Association of General Fatigue With Cellular Immune Indicators Among Healthy White-Collar Employees

Akinori Nakata, DMSc, Masahiro Irie, MD, DMSc, and Masaya Takahashi, DMSc

Objective: Although fatigue is a common complaint in the working population, underlying immunological mechanisms are not well understood. This study investigated the association of general fatigue with cellular immune indicators. **Methods:** A total of 148 healthy white-collar employees (70% men) underwent a blood draw for the measurement of natural killer (NK), B, and T cell counts as well as NK cell cytotoxicity (NKCC) and completed two different fatigue scales, that is, Profile of Mood State (POMS) and Maastricht Questionnaire (MQ). **Results:** Multiple linear regression analyses revealed that POMS fatigue score was significantly associated with decreases of NK cells ($\beta = -.407$) and NKCC ($\beta = -.215$), whereas MQ fatigue score was significantly associated with reduced NK cells ($\beta = -.290$) but not with NKCC ($\beta = -.127$). **Conclusion:** The results suggest that general fatigue may be related to impaired NK cell competency among healthy employees.

Fatigue is a common complaint in the working population, with reported prevalence varying from 8% to 38%.[1–6] Prolonged fatigue has been identified as an independent risk factor for long-term sickness absence,[1,7] impaired work ability and productivity loss,[8] occupational injuries,[9] and adverse health conditions including chronic disorders,[10,11] infection,[12] and obesity.[13] Fatigue is more prevalent among workers with high job stress,[7,14–17] irregular work schedules,[7,13] long work hours,[18–21] and poor sleep.[16,22,23] Although fatigue has drawn a considerable attention in recent occupational health research,[24] the underlying biological mechanisms of fatigue is largely unknown.

A number of studies have reported that chronic fatigue syndrome (CFS), which is a condition characterized by profound, disabling, and unexplained sensation of fatigue lasting more than 6 months accompanied by a constellation of nonspecific symptoms,[25] is related to immune abnormalities.[26,27] These abnormalities include alterations of cytokine profile, reduced natural killer cell cytotoxicity (NKCC), decreased responses to T cell mitogens, and a presence of autoantibodies.[27,28] In contrast to a large body of CFS research, little is known about the immunological characteristics of general or mild/frequent fatigue. Such fatigue is normally restored by sufficient rest and sleep, but can cause serious health issues when it becomes persistent. A limited amount of studies that directly associated fatigue and immune outcomes found that prolonged fatigue is related to decreased NKCC[29] and cytokines such as interleukin (IL)-4 and interferon (IFN)-γ,[30] and increased inflammatory markers including C-reactive protein (CRP)[31–33] and white blood cell counts.[32] It has also been reported that work-related fatigue is associated with reactivation of latent viruses such as human herpesvirus (HHV)-6 and -7.[34] Nevertheless, due to a restricted amount of information the immunologic basis of general fatigue is still not well understood.

In addition to reports on fatigue and immunity as described earlier, there are studies that investigated the immunological effects of affective states that define fatigue as a core element, that is, burnout syndrome and vital exhaustion. Burnout syndrome that is characterized by a constellation of emotional exhaustion, depersonalization, and diminished personal accomplishment, has been consistently associated with impaired immune activity.[35–40] Workers with a tendency of burnout had decreased T cell subsets (CD4 +, CD8 +, and CD3 + T cells),[35] NK cells,[36] NKCC,[36] and IL-4,[37] as well as increased TNF-α,[37,39] IL-10,[38] and CRP.[40] Meanwhile, vital exhaustion is conceptualized as an unusual state of fatigue, loss of energy, increased irritability, and feelings of demoralization.[41] Vital exhaustion has also been reported to be related to immune disruption as represented by increased IL-1ra, IL-6, CRP, IL-10, and TNF-α, especially in patients with cardiovascular disorders.[42–44]

Although fatigue seemed to be a core component of burnout syndrome and vital exhaustion, it should be acknowledged that fatigued workers are not always burnt out and burnt out workers might not experience fatigue as a major complaint.[3] In the same way, fatigued workers may not necessarily experience demoralization or depressive feeling by definition as vitally exhausted workers do. Collectively, fatigue seems to overlap with both burnout syndrome and vital exhaustion to some extent, but it is not entirely redundant with these concepts. Therefore, it seems important to elucidate the direct association of fatigue with the immune system, which may help one to understand various health problems related to fatigue at work.

The aim of this study was to investigate the association of fatigue with cellular immune indicator in a cross-sectional study design. We measured NKCC and circulating NK (CD3-CD56 +) cells together with B (CD19 +) and total T (CD3 + CD56-) cells among 148 white-collar employees. The conceptual model for this study links work-related factors, heath behaviors, and sociodemographic factors to immunological outcomes through fatigue (Figure 1). In this model, poor health behaviors (eg, insufficient sleep), high work stress, long work hours, and low socioeconomic status are presumed to increase the level of fatigue leading to poor immune outcomes. Direct pathways of work-related factors, heath behaviors, and sociodemographic factors to immune outcomes are depicted but are not investigated in this article.

SUBJECTS AND METHODS

Study Participants

The study was conducted as a part of annual occupational health examination in April 2002. All participants were full-time, white-collar, and daytime Japanese employees working at a trading company. A total of 217 employees who underwent health examination were invited to participate in this study and the survey questionnaire, including purpose, instruction, and informed consent was given to them. Overall, 216 employees agreed to participate in the questionnaire survey and blood test, and replied with a signed consent form. Of these employees, 47 were excluded because of missing data in essential study parameters. An additional 21 employees

From the Division of Applied Research and Technology (Dr Nakata), National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, Ohio; Institute of Health Science (Dr Irie), Kyushu University, Japan; and National Institute of Occupational Safety and Health (Dr Takahashi), Kawasaki, Japan.

This research was partly supported by the base funding of the Japan National Institute of Occupational Safety and Health, Kawasaki, Japan.

The authors declare that they have no competing interests regarding this article.

Address correspondence to: Akinori Nakata, PhD, Division of Applied Research and Technology, MS-C24, National Institute for Occupational Safety and Health, 4676 Columbia Pkwy, Cincinnati, OH 45226 (nakataatky@umin.ac.jp or cji5@cdc.gov).

DOI: 10.1097/JOM.0b013e318229a938

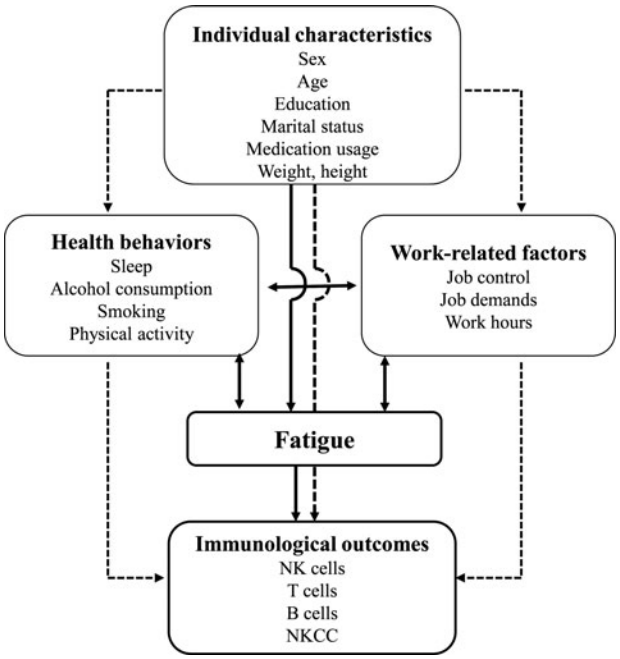

FIGURE 1. Conceptual model for the relationship among work-related factors, heath behaviors, sociodemographic factors, fatigue, and immunological outcomes.

reporting physical/mental disorders were excluded (see "Covariates" section for detail), which resulted in a sample of 148 participants. 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.

Measures

Fatigue

Fatigue was measured by two different scales. First, we used the three-item modified version of the Profile of Mood State (POMS)[45] validated in Japanese.[46] Participants were asked about their feeling during the past month: (*a*) I felt fatigued, (*b*) I felt exhausted, and (*c*) I felt sluggish. Responses to the questionnaire were coded as almost never = 1, sometimes = 2, often = 3, and almost always = 4. Responses are summed to obtain total POMS fatigue score, which ranges from 3 to 12, with higher scores reflecting more fatigue. Selection of items from the original POMS was based on factor analysis of item loading from a large scale study in Japan.[47] Chronbach's α of the POMS fatigue scale was 0.90. The test–retest stability over 1 year was $r = .465$ ($P < 0.001$). The modified POMS fatigue scale was chosen because the original POMS fatigue scale is one of the most widely adopted measures of subjective fatigue. The modified version has been frequently used in prior studies and has been shown to hold a high reliability.[48–50] Second, we used 21-item Maastricht Questionnaire (MQ)[41] validated in Japanese[51] to develop an original fatigue construct from the questionnaire; the reliability of the total scale was good ($\alpha = .90$). Briefly, principal component analysis with oblimin rotation was used to determine the underlying structure of MQ. Kaiser criterion was adopted to identify the number of components, and subsequent Kaiser-Meyer-Olkin criteria and Bartlett test of sphericity were applied as fit indices. Those items with component loadings of more than .40 and cross-loading of more than .20 were selected. As a result, items for fatigue taken out from the original 21-item MQ were questions 1, 4, 12, 14, and 20. These items are "Do you often feel tired? (Q1)," "Do you feel weak all over? (Q4)," "Do little things irritate you more than they used to? (Q12)," "I feel fine (reverse) (Q14)," and "Do you ever wake up with a feeling of exhaustion and fatigue (Q20)?" Responses to the questionnaire were coded as no = 0, don't know = 1, and yes = 2. Responses are summed to obtain total MQ fatigue score, which ranges from 0 to 10, with higher scores representing increased fatigue. Chronbach's α of the MQ fatigue scale was 0.77. The test–retest stability over 1 year with this sample was high ($r = .689$, $P < 0.001$). We selected the MQ to measure fatigue based on the fact that the scale predominately assesses two distinct dimensions, that is, fatigue and depression.[52] The MQ fatigue scale is often used in a clinical setting and reported to predict future myocardial infarction or new cardiac events in both healthy and cardiac populations.[53,54]

Preparation of Blood Samples

Fasting blood samples were collected between 9 and 11 AM from participants to control for diurnal variations. Ethylenediaminetetraacetic acid dipotassium (2K-EDTA) was used as an anticoagulant to collect 2 mL of venous blood from subjects for measurement of leukocytes counts and immunofluorescence staining. Similarly, 5 mL heparinized venous blood was collected to measure NKCC. All samples were transported and handled at room temperature (ie, 15°C–20°C). Immunofluorescence staining analysis and measurement of NKCC were conducted within 24 and 12 hours of blood collection, respectively. We determined counts of total leukocytes and total lymphocytes by an automated cell counter (Coulter Counter SP-VI, Coulter Electronics, Hialeah, FL), and lymphocyte subpopulations by flow cytometry analysis (EPICS XL, Beckman Coulter Inc, CA), as described in detail elsewhere.[55–57]

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. Anti-CD45-FITC antibody was used to identify and differentiate lymphocytes from nonlymphocytes and debris. 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. 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 (EPICS XL, Beckman Coulter Inc, Fullerton, CA).

With regard to functional roles of selected lymphocytes, T and B cells bear central roles in cellular and humoral immunity; subsets of T (CD4 + and CD8 +) cells control production of immunoglobulins from B cells and secretion of cytokines. NK cells are large granular cells possessing killer activity against certain tumor cells and virus-infected cells without prior sensitization. Although interpretation of changes in number of lymphocyte subsets needs 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.[58] Similarly, an extreme decrease of B cells is associated with suppressed humoral immune function resulting in inhibited production of immunoglobulins, whereas a decrease of NK cells is associated with reduced effectiveness in killing infected and cancerous cells.[59]

Cytotoxicity Assay

A standard 4-hour Chromium-51 (^{51}Cr) release assay was used to determine NKCC with effector cells at an effector/target [E/T] cell ratio of 20:1.[60] K562 was used as target cells and labeled with [^{51}Cr]-sodium chromate (New England Nuclear, Boston, MA) at 37°C for an hour, washed and resuspended at 2×10^5/mL in Roswell Park Memorial Institute (RPMI)-1640 medium containing 10% Fetal Calf Serum, 2 m*M* 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 hours. Radioactivity in the supernatant was determined by 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)]. We chose the E/T cell ratio of 20:1 because a large study of Japanese population ($n = 3625$) identified that the differences among individuals cytotoxic activity were most distinguishable.[61]

Covariates

Covariates included sex, age (in years), education (in years), marital status (unmarried/married), smoking (number of cigarettes smoked per day), alcohol consumption (g ethanol/week), leisure-time physical activity, subjective sleep sufficiency, height, weight, typical work hours per day, job control, job demands, self-reported illness, and regular medication usage. Alcohol consumption was estimated by asking the usual amount of alcoholic drinks consumed per day multiplied by the number of occasions in a week that alcoholic drinks were consumed. 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).[62] Subjective sleep sufficiency was determined by a single question[63]: Do you think your daily sleep is sufficient? Response options were: (1) very insufficient, (2) somewhat insufficient, (3) fairly sufficient, or (4) very sufficient. Height (m) and weight (kg) were measured anthropometrically to assess body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters. Job control and job demands were measured using the Brief Job Stress Questionnaire; both scales consisted of three items.[47] Examples of items include "I can work at my own pace (job control)" and "I have an extremely large amount of work to do (job demands)." These scales were developed with a research grant for Japanese Ministry of Labor with referring to Karasek's Job Content Questionnaire and the National Institute for Occupational Safety and Health Generic Job Stress Questionnaire.[47]

Regarding physical/psychological illness, participants were asked by occupational health doctors/nurses if they had been diagnosed or being treated for any of the following symptoms or disorders at the time of the study: hypertension, diabetes mellitus, depression, asthma, allergies, cancer, angina pectoris, cardiac infarction, gout, renal disease, colonic polyp, skin disease, anxiety disorders, musculoskeletal disorders, arrhythmia, cholelithiasis, kidney and urinary track diseases, liver disease, cerebrovascular disease, hyperlipidemia, 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 disorders were identified; hypertension ($n = 13$), hyperlipidemia ($n = 10$), diabetes mellitus ($n = 4$), gastric/duodenal ulcer ($n = 3$), depression ($n = 2$), asthma ($n = 2$), liver diseases ($n = 2$), autonomic imbalance ($n = 2$), anxiety disorders ($n = 1$), severe allergies ($n = 1$), and the common cold ($n = 1$); 20 participants reported 2+ disorders. To eliminate the potential effects of health status on immune parameters, we excluded all participants who reported the above disorders ($n = 21$) from the analyses. We also obtained data on the use of the following medications; aspirin ($n = 31$), β-Blockers ($n = 1$), acetaminophen ($n = 23$), corticosteroids ($n = 1$), antidepressants ($n = 1$), and anxiolytic drugs ($n = 1$). All participants with self-reported illnesses as described earlier were eliminated, leaving only aspirin ($n = 26$) and acetaminophen ($n = 18$) users in the subsequent analyses; these users were categorized as medication users (yes/no) in the analyses.

Statistical Analyses

Variables (age, alcohol consumption, BMI, POMS, and MQ fatigue scores) with skewed distributions were logarithmically transformed to achieve a more normal distribution in values. Alcohol consumption and MQ score were scaled for a nonnegative value by adding 1. Intercorrelations among fatigue, immune markers, and covariates were initially tested by the Pearson product-moment correlation coefficient.

Multiple linear regression analysis was used to examine the relationship between fatigue (dependent variable) and covariates (independent variables). Hierarchical multiple linear regression analyses were performed to test the association of fatigue scores with immune indicators. In step 1, we entered age, sex, and education as covariates. In step 2, we added marital status, smoking, alcohol consumption, physical activity, subjective sleep sufficiency, BMI, medication usage, work hours, job control, and job demands. In the analytic process, we considered the interactions of sex × fatigue but there were no significant ($P < 0.05$) interactions thus were not incorporated into the further analyses.

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).

RESULTS

Sample Characteristics

Characteristics of study participants are shown in Table 1. More than 70% were men and 63% were married. On average, participants aged 40, educated 15 years, and worked 10 hours per day. No participants in this sample showed clinically overt abnormalities of immune indicators (Table 1).

TABLE 1. Characteristics of Study Participants ($N = 148$)*

Characteristics	Mean ± SD or *n* (%)
POMS Fatigue score (range: 3–12)†	6.1 ± 2.1
MQ fatigue score (range: 0–10)†	5.4 ± 2.1
Sex, % men	104 (70.3)
Age (in years) (range: 23–59)	39.9 ± 11.1
Education (in years) (range: 12–20)	15.3 ± 1.5
Marital status, % married	93 (62.8)
Smoking (number of cigarettes smoked/day) (range: 0–60)	7.1 ± 11.3
Alcohol consumption (g ethanol/week)	134.4 ± 138.3
Leisure-time physical activity (METs/week)	5.8 ± 8.9
Subjective sleep sufficiency‡	2.4 ± 0.7
BMI (kg/height (m)^2)	22.5 ± 2.9
Work hours/day (range: 7–15)	9.9 ± 1.9
Job demands (range: 7–24)	17.3 ± 3.3
Job control (range: 3–12)	8.2 ± 1.7
Medication usage§, % yes	44 (29.7)
Immune indicators	
NK (CD3-CD56+) cells (cells/mm^3)	312 ± 196
Total T (CD3+CD56-) cells (cells/mm^3)	1169 ± 417
B (CD19+) cells (cells/mm^3)	250 ± 145
NKCC (% cytotoxicity)	50.6 ± 15.9

*Participants who reported physical/psychological disorders were excluded to eliminate the potential effects of health status on immune parameters.

†Higher scores indicate increased fatigue.

‡Subjective sleep sufficiency (1 = very insufficient, 2 = somewhat insufficient, 3 = fairly sufficient, 4 = very sufficient).

§Use of acetaminophen or aspirin.

TABLE 2. Pearson Correlation Matrix for Continuous Variables ($N = 148$)

	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15	
Variable	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
1. POMS fatigue score*	–	–																												
2. MQ fatigue score*	**.626**	**<0.001**	-	-																										
3. NK (CD3–CD56+) cells (cells/mm^3)	**−.356**	**0.001**	**−.353**	**<0.001**	-	-																								
4. T (CD3+CD56-) cells (cells/mm^3)	−.070	0.398	−.069	0.405	−.047	0.574	-	-																						
5. B (CD19+) cells (cells/mm^3)	−.016	0.848	.021	0.801	.009	0.914	**.315**	**<0.001**	-	-																				
6. NKCC	−.156	0.058	**−.163**	**0.049**	**.466**	**<0.001**	**−.192**	**0.020**	**−.170**	**0.038**	-	-																		
7. Age*	**−.323**	**<0.001**	**−.255**	**0.002**	.092	0.267	.059	0.478	**.194**	**0.018**	−.093	0.263	-	-																
8. Education (in years)	−.033	0.693	−.123	0.137	.112	0.174	.006	0.938	−.004	0.957	**.203**	**0.013**	**−.454**	**<0.001**	-	-														
9. Smoking (number of cigarettes/day)	−.037	0.652	−.109	0.189	.031	0.705	**.387**	**<0.001**	**.285**	**<0.001**	−.032	0.697	.029	0.726	**.213**	**0.009**	-	-												
10. Alcohol consumption (g ethanol/week)	.000	0.998	−.124	0.133	.108	0.190	.008	0.920	−.025	0.763	.159	0.053	.080	0.334	**.251**	**0.002**	**.275**	**0.001**	-	-										
11. Leisure-time physical activity (METs/week)	−.079	0.338	−.060	0.466	−.054	0.516	.021	0.800	.003	0.967	.063	0.446	.037	0.658	.005	0.948	.021	0.804	**.165**	**0.045**	-	-								
12. Subective sleep sufficiency	**−.350**	**<0.001**	**−.346**	**<0.001**	.085	0.303	**.217**	**0.008**	.115	0.165	−.003	0.973	.145	0.079	.068	0.413	.118	0.153	.117	0.158	.007	0.932	-	-						
13. BMI (kg/height (m)^2)*	.053	0.519	−.076	0.356	**.184**	**0.026**	.087	0.291	**.202**	**0.014**	.155	0.060	**.235**	**0.004**	.060	0.468	**.233**	**0.004**	**.188**	**0.022**	.072	0.387	−.039	0.635	-	-				
14. Work hours/day	**.273**	**<0.001**	**.163**	**0.047**	−.023	0.784	−.089	0.282	−.028	0.734	.084	0.313	**−.260**	**0.001**	**.355**	**<0.001**	.145	0.079	**.167**	**0.043**	−.029	0.724	**−.288**	**<0.001**	**.311**	**<0.001**	-	-		
15. Job demands	**.390**	**<0.001**	**.181**	**0.028**	−.068	0.409	−.054	0.514	.031	0.713	.008	0.919	−.117	0.157	.092	0.269	−.100	0.228	.001	0.988	−.004	0.962	**−.288**	**<0.001**	.100	0.226	**.477**	**<0.001**	-	-
16. Job control	**−.236**	**<0.001**	**−.275**	**<0.001**	**.259**	**0.001**	.113	0.170	.013	0.872	**.164**	**0.046**	.051	0.536	−.042	0.614	.030	0.722	.001	0.995	.017	0.834	**.169**	**0.040**	.087	0.294	−.120	0.145	**−.261**	**0.001**

*Log-transformed.
Bold type indicates variables at $P < 0.05$ level.

TABLE 3. Multiple Regression Analyses With POMS and MQ Fatigue Scores as Dependent Variables and Covariates as Independent Variables ($N = 148$)

	POMS Fatigue score*		MQ Fatigue score*	
	β†	*P*	β†	*P*
Covariates:	Adjusted $R^2 = .309$ ($P < 0.001$)		Adjusted $R^2 = .205$ ($P < 0.001$)	
Age (years)*	− .461	<0.001	− .317	0.005
Sex (men = 1, women = 2)	.063	0.638	.099	0.490
Education (in years)	− .279	0.006	− .253	0.020
Marital status (1 = unmarried, 2 = married)	.073	0.450	.024	0.819
Smoking (number of cigarettes smoked/day)	.028	0.715	− .010	0.900
Alcohol consumption (g ethanol/week)*	.122	0.145	.020	0.825
Leisure-time physical activity (METs/week)	− .073	0.314	− .039	0.614
Subjective sleep sufficiency	− .165	0.038	− .201	0.019
BMI (kg/height $(m)^2$)*	.138	0.137	.032	0.749
Work hours/day	.012	0.905	.123	0.246
Job demands	.254	0.003	.003	0.970
Job control	− .163	0.028	− .210	0.009
Medication usage (no = 1, yes = 2)	− .011	0.892	.017	0.841

*Log-transformed.
†Standardized regression coefficient.

Pearson Correlation Between POMS/MQ Fatigue Scores, Immune Indicators, and Covariates

Intercorrelations among fatigue scores, immune indicators, and covariates are shown in Table 2. Correlation between POMS and MQ fatigue scale was high ($r = .626$). POMS and MQ fatigue scores were both inversely correlated with NK cells. NKCC was significantly correlated with MQ fatigue score whereas POMS fatigue score was marginally correlated. Neither POMS nor MQ fatigue scores were correlated with T or B cells. Age, subjective sleep sufficiency, and job control were both inversely correlated with POMS and MQ fatigue scores. Work hours and job demands were positively correlated with POMS and MQ fatigue scores (Table 2).

Association Between POMS/MQ Fatigue Scores and Covariates

The relationships between POMS and MQ fatigue scores with covariates are shown in Table 3. POMS and MQ fatigue scores were significantly correlated with younger age, lower educational status, insufficient sleep, and low job control. In addition, only POMS fatigue score was significantly associated with high job demands (Table 3).

Association Between POMS/MQ Fatigue Scores and Immune Indicators

Hierarchical multiple regression analyses revealed that POMS fatigue score was inversely associated with NK cells and NKCC even after adjustment of an array of potential confounders (Table 4 and Figure 2). MQ fatigue score was also inversely associated with NK cells but not with NKCC. Figure 2 illustrates the dot plots for the relationship between fatigue scores and NK markers. Neither POMS nor MQ fatigue scores were correlated with T or B cells.

DISCUSSION

The current study investigated the relationship between the levels of fatigue and cell-mediated immune indicators in 148 healthy employees. There were four key findings from this study. First, POMS fatigue score was inversely associated with NK cells and NKCC. Second, MQ fatigue score was also inversely associated with NK cells but not with NKCC. Third, neither POMS nor MQ fatigue scores were associated with T or B cells. And finally, factors related to POMS and MQ fatigue had similar conditions; it was defined by multiple factors including age, education, sleep, and job stress. Although the results must be interpreted with caution due to the cross-sectional nature of the study, fatigue related to high job stress, insufficient sleep, and low socioeconomic status may result in impaired NK cells in healthy white-collar workers.

In this study, we found a decrease of NK cell immunity by increased fatigue level. This finding is consistent with one study that reported a reduction of NKCC in fatigued individuals using the within subjects design with two point estimates.[29] Authors found that an increase in the amount of sleep and a decrease in levels of fatigue were related to an increase of NKCC. However, authors did not find a relationship between fatigue and NKCC in cross-sectional analyses, possibly due to small number of subjects in the study ($n = 45$). Our results are also in accordance with a large-scale prospective study ($n = 12{,}140$) showing that a high level of fatigue is associated with 20% increase of being absent due to common infection[12] because NK cells appear to play a major role in killing virally infected cells.[59] Studies have reported that reduced NKCC is a significant prognostic indicator of infection among healthy individuals. According to several prospective studies, healthy subjects with persistently low NKCC exhibited a higher risk for developing infections within 6 to 12 months.[64] Thus our results imply that fatigue may compromise NK cell function resulting in frequent/common infection.

No significant associations between fatigue and T or B cells were found in this study. Although we are not aware of any studies demonstrating the relationship between general fatigue and immunity, a review specifically focused on immunology of CFS concluded that (1) quantity and function of B cells are not affected by CFS, and (2) CFS may relate to T cell activation but the quantity of T cell subsets in relation to CFS is inconclusive.[65] Clearly, more evidence is needed to reach a valid conclusion regarding the relationship between general fatigue and T and B cells.

The multiple regression analyses with fatigue scales as outcomes revealed that reduced sleep sufficiency and high job stress (low job control and/or high job demands) are significantly related to increased fatigue (Table 3). This finding is consistent with those

TABLE 4. Summary of Hierarchical Multiple Linear Regression Analysis for the Association of POMS and MQ Fatigue Scores With Cellular Immune Markers ($N = 148$)

Immunological outcomes (dependent variable)	Step 1*								Step 2†							
	NK cells		T cells		B cells		NKCC		NK cells		T cells		B cells		NKCC	
	β§	*P*	β§	*P*	β§	*P*	β§	*P*	β§	*P*	β§	*P*	β§	*P*	β§	*P*
POMS Fatigue score‡	−.366	<0.001	−.054	0.559	.091	0.310	−.218	0.013	−.407	<0.001	−.001	0.994	.068	0.481	−.215	0.028
MQ Fatigue score‡	−.334	<0.001	−.052	0.562	.102	0.248	−.158	0.067	−.290	<0.001	.014	0.875	.117	0.177	−.127	0.167

*Adjusted for sex, age, and education.
†Adjusted for sex, age, education, marital status, smoking, alcohol consumption, physical activity, subjective sleep sufficiency, BMI, medication usage, work hours, job demands, and job control.
‡Log-transformed.
§Standardized regression coefficients for each variable's unique contribution.

of past studies in different working populations. For example, in two consecutive surveys during 2003 to 2004 ($n = 350$–383), reduced daily sleep hours was the strongest factor related to accumulated fatigue in Japanese manufacturing workers.[22] A study of 5720 healthy employed men and women in Sweden reported that fatigue was predicted by disturbed sleep (odds ratio [OR], 4.31) and high work demands (OR, 2.39) but not by overtime (OR, 0.87–1.32).[16] A cross-sectional survey of medical interns revealed that poor sleep quality and greater perceived stress were significantly associated with fatigue but working longer than 80 h/week was not directly associated with fatigue.[23] In healthy working employees, it seems that insufficient sleep and job stresses are two major modifiable factors related to increased fatigue, which may impair NK cell competency.

The regression analysis also found that age is inversely correlated with the level of fatigue. Several studies have reported that age is positively related to an increase of fatigue,[66,67] whereas other studies found no relationship between the two.[2,68,69] Meanwhile, there is also evidence suggesting that fatigue is inversely correlated with age. In a national cross-sectional telephone survey of US workers, the 2-week period prevalence of fatigue was 40.2% for 18 to 29 years old, 40.7% for 30 to 39 years old, 37.2% for 40 to 49 years old, and 33.7% for 50 to 65 years old.[8] As such, the evidence for age being a correlate of fatigue has been inconsistent across studies. With regard to our findings, younger workers tend to work longer hours with insufficient sleep, which may constitute an inverse correlation between age and fatigue (Table 2). Thus, the relationship between age and fatigue seems to be complex and may depend on nature of the target population.

The current study may provide further implications for strategies to reduce fatigue at the workplace and improve immunological health of workers. Several prior studies have pointed out that long work hours or excessive overtime are associated with fatigue,[16,19,22,23] but the findings are not always consistent. We speculate that this inconsistency may be attributable to the fact that work hour-fatigue relationship may be confounded by sleep.[70,71] Workers with insufficient/short sleep due to long work hours may have suffered from fatigue, whereas workers who worked long but have had good sleep may not complain much about their fatigue. In conjunction with this speculation, we propose that an efficient measure to reduce workers' fatigue is to have control over their sleep and work schedules. Epidemiological studies have indicated that having control over work time (as characterized by control over the starting and ending times of a workday, the opportunities to take breaks and to deal with private matters during the workday, the scope for influencing, the scheduling of shifts, the scheduling of paid days off and vacations, and the opportunities to take unpaid leave) as well as control over nonworking hours (eg, sleep/rest hours and physical activities) can have significant positive impacts of the health including fatigue outcomes.[72–75] Such strategy may be promising to reduce job stress, recover from fatigue and insufficient sleep, and improvement of immune response simultaneously.

This study has strengths and limitations that should be considered for the interpretation of the results. The specific strengths of our study are that we controlled for a broad array of potential confounders and applied two different fatigue scales. In addition, participants who reported illnesses were excluded to minimize sampling bias, that is, fatigued as a consequence of health conditions. Limitations include the following. First, since this study is of cross-sectional data, the association could be in either direction, that is, subjective fatigue may reduce NK cells or that reduced NK cells may be the cause for increased perception of fatigue. Second, sample size was not large, which might have contributed to underestimation of effect size, that is, MQ fatigue and NKCC. Third, although we used two distinct fatigue scales, it is desirable to reconfirm our findings using other fatigue scales such as the visual analog scale, Brief Fatigue Inventory,[76] or Checklist Individual Strength[1] to support our

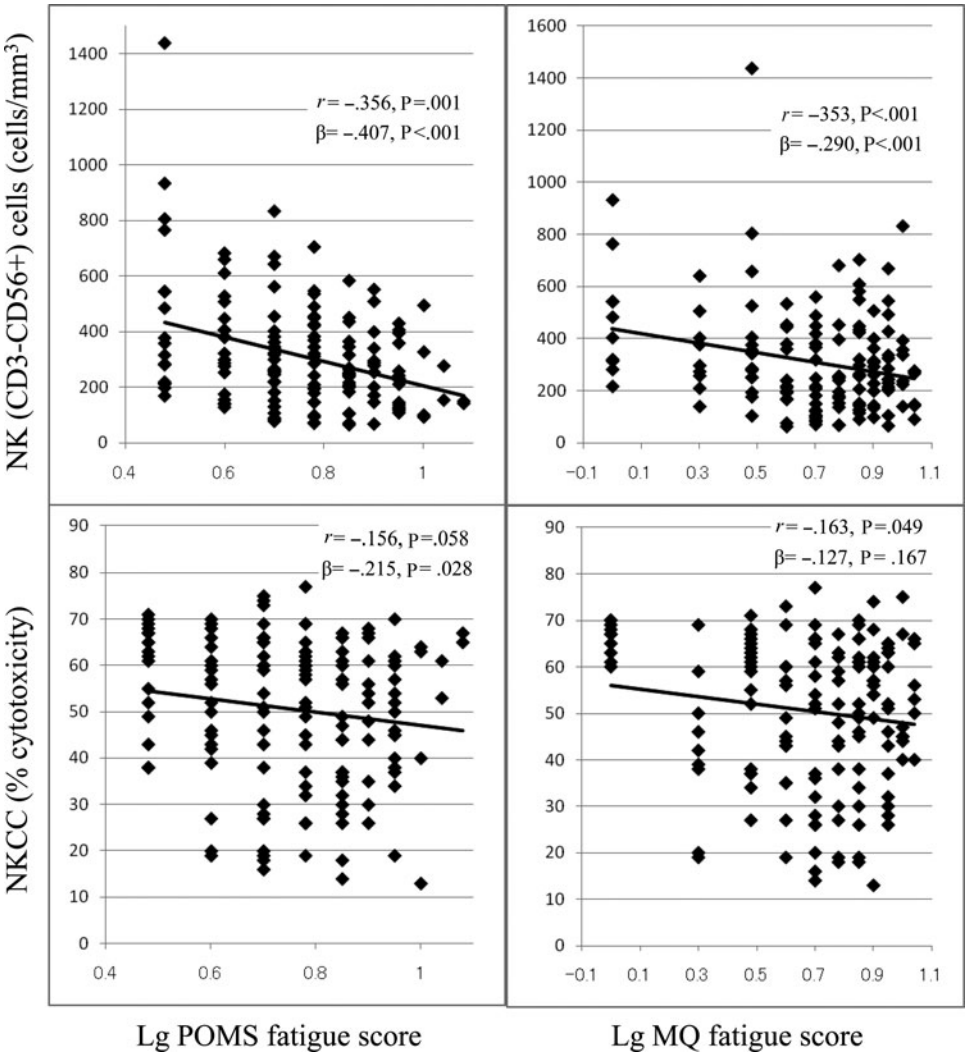

FIGURE 2. The dot plots for the relationships between POMS and MQ fatigue scores with NK cell counts (upper) and POMS and MQ fatigue scores with NKCC (lower).
Note. Lg indicates logarithmically transformed; POMS, profile of mood state, MQ, Maastricht Questionnaire.

findings. Fourth, participants were employees from specific occupations and are not representative of the entire Japanese workforce or workers of other racial/ethnic groups. Fifth, we could not obtain data on menstrual phase or oral contraceptive use in women, which might have some effects on immunological outcomes. Sixth, although the chance seems to be low, participants with CFS or fibromyalgia may be included in the analysis because these disorders were not explicitly listed in the questionnaire. Seventh, we only measured cellular immune markers, which limit the interpretation of our findings. And finally, even though we adjusted for a variety of confounders, we could not exclude the possibility that unadjusted factors, that is, personality traits, genetic components, other social/occupational factors, as well as unknown or unmeasured factors may have affected our findings.

In conclusion, this study examined the association between fatigue and cellular immune status in a sample of 148 healthy Japanese white-collar daytime employees. The results suggested that fatigue is associated with impaired NK cell immune response but not T or B cell counts. Although the precise mechanisms and pathways underlying the observed associations have yet to be determined, the findings of the present study provides some support for the biological evidence of the relationship between fatigue and the immune system. Further research is needed to confirm the relationships between fatigue, immunity, and long-term health outcomes in a prospective manner.

ACKNOWLEDGMENTS

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the US National Institute for Occupational Safety and Health.

REFERENCES

1. Bultmann U, Huibers MJ, van Amelsvoort LP, Kant I, Kasl SV, Swaen GM. Psychological distress, fatigue and long-term sickness absence: prospective results from the Maastricht Cohort Study. *J Occup Environ Med*. 2005;47:941–947.
2. Bultmann U, Kant I, Kasl SV, Beurskens AJ, van den Brandt PA. Fatigue and psychological distress in the working population: psychometrics, prevalence, and correlates. *J Psychosom Res*. 2002;52:445–452.
3. Huibers MJ, Beurskens AJ, Prins JB, et al. Fatigue, burnout, and chronic fatigue syndrome among employees on sick leave: do attributions make the difference? *Occup Environ Med*. 2003;60(Suppl 1):i26–31.

4. Jansen NW, van Amelsvoort LG, Kristensen TS, van den Brandt PA, Kant IJ. Work schedules and fatigue: a prospective cohort study. *Occup Environ Med*. 2003;60(Suppl 1):i47–53.
5. Kristal-Boneh E, Froom P, Harari G, Ribak J. Fatigue among Israeli industrial employees. *J Occup Environ Med*. 1996;38:1145–1150.
6. de Fatima Marinho de Souza M, Messing K, Menezes PR, Cho HJ. Chronic fatigue among bank workers in Brazil. *Occup Med (Lond)*. 2002;52:187–194.
7. Huibers MJ, Bultmann U, Kasl SV, et al. Predicting the two-year course of unexplained fatigue and the onset of long-term sickness absence in fatigued employees: results from the Maastricht Cohort Study. *J Occup Environ Med*. 2004;46:1041–1047.
8. Ricci JA, Chee E, Lorandeau AL, Berger J. Fatigue in the U.S. workforce: prevalence and implications for lost productive work time. *J Occup Environ Med*. 2007;49:1–10.
9. Swaen GM, Van Amelsvoort LG, Bultmann U, Kant IJ. Fatigue as a risk factor for being injured in an occupational accident: results from the Maastricht Cohort Study. *Occup Environ Med*. 2003;60(Suppl 1):i88–92.
10. Watt T, Groenvold M, Bjorner JB, Noerholm V, Rasmussen NA, Bech P. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. *J Epidemiol Community Health*. 2000;54:827–833.
11. Franssen PM, Bultmann U, Kant I, van Amelsvoort LG. The association between chronic diseases and fatigue in the working population. *J Psychosom Res*. 2003;54:339–344.
12. Mohren DC, Swaen GM, Kant I, van Schayck CP, Galama JM. Fatigue and job stress as predictors for sickness absence during common infections. *Int J Behav Med*. 2005;12:11–20.
13. Yamada Y, Kameda M, Noborisaka Y, Suzuki H, Honda M, Yamada S. Excessive fatigue and weight gain among cleanroom workers after changing from an 8-hour to a 12-hour shift. *Scand J Work Environ Health*. 2001;27:318–326.
14. Bultmann U, Kant IJ, Schroer CA, Kasl SV. The relationship between psychosocial work characteristics and fatigue and psychological distress. *Int Arch Occup Environ Health*. 2002;75:259–266.
15. Bultmann U, Kant IJ, Van den Brandt PA, Kasl SV. Psychosocial work characteristics as risk factors for the onset of fatigue and psychological distress: prospective results from the Maastricht Cohort Study. *Psychol Med*. 2002;32:333–345.
16. Akerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Mental fatigue, work and sleep. *J Psychosom Res*. 2004;57:427–433.
17. Eriksen W. Work factors as predictors of persistent fatigue: a prospective study of nurses' aides. *Occup Environ Med*. 2006;63:428–434.
18. Suwazono Y, Dochi M, Kobayashi E, et al. Benchmark duration of work hours for development of fatigue symptoms in Japanese workers with adjustment for job-related stress. *Risk Anal*. 2008;28:1689–1698.
19. Nagashima S, Suwazono Y, Okubo Y, et al. Working hours and mental and physical fatigue in Japanese workers. *Occup Med (Lond)*. 2007;57:449–452.
20. Akerstedt T, Fredlund P, Gillberg M, Jansson B. Work load and work hours in relation to disturbed sleep and fatigue in a large representative sample. *J Psychosom Res*. 2002;53:585–588.
21. Otsuka Y, Sasaki T, Iwasaki K, Mori I. Working hours, coping skills, and psychological health in Japanese daytime workers. *Ind Health*. 2009;47:22–32.
22. Sasaki T, Iwasaki K, Mori I, Hisanaga N, Shibata E. Overtime, job stressors, sleep/rest, and fatigue of Japanese workers in a company. *Ind Health*. 2007;45:237–246.
23. Friesen LD, Vidyarthi AR, Baron RB, Katz PP. Factors associated with intern fatigue. *J Gen Intern Med*. 2008;23:1981–1986.
24. Van Dijk FJ, Swaen GM. Fatigue at work. *Occup Environ Med*. 2003;60(Suppl 1):i1–2.
25. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med.* 1994;121:953–959.
26. Silverman MN, Heim CM, Nater UM, Marques AH, Sternberg EM. Neuroendocrine and immune contributors to fatigue. *PM R*. 2:338–346.
27. Lorusso L, Mikhaylova SV, Capelli E, Ferrari D, Ngonga GK, Ricevuti G. Immunological aspects of chronic fatigue syndrome. *Autoimmun Rev*. 2009;8:287–291.
28. Fletcher MA, Zeng XR, Maher K, et al. Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell function and dipeptidyl peptidase IV/CD26. *PLoS One*. 2010;5:e10817.
29. Shakhar K, Valdimarsdottir HB, Guevarra JS, Bovbjerg DH. Sleep, fatigue, and NK cell activity in healthy volunteers: significant relationships revealed by within subject analyses. *Brain Behav Immun*. 2007;21:180–184.
30. Hickie IB, Bansal AS, Kirk KM, Lloyd AR, Martin NG. A twin study of the etiology of prolonged fatigue and immune activation. *Twin Res*. 2001;4:94–102.
31. Valentine RJ, McAuley E, Vieira VJ, et al. Sex differences in the relationship between obesity, C-reactive protein, physical activity, depression, sleep quality and fatigue in older adults. *Brain Behav Immun*. 2009;23:643–648.
32. Raison CL, Lin JM, Reeves WC. Association of peripheral inflammatory markers with chronic fatigue in a population-based sample. *Brain Behav Immun*. 2009;23:327–337.
33. Cho HJ, Seeman TE, Bower JE, Kiefe CI, Irwin MR. Prospective association between C-reactive protein and fatigue in the coronary artery risk development in young adults study. *Biol Psychiatry*. 2009;66:871–878.
34. Kondo K. Chronic fatigue syndrome and herpesvirus reactivation [in Japanese]. *Nippon Rinsho*. 2007;65:1043–1048.
35. Bargellini A, Barbieri A, Rovesti S, Vivoli R, Roncaglia R, Borella P. Relation between immune variables and burnout in a sample of physicians. *Occup Environ Med*. 2000;57:453–457.
36. Nakamura H, Nagase H, Yoshida M, Ogino K. Natural killer (NK) cell activity and NK cell subsets in workers with a tendency of burnout. *J Psychosom Res*. 1999;46:569–578.
37. von Kanel R, Bellingrath S, Kudielka BM. Association between burnout and circulating levels of pro- and anti-inflammatory cytokines in schoolteachers. *J Psychosom Res*. 2008;65:51–59.
38. Mommersteeg PM, Heijnen CJ, Kavelaars A, van Doornen LJ. Immune and endocrine function in burnout syndrome. *Psychosom Med*. 2006;68:879–886.
39. Grossi G, Perski A, Evengard B, Blomkvist V, Orth-Gomer K. Physiological correlates of burnout among women. *J Psychosom Res*. 2003;55:309–316.
40. Toker S, Shirom A, Shapira I, Berliner S, Melamed S. The association between burnout, depression, anxiety, and inflammation biomarkers: C-reactive protein and fibrinogen in men and women. *J Occup Health Psychol*. 2005;10:344–362.
41. Appels A, Hoppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. *Int J Cardiol*. 1987;17:15–24.
42. Janszky I, Lekander M, Blom M, Georgiades A, Ahnve S. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. *Brain Behav Immun*. 2005;19:555–563.
43. Meyer T, Stanske B, Kochen MM, et al. Elevated serum levels of interleukin-10 and tumor necrosis factor are both associated with vital exhaustion in patients with cardiovascular risk factors. *Psychosomatics*. 2010;51:248–256.
44. Wirtz PH, von Kanel R, Schnorpfeil P, Ehlert U, Frey K, Fischer JE. Reduced glucocorticoid sensitivity of monocyte interleukin-6 production in male industrial employees who are vitally exhausted. *Psychosom Med*. 2003;65:672–678.
45. McNair D, Lorr M, Droppleman L. *Profile of Mood States*. San Diego, CA: Educational and Industrial Testing Service; 1992.
46. Yokoyama K, Araki S, Kawakami N, Tkakeshita T. Production of the Japanese edition of profile of mood states (POMS): assessment of reliability and validity [in Japanese]. *Nippon Koshu Eisei Zasshi*. 1990;37:913–918.
47. Shimomitsu T, Yokoyama K, Ono Y, Maruta T, Tanigawa T. Development of a novel brief job stress questionnaire. In: Kato M, ed. *Report of the Research Grant of a Prevention of Work-Related Diseases from the Ministry of Labour [in Japanese]*. Tokyo, Japan: Tokyo Medical University; 1998:107–115.
48. Takada M, Ebara T, Kamijima M. Heart rate variability assessment in Japanese workers recovered from depressive disorders resulting from job stress: measurements in the workplace. *Int Arch Occup Environ Health*. 2010;83:521–529.
49. Kawakami N, Kobayashi Y, Takao S, Tsutsumi A. Effects of web-based supervisor training on supervisor support and psychological distress among workers: a randomized controlled trial. *Prev Med*. 2005;41:471–478.
50. Shimazu A, Okada Y, Sakamoto M, Miura M. Effects of stress management program for teachers in Japan: a pilot study. *J Occup Health*. 2003;45:202–208.
51. Watanabe T, Sugiyama Y, Sumi Y, et al. Effects of vital exhaustion on cardiac autononomic nervous functions assessed by heart rate variability at rest in middle-aged male workers. *Int J Behav Med*. 2002;9:68–75.
52. McGowan L, Dickens C, Percival C, Douglas J, Tomenson B, Creed F. The relationship between vital exhaustion, depression and comorbid illnesses in patients following first myocardial infarction. *J Psychosom Res*. 2004;57:183–188.
53. Appels A, Mulder P. Excess fatigue as a precursor of myocardial infarction. *Eur Heart J*. 1988;9:758–764.
54. Kop WJ, Appels AP, Mendes de Leon CF, de Swart HB, Bar FW. Vital exhaustion predicts new cardiac events after successful coronary angioplasty. *Psychosom Med*. 1994;56:281–287.

55. Nakata A, Araki S, Tanigawa T, et al. 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. *J Occup Environ Med*. 2000;42:143–150.
56. Nakata A, Takahashi M, Irie M, Swanson NG. Job satisfaction is associated with elevated natural killer cell immunity among healthy white-collar employees. *Brain Behav Immun*. 2010;24:1268–1275.
57. Nakata A, Tanigawa T, Fujioka Y, Kitamura F, Iso H, Shimamoto T. 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. *Ind Health*. 2002;40:142–148.
58. Westermann J, Pabst R. Lymphocyte subsets in the blood: a diagnostic window on the lymphoid system? *Immunol Today*. 1990;11:406–410.
59. Whiteside TL, Herberman RB. Role of human natural killer cells in health and disease. *Clin Diagn Lab Immunol*. 1994;1:125–133.
60. Pross HF, Baines MG, Rubin P, Shragge P, Patterson MS. Spontaneous human lymphocyte-mediated cytotoxicity against tumor target cells. IX. The quantitation of natural killer cell activity. *J Clin Immunol*. 1981;1: 51–63.
61. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *Lancet*. 2000;356: 1795–1799.
62. Suzuki I, Kawakami N, Shimizu H. Reliability and validity of a questionnaire for assessment of energy expenditure and physical activity in epidemiological studies. *J Epidemiol*. 1998;8:152–159.
63. Nakata A, Haratani T, Kawakami N, Miki A, Kurabayashi L, Shimizu H. Sleep problems in white-collar male workers in an electric equipment manufacturing company in Japan. *Industrial Health*. 2000;38: 62–68.
64. Ogata K, An E, Shioi Y, et al. Association between natural killer cell activity and infection in immunologically normal elderly people. *Clin Exp Immunol*. 2001;124:392–397.
65. Lyall M, Peakman M, Wessely S. A systematic review and critical evaluation of the immunology of chronic fatigue syndrome. *J Psychosom Res*. 2003;55: 79–90.
66. Beckers DG, van der Linden D, Smulders PG, Kompier MA, van Veldhoven MJ, van Yperen NW. Working overtime hours: relations with fatigue, work motivation, and the quality of work. *J Occup Environ Med*. 2004;46:1282–1289.
67. Verdonk P, Hooftman WE, van Veldhoven MJ, Boelens LR, Koppes LL. Work-related fatigue: the specific case of highly educated women in the Netherlands. *Int Arch Occup Environ Health*. 2010;83:309–321.
68. Janssen N, Nijhuis FJ. Associations between positive changes in perceived work characteristics and changes in fatigue. *J Occup Environ Med*. 2004;46:866–875.
69. Wada K, Arimatsu M, Yoshikawa T, et al. Factors on working conditions and prolonged fatigue among physicians in Japan. *Int Arch Occup Environ Health*. 2008;82:59–66.
70. Nakata A. Effects of long work hours and poor sleep characteristics on workplace injury among full-time male employees of small- and medium-scale businesses. *J Sleep Res*. [published ahead of print February 7, 2011] doi: 10.1111/j.1365-2869.2011.00910.x.
71. Nakata A. Work hours, sleep sufficiency, and prevalence of depression among full-time employees: a community-based cross-sectional study. *J Clin Psychiat*. 2011;72:605-614.
72. Grzywacz JG, Casey PR, Jones FA. The effects of workplace flexibility on health behaviors: a cross-sectional and longitudinal analysis. *J Occup Environ Med*. 2007;49:1302–1309.
73. Takahashi M, Iwasaki K, Sasaki T, Kubo T, Mori I, Otsuka Y. Worktime control-dependent reductions in fatigue, sleep problems, and depression. *Appl Ergon*. 2011;42:244–250.
74. Ala-Mursula L, Vahtera J, Linna A, Pentti J, Kivimaki M. Employee worktime control moderates the effects of job strain and effort-reward imbalance on sickness absence: the 10-town study. *J Epidemiol Community Health*. 2005;59:851–857.
75. Ala-Mursula L, Vahtera J, Pentti J, Kivimaki M. Effect of employee worktime control on health: a prospective cohort study. *Occup Environ Med*. 2004;61:254–261.
76. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer*. 1999;85:1186–1196.

ERRATUM

Pulmonary Function in a Cohort of New York City Police Department Emergency Responders Since the 2001 World Trade Center Disaster: Erratum

In the article, Pulmonary Function in a Cohort of New York City Police Department Emergency Responders Since the 2001 World Trade Center Disaster," published in the June 2011 issue, a portion of the 2007 data was omitted and is herein clarified.

In 2002, 11 of 206 subjects (5.3%) exhibited mild pulmonary dysfunction (60% to 80% of predicted; 95% CI: 3.0% to 9.4%). Upon reevaluation in 2007, the abnormalities had resolved in 4 of the 11 affected individuals (36.4%), whereas 6 individuals (54.5%) continued to exhibit mild pulmonary dysfunction, and 1 individual did not return for testing. Ten additional individuals (7.2%) of 139 returning subjects exhibited mild pulmonary dysfunction (95% CI: 3.9% to 12.9%), raising the number of affected individuals to 16 (11.5%; 95% CI: 7.2% to 18.0%). This increase in prevalence, however, was not statistically significant (McNemar test with continuity correction, $P = 0.18$) and does not affect the conclusions.

REFERENCE

1. Kleinman EJ, Cucco RA, Martinez C, et al. Pulmonary function in a cohort of New York City Police Department emergency responders since the 2001 World Trade Center disaster. *J Occup Environ Med*. 2011;53:618–626.

DOI: 10.1097/JOM.0b013e31822c9e64

