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Effort-reward imbalance, overcommitment, and cellular immune measures among white-collar employees☆

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ABSTRACT

We investigated whether chronic job stress, i.e., effort-reward imbalance (ERI) and overcommitment is associated with cellular immunity among 190 male and 157 female white-collar daytime employees (mean age 38; range 22–69 years). Participants provided a blood sample for the measurement of circulating immune (natural killer (NK), B, and T) cell counts and NK cell cytotoxicity (NKCC) and completed a questionnaire survey during April to June 2002. Stepwise multiple linear regression analyses revealed that NK cells were associated with effort ($\beta = -.230$; $p = .013$), reward ($\beta = .169$; $p = .047$), and ERI ($\beta = -.182$; $p = .047$) scores but not with overcommitment in men; reward score was positively associated with NKCC ($\beta = .167$; $p = .049$) and inversely associated with B cells ($\beta = -.181$; $p = .030$). No significant associations were found in women. Although the picture remains less clear in women, our findings suggest a potential immunological pathway linking adverse working conditions and stress-related disorders in men.

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1. Introduction

Over the past few decades, numerous studies have tested and identified the link between psychological job stress and adverse health, mainly based on two job stress models, i.e., the job demand-control (JDC) model (Karasek, 1979) and the effort-reward imbalance (ERI) model (Siegrist, 1996). The JDC model states that employees who face too much work with little control over their jobs experience high job strain; the model exclusively focuses on the job task profile. Meanwhile, the ERI model postulates that job strain is not merely a product of employee efforts but results from an imbalance between the efforts spent and the rewards (money, career opportunities, esteem, respect, and job security) received. The ERI model also considers a personal characteristic referred as overcommitment. Overcommitment refers to a set of attitudes, behaviors, and emotions reflecting excessive endeavor in combination with a strong desire for approval and esteem (Siegrist, 2001). Reviews of the ERI model concluded that employees reporting overcommitment and exerting a high level of effort, but receiving a low level of rewards may experience an increased risk of psychological and physical health disorders (Tsutsumi and Kawakami, 2004; van Vegchel et al., 2005).

To date, a number of studies have demonstrated that JDC and ERI job stress components are related to an alteration of physiological measures such as heart rate (HR), HR variability (HRV), blood pressure (BP), and secretion of hypothalamus-pituitary-adrenal (HPA) axis hormones, which are considered to mediate the stress–illnesses relationship (Chandola et al., 2010; Chida and Steptoe, 2009; Hansen et al., 2009; Siegrist, 2010). Although some studies have observed sex differences in the physiological response to job stress using these models (Hintsanen et al., 2007; Steptoe et al., 2004), other studies have consistently reported that high job demands, low job control, high job strain, high ERI, and high overcommitment are associated with increased HR (Hintsanen et al., 2007), elevated BP (Kjeldsen et al., 2006; Schnall et al., 1998), decreased HRV (Chandola et al., 2008; Hintsanen et al., 2007), and increased secretion of catecholamines (Lee et al., 2010) and cortisol (Chandola et al., 2008; Eller et al., 2006; Steptoe et al., 2004).

In addition to the findings as described above, considerable attention has been drawn to identifying immunological pathways that may mediate the relationship between job stress and health. Studies using the JDC model revealed that high job demands are associated with reduced counts of circulating natural killer (NK) cells (Nakata et al., 2000a) and CD4+ T cells (Meijman et al., 1995), while low job control is related to decreases of memory

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CD4+ (CD4+CD45RO+ or CD4+CD29+) T cells (Kawakami et al., 1997; Nakata et al., 2000a) and CD4+/CD8+ ratio (Meijman et al., 1995). As a consequence, high job strain, defined as a combination of high job demands and low job control, was associated with decreased NK cells (Nakata et al., 2002) and naïve CD4+ (CD4+CD45RA+) T cells (Nakata et al., 2002), and increased serum immunoglobulin G (IgG) (Nakata et al., 2000a; Theorell et al., 1990) and IgM (Nakata et al., 2000a). In addition, some studies have examined the association of the JDC model with low-grade inflammatory markers such as interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α and C-reactive protein (CRP). Among four studies reported to date, three found no significant relationships between job stress and inflammatory markers (Clays et al., 2005; Hemingway et al., 2003; Shirom et al., 2008) while one study reported a significant positive correlation between job demands and CRP and an inverse correlation between job control and TNF-α (Schnorpfeil et al., 2003). These inconsistent findings suggest that there may be alternative pathways linking job stress and cardiovascular health in addition to inflammatory processes.

In sharp contrast to studies using the JDC model, only several studies have explored the relationship between job stress and immune-related outcomes using the ERI/overcommitment model. In a sample of 537 German factory workers (89% male), Bosch and colleagues examined the link between ERI measures and CD4+/CD8+ ratio and late-differentiated (CD27-CD28-) CD8+ cytotoxic T cells (Bosch et al., 2009). They found that reduced reward was associated with a significantly lower CD4+/CD8+ ratio, and decreased rewards and heightened ERI were related to an increased relative proportion and counts of late-differentiated cytotoxic T cells, suggesting that exposure to such chronic stress may promote immunosenescence. More recently, a study of German school teachers (34 women and 21 men) examined whether high ERI and overcommitment modulate the immune response after exposure to acute experimental tasks (an extemporaneous speech followed by mental arithmetic) (Bellingrath et al., 2010). Authors hypothesized that those who perceived high job stress may maintain poor immune status but their immune system can also be vulnerable when confronted with novel/acute stressors. The results revealed that the high ERI stress group at baseline was accompanied by lowered CD4+ T cells, CD16+/CD56+ NK cells, and IL-10 and elevated TNF-α and IL-6 compared to the low ERI stress group, but immune responses to a subsequent acute experimental task were somewhat different between the high and low stress groups. Both the high and low stress groups showed an increment of CD4+ T and CD16+/CD56+ NK cells but an increase of these cells in response to acute stress in high stress group was dampened compared to the response of the low stress group. In addition, those under low stress had an increased secretion of anti-inflammatory (IL-10) cytokine and decreased pro-inflammatory (IL-2) cytokine when exposed to acute stressors but those with high stress showed an opposite reaction, i.e., a decrease of IL-10 and an increase of IL-2, after exposure to acute stressors. This means that the immune responses of those with low stress at baseline could be flexible with additional stress exposure but the immune responses those under high stress may not be adaptable. Another study with a similar experimental protocol demonstrated that the ERI score was significantly and positively associated with high-sensitive CRP after exposure to acute mental stress in a sample of 92 healthy working men (Hamer et al., 2006). These findings are also in line with meta-analytic studies showing that exposure to chronic stress is associated with reduced NK and cytotoxic T cells and increased inflammatory substances as represented by IL-6 and CRP while exposure to acute stress is related to enhancement of these markers (Segerstrom and Miller, 2004; Zorrilla et al., 2001).

These investigations suggest that higher ERI/overcommitment may compromise future health conditions through dysfunction of the immune system, but there are still some important issues that need to be resolved. First, the findings were obtained from western countries (two from Germany and one from the UK) with limited sample sizes ($n < 100$ for 2 studies) that may limit generalizability and replicability. Because the ERI model has now been widely adopted not only in western countries but also in Asian countries including Japan (Irie et al., 2004; Shimazu and de Jonge, 2009; Tsutsumi et al., 2002a), it seems desirable to validate these findings with a sizable and culturally diverse population. Second, previous studies have not yet systematically dealt with potential gender-specific effects. It is possible that the affective response and immune reaction to stress is unique by sex (Edwards et al., 2006; Shirom et al., 2006), which deserves attention. With respect to the immune response alone, NK cell function has been reported to vary between men and women (Yovel et al., 2001). In addition, men and women may share occupational roles and responsibilities in different ways and work under different styles/conditions. In Japan, men tend to work in managerial positions with longer work hours and generally report higher levels of job stress than women (Nakata et al., 2008; Utsugi et al., 2009).

Therefore, our study was undertaken to fill a gap in the current knowledge about the psychoneuroimmunologic mechanism of ERI/overcommitment by assessing cellular immune parameters in Japanese working men and women. We measured NK cell cytotoxicity (NKCC) and circulating NK (CD3−CD56+) cells together with B (CD19+) and total T (CD3+CD56−) cells among 404 white-collar employees. We selected these immune markers because the reduction of NKCC and circulating NK and T cells is reported to be associated with poor working conditions (Bellingrath et al., 2010; Boscolo et al., 2008; Cohen et al., 2007; Di Donato et al., 2006; Hintsanen et al., 2007; Morikawa et al., 2005; Nakata et al., 2000a, 2002; Okamoto et al., 2008), and these markers are commonly measured in human psychoneuroimmunologic studies (Segerstrom and Miller, 2004).

With regard to the function and role of selected lymphocytes, NK cells are large granular cells possessing killer activity against certain tumor cells and virus-infected cells without prior sensitization. Meanwhile, T and B cells bear central roles in cellular and humoral immunity; subsets of T (CD4+ and CD8+) cells control the production of immunoglobulins from B cells and the secretion of cytokines. Although interpretation of changes in number of lymphocyte subsets needs to be done with great care, an excessive increase of T cells is known to be associated with systemic inflammation, whereas a persistent decrease of T cells is related to immunodeficiency and psychological disorders such as depression (Herbert and Cohen, 1993; Westermann and Pabst, 1990). Similarly, an extreme decrease of B cells is associated with suppressed humoral immune function resulting in inhibited production of immunoglobulins, while decreases of NK cells and NKCC are associated with reduced effectiveness in killing infected and cancerous cells (Whiteside and Herberman, 1994). NKCC has also been suggested as a significant prognostic indicator of poor lifestyle practices and infection among healthy individuals. People with poor lifestyle practices, such as smoking and no habitual exercise, exhibited a 15–20% decrease in NKCC than those with good lifestyle practices (i.e., nonsmoking or regular habitual exercise) (Kusaka et al., 1992). Among healthy subjects, persistently low NKCC are known to be associated with a higher risk for developing infections within 6–12 months (Levy et al., 1989; Zorrilla et al., 2001). Similarly, people with a low level of NKCC had a 1.6–1.7 times higher risk of cancer incidence than those with medium or higher NKCC levels after 11 years of observation (Imai et al., 2000).

Our aim was to clarify the following three questions: (1) Are effort, reward, ERI, and overcommitment associated with immune markers in white-collar Japanese workers? (2) If so, are there any

gender differences in such associations? and (3) What is the influence of covariates on such associations?

2. Methods

2.1. Subjects and procedure

The study design was cross-sectional and data were collected with a self-administered questionnaire at a pharmaceutical company and a trading company in Japan. The study was conducted as a part of occupational health examinations during April through June 2002. We established the following inclusion and exclusion criteria for this study. Those participants who had worked full-time at least one year, had worked during daytime hours only, and were working white-collar jobs, were included while those who had worked part-time, had worked under contract, had missing responses in sociodemographic variables, and were on medical leave were excluded from the analyses. A total of 643 employees were initially recruited for this study. The survey questionnaire, including purpose, instruction, and informed consent was given to a total of 626 employees (17 employees could not be reached because they were out due to sickness, mostly because of psychiatric illnesses, or maternity leave). Four hundred and four employees agreed to participate in the questionnaire survey and blood test, and replied with a signed consent form (response rate 64.5%). Among participants, those who had missing data, reported immune-related disorders, were pregnant, or were using immunomodulating drugs were excluded (see Section 2.2.5 for detail), which resulted in a sample size of 347 participants (190 men and 157 women).

The study protocol was reviewed and approved by the Institutional Review Board of the National Institute of Occupational Safety and Health, Japan and by the Ethical Committee of the Kyushu University.

2.2. Measures

2.2.1. Effort-reward imbalance and overcommitment

Effort-reward imbalance and overcommitment were assessed by the validated Japanese version (Tsutsumi et al., 2001, 2002b) of the questionnaire (ERI-Q) (Siegrist, 1996; Siegrist et al., 2004). Effort and reward at work were measured by 6 and 11 items, respectively. Reward was composed of 3 subscales 'esteem (respect and support)', 'job promotion and salary', and 'job security and career opportunities', which were measured by 5, 4, and 2 items, respectively. For the effort and reward scales, the respondent responds 'yes' or 'no' as to whether a stressful situation exists at work. If 'yes' the respondent is further asked to indicate the distressfulness of this condition on a 4-point scale ranging from 1 (not at all distressed) to 4 (very distressed). Examples of the items are: 'Over the past years, my job has become more and more demanding' (effort); 'I receive the respect I deserve from my superiors' (reward). With regard to the effort scale, we excluded one item, 'My job is physically demanding,' because the study participants were white-collar office workers with less physically demanding work. The total score varies between 5 and 25 for effort and between 11 and 55 for reward.

The ERI ratio score was calculated based on the following equation: effort (5 items)/reward (11 items) × correction factor (0.4545). The correction factor was used to compensate for the unequal number of items in the effort and reward scale. The ERI ratio score was logarithmically transformed for analyses following the procedure recommended by Siegrist et al. (2004).

Overcommitment was assessed by 6 items with a 4-point scale ranging from 1 (strongly disagree) to 4 (strongly agree); the total score varies between 6 and 24. Examples of these items include 'Even the slightest interruption bothers me' and 'I start thinking about work problems as soon as I get up in the morning.' The Cronbach's alpha was 0.856 for effort, 0.898 for reward, and 0.741 for overcommitment.

2.2.2. Preparation of blood samples

Fasting blood samples were collected between 9.00 and 11.00 a.m. from participants to control for diurnal variations. Ethylenediaminetetraacetic acid dipotassium was used as an anticoagulant to collect 2 ml of venous blood from subjects for measurement of leukocyte counts and immunofluorescence staining. Similarly, 5 ml of heparinized venous blood was collected to measure NKCC. All samples were transported and handled at room temperature (i.e., 15–20 °C). Immunofluorescence staining analysis and measurement of NKCC were conducted within 24 and 12 h of blood collection, respectively. We determined counts of total leukocytes and total lymphocytes with an automated cell counter (Coulter Counter SP-VI, Coulter Electronics, Hialeah, FL, USA), and lymphocyte subpopulations by flow cytometry analysis (EPICS XL, Beckman Coulter Inc, CA, USA), as described in detail elsewhere (Nakata et al., 2000a, 2002).

2.2.3. Cell surface marker analysis

The following sets of monoclonal antibodies were used to perform four-color direct immunofluorescence surface-marker analysis: anti-CD45-FITC/anti-CD56-RD1/anti-CD19-ECD/anti-CD3-PC5. A combination of Mouse IgG1-FITC/Mouse IgG1-RD1/Mouse IgG1-ECD/Mouse IgG1-PC5 was used as the negative control. All monoclonal antibodies were purchased from Beckman Coulter Inc., USA. We calculated the number in each lymphocyte subset by multiplying lymphocyte counts by the percentage of positive cells in each category, as determined by flow cytometer.

2.2.4. Cytotoxicity assay

A standard 4-h Chromium-51 (^{51}Cr) release assay was used to determine NKCC (Pross et al., 1981). K562 was used as the target cells and labeled with [^{51}Cr]-sodium chromate (New England Nuclear, Boston, MA, USA) at 37 °C for an hour, washed and re-suspended at 2×10^5 ml^{-1} in Roswell Park Memorial Institute (RPMI)-1640 medium containing 10% Fetal Calf Serum, 2 mM glutamine, 100 U/ml penicillin and 100 U/ml streptomycin. Labeled target cells were incubated with effector cells at an effector/target [E/T] cell ratio of 20:1 in U-bottomed 96-well plates at 37 °C for 4 h. Radioactivity in the supernatant was determined with a gamma counter. The assay was performed in quadruplicate. The percentage of specific lysis as cytotoxicity was determined according to the following formula: percentage of specific lysis = [(mean experimental cpm release − mean spontaneous cpm release)/(mean maximal cpm release − mean spontaneous cpm release)].

2.2.5. Covariates

Covariates included age (in years), education (in years), smoking (number of cigarettes smoked per day), alcohol consumption (g ethanol per week), leisure-time physical activity, caffeine intake (cups of coffee or tea per day), subjective sleep sufficiency, depressive symptoms, interpersonal (intragroup) conflict at work, height, weight, occupational grade (managerial or non-managerial), company type (pharmaceutical or trading), typical work hours per day including overtime, one-way commute time (<30 min, 30–59 min, 60–89 min, 90–119 min, and 120+ min), self-reported illness, and regular medication usage.

Alcohol consumption was estimated by asking about the usual amount of alcoholic drinks consumed per day and the number of occasions in a week that alcoholic drinks were consumed. We converted gross liquor consumption into net ethanol intake. We assessed leisure-time physical activity by calculating the energy expenditure of habitual physical exercise. We asked frequency, type, and length of physical exercise per month and converted these data to metabolic equivalents (METs). Estimated METs were assigned to the physical activities according to their mean intensity levels. One MET corresponds to an energy expenditure of approximately 1 kcal/kg/h. Weekly leisure-time physical activity was calculated from the questionnaire. For example, one hour of moderate intensity physical activity such as bicycling, walking, and calisthenics is equivalent to 3.0 METs, 3.3 METs, and 3.5 METs, respectively, while one hour of vigorous intensity physical activities such as jogging, tennis, and swimming is equivalent to 7.0 METs, 7.0 METs, and 8.0 METs, respectively. If a respondent reported 3 days of bicycling for an hour and one day of tennis for 2 h, the total METs/week was calculated by the following formula: 3 days × 1 h × 3.0 METs + 1 day × 2 h × 7.0 METs = 23.0 METs/week. Validity and test-retest reliability were previously confirmed with this questionnaire (Suzuki et al., 1998). Subjective sleep sufficiency was determined by a single question (Nakata et al., 2000b): Do you think your daily sleep is sufficient? Response options were: (1) very insufficient, (2) somewhat insufficient, (3) fairly sufficient, or (4) very sufficient. Depressive symptoms were measured by a Japanese version of the Center for Epidemiologic Studies Depression scale (CES-D) (Shima et al., 1985). The 20-item depressive symptom scale measures the level of depressive symptoms experienced in the past week (Radloff, 1977). The internal consistency of the CES-D scale for the study sample was 0.84. Interpersonal (intragroup) conflict at work was assessed by an 8-item scale included in the GJSQ (Hurrell and McLaney, 1988; Nakata et al., 2007), which measures how much the worker feels the relationships within their working group are harmonious, cooperative, and supportive (possible range, 8–40). Items are rated on a five-point scale ranging from 1 (disagree strongly) to 5 (strongly agree). Examples of these items include 'There is harmony within my group' and 'In our group, we have lots of bickering over who should do what.' A higher score indicates higher conflict within the working group. The internal consistency of this scale was 0.83. Information on height (m) and weight (kg) were obtained to assess body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters. For self-reported illness, participants were asked if they had been diagnosed or treated for any of the following symptoms or disorders at the time of the study: hypertension, diabetes mellitus, menopause disorder, depression, asthma, allergies, cancer, cardiovascular disease, arrhythmia, angina pectoris, liver disease, cerebrovascular disease, hyperlipidemia, hyperthyroidism, gastric/duodenal ulcer, autonomic imbalance, or other diseases. If the subjects reported 'other diseases,' they were asked to specify the condition. As a result, participants with the following symptoms or disorders were identified; hypertension ($n = 18$), diabetes mellitus ($n = 6$), menopause ($n = 3$), depression ($n = 4$), asthma ($n = 2$), severe allergies ($n = 12$), liver diseases ($n = 2$), gastric/duodenal ulcer ($n = 4$), autoimmune disorders ($n = 2$), hyperlipidemia ($n = 13$), autonomic imbalance ($n = 2$), and the common cold ($n = 10$); no other symptoms/disorders (including cancer) were reported from the participants. In order to eliminate the potential effects of health status on immune parameters, we excluded employees reporting immune-related disorders (asthma, autoimmune disorders, severe allergies, or common cold) and those who were pregnant from the analyses ($n = 16$). The number of other symptoms/disorders was counted and included as a covariate (no = 0, yes = 1+). We also obtained data on the use of the following medications; aspirin ($n = 38$), β-blockers ($n = 2$), acetaminophen ($n = 30$), corticosteroids ($n = 1$), antidepressants ($n = 2$), and anxiolytic drugs ($n = 1$), and grouped participants into medication users/non-users. Those who were using immunomodulating drugs (β-blockers, corticosteroids, antidepressants, or anxiolytic drugs) were eliminated from the subsequent analyses ($n = 4$).

Table 1
Characteristics of study participants stratified by sex.[a]

Characteristics	Men (n = 190)		Women (n = 157)		p[b]
	Mean ± SD or n (%)	Range	Mean ± SD or n (%)	Range	
Effort-reward scores					
Effort[c]	11.1 ± 4.0	5–23	10.9 ± 4.2	5–25	.760
Reward[d]	47.9 ± 7.3	15–55	45.6 ± 7.9	16–55	.006
Effort-reward imbalance[c,e]	0.56 ± 0.34	0.20–2.89	0.58 ± 0.36	0.20–2.32	.614
Overcommitment[c]	13.6 ± 2.3	7–24	13.0 ± 3.1	6–22	.038
Immune markers					
NKCC (% cytotoxicity)	50.1 ± 16.9	5–77	37.5 ± 16.7	4–74	<.001
NK (CD3-CD56+) cells (cells/mm^3)	323 ± 209	57–1,438	239 ± 139	38–765	<.001
Total T (CD3+CD56-) cells (cells/mm^3)	1,167 ± 414	353–3,208	1,182 ± 304	471–2,315	.702
B (CD19+) cells (cells/mm^3)	242 ± 141	18–736	227 ± 114	25–911	.251
Sociodemographic and lifestyle factors					
Age (in years)[e]	40.2 ± 11.9	23–69	34.5 ± 9.6	22–58	<.001
Education (in years)	15.9 ± 1.3	12–21	14.6 ± 1.7	12–21	<.001
Smoking (number of cigarettes smoked/day)	9.5 ± 12.7	0–60	2.3 ± 5.9	0–40	<.001
Alcohol consumption (g thanol/week)	158.9 ± 141.6	0–805	45.8 ± 79.2	0–483	<.001
Leisure-time physical activity (METs/week)	5.9 ± 9.7	0–52.5	5.4 ± 9.2	0–52.5	.618
Subjective sleep sufficiency[f]	2.3 ± 0.8	1–4	2.3 ± 0.8	1–4	.452
Caffeine intake (cups of coffee or tea/day)	3.2 ± 1.0	1–5	3.5 ± 1.0	1–5	.008
BMI (kg/height (m)^2)[e]	23.5 ± 2.8	17.2–32.8	20.0 ± 2.1	15.4–28.9	<.001
Regular medication usage (yes)[g]	12 (6.3)		51 (32.5)		<.001
Chronic condition (yes)[h]	25 (13.2)		16 (10.2)		.394
Occupational factors					
Work hours/day	10.2 ± 1.7	7–15	8.9 ± 1.3	7–13	<.001
One-way commute time[i]	2.2 ± 0.8	1–5	2.4 ± 0.8	1–5	.043
Interpersonal (intragroup) conflict at work[c]	18.8 ± 4.9	8–33	19.8 ± 5.9	8–40	.071
Depressive symptoms (CES-D Scale score)[c,e]	12.3 ± 5.6	0–34	14.4 ± 7.0	0–43	.003
Company type					<.001
Pharmaceutical	57 (30.0)		101 (64.3)		
Trading	133 (70.0)		56 (35.7)		
Job position					<.001
Managerial	57 (30.0)		4 (2.5)		
Non-managerial	133 (70.0)		153 (97.5)		

[a] Participants who reported immune-related disorders at the time of study was excluded to eliminate the potential effects of health status on immune parameters (see text for detail).
[b] p-Value derived from χ^2-test for categorical variables and Student's t-test or Welch's test for continuous variables.
[c] Negatively oriented.
[d] Positively oriented.
[e] Although log-transformed values were used to approximate normal distribution in statistical analyses, mean values, SDs, and ranges are presented without log transformation to allow comparison with other studies.
[f] Subjective sleep sufficiency (1 = very insufficient, 2 = somewhat insufficient, 3 = fairly sufficient, 4 = very sufficient).
[g] Medications include, aspirin, acetaminophen, ibuprofen, and naproxen.
[h] Chronic condition includes hypertension, diabetes mellitus, menopausal disorder, depression, liver diseases, gastric/duodenal ulcer, hyperlipidemia, and autonomic imbalance.
[i] One-way commute time (1 = <30 min, 2 = 30–59 min, 3 = 60–89 min, 4 = 90–119 min, 5 = 120+ min).

2.3. Statistical analyses

Variables (age, BMI, and CES-D scale score) with skewed distributions were logarithmically transformed to achieve a more normal distribution in values. To examine sex differences of independent and dependent variables, the Student's t-test or Welch's test were used for continuous variables and the χ^2-test for categorical variables. Since there were significant differences in variables by sex, and given the fact that the affective response and immune reaction to stress differed by sex (Edwards et al., 2006; Shirom et al., 2006), subsequent regression analyses were carried out separately for men and women. Intercorrelations between job stress variables and immune markers were tested with the Pearson product–moment correlation coefficient.

Stepwise multiple linear regression analysis was performed to test the relationship between immune markers (dependent variables) and ERI-Q scores including reward subscales and covariates (independent variables). The first step included ERI-Q scores, age, and education as covariates (Model 1). In the second step, we added smoking, alcohol consumption, physical activity, caffeine intake, subjective sleep sufficiency, and BMI, in addition to Model 1 covariates (Model 2). Finally, we adjusted for all potential confounders included in Model 2 and use of medication, depressive symptoms, interpersonal (intragroup) conflict at work, chronic condition(s), and occupational factors (occupational grade, company type, work hours, and commuting time) (Model 3). The independent variables of medication usage, chronic condition(s), occupational grade, and company type were treated as categorical variables while the remaining variables were treated as continuous variables. The covariates were selected based on a recent review with regard to confounders in psychoneuroimmunology studies (Hansen et al., 2009) and possible associations with job stress and immunity (Bellingrath et al., 2010; Bosch et al., 2009; Clays et al., 2005; Nakata et al., 2000a, 2002; Shirom et al., 2008).

To provide further illustration of the association between ERI stress and immune markers, we conducted a two-way analysis of covariance (ANCOVA) with sex (men and women) and ERI stress (median split) as independent variables and age and education as covariates (Model 1), age, education, smoking, alcohol consumption, physical activity caffeine intake, subjective sleep sufficiency, and BMI as covariates (Model 2), and age, education, smoking, alcohol consumption, physical activity caffeine intake, subjective sleep sufficiency, BMI, chronic condition, depressive symptoms, intragroup conflict, work hours, and commuting time as covariates (Model 3). Significant differences in group means were further examined using Tukey's post hoc test when the main effects of ERI scales were significant.

The significance level for all statistical analyses was $p < 0.05$ (two-tailed test). We analyzed the data using the Statistical Package for the Social Sciences version 15.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Sample characteristics

Characteristics of the study participants and the differences between men and women are shown in Table 1. As shown in this table, most variables measured in this sample differed by sex. Reward score, overcommitment, NK cell counts, NKCC, age, years of education, cigarettes smoked per day, alcohol consumption, BMI, and work hours were significantly higher in men than in women. By contrast, caffeine intake, commuting time, and CES-D scale score

in women were significantly higher than in men. Managerial positions were predominant for men while regular medication usage was more frequent for women than for men.

3.2. Crude association between ERI scores and immune markers

Pearson correlations among ERI-Q scores and immune variables are shown in Table 2. The table is presented with men in the upper diagonal and women in the lower. In men, a significant inverse relationship of NK cells with effort, ERI, and overcommitment scores was found; the reward score was significantly and positively associated with NK cells and NKCC. The effort score and total T cells were marginally associated. In women, NKCC was marginally associated with ERI and reward scores.

3.3. Multivariate relationship between ERI-Q scores and immune markers

The results of the stepwise multiple linear regression analysis revealed that effort, reward, and ERI scores were consistently associated with NK cells in men (Table 3); the reward score was also consistently associated with NKCC. The overcommitment score was inversely associated with NK cells but the association was not significant when all covariates were adjusted for (Model 3). The reward score was significantly correlated with B cells only in the fully adjusted model (Model 3); this association was not significant in Models 1 and 2.

In women, none of the ERI-Q scores were significantly ($p < .05$) associated with immune markers; NKCC was only marginally associated with the reward scores and ERI scores while the reward score was weakly related with NK cells (Model 1); however, none of these reached significance ($p < .05$) after further adjustment.

3.4. Relationship between reward subscales and immune markers

Since we found a consistent association between reward scores and NK cell immunity, we explored in detail which subscale was more strongly associated with NK cells (Table 4). In men, two of the reward subscales 'respect and support' and 'job promotion and salary' were significantly associated with NK cells and NKCC while 'job security' was marginally related to NKCC (Models 1 and 2). In contrast, 'job security and career opportunities' was inversely correlated with B cells in Models 2 and 3, while 'respect and support' was inversely correlated with B cells in Model 3 only.

In women, none of the ERI-Q scores were significantly associated with immune markers but 'job promotion and salary' was marginally associated with NKCC (in Models 1 and 2) and NK cells (in Model 1 only).

3.5. Association of ERI scales and sex with immune markers (two-way ANCOVA)

The results of the two-way (ERI scales × sex) ANCOVA controlling for different covariates are shown in Table 5 and Fig. 1. The main effect of reward on NKCC ($F(1/333) = 9.894$, $p = .002$) as well as main effects of reward ($F(1/333) = 5.431$, $p = .020$) and ERI ($F(1/333) = 5.431$, $p = .020$) on NK cells were significant in the ANCOVA (Model 3). The interaction effects of reward × sex on NKCC and NK cells, and an interaction effect of ERI × sex on NK cells were not significant, thus simple-effects analyses were not pursued. Fig. 1 illustrates the effects of reward and sex on NKCC (A) and NK cells (B), as well as the effect of ERI and sex on NK cells (C).

Table 2
Pearson correlation matrix for effort, reward, ERI, overcommitment, and immune variables stratified by sex ($n = 190$ for men and $n = 157$ for women; upper diagonal is men and lower diagonal is women).

Variable	1		2		3		4		5		6		7		8	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
1. Effort[a]			−.545	<.001	.898	<.001	.434	<.001	−.093	.200	−.247	.001	−.126	.084	−.110	.129
2. Reward[b]	−.444	<.001			−.816	<.001	−.384	<.001	.191	.008	.199	.006	.055	.451	−.068	.354
3. Effort-reward imbalance (ERI)[a,c]	.887	<.001	−.764	<.001			.468	<.001	−.118	.105	−.218	.003	−.087	.235	−.015	.842
4. Overcommitment[a]	.474	<.001	−.366	<.001	.509	<.001			−.041	.575	−.148	.041	−.009	.902	.015	.838
5. NKCC (% cytotoxicity)	−.119	.137	.142	.075	−.155	.053	−.011	.894			.513	<.001	−.211	.003	−.134	.066
6. NK (CD3−CD56+) cells (cells/mm^3)	−.085	.289	.131	.101	−.113	.157	.024	.770	.467	<.001			−.047	.516	.073	.320
7. Total T (CD3+CD56−) cells (cells/mm^3)	.065	.422	−.090	.263	.118	.143	.034	.676	−.272	.001	−.145	.069			.265	<.001
8. B (CD19+) cells (cells/mm^3)	.031	.696	.051	.530	.018	.823	−.107	.180	−.011	.888	.028	.730	.304	<.001		

[a] Negatively oriented.
[b] Positively oriented.
[c] Log-transformed.

Table 3
Summary of stepwise multiple linear regression analysis for the association of effort, reward, effort-reward imbalance, and overcomittment with immune markers stratified by sex (n = 190 for men and n = 157 for women).

Immune marker (dependent variable)	Model 1[a]				Model 2[b]				Model 3[c]			
	Men		Women		Men		Women		Men		Women	
	β[d]	p	β[d]	p	β[d]	p	β[d]	p	β[d]	p	β[d]	p
Effort[e]												
NKCC (% cytotoxicity)	−.092	.213	−.111	.162	−.111	.161	−.106	.207	−.066	.465	−.068	.482
NK (CD3−CD56+) cells (cells/mm^3)	**−.240**	**.001**	−.088	.274	**−.265**	**.001**	−.090	.290	**−.230**	**.013**	−.043	.671
Total T (CD3+CD56−) cells (cells/mm^3)	−.119	.104	.063	.433	−.049	.504	.019	.818	−.015	.854	−.003	.973
B (CD19+) cells (cells/mm^3)	−.102	.163	.037	.628	−.059	.434	.040	.614	−.027	.759	.033	.734
Reward[f]												
NKCC (% cytotoxicity)	**.192**	**.008**	.135	.090	**.211**	**.005**	.129	.114	**.167**	**.049**	.102	.281
NK (CD3−CD56+) cells (cells/mm^3)	**.201**	**.006**	.134	.096	**.202**	**.008**	.133	.111	**.169**	**.047**	.122	.221
Total T (CD3+CD56−) cells (cells/mm^3)	.058	.794	−.088	.274	−.090	.899	−.053	.506	.012	.883	−.032	.740
B (CD19+) cells (cells/mm^3)	−.065	.373	.043	.576	−.122	.094	.049	.529	**−.181**	**.030**	.050	.595
Effort-reward imbalance[e]												
NKCC (% cytotoxicity)	−.166	.111	−.147	.064	−.141	.074	−.146	.082	−.090	.309	−.130	.205
NK (CD3−CD56+) cells (cells/mm^3)	**−.214**	**.003**	−.118	.144	**−.233**	**.003**	−.127	.134	**−.182**	**.047**	−.096	.374
Total T (CD3+CD56−) cells (cells/mm^3)	−.084	.251	.117	.148	−.009	.899	.071	.388	.018	.826	.065	.540
B (CD19+) cells (cells/mm^3)	−.011	.884	.026	.749	.040	.600	.036	.675	.099	.257	.019	.865
Overcommitment[e]												
NKCC (% cytotoxicity)	−.043	.555	.023	.766	−.056	.461	.016	.844	−.036	.645	.009	.926
NK (CD3−CD56+) cells (cells/mm^3)	**−.150**	**.037**	.020	.801	**−.152**	**.046**	.039	.655	−.104	.200	.073	.442
Total T (CD3+CD56−) cells (cells/mm^3)	−.004	.957	.032	.694	.078	.258	−.031	.710	.118	.105	−.035	.702
B (CD19+) cells (cells/mm^3)	.018	.804	−.101	.191	.062	.388	−.120	.138	.100	.197	−.132	.137

Bold values indicates $p < .05$.
[a] Adjusted for age and education.
[b] Adjusted for age, education, smoking, alcohol consumption, physical activity, caffeine intake, subjective sleep sufficiency, and BMI.
[c] Adjusted for age, education, smoking, alcohol consumption, physical activity, caffeine intake, subjective sleep sufficiency, BMI, medication usage, depressive symptoms, intragroup conflict score, chronic condition, work hours, occupational grade, company type, and commuting time.
[d] Standardized regression coefficients for each variable's unique contribution.
[e] Negatively oriented.
[f] Positively oriented.

4. Discussion

The current study investigated the association of ERI/overcommitment with cell-mediated immunity in a cross-section of 347 healthy white-collar Japanese daytime employees and the following findings were obtained. In men, psychologically adverse work environment as indicated by high effort, low reward, and a high ERI ratio was negatively associated with NK cell measures; among three reward components, 'low respect and support' and 'diminished job promotion and salary' were major contributors decreasing the NK cell immune response. Similarly, reward (total) and its 2 subscales, 'low respect and support' and 'diminished job security and career opportunities,' were related to an increase of B cells when the covariates were fully controlled for. Overcommitment was only weakly related to a decrease of NK cells in men. The results for women were less clear as compared to those

Table 4
Summary of stepwise multiple linear regression analysis for the association of reward subscales with immune markers stratified by sex (n = 190 for men and n = 157 for women).

Immune marker (dependent variable)	Model 1[a]				Model 2[b]				Model 3[c]			
	Men		Women		Men		Women		Men		Women	
	β[d]	p	β[d]	p	β[d]	p	β[d]	p	β[d]	p	β[d]	p
Respect and support (esteem)[e]												
NKCC (% cytotoxicity)	**.204**	**.005**	.114	.152	**.221**	**.003**	.111	.173	**.187**	**.025**	.100	.289
NK (CD3−CD56+) cells (cells/mm^3)	**.202**	**.005**	.111	.169	**.200**	**.009**	.118	.150	**.172**	**.047**	.099	.318
Total T (CD3+CD56−) cells (cells/mm^3)	.050	.498	−.059	.463	−.026	.706	−.035	.659	−.014	.858	−.011	.911
B (CD19+) cells (cells/mm^3)	−.057	.435	.036	.636	−.119	.099	.039	.618	**−.174**	**.035**	.040	.670
Job promotion and salary[e]												
NKCC (% cytotoxicity)	**.152**	**.037**	.144	.071	**.175**	**.022**	.137	.095	**.184**	**.038**	.084	.368
NK (CD3−CD56+) cells (cells/mm^3)	**.215**	**.003**	.135	.094	**.228**	**.003**	.133	.111	**.189**	**.029**	.102	.299
Total T (CD3+CD56−) cells (cells/mm^3)	.093	.203	−.087	.280	.045	.522	−.049	.542	.070	.368	−.035	.713
B (CD19+) cells (cells/mm^3)	−.032	.662	.054	.486	−.072	.325	.062	.427	−.111	.181	.060	.518
Job security and career opportunities[e]												
NKCC (% cytotoxicity)	**.145**	**.048**	.089	.265	.138	.065	.081	.321	.085	.288	.064	.449
NK (CD3−CD56+) cells (cells/mm^3)	.067	.360	.114	.156	.049	.517	.120	.146	.012	.888	.116	.193
Total T (CD3+CD56−) cells (cells/mm^3)	−.020	.784	−.116	.151	−.064	.352	−.079	.323	−.043	.561	−.048	.582
B (CD19+) cells (cells/mm^3)	−.120	.100	.011	.888	**−.159**	**.026**	.017	.827	**−.204**	**.009**	.015	.862

Bold values indicates $p < .05$.
[a] Adjusted for age and education.
[b] Adjusted for age, education, smoking, alcohol consumption, physical activity, caffeine intake, subjective sleep sufficiency, and BMI.
[c] Adjusted for age, education, smoking, alcohol consumption, physical activity, caffeine intake, subjective sleep sufficiency, BMI, medication usage, depressive symptoms, intragroup conflict score, chronic condition, work hours, occupational grade, company type, and commuting time.
[d] Standardized regression coefficients for each variable's unique contribution.
[e] Positively oriented.

Table 5
Two-way analysis of covariance of immune markers by ERI components × sex ($n = 347$).

Immune marker (dependent variable)	NKCC $F(d.f.)$, p	NK cells $F(d.f.)$, p	T cells $F(d.f.)$, p	B cells $F(d.f.)$, p
Model 1[a]				
Effort (main effect)	$F(1/341) = 1.308$, $p = .254$	$F(1/341) = 3.507$, $p = .062$	$F(1/341) = 1.345$, $p = .247$	$F(1/341) = 0.199$, $p = .655$
Sex (main effect)	**$F(1/341) = 24.84$, $p < .001$**	**$F(1/341) = 10.37$, $p = .001$**	$F(1/341) = 0.014$, $p = .907$	$F(1/341) = 0.238$, $p = .626$
Effort × Sex (interaction)	$F(1/341) = 0.223$, $p = .637$	$F(1/341) = 0.498$, $p = .481$	$F(1/341) = 3.119$, $p = .078$	$F(1/341) = 1.045$, $p = .307$
Model 2[b]				
Effort (main effect)	$F(1/335) = 1.087$, $p = .298$	$F(1/335) = 3.013$, $p = .084$	$F(1/335) = 1.136$, $p = .287$	$F(1/335) = 0.237$, $p = .627$
Sex (main effect)	**$F(1/335) = 11.87$, $p = .001$**	$F(1/335) = 3.039$, $p = .082$	$F(1/335) = 3.218$, $p = .074$	**$F(1/335) = 5.077$, $p = .025$**
Effort × Sex (interaction)	$F(1/335) = 0.244$, $p = .622$	$F(1/335) = 0.442$, $p = .506$	$F(1/335) = 2.961$, $p = .086$	$F(1/335) = 1.077$, $p = .300$
Model 3[c]				
Effort (main effect)	$F(1/333) = 1.566$, $p = .212$	$F(1/333) = 1.506$, $p = .221$	$F(1/333) = 0.010$, $p = .922$	$F(1/333) = 0.425$, $p = .515$
Sex (main effect)	**$F(1/333) = 16.42$, $p < .001$**	**$F(1/333) = 6.110$, $p = .014$**	**$F(1/333) = 6.682$, $p = .010$**	**$F(1/333) = 6.309$, $p = .012$**
Effort × Sex (interaction)	$F(1/333) = 0.077$, $p = .782$	$F(1/333) = 0.565$, $p = .453$	$F(1/333) = 2.367$, $p = .125$	$F(1/333) = 0.778$, $p = .378$
Model 1[a]				
Reward (main effect)	**$F(1/341) = 9.481$, $p = .002$**	**$F(1/341) = 8.222$, $p = .004$**	$F(1/341) = 1.500$, $p = .221$	$F(1/341) = 0.011$, $p = .916$
Sex (main effect)	**$F(1/341) = 22.32$, $p < .001$**	**$F(1/341) = 8.617$, $p = .004$**	$F(1/341) = 0.020$, $p = .887$	$F(1/341) = 0.172$, $p = .679$
Reward × Sex (interaction)	$F(1/341) = 0.025$, $p = .874$	$F(1/341) = 2.068$, $p = .151$	$F(1/341) = 0.538$, $p = .464$	$F(1/341) = 0.104$, $p = .748$
Model 2[b]				
Reward (main effect)	**$F(1/335) = 8.950$, $p = .003$**	**$F(1/335) = 8.007$, $p = .005$**	$F(1/335) = 2.273$, $p = .133$	$F(1/335) = 0.013$, $p = .909$
Sex (main effect)	**$F(1/335) = 9.929$, $p = .002$**	$F(1/335) = 2.095$, $p = .149$	**$F(1/335) = 4.160$, $p = .042$**	**$F(1/335) = 5.407$, $p = .021$**
Reward × Sex (interaction)	$F(1/335) = 0.084$, $p = .773$	$F(1/335) = 1.767$, $p = .185$	$F(1/335) = 0.756$, $p = .385$	$F(1/335) = 0.070$, $p = .791$
Model 3[c]				
Reward (main effect)	**$F(1/333) = 9.894$, $p = .002$**	**$F(1/333) = 5.431$, $p = .020$**	$F(1/333) = 0.505$, $p = .478$	$F(1/333) = 0.012$, $p = .913$
Sex (main effect)	**$F(1/333) = 14.20$, $p < .001$**	**$F(1/333) = 5.376$, $p = .021$**	**$F(1/333) = 7.236$, $p = .008$**	**$F(1/333) = 6.716$, $p = .010$**
Reward × Sex (interaction)	$F(1/333) = 0.007$, $p = .934$	$F(1/333) = 2.370$, $p = .125$	$F(1/333) = 0.559$, $p = .455$	$F(1/333) = 0.101$, $p = .751$
Model 1[a]				
ERI (main effect)	$F(1/341) = 2.286$, $p = .131$	**$F(1/341) = 9.637$, $p = .002$**	$F(1/341) = 0.368$, $p = .544$	$F(1/341) = 0.493$, $p = .483$
Sex (main effect)	**$F(1/341) = 25.17$, $p < .001$**	**$F(1/341) = 9.402$, $p = .002$**	$F(1/341) = 0.029$, $p = .865$	$F(1/341) = 0.139$, $p = .710$
ERI × Sex (interaction)	$F(1/341) = 0.401$, $p = .527$	$F(1/341) = 0.873$, $p = .351$	$F(1/341) = 3.325$, $p = .069$	$F(1/341) = 1.533$, $p = .216$
Model 2[b]				
ERI (main effect)	$F(1/335) = 1.916$, $p = .167$	**$F(1/335) = 9.404$, $p = .002$**	$F(1/335) = 0.385$, $p = .535$	$F(1/335) = 0.310$, $p = .578$
Sex (main effect)	**$F(1/335) = 11.93$, $p = .001$**	$F(1/335) = 2.382$, $p = .124$	**$F(1/335) = 4.203$, $p = .041$**	**$F(1/335) = 5.567$, $p = .019$**
ERI × Sex (interaction)	$F(1/335) = 0.680$, $p = .410$	$F(1/335) = 0.718$, $p = .397$	$F(1/335) = 3.568$, $p = .060$	$F(1/335) = 2.037$, $p = .154$
Model 3[c]				
ERI (main effect)	$F(1/333) = 2.792$, $p = .096$	**$F(1/333) = 7.232$, $p = .008$**	$F(1/333) = 0.260$, $p = .611$	$F(1/333) = 0.845$, $p = .359$
Sex (main effect)	**$F(1/333) = 16.01$, $p < .001$**	**$F(1/333) = 4.905$, $p = .027$**	**$F(1/333) = 7.270$, $p = .007$**	**$F(1/333) = 6.573$, $p = .011$**
ERI × Sex (interaction)	$F(1/333) = 0.296$, $p = .587$	$F(1/333) = 1.081$, $p = .299$	$F(1/333) = 3.345$, $p = .068$	$F(1/333) = 1.644$, $p = .201$
Model 1[a]				
Overcommitment (main effect)	$F(1/341) = 0.329$, $p = .567$	$F(1/341) = 1.341$, $p = .248$	$F(1/341) = 0.169$, $p = .681$	$F(1/341) = 0.825$, $p = .364$
Sex (main effect)	**$F(1/341) = 24.26$, $p < .001$**	**$F(1/341) = 9.221$, $p = .003$**	$F(1/341) = 0.028$, $p = .867$	$F(1/341) = 0.391$, $p = .532$
Overcommitment × Sex (interaction)	$F(1/341) = 0.125$, $p = .724$	$F(1/341) = 1.998$, $p = .158$	$F(1/341) = 1.773$, $p = .184$	$F(1/341) = 0.341$, $p = .560$
Model 2[b]				
Overcommitment (main effect)	$F(1/335) = 0.576$, $p = .448$	$F(1/335) = 1.631$, $p = .202$	$F(1/335) = 0.175$, $p = .676$	$F(1/335) = 0.988$, $p = .321$
Sex (main effect)	**$F(1/335) = 11.93$, $p = .001$**	$F(1/335) = 2.560$, $p = .111$	**$F(1/335) = 3.939$, $p = .048$**	**$F(1/335) = 4.498$, $p = .035$**
Overcommitment × Sex (interaction)	$F(1/335) = 0.096$, $p = .757$	$F(1/335) = 1.812$, $p = .179$	$F(1/335) = 0.735$, $p = .392$	$F(1/335) = 0.686$, $p = .408$
Model 3[c]				
Overcommitment (main effect)	$F(1/333) = 0.768$, $p = .382$	$F(1/333) = 0.701$, $p = .403$	$F(1/333) = 0.163$, $p = .687$	$F(1/333) = 0.246$, $p = .621$
Sex (main effect)	**$F(1/333) = 17.54$, $p < .001$**	**$F(1/333) = 6.155$, $p = .014$**	**$F(1/333) = 7.563$, $p = .006$**	**$F(1/333) = 6.248$, $p = .013$**
Overcommitment × Sex (interaction)	$F(1/333) = 0.066$, $p = .797$	$F(1/333) = 1.694$, $p = .194$	$F(1/333) = 0.589$, $p = .443$	$F(1/333) = 0.486$, $p = .486$

Bold values indicates $p < .05$.

[a] Model 1: adjusted for age and education.

[b] Model 2: Model 1 + smoking, alcohol consumption, physical activity, caffeine intake, subjective sleep sufficiency, and BMI.

[c] Model 3: Model 2 + depressive symptoms, work hours, chronic condition, and medication usage.

for men in the regression analyses, suggesting that the ERI model may not explain stress-related changes in immunity in Japanese working women. The results of a two-way ANCOVA showed that reward had a significant main effect on NKCC and NK cells whereas ERI had a significant main effect on NK cells, although this was only true for men. While more research is needed to elucidate causal pathways and reasons for sex differences, the results of our study provide additional information for a possible psychoneureoimmune link between ERI and stress-related disorders as evidenced by inhibited innate (NK) immune response in men.

In this study, we used stepwise regression analyses and ANCOVA to identify the influence of covariates on the association of ERI scales and immune markers. The relationship between the reward and NK cells markers remained statistically significant even after controlling for a number of important confounders in a step-by-step fashion. In contrast, the relationship between B cells and the total reward and 'job promotion and salary' subscale became apparent after controlling for a full set of confounders. In many psychoneuroimmunology studies in occupational health, some of the important covariates such as sleep, work hours, occupational grade, commuting time, depressive symptoms, chronic condition(s), and use of medications are not always taken into account. Therefore, the relationship between ERI scales and immune markers may be underestimated. The finding that rewards related to B cells in this study is unique in terms of the work stress–immune relationship and may help further the understanding of the role of B cells in response to job stress.

To our knowledge, there are two studies which explored the direct link between the ERI stress model and immune parameters. Our finding is consistent with one study which reported that a high level of ERI is associated with lower NK cell (CD16+/CD56+) counts after exposure to an acute experimental task (Bellingrath et al., 2010). We also confirmed consistent relationships between reward and ERI scores and two of the reward subscales with NKCC. These findings confirm that not only counts of NK cells but also the cytolytic capacity of NK cells is adversely associated with high

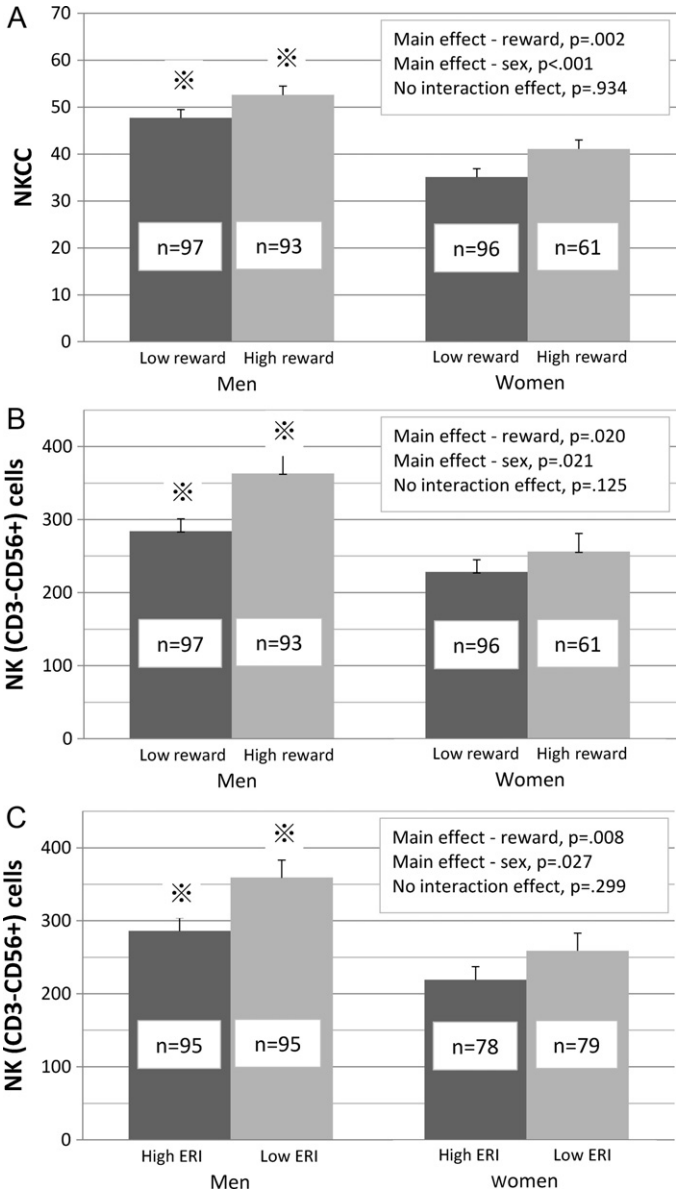

Fig. 1. The main effects of reward/ERI and sex on NK cell markers. There were significant main effects of reward and sex on NKCC (A) and NK cells (B), as well as significant main effects of ERI and sex on NK cells (C). Values are displayed as mean ± standard error of the mean. * Indicates a significant difference ($p < .05$).

ERI stress. Our study also found a significant inverse relationship between two reward subscales and B cell counts suggesting an activation of humoral immune function.

The present finding is consistent with a series of studies reporting suppression of NKCC or NK cells from exposure to negative work environment stressors such as increased quantitative workload (Kawaguchi et al., 2007; Miyazaki et al., 2005; Morikawa et al., 2005; Nakata et al., 2000a; Okamoto et al., 2008), high job strain (Nakata et al., 2000a), elevated job insecurity (Boscolo et al., 2008), increased overall job stress (Di Donato et al., 2006), decreased decision latitude (Boscolo et al., 2008), and reduced job satisfaction (Nakata et al., 2010) as well as unemployment (Cohen et al., 2007). Given the fact that NK cells bear a higher density of β-adrenergic receptors than other lymphocytes such as T cells (Khan et al., 1986; Landmann, 1992; von Kanel et al., 2006), exposure to chronic job stress may induce excessive activation of the sympathetic nervous system leading to chronically high circulating catecholamine levels which desensitizes β-adrenergic receptor function on NK cells through decreases in receptor density, binding affinity, and receptor sensitivity (Dimsdale et al., 1994; Mausbach et al., 2008; Miller et al., 1999) resulting in a suppression of NK cell immunity.

The association between the ERI model and NK cells may relate to inflammatory disorders such as cardiovascular disease (CVD) because NK cells appear to play a major role in killing virally infected cells (Whiteside and Herberman, 1994), and chronic infection has been suggested as a possible mediating mechanism (De Backer et al., 2002; Gattone et al., 2001; Pasceri et al., 1998). This assumption may be partly supported by the fact that employees with high ERI experience frequent sick leave (Fahlen et al., 2009; Godin and Kittel, 2004; Hanebuth et al., 2006; Head et al., 2007) because infection-related symptoms (respiratory disorders and gastroenteritis) are reported to explain 50–60% of all spells of sick leave (Feeney et al., 1998). If high ERI status persists for long term, it could be speculated that employees with such characteristics may become more susceptibility to ubiquitous infectious agents such as Cytomegalovirus, Helicobacter pylori, and Chlamydia pneumonia leading to CVD. Although the chronic infection–CVD relationship has yet to reach universal agreement (Danesh et al., 2000), our result still raise the possibility that increased ERI stress may enhance susceptibility to infection by attenuating NK cell immunity, which may consequently contribute to elevated inflammatory activity and hence to the development of CVD. However, clearer evidence is needed to confirm this speculation.

No significant association between ERI scales and total T (CD3+CD56−) cells was found in this study. Bosch et al. (2009) found decreases of CD4+/CD8+ ratio and cytotoxic T cells but did not report a decrease of total T cells. The association of the ERI model and T cells may be reflected in components of T cells, i.e., CD4+ and CD8+ T cells or CD4+/CD8+ ratio (Amati et al., 2010; Bosch et al., 2009; Kawakami et al., 1997; Meijman et al., 1995; Nakata et al., 2000a; Okamoto et al., 2008) rather than merely total numbers of T cells.

In this study, we analyzed men and women separately to see if there are any sex differences in the ERI-immune relationship and some differences were identified. Although the sample sizes of men and women were similar, there was a significant association between ERI-Q scores and NK immune markers for men but there were, at most, only marginally significant associations for women. The inconsistent findings between men and women may be explained, at least partly, by the following. First, two studies relating the ERI model with salivary cortisol levels reported a much weaker relationship between the two in women than in men suggesting that the ERI-Q may be a more suitable measure to detect physiological changes in men than in women (Eller et al., 2006; Steptoe et al., 2004). Second, stresses outside the job or other job stressors might be more important factors modulating the immune system in women, which may have contributed to confound the direct association between ERI and immunity. As the present results may be a sample-specific finding, more comprehensive evidence is needed to determine the sex difference of the ERI–immune relationship than has been gathered.

Our findings should be interpreted in the context of the following limitations. To begin with, the study was cross-sectional in nature; thus no causal interpretations can be made. Furthermore, as a nature of the cross-sectional design, it is conceivable that immunologically weaker individuals (in this case reduced NKCC and NK cell counts) may indicate higher levels of job stress compared to those maintaining a higher NK cell immune response, because they may be physically/mentally vulnerable. Additional studies are required to determine the causal inference of the present findings. Second, participants were employees from specific occupations and do not represent the entire Japanese workforce or workers of other racial/ethnic groups. Third, we failed to control for menstrual phase or oral contraceptive use in women,

which might have affected immunologic outcomes. Fourth, data on illness medical records were collected through self-report rather than medical diagnosis, which may introduce recall/reporting bias. Fifth, we did not measure cellular and inflammatory immune measures simultaneously, which limits the interpretation of our findings. And finally, although we adjusted for a variety of confounders, we could not exclude the possibility that unadjusted factors, i.e., personality traits, genetic components, other work-related factors, and concurrent life stressors outside work such as marital discord, work-family conflict, interpersonal and financial difficulties, as well as unknown third factor(s) could affect both the dependent and independent variables.

Despite these limitations, our study has several strengths. The study used a well-established measure of ERI-Q and controlled for a broad array of potential confounders in a stepwise fashion with a large and relatively homogenous sample, i.e., white-collar healthy daytime Japanese employees working full-time. Thus, the perception of job stress within this group could be conceptually equivalent and the results may be at least generalized to this population. The analyses were carried out separately for men and women (with approximately equal sample sizes), which contributed to the investigation of unique sex differences. In addition, the study provided evidence linking ERI with immune markers in an Asian (Japanese) population, which was supportive of the findings obtained in western countries.

In conclusion, this study examined the cross-sectional association of effort-reward imbalance with cellular immunity in a sample of 347 healthy white-collar daytime employees. The results suggested that effort-reward imbalance components were associated with NK cell immunity in men, while the association was much weaker in women. Although the precise mechanisms and pathways underlying the observed associations have yet to be determined, the findings of the present study provide some support for the psychoneuroimmunologic plausibility of the relationship between effort-reward imbalance and health. Future studies should make an effort to investigate mechanistic causal associations between ERI, NK cells, cytokines, humoral and inflammatory markers, and long-term health.

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References

Amati, M., Tomasetti, M., Ciuccarelli, M., Mariotti, L., Tarquini, L.M., Bracci, M., Baldassari, M., Balducci, C., Alleva, R., Borghi, B., Mocchegiani, E., Copertaro, A., Santarelli, L., 2010. Relationship of job satisfaction, psychological distress and stress-related biological parameters among healthy nurses: a longitudinal study. Journal of Occupational Health 52, 31–38.

Bellingrath, S., Rohleder, N., Kudielka, B.M., 2010. Healthy working school teachers with high effort-reward-imbalance and overcommitment show increased pro-inflammatory immune activity and a dampened innate immune defence. Brain, Behavior, and Immunity 24, 1332–1339.

Bosch, J.A., Fischer, J.E., Fischer, J.C., 2009. Psychologically adverse work conditions are associated with CD8+ T cell differentiation indicative of immunesenescence. Brain, Behavior, and Immunity 23, 527–534.

Boscolo, P., Di Donato, A., Di Giampaolo, L., Forcella, L., Reale, M., Dadorante, V., Alparone, F., Pagliaro, S., Kouri, M., Magrini, A., Fattorini, E., 2009. Blood natural killer activity is reduced in men with occupational stress and job insecurity working in a university. International Archives of Occupational and Environmental Health 82, 787–794.

Chandola, T., Britton, A., Brunner, E., Hemingway, H., Malik, M., Kumari, M., Badrick, E., Kivimaki, M., Marmot, M., 2008. Work stress and coronary heart disease: what are the mechanisms? European Heart Journal 29, 640–648.

Chandola, T., Heraclides, A., Kumari, M., 2010. Psychophysiological biomarkers of workplace stressors. Neuroscience and Biobehavioral Reviews 35, 51–57.

Chida, Y., Steptoe, A., 2009. Cortisol awakening response and psychosocial factors: a systematic review and meta-analysis. Biological Psychology 80, 265–278.

Clays, E., De Bacquer, D., Delanghe, J., Kittel, F., Van Renterghem, L., De Backer, G., 2005. Associations between dimensions of job stress and biomarkers of inflammation and infection. Journal of Occupational and Environmental Medicine 47, 878–883.

Cohen, F., Kemeny, M.E., Zegans, L.S., Johnson, P., Kearney, K.A., Stites, D.P., 2007. Immune function declines with unemployment and recovers after stressor termination. Psychosomatic Medicine 69, 225–234.

Danesh, J., Whincup, P., Walker, M., Lennon, L., Thomson, A., Appleby, P., Wong, Y., Bernardes-Silva, M., Ward, M., 2000. Chlamydia pneumoniae IgG titres and coronary heart disease: prospective study and meta-analysis. British Medical Journal 321, 208–213.

De Backer, J., Mak, R., De Bacquer, D., Van Renterghem, L., Verbraekel, E., Kornitzer, M., De Backer, G., 2002. Parameters of inflammation and infection in a community based case-control study of coronary heart disease. Atherosclerosis 160, 457–463.

Di Donato, A., Di Giampaolo, L., Reale, M., Dadorante, V., Alparone, F., Stocchi, M., Fattorini, E., Di Gioacchino, M., Magrini, A., Boscolo, P., 2006. Effect of occupational stress and anxiety on natural killer lymphocyte activity of men and women employed in a university. International Journal of Immunopathology and Pharmacology 19, 79–84.

Dimsdale, J.E., Mills, P., Patterson, T., Ziegler, M., Dillon, E., 1994. Effects of chronic stress on beta-adrenergic receptors in the homeless. Psychosomatic Medicine 56, 290–295.

Edwards, K.M., Burns, V.E., Ring, C., Carroll, D., 2006. Sex differences in the interleukin-6 response to acute psychological stress. Biological Psychology 71, 236–239.

Eller, N.H., Netterstrom, B., Hansen, A.M., 2006. Psychosocial factors at home and at work and levels of salivary cortisol. Biological Psychology 73, 280–287.

Fahlen, G., Goine, H., Edlund, C., Arrelov, B., Knutsson, A., Peter, R., 2009. Effort-reward imbalance, locked in at work, and long-term sick leave. International Archives of Occupational and Environmental Health 82, 191–197.

Feeney, A., North, F., Head, J., Canner, R., Marmot, M., 1998. Socioeconomic and sex differentials in reason for sickness absence from the Whitehall II Study. Occupational and Environmental Medicine 55, 91–98.

Gattone, M., Iacoviello, L., Colombo, M., Castelnuovo, A.D., Soffiantino, F., Gramoni, A., Picco, D., Benedetta, M., Giannuzzi, P., 2001. Chlamydia pneumoniae and cytomegalovirus seropositivity, inflammatory markers, and the risk of myocardial infarction at a young age. American Heart Journal 142, 633–640.

Godin, I., Kittel, F., 2004. Differential economic stability and psychosocial stress at work: associations with psychosomatic complaints and absenteeism. Social Science and Medicine 58, 1543–1553.

Hamer, M., Williams, E., Vuonovirta, R., Giacobazzi, P., Gibson, E.L., Steptoe, A., 2006. The effects of effort-reward imbalance on inflammatory and cardiovascular responses to mental stress. Psychosomatic Medicine 68, 408–413.

Hanebuth, D., Meinel, M., Fischer, J.E., 2006. Health-related quality of life, psychosocial work conditions, and absenteeism in an industrial sample of blue- and white-collar employees: a comparison of potential predictors. Journal of Occupational and Environmental Medicine 48, 28–37.

Hansen, A.M., Larsen, A.D., Rugulies, R., Garde, A.H., Knudsen, L.E., 2009. A review of the effect of the psychosocial working environment on physiological changes in blood and urine. Basic Clin Pharmacol Toxicol 105, 73–83.

Head, J., Kivimaki, M., Siegrist, J., Ferrie, J.E., Vahtera, J., Shipley, M.J., Marmot, M.G., 2007. Effort-reward imbalance and relational injustice at work predict sickness absence: the Whitehall II study. Journal of Psychosomatic Research 63, 433–440.

Hemingway, H., Shipley, M., Mullen, M.J., Kumari, M., Brunner, E., Taylor, M., Donald, A.E., Deanfield, J.E., Marmot, M., 2003. Social and psychosocial influences on inflammatory markers and vascular function in civil servants (the Whitehall II study). American Journal of Cardiology 92, 984–987.

Herbert, T.B., Cohen, S., 1993. Depression and immunity: a meta-analytic review. Psychological Bulletin 113, 472–486.

Hintsanen, M., Elovainio, M., Puttonen, S., Kivimaki, M., Koskinen, T., Raitakari, O.T., Keltikangas-Jarvinen, L., 2007. Effort-reward imbalance, heart rate, and heart rate variability: the Cardiovascular Risk in Young Finns Study. International Journal of Behavioral Medicine 14, 202–212.

Hurrell Jr., J.J., McLaney, M.A., 1988. Exposure to job stress—a new psychometric instrument. Scandinavian Journal of Work, Environment and Health 14 (Suppl. 1), 27–28.

Imai, K., Matsuyama, S., Miyake, S., Suga, K., Nakachi, K., 2000. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. Lancet 356, 1795–1799.

Irie, M., Tsutsumi, A., Shioji, I., Kobayashi, F., 2004. Effort-reward imbalance and physical health among Japanese workers in a recently downsized corporation. International Archives of Occupational and Environmental Health 77, 409–417.

Karasek, R., 1979. Job demand, job decision latitude, and mental strain: implications for job redesign. Administrative Science Quarterly 24, 285–308.

Kawaguchi, Y., Toyomasu, K., Yoshida, N., Baba, K., Uemoto, M., Minota, S., 2007. Measuring job stress among hospital nurses: an attempt to identify biological markers. Fukuoka Acta Medica 98, 48–55.

Kawakami, N., Tanigawa, T., Araki, S., Nakata, A., Sakurai, S., Yokoyama, K., Morita, Y., 1997. Effects of job strain on helper-inducer (CD4+CD29+) and suppressor-inducer (CD4+CD45RA+) T cells in Japanese blue-collar workers. Psychotherapy and Psychosomatics 66, 192–198.

Khan, M.M., Sansoni, P., Silverman, E.D., Engleman, E.G., Melmon, K.L., 1986. Beta-adrenergic receptors on human suppressor, helper, and cytolytic lymphocytes. Biochemical Pharmacology 35, 1137–1142.

Kjeldsen, S.E., Knudsen, K., Ekrem, G., Fure, T.O., Movinckel, P., Erikssen, J.E., 2006. Is there an association between severe job strain, transient rise in blood pressure and increased mortality? Blood Pressure 15, 93–100.

Kusaka, Y., Kondou, H., Morimoto, K., 1992. Healthy lifestyles are associated with higher natural killer cell activity. Preventive Medicine 21, 602–615.
Landmann, R., 1992. Beta-adrenergic receptors in human leukocyte subpopulations. European Journal of Clinical Investigation 22 (Suppl. 1), 30–36.
Lee, K.H., Yoon, K., Ha, M., Park, J., Cho, S.H., Kang, D., 2010. Heart rate variability and urinary catecholamines from job stress in korean male manufacturing workers according to work seniority. Industrial Health 48, 331–338.
Levy, S.M., Herberman, R.B., Simons, A., Whiteside, T., Lee, J., McDonald, R., Beadle, M., 1989. Persistently low natural killer cell activity in normal adults: immunological, hormonal and mood correlates. Natural Immunity and Cell Growth Regulation 8, 173–186.
Mausbach, B.T., Aschbacher, K., Mills, P.J., Roepke, S.K., von Kanel, R., Patterson, T.L., Dimsdale, J.E., Ziegler, M.G., Ancoli-Israel, S., Grant, I., 2008. A 5-year longitudinal study of the relationships between stress, coping, and immune cell beta(2)-adrenergic receptor sensitivity. Psychiatry Research 160, 247–255.
Meijman, T.F., van Dormolen, M., Herber, R.F.M., Rogen, H., Kuiper, S., 1995. Job strain, neuroendocrine activation, and immune status. In: Sauter, S.L., Murphy, L.R. (Eds.), Organizational Risk Factors for Job Stress. American Psychological Association, Washington, DC, pp. 113–126.
Miller, G.E., Cohen, S., Rabin, B.S., Skoner, D.P., Doyle, W.J., 1999. Personality and tonic cardiovascular, neuroendocrine, and immune parameters. Brain, Behavior, and Immunity 13, 109–123.
Miyazaki, T., Ishikawa, T., Nakata, A., Sakurai, T., Miki, A., Fujita, O., Kobayashi, F., Haratani, T., Iimori, H., Sakami, S., Fujioka, Y., Kawamura, N., 2005. Association between perceived social support and Th1 dominance. Biological Psychology 70, 30–37.
Morikawa, Y., Kitaoka-Higashiguchi, K., Tanimoto, C., Hayashi, M., Oketani, R., Miura, K., Nishijo, M., Nakagawa, H., 2005. A cross-sectional study on the relationship of job stress with natural killer cell activity and natural killer cell subsets among healthy nurses. Journal of Occupational Health 47, 378–383.
Nakata, A., Araki, S., Tanigawa, T., Miki, A., Sakurai, S., Kawakami, N., Yokoyama, K., Yokoyama, M., 2000a. Decrease of suppressor-inducer (CD4+ CD45RA) T lymphocytes and increase of serum immunoglobulin G due to perceived job stress in Japanese nuclear electric power plant workers. Journal of Occupational and Environmental Medicine 42, 143–150.
Nakata, A., Haratani, T., Kawakami, N., Miki, A., Kurabayashi, L., Shimizu, H., 2000b. Sleep problems in white-collar male workers in an electric equipment manufacturing company in Japan. Industrial Health 38, 62–68.
Nakata, A., Takahashi, M., Ikeda, T., Haratani, T., Hojou, M., Araki, S., 2007. Perceived job stress and sleep-related breathing disturbance in Japanese male workers. Social Science and Medicine 64, 2520–2532.
Nakata, A., Takahashi, M., Ikeda, T., Hojou, M., Araki, S., 2008. Perceived psychosocial job stress and sleep bruxism among male and female workers. Community Dentistry and Oral Epidemiology 36, 201–209.
Nakata, A., Takahashi, M., Irie, M., Swanson, N.G., 2010. Job satisfaction is associated with elevated natural killer cell immunity among healthy white-collar employees. Brain, Behavior, and Immunity 24, 1268–1275.
Nakata, A., Tanigawa, T., Fujioka, Y., Kitamura, F., Iso, H., Shimamoto, T., 2002. Association of low job control with a decrease in memory (CD4+ CD45RO+) T lymphocytes in Japanese middle-aged male workers in an electric power plant. Industrial Health 40, 142–148.
Okamoto, H., Tsunoda, T., Teruya, K., Takeda, N., Uemura, T., Matsui, T., Fukazawa, S., Ichikawa, K., Takemae, R., Tsuchida, K., Takashima, Y., 2008. An occupational health study of emergency physicians in Japan: health assessment by immune variables (CD4, CD8, CD56, and NK cell activity) at the beginning of work. Journal of Occupational Health 50, 136–146.
Pasceri, V., Cammarota, G., Patti, G., Cuoco, L., Gasbarrini, A., Grillo, R.L., Fedeli, G., Gasbarrini, G., Maseri, A., 1998. Association of virulent Helicobacter pylori strains with ischemic heart disease. Circulation 97, 1675–1679.
Pross, H.F., Baines, M.G., Rubin, P., Shragge, P., Patterson, M.S., 1981. Spontaneous human lymphocyte-mediated cytotoxicity against tumor target cells. IX. The quantitation of natural killer cell activity. Journal of Clinical Immunology 1, 51–63.
Radloff, L., 1977. The CES-D Scale: a self-reported depression scale for research in general population. Applied Psychological Measurement 1, 385–401.
Schnall, P.L., Schwartz, J.E., Landsbergis, P.A., Warren, K., Pickering, T.G., 1998. A longitudinal study of job strain and ambulatory blood pressure: results from a three-year follow-up. Psychosomatic Medicine 60, 697–706.
Schnorpfeil, P., Noll, A., Schulze, R., Ehlert, U., Frey, K., Fischer, J.E., 2003. Allostatic load and work conditions. Social Science and Medicine 57, 647–656.
Segerstrom, S.C., Miller, G.E., 2004. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychological Bulletin 130, 601–630.
Shima, S., Shikano, Kitamura, T., Asai, M., 1985. Reliability and validity of CES-D. Japanese Journal of Clinical Psychiatry 27, 717–723 (in Japanese).
Shimazu, A., de Jonge, J., 2009. Reciprocal relations between effort-reward imbalance at work and adverse health: a three-wave panel survey. Social Science and Medicine 68, 60–68.
Shirom, A., Toker, S., Berliner, S., Shapir, I., Melamed, S., 2006. Work-related vigor and job satisfaction relationships with inflammation biomarkers among employed adults. In: Fave, A.D. (Ed.), Dimensions of Well-being: Research and Intervention. Franco Angeli, Milano, Italy, pp. 254–274.
Shirom, A., Toker, S., Berliner, S., Shapira, I., 2008. The Job Demand-Control-Support Model and stress-related low-grade inflammatory responses among healthy employees: a longitudinal study. Work and Stress 22, 138–152.
Siegrist, J., 1996. Adverse health effects of high-effort/low-reward conditions. Journal of Occupational Health Psychology 1, 27–41.
Siegrist, J., 2001. A theory of occupational stress. In: Dunham, J. (Ed.), Stress in the Workplace: Past, Present, and Future. Whurr Publishers, London, pp. 53–66.
Siegrist, J., 2010. Effort-reward imbalance at work and cardiovascular diseases. International Journal of Occupational Medicine and Environmental Health 23, 279–285.
Siegrist, J., Starke, D., Chandola, T., Godin, I., Marmot, M., Niedhammer, I., Peter, R., 2004. The measurement of effort-reward imbalance at work: European comparisons. Social Science and Medicine 58, 1483–1499.
Steptoe, A., Siegrist, J., Kirschbaum, C., Marmot, M., 2004. Effort-reward imbalance, overcommitment, and measures of cortisol and blood pressure over the working day. Psychosomatic Medicine 66, 323–329.
Suzuki, I., Kawakami, N., Shimizu, H., 1998. Reliability and validity of a questionnaire for assessment of energy expenditure and physical activity in epidemiological studies. Journal of Epidemiology 8, 152–159.
Theorell, T., Orth-Gomer, K., Eneroth, P., 1990. Slow-reacting immunoglobulin in relation to social support and changes in job strain: a preliminary note. Psychosomatic Medicine 52, 511–516.
Tsutsumi, A., Ishitake, T., Peter, R., Siegrist, J., Matoba, T., 2001. The Japanese version of the effort-reward imbalance questionnaire: a study in dental technicians. Work and Stress 15, 86–96.
Tsutsumi, A., Kawakami, N., 2004. A review of empirical studies on the model of effort-reward imbalance at work: reducing occupational stress by implementing a new theory. Social Science and Medicine 59, 2335–2359.
Tsutsumi, A., Kayaba, K., Nagami, M., Miki, A., Kawano, Y., Ohya, Y., Odagiri, Y., Shimomitsu, T., 2002a. The effort-reward imbalance model: experience in Japanese working population. Journal of Occupational Health 44, 398–407.
Tsutsumi, A., Nagami, M., Morimoto, K., Matoba, T., 2002b. Responsiveness of measures in the effort-reward imbalance questionnaire to organizational changes: a validation study. Journal of Psychosomatic Research 52, 249–256.
Utsugi, M., Saijo, Y., Yoshioka, E., Sato, T., Horikawa, N., Gong, Y., Kishi, R., 2009. Relationship between two alternative occupational stress models and arterial stiffness: a cross-sectional study among Japanese workers. International Archives of Occupational and Environmental Health 82, 175–183.
van Vegchel, N., de Jonge, J., Bosma, H., Schaufeli, W., 2005. Reviewing the effort-reward imbalance model: drawing up the balance of 45 empirical studies. Social Science and Medicine 60, 1117–1131.
von Kanel, R., Kudielka, B.M., Preckel, D., Hanebuth, D., Fischer, J.E., 2006. Delayed response and lack of habituation in plasma interleukin-6 to acute mental stress in men. Brain, Behavior, and Immunity 20, 40–48.
Westermann, J., Pabst, R., 1990. Lymphocyte subsets in the blood: a diagnostic window on the lymphoid system? Immunology Today 11, 406–410.
Whiteside, T.L., Herberman, R.B., 1994. Role of human natural killer cells in health and disease. Clinical and Diagnostic Laboratory Immunology 1, 125–133.
Yovel, G., Shakhar, K., Ben-Eliyahu, S., 2001. The effects of sex, menstrual cycle, and oral contraceptives on the number and activity of natural killer cells. Gynecologic Oncology 81, 254–262.
Zorrilla, E.P., Luborsky, L., McKay, J.R., Rosenthal, R., Houldin, A., Tax, A., McCorkle, R., Seligman, D.A., Schmidt, K., 2001. The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain, Behavior, and Immunity 15, 199–226.