.14) in subjects who had high stress. In contrast, there was no association between cortisol (AUC) and MtS in the nonstressed group. Stressed subjects with either middle or low cortisol (AUC) tertile did not differ from the nonstressed subjects for all tertiles of cortisol (AUC) (Figure 2).

ERI and MtS through inflammatory pathway. Overall, the mean CRP ($n = 146$) was 2.04 ± 0.82. There was a significant difference between the mean values of CRP for the stressed group (2.14 ± 0.8, $n = 98$) compared to the nonstressed group (1.85 ± 0.82, $n = 48$; $p \leq .05$). A significant difference in mean CRP was also observed between the MtS group (2.47 ± 0.67, $n = 43$) and the group without MtS (1.87 ± 0.82, $n = 103$; $p \leq .001$).

Table 3 shows the regression analysis of ERI adjusted for CRP. The ERI ratio after adjustment for other factors remained significantly associated with MtS. In addition, CRP was significantly associated with MtS. However, further adjusting by entering CRP into the model resulted in the association between ERI ratio and MtS being attenuated. The interaction between ERI ratio and CRP levels in predicting the chance of MtS was significant.

Accordingly, we stratified our logistic regression analyses to compare the stressed and nonstressed group. For the stressed group, the adjusted CRP remained associated with MtS, but there was no association in the nonstressed group (Table 3). Fisher's

Table 1. *Psychological, Physical, Physiological, and Biochemical Characteristics of Jordanian Male Workers* (n = *204) Comparison Between Stressed and Nonstressed Group*

	$n = 204$ Mean (*SD*)	Stressed ($n = 132$) Mean (*SD*)	Nonstressed ($n = 72$) Mean (*SD*)	p*
Age (year)	35.3 (8.8)	35.6 (9.1)	34.7 (8.1)	*ns*
Waist (cm)	94.1 (12.6)	96.2 (12.3)	90.3 (12.1)	≤ .001
BMI (kg.m^{-2})	26.9 (3.7)	27.4 (3.6)	26.0 (3.6)	< .05
Perceived stress	25.6 (6.9)	25.3 (6.7)	26.1 (7.2)	*ns*
Overcommitment	14.3 (3.9)	14.1 (3.7)	14.7 (4.1)	*ns*
Physical activity (MET-min/week)	1,210 (1,948)	1,138 (1,946)	1,341 (1,958)	*ns*
Total sleep quality	5.4 (3.1)	5.3 (2.9)	5.7 (3.3)	*ns*
Fasting blood glucose(mg/dL)	91.1 (12.2)	91.9 (12.4)	89.6 (11.3)	*ns*
Low-density lipoprotein (mg/dL)	111.2 (31.6)	111.9 (33.3)	109.9 (28.3)	*ns*
Total cholesterol (mg/dL)	187.1 (36.6)	188.3 (39.9)	184.8 (29.6)	*ns*
High-density lipoprotein (mg/dL)	42.1 (8.7)	42.2 (8.7)	41.9 (8.8)	*ns*
Triglycerides (mg/dL)	155.3 (85.4)	155.9 (84.9)	154.3 (86.9)	*ns*
Systolic blood pressure (mmHg)	122 (9)	120 (8)	123 (9)	< .05
Diastolic blood pressure (mmHg)	80 (6)	81 (8)	81 (5)	*ns*
Saliva cortisol 0 time (nmol/L)	11.3 (5.2)	11.8 (5.6)	10.4 (4.3)	*ns*
Saliva cortisol 10 time (nmol/L)	14.7 (6.6)	15.5 (7.1)	13.2 (5.3)	< .05
Saliva cortisol 20 time (nmol/L)	18.2 (7.9)	19.1 (8.5)	16.6 (6.4)	< .05
(Δ cortisol) (20 min–0 min) (nmol/L)	6.9 (4.9)	7.3 (5.1)	6.2 (4.1)	*ns*
Cortisol° (nmol/L)	305.9 (139.4)	326.9 (153.3)	267.3 (99.2)	< .05

Note. ns = not significant.
*Two-tailed p value based on independent sample t test.
°Cortisol calculated from area under the curve (AUC).

Table 2. *Association Between Work Stress, Cortisol, and Metabolic Syndrome (*n = *192)*

	Unadjusted *OR* (95% CI)	Adjusted+ *OR* (95% CI)	Adjusted++ *OR* (95% CI)
Effort-reward ratio[a]	4.78* (2.31–9.88)	4.74* (2.13–10.55)	2.80** (1.15–6.78)
Cortisol°	3.03* (2.08–4.40)	2.86* (1.92–4.25)	
Effort-reward ratio and cortisol interaction	1.84* (1.50–2.26)	1.83* (1.47–2.28)	
Stressed group ($n = 126$)			
Cortisol°	3.96* (2.39–6.56)	3.90* (2.23–6.81)	
Effort-reward ratio and cortisol interaction	2.12* (1.60–2.81)	2.14* (1.53–2.98)	
Nonstressed group ($n = 66$)			
Cortisol	1.23 *ns* (0.68–2.20)	1.15 *ns* (0.52–2.55)	
Effort-reward ratio and cortisol interaction	1.32 *ns* (0.75–2.32)	1.15 *ns* (0.55–2.39)	

Note. ns = not significant.
[a]per one unit increase in the effort reward ratio (0.1). °per *SD* increase in the area under the curve (AUC) of three timed cortisol measurements.
+Adjusted for age, type of work, physical activity, awakening time, and work overcommitment. ++Adjusted for age, type of work, physical activity, awakening time, work overcommitment, and cortisol expressed in AUC.
*$p \leq .001$. **$p < .05$.

exact test showed that MtS was most prevalent among stressed subjects in the highest CRP tertile (Figure 3; $p \leq .001$).

ERI and MtS Components

ERI and MtS components through the cortisol pathway. Table 4 shows that the ERI ratio was associated with the MtS components of waist circumference and SBP after adjusting for age, type of work, physical activity, awakening time, and work overcommitment. The adjusted cortisol level AUC showed a significant positive association with waist circumference, SBP, and FBG, and a negative association with HDL. Moreover, there was a significant interaction between ERI ratio and cortisol AUC level in predicting the level of waist circumference, SBP, FBG, and HDL.

High cortisol AUC level was significantly associated with large waist circumference, high triglyceride level, low HDL level, high SBP, and high DBP only in the stressed group (Table 4). In contrast, in the nonstressed group, cortisol (AUC) was not associated with any of the MtS components (Table 4).

ERI and MtS components through the inflammatory pathway. Table 4 shows that CRP was associated with waist circumference and triglycerides. There was a significant interaction between ERI ratio and CRP levels in predicting the levels of waist circumference, triglycerides, and SBP.

In the stressed group, the CRP levels were higher than in the nonstressed group. Within the stressed group, CRP was significantly associated with waist circumference (Table 4). In the nonstressed group, CRP was only associated with triglyceride level.

In a separate analysis, the binary regression was repeated only among subjects with upper tertile waist circumference of ≥ 98.5 cm ($n = 49$). The data showed that, after adjustment, CRP was significantly associated with MtS (*OR* = 4.26, 95% CI: 1.40–13.05; $p < .05$), but was no longer significantly associated

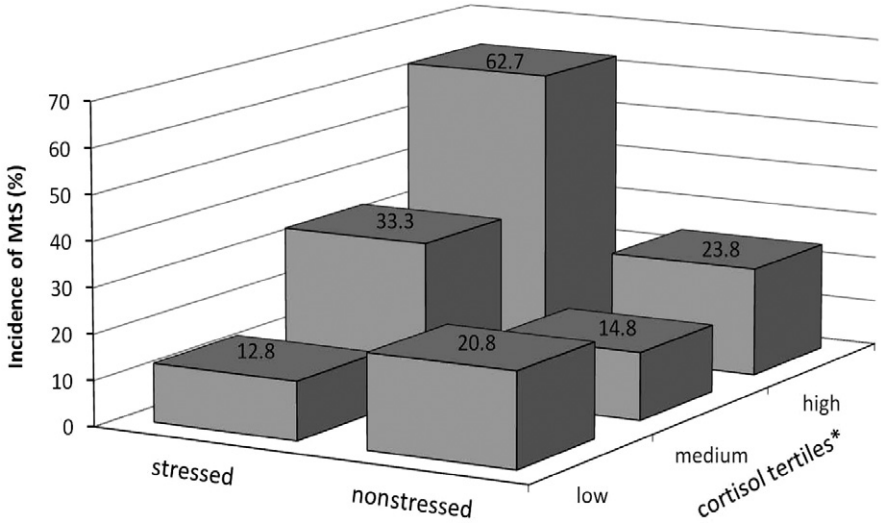

Figure 2. Incidence of MtS across work stress status and tertiles of cortisol. *Cortisol calculated from area under the curve (AUC). Low cortisol tertile < 230.5 nmol/L, middle tertile ≥ 230.5 < 340 nmol/L, high tertile ≥ 340 nmol/L.

Table 3. *Association Between Work Stress, C-Reactive Protein, and Metabolic Syndrome (*n = *146)*

	Unadjusted *OR* (95% CI)	Adjusted+ *OR* (95% CI)	Adjusted++ *OR* (95% CI)
Effort-reward ratio[a]	2.65** (1.13–6.25)	3.35** (1.32–8.53)	2.36 *ns* (0.89–6.24)
C-reactive protein[1]	2.49 * (1.55–4.01)	2.51* (1.50–4.20)	
Effort-reward ratio and C-reactive protein interaction	1.80* (1.33–2.42)	1.85* (1.33–2.57)	
Stressed group ($n = 98$)			
C-reactive protein	3.02* (1.67–5.47)	4.14* (1.99–8.62)	
Effort-reward ratio and C-reactive protein interaction	1.80* (1.34–2.42)	2.03* (1.39–2.98)	
Nonstressed group ($n = 48$)			
C-reactive protein	1.28 *ns* (0.53–3.06)	5.62 *ns* (0.67–47.40)	
Effort-reward ratio and C-reactive protein interaction	0.79 *ns* (0.35–1.78)	1.90 *ns* (0.46–7.87)	

Note. *ns* = not significant.
[a]per one unit increase in the effort reward ratio (0.1). [1]per one unit increase in C-reactive protein, Log(1 mg/L).
*$p \leq .001$. **$p < .05$.
+Adjusted for age, type of work, physical activity, awakening time, and work overcommitment. ++Adjusted for age, type of work, physical activity, awakening time, work overcommitment, and Log value of C-reactive protein.

among subjects in the middle tertile waist circumference, 88.0 cm to 98.5cm group ($n = 45$). The middle waist circumference tertile but not the lower tertile (waist circumference of < 88cm, $n = 52$) was used as the reference group, since none of the subjects on the lower tertile group had MtS.

ERI, MtS, and Inflammation with Central Obesity

Further analysis of subjects with upper tertile waist circumference (≥ 98.5cm) and high stress (ERI ≥ 1, $n = 39$) showed that, after adjustment for other factors, CRP was significantly associated with MtS (*OR* = 5.23, 95% CI: 1.41–19.45, $p < .05$). This association was not significant in the nonstressed group (ERI < 1, $n = 9$).

The interaction between CRP and cortisol (AUC) was a significant predictor of MtS for the stressed group, even after adjustment for other factors ($p \leq .001$), whereas the prediction was not significant for the nonstressed group.

Cortisol Measurement Immediately on Awakening and MtS

Adjustment for cortisol using cortisol measured at awakening (time = 0) attenuated the association between ERI and MtS (*OR* = 3.70, 95% CI: 1.60–8.60, $p < .05$). Even after adjustment for the confounders, the cortisol at time = 0 remained significantly associated with MtS (*OR* = 1.93, 95% CI: 1.35–2.76, $p \leq .001$). In addition, the interaction between ERI ratio and cortisol time = 0 was significantly associated with MtS (*OR* = 1.68, 95% CI: 1.35–2.10, $p \leq .001$). Among the stressed group, the adjusted cortisol at time = 0 and the interaction between cortisol at time = 0 and ERI was significantly associated with MtS (*OR* = 2.39, 95% CI: 1.47–3.90, $p \leq .001$; *OR* = 1.89,

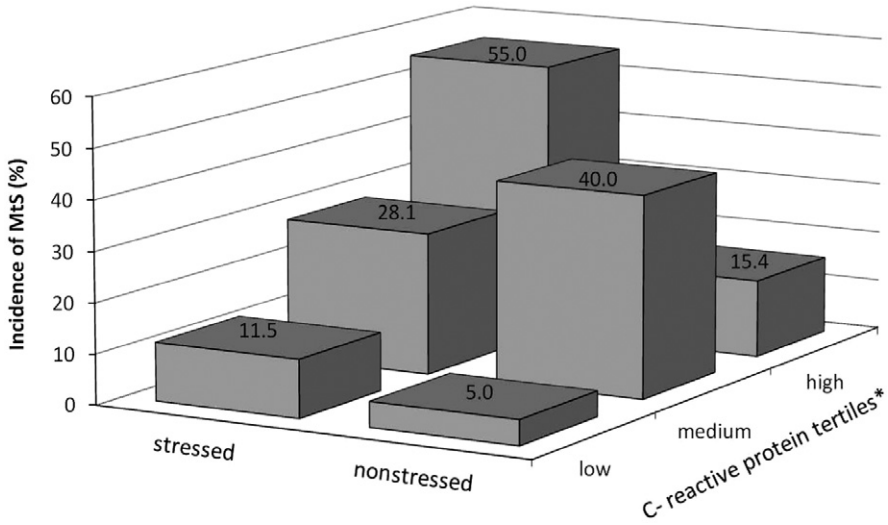

Figure 3. Incidence of MtS across work stress status and tertiles of CRP. *Low C-reactive protein tertile < 1.44 mg/L, middle tertile ≥ 1.44 < 3.50 mg/L, high tertile ≥ 3.50 mg/L.

Table 4. *Associations Between Work Stress, Cortisol, C-Reactive Protein, and Components of Metabolic Syndrome, Adjusted for Age, Type of Work, Physical Activity, Wakening Time, and Work Overcommitment*

	Waist circumference		Triglycerides		HDL		SBP		DBP		FBG	
	ß	*t*	ß	*t*	ß	*t*	ß	*t*	ß	*t*	ß	*t*
Effort-reward ratio[a]	.22*	3.61	.02 *ns*	0.28	–.01 *ns*	0.01	.18**	0.24	.02 *ns*	0.24	.12 tr	1.79
Cortisol°	.17*	2.81	.08 *ns*	1.14	–.20**	–2.67	.26*	3.60	.12 *ns*	1.54	.14**	2.10
C-reactive protein[1]	.31*	4.22	.23**	2.66	–.16 tr	–1.84	.11 *ns*	1.26	.05 *ns*	0.54	.11 *ns*	1.30
Effort-reward ratio and cortisol interaction	.25*	4.00	.11 *ns*	1.45	–.15**	–2.00	.28*	3.87	.11 *ns*	1.43	.17**	2.46
Effort-reward ratio and C-reactive protein interaction	.32*	4.33	.18**	2.07	–.12 *ns*	–1.39	.19**	2.18	.54 ns	0.61	.13 *ns*	1.56
Stressed group												
Cortisol	.17**	2.18	.18**	2.06	–.25*	–2.70	.28**	3.14	.24**	2.75	.15 tr	1.87
Effort-reward ratio and cortisol interaction	.23**	2.86	.19**	2.09	–.20**	–2.19	.25**	2.70	.23**	2.46	.19**	2.28
C-reactive protein	.38*	4.20	.20 tr	1.91	–.20 tr	–1.96	.13 *ns*	1.23	.16 *ns*	1.58	.06 *ns*	0.67
Effort-reward ratio interaction C-reactive protein	.34*	3.97	.16 *ns*	1.58	–.19 tr	–2.37	.09 *ns*	0.90	.16 *ns*	1.55	.14 tr	1.76
Nonstressed group												
Cortisol	.14 *ns*	1.33	–.18 *ns*	–1.41	–.16 *ns*	–1.22	.07*ns*	0.52	–.08 *ns*	0.57	.04 *ns*	0.31
Effort-reward ratio and interaction cortisol	.19 tr	1.90	–.13 *ns*	–1.05	–.22 *ns*	–1.71	.06 *ns*	0.47	–.12 *ns*	0.39	–.01 *ns*	–0.10
C-reactive protein	.15 *ns*	1.07	.48**	2.88	.24 *ns*	1.31	.09 *ns*	0.51	.15 *ns*	0.79	.23 *ns*	1.22
Effort-reward ratio and interaction C-reactive protein	.12 *ns*	0 .96	.41**	2.97	–.31**	–2.03	–.01 *ns*	–0.04	–.21 *ns*	–1.27	.19 *ns*	1.16

Note. ß = standardized coefficients; *t* = *t* value; tr = trend ($p > .05 \leq .08$); *ns* = not significant.
[a]per one unit increase in the effort reward ratio (0.1). °per *SD* increase in the area under the curve (AUC) of three timed cortisol measurements. [1]per one unit increase in C-reactive protein, Log(1 mg/L).
*$p \leq .001$. **$p < .05$.

95% CI: 1.37–2.61, $p \leq .001$, respectively). In contrast, there was no association between cortisol at time = 0 or the interaction between cortisol at time = 0 and ERI with MtS in the nonstressed group.

Change in Cortisol Level and MtS

When change in cortisol level (Δ cortisol) (expressed as cortisol level at 20 min—cortisol level at time = 0) was used in the regression analysis instead of the cortisol (AUC), the association between the ERI ratio and MtS was attenuated (*OR* = 3.26, 95% CI: 1.41–7.50, $p < .05$). Change in cortisol was significantly associated with MtS (*OR* = 2.00, 95% CI: 1.37–2.93, $p \leq .001$). Further, there was a significant interaction between ERI ratio and change in cortisol and of MtS (*OR* = 1.69, 95% CI: 1.33–2.14, $p \leq .001$). Among the stressed group, we found a significant association between change in cortisol level and MtS (*OR* = 2.49, 95% CI: 1.48–4.17, $p \leq .001$). In addition, the interaction between change in cortisol and ERI was significantly associated with MtS (*OR* = 1.67, 95% CI: 1.26–2.22, $p \leq .001$). In contrast, no such associations were found in the nonstressed group.

Discussion

Despite overall good health, a high proportion of Jordanian workers in this study had large waist circumference, undertook little physical activity, and were active smokers. When stratified by ERI ratio, there were clear differences in waist circumference, BMI, SBP, cortisol at awakening, and CRP. In accordance with the stress model, the HPA axis and the SMA axis become activated, resulting in effects on cortisol and CRP, which are central to the development of MtS. In this study, we established a relationship between work-related stress, cortisol, and CRP in predicting MtS.

First, we showed that a high level of work-related stress (ERI ratio ≥ 1) was significantly associated with a large waist circumference, high DBP, and, to some extent, with high FBG level, as well as with a greater number of cases of MtS. These results are consistent with studies examining the relationship between chronic stress and MtS (Chandola, Brunner, & Marmot, 2006; Raikkonen, Matthews, & Kuller, 2007). In contrast, nonstressed subjects (ERI ratio < 1) showed no association with the MtS or any of its components.

To our knowledge, this is the first study addressing this link through two pathways, the HPA and SMA pathways, through their effects on the endocrine system (cortisol) and inflammatory markers (CRP). Rosmond (2005) has hypothesized that stress-related high cortisol secretion is strongly associated with MtS. Few studies have investigated cortisol levels at awakening and ERI association, and some showed positive associations (Eller et al., 2012). However, other studies have shown inconsistent findings for cortisol levels on awakening that were associated with ERI (Bellingrath, Weigl, & Kudielka, 2008; Steptoe et al., 2004). These inconsistent findings may be due to improper saliva cortisol collection, such as noncompliance with saliva sampling procedures or incorrect timing of sample collection. It can be difficult to guarantee true cortisol levels collected in ambulatory settings (Kudielka, Broderick, & Kirschbaum, 2003). Exposure to light following morning awakening may also affect the morning cortisol levels (Clow et al., 2004). In this study, the cortisol samples were collected with care, but while all precautions were taken, subjects' compliance could not be guaranteed. Although the awakening response of cortisol measured by AUC shows a high degree of intraindividual stability when measured over several days or weeks (Pruessner et al., 1997), this stability has not been tested in the current study, where only one set of samples was taken for the AUC analysis.

We further demonstrated the possible role of saliva cortisol and CRP in the development of MtS. Adjusting for saliva cortisol or CRP attenuated the association between stress and MtS. CRP elevation may also be a result of activation of the stress system (HPA and SMA) (Bruce, Rodman, & Newman, 2007; Rippe, 2012). Although hypercortisolemia-related stress appears to be a specific risk factor for MtS, the association for high CRP-related stress was only found in those with central obesity, consistent with many other studies (Hak et al., 1999; Lemieux et al., 2001; Saijo et al., 2004). A mechanism that explains the elevated CRP levels is that adipose tissues secrete proinflammatory cytokines (Kern et al., 2001), which in turn induce the synthesis and secretion of CRP by the liver (Papanicolaou, Wilder, Manolagas, & Chrousos, 1998). A synergistic effect of central obesity and work stress, acting together to intensify CRP production, is highly plausible (Dixon et al., 2008; Laaksonen et al., 2004; Visser, Bouter, McQuillan, Wener, & Harris, 1999). Indeed, weight loss was not only associated with a decrease in CRP level (Selvin, Paynter, & Erlinger, 2007), but also a reduction in psychological stress (Bruce et al., 2007; Rippe, 2012). This attenuates HPA and SMA activation, and in turn reduces cytokines and CRP production. In addition, visceral fat loss may lead to a decreased number of glucocorticoid receptors within visceral areas. Eventually, decreases in cortisol activity may lead to less abdominal fat deposition.

There are additional limitations to our study, such as the relatively small sample size, particularly the small number of centrally obese subjects, which limits the statistical power of this study. The strength of this study is the application of strict subject inclusion/exclusion criteria that excluded all medical conditions that may elevate cortisol or CRP level. The ERI questionnaire is a commonly used scale that is designed to measure work stress, which has been linked to poor health outcomes. Thus, persons with psychiatric diagnoses of work-related stress would be expected to show a stronger positive association with MtS. In addition, this study indicated that Jordanian workers reported a generally high level of work stress when assessed on the ERI questionnaire compared to other cohorts from European countries (Siegrist et al., 2004). This higher level of stress suggests Jordanian workers had higher perceived work effort and higher job demand, but job satisfaction was lower than workers in the samples from other nations. Additional research is recommended to explore the work-stress relationship (high ERI ratio) and its long-term health impact on workers in Jordan.

In conclusion, our results suggest that work-related stress, and its resulting hypercortisolemia and augmented CRP, synergistically contribute to the development of MtS in middle-aged Jordanian workers. High work-related stress in the presence of central obesity predisposes Jordanian workers to increased risk of MtS, potentially working through inflammatory pathways. These measures could also lead to an increased risk for developing cardiovascular disease or diabetes. These findings have important health implications for stress at work. Further research involving prospective studies should confirm our findings and investigate the causality and direction of the relationships among ERI, cortisol, inflammation (CRP), central obesity, and MtS.

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