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Full paper

Inhibitory effects of pine nodule extract and its component, SJ-2, on acetylcholine-induced catecholamine secretion and synthesis in bovine adrenal medullary cells

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ABSTRACT

Extract of pine nodules (matsufushi) formed by bark proliferation on the surface of trees of *Pinus tabulaeformis* or *Pinus massoniana* has been used as an analgesic for joint pain, rheumatism, neuralgia, dysmenorrhea and other complaints in Chinese traditional medicine. Here we report the effects of matsufushi extract and its components on catecholamine secretion and synthesis in cultured bovine adrenal medullary cells. We found that matsufushi extract (0.0003–0.005%) and its component, SJ-2 (5-hydroxy-3-methoxy-trans-stilbene) (0.3–100 μ M), but not the other three, concentration-dependently inhibited catecholamine secretion induced by acetylcholine, a physiological secretagogue. Matsufushi extract (0.0003–0.005%) and SJ-2 (0.3–100 μ M) also inhibited ⁴⁵Ca²⁺ influx induced by acetylcholine in a concentration-dependent manner, similar to its effect on catecholamine secretion. They also suppressed ¹⁴C-catecholamine synthesis and tyrosine hydroxylase activity induced by acetylcholine. In *Xenopus* oocytes expressing α 3β4 nicotinic acetylcholine receptors, matsufushi extract (0.0003–0.001%) and SJ-2 (1–100 μ M) directly inhibited the current evoked by acetylcholine. The present findings suggest that SJ-2, as well as matsufushi extract, inhibits acetylcholine-induced catecholamine secretion and synthesis by suppression of nicotinic acetylcholine receptor-ion channels in bovine adrenal medullary cells.

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1. Introduction

Pine nodules (matsufushi) of *Pinus tabulaeformis* or *Pinus massoniana* are formed by pine bark proliferation at places on the trunk or limbs that have undergone damage, either by pests or physical injury. The effective curative components in the matsufushi have been used as an analgesic for joint pain, rheumatism, neuralgia,

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dysmenorrhea and other complaints in Chinese traditional medicine.¹ Previous studies reported that the oxidation products of oleum terebinthinae have been reported to protect conscious guinea pigs against histamine-induced bronchoconstriction.² α -Pinene, a natural compound isolated from pine needle oil, has antiliver cancer cell growth activity.³

In the human body, the most abundant catecholamines are adrenaline, noradrenaline, and dopamine, all of which are produced from phenylalanine and/or tyrosine. Catecholamines are produced mainly in the chromaffin cells of the adrenal medulla, the postganglionic fibers of the sympathetic nervous system, and the

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central nervous system. Catecholamines play very important roles in modulating heart rate, blood pressure, and blood glucose levels, and in the general reactions of the sympathetic nervous system.⁴

Adrenal medullary cells are derived from embryonic neural crests and share many properties with sympathetic postganglionic neurons. In cultured bovine adrenal medullary cells, there are at least three distinct types of ionic channels involved in catecholamine secretion⁵: nicotinic acetylcholine receptor (nAChR)-ion channels, voltage-dependent Na⁺ channels, and voltage-dependent Ca²⁺ channels. ACh induces Na⁺ influx via nAChR-ion channels, and then it induces Ca²⁺ influx and subsequent catecholamine secretion.⁵ Veratridine and high K⁺ stimulate voltage-dependent Na⁺ channels and voltage-dependent Ca²⁺ channels, respectively, which also induce catecholamine secretion from the cells. On the other hand, stimulation of catecholamine synthesis induced by ACh is associated with the activation of tyrosine hydroxylase, the ratelimiting step of catecholamine biosynthesis⁶ in cultured bovine adrenal medullary cells.⁷ Adrenal medullary cells are a good model for the detailed analysis of a drug's actions on catecholamine secretion and synthesis.^{8,9}

Previous studies have reported that pine oil extract has analgesic and antitumor effects and a dissolving effect on gallstones.¹⁰ Extract of the oil from Siberian pine (*Pinus sibirica*) has been found to have an anti-inflammatory effect.¹¹ The pharmacological effects of matsufushi extract, however, have not been studied in the sympathetic nervous system. In the present study, we investigated the effects of matsufushi extract and compounds isolated from matsufushi extract on catecholamine secretion and synthesis. We found that matsufushi extract and SJ-2, but not the other three components, inhibited ACh-induced catecholamine secretion and synthesis by suppression of nAChR-ion channels in the cell.

2. Materials and methods

2.1. Materials

Oxygenated Krebs–Ringer phosphate (KRP) buffer was used throughout. Its composition is as follows (in mM): 154 NaCl, 5.6 KCl, 1.1 MgSO₄, 2.2 CaCl₂, 0.85 NaH₂PO₄, 2.15 Na₂HPO₄, and 10 glucose, adjusted to pH 7.4. Drugs and reagents were obtained from the indicated sources as followings: Eagle's minimum essential medium (Eagle's MEM) was from Nissui Pharmaceutical (Tokyo, Japan); collagenase was from Nitta Zerachin (Osaka, Japan); calf serum was from Cell Culture Technologies (Gravesano, Switzerland). ACh and veratridine were from Sigma (St. Louis, MO, USA). L-[U-¹⁴C]Tyrosine was from American Radiolabeled Chemicals Inc. (St. Louis, MO, USA); ⁴⁵CaCl₂, ²²NaCl, and L-[1-¹⁴C]tyrosine from Perkin–Elmer Life Sciences (Boston, MA, USA).

2.2. Isolation and purification of ethanol extracts from matsufushi

Pine nodules (matsufushi) of *Pinus tabulaeformis carr.* were purchased from Anguoshi Tongli Herbal Medicine CO., Ltd. (Lot No. songje201206) (Anguo, Hebei, China). SJ-2 (5-hydroxy-3-methoxytrans-stilbene), SJ-3 (Stigmast-5-en-3-ol), SJ-4 (Phenol, 3-[(1E)-2-(4-hydroxyphenyl)ethenyl]-5-methoxy) and SJ-16 (15- hydroxydehydroabietic acid) were purified from matsufushi by high performance liquid chromatography (HPLC) (Waters, Milford, Massachusetts, USA). In brief, baked and crushed, the pine nodule powder was dissolved in pure water and filtered through a fiber membrane to remove macro-impurities. The filtrate was concentrated by gradually extracting with petroleum ether. The final extract was dissolved in 95% ethanol in the rest and used for the present study as matsufushi extract. The extract of matsufushi (100 g) was subjected to silica gel column chromatography (Qingdao Haiyang Chemical Co., Ltd., Qingdao, Shandong, China) $[CH_2Cl_2-EtOAc-MeOH (8:1:0.1 \rightarrow 0:0:100), v/v/v]$ to give eleven fractions (Fr. A1-11). Fraction A1 (15.4 g) was subjected to silica gel chromatography [petroleum ether-EtOAc-MeOH column $(12:1:0.1 \rightarrow 10:1:0.1, v/v/v)$] to yield 5 fractions (Fr. A1-1–5). Fraction A1-3 (2.8 g) was purified by Sephadex LH-20 (MeOH) to yield SJ-2 (5-hydroxy-3-methoxy-trans-stilbene) (500 mg). Fraction A2 (3.5 g) was separated by silica gel column chromatography [petroleum ether-EtOAc-MeOH (12:1:0.1 \rightarrow 4:1:0.1, v/v/v)] to yield 6 fractions (Fr. A2-1-6). SJ-3 (Stigmast-5-en-3-ol) (11 mg) was obtained from Fr. A2-5 (20 mg) through recrystallization method. Fraction A2-7 (50 g) was subjected to Sephadex LH-20 (MeOH) to yield SJ-4 (Phenol, 3-[(1E)-2-(4-hydroxyphenyl)ethenyl]-5methoxy) (20 mg). Fraction A5 (11 g) was separated by silica gel column chromatography [petroleum ether-acetone (9:2 \rightarrow 3:2, v/ v)] to yield 12 fractions (Fr. A5-1–12). Fraction A5-12 (45 mg) was subjected to Sephadex LH-20 (MeOH) to yield SJ-16 (15-hydroxydehydroabietic acid) (7 mg). We decided the molecular weights of SJ-2, SJ-3, SJ-4, and SJ-16 by fast atom bombardment mass spectrometry (FAB-MS) (Micromass Co., Manchester, UK), 9.4T Apex Qe high-resolution-electrospray ionization-mass spectrometry (HR-ESI-MS) (Bruker Co., Karlsruhe, GER) and 9.4T Apex Qe quantum field theory-mass spectrometry (Q-FT-MS) (Bruker Co., Karlsruhe, GER). Their chemical structures of SJ-2, SJ-3, SJ-4, and SJ-16 were determined by the nuclear magnetic resonance (NMR) spectra which were recorded with Varian UNITYINOVA 600 at 599.8 (1H) and 150.8 MHz (13C) (Varian, Inc. CA, USA), chemical shifts given in δ [ppm] with tetramethylsilane (TMS) as internal standard. We identified the structures of SI-2, SI-3, SI-4, and SI-16 as 5-hvdroxy-3-methoxy-trans-stilbene. Their structures are shown in Fig. 3. Matsufushi extract, SI-2, and other compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and then diluted in a reaction medium before use at a final DMSO concentration not exceeding 0.5%, unless otherwise specified.

2.3. Isolation and primary culture of bovine adrenal medullary cells

Bovine adrenal glands, the medullary cells were isolated by collagenase digestion according to the method as reported previously.¹² The cells were plated at a density of 4×10^6 cells/dish (35 mm dish; Falcon, Becton Dickinson Labware, Franklin Lakes, NJ, USA) or 10^6 cells/well (24-well plate; Corning Life Sciences, Lowell, MA, USA).

2.4. Catecholamine secretion from cultured bovine adrenal medullary cells

Catecholamines were measured as described previously.¹² After preincubated with or without matsufushi (0.0001–0.005%), SJ-2 (0.3–100 μ M) or other components (10 μ M) at 37 °C for 10 min, cells (10⁶/well) were incubated with or without matsufushi (0.0001–0.005%), SJ-2 (0.3–100 μ M) or other components (10 μ M) in the presence or absence of various secretagogues (300 μ M ACh, 100 μ M veratridine or 56 mM K⁺) at 37 °C for another 10 min. Catecholamines (noradrenaline and adrenaline) secreted into the medium were measured.¹²

2.5. $^{45}Ca^{2+}$ influx by the cells

After preincubation with or without matsufushi extract (0.0001–0.005%) or SJ-2 (0.3–100 μ M) at 37 °C for 10 min, cells (4 × 10⁶/dish) were incubated with 1.5 μ Ci of ⁴⁵CaCl₂ at 37 °C for 5 min with or without 300 μ M ACh and matsufushi (0.0001–0.005%) or SJ-2 (0.3–100 μ M) in KRP buffer. The influx of ⁴⁵Ca²⁺ was measured, as reported previously.⁵

2.6. ¹⁴C-catecholamine synthesis from $[^{14}C]$ tyrosine in the cells

For measurement of $^{14}\text{C-Catecholamine synthesis, cells}(4\times10^6/\text{dish})$ were incubated with 20 μ M L-[U- ^{14}C]tyrosine (1.0 μ Ci) in KRP buffer in the presence or absence of various concentrations of matsufushi extract (0.0001–0.005%) or SJ-2 (0.3–100 μ M) and 300 μ M ACh at 37 °C for 20 min after preincubation for 10 min. $^{14}\text{C-Catecholamines}$ in the cells were separated using a Duolite C-25 columns (H+-type, 0.4 \times 7.0 cm) and counted for the radioactivity.⁷

2.7. Tyrosine hydroxylase activity

After preincubation for 10 min, cells with or without matsufushi extract (0.0001–0.005%) or SJ-2 (0.3–100 μ M) and 300 μ M ACh were exposed to 200 μ l of KRP buffer, supplemented with 18 μ M L-[1-¹⁴C]tyrosine (0.2 μ Ci) for 10 min at 37 °C. Tyrosine hydroxylase activity was measured to absorb the ¹⁴CO₂ released by the cells, and the radioactivity was counted.⁹

2.8. Expression of $\alpha 3\beta 4$ nAChRs in Xenopus oocytes and electrophysiological recordings

Isolation and microinjection of *Xenopus* oocytes was performed as previous studies.⁹ The cDNAs encoding the α 3 and β 4 subunits of rat neuronal nAChR were kindly provided from Dr. James W. Patrick (Division of Neuroscience, Baylor College of Medicine, TX, USA). Adult female *Xenopus laevis* frogs were obtained from Kyudo Co., Ltd. (Saga, Japan). cRNAs of α 3 and β 4 subunits were co-injected at a same ratio (10–20 ng/50 nL) into *Xenopus* oocytes, and electrophysiological recordings were performed 2–6 days after injection. Each oocytes was placed in a 100 µl recording chamber and perfused at 2 ml/min with extracellular Ringer solution (110 mM NaCl, 2.5 mM KCl, 10 mM HEPES, 1.8 mM BaCl₂, pH 7.5) containing 1.0 µM atropine, as previously reported.⁹ We examined the effects of matsufushi or SJ-2 on a concentration of ACh that produced 50% of the maximal effect (EC₅₀ = 0.2 mM) of ACh.

2.9. Statistical analysis

All experiments were performed in duplicate or triplicate, and each experiment was repeated at least three times. All values are given as means \pm SEM. The significance of differences between means was evaluated using one-way analysis of variance (ANOVA). When a significant F value was found by ANOVA, Tukey's test for multiple comparisons was used to identify differences among the groups. Values were considered statistically different when *P* was less than 0.05. Statistical analyses were performed using PRISM for Windows version 5.0J software (Abacus Concept, Berkeley, CA, USA).

3. Results

3.1. Inhibitory effects of matsufushi extract on basal and various secretagogue-induced catecholamine secretion in adrenal medullary cells

ACh (300 μ M), an agonist of nAChRs, caused catecholamine secretion corresponding to 17.76 \pm 0.22% of total catecholamines in the cells (Fig. 1). When the cells were treated with matsufushi extract at 0.001% for 10 min, the catecholamine secretion induced by ACh was reduced to 14.14 \pm 0.62%. Veratridine (100 μ M), an activator of voltage-dependent Na⁺ channels, and 56 mM K⁺, which depolarizes cell membranes and then activates voltage-dependent Ca²⁺ channels, also caused catecholamine secretion corresponding to 27.13 \pm 0.41% (Fig. 1) and 14.72 \pm 0.60% (Fig. 1) of

the total catecholamines, respectively. Matsufushi extract at 0.001% had little effect on basal or veratridine- and 56 mM K⁺-induced catecholamine secretion (Fig. 1).

3.2. Effects of various concentrations of matsufushi extract on AChinduced catecholamine secretion and ${}^{45}Ca^{2+}$ influx

The effects of matsufushi extract on ACh-induced catecholamine secretion and ${}^{45}Ca^{2+}$ influx were examined. Matsufushi extract (0.0001%–0.005%) significantly inhibited ACh-induced secretion of catecholamines (Fig. 2A). Matsufushi extract also concentration-dependently inhibited ACh-induced ${}^{45}Ca^{2+}$ influx (Fig. 2B). The half-maximal inhibitory concentrations (IC₅₀ values) of matsufushi in catecholamine secretion and ${}^{45}Ca^{2+}$ influx were calculated to be 0.0025% and 0.0013%, respectively.

3.3. The structures of four compounds isolated from matsufushi extract

Four compounds, SJ-2, SJ-3, SJ-4 and SJ-16, were isolated from matsufushi extract. The structures of these four compounds are shown in Fig. 3.

3.4. Effects of the four compounds on catecholamine secretion induced by ACh

When the cells were treated with each compound or their mixture at 10 μ M for 10 min, SJ-2 and the mixture of four compounds (Mix4) strongly reduced the catecholamine secretion induced by ACh (14.58 \pm 0.18% of total catecholamines) to 8.39 \pm 0.32% and 6.40 \pm 0.15% of the total, respectively, whereas the other three had little effect (Fig. 4).

3.5. Concentration-inhibition curves for the effects of SJ-2 on AChinduced catecholamine secretion and ${}^{45}Ca^{2+}$ influx

Treatment of cells with SJ-2 $(0.3-100 \ \mu\text{M})$ significantly inhibited ACh-induced secretion of catecholamines (Fig. 5A). SJ-2 also



Fig. 1. Effects of matsufushi extract on catecholamine secretion induced by various secretagogues in cultured bovine adrenal medullary cells. After preincubation of cells with or without matsufushi extract (0.001%) for 10 min, the cells (10⁶/well) were incubated with or without matsufushi extract (0.001%), ACh (300 μ M), veratridine (100 μ M) or 56 mM K⁺ for another 10 min at 37 °C. Catecholamines secreted into the medium were expressed as a percentage of the total catecholamines in the cells. Data are means \pm SEM from three separate experiments carried out in triplicate. "P < 0.01, compared with ACh alone.

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inhibited ACh-induced $^{45}\text{Ca}^{2+}$ influx in a concentration-dependent manner (Fig. 5B). The half-maximal inhibitory concentrations (IC₅₀ values) of SJ-2 in catecholamine secretion and $^{45}\text{Ca}^{2+}$ influx were determined to be 10.3 and 10.0 μM , respectively.

3.6. Effects of matsufushi extract and SJ-2 on ACh-induced response in $\alpha 3\beta 4$ nAChRs expressed in Xenopus oocytes

As shown in Fig. 6A and C, matsufushi extract and SJ-2 reversibly inhibited ACh (0.2 mM)-induced Na⁺ currents. Matsufushi extract (0.00003%–0.001%) (Fig. 6C) and SJ-2 (1–100 μ M) (Fig. 6D) significantly suppressed those currents. The half-maximal inhibitory concentrations (IC₅₀ values) of matsufushi extract and SJ-2 were found to be 0.00019% and 3.12 μ M, respectively.

3.7. Inhibitory effect of matsufushi extract and SJ-2 on ¹⁴Ccatecholamine synthesis and tyrosine hydroxylase activity

ACh (300 μ M) increased the synthesis of ¹⁴C-catecholamines from [¹⁴C]tyrosine about two-fold in bovine adrenal medullary cells. Treatment of cells with matsufushi extract and SJ-2 inhibited the stimulatory effect of ACh on ¹⁴C-catecholamine synthesis at concentrations of 0.001% and 0.003%, and 10 and 30 μ M, respectively (Fig. 7A). SJ-2, but not matsufushi extract, slightly but significantly inhibited the basal synthesis of ¹⁴C-catecholamines.

Matsufushi extract (0.001% and 0.003%) and SJ-2 (10 and 30 μ M) inhibited the tyrosine hydroxylase activity induced by ACh (Fig. 7B). SJ-2 also slightly inhibited the basal enzyme activity.

4. Discussion

Matsufushi are the nodules formed by pine bark proliferation at the sites of surface damage to a pine tree. In the present study, we examined the effects of matsufushi extract and its components, SJ-2, SJ-3, SJ-4, and SJ-16, on catecholamine secretion and ⁴⁵Ca²⁺ influx. We demonstrated that matsufushi extract and SJ-2, but not



Fig. 3. Chemical structures of SJ-2, SJ-3, SJ-4, and SJ-16.

the other three components, inhibited the secretion and synthesis of catecholamines induced by ACh in cultured bovine adrenal medullary cells. To the best of our knowledge, this is the first direct evidence of the inhibitory effects of matsufushi extract and its component SJ-2 on the catecholamine system.

4.1. Inhibitory effects of matsufushi extract and SJ-2 on AChinduced catecholamine secretion

Matsufushi extract significantly inhibited the catecholamine secretion induced by ACh, but not that induced by veratridine or 56 mM K⁺ in adrenal medullary cells. Our previous study⁵ reported that ACh and veratridine activated nAChR-ion channels and voltage-dependent Na⁺ channels, respectively, which, in turn, caused Na⁺ influx, subsequent Ca²⁺ influx, and finally catecholamine secretion. Addition of 56 mM K⁺ depolarizes cell membranes



Fig. 2. Effects of matsufushi extract on catecholamine secretion (A) and ${}^{45}Ca^{2+}$ influx (B) induced by ACh. (A) After preincubation for 10 min with or without matsufushi extract (0.0003–0.005%), cells were stimulated with ACh (300 μ M) in the presence or absence of matsufushi extract (0.0003–0.005%) for another 10 min at 37 °C. Catecholamines secreted into the medium were expressed as a percentage of the total catecholamines in the cells. (B) After preincubation for 10 min, cells were stimulated with ACh (300 μ M) and 1.5 μ Ci of ${}^{45}CaCl_2$ in the presence or absence of matsufushi extract (0.0003–0.005%) for another 5 min at 37 °C. ${}^{45}Ca^{2+}$ influxwas measured, and was expressed as nmol/4 × 10⁶ cells. Data are means ± SEM from three separate experiments carried out in triplicate. ${}^{*}P < 0.05$, ${}^{**}P < 0.001$, compared with ACh alone.

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Fig. 4. Effects of SJ-2, SJ-3, SJ-4, SJ-16, and their mixture on catecholamine secretion induced by ACh in cultured bovine adrenal medullary cells. After preincubation of cells with or without SJ-2 (10 μ M), SJ-3 (10 μ M), SJ-4 (10 μ M), C-16 (10 μ M) and their mixture (Mix 4) (10 μ M) for 10 min, the cells (10⁶/well) were incubated with or without each compound and their mixture for another 10 min at 37 °C. Catechol-amines secreted into the medium were expressed as a percentage of the total catecholamines in the cells. Data are means \pm SEM from three separate experiments carried out in triplicate. ****P* < 0.001, compared with ACh alone.

and activates voltage-dependent Ca²⁺ channels. In the present study, matsufushi extract had little effect on veratridine- and 56 mM K⁺-induced catecholamine secretion. Therefore, matsufushi extract seems to inhibit nAChR-ion channels but not voltage-dependent Na⁺ channels or voltage-dependent Ca²⁺ channels. Matsufushi extract and its component SJ-2 inhibited the Ca²⁺ influx induced by ACh in a concentration-dependent manner, which was similar to their effects on catecholamine secretion. Ca²⁺ plays an important role as the coupler in stimulus-secretion coupling.¹³ From these findings, it is likely that matsufushi extract and SJ-2 inhibit catecholamine secretion by suppressing the Ca²⁺ influx induced by ACh.

4.2. Structure—activity relationship of SJ-2 for inhibition of nAChRion channels

We used four compounds isolated from matsufushi extract. Of these, only SJ-2 inhibited the functioning of nAChR-ion channels. SJ-2 is structurally very similar to SJ-4. SJ-4 has a hydroxyl group at the 4 position, whereas SJ-2 has nothing at this position. Judging from the differences in their structures, this result suggests that the hydroxyl group at the 4 position of SJ-4 may induce stereo-specific interference when the flavonol glycoside interacts with nAChRs. On the other hand, we previously reported that resveratrol (trans-3, 4', 5-trihydroxystilbene), a grape polyphenol, inhibits catecholamine secretion induced by ACh, veratridine, and 56 mM K⁺ (IC₅₀ = 20.4, 11.0, and 62.8).⁹ The chemical structure of resveratrol (stilbene) is very similar to those of SJ-2 and SJ-4 whereas resveratrol has three hydroxyl groups at the 3, 4', and 5 positions. More information, however, will be needed to clarify the structural relation between the inhibitory effect of SJ-2 and the function of the ion channels.

4.3. Inhibitory mode of matsufushi extract and SJ-2 on the AChinduced inward current in Xenopus oocytes expressing $\alpha 3\beta 4$ nAChRs

To study the mechanism by which matsufushi extract and SJ-2 inhibit the ACh-induced catecholamine secretion and ACh-induced ⁴⁵Ca²⁺ influx, we examined their direct effect on ACh-induced currents in *Xenopus* oocytes expressing $\alpha 3\beta 4$ nAChRs. Matsufushi extract and SJ-2 directly inhibited the Na⁺ current in a concentration-dependent manner, suggesting that matsufushi and SJ-2 suppress ACh-induced catecholamine secretion and Ca²⁺ influx via inhibiting nAChR in adrenal medullary cells.

4.4. Inhibitory effect of matsufushi extract and SJ-2 on catecholamine synthesis and tyrosine hydroxylase activity

Matsufushi extract and SJ-2 inhibited ACh-induced catecholamine synthesis and ACh-induced tyrosine hydroxylase activity in



Fig. 5. Effects of SJ-2 on catecholamine secretion (A) and ${}^{45}Ca^{2+}$ influx (B) induced by ACh. (A) After preincubation for 10 min with or without SJ-2 (0.3–100 μ M), cells were stimulated with ACh (300 μ M) in the presence or absence of SJ-2 (0.3–100 μ M) for another 10 min at 37 °C. Catecholamines secreted into the medium were expressed as a percentage of the total catecholamines in the cells. (B) After preincubation for 10 min, cells were stimulated with ACh (300 μ M) and 1.5 μ Ci of ${}^{45}CaCl_2$ in the presence or absence of SJ-2 (0.3–100 μ M) for another 5 min at 37 °C. ${}^{45}Ca^{2+}$ influx was measured, and was expressed as nmol/4 × 10⁶ cells. Data are means ± SEM from three separate experiments carried out in triplicate. **P* < 0.05 and ****P* < 0.001, compared with ACh alone.

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Fig. 6. Effects of matsufushi extract and SJ-2 on peak ACh-induced inward currents in *Xenopus* oocytes expressing rat α 3 β 4 nAChRs. Representative traces from a single *Xenopus* oocyte are shown. The currents of matsufushi extract (Fig. 6A) and SJ-2 (Fig. 6C)-treated oocytes were recorded for 10 min after recording of the control currents, and the washout currents were obtained at 10 min after matsufushi extract and SJ-2 treatment. Matsufushi extract (0.0001%) and SJ-2 (10 μ M) suppressed the currents induced by the EC₅₀ (0.2 mM) of ACh, and the inhibitory effects were reversible. Concentration-response curve for the inhibitory effects of matsufushi extract (Fig. 6B) and SJ-2 (Fig. 6D) on ACh-induced currents. The peak current amplitude in the presence of matsufushi extract and SJ-2 was normalized to that of the control and the effects are expressed as percentages of the control. Data are presented as means \pm SEM from four separate experiments carried out in triplicate. **P* < 0.05 and ****P* < 0.001, compared to the control. Nonlinear regression analysis was performed and the mean values of IC₅₀ for matsufushi and SJ-2 are 0.00019% and 3.116 μ M, respectively.

the bovine adrenal medulla cells. It is well-known that Ca^{2+} plays an important role as a coupler in stimulus-synthesis coupling.⁷ In the present study, we observed that matsufushi extract and SJ-2 suppressed the ⁴⁵Ca²⁺ influx by inhibiting nAChR-ion channels. Therefore, it is likely that matsufushi extract and SJ-2 inhibit the catecholamine synthesis and tyrosine hydroxylase activity induced by ACh via the suppression of Ca²⁺ influx in cultured bovine adrenal medulla cells.

4.5. Pharmacological significance of the inhibitory effects of matsufushi extract and SJ-2 on the catecholamine system

Although the human serum concentrations of matsufushi extract and SJ-2 have not been reported yet, extracts of *P. massoniana* bark (140 μ g/ml = 0.014%) showed an anti-metastatic effect in Hela cells.¹⁴ In addition, ethanol extracts of *Pinus densiflora Sieb. et Zucc.* (100 μ g/ml = 0.01%) were shown to alleviate lipogenesis and oxidative stress during oleic acid-induced steatosis in HepG2 cells.¹⁵ In *in vivo* studies, *Pinus sibirica* oil extracts administered orally at a dose of 300 mg/kg showed anti-inflammatory effects.¹¹ In the near future, it should be clarified whether SJ-2 used in the

present study would be relevant as potential supplements for human health.

Although catecholamines play an important role in the regulation of normal function in the central and peripheral sympathetic nervous systems, strong and prolonged stress causes their release in massive amounts, which can lead to cardiovascular diseases such as hypertension, atherosclerosis, coronary heart disease, and heart failure.^{4,16} Chronic heart failure is reported to be associated with the activation of the sympathetic nervous system as manifested by increased circulating catecholamines.^{4,17} Furthermore, the stress hormone adrenaline stimulates β_2 -adrenoceptors, an effect that in turn activates the Gs protein/cyclic AMP-dependent protein kinase and the β -arrestin-mediated signaling pathway, reduces the p53 level, and induces DNA damage.¹⁸

Our recent review¹⁶ and studies reported that daidzein, a soy isoflavone,¹⁹ nobiletin, a citrus polymethoxy flavones,²⁰ and ikarisoside A, a natural flavonol glycoside derived from plants of the genus *Epimedium*,²¹ suppress the secretion and synthesis of catecholamines induced by ACh in cultured bovine adrenal medullary cells. The present findings would support the idea that matsufushi extract and its constituent SJ-2 suppress the induction of catecholamine system hyperactivity by strong stress or emotional

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Fig. 7. Effects of matsufushi extract and SJ-2 on ¹⁴C-catecholamine synthesis from [¹⁴C]tyrosine (Fig. 7A) and tyrosine hydroxylase activity (Fig. 7B) in the cells. After preincubation for 10 min with or without matsufushi extract and SJ-2, cells (4×10^6 /dish) were incubated with L-[U-¹⁴C] tyrosine (20μ M, 1 μ C) in the presence or absence of matsufushi extract (0.001 and 0.003%) and SJ-2 (10, 30 μ M) and with or without 300 μ M ACh at 37 °C for 20 min. The ¹⁴C-catecholamines formed were measured (Fig. 7A). After preincubation with or without matsufushi extract (0.001 and 0.003%) and SJ-2 (10 and 30 μ M) for 10 min, cells (10^6 /well) were incubated with L-[1-¹⁴C] tyrosine (18 μ M, 0.2 μ Ci) in the presence or absence of matsufushi extracts (0.001 and 0.003%) and SJ-2 (10 and 30 μ M) and with or without 300 μ M ACh at 37 °C for 10 min, and tyrosine hydroxylase activity was measured (Fig.7B). Data are means ± SEM from three separate experiments carried out in triplicate. ^{*}*P* < 0.05, ^{**}*P* < 0.001, compared with ACh alone or control (CON).

excitation which evokes the secretion of ACh from the splanchnic nerves. To confirm this possibility, further *in vivo* experiments will be required in the near future.

In summary, we have demonstrated that matsufushi extract and its component SJ-2 inhibit the catecholamine secretion and synthesis induced by ACh via inhibition of nAChRs-ion channels in the adrenal medulla and probably in the sympathetic neurons.

Conflicts of interest

The authors have conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jphs.2017.03.006.

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【特集 産業ストレスのバイオロジー:生物学的指標の現在と展望】

職業性ストレスの免疫学的指標 - 細胞性免疫とサイトカインを中心に

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抄録:本総説は職業性ストレスの免疫指標として、細胞性免疫と炎症マーカーに焦点を絞って現在までの 知見を整理したものである。これまでに蓄積された研究を概観した結果、職業上の心理社会的ストレスへ の曝露(高い要求度,低い裁量権,高い仕事のストレイン、低い職務満足感,高い努力報酬不均衡,オーバー コミットメント、失業、長時間残業)はNK細胞活性やNK細胞数の低下ならびに炎症マーカーの亢進に 測定しうる程度の影響をもたらすことが判明した。その結果、職業上の心理社会的ストレスは細胞性免疫 と炎症マーカーに負の影響をもたらすことが示されたが、因果関係をより明確化する研究や職業性ストレ スに対してより鋭敏で利用しやすい指標の開発が必要であることが示された。

Key words: Job stress (職業性ストレス), Inflammatory marker (炎症マーカー), cellular immunity (細胞性免疫), lymphocyte (リンパ球), Cytokine (サイトカイン), Psychosocial factor (心理社会的因子), Workers (労働者)

1. はじめに

過去30年の職業性ストレスの研究により、仕事のス トレスが健康にどのような影響を及ぼすか、多くのエ ビデンスが蓄積されてきた。最近になって、これらの エビデンスに基づきメタ分析が報告されるようになり. 職業性ストレスが様々な疾患の発症にどの程度の影響 を及ぼすかも明らかになりつつある。例えば、仕事の 要求度--コントロールモデルに基づく"仕事のストレ イン"に注目した場合、仕事のストレインが高い者は 低い者に比べ1.24倍脳卒中の発症リスク(相対危険度) が高く", 心疾患の発症リスクは1.26倍2 であること が明らにされている。同じく、2型糖尿病の発症リス クは1.29倍3. 高血圧の発症リスクは1.24倍4と報 告されている。さらに、呼吸器系では慢性閉塞性肺疾 . 患(COPD)の増悪は1.32倍⁵,うつ病の発症リスク は1.77 倍(未出版データのみでもリスクは1.27 倍で 有意)である。。一方、仕事のストレインはがん(前 立腺. 乳. 大腸)の発症⁷. 炎症性腸疾患⁸ や気管支 喘息の増悪⁹ を有意には増加させないことも報告され ている。これらのメタ分析に含まれている多くの研究 は. 欧米で行われたものを中心としているため我が国 の労働者において必ずしも当てはまるとは限らないが. 仕事のストレインという一つの指標だけをとっても多 様な疾患の発症にかかわっており. 疾患によっては明 白な影響を及ぼしていることが考えられる。

仕事のストレインはこれらの疾患の媒介因子となる 喫煙¹⁰,運動¹¹⁾,飲酒¹²⁾等の生活因子や肥満/低体 重¹³とも関連することがメタ分析によって示されてい る。例えば、喫煙者は非喫煙者よりも有意に仕事のス トレインが高く、また、仕事のストレインが高い喫煙 者は低い喫煙者に比べると1週間当たりの喫煙本数が 3本多いことが報告されており、仕事のストレインは 喫煙者の喫煙行動を促進する方向に働く¹⁰。一方、非 飲酒者や重度の飲酒者は、中等度の飲酒者よりも仕事 のストレインが高いことが横断研究の分析によって判

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図1 心理社会的職業性ストレッサーの神経・内分泌・免疫系を介しての生体への影響

注:心理社会的職業性ストレッサーは不健康な生活習慣を招き、神経・内分泌・免疫系に影響し、慢性炎 症の亢進ならびに細胞性免疫の機能の低下を導く。さらに、ネガティブ・フィードバックにより不健 康な生活習慣が強化され、精神的・身体的不調が引き起こされると考えられる。

明しているが、縦断研究の結果からは仕事のストレイ ンと飲酒の関連は明確には認められていない¹²⁾。また、 運動に関しては、仕事のストレインが高い者は運動不 足の者が多く、定期的な運動習慣があった者でもスト レインが高くなるに従って運動不足になることが示さ れている^{111,}肥満や低体重に関しては、横断的には標 準体重の者よりも低体重や肥満の者で仕事のストレイ ンが高く、縦断的には標準体重の者の仕事ストレイン が増加した場合肥満が増加し、逆に肥満であった者は 仕事ストレインの増加によって体重が低下するという 現象も認められている。これらのことから、職業性ス トレスは働く人々の健康行動を悪化させることによっ て長期的に悪影響を及ぼすものと考えられる(図1)。

さらに、最近では仕事のストレインが後年の認知症 の発症とも関連する証拠も提示されており^{14,15},仕事 のストレインが仕事から離れた後も長期間にわたって 影響することも明らかにされている。

2. 職業性ストレスと管性炎症

職業性ストレスと慢性炎症に関する研究は、主に欧 米において研究が活発に行われてきた。その理由とし て、主に白人や黒人において心理社会的ストレスとC 反応性蛋白 (C-reactive protein: CRP). インターロイ キン (Interleukin: IL) -6, TNF (腫瘍壊死因子 (Tumor Necrosis Factor: TNF) - a, 白血球数、単球数などの 炎症マーカーが中等度の相関を示し¹⁷⁾. これらの上昇 が循環器系疾患を予測する因子として有用と考えられ たからである¹⁸⁾。しかし, 黄色人種の炎症マーカー(CRP. IL-6)の値は白人や黒人に比べるとかなり低い¹⁹ こと から、欧米での知見が必ずしもアジア圏の人種に当て はまるとは限らないと考えられた。しかし、近年炎症 マーカーの一つである CRP の値が白人や黒人に比べ 低い人種(日本,中国、香港,韓国、マカオ、モンゴル、 台湾等)においても脳卒中などを予測する上で有用で あることが示されており²⁰⁾. 予測マーカーとしては信 頼性があると考えられている。

さて、職業性ストレスと炎症マーカーの関連につい ては、詳しくは本特集号の筆者の一人である江口尚先 生に譲るとして、測定結果の解釈や測定上の注意点。 数値のとらえ方についてこれまでの錐者の経験から気 付いた点をいくつか挙げておく。まず、これらの多く の研究では、炎症マーカーが1種類しか測定されてお らず、他のマーカーも並行して測定していないため結 果の解釈には十分注意が必要である。また、外れ値 (高値) があった場合に感染などの急性炎症による増 加なのか、あるいは測定上の問題(抗体のロットの違 いによる系統誤差等)なのか十分に考慮し、また、場 合によっては再測定するためにサンプルを保存してお く必要がある。逆に極端な低値は抗生物質等の薬物に よって低下している可能性もあり、検査対象者の薬物 使用の有無等についても記録し、交絡因子として考慮 する必要がある。このような対象者がいれば、解析に 含めた場合と含めない場合で結果がどのように異なる かも検討する必要があろう。疫学研究では大量のサン プルを同時測定するため、検査時にこの種の見落とし があると取り返しがつかなくなることもある。

筆者は可能な限り複数の炎症マーカーを測定し、測 定値のみの信頼性についても検討するようにしている。 男性健常者 191 名を対象に炎症マーカーを同時測定し たデータでは、高感度 CRP (hs-CRP)、IL-6 と TNFa は正の相関が認められた。スペアマンの順位相関係 数 (rs) を計算したところ、hs-CRP と IL-6 は rs=.412 (p<0.001)、hs-CRP と TNF- a は rs=.378 (p<0.001)、 IL-6 と TNF- a は rs=.436 (p<0.001) であった。異な る測定系で得られた値も得るようにすれば(この場合, hs-CRPとサイトカイン),測定値自身の信頼性も得ら れると考えられる。

その他、検査の値に関して正規分布を前提とした統 計解析を行う場合、対数変換等の変換処理を事前に行 う必要がある。対数変換によっても正規化しない場合 は、Box-Cox 変換、平方根変換や Blom's normal score 変換などによって正規分布に近づけるなどの工夫も必 要である。

3. 職業性ストレスと細胞性免疫

職業性ストレス研究において、細胞性免疫機能の測 定は比較的早くから行われていた。ナチュラル・キ ラー(Natural killer:NK)細胞活性やリンパ球幼若化 反応はリンパ球の機能を調べる上で有用であり、これ らの測定値が低ければ免疫機能の低下が疑われた。

欧米では1980年代に失業と細胞性免疫能の関連が活 発に研究され,失業直後よりも失業 12ヶ月後でリンパ 球幼若化反応が低下する現象が観察された 20。このこ とは、長引くストレスの影響が間隔を置いて免疫機能 に反映されることを示唆している。失業と NK 細胞活 性に着目した研究では、失業状態から再就職した(つ まりストレッサーが取り抜かれた)場合. 免疫機能が どのように回復するかという研究もなされている。 Cohen ら²⁰ は失業者 100 名と年齢と性別がマッチする 雇用が安定した就労者 100 名の NK 細胞活性を月1回 の割合で4ヶ月にわたって測定した。その結果、失業 者全体の NK 細胞活性は4ヶ月間一貫して就労者より も有意に低かった。経過観察の途中で就職が決まった 25 名の翌月の NK 細胞活性は前月に比べ 44-72%の 増加が認められた。この回復は生活習慣や NK 細胞率 の変化では説明されなかったことから、失業というス トレスから解放されると NK 細胞の機能は比較的速や かに回復する可能性があることが判明した。

次にNK 細胞の数と機能の両者と職業要因の関連を 検討した筆者らの一連の報告について言及する。我々 の研究では、男性労働者を対象に仕事の要求度-コン トロール-社会的支援モデルとリンパ球分画数の関連 を検討し、仕事の要求度とNK 細胞数との間に負の相 関、仕事のストレインとNK 細胞数の間に負の相関を 認めている²³。一方、社会的支援と細胞障害性 T 細胞 との間には正の相関を認めた。これらのことから職業



T=T細胞、Tc=Cytotoxic T細胞、Th1=T helper 1細胞、Th2=T helper 2細胞、IFN=Interferon

性ストレスの標的細胞は NK 細胞と推定し, 努力報酬 不均衡. 職務満足感ならびに長時間残業と NK 細胞の 関連を男女別に検討した。その結果, 男性では報酬の 低下は NK 細胞数と NK 活性の両者の低下と関連し, 努力は NK 細胞数の低下と関連した²⁰。女性では, 努 力, 報酬ならびに努力報酬不均衡はいずれも関連が認 められなかった。なお, オーバーコミットメントは男 性において弱い負の相関を示した。また, 職務満足感 は女性の NK 細胞数と NK 細胞活性の上昇と関連し, 男性は NK 細胞活性のみ上昇するという結果を得た²⁰。 さらに, 長時間の残業は NK 細胞数と負の相関を示す ことも示された²⁰。

これら一連の結果から、様々なストレスモデルに基 づく職業性ストレスの変数や労働時間はNK細胞と関 連するこどが判明し、NK細胞は職業性ストレスの免 疫指標として有用である可能性が示された。しかし、 これらの指標を健診などに取り入れるには実際上の問 題もある。例えば、NK細胞活性の測定には1検体に つき少なくとも5-7ml程度の全血が必要であり、リ ンパ球幼若化反応も同時に測定するとなると同じ程度 の量の血液量が必要になる。そうなると検査対象者の 負担は多く.健診などでは実用的ではない。その点を 考慮すると.細胞性免疫指標としては l ml 未満の血液 量で測定が行える NK 細胞数がより妥当と思われる。

健診の測定項目として取り入れることを考える場合. 血清 50μ1程度でサイトカインを一括して測定できる マルチプレックスサスペンションアレーというシステ ムも確立されていることから、複数の炎症性サイトカ インや抗炎症性サイトカインを同時測定する方が実用 上有用かもしれない。

なお,これまでに述べた知見を図として整理したも のを示す(図2)。

まとめ

本稿では、職業性ストレスと細胞性免疫、炎症マー カーとの関連について最新の知見を整理した。その結 果、過剰な仕事のストレスはNK細胞性の機能を抑制 し、炎症マーカーの増加を促すことが示唆された。し かし、産業保健の現場でこの知見を応用・利用するに はいくつかの課題が残されている。例えば、これまで の研究から、集団レベルにおいて過剰なストレスは免 疫機能を抑制することが判明しているが、個人単位で

図2 心理社会的職業性ストレッサーの細胞性免疫と炎症マーカーへの影響

みた場合、免疫系の抑制が仕事要因によるのか、それ とも仕事外要因によるのか、あるいは個人の遺伝的・ 素質的要因なのかの判別が難しい。また、ストレスの 影響が免疫系に対して同時期に反映されていれば因果 関係を理解しやすいが、急性ストレスでは免疫機能は 増強され、慢性ストレスによって抑制されることから、 免疫系に反映されるまでに時間差があることなどか ら、結果の解釈が難しい面もある。さらに、免疫指標 の測定はコストが高いこと、様々な測定条件を整えな ければならないという課題もある。そのため、ストレ スを鋭敏に定量化でき、現在よりも安価でリアルタイ ム (point-of-care) な測定が可能なマーカーの探索や測 定機器の開発が望まれる。これらの課題を踏まえて、 今後新たな知見が集積されることが期待される。

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Immune markers for job stress research: A focus on inflammatory and cellular immune markers

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Abstract The purpose of this review was to provide current knowledge about the possible association between psychosocial job stress and immunity focusing on inflammatory and cellular immune markers. In general, exposure to psychosocial job stressors (high job demands, low job control, high job strain, low job satisfaction, high effort-reward imbalance, over-commitment, unemployment, and excessive overtime) had a measurable impact on immune parameters including reduced NK cell activity and NK cell counts, and increased inflammatory responses. The evidence supports that psychosocial job stresses are related to disrupted immune responses but further research is needed to demonstrate cause-effect relationships and develop more sensitive and usable markers.

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【特集 産業ストレスのバイオロジー:生物学的指標の現在と展望】

毛髪・爪試料を利用した慢性的・蓄積的なストレスホルモン分泌の評価: 産業ストレス研究における展望

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抄録:ストレスホルモンとして知られているコルチゾールは心理社会的なストレスと冠動脈疾患やうつな どの疾患を結びつける生物学的なメカニズムとして考えられている。本総説では毛髪や爪の試料からのコ ルチゾールの評価について紹介した。毛髪や爪のコルチゾールは過去に遡って数か月,あるいは数週間に わたるホルモン産生を反映していると考えられている。職場環境における心理社会的ストレスと毛髪・爪 コルチゾールの関連を調べた研究はわずかな数であった。毛髪や爪の試料は職業性ストレスと健康の生物 学的なメカニズムを探索する上で大いに役に立つと考えられ,さらなる研究が必要である。

Key words: cortisol (コルチゾール), hair (毛髪), fingernail (爪), job stress (職業性ストレス)

1. コルチゾールと職業性ストレス

職場環境における心理社会的ストレスが健康を阻害 することが欧米では多く報告されている。その傾向は 日本においても同様であり、最近では、いくつかのコ ホート研究によって、職業性ストレスは脳血管疾患の 発症やうつなどのメンタルヘルスの悪化に関与してい ることが報告されている¹⁻³。

それとあわせて、職業性ストレスと健康を結びつけ る生物学的メカニズムについても多くの研究がおこな われている。そのうち、有力なものの一つにコルチ ゾールをあげることができる。コルチゾールは副腎皮 質から放出されるステロイドホルモンであり、急性の ストレスは血中や唾液中のコルチゾール濃度を増加さ せることが一般的に知られている4。また、それと同 時にコルチゾールは、免疫系、血管系、中枢神経系に 対して様々な生理的作用を有すことも知られており55、 また、精神疾患や心臓血管疾患との関わりも報告され ている⁶。そのようなことから、コルチゾールはスト レスと病気を結びつけるホルモンとして注目されてき ている。

職業性ストレスとコルチゾールの関連は過去に多く 調べられている。例えば、井澤ら⁷は、仕事の要求度 ーコントロールモデルと努力一報酬不均衡モデルによ り評価された職業性ストレスとコルチゾールの関連に ついて系統的なレビューを行っている。それによる と、仕事の要求度一コントロールモデルと唾液中コル チゾールの増加の関連は比較的一貫した傾向としては 観察されたものの、全体的には、関連を認めない結果 や逆に負の関連性を認める研究成果も報告されてお り、両者の間に一貫した関連性を認めているとは言い 難い状況である。

このような状況の原因としていくつかの点をあげる ことができる。一つの大きな問題は日内変動であり, コルチゾールは起床後に高く,夜にかけて徐々に低下 することがわかっている。したがって,コルチゾール

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の測定値は測定時刻や起床時刻による影響が大きく, この誤差が結果を大きく左右している可能性が考えら れる。また,急性ストレスの問題もあり,例えば,試 料の採取の前に一過性のストレスとなるような出来事 があった場合,このストレスによる影響が職業性スト レスの影響に混在してしまう可能性が考えられる。別 の問題としては,コルチゾールの評価の回数をあげる ことができる。職業性ストレスのような慢性的なスト レスと対応させるのであれば,コルチゾールを長期間 にわたって複数回評価するのが望ましいが,多くの研 究(特に血液サンプルを扱った研究)では,単回,あ るいは同一日に複数回コルチゾールを評価するにとど まっている。

2. 毛髪のコルチゾール

血液や唾液のサンプルに関する前述のような点を考 慮して,近年では毛髪に含まれるコルチゾールに注目 が集まっている。もとはスポーツ選手のステロイドな どの薬物使用の判別のために注目されていた方法であ るが,これをステロイドホルモンの一種であるコルチ ゾールに利用した形である。毛髪は,形成される際に 毛細血管からコルチゾールを含むステロイドが拡散す ると考えられている(図1)。毛髪は1か月で約1cm 伸びるため,例えば,根元から3cmの部分の毛髪に 含まれるコルチゾールは,3か月間に蓄積されたコル チゾールを表すといわれている。毛髪は過去のコルチ ゾール分泌の"記録媒体"として考えられている。

初期のパイロット研究では、例えば、失業¹⁰ や介 護¹¹⁾ などの慢性的なストレスを経験している人におい ては、毛髪のコルチゾール濃度が高いことが報告され ている。また、大うつ病¹²⁾ や急性心筋梗塞¹³⁾ との関 連も報告されている。

職業性ストレスとの関連については、研究数は多く ないものの、いくつかの結果が報告されている。 Manenschijn ら¹⁴は33名の交代勤務労働者と89名の 日勤労働者を比較し、交代勤務労働者では毛髪コルチ ゾールが高かったことを報告している。Steinisch ら¹⁵⁾ は衣料品工場の175名の労働者を対象に調査を行い. 仕事の要求度に関連する項目(今後の販売促進の見込 み)と毛髪コルチゾールの間に正の相関を報告してい る。Qiら¹⁶⁾は39名の幼稚園の先生を対象に調査を行 い. 努力-報酬不均衡の得点と毛髪のコルチゾールの 間に正の相関を報告している。Janssens ら ¹⁷⁾は 102 名 の製造会社で働く労働者を対象に調査を行い、自記式 のストレスの質問紙と毛髪コルチゾールの間に相関は 認めなかったが、抑うつ症状が高い者では毛髪コルチ ゾールが高かったことを報告している。Gidlowら¹⁸⁾は 132名のパブリック・セクターの労働者を対象に調査



図1 毛髪に含まれるコルチゾール

血中のコルチゾール(白い○で表現)は毛髪が形成される際に毛幹の中心部(髄質)に 受動的に拡散すると考えられている。汗腺や皮脂腺に含まれるコルチゾールの影響については明確なことはわかっていない(先行研究8,9)を参考に著者が図を作成)。 を行い.勤務中の自覚ストレスや努力―報酬不均衡モ デルによる職業性ストレスと毛髪コルチゾールの間に 有意な相関は認められなかったことを報告している。

毛袋試料の特徴的な点としては、把握できる期間の 長さである。個人の毛髪の長さにも依存するが、過去 6か月程度までのコルチゾールを評価することが可能 であると考えられている。なお、毛髪の先端にいくほ ど、コルチゾール濃度は低くなることが観察されてい る19)。一方で、毛髪からのコルチゾールの評価にあ たっては何点かの留意すべき点がある。例えば、コル チゾールの測定には数十本の毛髪が必要であり、また ハサミを利用して後頭部から採取するため、自身で採 取することは難しい。また太陽光やヘアダイ・染髪に よってコルチゾール値が低下することも指摘されてお り 20-22), 保存が長期間(2年以上)に及ぶ毛髪ではコ ルチゾール濃度が低かったことも報告されている 2%。 しかしながら、このような点を考慮しても、長期的な コルチゾールの動態を把握できるという点において毛 髪は非常に有用な試料であり、多くの研究で利用され 始めている。

3. 爪のコルチゾール

爪に関しては非常に研究数が少ない状況であるが、 毛髪と類似した原理であり、ステロイドなどのホルモンが爪母基(nail matrix)に受動拡散によって輸送され、ケラチンが形成される際に取り込まれると考えられている(図2)^{33.24}。手指の爪は10日間で約1mm



図2 爪に含まれるコルチゾール

血中のステロイドなどのホルモンは爪母基に受動拡散によって 輸送され、ケラチンが形成される際に取り込まれると考えられ ている(イラストの左側は皮膚や爪が透けて、その中の構造を 示している)。先端の1mmの爪は約10日分の長さに相当する。 ただし、爪の根元部分が先端部分に移動するまでに数か月を要 する。 伸びるため³⁰,例えば、1mmの爪であれば、過去の 10日間に蓄積されたコルチゾールを表すと考えられて いる。ただし、手指の爪は根元から先端までに伸びる のに数か月を要するため、先端の爪のコルチゾールは 数か月前のものを反映していると考えられている。こ の点について検討した最近の研究³⁰では、爪のコルチ ゾールは4か月前に評価した唾液中コルチゾールと中 程度の相関があることが報告されている。

ストレスとの関連について検討した研究としては. 例えば、Warnock ら²⁰は学生を対象に試験や論文締 め切りによるストレスと爪のコルチゾールやデヒドロ エピアンドロステロン(DHEA)の関連を検討してい る。爪が根元から先端に伸びる時間差を考慮して、爪 試料は、学生のストレスが低いと考えられる時期の3 か月後(ベースライン期)と、試験や論文提出の時期 の3か月後(ストレス期)にそれぞれ採取された。そ の結果、爪のコルチゾールは、ベースライン期とスト レス期の間では差は認められなかったが、コルチゾー ル/DHEA の値はストレス期で有意に高いという結果 が得られた(コルチゾールと DHEA の比は一つのス トレスの指標として考えられている 27)。しかしなが ら、この研究では対照群は設けられておらず、ホルモ ン値や爪の成長速度の季節による変化が結果に影響を 与えている可能性を否定できない。また、最近の著者 らの研究²⁸⁾では、ライフイベントや職業性ストレスと 爪コルチゾールの関連を検討し、ライフイベントを経 験している人やコントロール度に対する要求度の比が 高い人は、コルチゾールが高かったことが報告されて いる。これらの結果はいずれも予備的なものであり. 今後の研究が待たれる。

爪試料の特徴的な点としては、まず、採取が簡便である点があげられる。採取量も少なく済み、自身で採取することが可能である。爪が短い場合でも1~2週間の期間を設ければ、必要量を採取することは可能である。また、室温による保存が可能であり、郵送で回収することも可能である。このような側面は疫学研究などでの利用に適している。また、毛髪と比較して爪は構造上の劣化が少ないことが予想され、また、コルチゾールはケラチンとの結合性が高いため、日常生活における外的な要因の影響を受けにくいことが示唆されている²⁰⁾。一方で、他試料との相関について検討した研究はまだ-つであり²⁰⁾、今後、妥当性に関する

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データの蓄積は必要である。まだ交絡要因について不 明な点も多く、例えば、マニキュアなどの影響や爪の 成長速度の影響などについてもあわせて検討が必要で ある。

4. まとめ

本総説では、コルチゾールの評価の方法として、近 年、注目されている毛髪や爪の試料の研究を紹介した。 各試料の特徴を表1にまとめた。従来までの血液や唾 液の試料は"その時点"のホルモン値を強く反映する のに対して,毛髪や爪は,数週間から数か月にわたる ホルモンの長期的な動態を反映する点が特徴的であ る。職場の慢性的なストレスやそれに伴う慢性的なコ ルチゾールの上昇が健康に悪影響を及ぼすことを考え ると,このような特徴は研究などでストレスの現象を 検討する上では非常に有利な点である。研究数はまだ 少なく,まだ不明な点も多いが,毛髪や爪の試料を積 極的に研究に取り入れることによって,職業性ストレ スと健康の関連の解明がさらに進むことが期待される。

表1 コルチゾールの評価における各試料の特徴

	血液・唾液	毛髪	Л
慢性ストレスの評価	急性ストレスや日内変動に よる影響が大きい	数か月単位の状態を把握	数週間単位の状態を把握 (ただし数か月前)
検体採取の容易さ	侵襲的(血液) 安静状態の確保が必要 冷凍保存が必要	自己採取難しい 検体量必要(毛髪が短い人 やない人からは採取できな い) 冷凍手続き不要	自己採取可能 少ない検体量 冷凍手続き不要
検体の状態による測定結果へ の影響	検体が冷凍保存されていれ ば問題ない	ヘアダイ・パーマ、太陽光 による試料の劣化の可能性	(未検討)
妥当性の検証(他試料との相 関)	血液と強い相関(唾液)	唾液との相関を認める研究 (特に爪試料)	もあるが,研究数は少ない

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Assessments of accumulated stress-related hormones by using hair and fingernail samples: A perspective on job stress research

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Abstract Cortisol, one of stress-related hormones. has been considered a mediator linking psychosocial stress and various diseases such as coronary heart disease and depressive disorder. This review introduced assessments of cortisol by using hair and fingernail samples. Cortisol levels in hair and fingernail samples may retrospectively represent hormone productions during a few months and weeks, respectively. Only a few studies previously investigated the associations between psychosocial stress in work environments and cortisol in hair and fingernail samples. Further studies are needed because hair and fingernail samples could largely contribute to exploring the biological links between job stress and health.

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Long working hours, job satisfaction, and depressive symptoms: a community-based cross-sectional study among Japanese employees in small- and medium-scale businesses

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ABSTRACT

Although long working hours have been suspected to be a risk factor for depressive symptoms (DS), it is not well understood the conditions under which long working hours are associated with it. This study investigated the moderating effect of job satisfaction on the relationship between working hours and DS. A total of 2,375 full-time non-shift day workers (73% men), aged 18-79 (mean 45) years, in 296 small- and medium-scale businesses were surveyed using a self-administered questionnaire evaluating working hours, job satisfaction, DS and covariates. The Center for Epidemiologic Studies Depression scale (CES-D) was used to assess DS. Risk of DS (CES-D \geq 16) by working hours, job satisfaction, and both combined was estimated by multivariable logistic regression analysis. Compared to participants working 6-8 hrs/day, those working 12+ hrs/day had significantly higher odds of DS (adjusted odds ratio [aOR] 1.49), while participants with low satisfaction, as opposed to high satisfaction, had increased odds of DS (aOR 1.81). Furthermore, compared to those working 6–8 hrs/day with high satisfaction (reference group), participants working 6-8 hrs/day, > 8 to 10 hrs/day, and > 10 hrs/day combined with low satisfaction had dose-response increase of DS (aOR 1.48, 2.21 and 2.31, respectively, p < 0.05), whereas those working > 8 to 10 hrs/day and > 10 hrs/day combined with high satisfaction had not (aOR 0.93 and 1.39, respectively, p > 0.10). The results suggest that long working hours are associated with increased risk of DS only under reduced job satisfaction condition, which highlights the importance of improving job satisfaction, particularly among those working excessive hours.

INTRODUCTION

Depression/depressive symptoms (DDS) is one of the most common and most costly mental health disorders, contributing to work impairment and reduced productivity affecting a large number of working people [1]. According to a report by the World Health Organization in 2012, it was estimated that 350 million people suffered from depression worldwide [2]. In Japan, nearly 2 million people were thought to have suffered from depression in 2005 [3]. A study that addressed the economic impact of depression in Japan estimated that the yearly cost was approximately \$11 billion and of this cost 62.8% was work-related depression [4].

Long working hours and overtime have been suspected to be a critical risk factor for DDS, although the findings are not always consistent [5]. To my knowledge, there are a total of 33 studies that have examined the relationship between long working hours/overtime and DDS, and of these reports, 21 studies found significant positive associations [6–26], while 12 studies reported insignificant or even an inverse relationship between the two [27–38]. Inconsistent findings across studies may be due partly to differences in sample sizes, characteristic of study populations, definition of working hours/depression, analytic approaches, and covariates adjusted for, as well as study designs (leading to possible cause-effect reversals), as pointed out by some researchers [15, 18, 19, 35]. However, there are also other potentially important workrelated factors that may have contributed to mixed results. It is becoming increasingly clear that the perception of psychosocial work conditions affect the relationship between work hours and psychological health [39-41]. For example, if employees are satisfied with or enjoying their job they may work long without suffering from DDS, whereas those who are dissatisfied with their job may not or could not work long because of depressed mood. Indeed, a metaanalysis on the relationship between job satisfaction and health confirmed that increased job satisfaction is protective against DDS [42]. Furthermore, a study that investigated the relationship between overtime and psychological health found that employees working overtime combined with low rewards had an elevated risk of poor recovery, burnout, negative home-to-work interference, and negative work-tohome interference compared to those with no overtime/high rewards (reference group), whereas those with overtime/ high rewards did not show such an increase compared to the reference group [39].

Other work conditions that deserve attention are the influence of work schedule and status of employment. Regarding work schedule, a growing body of evidence suggests that night/rotating/irregular shift work is more harmful to mental health than daytime work condition [15, 37, 43-45], suggesting that the research on the relationship between work hours and DDS should rule out or at least statistically control for the influence of work schedules to produce more accurate estimates [5]. With respect to employment status, part-time employment has been reported to be more detrimental to health than fulltime employment, especially among those involuntarily working part-time [32, 46, 47]. In accordance with these reports, one study confirmed the importance of distinguishing between overtime and long working hours among full- and part-time employees in relation to workrelated outcomes, i.e., motivation and fatigue [48].

Based on these assumptions, the present study was designed to investigate the possible moderating role of job satisfaction in the relationship between working hours and depressive symptoms in full-time employees working under non-shift daytime condition. The aim of this study was to answer three research questions: 1) Is there an association between long working hours and depressive symptoms? 2) Is there an association between job satisfaction and depressive symptoms? 3) Do the combination of working hours and job satisfaction together relate to depressive symptoms? If so, which factor is mainly related to depressive symptoms? I address these questions using a sample of 2,375 full-time employees from 329 small and medium-scale businesses (SMBs) comprised of various industry sectors and occupations.

RESULTS

Descriptive statistics for participants are shown in Table 1. Roughly 73% and 27% of participants were men and women, respectively. Overall, 45% of participants were aged 50 years and older, 68% married, 80% had high school education or higher, 48% current smoker, 68% alcohol drinker, 91% coffee/tea drinker, 38% slept less than 6 hrs/day, 21% had BMI 25 or higher, 76% had no physical/psychological symptoms, and 14% used medications. Regarding occupational factors, 43% worked in production/manufacturing, 44% metalworking, and 38% working in a business with employees less than 18 people.

Overall prevalence and prevalence of depressive symptoms (CES-D \geq 16) by working hours and job satisfaction are shown in Table 2. The prevalence of depressive symptoms among this population was 30.3% (95% CI 28.4–32.1). Working 12 hrs/day or more (compared to 6–8 hrs/day) and reduced job satisfaction were associated with increased depressive symptoms in a dose-response manner, but the strength of association with depressive symptoms seemed to be more pronounced for job satisfaction than for working hours. Prevalence of depressive symptoms among those who reported 'very satisfied' with their job had 16.8% while those reporting 'somewhat satisfied,' 'not too satisfied,' and 'not at all satisfied' had 27.6%, 36.0%, and 51.4%, respectively.

Direct associations of working hours and job satisfaction with depressive symptoms as estimated by multivariable logistic regression analyses are shown in Table 3. Participants working 12+ hrs/day had significantly higher odds of depressive symptoms than those working 6 to 8 hrs/day (reference group) even after controlling for confounders. Furthermore, the trichotomized analysis found that participants working > 10 hrs/day had significantly increased odds of depressive symptoms than the reference category.

Regarding job satisfaction, participants reporting 'not at all satisfied,' 'not too satisfied,' and 'somewhat satisfied' had significantly increased odds of depressive symptoms compared to those reporting 'very satisfied' with their job (reference group). The dichotomized analysis found that participants reporting low job satisfaction had 75% to 88% increase of depressive symptoms than those with high satisfaction.

The combined association of working hours and job satisfaction with depressive symptoms are shown in Table 4 and Figure 1. As compared with a reference group that had a 6 to 8 hrs/day working hours with high job satisfaction, the odds of depressive symptoms were significantly higher among participants working 6 to 8 hrs/day, > 8 to 10 hrs/day or > 10 hrs/day with low job satisfaction. Although participants working > 10 hrs/ day with high job satisfaction had increased depressive symptoms compared with the reference group in models 1

Characteristics	N	(%)
Total participants	2,375	(100)
Sociodemographic and socioeconomic factors:		
Sex		
Men	1,739	(73.2)
Women	636	(26.8)
Age group, years		
18–29	383	(16.1)
30–39	522	(22.0)
40-49	399	(16.8)
50–59	723	(30.4)
60+	348	(14.7)
Marital status		
Married	1,613	(67.9)
Single	605	(25.5)
Separated/divorced/widowed	157	(6.6)
Educational level		
Junior high school	486	(20.5)
High school	1,166	(49.1)
Vocational/junior college	336	(14.1)
College/graduate school	387	(16.3)
Health indicators:		
Smoking status		
Lifetime nonsmoker	987	(41.6)
Former smoker	240	(10.1)
Current smoker (> 0 to \leq 10 cigarettes/day)	192	(8.1)
Current smoker (> 10 to \leq 20 cigarettes/day)	639	(26.9)
Current smoker (> 20 cigarettes/day)	317	(13.3)
Drinking habit		
Non-drinker	757	(31.9)
Occasional (> 0 to \leq 3 times/week)	578	(24.3)
Frequent (≥ 4 times/week)	1,040	(43.8)
Caffeine intake (cups of coffee or tea/day)		
Almost none	212	(8.9)
1 to 2	1,119	(47.1)
3+	1,044	(44.0)
Sleep hours per day		
< 6	912	(38.4)
≥ 6	1,463	(61.6)
Body Mass Index		
< 20	419	(17.6)
\geq 20 to < 22.5	772	(32.5)
\geq 22.5 to < 25.0	684	(28.8)
≥ 25.0	500	(21.1)
Number of physical/psychological symptoms ^a		
None	1,801	(75.8)
1	491	(20.7)

Table 1: Sample descriptive statistics (N = 2,375)

2 or more	83	(3.5)
Use of medication ^b		
No	2,035	(85.7)
Yes	340	(14.3)
Occupational factors:		
Job type		
Managerial/clerical	642	(27.0)
Sales/service	170	(7.2)
Technical	97	(4.1)
Production/Manufacturing	1,026	(43.2)
Other	440	(18.5)
Industry sector		
Ceramic/clay/stone	46	(1.9)
Textile	40	(1.7)
Papermaking	128	(5.4)
Printing	41	(1.7)
Chemical	308	(13.0)
Leather	15	(0.6)
Metalworking	1,033	(43.5)
Food	127	(5.3)
Machinery	376	(15.8)
Other	261	(11.0)
Size of company by number of employees (in quintiles)		
1–8 workers	412	(17.3)
9–18 workers	506	(21.3)
19–31 workers	495	(20.8)
32–61 workers	515	(21.7)
62+ workers	447	(18.8)
Job control (in tertiles)		
High	798	(33.6)
Medium	795	(33.5)
Low	782	(32.9)
Quantitative workload (in tertiles)	l l	
Low	895	(37.7)
Medium	770	(32.4)
High	710	(29.9)

^aPhysical/psychological symptoms include hypertension, hyperlipidemia, diabetes mellitus, menopausal syndrome, cardiovascular disease, cancer, stomach/duodenal ulcer, arrhythmia, gout, hyperuricemia, renal disease, liver disease, stroke, gynecologic diseases, hyperthyrodism, peptic ulcer, severe allergy, hernia, back pain, rheumatoid arthritis, and panic disorder. ^bMedications include aspirin, acetaminophen, β-blockers, cold/flu medicine, anti-hypertensives, naproxen, corticosteroids, and ibuprofen.

and 2 (p < 0.05), the significance disappeared after further adjustment for additional covariates (models 3 and 4).

DISCUSSION

The purpose of this study was to investigate the independent and combined association of working hours and job satisfaction with depressive symptoms in a

large number of SMB employees in a suburb of Tokyo. The current study produced three main findings. First, long working hours, particularly those working 12+ hrs/ day (compared to those working 6 to 8 hrs/day), were weakly but significantly associated with increased risk of depressive symptoms. Second, reduced job satisfaction was strongly related to depressive symptoms in a dose-response manner. Third and most importantly, the combination of

Variables	Ν	(%)	CES-D Score ≥ 16, % (95% CI)
Overall prevalence	2,375	(100.0)	30.3 (28.4 to 32.1)
Working hours per day: ^a			
6 to 8	1,144	(48.2)	28.4 (25.8 to 31.0)
9	506	(21.3)	28.9 (24.9 to 32.8)
10	416	(17.5)	31.5 (27.0 to 36.0)
11	121	(5.1)	37.2 (28.6 to 45.8)
12+	188	(7.9)	38.3 (31.3 to 45.2)
Working hours per day: ^b			
6 to 8	1,144	(48.2)	28.4 (25.8 to 31.0)
> 8 to 10	922	(38.8)	30.0 (27.1 to 33.0)
> 10	309	(13.0)	37.9 (32.5 to 43.3)
Job satisfaction: ^c			
Very satisfied	280	(11.8)	16.8 (12.4 to 21.2)
Somewhat satisfied	1,306	(55.0)	27.6 (25.2 to 30.1)
Not too satisfied	614	(25.9)	36.0 (32.2 to 39.8)
Not at all satisfied	175	(7.4)	51.4 (44.0 to 58.8)
Job satisfaction: ^c			
Very satisfied/Somewhat satisfied	1,586	(66.8)	25.7 (23.6 to 27.9)
Not too satisfied/Not at all satisfied	789	(33.2)	39.4 (36.0 to 42.8)

Fable 2: Prevalence of	depressive sympt	oms by working hours	s and job satisfaction	(N = 2,375)
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 $^{a}p < 0.05$, $^{b}p < 0.01$, $^{c}p < 0.001$ (Chi-squared test).

working hours with job satisfaction had a synergistic association with depressive symptoms, but this association was observed only when different working hours were combined with low job satisfaction (compared to those working 6–8 hours/day with high satisfaction). Although the results of this study should be interpreted with caution

in light of self-reporting and cross-sectional design, these data imply that job redesign/crafting aimed at enhancing job satisfaction may prevent, or at least reduce, occurrence of workplace DDS associated with long working hours.

Data from past studies have suggested that long working hours are associated with increased risk of





	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
Variables	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Working hours per day:				
6 to 8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
9	1.02 (0.81 to 1.29)	1.04 (0.82 to 1.32)	1.03 (0.81 to 1.31)	1.09 (0.84 to 1.42)
10	1.16 (0.91 to 1.48)	1.25 (0.96 to 1.62)	1.20 (0.92 to 1.56)	1.16 (0.87 to 1.55)
11	1.49 (1.01 to 2.21) ^e	1.56 (1.04 to 2.35) ^e	1.45 (0.96 to 2.20)	1.51 (0.96 to 2.37)
12+	1.56 (1.14 to 2.16) ^e	1.64 (1.17 to 2.30) ^e	1.44 (1.02 to 2.04) ^e	1.49 (1.00 to 2.22) ^e
Working hours per day:				
6 to 8	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
> 8 to 10	1.08 (0.89 to 1.31)	1.12 (0.92 to 1.38)	1.10 (0.89 to 1.35)	1.12 (0.89 to 1.40)
> 10	$1.54 (1.18 \text{ to } 2.00)^{\text{f}}$	$1.60 (1.20 \text{ to } 2.13)^{\text{f}}$	1.43 (1.07 to 1.92) ^e	1.49 (1.07 to 2.08) ^e
Job satisfaction:				
Very satisfied	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Somewhat satisfied	1.89 (1.35 to 2.65) ^f	1.79 (1.28 to 2.52) ^f	1.82 (1.29 to 2.56) ^f	2.04 (1.42 to 2.92) ^f
Not too satisfied	2.79 (1.96 to 3.97) ^f	2.52 (1.76 to 3.61) ^f	2.55 (1.78 to 3.67) ^f	$2.92 (1.99 \text{ to } 4.30)^{\text{f}}$
Not at all satisfied	5.25 (3.41 to 8.08) ^f	4.52 (2.92 to 7.01) ^f	4.50 (2.90 to 7.00) ^f	5.51 (3.41 to 8.89) ^f
Job satisfaction:				
Very satisfied/Somewhat satisfied (high)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Not too satisfied/Not at all satisfied (low)	1.88 (1.57 to 2.25) ^f	1.75 (1.46 to 2.11) ^f	1.75 (1.45 to 2.11) ^f	1.81 (1.47 to 2.22) ^f

Table 3: Association of working hours and job satisfaction with depressive symptoms (N = 2,375)

^aUnadjusted.

^bAdjusted for sex, age group, marital status, and educational level.^c Adjusted for sex, age group, marital status, educational level, smoking, drinking, caffeine intake, sleep duration, and BMI.^d Adjusted for sex, age group, marital status, educational level, smoking, drinking, caffeine intake, sleep duration, BMI, number of physical/psychological symptoms, use of medication (yes/no), job type, industry sector, company size, job control (high, medium, low), and male/female ratio.^e p < 0.05, ^fp < 0.001.

DDS [6–26]. At the same time, there are also studies that reported no significant relationship [27–36] or even an inverse relationship between the two [37, 38]. As stated earlier in the Introduction, several plausible explanations have been proposed for its inconsistent findings. In addition to these explanations, this study yielded an alternative explanation as to why work hour-DDS relationship is not simple or straightforward. The results of this study suggested that long working hours do not necessarily have negative psychological health consequences if employees are working under favorable/ positive working condition, i.e., high job satisfaction. Conversely, the risk of DDS associated with long working hours are more pronounced if employees are working under poor/negative condition, i.e., low job satisfaction. The finding is supported by several studies that considered working condition in relation to long work hours and health [39, 40]. One study reported that long work hours are not necessarily related to adverse psychological health if job rewards are high, even under high pressure to work overtime among postal service employees [39]. Another study observed a positive association between weekly working hours and poor physical health among train drivers who worked overtime with high pressure and low social support, whereas those under high pressure with high social support yielded an inverse relationship [40]. These findings, together with the current results, support the notion that psychosocial work condition could serve as a moderator in the relationship between working hours and health.

			Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
Variables	N	(%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Working hours and job satisfaction:						
Working 6 to 8 h/day with high job satisfaction	768	(32.3)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Working 6 to 8 h/day with low job satisfaction	376	(15.8)	1.58 (1.21 to 2.07) ^g	1.48 (1.13 to 1.94) ^f	1.47 (1.12 to 1.93) ^f	1.48 (1.11 to 1.98) ^f
Working > 8 to 10 h/day with high job satisfaction	618	(26.0)	0.92 (0.72 to 1.18)	0.97 (0.75 to 1.25)	0.93 (0.72 to 1.21)	0.93 (0.70 to 1.23)
Working > 8 to 10 h/day with low job satisfaction	304	(12.8)	2.21 (1.67 to 2.92) ^g	2.16 (1.61 to 2.89) ^g	2.13 (1.59 to 2.86) ^g	2.21 (1.60 to 3.05) ^g
Working more than 10 h/day with high job satisfaction	200	(8.4)	1.49 (1.07 to 2.09)e	1.56 (1.09 to 2.22)e	1.41 (0.98 to 2.20)	1.39 (0.94 to 2.07)
Working more than 10 h/day with low job satisfaction	109	(4.6)	2.51 (1.66 to 3.78) ^g	2.45 (1.59 to 3.76) ^g	2.13 (1.38 to 3.30) ^g	2.31 (1.42 to 3.74) ^g

Table 4: Combined association of working hours and job satisfaction with depressive symptoms (N = 2,375)

^aUnadjusted.

^bAdjusted for sex, age group, marital status, and educational level.

^cAdjusted for sex, age group, marital status, educational level, smoking, drinking, caffeine intake, sleep duration, and BMI. ^dAdjusted for sex, age group, marital status, educational level, smoking, drinking, caffeine intake, sleep duration, BMI, number of physical/psychological symptoms, use of medication (yes/no), job type, industry sector, company size, job control (high, medium, low), and male/female ratio.

p < 0.05, f p < 0.01, g p < 0.001.

Interestingly, those who worked moderately long hours (> 8 to 10 hrs/day) with high job satisfaction had the lowest risk of depressive symptoms compared to those working 6–8 hrs/day with high job satisfaction (aOR=0.92 to 0.97). Although the results only yielded a small difference, it seems reasonable to think that this population is consisted of healthiest group of employees who are working voluntarily with high motivation. Two studies from Netherlands suggested that moderate overtime is not always harmful to health outcomes [49, 50]. For instance, a study using a representative sample of a Dutch full-time workforce found that voluntary overtime workers were non-fatigued and satisfied with their job even without rewards while involuntary overtime workers exhibited high fatigue level and less satisfaction [49].

More than a half of the participants who were 'not at all satisfied' with their job had depressive symptoms. This finding is in line with several empirical researches [51, 52] as well as a result of meta-analysis based on 485 studies of job satisfaction and health which reported that workers with low levels of satisfaction were more likely to experience DDS ($\rho = .428$) [42], indicating that job satisfaction is an important predictor of psychological health. Therefore, those with extremely low levels of job satisfaction may need an immediate care to prevent workplace depression.

In this study, 30.3% of participants had CES-D scores of 16 or higher. The prevalence is similar to several studies using same criteria among the working populations (ranging from 24.5% to 33.9%) [53–55]. In contrast, an estimate based on diagnostic criteria are often much lower. For example, a median 12-month prevalence of

major depressive disorder based on 42 different studies yielded 5.3% with an interquartile range of 3.6% to 6.5% [56]. Similarly, lifetime and 12-month prevalence of major depressive disorder was reported to be 6.1% and 2.2%, respectively, based on the World Mental Health Japan Survey [57]. The prevalence gap between the former and latter studies could be attributable to different criteria for defining DDS, i.e., questionnaire vs. diagnostic criteria. In consideration of these facts, studies using both methodology/definition simultaneously may help understand the relationship between long working hour and DDS more precisely.

Strengths and limitations

A principal strength of this study is that it not only explored the independent association of working hours and job satisfaction with depression but also examined the combined associations of working hours and job satisfaction on depressive symptoms in a fairly large number of fulltime employees of SMBs representing various industry sectors and occupations. Furthermore, participants under shift work and non-full-time condition, who reported major depressive disorders and anxiety disorders, as well as those working < 6 h/day and > 20 h/day were excluded to minimize selection bias leading to under- or overestimation. The limitations of this study are as follows. First, since this is a cross-sectional data, the association could be in either direction, i.e., long work hours and diminished job satisfaction may increase the risk of depressive symptoms or that undiagnosed depression or depressive personality traits may be the cause for reduced job satisfaction and short working hours. Second, work hours, job satisfaction, and depressive symptoms were assessed by self-report rather than through the use of objective measures or diagnostic criteria. Third, response bias may have occurred if nonrespondents differed from respondents; in particular, those who worked extremely long hours may have had less time available to respond to the questionnaire. Fourth, although the study included a fairly large number of confounders, information on unmeasured work-related factors such as work-family conflict and organizational justice and nonwork-related variables such as personality traits and genetic components, as well as unknown common factors for both depressive symptoms and job satisfaction were not included in the analyses.

MATERIALS AND METHODS

Study participants and procedure

The study design was cross-sectional and data were collected using a self-administered questionnaire between August and December 2002. The study sample consisted of full-time employees of SMBs in a size ranging from 1 to 158 workers in the city of Yashio, Saitama, and in the Ohta ward of Tokyo. Yashio has the highest percentage of manufacturing plants in Saitama prefecture. The ward of Ohta, which is a so-called "industrial area," is unique for its number of SMBs. About 20% of SMBs in both areas were selected weighted by distribution of industry sector types, resulting in 329 SMBs from Yashio and 61 from the Ohta ward. An occupational health nurse/physician contacted each representative of the company to request participation in the questionnaire survey. Among these businesses, 248 in Yashio and 52 in Ohta agreed to participate. Questionnaires were distributed during visits to each business and were given to 2,591 employees in Yashio and 1,102 employees in Ohta (n = 3,693). Finally, responses were obtained from 2,884 employees (2,022 men and 862 women) from 296 businesses (response rate 78.1%). Those who had missing responses to sex, age, working hours, and job satisfaction were eliminated from the analyses (n = 126). Similarly, those who had 6 or more missing responses on the Center for Epidemiologic Studies Depression Scale (CES-D) (see 'Measurements' section for detail) and those who had been diagnosed with major depressive disorder or anxiety disorders were excluded from the analysis (n = 64). In addition, those who reported working < 6 hrs/day or > 20 hrs/day, working under non-day shifts or < 18years old were excluded (n = 131). Since there were less than 5% missing responses for all the covariates in this study, Missing Value Analysis was performed using IBM SPSS Statistics 21.0 software (SPSS, Inc., Chicago, IL, USA) [58]. The 'expectation-maximization method' of imputing missing values was utilized. As a result, following variables, i.e., marital status, educational level, smoking status, drinking habit, caffeine intake, sleep

hours, BMI, number of physical/psychological symptoms, use of medication, job type, job control, and quantitative workload were imputed. Thus, data on a total of 2,375 participants (1,739 men and 636 women) working under non-shift daytime condition were used in the final analyses. The study was approved by the Medical Ethical Committee of the University of Tokyo. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the studies presented.

Variables

Working hours

Working hours were determined by an open-ended question: How many hours do you usually work in a typical working day? Number of hours were grouped into three categories (i) 6 to 8 hrs/day, (ii) > 8 to 10 hrs/day, and (iii) > 10 hrs/day.

Job satisfaction

Job satisfaction was assessed by a single-item assessment tool included in the Japanese version of the generic job stress questionnaire (GJSQ) developed by the U.S. National Institute for Occupational Safety and Health (NIOSH) which is a well-established means of measurement [59–61]. Item/response for the scale is as follows: All in all, how satisfied would you say you are with your job? (1) not at all satisfied, (2) not too satisfied, (3) somewhat satisfied, (4) very satisfied. The item has been frequently used in past studies to measure job satisfaction at the workplaces [51]. Job satisfaction was dichotomized into low (not at all satisfied/not too satisfied) and high (somewhat satisfied/very satisfied) levels.

Depressive symptoms

Depressive symptoms was measured using a Japanese version of the Center for Epidemiologic Studies Depression scale (CES-D) [62]. The 20-item depressive symptom scale measures the level of depressive symptoms experienced in the past week. The CES-D scale cut-off score is 16, which differentiates between those exhibiting high levels of depressive symptoms (score \geq 16) and those with lower levels of such symptoms (score < 16) [63]. The internal consistency of the CES-D scale for the study sample was 0.84.

Covariates

Covariates considered included sociodemographic and socioeconomic factors, health behaviors, biological factors, medication usage, and occupational factors as listed in Table 1. Daily sleep hours during the previous 1-year period were assessed by a following questionnaire: On average, how much sleep at night do you usually get? Response options were: < 5 hrs/5 to < 6 hrs/6 to < 7 hrs/7to < 8 hrs/8 to < 9 hrs/9+ hrs. A previous study confirmed a strong convergent and discriminant validity as well as a high level of test-retest stability over 1 year for this question [64]. Information on height and weight were obtained to assess body mass index (BMI), calculated as weight (kg) divided by height (m) squared, and divided into four groups. Job control and quantitative workload were evaluated by the Japanese version of the NIOSH GJSQ. Job control measures how much the worker feels that tasks, workplace setting, and decisions at work are controllable and is assessed based on 16-items, while quantitative workload estimates how much work must be done on daily basis and is based on 4-items. Internal consistency (Cronbach's alpha) for these scales was 0.96 and 0.88, respectively.

Participants were asked if they were treated for any of the following disorders or symptoms: hypertension, hyperlipidemia, diabetes mellitus, major depressive disorder, menopausal syndrome, or other. If the participants reported 'other disorders,' they were asked to specify the condition. Participants reported various disorders as listed on the bottom of Table 1. The numbers of disorders among the participants were counted and were included as a covariate.

Statistical analyses

Prevalence of depression by working hours and job satisfaction was analyzed by Chi-squared test. The risk of depression by working hours and job satisfaction was estimated by multivariable logistic regression with odds ratios (ORs) and 95% confidence intervals (CIs) as measures of association. Combined associations of working hours and job satisfaction were examined by a similar analytic method. They were divided into six groups as follows: three groups of working hours (< 6 hrs/ day, 6 to < 8 hrs/day, or 8 + hrs/day) \times two groups of job satisfaction (low versus high). The interactive associations of working hours and job satisfaction on depression were also examined. Adjustments for covariates were made in a stepwise fashion. A crude OR was computed in Model 1. The second model included sociodemographic and socioeconomic factors as covariates (Model 2). The third model included health behaviors and biological factors in addition to model 2 covariates (Model 3). And finally, occupational factors were included in addition to model 3 covariates (Model 4). Quantitative workload was left out of multivariable logistic regression analyses because of a strong intercorrrelation with working hours and some recent studies indicated that work demands should be treated as an intermediate variable but not as a confounder [17, 22]. The significance level for all statistical analyses was P < 0.05(two-tailed test). Data were analyzed using IBM SPSS version 21.0 software (SPSS, Inc., Chicago, IL, USA).

CONCLUSIONS

This study found independent associations of working hours and job satisfaction with depressive symptoms. However, when the combined associations of working hours and job satisfaction were tested, job satisfaction turned out to be the main factor related to depressive symptoms. Furthermore, a combination of long working hours with reduced job satisfaction exerted a reciprocal association on depressive symptoms, but a combination of long working hours with high satisfaction did not show such an effect. Prospective research is warranted to determine the causal mechanisms underlying the present findings.

Abbreviations

DDS: depression/depressive symptoms; CES-D: Center for Epidemiologic Studies Depression scale; SMB: small and medium-scale business; NIOSH: National Institute for Occupational Safety and Health; GJSQ: generic job stress questionnaire; OR: odds ratio; aOR: adjusted odds ratio; CIs: confidence intervals; BMI: body mass index

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CONFLICTS OF INTEREST

There is no conflicts of interest.

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Association of Suicidal Ideation with Job Demands and Job Resources: a Large Cross-Sectional Study of Japanese Workers

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Abstract

Purpose This study aimed to identify the association of suicidal ideation with job demands and job resources among Japanese workers.

Methods Valid data from questionnaires that were precollected from 42,499 workers (34,882 males and 7617 females) were used for multilevel logistic regression analyses. Job demands and job resources were selected as potential predictors of suicidal ideation. Lifestyle variables, support from family and friends, and suffering from depressive or eating disorders were used as covariates.

Results In the employee-level, most job demands and job resources had significant associations with the risk of suicidal ideation in both sexes. High coworker support had a significant negative association with the risk of suicidal ideation in the organization-level, irrespective of their gender. High physical demands and poor physical environment in the organization-level had significant positive associations with increased risk of suicidal ideation only among females.

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Conclusions The risk of suicidal ideation among Japanese workers is associated with job demands and job resources in the employee-level, and coworker support in the organization-level may be important as well.

Keywords Suicidal ideation · Job demands · Job resources · Japanese · Multi-level analysis

Introduction

Suicide is one of the largest health and behavioral problems since the late twentieth century in most parts of the world, irrespective of the levels of industrialization or wealth. Figures from the World Health Organization (WHO) [1] indicate that one suicide occurs every 40 s, and it is the third leading cause of death in the world. In Japan, around 30,000 people have died from suicide every year since 1998; this equates to 25 deaths from suicide per 100,000 people each year. The Japan Cabinet Office reported that 27,283 people died from suicide in 2013 [2]. Although the total number of suicides has been decreasing continuously since 2010, suicide is still the largest cause of death especially in the younger population in Japan [3]. The number of worker suicides in 2013 reached 9401 [2]; this means that 34.5 % of Japanese people who committed suicide had a job at the time of suicide. Employmentrelated problems have been the fourth-ranked cause of suicide for several years [2, 4, 5] and have broadly been defined as karojisatsu (suicide due to overwork) in Japan [6-8]. Therefore, it is important to identify work-related risk and protective factors associated with suicide among the working population at a more detailed level.

Mann [9] proposed a suicide prevention strategy based on three components: (1) mood or other psychiatric disorders, (2) suicidal ideation, and (3) factors involved in suicidal behavior. Suicidal ideation, which is a serious thought about killing oneself [10], was deemed to have a direct association with suicidal action. Suicidal ideation has a strong association with completed suicide [11, 12]. It is also a phenomenon that occurs commonly with suicide action; thus, it may be beneficial to identify risk factors for suicidal ideation.

As mentioned earlier, it is important to consider both risk factors and protective factors for suicidal ideation among workers. Within the work stress literature, the Job Demands Resources (JD-R) model [13-15], which considers both health impairment process with job demands and motivation improvement process with job resources, has been one of the most frequently cited theoretical frameworks. In this model, job demands are defined as "physical, social, or organizational aspects of the job that require sustained physical or mental effort and are associated with certain physiological and psychological costs," (p. 501) and job resources are defined as "physical, psychological, social, or organizational aspects of the job that may do any of the following: (a) be functional in achieving work goals; (b) reduce job demands at the associated physiological and psychological costs; (c) stimulate personal growth and development" (p. 501) [13]. For example, high quantitative job demands, numerous or intensive interpersonal conflicts, or long work hours are classified as job demands, while substantial job control or strong support from supervisors or coworkers are classified as job resources. In the JD-R model, specific contents of both job demands and job resources are considered to vary by occupations mainly due to the differences in the nature of their work [13]. Compared to the other prevalent job stress models (e.g., Job Demands Control model [16], NIOSH Generic Job Stress model [17]), the advantage of the JD-R model is its flexibility to include various job demands and job resources in each domain. However, this may also be a downside of the JD-R model, especially when considering the general approach for decreasing suicidal ideation that is applicable to many occupations.

Based on these discussions, this study aimed to identify the association of suicidal ideation with job demands and job resources among Japanese workers in a large sample of working adults. To our knowledge, only a few studies have focused on this topic using a large sample of Japanese workers. Suicidal ideation is one of the common symptoms of the major depression, and thus having such thoughts frequently may reflect one's unhealthy mental status. The study analyses were conducted separately for each gender because, in Japan, males have been shown to have higher suicide rates compared with females [2]. This may reflect social, biological, or psychological differences in the causes of suicidal ideation.

Method

Study Participants

A total of 62,408 Japanese workers representing various industries and occupations were included in this crosssectional study. Data were drawn from the Mental Health and Life Style Inventory survey conducted in Tokyo, Japan (April 2008 to December 2010), which was distributed to 61 organizations in nine industry sectors. Overall, 55,242 workers completed and returned the questionnaire (response rate = 88.5 %). Informed consent was obtained from all study participants. After excluding 12,743 participants who left certain questionnaire items incomplete, the responses of the remaining 42,499 workers (34,882 males and 7617 females) in 61 organizations were selected for the present analysis (valid response rate = 76.9 %). The number of workers within each organization ranged from 11 to 24,156 (median = 158). The study protocol was approved by the Ethical Committee of the University of Occupational and Environmental Health (H26-029).

Measures

Suicidal Ideation

Suicidal ideation was measured by a single item "I seriously consider that I would feel better if I were to die," during the past 2 weeks, followed by four choices: "1=never or almost never," "2=a little or occasionally," "3=often or fairly often," and "4=very often or always." In this study, we classified responses into two categories: little or no suicidal ideation ("1=never or almost never" or "2=a little or occasionally") and having suicidal ideation ("3=often or fairly often" or "4=very often or always"). Kessler et al. [10] defined the suicidal ideation as a serious thought about killing oneself; thus, we set a cutoff point between the answering choices "2=a little or occasionally" and "3=often or fairly often."

Potential Predictors

Job demands and job resources were chosen as potential predictors of suicidal ideation. Job demands and job resources were measured with the Brief Job Stress Questionnaire (BJSQ) developed by The Japanese Ministry of Health, Labour and Welfare [18]. In the BJSQ, job demands consisted of five subscales, namely "quantitative job demands" (three items, $\alpha = 0.75$; e.g., I have an extremely large amount of work to do.), "qualitative job demands" (three items, $\alpha = 0.67$; e.g., I have to pay very careful attention.), "physical demands" (one item; My job requires a lot of physical work.), "interpersonal conflict" (three items, $\alpha = 0.64$; e.g., There are differences of opinion within my department.), and "poor physical environment" (one item; My working environment is poor.). Job resources consisted of five subscales, namely "job control" (three items, $\alpha = 0.68$; e.g., I can work at my own pace.), "suitable jobs" (one item; This job suits me well.), "meaningfulness of work" (one item; My job is worth doing.), "supervisor support" (three items, $\alpha = 0.79$; e.g., How freely can you talk with your supervisor?), and "coworker support" (three items, $\alpha = 0.78$; e.g., How freely can you talk with your coworker?). Each item for the job demands and job resources was answered by participants using a four-point Likert-type scale: "1 = strongly disagree," "2 = disagree," "3 = agree," and "4 = strongly agree." Overtime work, which was considered to be a one component of job demands, was measured with a single item asking, "How long did you work overtime, including work done during holidays, in the last month?" followed by six choices: "less than 15 h," "15 to <30 h," "30 to <45 h," "45 to <60 h," "60 to <80 h," and "80 h or more."

Covariates

Lifestyle variables (hours slept per day, smoking status, and alcohol consumption), support from family and friends, and suffering from depressive or eating disorders were considered as covariates in the analyses. Support from family and friends were measured with three items (α =0.84; e.g., How freely can you talk with family or friends?), which were included in the BJSQ [18]. Participants answered each item with a 4-point Likert-type scale: "1=strongly disagree," "2=disagree, "3=agree," and "4=strongly agree". In this study, the presence of depressive or eating disorders were not defined clearly by asking the participants whether they are currently suffering from each of the disorder or not. Thus, the response categories were "yes" or "no" for each disorder.

Statistical Analyses

Participants were divided by each mean subscale score for job demands or job resources. The lower score for each scale was considered as reference group. Overtime work of less than 80 h per month was also considered as reference group. The criteria of 80 overtime hours a month were adopted from the Comprehensive Program for the Prevention of Health Impairment Due to Overwork [19]. Under the Japanese law, if the number of overtime hours exceeds 80 h per month and an employee requests administrative guidance or the number of overtime hours exceeds 80 h per month for two to six consecutive months, the employer should make an effort to provide the employee with administrative guidance through an occupational physician.

The risks of suicidal ideation associated with job demands and job resources were estimated using multilevel logistic regression analysis, controlling for lifestyle variables (number of hours slept per day, smoking status, and alcohol consumption), support from family and friends, and suffering from depressive or eating disorders. We considered the workers as a level 1 variable (employee-level) and the organization as a level 2 variable (organization-level) because each worker can be nested within only one organization. Organization-level job demand and job resource scores were calculated by averaging employee-level scores for each organization. All independent variables in the employee-level were centered by group mean and those in the organizationlevel were centered by grand mean.

IBM SPSS Statistics version 22 (IBM Corp., NY) and Mplus version 7.11 (Muthén & Muthén, LA) were used for statistical analyses. We calculated only employee-level odds ratios (ORs) because Mplus version 7.11 cannot calculate OR in the organization-level, nor calculate the 95 % confidence intervals for each ORs in the employee-level. All analyses were carried out separately for males and females.

Results

Characteristics of the participants stratified by gender are shown in Table 1. To check whether the distributions of each variable differed by gender, χ^2 tests were conducted. The prevalence of suicidal ideation was 4.6 % in males and 4.7 % in females; there was no significant gender difference. These percentages were almost identical to a study with 5238 US adults (5.6 % for males and females) [20]. Overall, most males were older (approximately 40 % of males were more than 40 years old) and worked as full-time workers (96.3 %). The percentage of night shift workers was significantly higher in males (21.2 %) than that in females (2.0 %). Most females were lifetime non-smokers (80.3 %). Approximately 24 % of males drank alcohol almost everyday. The prevalence of eating disorder was significantly higher in females; however, no significant gender difference was found in the prevalence of depressive disorder. Job demands scores were generally higher in males than those in females, but job resources scores were generally lower in males than those in females. Compared to the study samples, samples with missing data (n=12,743) were more often females (n=2,793, 21.9 %), slightly older (more than 50 years old: n=3519, 27.6 %), working the night shift (n = 2835, 22.2 %), and belonging in public affairs (n=6135, 48.1 %). Fifty-eight percent of the participants who had some missing data did not answer their current employment status.

To check the hierarchy of our data, intra-class correlation coefficients (ICC(1)) were calculated for each variable. Among subscales of job demands and job resources, all ICC(1) excluding ICC(1) for overtime work in females were significant in both sexes. Internal consistencies of all variables within each organization (ICC(2)) ranged from 0.90 to 0.98 in males and 0.70 to 0.98 in females (Table 2). Thus, we

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Table 1 Characteristics of the study participants and the results of the χ^2 tests for each variable by gender

		Male		Female		Chi-square
		n	%	n	%	
Suicidal ideation	No	33,279	(95.4)	7262	(95.3)	0.1
	Yes	1603	(4.6)	355	(4.7)	
Demographic variables						
Age groups						2574.3***
Less than 20 years		358	(1.0)	118	(1.5)	
20 to 29 years		7062	(20.2)	3410	(44.8)	
30 to 39 years		12,826	(36.8)	2775	(36.4)	
40 to 49 years		9262	(26.6)	933	(12.2)	
50 to 59 years		4638	(13.3)	332	(4.4)	
60 years or more		736	(2.1)	49	(0.6)	
Employment status						448.6***
Full-time		33,601	(96.3)	6906	(90.7)	
Part-time		1281	(3.7)	711	(9.3)	
Work shift						1576.9***
Day shift		27,493	(78.8)	7465	(98.0)	
Night shift		7389	(21.2)	152	(2.0)	
Industry sector						1834.4***
Agriculture		778	(2.2)	303	(4.0)	
Manufacturing		22,843	(65.5)	3478	(45.7)	
Wholesale/retail		708	(2.0)	332	(4.4)	
Information technology		2982	(8.5)	1092	(14.3)	
Finance/insurance		2656	(7.6)	1324	(17.4)	
Real estate		1750	(5.0)	411	(5.4)	
Human health/social work		15	(0.0)	93	(1.2)	
Media/publication		264	(0.8)	77	(1.0)	
Public affairs		2886	(8.3)	507	(6.7)	
Lifestyle variables						
Sleep hours per day						12.4**
Less than 5 h		2870	(8.2)	613	(8.0)	
5 to <7 h		22,047	(63.2)	4972	(65.3)	
7 h or more		9965	(28.6)	2032	(26.7)	
Smoking status						4607.4***
Current smoker		15,401	(44.2)	924	(12.1)	
Nonsmoker		13,148	(37.7)	6118	(80.3)	
Past smoker		6333	(18.2)	575	(7.5)	
Alcohol consumption (days)						1996.9***
0		5361	(15.4)	1794	(23.6)	
1 to 3/month		8284	(23.7)	3000	(39.4)	
1 to 2/week		6314	(18.1)	1554	(20.4)	
3 to 4/week		3833	(11.0)	463	(6.1)	
5 to 6/week		2651	(7.6)	207	(2.7)	
Almost everyday		8439	(24.2)	599	(7.9)	
Health-related variables						
Depressive disorder	No	34,392	(98.6)	7520	(98.7)	0.8
	Yes	490	(1.4)	97	(1.3)	
Eating disorder	No	34,866	(100.0)	7576	(99.5)	113.2***
	Yes	16	(0.0)	41	(0.5)	
Work-related variables						

Job demands

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Table 1 (continued)

		Male		Female		Chi-square
		п	%	n	%	
Quantitative job demands	Low	13,909	(39.9)	4301	(56.5)	702.8***
	High	20,973	(60.1)	3316	(43.5)	
Qualitative job demands	Low	14,710	(42.2)	4598	(60.4)	834.8***
	High	20,172	(57.8)	3019	(39.6)	
Physical demands	Low	23,696	(67.9)	6345	(83.3)	712.6***
	High	11,186	(32.1)	1272	(16.7)	
Interpersonal conflict	Low	19,632	(56.3)	4810	(63.1)	120.6***
	High	15,250	(43.7)	2807	(36.9)	
Poor physical environment	Low	21,145	(60.6)	4331	(56.9)	36.8***
	High	13,737	(39.4)	3286	(43.1)	
Overtime work per month						111.2***
Less than 80 h		33,702	(96.6)	7532	(98.9)	
80 h or more		1180	(3.4)	85	(1.1)	
Job resources						
Job control	Low	15,903	(45.6)	3047	(40.0)	79.0***
	High	18,979	(54.4)	4570	(60.0)	
Suitable jobs	Low	11,750	(33.7)	2443	(32.1)	7.3**
	High	23,132	(66.3)	5174	(67.9)	
Meaningfulness of work	Low	12,179	(34.9)	2819	(37.0)	12.0***
	High	22,703	(65.1)	4798	(63.0)	
Supervisor support	Low	17,890	(51.3)	4343	(57.0)	82.3***
	High	16,992	(48.7)	3274	(43.0)	
Coworker support	Low	20,513	(58.8)	4139	(54.3)	51.2***
	High	14,369	(41.2)	3478	(45.7)	

p* < 0.01; *p* < 0.001

 Table 2
 Intra-class correlation coefficients and internal consistencies of job demands and job resources

	ICC(1)		ICC(2))
	Male	Female	Male	Female
Job demands				
Quantitative job demands	0.04***	0.08***	0.96	0.92
Qualitative job demands	0.02***	0.07**	0.93	0.90
Physical demands	0.09***	0.26**	0.98	0.98
Interpersonal conflict	0.03**	0.06***	0.94	0.88
Physical environment	0.04***	0.04**	0.96	0.83
Overtime work	0.05**	0.06	0.97	0.89
Job resources				
Job control	0.02***	0.03*	0.93	0.81
Suitable jobs	0.02***	0.02**	0.92	0.70
Meaningfulness of work	0.03***	0.05**	0.95	0.86
Supervisor support	0.02**	0.02*	0.91	0.75
Coworker support	0.02*	0.03***	0.90	0.76

ICC(1) intra-class correlation coefficient, ICC(2) internal consistency within the organization

p* < 0.05;*p* < 0.01; ****p* < 0.001

considered that all job demands and job resources excluding overtime work among females had both employee-level and organization-level information.

Table 3 shows the standardized estimates and odds ratios of multilevel logistic regression analyses controlling for lifestyle variables, support from family and friends, and suffering from depressive or eating disorders, stratified by gender. Among males, all job demands had positive associations with the risk of suicidal ideation in the employee-level. No significant associations were found between any job demands and suicidal ideation in the organization-level. All job resources excluding coworker support were negatively associated with the risk of suicidal ideation in the employee-level. Among job resources, high coworker support had significant negative association with the risk of suicidal ideation in the organization-level.

Among females, all job demands excluding high quantitative job demands and overtime work had positive association with the risk of suicidal ideation in the employee-level. High quantitative job demands had a negative association with the risk of suicidal ideation, and overtime work had no significant association with the risk of suicidal ideation in the employeelevel. For the organization-level, high physical demands and

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Table 3 Standardized estimates and odds ratios of suicidal ideation among male and female workers

	Male				Female					
	Employee - level		Organization - level Employ		Employee -	e - level		Organization - level		
	Estimate ^c	SE	OR ^{a,b}	Estimate ^c	SE	Estimate ^c	SE	OR ^{a,b}	Estimate ^c	SE
Job demands										
High quantitative job demands	0.05**	0.02	1.23	-0.36	0.28	-0.05**	0.02	0.80	0.14	0.26
High qualitative job demands	0.09***	0.01	1.48	-0.15	0.25	0.12***	0.02	1.68	-0.34	0.32
High physical demands	0.07***	0.01	1.40	0.50	0.26	0.05**	0.02	1.31	0.46*	0.23
High interpersonal conflict	0.13***	0.01	1.70	0.00	0.25	0.10***	0.02	1.56	-0.17	0.24
Poor physical environment	0.06***	0.01	1.30	-0.18	0.26	0.06*	0.02	1.27	0.61*	0.29
Overtime work (80 h or more/month)	0.03**	0.01	1.39	0.22	0.15	-0.02	0.03	0.66-	-	_
Job resources										
High job control	-0.06***	0.01	0.77	-0.19	0.29	-0.05	0.04	0.82	-0.14	0.15
Suitable jobs (yes vs. no)	-0.12***	0.01	0.59	0.07	0.46	-0.08**	0.03	0.71	-0.14	0.21
Meaningfulness of work (yes vs. no)	-0.14***	0.01	0.55	-0.31	0.37	-0.08***	0.02	0.69	-0.22	0.28
High supervisor support	-0.04***	0.01	0.85	0.07	0.39	-0.07**	0.03	0.74	0.34	0.21
High coworker support	-0.01	0.01	0.96	-0.61*	0.26	-0.08***	0.02	0.71	-0.78**	0.23

SE standard error

OR odds ratio

p*<0.05; *p*<0.01; ****p*<0.001

^a Low score for each scale as reference group

^b Controlling for lifestyle variables (sleep hours per day, smoking status, and alcohol consumption), support from family and friends, and suffering from depressive or eating disorders

^c Standardized

poor physical environment had positive association with the risk of suicidal ideation. Among job resources, all job resources excluding job control had negative association with the risk of suicidal ideation in the employee-level. High coworker support had negative association with the risk of suicidal ideation in the organization-level.

Discussion

This study examined the associations between job demands and job resources and the risk of suicidal ideation among a large cross-sectional cohort of Japanese workers. Multilevel logistic regression analyses revealed that at the employeelevel, job demands and job resources had significant associations with the risk of suicidal ideation in both genders. At the organization-level, high physical demands and poor physical environment had positive associations with the risk of suicidal ideation only among females, and high coworker support had negative association with the risk of suicidal ideation in both genders. These results, in particular those at the organization-level, may be the first reported evidence published in work stress literature with regard to the risk of workers' suicidal ideation.

At the organization-level, high coworker support was negatively associated with the risk of suicidal ideation in both genders. Compared to the supervisors, coworkers generally pose as lesser risk and most workers may easily talk about their negative feelings associated with suicidal ideation and thus lessen these feelings through a "cathartic effect". In fact, Fridner et al. [21] revealed that supportive environments when facing difficulties have protective effects on the risk of suicidal ideation among Swedish doctors. Other evidence from cross-sectional studies revealed that organizing a supportive meeting in the workplace had a favorable effect on reducing the risk of suicidal ideation [22, 23]. Although suicidal ideation can be considered as the mentally unhealthy status of workers, organization-level support such as creating a supportive atmosphere, especially from their coworkers, may contribute to reduce workers' suicidal ideation regardless of their gender. Notably, among males, coworker support had no significant association with the risk of suicidal ideation at the employee-level. This may imply that nurturing the coworker support at the organization-level is more important to prevent suicidal ideation, especially for male workers.

With regard to job demands, high physical demands and poor physical environment were positively associated with the risk of suicidal ideation at the organization-level, but only among females. One potential interpretation of these results may be attributed to the specific biological characteristics of females, which is a regular menstrual period. Within a regular menstrual period, many females suffer from severe body pain such as abdominal pain, low back pain, or headaches [24, 25]. Females who are menstruating are also sensitive to fatigue [25]. Therefore, due in part to menstruation, most females may be more easily be affected by high physical demands and poor physical environment such as moving heavy objects or exposure to heat environment and suffer more from negative feelings, and this may finally lead to suicidal ideation in some cases. However, physical demands and physical environment can easily be improved through organizational change, for example, providing protective equipment for employees, setting up air conditioning equipment, or increasing air ventilation, usually accomplished by adopting some kind of action checklists [26-28]. Based on our study results, ameliorating the physical demands and work environment may be important to counter workers' suicidal ideation, especially for female workers.

At the employee-level, most job demands had a positive association with the risk of suicidal ideation. In a crosssectional study, Chin et al. [29] revealed a significant association between work-related stress and suicidal ideation in a sample of 6969 Korean male and female workers. Takada et al. [30] also showed a significant association between job stressors and suicidal ideation with 2834 Japanese male workers in a cross-sectional study. However, this association was not found in 1284 female workers. Although a further repeat study should be undertaken, differences between our results and Takada et al. [30] might partly be attributed to the different measurement process of job demands; Takada et al. [30] summed up each scores of job demands and reversed scores of job resources as an indicator of "job stressors." Other proceeding studies revealed a significant association between interpersonal conflict and suicidal ideation. Wall et al. [22] demonstrated a cross-sectional association between interpersonal conflicts such as "recent degrading experiences" or "harassment at work" and the risk of suicidal ideation among a total of 421 Italian and Swedish doctors. In Japan, Wada et al. [31] conducted a cross-sectional study with 3862 doctors and found a significant association between interpersonal conflicts (unreasonable patient demands and complaints) reported in the previous 6 months and their suicidal ideation. Our results also presented that interpersonal conflict had higher levels of OR with the risk of suicidal ideation in both genders. Thus, interpersonal conflict may be one of the crucial factors associated with Japanese workers' suicidal ideation.

Moreover, our results showed a significant association between overtime work and suicidal ideation in males. We found that when overtime work exceeded 80 h per month, the risk of suicidal ideation increased. These results are consistent with the cross-sectional evidence shown by 67,471 Korean workers [32]. Although the prevalence of suicide attempts is generally lower in males than that in females, the ratio of suicide completion is higher in males [33]. This evidence suggests that males might enhance hidden suicidal ideation when levels of job demands including overtime work become excessive. It is well known that job demands lead to adverse psychological, physiological, and behavioral stress reactions [17, 34–37]. Thus, we should pay more attention to workers' psychological functioning to prevent workplace suicide, especially for males who are determined to accomplish suicide without any consultation with others.

Contrary to the findings from job demands-suicidal ideation relationship, most job resources had a favorable effect on the risk of suicidal ideation. On the JD-R model [13-15], job resources are established at the beginning of the motivation process, enhancing work engagement and diminishing burnout. Our recent study [38] revealed that high levels of job resources such as job control and supervisor or coworker support enhanced work engagement, and these associations were mediated by positive affect and meaningfulness of work. These positive aspects of human emotions may have the potential to prevent the risk of suicidal ideation through cultivating psychological strength against stressful situations, although no significant association was found between job control and suicidal ideation in females. In a cross-sectional study, Fridner et al. [21] revealed a significant negative association between job control such as controllability for their own work hours or amount of work assigned and the risk of suicidal ideation among 241 male physicians. Although our study measured a "general" controllability of their work, controllability for their work hours or amount of tasks may be important to consider male workers' risk of suicidal ideation.

With regard to females, there was an unexpected finding of an inverse association between quantitative job demands and the risk of suicidal ideation at the employee-level. This observation is difficult to interpret but we speculate that females who are extremely competent but have a reduced job quantity may feel frustrated with their work which can cause reduced self-esteem leading to increase suicidal ideation. However, this is just one possible explanation and our study design is cross-sectional with limited variables; further longitudinal study design is needed to confirm this hypothesis.

Several limitations of our study should be noted. First, our data were derived from self-reports; thus, we cannot disregard recall reporting and social desirability bias. Overtime work usually can be measured objectively with registered data from each company. However, we did not collect these types of registered data; the methods mentioned above should be adopted in future research to confirm our results. Second, because our study design was cross-sectional, we could not establish causal relations between independent variables and suicidal ideation. Although we found significant associations between several potential predictors and suicidal ideation, reverse causation is possible. A longitudinal cohort study is required to determine causality of the relationships. Third, although the response rate was relatively high (88.5 %), the non-participants in this population may have had a higher prevalence of suicidal ideation than those who participated. These workers might not have been able to answer the questionnaire; thus, we cannot neglect the healthy worker effect. Fourth, although the prevalence of suicidal ideation was almost identical between males and females presented in past studies [20, 30], it is known that males generally commit suicide more frequently than females [39]. One possible explanation for this difference is that, in general, females may easily share their suicidal ideation with others compared to males [40], but may not take suicide actions. Further study should be undertaken to confirm this assumption. Fifth, although the response rate was relatively high, the representativeness of employees in each organization may not be guaranteed. In this study, we calculated the organization-level job demand and job resource scores based on the individual-level scores, but it was speculated that we can successfully obtained the representative sample in every organization. Because most scores of ICC(1) were significant but small, it also be speculated whether all job demands and job resources had enough information in organization-level. Other organization-derived work-related characteristics should be measured to assess their effects on the associations of the individual-level job demands and job resources with suicidal ideation in the future.

Notwithstanding these limitations, we conclude the following for Japanese workers. In both genders, job demands such as qualitative and physical demands, interpersonal conflict, and physical environment and job resources such as suitable jobs, meaningfulness of work, and supervisor support had significant association with the risk of suicidal ideation at the employee-level. At the organization-level, high physical demands and poor physical environment had positive associations with the risk of suicidal ideation among females, and high coworker support had a negative association with the risk of suicidal in both genders. Organizational campaigns to improve coworker support may have the potential to decrease Japanese workers' suicidal ideation in practice.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the studies presented.

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Interrelationships Between Job Resources, Vigor, Exercise Habit, and Serum Lipids in Japanese Employees: a Multiple Group Path Analysis Using Medical Checkup Data

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Abstract

Background Physical inactivity is one of the major risk factors for dyslipidemia and coronary heart disease. Job resources have been identified as determinants of employees' vigor and physical activity habits.

Purpose Our first purpose was to comprehensively analyze the series of relationships of job resources, through vigor and exercise habit (i.e., one aspect of physical activity), to serum lipid levels in a sample of Japanese employees in a manufacturing company. Our second purpose was to investigate sex differences in these relationships using a multiple-group path analysis.

Methods Data were collected from 4543 employees (men = 4018, women = 525) during a medical checkup conducted in February and March 2012. Job resources (job control, skill utilization, suitable jobs, and meaningfulness of work), vigor,

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exercise habit, triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured cross-sectionally.

Results Job resources and vigor were positively associated with exercise habit in both sexes. Exercise habit was inversely associated with triglyceride (-0.03 in men and -0.01 in women, ps < 0.05) and LDL-C (-0.07 in both sexes, ps < 0.05). HDL-C was positively associated with exercise habit (0.03 in both sexes, ps < 0.05). There was no significant difference by sex in path coefficients, except for the covariance between suitable jobs and meaningfulness of work.

Conclusion Higher levels of job resources were associated with greater vigor, leading to exercise habit, which in turn, improved serum lipid levels. Longitudinal studies are required to demonstrate causality.

Keywords Job resources \cdot Vigor \cdot Physical activity \cdot Exercise habit \cdot Serum lipids

Introduction

Physical inactivity is considered one of the risk factors for mortality [1] and coronary heart disease [2] in the modern society. The Japan Ministry of Health, Labour and Welfare [3] has set improvement of physical activity and exercise as one of the national goals for Japanese health promotion. Several meta-analyses have indicated negative relationships between physical activity and dyslipidemias such as abnormalities in levels of triglyceride, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), which are considered to be main risk factors for coronary heart disease [4–7]. These studies suggest that regular physical activity may improve serum lipid levels. Hence, identifying the critical factors that increase physical activity is important.

Preceding studies have revealed that biological, psychosocial, or environmental factors are effective in increasing physical activity. According to a review by Bauman et al. [8], physical activity is determined in various dimensions. Sallis et al. [9] suggested an ecological model that defined many multi-level factors as determinants of physical activity and emphasized the interactions among these factors. In Japan, ecological models stressing self-efficacy, social support, and neighborhood environment, to increase physical activity, were proposed by Ishii et al. and Oka et al. [10, 11]. In addition, health behaviors of employees could be influenced by jobrelated factors. In occupational research, employees' positive feelings, such as vigor, were also found to be associated with physical activity [12-14]. In these studies, greater levels of vigor which was one of the positive feelings or which was a subordinate factor of work engagement [15] were related to higher levels of physical activity. A 20-year follow-up study conducted by Shirom et al. [16] suggested that vigor for work at baseline influenced physical activity and mortality 20 years later. Employees who are vigorous at work not only are likely to have vigorous lifestyles but also engage in physical activities in their personal lives.

The "job demands-resources model" [17] was proposed to enhance these positive aspects at the worksite and has drawn attention in the past decades. In this model, the "health impairment process" is considered important to promote the positive aspects, preventing burnout and negative health outcomes by reducing job demands [18]. The "motivational process," which promotes mental health by enriching job resources, has also gained significance. Several preceding studies have revealed that job resources such as job control, skill utilization, suitable jobs, and meaningfulness of work could promote employees' positive outcomes [19-21]. Job-related factors could promote or inhibit employees' health behaviors through work-home spillover effects [22, 23]. The workplace can be considered a suitable place to promote healthy behaviors in employees because they spend a considerable amount of time there [24, 25]. In addition, the ecological model [9] suggests that multi-level interventions, including not only the domestic environment but also the occupational environment, are effective in promoting physical activity. Therefore, it is important to investigate the association between job-related factors and physical activity. However, to the best of our knowledge, no study to date has assessed these relationships.

In addition, sex differences in these relationships have not been fully investigated. Because sex is an important biological risk factor for atherosclerotic cardiovascular disease [26, 27], men and women are likely to show a different pattern in these relationships. Additionally, although few studies have investigated the relationships between job-related factors and physical activity, sex differences in neighborhood environment and physical activity have been reported [28]. Thus, it is reasonable to consider the relationship between occupational environment and physical activity separately by sex. In this study, we analyzed the relationships among job resources, vigor, exercise habit (i.e., one aspect of physical activity), and serum lipids in Japanese employees in a manufacturing company. We employed a multiple group path analysis to assess sex differences in these relationships. This study could provide an opportunity to integrate previous evidence into one study by using multivariate analysis and demonstrate the effects of job resources on serum lipids. In addition, this study will encourage occupational health staff to pay attention to job-related factors in order to prevent coronary heart disease. It could thus be hypothesized that employees who have higher levels of job resources at worksites would be vigorous and have more intensive exercise habit. Increasing the intensity of exercise habit would in turn lead to improvement of serum lipid levels.

Methods

Participants

Data were collected at a medical checkup conducted by a manufacturing company that makes beverages in February and March of 2012. A total of 5141 employees were asked to participate in this study, and 4543 employees (men=4018, women=525, mean age=38.7, SD=9.9) who completed the examination and had no missing data during the analysis (valid response rate=88.4 %) were included in the study. We obtained informed consent from all participants before the medical checkup, through an instruction on the questionnaire. The instruction assured protection of personal information, citing that the data would only be used by health care professionals, and only anonymized data would be offered to others strictly for academic use. The study protocol was approved by the ethical committee of the University of Occupational and Environmental Health, Japan (No. H25-120).

Measurements

The self-answered questionnaire was distributed, and blood sample was collected from all participants simultaneously.

The questionnaire assessed the following fields.

Job Resources

The questions on job control (three items, e.g., "I can work at my own pace"), skill utilization (one item [reversed], "My knowledge and skills are rarely used at work"), suitable jobs (one item, "This job suits me well"), and meaningfulness of work (one item, "My job is worth doing") from the Brief Job Stress Questionnaire (BJSQ) were used for assessment [29]. All items were rated on a 4-point Likert scale, ranging from 1 (strongly disagree) to 4 (strongly agree). The internal consistency of job control in this study measured by Cronbach's alpha was 0.66.

Vigor

Vigor also was measured by questions from the BJSQ (three items, e.g., "I have been very active") [29]. The items were rated on a 4-point Likert scale, ranging from 1 (hardly) to 4 (almost). Cronbach's alpha of vigor was 0.89.

Exercise Habit

Exercise habit was measured by a single question that was scored along three points, "(1) do not exercise," "(2) do modest exercise (walking, golf, etc.)," and "(3) do intensive exercise (sports, match, etc.)." Participants were instructed to "please check a point that was most appropriate." A higher point meant a more intensive exercise habit.

Serum Lipids, i.e., Triglyceride, HDL-C, and LDL-C

Triglyceride, HDL-C, and LDL-C levels measured as part of the medical checkup were used. Blood samples were collected from antecubital veins, using fasting measurements. Participants were instructed in advance to fast before the medical checkup. Following the separation of serum, lipids were measured by an enzymatic procedure.

Analyses

Data were analyzed using a multiple group path analysis, stratified by sex (men=4018, women=525). Before the analysis, we conducted an ex ante analysis on all participants (N= 4543) to compare our hypothesized model with the reversed relationships model between vigor and exercise habit (Fig. 1). After the ex ante analysis, we conducted the multiple group path analysis. First, four paths were drawn from job control, skill utilization, suitable jobs, and meaningfulness of work to vigor. Then, we drew a path from vigor to exercise habit. Finally, the three physiological outcomes (triglyceride, HDL-C, and LDL-C) were positioned as dependent variables of exercise habit. Covariances were assumed among four job resources.

We presumed equality constraints to parameters between male and female groups and constructed six different models. The greater the model number was, the stronger the constraints were. Model 1 was not constrained by any parameter. Constraints were added for paths coefficients in model 2, variances of job resources in model 3, covariances in model 5, and all parameters in model 6. In model 4, constraints were assumed partially for covariances (refer to Table 2 for details of model constraints). We adopted the best model, using



Fig. 1 Two models of the ex ante analysis on the association between vigor and exercise habit in all participants (N=4543)

results of a likelihood ratio test and model fit indices. We calculated the goodness of fit index (GFI), adjusted goodness of fit index (AGFI), root mean square error of approximation (RMSEA), and Akaike's information criterion (AIC) for the same. All paths in the model were standardized. SPSS and Amos 22.0 version were used for analyses.

Results

Internal Validity Analysis

At first, we conducted a *t* test and a χ^2 test between participants who completed the study and those who did not to confirm whether non-response bias was present. Employees who completed were significantly younger (*M*=38.7) than those who did not (*M*=45.3, *t* (5139)=14.65, *p*<0.05). In addition, the proportion of men in the completed group (88.4 %) was significantly higher than that in those who did not complete (42.3 %, χ^2 (1)=800.06, *p*<0.05).

Descriptive Statistics and Differences in Study Variables Between Sexes

Table 1 shows the descriptive statistics of variables measured in this study by sex. Mean scores of meaningfulness of work, vigor, and exercise habit in men were significantly higher than those in women. Regarding serum lipids, means of triglyceride and LDL-C were significantly higher in men than they were in women. On the other hand, mean HDL-C was significantly lower in men than it was in women. Table 1Descriptive statistics ofage, job resources, vigor, exercisehabit, and values of serum lipids,and mean differences betweensexes (N=4543)

Variables	Mean (SD) men $(N = 4018)$	Mean (SD) women $(N-525)$	t value
	(N=4018)	(N=525)	(df=4541)
Age	38.73 (9.9)	38.04 (9.9)	1.52 n.s.
Job resources			
Job control (3 items)	8.06 (1.8)	8.03 (1.8)	0.40 n.s.
Skill utilization (1 item)	2.78 (0.7)	2.73 (0.7)	1.50 n.s.
Suitable jobs (1 item)	2.81 (0.7)	2.88 (0.8)	-1.92 n.s.
Meaningfulness of work (1 item)	2.79 (0.8)	2.71 (0.8)	2.26*
Vigor (3 items)	6.98 (2.2)	6.67 (2.3)	2.94*
Exercise habit (1 item)	1.64 (0.7)	1.45 (0.6)	6.11*
Serum lipids			
Triglyceride (mg/dl)	120.83 (107.2)	86.39 (252.9)	5.60*
HDL-C (mg/dl)	58.33 (14.9)	72.93 (17.3)	-20.66*
LDL-C (mg/dl)	120.98 (31.5)	110.91 (30.3)	6.91*

df degree of freedom, n.s. not significant

*p<0.05

Multiple Group Path Analysis

First, we conducted the ex ante analysis in all participants (N= 4543). Path coefficients between vigor and exercise habit were almost identical between our hypothesized model (0.13, p<0.05) and the reversed model (0.11, p<0.05). However, the χ^2 value and AIC of our hypothesized model ($\chi^2(22)$ = 774.17, AIC=820.17) were slightly better than those of the reversed model ($\chi^2(22)$ =781.13, AIC=827.13). Accordingly, we adopted our hypothesized model and conducted the multiple group path analysis.

Table 2 shows the results of the likelihood ratio test and model fit indices across the six models (with different equality constraints as described previously). Model 5 had a significantly worse model fit than model 4 (χ^2 (1)=6.46, p<0.05), as

did model 6 in comparison to model 5 (χ^2 (5)=1064.43, p<0.05). Models 1, 2, 3, and 4 did not have any significant differences. In addition, model 4 had the strongest quality constraints to the parameters. Although model 4 had poorer GFI (0.956) than the other three models, its AGFI, RMSEA, and AIC were the best (AGFI=0.936, RMSEA=0.056, AIC= 988.10). We prioritized statistical parsimony and adopted model 4 as the best model. Therefore, we estimated the covariance between suitable jobs and meaningfulness of work, and residual variances between the groups.

Results of the multiple group path analysis using job resources, vigor, exercise habit, and serum lipids are shown in Fig. 2 (men) and Fig. 3 (women). Most parameters estimated in this model were equal between the groups. All paths in the model were standardized.

Table 2	Likelihood ratio test and model fit indices of models with equ	uality constraints of parameters (grouping=men and women)
	Enternice ou rune test und meder ne marees er models what equ	anty constraints of parameters (grouping men and women)

Model	Equality constraints	χ^2 (df)	$\Delta\chi^2$ (df)	GFI	AGFI	RMSEA	AIC
1	No constraints	912.41 (44)	_	0.957	0.913	0.066	1004.41
2	Path coefficients	921.13	10.89 (8) n.s.	0.957	0.925	0.061	997.13
3	Variances of job resources	923.30 (56)	2.16 (4) n.s.	0.957	0.930	0.058	991.30
4	Covariances of job resources except between suitable jobs and meaningfulness of work	930.10 (61)	6.81 (5) n.s.	0.956	0.936	0.056	988.10
5	Covariances of job resources	936.56 (62)	6.46 (1)*	0.956	0.936	0.056	992.56
6	Residual variances	2000.99 (67)	1064.43 (5)*	0.875	0.833	0.080	2046.99

Note. We used Amos version 22.0 for model comparison

df degree of freedom, n.s. not significant

*p<0.05

Fig. 2 Results of the multiple group path analysis using job resources, vigor, exercise habit, and serum lipid levels in men. Note: All paths were standardized. Parameters differing between the groups are shown in *bold*. GFI = 0.956, AGFI = 0.936, RMSEA = 0.056, AIC = 988.10. *p<0.05



All paths from job resources to vigor were significantly positive in both sexes. Of the job resources, meaningfulness of work had the strongest association with vigor (0.30 in men and 0.27 in women). All covariances among job resources were positively associated with each other, with suitable jobs and meaningfulness of work having the strongest association (0.64 in men and 0.58 in women). The four job resources explained 24 % of the variance of vigor in men and 19 % in women (ps < 0.05). The path coefficients from vigor to exercise had significant positive relationships (0.12 in men and 0.14 in women). Exercise habit and triglyceride had significant negative relationships in both men and women (-0.03 in men and -0.01 in women). LDL-C had significant negative relationships in both sexes (-0.07). Further, exercise habit and HDL-C had significant positive relationships in both sexes (0.03). Exercise habit could explain 0.0-0.4 % of the variances of serum lipids in both sexes (ps < 0.05).

Discussion

The purpose of this study was to analyze the relationships among job resources, vigor, exercise habit (i.e., one aspect of physical activity), and serum lipids in Japanese employees. We also analyzed sex differences of these relationships, using the multiple group path analysis. Results indicated that a comprehensive series of relationships from job resources, through vigor and exercise habit, to serum lipid levels, exist in both sexes, integrating previous evidence into one study. Higher levels of job resources were associated with greater vigor, vigor to more intensive exercise habit, and this in turn led to improve serum lipid levels in both sexes.

The associations between exercise habit and serum lipid levels were in line with the preceding studies [4-7]. Our results may provide additional evidence that more intensive exercise habit likely improves serum lipid levels in both sexes. However, R^2 values of serum lipids were very small (0.000– 0.004). Although these values were statistically significant, the explanatory power of exercise habit was not high. Accordingly, many other factors, in addition to exercise habit, could be associated with serum lipids. Lower level of dyslipidemia among the Japanese in comparison with the European or American population may also explain the weak associations found in this study. For example, the prevalence of abnormal HDL-C levels in Japan was 8.3 % [30], which was much lower than those in European countries and in the USA (30-49 %) [31–33]. Therefore, associations between exercise habit and serum lipids may be weaker in our sample, owing to the fact that majority of our sample had healthy values in serum lipids.

Vigor and exercise habit had a significant positive association in both sexes. In addition, our hypothesized direction model had slightly better model fit than did its reversed model in the ex ante analysis. Vigor has been found to positively

Fig. 3 Results of the multiple group path analysis using job resources, vigor, exercise habit, and serum lipid levels in women. Note: All paths were standardized. Parameters differing between the groups are shown in *bold*. GFI=0.956, AGFI=0.936, RMSEA=0.056, AIC=988.10. *p<0.05



predict employees' good health and proactive behaviors in occupational health studies [34]. It has been suggested that one of the major reasons for this association is that people who are vigorous could be more motivated for physical activity so that they can experience an enhanced vigorous feeling [16, 35]. Therefore, although several studies have mentioned reverse, reciprocal, or other relationships between physical activity and vigor [36–38], being vigorous is also likely to be a determinant of intensive exercise habit. Because this study was cross-sectional, further investigation is needed to establish a causal relationship among these variables.

All four job resources had a positive relationship with vigor in both sexes. This finding validates the results of preceding studies [17, 19–21] and our hypothesis. An increase in job control, which was one of the job resources measured in this study, has been suggested to be predictive of an increase in vigor [19]. It is likely that employees with higher levels of job resources are better able to choose adequate strategies to handle their tasks and reach their goals, and thus have high vigor [20].

Meaningfulness of work, in particular, had a strong association with vigor. Meaningfulness of work, considered to be an intrinsic reward for employees [21], has been proposed to play an important role in increasing positive affect and vigor [20]. A sense of significance for employees' task could serve to energize, reinforce, and maintain work behavior, and may be associated with vigor [39].

Contrary to our expectations, these relationships did not differ between men and women. Although mean scores were significantly different, especially for HDL-C, our results indicated that these associations are almost identical. Sex differences in the effect of exercise or physical activity on improving serum lipid levels have often been discussed [40, 41]. For example, Skoumas et al. [41] indicated that the benefits of being physically active on serum lipids were significant in women but not in men. However, physical activity with sufficient amount, frequency, and duration improved various kinds of serum lipids, regardless of sex [6, 42]. For example, Suzuki et al. [42] revealed that a physical activity routine of 180 min/week had beneficial effects on serum lipids in both sexes, but one of 90 min/week had beneficial effects only in women. Our study could suggest that the association between exercise habit intensity and serum lipid levels is linear, and that more intensive exercise habit is associated with lower triglyceride and LDL-C and higher HDL-C, regardless of sex. The relationships between job resources, vigor, and exercise habit did not differ by sex. This is inconsistent with findings from a community-based survey [28] that showed sex difference in the patterns of relationships between neighborhood environment and physical activity. This discrepancy may be explained by the fact that all participants in our study were employed, while the community-based survey [28] included unemployed people. The unemployment rate in the community-based survey [28] was much higher among women (48.9 %) than among men (16.7 %). Because unemployed people may be more exposed to neighborhood environment than employed people, nonworking women may be more influenced by neighborhood environment than men outside the home. Therefore, the sex difference in the relationship between environment and physical activity observed in the community-based survey [28] may be explained by the sex difference in employment status. Sex differences in the relationship between environment and physical activity may be much smaller among the working population than in the general population.

Although our study design was cross-sectional, it has several practical implications. Enhancing job resources could improve exercise habit and thereby improve serum lipid levels. This possibility, suggested by our study, could encourage occupational health staff to pay attention to job-related factors in order to prevent coronary heart disease. Kouvonen et al. [43] suggested that lack of job resources could spill over to leisure time and may be connected to feelings of helplessness, and insufficient physical activity. Job resources may improve exercise habit through a positive affect like vigor. Although interventions in job resources in order to promote employees' health have been already conducted [44], only few have tried to promote physical activity. In studies focusing on other factors related to physical activity [45], employees are likely to be reluctant to put additional efforts due to time constraints [46]. On the other hand, job resources and employees' vigor are primarily effective in improving performance and commitment towards work and productivity [47], thus directly benefitting the organization.

This study being cross-sectional, a causal relationship could not be established. In particular, the causal relationship between vigor and exercise habit needs to be further investigated. The generalizability of our results needs to be further examined, given that the sample consisted of predominantly male employees from a single company. Available job resources may differ considerably across companies, worksites, job types, and departments. In addition, the small percentage of women (11.6 %) in this study may make it difficult to accurately compare sex differences in the relationships. The internal validity of this study could be questionable due to non-response bias, as participants who completed this study were significantly younger and predominantly male. The path coefficients may have been confounded by age and educational, economic, and marital status. We did not include these covariates in order to avoid complexity of the model. The validity and reliability of the scales used in this study could be questioned, as a single item measured some variables. In particular, we did not measure the frequency, duration, and maintenance of exercise habit. The present findings may also be explained by an incorrect measurement of exercise habit. The frequency, duration, and maintenance of exercise habit might have led to more accurate measurement. The internal consistency of job control was not too high (Cronbach's al-pha=0.66). These limitations need to be addressed in future studies. Moreover, physical activity is constituted not only by exercise in leisure time. The Japan Ministry of Health, Labour and Welfare [3] suggests that all types of activities are effective for health. Future studies also need to assess how worksite support can be effective even to marginally increase physical activity of employees.

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Compliance with Ethical Standards

Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants for being included in the study.

Conflict of Interest The authors declare that they have no competing interests.

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