monoclonal antibodies (DAKO Inc., Carpinteria, CA): mouse IgG1, CD3+ T cells, CD3+/CD4+ helper T cells, CD3+/CD8+ cytotoxic T cells, CD3+/CD19+ B cells, and CD3+/CD16+/CD56+ NK cells.

A chromium release assay was used to determine natural killer cell activity (NKCA). Effector and ^{51}Cr-labeled K562 target cells were incubated for 3.5 h in 96-well round-bottomed plates. Wells contained effector and target cells at ratios of 20:1. Wells with K562 in medium alone or with 1N HCL were used to assess spontaneous and maximum release. Radioactivity was counted in a γ-counter and the percentage-specific lysis was determined according to the formula: (mean experimental cpm − mean spont. release cmp)/(mean maximal cmp − mean spont. release cmp) × 100.

To determine the volume of secreted saliva and the concentration of S-IgA, samples of unstimulated saliva were collected using cotton swabs (Salivettes; Sarstedt, Ltd., Leicester, UK). A cotton swab was placed underneath the tongue of each participant for 5 min. Subsequently, the cotton swab was removed and saliva was extracted from the cotton by centrifugation at 3.5×10^3 rpm for 10 min. Saliva was stored frozen in capped test tubes at −20 °C until assay. The S-IgA concentration (in salivain micrograms per milliliter) was determined by enzyme-linked immunoabsorbent assay using an IgA test (MBL Inc., Nagoya, Japan). The thawed saliva aliquots (10 μl) were diluted 40 times. Saliva samples were reacted with polystyrene beads that labeled the antihuman secretory component. After incubation at 37 °C for 1 h, the beads were washed twice and reacted with peroxidase standard antihuman IgA (rabbit IgG/Fab′) (second reaction). After incubation at room temperature for 1 h, the beads were washed three times, and then enzyme metrical fluid (orthophenylenediamine + 4 mM H_2O_2) (third reaction) was added. After incubation at room temperature for 30 min, the reaction was stopped by the addition of H_2SO_4. The reaction product was quantified spectrophotometrically at 492 nm with a microplate reader (model 550; Bio-Rad Inc., Hercules, CA). The S-IgA secretion rate (in micrograms per min) was calculated as the product of S-IgA concentration and saliva flow rate.

In this study, we measured the proportions of lymphocyte subsets and S-IgA at five points (baseline, just after the task, and 15 min, 30 min, and 1 h after the task) and NKCA at three points (baseline, just after the task, and 1 h after the task). Sampling points for NKCA were fewer mainly due to the limits of the Mie Prefectural College of Nursing on the total allowable quantity of blood drawn: 5 ml blood is necessary for the assay of NKCA, but only 1 ml blood is necessary to measure other immune indices. In addition, the sampling timing for the NKCA assay was determined based on a previous study in which NKCA was increased immediately after a 15-min stress task and decreased 15 min after termination of the task (Peters et al., 1999).

2.3. Cortisol measures

Samples of saliva for measurement of the concentration of salivary cortisol were obtained by the same method as that used for S-IgA and stored at −20 °C until assay. The concentration of cortisol in the saliva (in micrograms per milliliter) was determined by an enzyme-linked immunoabsorbent assay. Ninety-six-well Costar™ microplates precoated with anti-Cortisol rabbit antibody were prepared. A saliva sample of 50 μl was added to each well in triplicate. Then an enzyme conjugate of 50 μl was added to each well and incubated at room temperature for 1 h. After incubation, each well was washed three times. A substrate of 50 μl was added to each well and incubated at room temperature for 30 min. Subsequently, 1N HCL 50 μl was added to each well to stop the enzyme reaction. To measure the concentration of cortisol, the plate was read at 450 nm with a microplate reader (model 550; Bio-Rad Inc.).

2.4. Cardiovascular measures

Cardiodynamic activity was recorded by electrocardiography (ECG) and non-invasive finger blood pressure (FINAP) measurements. To determine HR, ECG was recorded using an MP 100 system (BIOPAC Systems Inc., Santa Barbara, CA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded through the finger cuff of a Portapres Model 2 (TNO Biomedical Instrumentation Inc., Amsterdam, The Netherlands) attached to the third finger of the non-dominant arm of each subject. Each indicator was recorded continuously during the task and the rest periods. The ECG data were subsequently analyzed to yield HRV. The data were first subject to visual inspection, and only completely artifact-free data were used for estimation of the R–R intervals. The R–R interval data were resampled at 4 Hz to obtain equidistant time series values. A power spectrum density was then obtained through a fast Fourier transformation of the tachogram. In connection with the fast Fourier transformation, the data were detrended linearly and filtered through a rectangular window. We studied the integral of the power spectrum in two major frequency bands, a high frequency band (HF, 0.15–0.5 Hz) and a low frequency band (LF, 0.05–0.15 Hz). The former is correlated with respiratory sinus arrhythmia and is exclusively attributable to parasympathetic influence, and the latter mirrors the baroreceptor feedback loop that controls blood pressure and appears to reflect both sympathetic and parasympathetic activity (Sayers, 1973). In the present study, we examined the HF component expressed as a percentage of the total power in the spectrum (Perini et al., 2000) and the relative contributions of LF and HF power (LF/HF), which reflects sympathovagal balance. Two subjects in the C group, two subjects in the UC group, all subject in the control group were excluded from analyses of HRV due to technical problems. Thus the HRV analyses were performed for 16 subjects in the C group and 16 subjects in the UC group. Analyses of ECGs and FINAP waveforms were performed using the software package AcqKnowledge for the MP 100.

2.5. Psychological measures

The subjects were asked to evaluate subjectively the intensity of their stress, physical fatigue, and mental fatigue on visual–analog scales (0–100%). Additionally, they were asked to rate their sense of control over the task on a scale from 0% (not controllable at all) to 100% (perfectly controllable). In addition, they completed a Japanese version (Kazuhito et al., 1990) of the Profile of Mood States (POMS) (Usala and Hertzog, 1989) and a Japanese version (Katsuharu and Tadanobu, 1982) of the State-Trait Anxiety Inventory (STAI) (Speilberger et al., 1970). POMS is composed of six sub-scales (Tension-Anxiety (T-A), Depression-Dejection (D), Anger-Hostility (A-H), Vigor (V), Fatigue (F), and Confusion (C); 65 items). STAI is composed of two sub-scales to measure state and trait anxiety and consists of 40 items.

2.6. Stress task and manipulation of controllability

The subjects in the C and the UC groups performed mental arithmetic for 15 min. The subjects were told to add the currently displayed number (from 2 to 9) to the next one shown on the PC monitor, and to indicate the last digit of the resulting number by pressing a key (from 0 to 9). Each number was displayed for 500 ms and followed by a 1500-ms interval. The task included 34 sets (one set consists of 10 answers). During the task, bursts of aversive noise (approximately 100 dB) were delivered continuously when the error rate exceeded 20% in a set, and the noise was stopped when the rate of correct answers exceeded 80% in the next set. Subjects in the C and UC groups were told that they had to calculate a correct answer 90% of the time, and that if their accuracy rate was lower than this, none of their data would be used for the analysis.

As a manipulation of controllability, the noise was administered to the subjects in the C group. On the other hand, in the UC group the noise yoked to the C group was administered irrespective of the subjects' performance. Thus, subjects in the UC group could not stop the noise by achieving a high rate of correct answers. The subjects in the control group did not perform the mental arithmetic task and thus received no aversive noise.

2.7. Procedure

The subjects were instructed to eat a light breakfast on the morning of the experiment, and caffeine-containing beverages were not allowed. Also, the subjects were told to paste a monoanesthetic seal (PENLES; Wyeth Lederle Inc., Tokyo, Japan) at the location of the cannula insertion in their arms about 1 h before the experimental sessions to reduce pain. Subjects suffering from an infectious illness within 2 weeks of the experiment were rescheduled.

The experimental sessions were composed of a mental arithmetic task and four rest periods. The subjects were tested individually between 9:00 a.m. and 12:00 p.m. in a temperature- and humidity-controlled room. After a subject entered the experiment room, a cannula was inserted into the forearm vein of her non-dominant arm. Next, electrodes for electrocardiographic measurements and a finger cuff for blood pressure recording were attached. For the next 15 min, the subject filled out psychological questionnaires. After a rest period of 15 min, the first blood sample (for assays of female sex hormones and immunological parameters) and the first saliva sample (for assays of S-IgA and cortisol) were taken. Next, instructions were given for the mental arithmetic task, and the subjects were allowed to practice the mental arithmetic task for 2 min. The subjects then performed the mental arithmetic task for 15 min. Immediately after the task, the second blood and saliva samples were taken, and each subject filled out the questionnaire again. After each rest period (15, 30, and 60 min), the third, fourth, and fifth blood and saliva samples were taken, respectively, and the questionnaires were filled out. Autonomic indices (ECG and BP) were measured continuously throughout the experimental session. After the end of the procedure, the electrodes, blood-pressure cuff, and cannula were removed, and the subjects were fully debriefed and thanked. Each subject was paid 2400 Japanese yen for participating in the study.

2.8. Statistical analysis

Prior to statistical analysis, the mean values of HR, SBP, and DBP were calculated for the last 5 min of the pre-experimental baseline period, for the periods during the stress task (0–5 min, 5–10 min, and 10–15 min), and for the last 5 min of each rest period after the task. Means of the cardiovascular parameters were determined every 5 min to examine their temporal variations during the stress task (e.g., habituation to the task). The cardiovascular data were analyzed using repeated-measures analyses of variance (ANOVAs): Group (C, UC, and control group) × Period (baseline, $stress_{5\,min}$, $stress_{10\,min}$, $stress_{15\,min}$, $rest_{15\,min}$, $rest_{30\,min}$, $rest_{60\,min}$). The immune, endocrine, and psychological measures and the HF components of HRV and the LF/HF ratio were analyzed using repeated-measures ANOVAs: Group × Period (baseline, stress, $rest_{15\,min}$, $rest_{30\,min}$, $rest_{60\,min}$). The components of HRV were calculated during 15-min epochs of each baseline, stress and rest period. The Greenhouse–Geisser epsilon correction factor, ε (Jennings and Wood, 1976), was used where appropriate. Corrected degrees of freedom are reported; the P-values reflect the epsilon correction. In cases where significant interactions were found in the ANOVAs, post hoc analyses using LSD tests ($P < 0.05$) were conducted to examine which combinations of data points differed significantly. For perception of subjective controllability, a Student's *t*-test was used on only the C and UC groups, both of which had performed the mental arithmetic task. For each group, Pearson correlation coefficients were computed among change scores (scores at the stress period − scores at the baseline) of these indices to examine the relationship between immune, cardiovascular, and endocrine reactivity. Additionally, analyses comparing the strength of correlation coefficients between the C and UC groups were carried out using *z*-scores of the normal distribution for all correlation coefficients that showed significant correlations in the C group, the UC group, or both.

3. Results

3.1. Immunological measures

The immune data at the baseline, stress, and rest periods are summarized in Table 1. Fig. 1 illustrates changes in the percentages of CD3+ T cells, NK cells, B cells, and NKCA. The main effects of Period were significant for WBCs, lymphocytes, NK cells, NKCA, CD3+ T cells, CD19+ B cells, CD4+ T cells, and CD8+ T cells ($Fs(1\text{–}2,34\text{–}113) = 9.47\text{–}50.11$, $Ps < 0.001$).

A previous study has shown that salivary flow is often correlated with a change in the concentration of S-IgA (Stone et al., 1987). Because the present data also yielded a significant negative correlation between S-IgA concentration and salivation ($r(42) = -0.523$, $P < 0.01$), a finding in accord with previous research (Herbert and Choen, 1993), the secretion rate of S-IgA was calculated by multiplying the saliva S-IgA concentration (μg/ml) and saliva volume (ml/min) for statistical analysis. In parameters of mucosal immunity, the main effects of Period were significant for S-IgA concentration and S-IgA secretion rate ($F(34,109) = 2.78$, $P < 0.05$, $F(3,111) = 3.59$, $P < 0.05$). In addition, the main effects of Group were significant for S-IgA concentration ($F(2,36) = 5.65$, $P < 0.01$).

Table 1
Means (S.D.s) of immunological measures and results of ANOVAs

	Group	Baseline	Stress	Rest 15 min	Rest 30 min	Rest 60 min	*N*	Effect[a]
WBC (×10³/μl)	C	5.01 (1.46)	5.29 (1.45)	5.19 (1.42)	5.37 (1.44)	5.38 (1.47)	17	
	UC	4.45 (1.10)	4.73 (1.06)	4.62 (1.03)	4.71 (1.03)	4.78 (1.04)	18	Period**
	Control	3.85 (0.45)	3.95 (0.48)	4.08 (0.46)	4.13 (0.50)	4.17 (0.46)	6	
Lymphocyte (×10³/μl)	C	1.59 (0.45)	1.76 (0.51)	1.61 (0.46)	1.72 (0.50)	1.77 (0.55)	17	
	UC	1.44 (0.23)	1.66 (0.33)	1.57 (0.25)	1.59 (0.28)	1.69 (0.33)	18	Period**
	Control	1.15 (0.36)	1.23 (0.12)	1.33 (0.15)	1.38 (0.12)	1.69 (0.42)	6	
Monocyte (×10³/μl)	C	0.46 (0.21)	0.51 (0.20)	0.47 (0.19)	0.45 (0.18)	0.47 (0.16)	17	
	UC	0.44 (0.18)	0.43 (0.19)	0.40 (0.15)	0.46 (0.19)	0.41 (0.16)	18	n.s.
	Control	0.43 (0.12)	0.43 (0.15)	0.42 (0.13)	0.40 (0.06)	0.30 (0.10)	6	
Granulocyte (×10³/μl)	C	2.95 (1.08)	3.02 (1.01)	3.11 (1.11)	3.2 (1.16)	3.14 (1.11)	17	n.s.
	UC	2.56 (1.02)	2.64 (1.03)	2.65 (0.98)	2.66 (0.91)	2.67 (0.86)	18	
	Control	2.27 (0.42)	2.28 (0.41)	2.33 (0.48)	2.3 (0.49)	2.3 (0.43)	6	
CD3+ CD4+ (%)	C	49.68 (7.53)	42.47 (10.48)	47.09 (7.55)	45.90 (7.21)	44.85 (6.32)	17	
	UC	48.29 (6.68)	39.57 (7.78)	44.45 (7.03)	44.58 (8.07)	43.81 (6.98)	18	Period** Group ×
	Control	46.73 (3.45)	45.45 (4.28)	44.62 (3.33)	43.86 (3.68)	42.64 (4.34)	6	Period*
CD3+ CD4+ (%)	C	28.66 (6.85)	27.25 (6.16)	28.52 (6.21)	28.11 (5.84)	27.87 (5.72)	17	
	UC	30.41 (5.74)	29.09 (5.53)	30.20 (5.58)	29.59 (5.26)	29.40 (5.33)	18	Period*
	Control	28.69 (2.94)	27.38 (3.42)	27.92 (3.50)	27.58 (3.69)	27.40 (3.44)	6	
Saliva flow rate (ml/min)	C	0.24 (0.16)	0.29 (0.10)	0.27 (0.14)	0.22 (0.13)	0.21 (0.11)	17	
	UC	0.28 (0.14)	0.30 (0.10)	0.28 (0.12)	0.23 (0.12)	0.24 (0.14)	18	n.s.
	Control	0.20 (0.14)	0.17 (0.16)	0.13 (0.14)	0.15 (0.15)	0.22 (0.12)	7	
sIgA secretion rate (μg/min)	C	12.98 (7.41)	15.23 (4.45)	13.86 (6.55)	10.97 (5.97)	11.03 (5.57)	17	
	UC	15.92 (5.73)	16.03 (2.84)	14.96 (5.04)	13.11 (5.09)	14.62 (8.50)	16	Period*
	Control	11.96 (9.16)	11.17 (12.11)	7.81 (8.05)	8.25 (7.90)	13.24 (7.60)	7	
sIgA concentration (μg/ml)	C	56.54 (8.15)	54.59 (7.40)	52.18 (5.37)	52.46 (5.03)	54.39 (6.09)	17	
	UC	54.20 (8.19)	51.97 (4.83)	51.08 (3.87)	53.28 (4.93)	56.03 (8.02)	16	Group**, Period*
	Control	56.58 (9.14)	67.04 (16.64)	61.83 (11.25)	60.88 (11.12)	62.23 (9.93)	7	
Cortisol (ng/ml)	C	2.83 (0.67)	2.79 (0.59)	2.60 (0.76)	2.53 (0.76)	2.95 (0.58)	17	
	UC	2.79 (0.56)	2.61 (0.62)	2.52 (0.72)	2.68 (0.59)	2.68 (0.57)	17	Period*
	Control	2.89 (0.39)	2.73 (0.66)	2.52 (0.79)	2.48 (0.92)	2.77 (0.96)	5	

C: controllable group; UC: uncontrollable group; Control: control group.
[a] Main effects and interactions as results of ANOVAs.
* $P < 0.05$.
** $P < 0.01$.

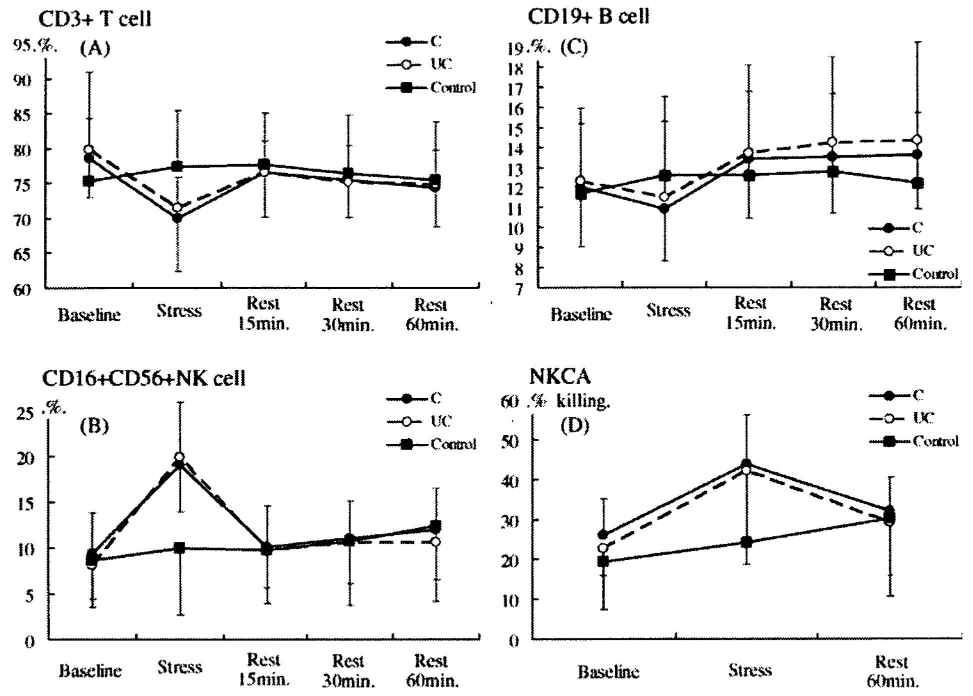

Fig. 1. Percentage of CD3+ (A); NK cells (B); CD19+ (C); and NKCA (D) at the five measurement points. Vertical bars indicate standard deviations. C: controllable group; UC: uncontrollable group; Control: control group.

In the C and the UC groups, indices of innate immunity (percentages of NK cells and NKCA) were significantly higher, and indices of specific immunity (percentages of CD3+, 19+, CD4+ and CD8 cells) were significantly lower, after the stress task than at the respective baseline (see Fig. 1). The C and UC groups differed significantly from the control group in all immune measures during the task periods ($Fs(4–8,34–156) = 2.28–9.56$, $Ps < 0.001–0.05$) but not during the rest periods ($Ps > 0.01$). Notably, there were no significant differences between the C and the UC groups in any indices.

3.2. Cardiovascular measures

Changes in cardiovascular indices are illustrated in Fig. 2. ANOVAs yielded significant main effects of Group for HR and DBP ($F(2,39) = 4.09$, $P < 0.05$, $F(2,39) = 4.90$, $P < 0.05$). Additionally, there were significant main effects of Period for HR, SBP, and DBP ($Fs(1–2,64–83) = 25.62–38.85$, $P < 0.001$). In the C and UC groups, all cardiovascular parameters were significantly higher during the stress task than at the respective baseline. These parameters remained at high levels and did not change during the task, suggesting that habituation did not take place during the 15-min task. The C and UC groups differed significantly from the control group in all cardiovascular measures during the task periods ($Fs(12,234) = 4.33–20.93$, $P < 0.001$) but not during the rest periods ($Ps > 0.01$). On the other hand, the main effects of Period were shown in HRV parameters: the HF component of HRV was significantly reduced during the task period compared with the baseline ($F(1,30) = 13.26$, $P < 0.01$), and the LF/HF ratio showed a significant increase in the task period ($F(1,30) = 6.07$, $P < 0.01$). The decrease in the HF component and the increase in the LF/HF ratio suggest that the mental arithmetic task induced a dominant state of sympathetic activity. For the cardiovascular measures, there were no significant differences between the C and the UC groups in any indices.

3.3. Cortisol measures

The cortisol levels at the baseline, after the stress task, and during the rest periods are presented in Table 1. In all groups, the cortisol level continued to significantly decrease to the $rest_{30\ min}$ compared with the baseline, and significantly increased after the $rest_{60\ min}$ compared with the baseline. There were no significant main effects of Group and no significant interactions between Group and Period. Notably, there were no significant differences between the C and the UC groups.

3.4. Psychological measures

The psychological data at baseline, after the stress task, and during the rest periods are presented in Table 2. Concerning the perceived controllability of the groups, the mean value of this parameter was 49.22 (S.D. = 17.20) in the C group, and 38.56 (S.D. = 16.64) in the UC group. That of the C group was marginally higher than that of the UC group ($t(34) = 1.77$, $P = 0.08$). ANOVAs yielded significant main effects of Group for perception of stress, state anxiety, and T-A, D, A-H, C of POMS ($Fs(2,34–39) = 3.53–6.72$,

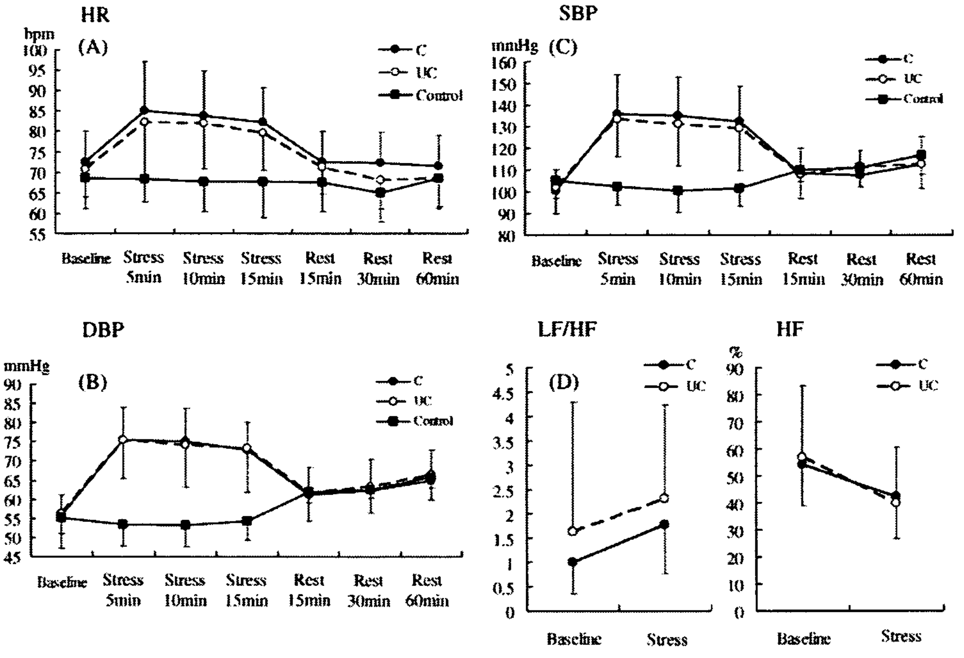

Fig. 2. HR (A); DBP (B); and SBP (C) at the seven measurement points; and HF and LF/HF (D) during baseline and task periods. Vertical bars indicate standard deviations. Vertical bars indicate standard deviations. C: controllable group; UC: uncontrollable group; Control: control group.

$Ps < 0.01$–0.05). In addition, there were significant main effects of Period for physical fatigue, mental fatigue, perception of stress, state anxiety, and T-A, D, A-H, V, C of POMS ($Fs(1$–$2,54$–$109) = 3.83$–18.44, $Ps < 0.001$–0.05). Significant Group × Period interactions were observed for mental fatigue, perception of stress, state anxiety, and T-A, V, C of POMS ($Fs(4$–$8,68$–$156) = 2.72$–4.92, $Ps < 0.001$–0.05). Post hoc analyses ($P < 0.05$) indicated that mental

Table 2
Means (S.D.s) of psychological measures and results of ANOVAs

	Group	Baseline	Stress	Rest 15min	Rest 30min	Rest 60min	*N*	Effect[a]
Perception of stress	C	26.29 (25.80)	46.59 (21.36)	35.59 (21.60)	36.29 (25.40)	38.89 (26.27)	17	Group*, Period**,
	UC	26.06 (21.53)	53.83 (27.89)	26.22 (15.44)	20.94 (14.74)	20.72 (17.83)	18	Group × Period**
	Control	10.43 (9.68)	16.86 (12.39)	18.29 (14.45)	19.43 (14.26)	18.43 (15.75)	7	
Mental fatigue	C	27.29 (23.59)	41.71 (21.67)	36.94 (20.64)	37.29 (24.89)	39.59 (24.62)	17	Period**,
	UC	33.67 (24.15)	53.33 (23.93)	33.22 (18.27)	25.83 (16.88)	25.39 (19.01)	18	Group × Period**
	Control	16.29 (14.60)	21.86 (17.49)	23.14 (18.22)	24.29 (17.54)	25.43 (17.89)	7	
STAI								
State-anxiety	C	41.82 (8.20)	48.53 (8.55)	40.76 (7.44)	40.41 (7.95)	39.35 (8.02)	17	Group**, Period**,
	UC	38.83 (5.26)	50.83 (10.06)	37.78 (4.81)	37.17 (4.63)	34.72 (5.49)	18	Group × Period**
	Control	36.57 (3.15)	33.86 (4.34)	32.71 (4.31)	33.14 (5.27)	31.14 (5.37)	7	
POMS								
Tension-anxiety	C	10.00 (6.77)	10.21 (7.01)	–	–	6.71 (5.89)	14	Group**, Period**,
	UC	13.19 (4.83)	18.13 (8.34)	–	–	7.75 (3.40)	16	Group × Period**
	Control	8.71 (5.47)	4.57 (2.57)	–	–	3.14 (2.79)	7	
Vigor	C	12.25 (6.07)	8.38 (6.04)	–	–	9.25 (6.14)	16	Period**,
	UC	13.76 (4.28)	8.35 (5.20)	–	–	12.41 (5.36)	17	Group × Period*
	Control	10.14 (4.41)	10.14 (4.41)	–	–	10.14 (3.53)	7	
Fatigue	C	8.06 (6.94)	7.56 (7.04)	–	–	8.13 (5.86)	16	Group × Period*
	UC	12.53 (7.09)	10.24 (7.00)	–	–	7.47 (4.62)	17	
	Control	4.86 (3.53)	5.29 (3.55)	–	–	5.14 (3.93)	7	

Only the parameters that interaction was found in is shown in Table 2; An effect of periods was found in the following parameters: Physical fatigue** and Depression-Dejection**, Confusion** and Anger-Hostility** of POMS; An effect of group was found in the following parameters: Depression-Dejection* and Anger-Hostility* of POMS; There was no significantly all effect for Trait-anxiety. C: controllable group; UC: uncontrollable group; Control: control group.

[a] Main effects and interactions as results of ANOVAs.

* $P < 0.05$.

** $P < 0.01$.

Table 3
Correlations between changes in immune, cardiovascular, and endocrine measures (each group)

Controllable	$HR_{5\ min}$	$HR_{10\ min}$	$HR_{15\ min}$	$SBP_{5\ min}$	$SBP_{10\ min}$	$SBP_{15\ min}$	$DBP_{5\ min}$	$DBP_{10\ min}$	$DBP_{15\ min}$	HF	Cortisol
Granulocyte											0.07
CD3+	0.01	−0.15		−0.04	−0.16	−0.14	0.00	−0.04	−0.04		
CD4+				−0.24	−0.28	−0.28	−0.14	−0.19	−0.16		
CD8+											
CD19+	−0.46	−0.43	−0.41	−0.35	−0.39	−0.42	−0.19	−0.12			
NKcell	0.19	0.33	0.32	0.19	0.33	0.32	0.08	0.10	0.15		0.20
NKCA	0.78*									0.23	
Cortisol	0.09	−0.04									
Granulocyte											−0.55*
CD3+	−0.54*	−0.51*		−0.63**	−0.66**	−0.64**	−0.55**	−0.69**	−0.68**		
CD4+				−0.58**	−0.74**	−0.70**	−0.51**	−0.70**	−0.73**		
CD8+											
CD19+	−0.46**	−0.44*	−0.42**	−0.43**	−0.45*	−0.42**	−0.32*	−0.31*			
NKcell	0.64**	0.58**	0.52**	0.65**	0.69**	0.68**	0.49*	0.62**	0.60**		0.59*
NKCA	0.33									−0.79**	
Cortisol	0.54*	0.53*									

The underline indicates significant differences between correlation coefficients in the controllable vs. uncontrollable groups. In control group, there were significant correlations between $SBP_{10\ min}$ and Monocyte ($r = 0.80^*$), CD19+ ($r = -0.77^*$), or NKCA ($r = 0.91^*$).
* $P < 0.05$.
** $P < 0.01$.

fatigue of the UC group and perception of stress and state anxiety of the C and the UC groups were higher than those of the control group after the task. In POMS, TA of the UC groups was higher than that of the C and control groups after the task.

3.5. Associations among immune, cardiovascular, and endocrine reactivity

Controllability was not shown to have any effect on cardiovascular or immune parameters by ANOVA. Thus, to further examine the effects of controllability on functional associations among the autonomic nervous, endocrine, and immune systems during the acute stress task, we performed correlation analyses among changes in cardiovascular, endocrine, and immune parameters in each experimental group separately. Furthermore, to examine the temporal characteristics of the influences of autonomic activity on the immune functions, we determined the mean changes of cardiovascular parameters in three time windows during the task: 0–5 min, 5–10 min, and 10–15 min; the correlations between these cardiovascular parameters and the immune parameters were then calculated for each time window. The results in the C and UC groups are presented in Table 3. There were no significant correlations except those between HR and NKCA in the C group. On the other hand, in the UC group, there were many strong correlations among the endocrine, cardiovascular, and immune measures (see Table 3). To prove that these correlations in the UC group were not merely artifacts, we performed a scatterplotting of the SBP and immune parameters in the UC and the C group, respectively, as shown in Fig. 3. All cardiovascular measures in the UC group correlated positively with the change in the percentage of NK cells, and negatively with the change in the percentage of CD3+ T cells and CD19+ B cells, and blood pressure correlated positively with the change in the percentage of NK cells, and negatively with the change in the percentages of CD3+ T cells, CD4+ T cells, and CD19+ B cells. Further, remarkably high correlations of the autonomic and the immune parameters were found continuously from the initiation to the end of the acute stress task. The HF component of HRV showed a remarkably significant negative correlation with NKCA ($r = -0.79$, $P < 0.01$) only in the UC group, suggesting that reduction of vagal activity led directly to upward regulation of the cytotoxicity of NK cells in the uncontrollable stress condition.

Analyses comparing the strength of the correlation coefficients between the C and UC groups showed that the correlation coefficients relating SBP or DBP at all time points and CD3+ T cells, CD4+ T cells, or NK cells in the UC group were significantly larger than those in the C group ($zs = 1.99$–2.39, $P < 0.05$).

4. Discussion

4.1. Cardiovascular and immune reactions to acute stress

During the mental arithmetic task, enhanced cardiovascular responses (HR, SBP, and DBP) were observed. Additionally, results of HRV parameters (LF/HF ratio and HF) suggested activation of the sympathetic nervous system and deactivation of the parasympathetic nervous system. Furthermore the proportion of NK cells in peripheral blood increased and the proportions of T cells, helper T cells, and B cells in blood decreased. Such lymphocyte trafficking by

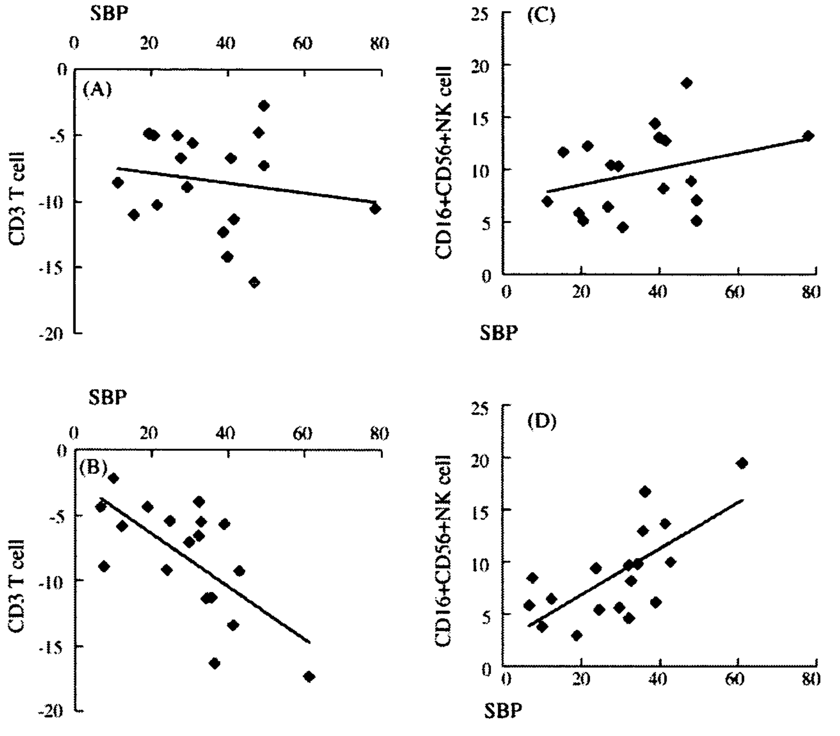

Fig. 3. Scatterplotting of SBP and immune parameters in controllable and uncontrollable groups. A and C: controllable group; B and D: uncontrollable group.

acute stress has been suggested to be adaptive for survival (Engler et al., 2004; Segerstrom and Miller, 2004). An increase of antigen-nonspecific peripheral innate immune cells, here represented by NK cells, might be interpreted as preparation for the potential invasion of bacteria or other antigens by injuring accompanying fight/flight behaviors. A decrease of T cells and B cells might represent trafficking of such cells into the lymph nodes, where helper T cells are sensitized to antigens and cascades of antigen-specific immune responses are initiated. Additionally, the increased NKCA and S-IgA secretion rate by the acute stress task might represent enhancement of functional aspects of innate and mucosal immunity, which might also be adaptive for survival under acute stress. These responses in cardiovascular and immune parameters are consistent with previous studies (Delahanty et al., 2000, 1996; Willemsen et al., 2002; Isowa et al., 2004; Kimura et al., 2005).

It has been suggested that increase of NK cells during acute stress should be mediated by increased blood flow and blood pressure, and effects by E and NE through surface receptors (mainly, β2- and α-adrenoreceptors) (Benschop et al., 1993; Mills et al., 2000; Farag et al., 2002). Although we did not measure catecholamines directly, HRV parameters were evaluated as indirect indices of autonomic activity. As our results indicated, changes in the proportion of NK cells robustly correlated with cardiovascular indices whereas they showed only a limited correlation with HRV. These results suggest that the redistribution of NK cells observed in this study is considered to be mainly caused by an increase of blood pressure rather than an enhancement of autonomic activity. Because blood pressure levels are regulated not only by autonomic activity but also many other endocrine factors (e.g., vasopressin, atrial natriuretic peptide, opioids, oxytocin, angiotensin and so on), the observed increase of peripheral NK cells likely took place as the result of the integrated effects of such cardiovascular and neuroendocrine activities. On the other hand, because the physical effects of increased blood pressure cannot explain the decrease of T cells and B cells in peripheral circulation and the increase of NKCA, such immune changes under acute stress might be mediated mainly by neuroendocrine factors. This speculation is supported by reports that T cells and B cells have receptors for various neuroendocrine substances (Landmann et al., 1984; Van Tits et al., 1990; Kohm and Sanders, 2001).

4.2. *Effects of controllability*

Contrary to our prediction, no effects of controllability of the acute stress task were observed in any immune parameters. These results are consistent with the previous study by Peters et al. (1998), who reported that there were no effects of stress controllability on immune parameters except IL-6 concentration. On the other hand, although Peters et al. (1998, 1999) suggested that an effect of controllability appeared in cortisol level as an index of the HPA axis, we did not observe any effects of stress controllability in cortisol. Considering the null effect in the present study and the inconsistent and mixed results in previous studies (Weisse et al., 1990; Sieber et al., 1992; Gomez et al., 1994; Peters et al., 1998, 1999, 2003), immune and endocrine reactivity to acute stress might not be as sensitive to the controllability of stressors as previously thought.

However before reaching any definitive conclusions, some caveats regarding the present study must be recognized. First, in this study, the difference of perceived controllability between the C and UC conditions was only marginally significant, and thus we must suspend the conclusion that the experimental manipulation of controllability was substantially valid. Second, effects of controllability on the immune system and the HPA axis might have been concealed by the relatively wide inter-individual differences and the small sample size. Third, as regards to the HPA axis, circadian variation might have affected the results of cortisol in this study. The observed trend that the concentration of cortisol decreased according to the progress of the experimental session in all groups suggests such effects of circadian variation. During the time period in the present experiment (i.e., 9:00 a.m.–2:00 p.m.), cortisol levels usually drop; this circadian variation might be contaminated in the reported results. Further studies to control such factors more rigorously are awaited.

4.3. Associations among immune, cardiovascular, and endocrine reactivity in uncontrollable acute stress

As unpredicted results, correlations between the cardiovascular parameters, specifically SBP and DBP, and the immune parameters, especially T cells, helper T cells, and NK cells, were prominent in the UC condition, whereas few and slight correlations among those parameters were found under the C condition (see Table 3). In addition, beginning at 5 min after the start of the task and continuing until the end of the task, uncontrollability served to consistently strengthen the association between cardiovascular and immune parameters. Further, the scatterplotting of indices of blood pressure and immune parameters (see Fig. 3) appeared to suggest that those effects were not just artifacts. Taken together, the findings in the present study for the first time suggest that uncontrollability of acute stress, at least in some situations, might have the effect of strengthening the correspondence between the autonomic nervous and immune systems rather than increasing the reactivity in each system.

Recent neuroanatomical and functional neuroimaging findings can offer suggestions in considering the mechanisms underlying such effects. Much evidence has indicated that the contingency between a stimulus and reward or punishment in a situation should be represented in the orbitofrontal cortex (OFC) in the frontal lobe (O'Doherty et al., 2001a,b). The OFC receives inputs from sensory associative cortices of all modalities and from limbic structures such as the amygdala and the hippocampus (Carmichael et al., 1994; Carmichael and Price, 1995), and has rich connections to the hypothalamus and the periaqueductal gray matter (PAG), that have been implicated in the modulation of autonomic and endocrine functions (Price, 1999; Kringelbach and Rolls, 2004). Based on this neuroanatomical architecture, the OFC might evaluate how one can control the current situation and regulate autonomic and endocrine systems to optimize levels of their activity to meet the current demand. In an uncontrollable situation, when the situation is evaluated as still somewhat controllable and worthy of allocating more resources, sympathetic nervous and endocrine systems might be more activated, and thus enhancement of innate immunity and suppression of specific immunity might be emphasized through increased secretion of catecholamines and glucocorticoid (Peters et al., 1998; Swenson and Vogel, 1983). On the other hand, when the situation is evaluated as totally uncontrollable, the OFC might tune the activity of autonomic and endocrine systems to minimum levels to avoid allocation of resources in vain, in order to increase the chances of survival. In such a case, influences on innate and specific immunity should also decrease. Such processes will lead to relatively wide individual differences in levels of activity in the autonomic, endocrine, and immune systems. Consequently, the correspondence between autonomic activity and immune activity might be strengthened in an uncontrollable stress situation. While, this is speculation because measurement of brain activity was not conducted in this study, our previous research has documented significant activation in lateral and medial OFC under uncontrollable compared with controllable stress using position emission tomography (PET) (Ohira et al., 2004).

4.4. Limitations of the study

First, the relatively small sample size ($N = 43$) and large standard deviation in each parameter suggest that the observed effects in this study might not be robust, although they were statistically significant. Second, the levels of S-IgA secretion at baseline and after stress treatment in the current study were lower than those observed in previous studies (Willemsen et al., 1998; Ring et al., 1999). This inconsistency may be attributable to differences in the methodologies. The S-IgA assay employing ELISA in the studies of Willemsen et al. (1998) and Ring et al. (1999) measured the volume both of IgA monomer of fragment of IgA and S-IgA. However, we measured only the volume of S-IgA secreted in saliva. In addition, values of S-IgA reported in our previous experiments (Isowa et al., 2004; Kimura et al., 2005) are similar to values of S-IgA in the present study. Third, it is still unclear whether the reported results are limited for the mental arithmetic task or can be generalized for other acute stress tasks. The present findings must be replicated using other acute stress tasks and manipulations of controllability over the tasks.

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Low Control at Work and the Risk of Suicide in Japanese Men: A Prospective Cohort Study

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Key Words
Suicide · Psychological stress · Psychosocial job characteristic

Abstract
Background: Although adverse psychosocial job characteristics are suspected predictors of suicide death, prospective studies based on established stress instruments are limited. ***Methods:*** In a multicenter community-based Japanese cohort study, we prospectively investigated the association between psychosocial job characteristics and the risk of death from suicide among male workers. Baseline examination was conducted from 1992 to 1995 to determine the socioeconomic, behavioural and biological variables in addition to the psychosocial job characteristics of 3,125 male workers aged 65 and under and free from major illness. Low job control and high job demands were measured as adverse psychosocial job characteristics according to a job demand-control model questionnaire. Suicide deaths were identified using the Cause-of-Death Register. ***Results:*** During the 9-year follow-up, 14 suicides were identified. The suicide death rate was 48.1 per 100,000 person years. Multivariate analysis revealed a more than fourfold increase in the risk of suicide among men with low control at work (relative risk: 4.10; 95% confidence interval: 1.31–12.83) compared with counterpart men after adjustment for age, marital status, educational attainment, occupation, smoking status, alcohol consumption, total cholesterol level, and study area. Job demands were not associated with risk of death from suicide. ***Conclusions:*** By using a job demand-control model questionnaire, low control at work was revealed as a predictor of suicide death among Japanese male workers. The finding implies that job redesign aimed at increased worker control could be a worthwhile strategy in preventing, or at least reducing, the risk of suicide death.

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Introduction

Since 1998, more than 30,000 suicide deaths have been recorded annually in Japan. The suicide death rate among Japanese men drastically rose from 26.0 per 100,000 in 1997 to 36.5 per 100,000 in 1998 [1], mainly as a result of an increase among middle-aged men; it is suspected that the collapse of the Japanese economic bubble in the early 1990s and subsequent adverse living conditions played an important role in causing this phenomenon. Psychoso-

[1] For members, see the appendix.

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cial job characteristics are one factor affecting suicide rates [2].

Adverse psychosocial job characteristics can potentially lead to suicide via depression or psychiatric disorders. Many cross-sectional studies have revealed a positive association between adverse job characteristics and poor mental health, including major depressive episodes, depressive symptoms, and psychiatric morbidity [3–14]. Moreover, with a few exceptions [15], prospective analyses have also confirmed associations between job characteristics and subsequent burnout, depressive symptoms and psychiatric disorders [16–29]. However, to the best of our knowledge, only one study has prospectively shown that stress at work predicts suicide death [30]. In this study, work stress was assessed by asking participants to rate their experience of stress at work as minimal, light, moderate, or severe. However, such simple assessment of self-perceived stress might be too vague to be informative for suicide prevention, because it is not clear which specific sources of job stress are responsible for an increase in suicide risk.

The job demand-control model is currently the most prevalent job stress model [31]. It includes two components: psychological demands, which tap the quantitative and conflicting demands of work, and job control, which measures decision authority and skill utilization during a task. The two model components can be used to manipulate the work environment in an aim to reduce stress in the workplace [32]. The job demand-control model posits that workers with a combination of high psychological job demand and low job control are at risk of developing illnesses. The majority of studies support this hypothesis with respect to mental illness [22, 23, 25–28]. Moreover, many recent analyses have predicted an association between low control and mental health risks such as depression, revealing significant predictive associations [19, 22, 23, 25, 26, 33–37]. Low control has also been shown to explain health inequality by socioeconomic status [38]. Low control therefore seems to be a promising predictor of suicide. In this study, we investigate the extent to which psychosocial job characteristics are related to death from suicide among men in a Japanese community-based study.

Subjects and Methods

The Jichi Medical School Cohort Study

The Jichi Medical School Cohort Study began in 1992 and ultimately included 12,490 Japanese (4,911 men and 7,579 women) from 12 communities located across Japan [39]. Baseline data were collected between 1992 and 1995 using a standardized questionnaire and physical examination, which took place in each community. The questionnaire was distributed to the subjects to complete on their own before their health examination. In accordance with the provisions of the Health and Medical Service Law for the Aged, a mass screening examination program concerned with cardiovascular risk factors has been conducted in Japan since 1983. The law requires municipal governments to manage the program efficiently and offer it to all residents who are willing to participate. The target subjects vary according to each community, from all residents to those not offered physical examinations at their workplace or elsewhere, including subjects of the National Health Insurance program. Residents aged 40–69 years were the subjects for the mass screening examination program in 8 of the 12 communities, those aged 20–69 years were the subjects in one of the programs, those aged 35 years and older were included in one, and all adult residents were included in the remainder. In each community, the local government office invited all potential participants to participate by sending letters or using public information sources. The invitation mentioned that persons visiting hospitals or clinics because of cardiovascular diseases did not have to take the examination. People other than those in the initially defined age groups also participated in the study and are included in the database. The overall response rate was 65.4%.

Endpoint

The follow-up system established ensures that participants are annually contacted by direct interview or telephone/letter to determine their health status. Those who moved out of the study communities during the follow-up period remained in the study until the date of emigration. Data on emigration were obtained every year from municipal governments. Mortality data were collected from the Cause-of-Death Register at public health centers in each community with permission from the Agency of General Affairs and the Ministry of Health, Labor, and Welfare. We were able to ascertain the endpoint of all followed-up participants who died between the date of their health examination and end of 2002. The endpoint in our study comprised all cases of suicide (ICD 10th revision codes X60 to X84).

Psychosocial Job Characteristics

Job characteristics were derived at baseline using a Japanese version of the demand-control questionnaire translated from the WHO MONICA Psychosocial Study Questionnaire [40, 41]. The psychometric properties of the questionnaire have been reported elsewhere [42]. The job characteristics studied were job control and psychological demands. Job control was defined as the sum of two subscales each given equal weight: (1) skill discretion, measured using four parameters (possibility of learning new things, skills required, requirement for creativity, and the repetitious nature of the work), and (2) autonomy for decision making, measured using two parameters (right to make one's own decisions and freedom to choose the manner in which the work is performed). The second scale, psychological job demands, was defined using five parameters (speed in completing work, degree of difficulty, excessive workload, insufficient time allowed to complete the work, and conflicting demands). All questions were scored on a Likert scale of 1–4. Cronbach's coefficient alphas for the job control index and psychological demand index were 0.65

and 0.69, respectively. Job characteristics were also assessed as part of this cohort during the follow-up, demonstrating a moderate degree of stability with 5-year interval correlations of 0.63 (n = 377) for job control and 0.57 (n = 378) for job demands [43]. The variables were divided in such a way that the most adverse tertile indicated low control or high demands.

The Study Population

Since the aim of this analysis was to explore the effect of job characteristics on suicide, the study population was limited to 3,333 men with baseline ages of 65 and under who were currently working and whose occupations were defined. We excluded those with a history of cancer, myocardial infarction, and stroke. Workers without complete information on psychosocial job characteristics were also excluded. As a result, the final sample included 3,125 men.

The following occupations were included: farming and forestry (n = 960), fishery (236), security (17), transportation (87), construction (605), production (329), business (248), office work (198), professional (196), and the service industry (249). It should be noted that the sample population was not truly representative of the general working population of Japanese men. Workers engaged in farming, forestry, and fishery accounted for more than one third of the study population, among whom the health effect of psychosocial job characteristics has rarely been explored. More than 99% of the participants were employed by companies with fewer than 300 employees. According to the Industrial Safety and Health Law and related regulations in Japan, Japanese companies are required to conduct an annual health check-up of employees. For those not offered physical examinations at their workplace, such as workers with preindustrial occupations or those who are self-employed, the mass screening examination program is an opportunity to have their health status determined. As part of this cohort, we inferred from repeated surveys that changes in occupation or job position are not frequent in the rural settings included here [43]. Some part-time employees might have been included in the study population, but this was not ascertained.

The study design and procedures were reviewed and approved by each municipal government and the Ethics Committee for Epidemiological Research at Jichi Medical School. Written informed consent was obtained from all prospective participants.

Statistical Methods

Comparisons between psychosocial job characteristics and the studied variables at baseline were conducted using the χ^2 test for discrete variables and the t test for continuous variables. We counted person years of follow-up for each participant from the date of health examination to the date of death, date of emigration outside the study communities, or end of 2002, whichever occurred first. A total of 73 subjects (2.3% of the analytic cohort) moved out of the study communities during the study period and were analyzed as censored cases. The mean length of follow-up was 9.3 years and the total observed person years was 29,129. Cox's proportional hazard regression analysis was used to examine the association between psychosocial job characteristics and suicide death. The adjusted relative risks were estimated firstly after adjusting for age (<39, 40–49, 50–59, 60–65 years), occupation and study area (community), and then after adjusting for age, marital status (currently married, unmarried), educational attainment (lower or higher than the level of compulsory education), occupation, smoking status (nonsmoker, current smoker), alcohol consumption [nondrinker, <1 go daily (go, a traditional Japanese alcohol unit; 1 go = 28.9 g of alcohol), ≥1 go daily], total cholesterol and study area. Covariate variables were measured at baseline. Ordinal or nominal variables were represented by dummy variables, and serum total cholesterol was analyzed as a continuous variable. Statistical tests were two tailed. All analyses were conducted with SPSS for Windows, release 13.

Results

Of the participants free from overt major illnesses at baseline, 155 men died during the follow-up, and of these deaths, 14 were attributable to suicide. Suicide cases in this analysis ranged in age from 41 to 72 years. Three were in their 40s, 6 in their 50s, 4 in their 60s, and 1 in his 70s (median age: 55 years). Eleven of 14 cases occurred in 1998 or after, one occurred in 1993 and two in 1995. The present study showed a slightly lower suicide death rate (48.1 per 100,000 person years) than the Japanese national rate for men 40–69 years of age in 2000 (54.6 per 100,000 person years) [44]. Suicide cases were identified among farmers (n = 8), fishermen (1), businessmen (2), professional workers (1), construction workers (1) and production workers (1).

Table 1 shows the relationship between psychosocial job characteristics and the studied variables at baseline. Men reporting low job control were older, unmarried, and less educated compared with counterpart men. Among men with low job control, workers engaged in transportation and production were more prevalent, while businessmen and professional workers were less prevalent. Low job control was inversely associated with high job demands. Men with high job demands were younger, currently married, and more educated than counterpart men. Construction and production workers were more prevalent, while farmers were less prevalent among men with high demands. There were distributional differences in job characteristic levels across the studied areas. Low job control was significantly associated with a lower total cholesterol level, whereas high job demands were associated with a higher total cholesterol level.

Associations between job characteristics and suicide are presented in table 2. The incidence rate of suicide among men with low control at work (83.6 per 100,000 person years) was substantially higher than the reported Japanese national rate. Compared with counterpart men, the crude relative risk of suicide among men with low job

Table 1. Relationship between psychosocial job characteristics and the studied variables, the Jichi Medical School Cohort Study, baseline (1992/1995)

	Job control				p	Job demand				p
	low		others			high		others		
	n	%	n	%		n	%	n	%	
Age, years										
<39	145	12.5	298	15.2	<0.001	188	15.1	255	13.6	<0.001
40–49	278	24.0	641	32.6		415	33.3	504	26.8	
50–59	347	29.9	614	31.2		405	32.5	556	29.6	
60–65	389	33.6	413	21.0		239	19.2	563	30.0	
Marriage status										
Married	1,016	88.0	1,817	92.7	<0.001	1,148	92.5	1,685	89.9	0.012
Unmarried	139	12.0	144	7.3		93	7.5	190	10.1	
Education background										
Higher than compulsory	647	56.2	1,234	63.2	<0.001	775	62.8	1,106	59.2	0.046
Compulsory or lower	505	43.8	718	36.8		460	37.2	763	40.8	
Occupation										
Farming and forestry	342	29.5	618	31.4	<0.001	291	23.3	669	35.6	<0.001
Fisheries	90	7.8	146	7.4		94	7.5	142	7.6	
Business	67	5.8	181	9.2		80	6.4	168	8.9	
Office work	82	7.1	116	5.9		97	7.8	101	5.4	
Professional	44	3.8	152	7.7		96	7.7	100	5.3	
Security	15	1.3	2	0.1		1	0.1	16	0.9	
Service industry	84	7.2	165	8.4		102	8.2	147	7.8	
Transportation	71	6.1	16	0.8		28	2.2	59	3.1	
Construction	225	19.4	380	19.3		299	24.0	306	16.3	
Production	139	12.0	190	9.7		159	12.8	170	9.1	
Smoking status										
Nonsmoker	535	46.3	894	45.7	0.720	573	46.1	856	45.8	0.886
Current smoker	620	53.7	1,064	54.3		671	53.9	1,013	54.2	
Alcohol consumption										
Nondrinker	256	23.0	389	20.3	0.069	236	19.3	409	22.6	0.097
<28.9 g/day	303	27.2	588	30.6		369	30.2	522	28.8	
≥28.9 g/day	555	49.8	942	49.1		617	50.5	880	48.6	
Job demands										
High	304	26.2	943	48.0	<0.001					
Others	855	73.8	1,023	52.0						
Study area										
A	105	9.1	134	6.8	<0.001	71	5.7	168	8.9	0.001
B	208	17.9	536	27.3		291	23.3	453	24.1	
C	194	16.7	333	16.9		237	19.0	290	15.4	
D	38	3.3	61	3.1		31	2.5	68	3.6	
E	151	13.0	273	13.9		162	13.0	262	14.0	
F	142	12.3	179	9.1		150	12.0	171	9.1	
G	22	1.9	24	1.2		17	1.4	29	1.5	
H	157	13.5	212	10.8		147	11.8	222	11.8	
I	32	2.8	66	3.4		45	3.6	53	2.8	
J	35	3.0	26	1.3		16	1.3	45	2.4	
K	11	0.9	42	2.1		19	1.5	34	1.8	
L	64	5.5	80	4.1		61	4.9	83	4.4	
	Mean	SD	Mean	SD	p	Mean	SD	Mean	SD	p
Total cholesterol, mg/dl	183.3	34.6	187.2	34.1	0.003	187.2	34.4	184.7	34.2	0.047

Table 2. Incidence rates (IRs) and relative risks (RRs) of suicide by psychosocial job characteristics, the Jichi Medical School Cohort Study, 1992/1995–2002

Job characteristics	Suicide cases	IR[a]	Model 1			Model 2			Model 3		
			RR[b]	95% CI	p	RR[c]	95% CI	p	RR[d]	95% CI	p
Control											
High	5	27.2	1.00			1.00			1.00		
Low	9	83.6	3.07	1.03–9.16	0.044	4.07	1.31–12.59	0.015	4.10	1.31–12.83	0.015
Demand											
Low	10	57.4	1.00			1.00			1.00		
High	4	34.2	0.60	0.19–1.90	0.382	0.73	0.22–2.38	0.599	0.73	0.22–2.38	0.598

[a] Crude IR per 100,000 person years of follow-up.
[b] Crude RR.
[c] Adjusted for age, occupation and study area.
[d] Adjusted for age, occupation, study area, marital status, education, smoking, alcohol consumption, and total cholesterol.

control was 3.07 (95% confidence interval: 1.03–9.16). The relative risk with low job control increased after covariate variables were added to the model, and the adjusted relative risks indicated that men with low job control were more than fourfold likely to commit suicide than their counterparts. In contrast, high job demand had a rather protective but insignificant association with suicide. The crude relative risk indicated men with high job demands had a 40% lower risk of suicide than counterpart men, but adjusting for covariate variables made the association toward the null.

Discussion

A fourfold increase in risk of suicide death was revealed among men with low job control. The Nurses' Health Study prospectively showed for the first time that, compared with perceived light stress at work, suicide risk increased among women reporting severe stress [30]. This finding, which was revealed by simple assessment of self-perceived stress, therefore warranted a more extensive evaluation of work stress. In the present study, information about exposure to job characteristics was therefore obtained with a validated instrument. Psychosocial job characteristics were conceptualized using the job demand-control model, the most widely used conceptualization of unhealthy work stress in current epidemiological studies. The findings indicate that control at work is crucial for Japanese workers as previously shown among western working populations in terms of the association between low job control and mental health risk [22, 23, 25, 26, 33–35, 37]. Since modification of the work structure to give workers more control can be useful in stress reduction [32], our study provides implications for prevention of suicide death.

The age trend of suicide cases was similar to the national data on Japanese suicide mortality [44], but the present study showed a slightly lower suicide death rate for men than the reported Japanese national rate. This might be explained by the fact that follow-up of the study population started slightly before the surge of suicide deaths among Japanese men. In addition, we cannot deny the possibility that those with the worst work conditions selected to opt out of the study. Recent statistics show a high suicide incidence among men engaged in farming, forestry and fishery, administration, professional jobs, and the service industry, and a particularly increased incidence among those in the last three occupations, who are thought to suffer from the most harsh work conditions at present [45, 46]. Thus, the study population probably underrepresented the most at risk groups, other than farming, forestry, and fishery. Furthermore, a considerable number of the workers might have survived a long career. Moreover, a small at risk population (29,000) relative to the rare outcome of suicide might be vulnerable to sampling bias. Nevertheless, the adjusted relative risks of suicide among men exposed to low job control were notable, and the confidence intervals of these findings were acceptable.

Around the time when the study population was recruited, the average retirement age of Japanese employees was 63 years [47]; but some workers in the cohort are thought to have retired later because of the rather rural study setting, which included a large proportion of workers engaged in preindustrial occupations such as farming, employees of medium-small sized enterprises and self-employed individuals. Nonoccupational factors might have more strongly affected suicide, in particular among older cases, and might reflect the observed associations. However, analysis after excluding four cases who committed suicide at ages over 60 continued to reveal increased relative risks of suicide among men with low job control (crude relative risk: 3.99; 95% confidence interval: 1.03–15.43; p = 0.045, and multivariate relative risk: 6.12; 95% confidence interval: 1.45–25.82; p = 0.014, respectively).

A possible explanation for the association between low job control and suicide is that adverse job characteristics can cause depression or psychiatric disorders, which can lead to suicide [48, 49]. Well-designed prospective studies have confirmed the association between job characteristics and the risk of mental illness [19, 22, 23, 25, 26]. Another possibility is that long-term exposure to low job control leads to a sustained feeling of learned helplessness, which can make people vulnerable to stressors and in turn increase the risk of suicide [50]. Smoking, alcohol consumption and low serum total cholesterol might mediate the association between job characteristics and suicide [51–53], and thus, adjusting for these variables might lead to overadjustment. However, in this study, adjustment actually strengthened the associations. Low educational attainment, an indicator of socioeconomic status, predicted mortality in this cohort for both men and women [unpubl. data]. Moreover, in Japan, suicide among men is often associated with low socioeconomic status, including low income [54]. However, the observed association between low job control and suicide was independent of socioeconomic indicators such as education and occupation.

High job demands showed a weak protective effect with respect to suicide in the present study. This is inconsistent with the increased concern over suicide from overwork in Japan [55]. The present study related job demands at baseline with suicide during an average 9-year follow-up. As the less stable test-retest reliability indicates [43], job demands can change from time to time. Therefore, this study does not exclude the possibility that workers are at higher risk of suicide when they work extremely long hours or under extremely high job demands. It is also possible that an increase in job demands among workers whose ordinary work is less demanding is associated with a high risk of suicide. Recent observations of the unexpected associations between psychological demands and health outcome suggest the concept of psychological job demands should be more refined [56, 57]. Among a diverse population such as ours, the items of the demands scale might measure different dimensions [58]; that is, for some workers, high demands at work might imply a challenging or mentally stimulating job [57]. Another possibility is that workers with low psychological job demands might have included those with workloads reduced by redundancy [59].

A major limitation of the present study is that the prevalence of negative emotions such as depression [14] and hostility [60] was not ascertained at baseline. The observed association could be spurious if people with such tendencies exhibit a higher probability of reporting negative experiences at work [61]. Nevertheless, the protective (but insignificant) effect of job demands on suicide contradicts this conjecture. In addition, recent studies indicate that the impact of a tendency toward negative affectivity should not be overstated [26]. In the present study, the mean length of follow-up of the suicide cases was 5.6 (SD = 3.0) years. A previous 5-year follow-up study of Japanese middle-aged workers showed an association between depressive mood and subsequent suicide [62], but the actual 'induction time' was probably shorter than 5 years. It is unlikely therefore that a temporal depressive episode at baseline was responsible for an increased risk of suicide [63].

The alpha coefficient of the job control measurements was slightly low, and our exposure assessment was limited to one point in time, both of which could make the associations null. Nevertheless, the long-term stability of our measurements was shown to be statistically significant [43]. Some investigators have examined the duration or cumulativeness of exposure to adverse job characteristics, revealing the importance of cumulative job control [56, 64, 65]. The determination of death by suicide from death certificates can be problematic, since a proportion of suicides might be misclassified as deaths from other types of injury or accident. Misclassification of a suicide (that is, classification as an accident) could also bias the results towards the null.

On the other hand, our study had a number of strengths. For example, bias attributable to sample attrition is implausible as the follow-up rate was high. We excluded individuals with major illnesses at baseline, which might have influenced both the exposure (job characteristics) and outcome (the risk of suicide). Thus, selection bias due to ill subjects with certain types of jobs was unlikely. Furthermore, we took into account relevant risk factors of suicide, except factors such as low income and negative emotions.

Conclusion

Low job control was shown to be associated with an increased risk of suicide death among male workers in this Japanese community-based population. Since job control can be altered to help reduce stress in the workplace, increasing control at work could be one worthwhile strategy for preventing, or at least reducing, the risk of suicide death. Given the considerable impact of suicide on the society, the finding underlies the need for further research on the psychosocial risk factors of suicide in the workplace.

Appendix

The Jichi Medical School Cohort Study Group

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Association between Job Stressors and Heavy Drinking: Age Differences in Male Japanese Workers

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Abstract: The objective of the present study is to investigate the association between various occupational stressors and heavy drinking among male Japanese workers in different age groups. Using the Generic Job Stress Questionnaire, 13 occupational stressors and 2 workplace support indicators were assessed. The questionnaire survey was conducted of 25,104 workers, and the present study analyzed the data from 17,501 male workers. Heavy drinking was defined as weekly alcohol consumption of >275 g, and a total of 1,131 men (6.5%) were classified as heavy drinkers. After adjusting for shift work, occupational class, marital status and smoking, heavy drinking was related to "support from supervisor" for the 18–29 and 50–72 yr-old groups. For the 30–39 yr-old group, heavy drinking was related to "intragroup conflict", "job control" and "cognitive demands." For the 40–49 yr-old group, heavy drinking was related to "physical environment", "quantitative workload" and "underutilization of abilities." The present study clarified that certain occupational stressors relate to heavy drinking, and that this association varies among different age groups.

Key words: Alcohol, Stress, Workplace, Job stressor, Social support

Introduction

Numerous cross-sectional and longitudinal studies have been conducted to assess the association of occupational environment and stress with alcohol consumption, harmful drinking, and alcohol dependence[1–29]. However findings are still conflicting and inconclusive[1].

Most studies in this field have shown some association between drinking and job stress. For example, as far as cross-sectional studies are concerned, Hingson *et al.* conducted a household survey and reported that job stress was associated with mean alcohol consumption, heavy drinking, and drunkenness[2]. House *et al.* found that job tension was associated with average weekly alcohol consumption[3]. In addition, Ragland *et al.* studied urban transit operators and documented that those who often experienced job stress were likely to drink heavily[4]. As far as longitudinal studies are concerned, Crum *et al.* reported that, among men, even after adjusting for job insecurity and workplace support, alcohol dependence and abuse were associated with high-strain jobs[5].

However, Mensch *et al.* show low correlation between alcohol consumption and job stress among young men[6], and Cooper *et al.* documented no significant relationship between job pressure and alcohol consumption or problem drinking[7]. Head *et al.* also reported no significant association between objectively assessed stress and alcohol dependence among male workers by cohort study[8].

Many types of job stressors exist. Some of them have been suggested to correlate to drinking[9]. San José *et al.* reported that males and females in the range of 45–74 yr old reporting high hazardous physical working conditions

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