ISSN 0030-6096

OSAKA CITY MEDICAL JOURNAL

Vol. 68
No. 1

2022

PUBLISHED BY
OSAKA CITY MEDICAL ASSOCIATION
OSAKA JAPAN

Osaka City Medical Journal
Vol. 68, No. 1, June 2022

CONTENTS

Osaka City Med. J. Vol. 68, 1-10, 2022

Comparing the Effects of Intravenous Methylpredonisolone Pulse Therapy with the Conventional dose of Corticosteroids for the Treatment of Acute Facial Nerve Palsy: A Propensity Score Analysis

Masahiro Oishi[1)], Yuki Kouda[1)], Hisao Amatsu[2)], Hisako Yoshida[3)], Ayumi Shintani[3)], and Kishiko Sunami[1)]

Department of Otorhinolaryngology[1)] and Medical Statistics[3)], Osaka City University Graduate School of Medicine; and Department of Otorhinolaryngology[2)], Tane general hospital

Abstract

Background

To evaluate and compare the effectiveness of intravenous methylpredonisolone pulse therapy with conventional dose of corticosteroids for the treatment of facial nerve palsy.

Methods

The recovery rate and treatment period were compared between the intravenous methylpredonisolone pulse therapy and conventional dose of corticosteroids in this retrospective observational study. Patients with acute facial nerve palsy were treated within 7 days after onset.

Results

A total of 74 patients with facial nerve palsy were included: 48 were treated with intravenous methylpredonisolone pulse therapy and 26 with conventional doses of corticosteroids. The recovery rates were 70.8% and 84.6% in the intravenous methylpredonisolone pulse therapy and conventional treatment, respectively. The median treatment periods were 61 days and 30 days in the intravenous methylpredonisolone pulse therapy and conventional treatment, respectively. A statistically significant difference was observed between the two groups (log-rank test $p=0.014$), with the conventional treatment group having a shorter treatment period.

Conclusions

In conclusion, no results showed that intravenous methylpredonisolone pulse therapies were more effective than the conventional steroid treatment.

Key Words: Facial nerve palsy; Bell's palsy; Ramsay Hunt syndrome; Zoster sine herpete; Intravenous methylpredonisolone pulse therapy

Introduction

Facial nerve palsy may occur due to various reasons; however, its primary causes are Bell's palsy

Received August 18, 2021; accepted November 30, 2021.
Correspondence to: Masahiro Oishi, MD.
Depertment of Otorhinolaryngology Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3871; Fax: +81-6-6646-0515
E-mail: oishi1128@omu.ac.jp

and Ramsay Hunt syndrome (RHS). Bell's palsy, defined as an acute facial nerve paralysis of unknown origin, is recently presumed to be caused by reactivation of herpes simplex virus type 1 (HSV1)[1]. RHS occurs with vesicular eruption around the affected ear and with facial palsy caused by the reactivation of varicella-zoster virus (VZV)[2]. Zoster sine herpete (ZSH) is one of the atypical clinical manifestations of herpes zoster. ZSH is caused by the reactivation of VZV but without vesicular eruption. ZSH is one of the causes of facial nerve paralysis; however, distinguishing it from Bell's palsy is difficult. Therefore, it is commonly misdiagnosed as Bell's palsy[3-5]. ZSH is diagnosed with the detection of virus deoxyribonucleic acid (DNA) using polymerase chain reaction (PCR) or anti-VZV antibody in the serum[3,4]. It has also been reported in 8%-19% of patients clinically diagnosed with Bell's palsy[5]. Serological or PCR examinations should be performed to distinguish Bell's palsy from ZSH.

The prognosis of Bell's palsy is favorable, with approximately 70% of patients being completely resolved without treatment[6]. However, the prognosis of facial palsy caused by RHS and ZSH is worse than Bell's palsy[7]. Only 10% of complete facial palsy caused by RHS is resolved without treatment.

Reactivation of HSV1 or VZV in the geniculate ganglion causes facial nerve inflammation and edema, which resulted in facial nerve compression as it travels through the fallopian canal, the leading posited mechanism of Bell's palsy and facial paralysis of RHS. Corticosteroids target the inflammatory process and decrease nerve edema, thereby resulting in the return of facial nerve function.

Some randomized control trials (RCT) of the effectiveness of corticosteroid treatment for Bell's palsy, with higher recovery rate and shorter recovery time[8,9]. Some reports have described the effectiveness of corticosteroids for facial nerve palsy in RHS and ZSH[4,10].

Clinical practice guideline in the American Academy of Otolaryngology-Head, and Neck Surgery (AAO-HNS) recommends a 10-day course of oral steroids with at least 5 days at high dose [prednisolone {PSL} 50 mg/day for 10 days or 60 mg/day for 5 days then tapered for >5 days] to treat Bell's palsy[6]. The French Society of ENT (SFORL) recommends the PSL administration of 1 mg/kg/day for 7-10 days for the treatment of Bell's palsy and PSL 2 mg/kg/day for 10 days for the treatment of severe Bell's palsy[11]. The international guidelines for facial palsy in RHS are not yet established. The Japan Society of Facial Nerve Research proposed a dose of steroids according to the severity of facial palsy. PSL of 120-200 mg/day tapered within 10 days in complete facial palsy (<10 points in the Yanagihara score), PSL of 60 mg/day tapered in moderately facial palsy (18-10 points), PSL of 30 mg/day tapered in mild facial palsy (>20 points) are proposed in both Bell's palsy and RHS based on this guideline[12].

The efficacy of the intravenous methylprednisolone pulse therapy (methylprednisolone 1000 mg/day for 3-5 days) for central inflammatory diseases, such as multiple sclerosis, neuromyelitis optica, and acute transverse myelitis, has been already reported[13-15]. The intravenous methylpredonisolone pulse therapy is considered effective for acute facial nerve palsy but reports of their advisability have never been done before. The intravenous methylpredonisolone pulse therapy is a higher dose than the administration of the high dose steroids reported so far. There is no report comparing the effects of high-dose steroid administration and intravenous methylpredonisolone pulse therapy.

It is necessary to study whether ultra-high dose steroids have more effects to acute facial nerve palsy especially Bell's palsy and RHS than ever reporting.

In this study, we evaluated the effectiveness of intravenous methylprednisolone pulse compared

with the conventional dose of corticosteroids.

Methods

Study design and setting

A retrospective observational study was conducted at the Osaka City University Hospital and Tane General Hospital from April 2014 to March 2016. The ethical committee of Osaka City University Graduate School of Medicine approved this study (No. 2021-087). We included patients with acute facial palsy aged ≧16 years that occurred within 7 days of symptom onset. Precise history taking, thorough physical examination, stapedius reflex assessment, and serum test were performed on the first day. Electroneurography (ENoG) was measured 7-10 days after the symptom onset. Anti-HSV1 IgG and anti-VZV IgG in the serum were examined. A positive diagnosis was made when the HSV1 or VZV antibody was found to be 50 times higher. If both HSV1 and VZV antibodies were low, antibody testing was repeated 2 weeks after. If the increase doubled or higher, it was judged to be positive. HSV1-positive patients were diagnosed with Bell's palsy, VZV-positive with vesicular eruption as RHS, and VZV-positive without vesicular eruption as ZSH.

Patients were treated with (1) conventional dose of corticosteroid (PSL of -200 mg and 10 days tapering) or (2) intravenous methylpredonisolone pulse therapy (intravenous methylprednisolone 1000 mg for 3 days at 1-3 times). All the intravenous methylpredonisolone pulse therapy were performed at the Department of Neurology, Tane General Hospital.

Outcome measures

The facial movement was examined using the Yanagihara facial nerve grading system score at the first visit, one week after onset, the first month, and every month thereafter for up to 6 months. Recovery from the palsy was defined as a score ≧36 using the Yanagihara 40-point scoring system without facial contracture or synkinesis.

Statistical analysis

Continuous variables are represented by the median (interquartile range), and nominal variables are represented by the percentage (frequency). The chi-square test and Mann-Whitney test were used to describe the difference between the two groups. When ≧36 points indicated completely treated by the Yanagihara score, the duration for complete treatment between the normal treatment and steroid pulse groups was compared using the log-rank test with censoring. Patients who were not completely treated after 6 months or those who were lost to follow-up before 6 months were excluded. Next, we compared the time to complete treatment between the two groups using a Cox proportional hazards model with age, gender, and score at the start of treatment as regulators. In addition, a diagnosis was added to the model as interaction term and examined whether a difference in the therapeutic effect depends on the diagnosis. All statistical processing was performed using R (version 4.0.1), and the significance level was set to 5% on two sides.

Results

Among 80 patients diagnosed with acute facial nerve palsy, three were excluded because of diagnosis (facial nerve tumor, temporal bone fracture, and multiple sclerosis). Of 77 patients with facial nerve palsy, 52 were diagnosed as Bell's palsy and 25 as RHS and ZSH. Three of the patients with Bell's palsy not treated with steroid therapy were excluded from the analysis. Twenty-six patients in the conventional treatment group (17 with Bell's palsy, 9 with RHS and ZSH) and 48 in

the steroid pulse therapy group (32 with Bell's palsy, 16 with RHS and ZSH) were investigated. The baseline characteristics are shown in Table 1.

In the conventional treatment group, 17 patients (65.4%) were diagnosed with Bell's palsy and 9 (34.6%) as RHS and ZSH. In the steroid pulse therapy group, 32 patients (66.7%) were diagnosed with Bell's palsy and 16 (33.3%) as RHS&ZSH. No difference in the diagnosis was observed between the steroid pulse and conventional treatment groups. Stapedius reflex was negative in 14 patients (53.8%) in the conventional treatment group and 32 (66.7%) in intravenous methylpredonisolone pulse therapy group. No difference in the ratio of negative stapedius reflex between the steroid pulse therapy and conventional treatment groups. With regard to the ENoG value, the median value of ENoG in the conventional treatment and the intravenous methylpredonisolone pulse therapy was 37.4% and 33.3%, respectively, showing no significant difference. The proportion of patients with ENoG of <10% was 3.8% (1 patient) and 10.4% (5 patients) in the conventional treatment and the intravenous methylpredonisolone pulse therapy groups, respectively, showing no significant difference. The median values of the Yanagihara score observed at the start of treatment were 15.00

Table 1.

		Without steroid pulse	With steroid pulse	p	Overall
Number		26	48		74
Age (median [IQR])		49.00 [34.50-65.00]	61.00 [47.00-71.00]	0.006	58.00 [43.00-68.75]
Sex% (freq)	male	61.5 (16)	54.2 (26)	0.541	56.8 (42)
	female	38.5 (10)	45.8 (22)		43.2 (32)
Diagnosis% (freq)	Bell	65.4 (17)	66.7 (32)	0.911	66.2 (49)
	RHS &ZSH	34.6 (9)	33.3 (16)		33.8 (25)
SR%	negative	53.8 (14)	66.7 (32)	0.278	62.2 (46)
	positive	46.2 (12)	33.3 (16)		
ENoG%		37.40 [24.45-61.23]	33.30 [18.12-59.90]	0.365	33.75 [19.38-60.30]
ENoG 10%	more than 10%	96.2 (25)	89.6 (43)	0.323	91.9 (68)
	less than 10%	3.8 (1)	10.4 (5)		8.1 (6)
Baseline score		15.00 [7.50-18.00]	10.00 [6.00-14.00]	0.106	10.00 [6.00-17.50]

Baseline characteristics of all patients. Steroid pulse is intravenous methylpredonisolone pulse therapy. IQR, Interquartile Range; RHS, Ramsay Hunt syndrome; ZSH, Zoster sine herpete; SR, stapedius reflex; and ENoG, electroneurography.

Table 2.

	Percentage of cure	Treatment period
Treat with conventional treatment	22 (84.6%)	30 (95% CI 30-61)
Treat with steroid pulse	34 (70.8%)	61 (95% CI 30-122)

	Percentage of cure	Treatment period
RHS &ZSH	18 (72.0%)	61 (95% CI 30--)
Bell	33 (77.6%)	61 (95% CI 30-61)

The recovery rate and the treatment period. Steroid pulse is intravenous methylpredonisolone pulse therapy. RHS, Ramsay Hunt syndrome; and ZSH, Zoster sine herpete.

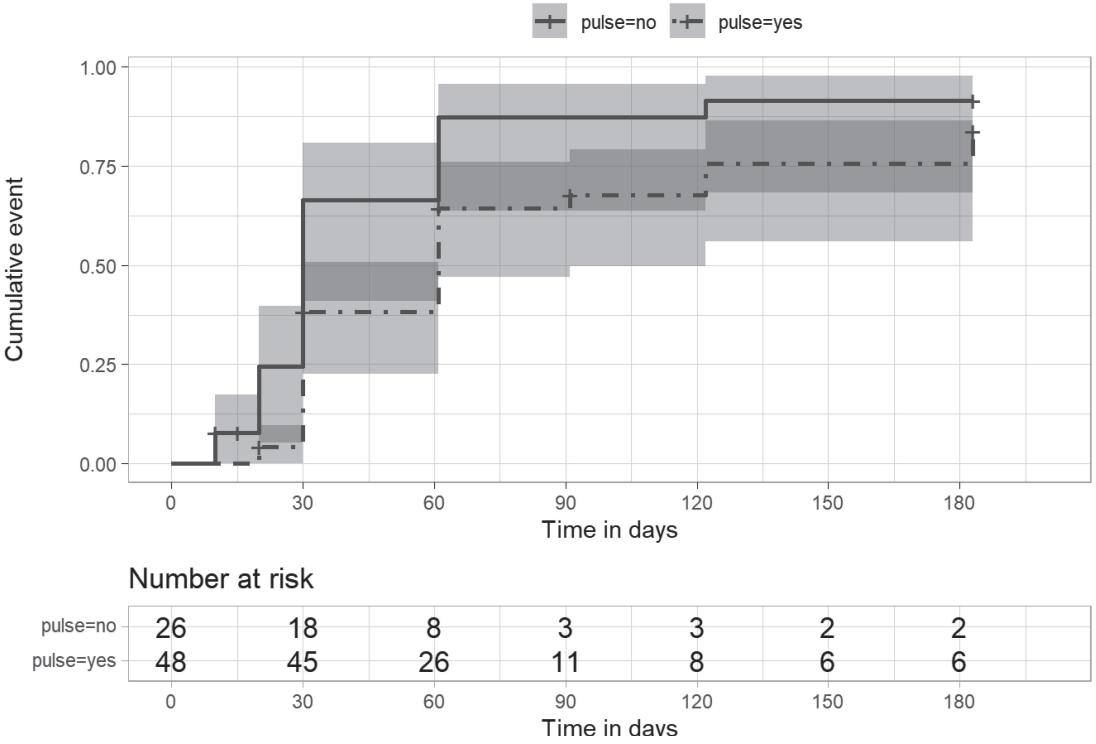


Figure 1. A Kaplan-Meier curve according to the treatment period of the steroid pulse therapy and the conventional treatment group. A statistically significant difference was observed between the two groups (log-rank test p=0.014), suggesting that the duration of for complete treatment the conventional treatment group is shorter than that in the s intravenous methylpredonisolone pulse therapy group. Pulse is intravenous methylpredonisolone pulse therapy. RHS, Ramsay Hunt syndrome; and ZSH, Zoster sine herpete.

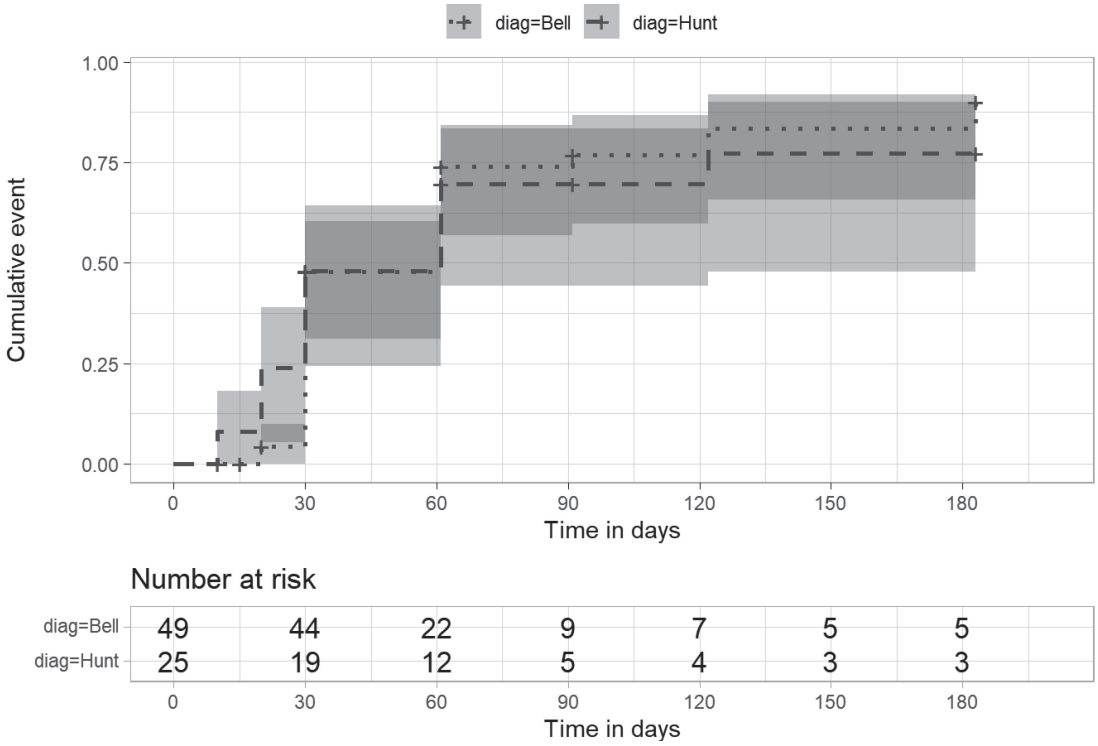


Figure 2. A Kaplan-Meier curve according to the treatment period of Bell's palsy and RHS and ZSH. Any difference between Bell's palsy and RHS and ZSH based on the treatment period were not detected.

and 10.00 points in the normal treatment and the intravenous methylpredonisolone pulse therapy groups, respectively, showing no significant difference.

The recovery rate of patients receiving the conventional treatment and the intravenous methylpredonisolone pulse therapy are shown in Table 2. Of 74 patients, 56 were completely treated with a Yanagihara score of ≧36 points. The rate of complete treatment was 70.8% (34 patients) and 84.6% (22 patients) in the intravenous methylpredonisolone pulse therapy and conventional treatment groups, respectively. The meaning values of the treatment period were 61 days and 30 days in the intravenous methylpredonisolone pulse therapy and conventional treatment groups, respectively. The rate of complete treatment was 77.6% (33 patients) and 72% (18 patients) in the Bell's palsy and RHS and ZSH, respectively. The median treatment period were 61 days in both Bell's palsy and RHS and ZSH groups (Table 2).

A Kaplan-Meier curve according to the treatment period of each group is shown in Figure 1. A statistically significant difference was observed between the two groups (log-rank test $p=0.014$), suggesting that the duration of for complete treatment in the conventional treatment group is shorter than that in the intravenous methylpredonisolone pulse therapy group.

Analysis of each disease is shown in Figure 2. We could not detect any difference between Bell's palsy and RHS and ZSH based on the treatment period.

Next, as a result of the Cox proportional hazard model adjusted for gender, age at the start of treatment, and Yanagihara score at the start of treatment, the hazard ratio for complete treatment in the intravenous methylpredonisolone pulse therapy to the conventional treatment group was 0.787 (95% confidence interval 0.359-1.722, $p=0.548$) (Fig. 3). Finally, when diagnostic were added as interaction, no difference was observed between the presence and absence of intravenous methylpredonisolone pulse therapy for complete treatment in patients with Bell's palsy (HR 1.051, 95% CI 0.504-2.194, $p=0.894$), but not in those with RHS and ZSH (HR 0.151, 95% CI 0.053-0.427, $p<0.001$) for complete treatment of the intravenous methylpredonisolone pulse therapy group, suggesting that the effectiveness of the intravenous methylpredonisolone pulse therapy differs depending on the cause of paralysis (p for interaction=0.003) (Fig. 4). In RHS and ZSH, treatment duration was longer when steroid pulse was administered.

Discussion

We evaluated the effectiveness of the intravenous methylpredonisolone pulse therapy for the treatment of Bell's palsy and RHS and ZSH. The results showed the steroid pulse therapy was not more effective than conventional therapy using 30-200 mg of prednisolone with several days of dose tapering.

Bell's palsy is one of the most common causes of acute facial nerve palsy with an annual incidence of 15-30/100000. Various diseases caused facial nerve paralysis (Table 3)[6]. Among them, Bell's palsy was considered as acute facial nerve palsy with unknown etiology but is currently considered as the reactivation of HSV1[1]. The prognosis of Bell's palsy is favorable, with approximately 70% of patients completely resolved without treatment[6].

RHS is acute facial nerve palsy with auricular vesicular eruptions and pain around the affected ear, with an annual incidence of 5/100000, and is caused by the reactivation of VZV. Its prognosis is worse than Bell's palsy, and spontaneous remission is available in only 30% of patients[10,16,17]. ZSH is an atypical clinical manifestation of herpes zoster, causing acute facial nerve palsy without vesicular

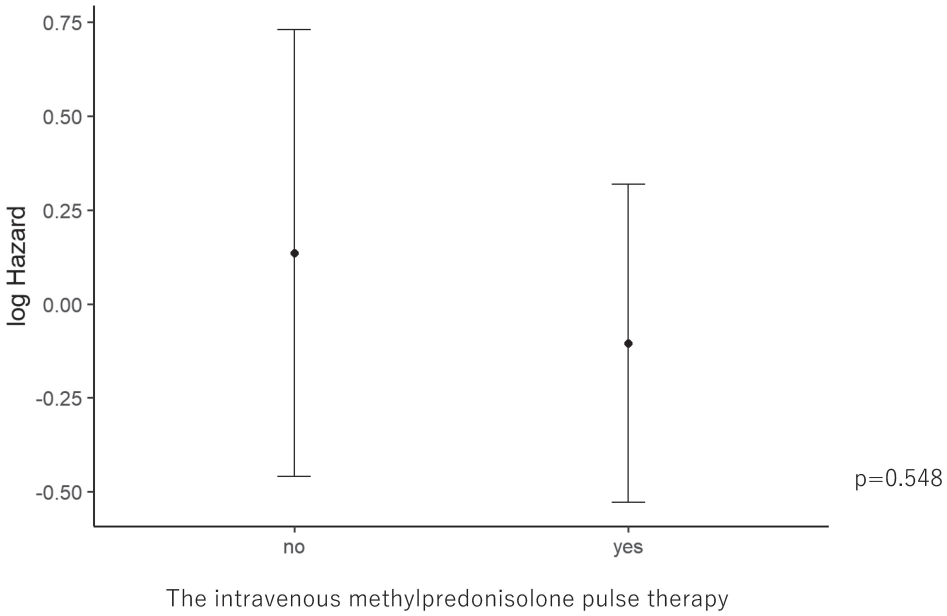
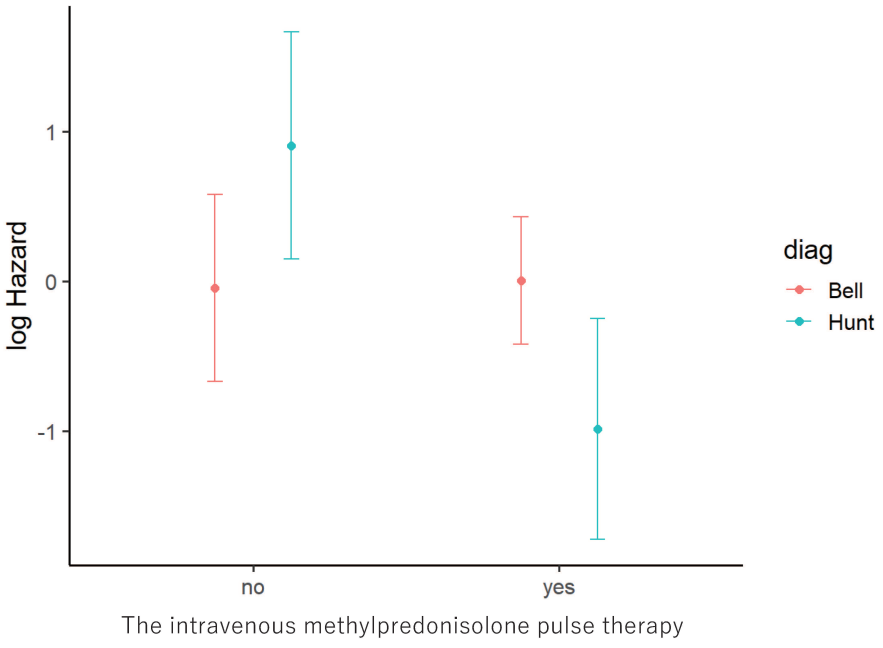


Figure 3. The hazard ratio for complete treatment in the intravenous methylpredonisolone pulse therapy and the conventional treatment group. The hazard ratio for complete treatment in the steroid pulse, intravenous methylpredonisolone pulse therapy to the conventional treatment group was 0.787 (95% CI 0.359-1.722, p=0.548). CI, confidence interval.



		Hazard ratio	95%CI	p value
RHS &ZSH	with/without steroid pulse	0.151	0.053-0.427	<0.001
Bell	with/without steroid pulse	1.051	0.504-2.194	0.894

Figure 4. The hazard ratio for complete treatment in the steroid pulse, intravenous methylpredonisolone pulse therapy and the conventional treatment group depending on the cause of paralysis. No difference was observed between the presence and absence of the steroid pulse therapy for complete treatment in patients with Bell's palsy (HR 1.051, 95% CI 0.504-2.194, p=0.894), but not in those with RHS and ZSH (HR 0.151, 95% CI 0.053-0.427, p< 0.001) for complete treatment of the steroid pulse, intravenous methylpredonisolone pulse therapy group. Steroid pulse is intravenous methylpredonisolone pulse therapy. HR, hazard ratio; RHS, Ramsay Hunt syndrome; ZSH, Zoster sine herpete; and CI, confidence interval.

eruptions and is also caused by the reactivation of VZV[18]. ZSH is diagnosed by increased anti-VZV antibody titer or virus DNA in the cerebrospinal fluid or serum[3]. ZSH is observed in 8%-19% of patients diagnosed with Bell's palsy[5] and involves pain around the affected ear; however, Bell's palsy is also sometimes accompanied by pain, and the degree of pain did not differ in both diseases[4]. Distinguishing Bell's palsy from ZSH is difficult based on physical findings alone. The prognosis of ZSH and RHS is poor. The poor prognosis of patients with Bell's palsy might be the presence of ZSH.

In this study, RHS and ZSH accounted for 31% of acute facial nerve palsy. The ratio of facial nerve palsy associated with VZV was higher than that of previous reports. Robillard et al reported that 185 (12.3%) of 1507 patients with facial nerve palsy were diagnosed as RHS[17] In our study, anti-VZV antibody titer and anti-HSV1 antibody titer were determined to diagnose acute facial nerve palsy; therefore, ZSH could be diagnosed as facial palsy associated with VZV. ZSH is likely to be diagnosed with Bell's palsy when testing for antibodies or PCR was not performed. Furuta et al reported that of 142 patients with acute facial nerve palsy, 56 were caused by reactivation of VZV and 86 by HSV1. They were diagnosed based on increased anti-VZV antibody titer in the serum or virus DNA in the saliva[19]. Our results of the RHS and ZSH ratio in acute facial nerve palsy were consistent with their findings.

Sullivav et al reported a double-blind, RCT about the effect of prednisolone (50 mg for 10 days) for the treatment of Bell's palsy. In their trial, 551 patients were divided into four groups (acyclovir plus prednisolone, acyclovir plus placebo, prednisolone plus placebo, and placebo). About 83% of patients randomized to prednisolone had recovered their facial nerve function, whereas 63.6% of those randomized to placebo had recovered 3 months after treatment ($p<0.01$). Moreover, 94.4% of patients randomized to prednisolone had recovered their facial nerve function, whereas 81.6% of those randomized to placebo had recovered 9 months after treatment[8]. Engström et al also had a substantially similar trial and reported a significant shortening of the treatment period by administering prednisolone (60 mg for 5 days with a 5-day taper)[9].

Based on these results, the AAO-HNS guideline recommends a 10-day course of oral steroid treatment (prednisolone of 50 mg for 10 days or prednisolone of 60 mg for 5 days with a 5-day taper) to treat Bell's palsy[6]. Conversely, Fujiwara et al reported that 50-60 mg prednisolone cannot adequately treat severe Bell's palsy. In their report, 120 mg of prednisolone (2 mg/kg) for 3 days with a 6-day taper can more effectively treat Bell's palsy than 60 mg of prednisolone[20,21].

No studies have reported the effectiveness of steroid pulse therapy for Bell's palsy to date. In our study, no significant effect was observed in administering conventional treatment and steroid pulse therapy, whereas short treatment periods were not observed. The steroid pulse therapy might not be necessary even for severe Bell's palsy.

Several studies have reported the effects of steroids in RHS; however, no RTC or meta-analysis has been conducted on steroid doses. In the review, Monsanto et al reported the difference in the effect of steroid type, each recovery rate was 69.2% in prednisone, 61.4% in prednisolone, 76.2% in hydrocortisone, and 81.3% in methylprednisolone[10]. Various reports have investigated steroid dosages for the treatment of RHS. Kinishi et al reported that 93.4% of patients had recovered facial nerve function using methylprednisolone of 500 mg for 1 day with a 6-day taper combined with acyclovir[16]. Only a few case reports have been published on intravenous methylpredonisolone pulse therapy for RHS. Donani et al reported that the patient who did not improve with initial therapy of oral prednisone (50 mg/day) recovered with the intravenous methylpredonisolone pulse therapy 37 days

after the onset[22]. The intravenous methylpredonisolone pulse therapy is possibly effective for RHS. However, in this study, intravenous methylpredonisolone pulse therapy did not effectively improve and reduce the treatment period compared to conventional treatment to treat RHS and ZSH.

The facial nerve grading system score identifies HSV-1 or VZV and ENoG as factors to predict the prognosis of facial movement. Antibody testing to confirm the cause takes approximately 1-2 weeks. The ENoG is considered as a valid prognosis from the 7th day to 14th days[23]. The administration of steroids to treat facial nerve palsy should be initiated within 72 h of symptom onset. Therefore, steroid doses are determined using the facial nerve grading system score only. In the guideline for facial paralysis of the Japan Society of Facial Nerve Research, the setting of the steroid doses is recommended by score, and if it is ≦8 points in the Yanagihara score, 120-200 mg of prednisolone is recommended[12]. Administration of steroids more than necessary should be avoided to prevent side effects, such as gastrointestinal disturbance, reactivation peptic ulcer disease, and loss of control of glucose level, elevated blood pressure, peripheral edema, and mood swings or episodes of acute psychosis.

In conclusion, the intravenous methylpredonisolone pulse therapy cannot be recommended for RHS and Bell's palsy. Bell's palsy does not require the intravenous methylpredonisolone pulse therapy because it has a good prognosis, but RHS & ZSH has a poor prognosis, so we considered the intravenous methylpredonisolone pulse therapy might be effective. However, the effectiveness of the steroid pulse therapy was not confirmed even in RHS & ZSH. Corticosteroids target the inflammatory process and decrease nerve edema, thereby resulting in the return of facial nerve function. For that purpose, even with severe paralysis, it is likely to be sufficient with 2 mg/kg/day prednisolone, and the steroid pulse therapy are not necessary.

Acknowledgements

All authors have no COI to declare regarding the present study.

The authors would gratefully acknowledge Dr. Shouichi Shiraishi and Ms. Mai Nakano for help with data collection.

References

1. Murakami S, Mizobuchi M, Nakashiro Y, et al. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med 1996;124:27-30.
2. Tomita H, Hayakawa W. Varicella-Zoster virus in idiopathic facial palsy. Arch Otolaryngol 1972;95:364-368.
3. Zhou J, Li J, Ma L, et al. Zoster sine herpete: a review. Korean J Pain 2020;33:208-215.
4. Lee HY, Kim MG, ParkDC, et al. Zoster sine herpete causing facial palsy. Am J Otolaryngol 2012;33:565-571.
5. Hato N, Yamada H, Kohno H, et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. Otol Neurotol 2007;28:408-413.
6. Baugh RF, Basura GJ, Ishii LE, et al. Clinical practice guideline: Bell's palsy. Otolaryngol Head Neck Surg 2013;149: S1-27.
7. Ikeda M, Abiko Y, Kukimoto N, et al. Clinical factors that influence the prognosis of facial nerve paralysis and the magnitudes of influence. Laryngoscope 2005;115:855-860.
8. Sullivan FM, Swan IR, Donnan PT, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. N Engl J Med 2007;357:1598-1607.
9. Engström M, Berg T, Stjernquist-Desatnik A, et al. Prednisolone and valaciclovir in Bell's palsy: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet Neurol 2008;7:993-1000.
10. Monsanto RD, Bittencourt AG, Bobato Neto NJ, et al. Treatment and prognosis of facial palsy on Ramsay Hunt Syndrome: results based on a review of the literature. Int Arch Otorhinolaryngol 2016;20:394-400.
11. Fieux M, Franco-Vidal V, Devic P, et al. French Society of ENT (SFORL) guidelines. Management of acute Bell's palsy. Eur Ann Otorhinolaryngol Head Neck Dis 2020;137:483-488.

12. Murakami S, Treatment of peripheral facial paralysis in acute phase. In: Japan Society of Facial Nerve Research, editor. Guideline for facial paralysis—Bell's palsy and Hunt syndrome. Tokyo: Kanehara shuppan; 2011:55-59.
13. Miller DM, Weinstock-Guttman B, Béthoux F, et al. A meta-analysis of methylprednisolone in recovery from multiple sclerosis exacerbations. Mult Scler 2000;6:267-273.
14. Yamasaki R, Matsushita T, FukazawaT, et al. Efficacy of intravenous methylprednisolone pulse therapy in patients with multiple sclerosis and neuromyelitis optica. Mult Scler 2016;22:1337-1348.
15. Defresne P, Meyer L, Tardieu M, et al. Efficacy of high dose steroid therapy in children with severe acute transverse myelitis. J Neurol Neurosurg Psychiatry 2001;71:272-274.
16. Kinishi M, Amatsu M, Mohri M, et al. Acyclovir improves recovery rate of facial nerve palsy in Ramsay Hunt syndrome. Auris Nasus Larynx 2001;28:223-226.
17. Robillard RB, Hilsinger RL Jr, Adour KK. Ramsay Hunt facial paralysis: clinical analyses of 185 patients. Otolaryngol Head Neck Surg 1986;95:292-297.
18. Nagel MA, Gilden DH. The protean neurologic manifestations of varicella-zoster virus infection. Cleve Clin J Med 2007;74:489-494, 496, 498-499 passim.
19. Furuta Y, Ohtani F, Mesuda Y, et al. Early diagnosis of zoster sine herpete and antiviral therapy for the treatment of facial palsy. Neurology 2000;55:708-710.
20. Fujiwara T, Haku Y, Miyazaki T, et al. High-dose corticosteroids improve the prognosis of Bell's palsy compared with low-dose corticosteroids: a propensity score analysis. Auris Nasus Larynx 2018;45:465-470.
21. Fujiwara T, Namekawa M, Kuriyama A, et al. High-dose corticosteroids for adult Bell's palsy: systematic review and meta-analysis. Otol Neurotol 2019;40:1101-1108.
22. Donati D, De Santi L, Ginanneschi F, et al. Successful response of non-recovering Ramsay Hunt syndrome to intravenous high dose methylprednisolone. J Neurol Sci 2012;318:160-162.
23. Mancini P, De Seta D, Prosperini L, et al. Prognostic factors of Bell's palsy: multivariate analysis of electrophysiological findings. Laryngoscope 2014;124:2598-2605.

Osaka City Med. J. Vol. 68, 11-18, 2022

Somatic Symptoms as Stress Responses among Japanese Workers Measured by the Brief Job Stress Questionnaire

Aya Kadowaki, Shinichi Iwasaki, Yasuhiko Deguchi, Tomoe Mitake, Yukako Okuda, Akihiro Niki, Tomoyuki Hirota, Yoshiki Shirahama, Yoko Nakamichi, and Koki Inoue

Department of Neuropsychiatry, Osaka City University Graduate School of Medicine

Abstract

Background

Occupational stressors cause physiological stress responses representing somatic symptoms and psychological stress responses such as a depressive mood and anxiety. However, few studies have investigated factors related to workers' physiological stress responses. Thus, this study examined the factors associated with stress-related somatic symptoms among Japanese workers.

Methods

Data were collected from 18513 Japanese public servants through the Brief Job Stress Questionnaire (BJSQ) in 2017, which was developed based on the National Institute for Occupational Safety and Health (NIOSH) stress model. Factors predicting higher physiological stress responses among demographic variables (sex and age), work-related variables (job title and job category), psychological stress responses, and two BJSQ factors (occupational stressors and social support) were identified using multiple linear regression analysis.

Results

After adjusting for demographic and work-related variables, higher psychological stress responses, being female, and being older were associated with having higher physiological stress responses. A higher score on psychological stress responses was the most potent factor. Neither greater occupational stressor nor lower social support was associated with a higher score of physiological stress responses when confounding was reduced.

Conclusions

Efforts should be made to identify employees' psychological stress responses in order to reduce workers' stress-related somatic symptoms.

Key Words: Physiological stress response; Psychological stress response; Occupational stress; Somatic symptom; Brief Job Stress Questionnaire

Received September 1, 2021; accepted November 30, 2021.

Correspondence to: Aya Kadowaki, MD.
Department of Neuropsychiatry, Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3821; Fax: +81-6-6636-0439
E-mail: ak.peridot@gmail.com

Introduction

Work-related stressors are widely known as major risk factors for physical and mental health problems among workers. For instance, burnout[1] is a well-known syndrome of exhaustion and disinterest typically in the work context, which can result in various negative effects such as anxiety, depression, and increased health problems[2]. In the meta-analysis by Alarcon[3], several studies have showed an association between workload and negative physical and psychological health outcomes. Other prospective studies suggested that high job demands, low job control, low co-worker support, low supervisor support, low procedural justice, low relational justice, and a high effort-reward imbalance predicted the incidence of stress-related diseases[4]. Limited to physical symptoms, research showed that most psychosocial stressors had small but significant lagged effects on the development of musculoskeletal problems, especially highly monotonous work and lower back pain[5]. The longitudinal and cross-sectional results from another meta-analysis provided some evidence of temporal consistency of the occupational stressor and physical symptom relationship[6].

According to the occupational stress model proposed by the National Institute for Occupational Safety and Health (NIOSH)[7], occupational stressors bring physiological stress responses which constitute somatic symptoms and psychological stress responses such as a depressive mood and anxiety. These stress responses are influenced by several factors such as individual (e.g., age, sex, and personality), non-work (e.g., domestic and family demands), and buffer factors (e.g., social support from supervisors, co-workers). Above all, somatic symptoms such as abdominal discomfort and musculoskeletal pain are frequent among the working population, as past studies have shown that nearly 80% of people have complaints about their health[8,9]. Somatic symptoms have a significantly negative impact on individuals and companies in the long term. They are a substantial cause for physician visits, multiple medical examinations, working disability, and other consequences with considerable socioeconomic impact[10]. Regarding occupational outcomes, high somatic symptom severity was a determinant of prolonged sick leave, prolonged disability, and health-related job loss[11]. In addition, compared to psychological stress responses such as depressive mood and anxiety, research on physiological stress response is scant, and there is no standard coping method that can be prescribed to both companies and individuals[12], which may make coping with it more difficult.

Despite the increasing number of workers in Japan who suffer from somatic symptoms[13], few studies have investigated the factors related to workers' somatic symptoms. Many questionnaires were developed to evaluate workers' occupational stress, including the Brief Job Stress Questionnaire (BJSQ)[14]. This questionnaire was based on the NIOSH occupational stress model mentioned above[7] and the job content questionnaire (JCQ)[15]. These occupational stress models and the validity of questionnaire categories and evaluation methods have already been established. Additionally, BJSQ is widely-used in Japan, known for the main component of the Stress Check Program[16], launched in 2015 as a Japanese annual survey aimed at identifying employees who experience high psychosocial stress in the workplace. Thus, this study aimed to examine the factors related to workers' somatic symptoms using the BJSQ among Japanese participants. According to the NIOSH occupational stress model[7], both of occupational stressors and social supports affect physiological and psychological stress response. Besides, occupational stressors is the only factor which directly affect physiological and psychological stress responses. Hence, it was hypothesized that workers' somatic symptoms were potently affected by occupational stressors and social supports, and they were most potently affected by occupational stressors.

Methods

Participants

This study employed a cross-sectional design. Initially, 18513 public servants at the municipal or the ward office of City A, located in the Kinki region of Japan were approached. In 2015, the Japanese government launched an occupational health policy to screen for workers with high psychosocial stress in a workplace with 50 or more employees[17]. The researchers of this study requested the municipal government of City A for the relevant study data in 2017. After acquiring the secondary data (already anonymized by the office staff), questionnaires with incomplete responses (n=1223) were excluded. Therefore, data from 17290 workers (93.4%) were analyzed for inclusion eligibility.

Demographic and work-related variables

The demographic variables were sex and age. Sex was included as a demographic variable as past studies have reported sex differences in the frequency of somatic symptoms[18,19]. The work-related variables were job title (non-manager and manager) and job category (clerical workers, technical workers, professional workers, and others). Clerical workers were defined as those who carried out clerical tasks related to construction, design, and management (among different roles) of buildings in the municipality; technical workers were those who carried out technical tasks requiring physical endeavors in the municipality; and professional workers comprised of nurses, care workers, public health nurses, and childcare workers, among others.

Brief Job Stress Questionnaire

The BJSQ[14] was originally created from the JCQ[15] and Generic Job Stress Questionnaire developed by the NIOSH[7]. It is a 57-item questionnaire that comprises four subscales and is responded to by using a 4-point Likert-type scale (1=disagree to 4=agree). Its factors are as follows: occupational stressors (17 items; score range: 17-68), which includes questions on work-related stressors (e.g., job demands; physical, psychological, social, or organizational aspects of the job that require sustained physical and/or psychological effort or skills and job control; the ability of a person to influence what happens in their work environment); stress responses (29 items; score range: 29-116) which has two subscales, namely psychological stress responses (PSY: 18 items; score range: 18-72) which includes 6 items for depression, 3 for anxiety, 3 for hostility, 3 for fatigue, and 3 for vigor; physiological stress responses (PHY: 11 items; score range: 11-44) which includes one item each for dizziness, body pain, headache, stiff shoulder, lower back pain, tired eyes, palpitation or shortness of breath, gastrointestinal symptoms, loss of appetite, constipation or diarrhea, and insomnia; social support (9 items; score range: 9-36), which includes questions on social support in the workplace (e.g., supervisor and co-worker support); and work and life satisfaction (2 items; score range: 2-8), which includes questions on employees' satisfaction with their work and personal lives. While calculating the BJSQ score, reversed scoring was used where necessary; higher scores indicated greater stress.

A large-scale investigation confirmed the reliability and validity of the BJSQ and its usefulness in assessing Japanese workers' mental health[20]. Another study conducted with a Japanese sample highlighted that the BJSQ is a well-established and widely used instrument for evaluating occupational stress. It has sufficient reliability and validity in the Japanese setting[21].

In the present study, the Cronbach's alpha coefficients for the factors and subscales were as follows: 0.80 for occupational stressors, 0.93 for psychological stress response (PSY), 0.85 for physiological stress response (PHY), 0.89 for social support, and 0.49 for work and life satisfaction. In

this study, the 2-item work and life satisfaction subscale were excluded because job dissatisfaction was regarded as a part of the stress response according to the occupational stress model by the NIOSH[7].

Statistical analysis

To examine whether demographic variables (sex and age), work-related variables (job title and job category), PSY, and the two BJSQ factors (occupational stressors and social support) predicted higher PHY, a multiple linear regression analysis was conducted. Differences were considered significant at $p<0.05$. All statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

As aforementioned, we acquired and utilized anonymous secondary data (i.e., workers' responses to the BJSQ, which had encrypted identification) in this study; this dataset had been previously collected by the healthcare center of City A through the Stress Check Program. Thus, given that the dataset already existed, the review committee waived the need to collect written informed consent from participants. Moreover, prior to data obtainment, the City A staff had already anonymized and de-identified the whole dataset. We provided a means to opt out of this study on the website. Finally, the Human Subjects Review Committee of Osaka City University approved the study protocol (authorization number: 2969), and this study conformed to the tenets of the Declaration of Helsinki.

Results

Table 1 shows the participants' characteristics and Brief Job Stress Questionnaire (BJSQ) scores (n=17290). In total, 64.5% (n=11145) were men and 35.5% (n=6145) were women. Participants' mean age (± standard deviation [SD]) was 45.6±10.3 years. Among the participants, 70.6% were non-managers (n=12215) and 29.4% were managers (n=5075). The most common job category was that of clerical workers (n=8584, 49.7%).

Table 1. Participants' characteristics and Brief Job Stress Questionnaire (BJSQ) scores (n=17290)

	Range	Total
n		17290
Age, years, mean (±SD)		45.6±10.3
Sex (n, %)		
Male		11145 (64.5)
Female		6145 (35.5)
Job Title (n, %)		
Non-manager		12215 (70.6)
Manager		5075 (29.4)
Job Category (n, %)		
Clerical worker		8584 (49.7)
Technical worker		3341 (19.3)
Professional worker		3328 (19.2)
Other categories		2037 (11.8)
Stress Response		
Psychological stress response	(18-72)	36.2±10.3
Physiological stress response	(11-44)	19.4±5.9
Occupational Stressor	(17-68)	41.9±6.9
Social Support	(9-36)	19.4±5.3

SD, standard deviation.

Table 2 shows the results of the hierarchical multiple linear regression analyses for higher PHY. Entering demographic and work-related variables, that is, age, sex, job title, and job category (Step 1) accounted for 3% of the variance. In Step 1, all variables were significant predictors. Namely, older age, female sex, a manager, and any job category predicted higher PHY. When the BJSQ subscales (PSY, occupational stressors and social support) were added (Step 2), PSY was the only significant predictor (explaining an additional 41% of the variance, $F=1512.440$, $p<0.05$). Namely, higher PSY predicted higher PHY (standard partial regression coefficient $\beta=0.661$: 95% confidence interval [CI], 0.37-0.39). For occupational stressors ($\beta=-0.01$; 95% CI, −0.03 to 0.01) and social support ($\beta=0.01$: 95% CI, −0.01 to 0.02), Step 2 of the model revealed no significant predictors.

Table 2. Related factors for higher physiological stress response by hierarchical multiple linear regression analyses (n=17290)

		Step 1		Step 2	
	Range	B	β	B	β
Age		0.02	0.0304***	0.04	0.061***
Sex		−1.89	−0.152***	−1.28	−0.103***
Job Title		−0.65	−0.05***	−0.20	−0.015*
Job Category					
Clerical worker					
Technical worker		2.38	0.201***	0.37	0.031**
Professional worker		2.40	0.16***	0.96	0.064***
Other categories		1.66	0.11***	−0.10	−0.01
Psychological Stress Response	(18-72)			0.38	0.661***
Occupational Stressor	(17-68)			−0.01	−0.01
Social Support	(9-36)			0.01	0.01
R		0.16		0.66	
R^2		0.03		0.44	
R^2 Change score		0.03		0.41	
F		76.591***		1512.440***	

Step 1: adjusted for age, sex (reference category: male), job title (reference category: non-manager), and job category (reference category: clerical worker).

Step 2: adjusted for the Brief Job Stress Questionnaire (BJSQ) subscales.

*p<0.05, **p<0.01, ***p<0.001.

Discussion

The present study aimed to examine the factors related to somatic symptoms as stress responses in an occupational context among Japanese workers. The results showed that a higher PSY, female sex, and higher age were related factors for a higher PHY (meaning somatic symptoms and subjective somatic complaints). Unexpectedly, neither greater occupational stressors nor lower social support were significantly associated with higher PHY. In the present study, a higher PSY was the most potent factor.

Physiological and psychological stress responses

The current study showed that neither higher occupational stressors nor lower social support was significantly associated with a higher PHY when confounding was reduced. This result seems contradictory to previous studies. Many studies have reported cross-sectional and longitudinal relationships between somatic symptoms and various occupational stressors. For instance, according

to Nixon's meta-analysis[6], somatic symptoms are related to a wide range of job stressors. This tendency was seen for both individual symptoms and composite symptom scales, and the effect sizes of these relationships varied by the stressor and the individual symptom. As for the social supports, studies examining the relationship between burnout[1] and Conservation of Resources theory[22] suggested work sources of support are strongly related to exhaustion, which is one of three main dimensions of burnout[2]. Non-work related sources of support are strongly related to depersonalization and personal accomplishment, the other two dimensions of burnout.

Unlike previous studies, this study measured PSY and PHY separately and simultaneously, and analyses were conducted to examine related factor of somatic symptoms, with confound factors including PSY. Previous studies have showed a close association between psychological symptoms such as depression and anxiety, and somatic symptoms. For instance, Löwe et al[23] found comorbidities between depression, anxiety, and somatization in over 50% of patients in primary care clinics. In a large study, Haug et al[18] showed that the number of somatic symptoms and the total score on the Hospital Anxiety and Depression Scale were linearly correlated. This finding corroborates the present study's finding that a higher PHY was associated with a higher PSY. Considering these past findings, there is the possibility that PSY act as mediators when somatic symptoms as stress responses (PHY) appear. In other words, when one confronted with occupational stressors, subjective somatic complaints appear secondarily. Indeed, past studies have indicated the possibility that depression and anxiety lowered the threshold for the perception of somatic symptoms[24], and depressive mood may foster illness-related memories and a negative view of one's health[25]. On the contrary, Rudy et al[26] suggested that chronic somatic symptoms may play a role in initiating or provoking depression and anxiety, indicating that somatic symptoms and somatic complaints can also contribute to psychological problems. Another possibility suggested by the current study is that PHY are more strongly affected by individual factors rather than occupational stressors or social supports. In any case, this study clarifies the importance of coping with workers' psychological problems to improve their somatic symptoms. Thus, the organizations should make an effort to care for workers' psychological stress responses such as depressive moods or anxiety. Efforts should be made to reduce somatic symptoms or complaints, and the necessary actions should be taken, such as referring workers to clinical doctors at the right time.

Sex and age

The present study also showed an association between a higher PHY and demographic variables such as female sex and older age. Regarding sex, many previous studies indicated that women report more somatic symptoms than men[18,19,27], which supports the results of the present study. There seem to be many reasons for the higher prevalence of somatic symptoms in women. First, previous studies have shown that compared to men, women have a higher prevalence of mental disorders associated with somatic symptoms, such as depression and anxiety disorders[18,28]. Participants in the present study did not have any active mental disorders; however, some psychological problems, which partially resembled depression symptoms and anxiety, may have increased their somatic symptoms. Sex differences in social roles and responsibilities, thresholds for healthcare, and the amplification of physical symptoms were considered[29,30].

Regarding age, several studies have suggested an association between age and somatic symptoms, but results are incoherent and difficult to interpret[19,28,31]. Although physiological functions change with age, somatic symptoms include medically explained symptoms as well as medically unexplained

symptoms or somatization, meaning the tendency to express psychological distress with somatic complaints, which results in inconsistent results caused by between-study differences in the definition of somatization problems, measurement instruments, and the setting of the research population. Several studies have reported somatization in older people, thereby concluding that clinically relevant somatization frequently occurring through somatization disorder in itself is rare among the aging population[32]. These studies can account for the current study's results, as medically explained and unexplained symptoms were not differentiated in this study.

Strengths and limitations

This study has several limitations. First, a cross-sectional design was employed and data were collected from self-reported questionnaires. Since this study used self-administered questionnaires, participants may have included people who exaggerated or diminished their actual degree of symptoms. Furthermore, the causal relationship between the two stress responses could not be determined because of the cross-sectional nature of the study design. A study using a structural equation modelling for two stress responses should be conducted to clarify these mechanisms. Second, as mentioned above, no information regarding the participants' medical history was collected in this study. This will likely increase the PHY in older people, although the participants of this study were clinically healthy enough to be engaged in full-time work. Third, this study's results may have been influenced by residual and unmeasured confounders such as personality[33], temperament[34], stress coping style, and length of employment. However, an understanding of the individual aspects of the stress response is limited. Thus, individual factors were not included in this study, except for age, sex, job title, and job category. Fourth, the data were obtained from public servants of one city in Japan, thus limiting the generalizability of these results to other jobs, regions, and countries. Last, PSY and PHY were not separately examined for their validity and reliability; though the validity and reliability of whole BJSQ and stress response was well established[14].

Despite the limitations, several strengths for our study deserve attention. To the best of authors' knowledge, this is the first investigation on the relationship between occupational stress and stress response dominance, and no previous study has simultaneously examined these two stress responses together. Though somatic symptoms as stress responses remain unclear and still difficult to deal with, our findings may be beneficial for individuals, supporters, and organizations to reduce workers' somatic symptoms. Additionally, few studies on occupational stress targeted for this large sample size in Japan. Moreover, this study utilized the BJSQ, widely-used in Japan as an assessment of workers' subjective stress response, known for the use of government's Stress Check Program. Since it is widely used in Japan, results of the current study is highly versatile for the future studies.

Acknowledgements

All authors have no COI to declare regarding the present study.

References

1. Maslach C, Schaufeli WB, Leiter MP. Job burnout. Annu Rev Psychol 2001;52:397-422.
2. Schaufeli WB, Taris TW, Van Rhenen W. Workaholism, burnout, and work engagement: three of a kind or three different kinds of employee well-being? Appl Psychol 2008;57:173-203.
3. Bowling NA, Alarcon GM. Bragg CB, et al. A meta-analytic examination of the potential correlates and consequences of workload. Work Stress 2015;29:95-113.
4. Nieuwenhuijsen K, Bruinvels D, Frings-Dresen M. Psychosocial work environment and stress-related disorders, a systematic review. Occup Med (Lond) 2010;60:277-286.
5. Lang J, Ochsmann E, Krause T, et al. Psychosocial work stressors as antecedents of musculoskeletal problems:

a systematic review and meta-analysis of stability-adjusted longitudinal studies. Soc Sci Med 2012;75:1163-1174.
6. Nixon AE, Mazzola JJ, Bauer J, et al. Can work make you sick? A meta-analysis of the relationships between job stressors and physical symptoms. Work Stress 2011;25:1-22.
7. Hurrell JJ, McLaney MA. Exposure to job stress: a new psychometric instrument. Scand J Work Environ Health 1988;14:27-28.
8. Ministry of Health Labour and Welfare Comprehensive Survey of Living Conditions. Available online: https://www.mhlw.go.jp/english/database/db-hss/cslc-report2019.html (accessed on Oct 1, 2021).
9. Ihlebaek C, Brage S, Eriksen HR. Health complaints and sickness absence in Norway, 1996-2003. Occup Med (Lond) 2007;57:43-49.
10. Barsky AJ, Orav EJ, Bates DW. Somatization increases medical utilization and costs independent of psychiatric and medical comorbidity. Arch Gen Psychiatry 2005;62:903-910.
11. Hoedeman R, Blankenstein AH, Krol B, et al. The contribution of high levels of somatic symptom severity to sickness absence duration, disability and discharge. J Occup Rehabil 2010;20:264-273.
12. Henningsen P, Zipfel S, Sattel H, et al. Management of functional somatic syndromes and bodily distress. Psychother Psychosom 2018;87:12-31.
13. Nakao M. Work-related stress and psychosomatic medicine. Biopsychosoc Med 2010;4:4.
14. Shimomitsu T, Haratani T, Nakamura K, et al. The final development of the brief job stress questionnaire mainly used for assessment of the individuals. The Ministry of Labor sponsored grant for the prevention of work-related illness 2000;126-164.
15. Karasek R, Brisson C, Kawakami N, et al. The job content questionnaire (JCQ): an instrument for internationally comparative assessments of psychosocial job characteristics. J Occup Health Psychol 1998;3:322-355.
16. Tsutsumi A, Shimazu, A. Eguchi H, et al. A Japanese stress check program screening tool predicts employee long-term sickness absence: a prospective study. J Occup Health 2018;60:55-63.
17. Kawakami N, Tsutsumi A. The stress check program: a new national policy for monitoring and screening psychosocial stress in the workplace in Japan. J Occup Health 2016;58:1-6.
18. Haug TT, Mykletun A, Dahl AA. The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-Ⅱ Study. Psychosom Med 2004;66:845-851.
19. Hiller W, Rief W, Brähler E. Somatization in the population: from mild bodily misperceptions to disabling symptoms. Soc Psychiatry Psychiatr Epidemiol 2006;41:704-712.
20. Kawakami N, Kobayashi F, Araki S, et al. Assessment of job stress dimensions based on the job demands-control model of employees of telecommunication and electric power companies in Japan: reliability and validity of the Japanese version of the job content questionnaire. Int J Behav Med 1995;2:358-375.
21. Endo M, Muto T, Haruyama Y, et al. Risk factors of recurrent sickness absence due to depression: a two-year cohort study among Japanese employees. Int Arch Occup Environ Health 2015;88:75-83.
22. Hobfoll SE. Conservation of resources. A new attempt at conceptualizing stress. Am Psychol 1989;44:513-524.
23. Löwe B, Spitzer RL, Williams JBW, et al. Depression, anxiety and somatization in primary care: syndrome overlap and functional impairment. Gen Hosp Psychiatry 2008;30:191-199.
24. Katon W, Lin E, Von Korff M, et al. Somatization: a spectrum of severity. Am J Psychiatry 1991;148:34-40.
25. Croyle RT, Uretsky MB. Effects of mood on self-appraisal of health status. Health Psychol 1987;6:239-253.
26. Rudy TE, Kerns RD, Turk DC. Chronic pain and depression: toward a cognitive-behavioral mediation model. Pain 1988;35:129-140.
27. Beutel ME, Wiltink J, Kerahrodi JG, et al. Somatic symptom load in men and women from middle to high age in the Gutenberg health study - association with psychosocial and somatic factors. Sci Rep 2019;9:4610.
28. Garrusi B, Danaei M, Aboosaeidi R. The prevalence and predictive factors of somatization and its relationship with anxiety and depression in Iranian population. J Prev Med Hyg 2019;60:E400-E406.
29. Barsky AJ, Wyshak G. Hypochondriasis and somatosensory amplification. Br J Psychiatry 1990;157:404-409.
30. Eagly AH. Sex Differences in social behavior: a social-role interpretation. 1st ed. New York: Psychology Press; 2013.
31. Hilderink PH, Collard R, Rosmalen JGM, et al. Prevalence of somatoform disorders and medically unexplained symptoms in old age populations in comparison with younger age groups: a systematic review. Ageing Res Rev 2013;12:151-156.
32. Sheehan B, Banerjee S. Review: Somatization in the elderly. Int J Geriatr Psychiatry 1999;14:1044-1049.
33. Iwasaki S, Deguchi Y, Inoue K. Effects of “Shinkeishitsu” on occupational stress in Japanese workers. SOJ Psychol 2014;1:1-7.
34. Deguchi, Y, Iwasaki S, Ishimoto H, et al. Relationships between temperaments, occupational stress, and insomnia among Japanese workers. PLoS ONE 2017;12:e0175346.

Osaka City Med. J. Vol. 68, 19-28, 2022

Association between Depression and Anxiety Symptoms and Changes in Neighborhood Interaction among Community-dwelling Older Adults before and after the COVID-19 Pandemic

Hideo Kurozumi[1)], Kentaro Uchida[1)], Jumpei Maruta[2)], Satoshi Nogi[1)], Satoshi Akada[1)], and Koki Inoue[1,3)]

Department of Neuropsychiatry[1)] and Center for Brain Science[3)], Osaka City University Graduate School of Medicine; and Department of Psychiatry[2)], Osaka City Kosaiin Hospital

Abstract

Background

The coronavirus disease (COVID-19) pandemic has changed people's daily lives globally. Specifically, there is concern regarding older adults who are at high risk of severe disease who have fewer opportunities to go out and interact with others, as they may develop psychological problems. This study investigated the relationship between changes in neighborhood interactions and psychological symptoms among older adults during the COVID-19 pandemic.

Methods

We conducted a questionnaire survey from January to May, 2021 and 460 responses were analyzed. We assessed depression and anxiety symptoms using the Kessler Psychological Distress Scale-6 (K6), and the frequency of neighborhood interaction before and after the start of the COVID-19 pandemic using a 4-point scale (1: always, 2: sometimes, 3: not often, and 4: never).

Results

The frequency of interaction with neighbors among community-dwelling older individuals decreased after the start of the pandemic, compared to before. Further, after the start of the pandemic, people who interacted less with their neighbors had higher K6 scores. Depression and anxiety symptoms may also have worsened among those whose frequency of interacting with neighbors decreased around the COVID-19 pandemic, compared with those whose frequency of interacting with neighbors did not change.

Conclusions

Our results suggest that older adults whose frequency of neighborhood interaction decreased are more likely to have psychological symptoms than those who do not. To prevent depression and anxiety symptoms among older adults, it is necessary to promote neighborhood interaction and social activities.

Received September 1, 2021; accepted November 30, 2021.
Correspondence to: Hideo Kurozumi, MD.
Department of Neuropsychiatry, Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3821; Fax: +81-6-6636-0439
E-mail: d18mb013@hg.osaka-cu.ac.jp

Key Words: COVID-19; Depression; Anxiety; Neighborhood; Older adults

Introduction

Japan is a super-aged society with a declining birthrate and an aging population; as of 2020, the number of people aged 65 years or older was 36.17 million, accounting for 28.7% of the total population. It is estimated that this number will reach 38.4% by 2065. The increasing costs of medical and nursing care for older adults place an enormous financial burden on Japan. Depression is a major mental health condition among older adults and in 2013, the prevalence of depression symptoms among the general older population ranged from 21.5% to 36.2%[1]. Depression symptoms are also strongly associated with the development of major depressive disorder[2] and suicide ideation in older adults[3-6]. Therefore, the prevention of depression symptoms in older adults is a crucial issue. Depression symptoms have been shown to be associated with a lack of interaction with others[7,8], social activities[9], and exercise[10], and it is recommended to engage in these activities from an early stage.

Originating in Wuhan, China, the coronavirus disease (COVID-19) has spread globally and was declared a pandemic by the World Health Organization on March 11, 2020[11]. Pandemics are generally said to exacerbate anxiety, due to fear of infection[12]; moreover, the COVID-19 pandemic has led to an increase in the number of people with depression symptoms in the United States[13]. In Japan, the pandemic has led to significant changes in various behavioral patterns, such as people preferring to stay home due to fear of being infected. It has been reported that people with comorbidities, such as diabetes and malignancy, as well as older people are at an increased risk of death from COVID-19[14,15]. Therefore, older people at high risk of severe disease are thought to be less likely to go out and interact with their neighbors. Kimura et al reported that restrictions on gyms, activities, and social participation may lead to increased depression[16]. The lockdown measures implemented after the pandemic began were found to be associated with greater depression and anxiety symptoms than before the pandemic[17-21]. Moreover, the prevalence of depression symptoms was reported to increase by nearly three times after the pandemic started, compared with before the pandemic, due to limited social activities[13]. Prior studies into these changes mostly consist of online questionnaires[13,17-26] and have not sufficiently examined older populations, who are more likely to lack access to Internet. Consequently, it is not yet clear how this change has affected the neighborhood relations of community-dwelling older adults, or whether it has changed or worsened their depression and anxiety symptoms.

To fill the gap in research, this study investigated the relationship between changes in neighborhood social interactions and depression and anxiety symptoms among community-dwelling older adults before and after the start of the COVID-19 pandemic.

Methods

Target population

The survey was conducted in Daito City in the Kansai region of Japan, a city where the proportion of older adults is 27.3% of the community, as of 2021, and the population is gradually aging. We obtained the cooperation of 60 stores operated by the drugstore company located in Daito City, and 510 individuals aged 65 years or older who used these drugstores on a daily basis were asked by store clerks to complete the questionnaire. The participants were not compensated for completing this

questionnaire, but were informed that they would receive compensation for participating in a future follow-up study. The store clerks assisted the participants in filling out the questionnaire. Those who had been diagnosed with dementia or mild cognitive impairment, and those who had visited a medical institution for cognitive impairment, were excluded from the survey. The questionnaire survey was administered from January 2021 to May 2021.

Questionnaire contents

The questionnaire contained items to record age, gender, education, medical history (diabetes, heart disease, stroke, hypertension, dyslipidemia, cancer, and deafness), drinking habits, smoking habits, subjective health, living arrangements, frequency of interacting with neighbors before the COVID-19 pandemic, frequency of interacting with neighbors during frequency of interacting with neighbors during the past three months, and current depression and anxiety symptoms. Diabetes, heart disease, stroke, hypertension, dyslipidemia, and cancer are some of the diseases listed as common among middle-aged and older people in the Japanese government's Longitudinal Study of Middle-aged and Older People[27]. In addition, it has been reported that older people with hearing loss have fewer interactions with others, and thus, feel lonelier. Therefore, in this questionnaire, these seven diseases were identified for the history of disease[28]. For the question on frequency of interaction with neighbors before COVID-19, the questionnaire was administered in a retrospective manner.

For the frequency of interaction with neighbors, the respondents were asked to choose from four options: "1: always", "2: sometimes", "3: not often", and "4: never". Participants were divided into four groups based on their answers, from group 1 'always' to group 4 'never'. The question on the frequency of interactions with neighbors was based on the quadrant method used in the Longitudinal Study of Middle-aged and Older People[27].

For drinking habits, the respondents were asked to choose from seven options: "1: every day", "2: 5-6 days a week", "3: 3-4 days a week", "4: 1-2 days a week", "5: 1-3 times a month", "6: rarely drink", and "7: never drink". The responses were tabulated and answers of 1-5 were judged to be "habitual drinkers", while answers of 6-7 were judged to be "non-drinkers".

For smoking habits, the respondents were asked to choose from among five options: "1: over 31 cigarettes a day", "2: 21-30 cigarettes a day", "3: 11-20 cigarettes a day", "4: 1-10 cigarettes a day", "5: never smoke". The responses were tabulated, and those who chose the responses 1-4 were determined to be "habitual smokers", while those who answered 5 were judged to be "non-smokers".

For subjective health, the respondents were asked to choose from the following six options: "1: very good", "2: good", "3: rather good", "4: rather bad", "5: bad", and "6: very bad". The responses were tallied and answers of 1-3 were categorized as "good subjective health" and 4-6 as "poor subjective health".

The Kessler Psychological Distress Scale-6 (K6) was used to assess depression and anxiety symptoms. The K6 is a self-administered scale developed by Kessler et al in 2002 to assess depression and anxiety symptoms during the previous month[29], and its reliability and validity (in Japanese) have been confirmed[30]. K6 items are answered with six items on a five-point scale ranging from "0: not at all" to "4: always". The score range is from 0 to 24, and scores of 13 or higher has been proposed as indicating serious mental disorders, while scores of 5 or higher has been proposed as indicating psychological stress in the general population[23].

Statistical analysis

Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for *R* (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0)[31].

To determine whether demographic and health characteristics affect the frequency of neighborhood interaction, cross tabulations were conducted in the four groups (mentioned below), according to the frequency of interaction in the neighborhood. The p-values of the tabulation table were examined for age and years of education using the Kruskal-Wallis test, and a chi-squared test was used for other categorical data. The pairwise comparisons using a chi-square test were used to compare the proportions between groups. The p-values were adjusted using the Bonferroni correction.

The participants were divided into four groups according to the frequency of neighborhood interaction in the three months after the start of the COVID-19 pandemic, and an inter-group comparison of K6 scores was performed using the Kruskal-Wallis test in the four groups. In addition, a Steel-Dwass multiple comparison correction was used to compare even pairs in the four groups.

A Wilcoxon signed rank test was performed to determine participants' frequency of neighborhood interactions before and after the COVID-19 pandemic started.

In addition, the frequencies of neighborhood interactions before and after the COVID-19 pandemic were compared individually for each person and divided into two groups: decreased, and non-decreased (unchanged or increased), and the groups were compared using the Mann-Whitney U test for K6 score.

The participants were divided into sixteen combinations according to the type of change in the frequency of neighborhood interactions before and after the start of the COVID-19 pandemic, and a pairwise comparison of K6 scores was performed using the Kruskal-Wallis test for the sixteen combinations. In addition, a Steel-Dwass multiple comparison correction was used to compare even pairs in the sixteen combinations.

In this study, the significance level was set at 5%.

Ethical considerations

Participants were provided with an explanatory document containing the details of the study at the time the questionnaire was provided, and were asked to sign a consent form if they agreed to participate. This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine (approval number: 2020-238).

Results

Our questionnaire survey produced responses from 510 community-dwelling older adults. A total of 460 completed questionnaires (125 male and 335 female participants, inclusion rate of 86.8%, mean age: 73.5 [standard deviation: ±6.8] years) were included in the analysis. Questionnaires with outliers were excluded from analysis.

Table 1 shows the participants' demographic and health characteristics. Participants were divided into four groups, based on the frequency of neighborhood interaction before or after the start of the COVID-19 pandemic. Before the COVID-19 pandemic, gender ($p<0.001$) and a history of diabetes ($p=0.049$) were both significantly associated with the frequency of neighborhood interaction. After the COVID-19 pandemic began, gender ($p=0.021$), drinking habits ($p=0.032$) and K6 score ($p=0.033$) were significantly associated with the frequency of neighborhood interaction. In the group

comparison, there was a significant difference in the K6 score between "1. always" and "4. never" (p= 0.041).

Table 2 shows the changes in the frequency of interactions with neighbors before and after the start of the pandemic. The frequency of interaction with neighbors after the start of the pandemic decreased, compared to before the pandemic (p<0.001).

Figure 1 shows the association between K6 scores and the change in frequency of interaction with neighbors before and after the start of the COVID-19 pandemic. The median (first quartile point [Q1], third quartile point [Q3]) K6 score was 2 (0, 5) in the decreased group, 1 (0, 3) in the non-decreased group. The participants in the group with decreased frequency of neighborhood interaction after the COVID-19 pandemic had significantly higher K6 scores than the non-decreased group (p=0.002).

Table 1. Descriptive statistics: overall and stratified by the frequency of interaction with neighbors before and after the start of the pandemic

Characteristics	Total	Frequency of interactions with neighbors								p	
		Always		Sometimes		Not often		Never			
Before or after the COVID-19 pandemic		Before	After	Before	After	Before	After	Before	After	Before	After
Demographics											
Overall, *n*	460	149	89	160	150	98	145	53	76		
Gender, *n*											
Male	125	25	15	43	39	33	42	24	29	<0.001[a]	0.021[b]
Female	335	124	74	117	111	65	103	29	47		
Age, mean years	73.5	74.5	75	73.2	73.6	72.4	72.5	73.3	73	0.137	0.050
Years of Education, mean years	12.3	12.1	12.3	12.4	12.3	12.6	12.4	12.1	12.1	0.140	0.636
Health and lifestyle											
Medical history, *n*											
Diabetes	63	13	8	21	17	17	23	12	15	0.049	0.151
Heart disease	43	14	7	15	18	8	10	6	8	0.939	0.452
Stroke	14	4	1	4	6	2	2	4	5	0.240	0.104
Hypertension	183	65	45	57	58	37	52	24	28	0.406	0.133
Dyslipidemia	84	31	23	29	24	15	24	9	13	0.734	0.232
Cancer	24	6	4	8	4	6	11	4	5	0.756	0.262
Deafness	48	13	8	17	14	12	19	6	7	0.835	0.655
Drinking habit, *n*	180	49	27	70	72	39	51	22	30	0.260	0.032
Smoking habit, *n*	36	7	4	13	12	11	15	5	5	0.284	0.421
Living arrangements, *n*											
More than one person	349	110	70	125	109	71	111	43	59	0.529	0.710
Living alone	111	39	19	35	41	27	34	10	17		
Subjective health, *n*											
Good	416	134	80	146	139	90	133	46	64	0.753	0.206
Bad	44	15	9	14	11	8	12	7	12		
K6, *n*											
score (0-4)	362		76		118		113		55		0.033[c]
score (5-12)	92		12		31		32		17		
score (13-24)	6		1		1		0		4		

COVID-19, coronavirus disease, SD, standard deviations, and K6, Kessler Psychological Distress Scale-6.

[a] pairwise comparisons of always vs not often, p=0.022, and pairwise comparisons of always vs. never, p<0.001.

[b] pairwise comparisons of always vs never, p=0.022.

[c] pairwise comparisons of always vs never, p=0.041.

Table 2. Changes in the frequency of interactions with neighbors before and after the start of the pandemic

		Frequency of interactions with neighbors after the start of the pandemic, *n*				Total
		Always	Sometimes	Not often	Never	
Frequency of interaction with neighbors before the start of the pandemic, *n*	Always	86	42	17	4	149
	Sometimes	3	100	53	4	160
	Not often	0	6	74	18	98
	Never	0	2	1	50	53
Total		89	150	145	76	460

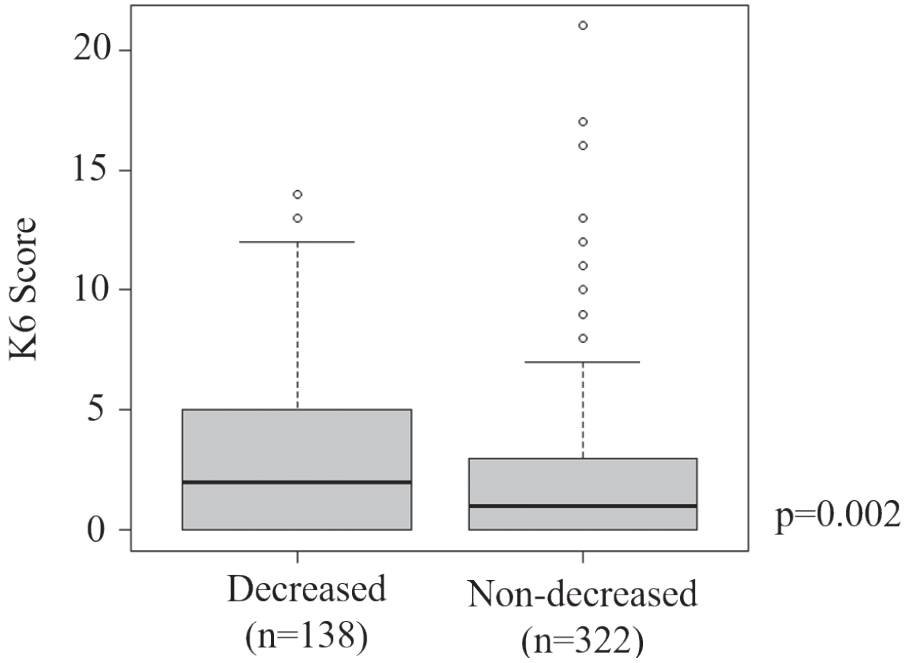


Figure 1. Boxplots of distribution of K6 scores stratified by change of frequency around the COVID-19 pandemic. K6, Kessler Psychological Distress Scale-6, and COVID-19, coronavirus disease.

There were no significant differences found between the 16 combinations according to the type of change in frequency of neighborhood interactions before and after the start of the COVID-19 pandemic.

Discussion

This study examined the relationship between the frequency of interacting with neighbors and depression and anxiety symptoms in community-dwelling older adults during the COVID-19 pandemic. Our study produced two important clinical observations. First, the frequency of interaction with neighbors among community-dwelling older adults decreased after the start of the pandemic, compared to before the pandemic. Second, participants who decreased the frequency of socializing with their neighbors may have worsened depression and anxiety symptoms, compared with those who did not change.

First, we address the decrease in the frequency of interaction with neighbors after the pandemic started. There are several reasons for community-dwelling older adults to limit their activities, such

as interacting with their neighbors. COVID-19 infection carries a very high mortality risk for older adults[22,32]; therefore, they may tend to take the government's request for self-restraint very seriously and increase the amount of time spent in the home. These requests were not intended to force people to take specific actions, as is the case with lockdowns in major cities globally, but rather to ask people to refrain from social activities. In particular, those who regularly consumed alcohol showed a decrease in the frequency of interacting with neighbors after the COVID-19 pandemic started. It has been reported that the isolation caused by COVID-19 increased drinking alone[23], and people with drinking habits may have been staying at home and drinking, limiting their interaction with their neighbors. Our results also showed a correlation between the frequency of neighborhood interactions and history of diabetes before the COVID-19 pandemic. Older adults with diabetes may have had less social interaction because many have diabetes-related complications and decreased activities of daily living than the general older population.

Our second finding is that the decrease in frequency of socializing with their neighbors may have worsened depression and anxiety symptoms, compared with those who did not decrease their frequency of socialization. The strong correlation between depression symptoms and the frequency of interaction with neighbors in older adults has been reported previously[8,33-35]. In this study, 92 patients (20%) had K6 scores of between 5 and 12, and 6 patients (1.3%) had K6 scores of 13 or higher, indicating serious mental disorders. In another Japanese study, the former was 36.6%, and the latter was 11.5%[24]. The reason for the difference in the results may be that the previous study targeted all ages and included a large number of young people who were strongly affected by the COVID-19 pandemic; their survey was conducted around May 2020, when COVID-19 began to spread and people may have felt more anxious. Many studies have pointed out an increase in depression and anxiety symptoms in younger people, rather than in older people[36,37]. One of the factors may be that younger people, who were more active, were more affected by the behavioral restrictions imposed by COVID-19 than older people. However, it has been reported that psychological distress is higher in older age groups[25,38]. This study revealed that depression symptoms worsened in older people who had less interaction with their neighbors, suggesting that interaction with others may be important for alleviating depression symptoms.

Less interaction with others could lead not only to depression, but also to an increased risk of needing nursing care, developing dementia, and early death[39-41]. It is therefore clear that a system to assist older adults socially is necessary. A variety of methods have been recommended to cope with the social isolation caused by the spread of COVID-19, including the use of Internet applications and video chat[42,43], as well as telephone support lines and support groups[26,44,45]. It is conceivable that preventing older adults from becoming isolated and engaging in social interaction from an early stage may help prevent depression and limit the progression of dementia.

One of the main strengths of this study is that it targeted older people in the community and invited them to complete the questionnaire at a location they were likely to use on a daily basis. Since the start of the pandemic, many studies have used online questionnaires to gather data. However, this study may have lower participant bias because physical questionnaires were administered in a drugstore, which allowed us to target people who do not have Internet access or who are uncomfortable with electronic devices.

This study had five limitations. First, in the present study, we used a subjective choice questionnaire, the information before the COVID-19 pandemic was collected retrospectively, the size

of the current study was small, and we did not conduct multivariate analysis, which may have introduced bias in the study results. However, we consider this study to be valuable because studies that investigated the actual situation of older people without using the Internet during the COVID-19 pandemic are distinctive. Second, we did not investigate the history of COVID-19 infection in this study. In total, 1151 people were infected with COVID-19 in Daito City from the beginning of the COVID-19 pandemic to May 2021, which is only 0.96% of the city's population. Therefore, the number of subjects with depressive symptoms as a reaction to the aftereffects of COVID-19 infection or the event of being infected was small, and we considered the effect to be minor. Third, during the study period, both the national and local governments were continuously appealing to people to refrain from social activities; it is therefore possible that the difference in whether the request was made by the Japanese government or the local government may have affected the frequency of people's socialization. Fourth, the survey was conducted at drugstores and the target population was active older adults who could come to the drugstore. Therefore, the frequency of depression and anxiety symptoms may have been lower than that of the total older population. Fifth, we could not determine an association between the degree of change in the frequency of neighborhood socializing and the change in K6 score. It is possible that the comparisons did not result in a significant difference due to the small sample size. Finally, this study did not determine causation between depression and anxiety symptoms worsening and the participants reducing their neighborhood interactions. Further studies are needed to understand this causation and how neighborhood association and depression change during the pandemic, including a larger number of participants by using a method to prospectively record neighborhood relations and depression.

This study found that the frequency of interaction with neighbors decreased due to the COVID-19 pandemic, and that depression and anxiety symptoms were exacerbated among those who interacted with neighbors less. We found that depression symptoms worsened not only in the younger age group as previous research has shown, but also among older adults whose social interaction with neighbors decreased. Older adults, who are likely to have limited social activities due to the COVID-19 pandemic, need to maintain neighborhood and social activities to prevent depression and anxiety symptoms, and social support is important for them to do so.

Acknowledgements

All authors have no COI to declare regarding the present study.

We would like to thank Editage (https://www.editage.com) for English language editing. The authors acknowledge the role of the Wellness Open Living Lab in conducting this study. We would also like to express our sincere gratitude to all the people who understood the purpose of this study and willingly cooperated.

References

1. Sasaki Y, Miyaguni Y, Tani Y, et al. Possibility of social supports as indicators for the community diagnosis of a community preventive approach for depression among older people: Japan Gerontological Evaluation Study (JAGES) 2013. Psychogeriatrics 2015;26:1019-1027. (In Japanese)
2. Beekman AT, Deeg DJ, Van Limbeek J, et al. Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. Psychol Med 1997;27:231-235.
3. Conwell Y, Olsen K, Caine ED, et al. Suicide in later life: psychological autopsy findings. Int Psychogeriatr 1991;3:59-66.

4. Harwood D, Hawton K, Hope T, et al. Psychiatric disorder and personality factors associated with suicide in older people: a descriptive and case-control study. Int J Geriatr Psychiatry 2001;16:155-165.
5. Préville M, Hebert R, Boyer R, et al. Physical health and mental disorder in elderly suicide: a case-control study. Aging Ment Health 2005;9:576-584.
6. Chiu HF, Yip PS, Chi I, et al. Elderly suicide in Hong Kong: a case-controlled psychological autopsy study. Acta Psychiatr Scand 2004;109:299-305.
7. Misawa J, Kondo K. Social factors relating to depression among older people in Japan: analysis of longitudinal panel data from the AGES project. Aging Ment Health 2019;23:1423-1432.
8. Santini ZI, Jose PE, Cornwell EY, et al. Social disconnectedness, perceived isolation, and symptoms of depression and anxiety among older Americans (NSHAP): a longitudinal mediation analysis. Lancet Public Health 2020;5:e62-e70.
9. Yamaguchi M, Inoue Y, Shinozaki T, et al. Community social capital and depressive symptoms among older people in Japan: a multilevel longitudinal study. J Epidemol 2019;29:363-369.
10. Kanamori S, Takamiya T, Inoue S, et al. Frequency and pattern of exercise and depression after two years in older Japanese adults: the JAGES longitudinal study. Sci Rep 2018;8:11224.
11. World Health Organization, Coronavirus disease (COVID-19) Pandemic. 2020. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on Aug 20, 2021)
12. Girdhar R, Srivastava V, Sethi S. Managing mental health issues among elderly during COVID-19 pandemic. J Geriatr Care Res 2020;7:32-35.
13. Ettman CK, Abdalla SM, Cohen GH, et al. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. JAMA Netw Open 2020;3:e2019686.
14. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430-436.
15. Russell B, Moss CL, Palmer K, et al. COVID-19 risk factors for cancer patients: a first report with comparator data from COVID-19 negative cancer patients. Cancers (Basel) 2021;13:2479.
16. Kimura M, Ojima T, Kondo K. Implications for older people's lifestyle during the coronavirus disease pandemic: The Japan Gerontological Evaluation Study. Japanese Journal of Health & Research 2020;41:3-13. (In Japanese)
17. Yamamoto T, Uchiumi C, Suzuki N, et al. The psychological impact of "mild lockdown" in Japan during the COVID-19 pandemic: a nationwide survey under a declared state of emergency. Int J Environ Res Public Health 2020;17:9382.
18. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. Int J Environ Res Public Health 2020;17:1729.
19. Tang W, Hu T, Hu B, et al. Prevalence and correlates of PTSD and depressive symptoms one month after the outbreak of the COVID-19 epidemic in a sample of home-quarantined Chinese university students. J Affect Disord 2020;274:1-7.
20. Moccia L, Janiri D, Pepe M, et al. Affective temperament, attachment style, and the psychological impact of the COVID-19 outbreak: an early report on the Italian general population. Brain Behav Immun 2020;87:75-79.
21. Mazza C, Ricci E, Biondi S, et al. A nationwide survey of psychological distress among Italian people during the COVID-19 pandemic: immediate psychological responses and associated factors. Int J Environ Res Public Health 2020;17:3165.
22. Huang Y, Zhao N. Generalized anxiety disorder, depressive symptoms and sleep quality during COVID-19 outbreak in China: a web-based cross-sectional survey. Psychiatry Res 2020;288:112954.
23. McPhee MD, Keough MT, Rundle S, et al. Depression, environmental reward, coping motives and alcohol consumption during the COVID-19 pandemic. Front Psychiatry 2020;11:574676
24. Stanton R, To QG, Khalesi S, et al. Depression, anxiety and stress during COVID-19: associations with changes in physical activity, sleep, tobacco and alcohol use in Australian adults. Int J Environ Res Public Health 2020; 17:4065.
25. Ping W, Zheng J, Niu X, et al. Evaluation of health-related quality of life using EQ-5D in China during the COVID-19 pandemic. PloS One 2020;15:e0234850.
26. Zhang Y, Ma ZF. Impact of the COVID-19 pandemic on mental health and quality of life among local residents in Liaoning Province, China: a cross-sectional study. Int J Environ Res Public Health 2020;17:2381.
27. Ministry of Health, Labour and Welfare. Longitudinal study of middle-aged and older people. Available online: https://www.mhlw.go.jp/toukei/list/29-6.html (accessed on Aug 20, 2021) (In Japanese)
28. Savikko N, Routasalo P, Tilvis RS, et al. Predictors and subjective causes of loneliness in an aged population. Arch Gerontol Geriatr 2005;41:223-233.

29. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med 2002;32:959-976.
30. Sakurai K, Nishi A, Kondo K, et al. Screening performance of K6/K10 and other screening instruments for mood and anxiety disorders in Japan. Psychiatry Clin Neurosci 2011;65:434-441.
31. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant 2013;48:452-458.
32. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.
33. Hawryluck L, Gold WL, Robinson S, et al. SARS control and psychological effects of quarantine, Toronto, Canada. Emerg Infect Dis 2004;10:1206-1212.
34. Reynolds DL, Garay JR, Deamond SL, et al. Understanding, compliance and psychological impact of the SARS quarantine experience. Epidemiol Infect 2008;136:997-1007.
35. Gerst-Emerson K, Jayawardhana J. Loneliness as a public health issue: the impact of loneliness on health care utilization among older adults. Am J Public Health 2015;105:1013-1019.
36. Daly M, Sutin AR, Robinson E. Depression reported by US adults in 2017-2018 and March and April 2020. J Affect Disord 2021;278:131-135.
37. Xiong J, Lipsitz O, Nasri F, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. J Affect Disord 2020;277:55-64.
38. El Hayek S, Cheaito MA, Nofal M, et al. Geriatric mental health and COVID-19: an eye-opener to the situation of the Arab countries in the Middle East and North Africa Region. Am J Geriatr Psychiatry 2020;28:1058-1069.
39. Saito M, Kondo K, Ojima T, et al. Criteria for social isolation based on associations with health indicators among older people. A 10-year follow-up of the Aichi Gerontological Evaluation Study. Nihon Koshu Eisei Zasshi 2015;62:95-105. (In Japanese)
40. Saito M, Kondo K, Ojima T, et al. Different association between the loss of healthy life expectancy and social isolation by life satisfaction among older people. Jap J Gerontology 2013;35:331-341. (In Japanese)
41. Aida J, Kondo K, Hirai H, et al. Assessing the association between all-cause mortality and multiple aspects of individual social capital among the older Japanese. BMC Public Health 2011;11:499.
42. Banskota S, Healy M, Goldberg EM. 15 smartphone apps for older adults to use while in isolation during the COVID-19 pandemic. West J Emerg Med 2020;21:514-525.
43. Holmes EA, O'Connor RC, Perry VH, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. Lancet Psychiatry 2020;7:547-560.
44. Brooks SK, Webster RK, Smith LE, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet 2020;395:912-920.
45. Wang H, Li T, Barbarino P, et al. Dementia care during COVID-19. Lancet 2020;395:1190-1191.

Osaka City Med. J. Vol. 68, 29-38, 2022

Comparison of Clinical Test Results in Pollen-food Allergy Syndrome: Multicenter Case Series Study

Taisuke Hashimoto[1)], Saki Kasuga[1)], Sakura Ando[1)], Naho Yamamoto[1)], Shiori Fujikawa[1)], Hiroko Fujitani[2)], and Takashi Hamazaki[1)]

Department of Pediatrics[1)], Osaka City University Graduate School of Medicine; and Fujitani Clinic[2)]

Abstract

Background

The crude antigen-specific immunoglobulin E (IgE) test does not necessarily have a high sensitivity and specificity for the diagnosis of pollen-food allergy syndrome (PFAS). The skin prick-to-prick test (PPT) has a high sensitivity; however, it can induce allergic symptoms, similar to the oral food challenge (OFC). A new *in vitro* test for the diagnosis of PFAS is required. This study aimed to compare the results of the basophil activation test (BAT) to the results of the other tests in PFAS.

Methods

To compare the sensitivities of the crude antigen-specific IgE test, PPT, and BAT-CD203c for diagnosing PFAS, we performed these tests on patients with PFAS. To examine the correlation between threshold doses and basophil CD203c expression levels, we also performed OFC on the patients and determined their threshold doses according to the results. We compared basophil CD203c expression levels in patients with oral symptoms and those with systemic symptoms in PFAS.

Results

Ten patients with PFAS induced by eating peach, watermelon, or tomato were analyzed. BAT-CD203c, crude antigen-specific IgE test, and PPT showed sensitivities of 93.3%, 86.7%, and 60%, respectively. There was a significant negative correlation between threshold doses and basophil CD203c expression levels. Basophil CD203c expression levels for the patient with systemic symptoms induced by eating peach were markedly higher than those for patients with oral symptoms.

Conclusions

BAT-CD203c has a high sensitivity in the diagnosis of PFAS and may be useful for predicting the threshold doses. BAT-CD203c may distinguish systemic and oral symptoms in peach allergy.

Key Words: Basophil degranulation test; Food allergy; Peach; Tomato; Watermelon

Received September 15, 2021; accepted November 30, 2021.

Correspondence to: Taisuke Hashimoto, MD.
Department of Pediatrics, Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3816; Fax: +81-6-6636-8737
E-mail: hashimotot.5591@gmail.com

Introduction

Pollen-food allergy syndrome (PFAS) is a food allergy based on cross-reactivity between pollens and food antigens. Its typical symptoms are isolated in the oropharynx, and systemic reactions are unusual[1]. The prevalence rates of PFAS have been reported to be 13%-58% in adults and 4.2% in children[2]. There is a concern that the number of children with PFAS will increase in the future as pollinosis develops at a younger age[3]. The symptoms of PFAS are mostly subjective, and a detailed medical history is important for the diagnosis of PFAS[4,5]. However, it is sometimes difficult to diagnose PFAS in children who have difficulty explaining their symptoms and medical history. Therefore, a superior test to assist the diagnosis of PFAS is needed.

Some objective tests for diagnosing PFAS have been verified, such as the allergen-specific immunoglobulin E (IgE) test, skin prick test, and oral food challenge (OFC)[1,6]. The crude antigen-specific IgE test has been reported to have a sensitivity of approximately 20%-70% and a specificity of approximately 60%-90%[7]. Therefore, it does not necessarily have high sensitivity and specificity for the diagnosis of PFAS. In addition, the crude antigen-specific IgE test result may be negative, even if systemic symptoms appear in PFAS. For example, the sensitivity of the peach-specific IgE test for severe peach allergy has been reported to be approximately 70%[8]. Therefore, the crude antigen-specific IgE test is insufficient to predict the risk of systemic symptoms. The allergen component-specific IgE test has been reported to be useful for predicting the risk of systemic symptoms[9,10]. However, it has not been sufficiently covered by medical insurance in Japan. The skin prick test, especially the prick-to-prick test (PPT), which is performed using fruit and vegetable pulps, has been reported to have higher sensitivity in the diagnosis of PFAS than the allergen-specific IgE test[7]. However, it is difficult to predict the risk of systemic symptoms using the skin prick test and crude antigen-specific IgE test[8], and the skin prick test has a high risk of inducing allergic symptoms in patients who have had systemic symptoms after ingestion of the causative food. If it is difficult to diagnose PFAS even after taking a detailed medical history and performing an allergen-specific IgE test and skin prick test, OFC is finally performed. A double-blind placebo-controlled food challenge (DBPCFC) is recommended because the symptoms of PFAS are mostly subjective[11]. Patients with systemic symptoms can be diagnosed with PFAS even with an open food challenge. Because OFC has a high risk of inducing allergic symptoms, a new *in vitro* test for the diagnosis of PFAS is needed.

The basophil activation test (BAT) is a less invasive test than PPT and OFC. In addition, it is a more useful method for identifying rare allergens compared to the allergen-specific IgE test, in which identifiable allergens are limited[12]. Basophils are activated by allergen-bound IgE antibodies, release inflammatory mediators such as histamine, and produce Th2-type cytokines [interleukin (IL)-4, IL-13] to induce allergic symptoms[13]. The basophil surface markers, CD63 and CD203c, indicate basophil activation, and BAT detects the levels of these markers using a flow cytometer[14]. The BAT has been reported to have high sensitivity and specificity for the diagnosis of peanut, milk, egg, and wheat allergy[15-17]. Regarding the usefulness of BAT in diagnosing PFAS, there are some reports demonstrating the sensitivity and specificity of BAT[18-21]. However, the allergens examined in these reports are limited. Regarding the usefulness of BAT in predicting the severity of PFAS, some studies have examined the difference in BAT between systemic and oral symptoms in PFAS[20,21]. However, the conclusions remain unclear. Furthermore, there are no reports examining the correlation between threshold doses and basophil CD203c expression levels in PFAS.

This study aimed to compare the result of BAT to the results of the other tests for PFAS.

Methods

Study design and study population

This was a multicenter case series study. Between October 2019 and March 2020, we enrolled patients who visited the Department of Pediatrics, Osaka City University Hospital or Fujitani Clinic in Osaka Prefecture and were diagnosed with PFAS. All patients were diagnosed with PFAS because they had a history of oral symptoms due to ingestion of raw fruits or vegetables and tested positive for specific IgE against the pollen that had been reported to be cross-reactive with the causative food. They underwent the crude antigen-specific IgE test, PPT, and BAT against the causative foods, and we examined the sensitivity of each test for the diagnosis of PFAS. OFC was performed on the patients who consented to the test, and their threshold doses were determined based on the results of OFC. We examined the correlation between threshold doses and basophil CD203c expression levels. Patients with systemic symptoms also underwent the crude antigen-specific IgE test, PPT, and BAT against the causative foods, and we compared the results with those of patients who had only oral symptoms. Furthermore, to compare basophil CD203c expression levels in patients with PFAS and healthy subjects, we also performed BAT-CD203c in healthy subjects who did not have food allergies.

Specific immunoglobulin E test

Allergen-specific IgE was measured using ImmunoCAP™ (Thermo Fisher Diagnostics, Uppsala, Sweden). We defined allergen-specific IgE antibody titers of <0.1 U_A/mL as 0 U_A/mL and of $\geqq 100$ U_A/mL as 100 U_A/mL. We also defined allergen-specific IgE antibody titer of $\geqq 0.35$ U_A/mL (CAP class 1) as positive.

Prick-to-prick test

Patients were instructed to stop taking antihistamines 3 days before undergoing PPT. Bifurcated Needle® (Allergy Laboratories, Ohio, Inc., USA) was used as the pricking needle. After piercing the pulp of raw fruits or vegetables with a pricking needle, it was pressed against the skin of the patient's forearm[22]. Allergen Scratch Extract Positive control (Torii) histamine dihydrochloride® (Torii Pharmaceutical Co., Ltd., Japan) and saline were used as positive and negative controls, respectively. Swelling more than twice the size of the positive control was defined as 4 (+), equivalent to that of 3 (+), half of that as 2 (+), less than half of that and larger than the size of the negative control as 1 (+), and equivalent or smaller than that of negative control as 0 (−).We defined 2 (+) or more as a positive response.

Extraction of fruit and vegetable allergens

In brief, the pulp of raw fruits or vegetables was minced and pureed in a food processor, and extraction buffer was added to it. The particles were separated by centrifugation for 10 min at 2000 rpm. The supernatant was collected for use as an extract and dialyzed against phosphate-buffered saline (PBS) overnight. The extracts were freeze-dried and stored at −80℃ until use. The frozen extracts were reconstituted in PBS, and the protein concentration in each extract was measured with a spectrophotometer (NanoDrop™ 2000c, Thermo Fisher Scientific, Wilmington, DE, USA) and diluted to 10 and 100 μg/mL with PBS at the time of use.

Basophil activation test (BAT-CD203c)

To quantify basophil CD203c expression, BAT was performed using a commercial kit (Allergenicity Kit, Beckman Coulter, Fullerton, CA, USA) in a manner similar to that in a previous study[17]. In brief, ethylenediaminetetraacetic acid-containing whole blood was incubated with each antigen extract at protein concentrations of 10 and 100 μg/mL for 10 min at 37℃ after the addition of activation solution

and the mixture of phycoerythrin-cyanine 7-labeled anti-CD3, fluorescein isothiocyanate-labeled anti-CRTH2, and phycoerythrin-labeled anti-CD203c for cell activation and staining of cell surface antigens. Anti-IgE antibody at 10 μg/mL was used as a positive control, and PBS was used as a negative control. The samples were analyzed using a flow cytometer (Gallios™, Beckman Coulter). Basophils were identified based on their forward- and side-scatter properties, the absence of CD3 expression, and the presence of CRTH2 expression. Upregulation of CD203c on basophils was determined using a threshold defined by the fluorescence of unstimulated cells (negative control). The ratio of CD203c expression level induced by a food allergen to that induced by PBS was expressed as the CD203c stimulation index (SI), and CD203c SI ≧2 was defined as positive[16]. Patients with CD203c expression levels induced by an anti-human IgE antibody <10% were defined as low responders and excluded from the analysis.

Oral food challenge

OFC was performed openly. The patients ingested 20g of raw fruits or vegetables at 5-min intervals and up to 100g. OFC was discontinued if subjective or objective symptoms were observed, and total intake was defined as the threshold dose.

Statistical analyses

Sensitivity was calculated as the positivity rate for each test in the patients with PFAS. The correlation between threshold doses and BAT-CD203c SI was analyzed using Spearman's rank correlation coefficient. The difference in BAT-CD203c SI between patients with PFAS and healthy subjects was analyzed using the Mann-Whitney U test. Statistical significance was set at $p<0.05$. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Ethics statement

This study was approved by the Ethical Committee of Osaka City University Graduate School of Medicine (#4411). Informed consent was obtained from the patients or their guardians.

Results

Characteristics of patients

Ten patients were enrolled and underwent clinical testing (Table 1). Patients aged 8 to 19 (median, 12) years were included, and six (60%) were male. Food allergens included peach (70%), watermelon (60%), and tomato (20%). Half of the patients had atopic dermatitis and bronchial asthma, and all patients had allergic rhinitis. The median total IgE levels were 1200 (range: 360-2700) IU/mL, and the median pollen-specific IgE levels were higher in the order Japanese cedar (83 U_A/mL), alder (64.7 U_A/mL), and orchard grass (2.13 U_A/mL). No low responders were found in BAT.

Sensitivity of tests

The sensitivities of the crude antigen-specific IgE antibody test, PPT, and BAT-CD203c against food allergens in the diagnosis of PFAS were examined (Table 2). The sensitivities of the crude antigen-specific IgE antibody test were 85.7%, 83.3%, and 100% for peach, watermelon, and tomato, respectively. Similarly, the sensitivities of PPT, BAT-CD203c in the extract at 10 μg/mL, and BAT-CD203c in the extract at 100 μg/mL were 71.4%, 50%, and 50%; 14.3%, 33.3%, and 100%; and 85.7%, 100%, and 100% for peach, watermelon, and tomato, respectively. For total food allergens, BAT-CD203c in the extract at 100 μg/mL showed the highest sensitivity (93.3%), followed by the crude antigen-specific IgE antibody test (86.7%), PPT (60%), and BAT-CD203c in the extract at 10 μg/mL

Table 1. Demographics and clinical test results of ten patients with PFAS

Subject	Age/Sex	AD	BA	AR	T-IgE	Japanese cedar sIgE	Alder sIgE	Orchard grass sIgE	Allergen	Crude antigen sIgE	PPT	BAT-CD203c SI (10 μg/mL)	BAT-CD203c SI (100 μg/mL)	Threshold doses
1	8/F	+	−	+	2700	90.7	100	11.5	Peach	84.4	2	1.02	39.36	NA
									Watermelon	5.8	2	4.22	66.79	NA
2	12/M	−	−	+	2000	100	86.7	9.14	Watermelon	5.54	3	13.24	76.35	20g
									Tomato	13.3	3	6.32	73.48	NA
3	9/F	+	+	+	1400	57.5	17.8	0.48	Peach	15.0	2	3.13	39.84	40g
4	14/M	+	+	+	576	100	27.8	32.5	Watermelon	1.47	3	0.44	146.79	NA
5	19/F	+	+	+	2339	29.0	0.89	2.16	Watermelon	0.82	0	1.62	157.86	NA
6	18/M	−	−	+	835	75.3	53.3	2.09	Peach	10.4	2	0.56	21.35	100g
7	12/F	−	−	+	360	0.14	8.07	0.19	Peach	0.1	0	0.60	1.31	80g
									Watermelon	0	0	1.21	81.0	40g
8	11/M	−	−	+	1207	100	100	24.7	Peach	50.5	4	1.40	15.55	NA
									Watermelon	1.78	0	1.47	17.65	NA
9	16/M	−	+	+	873	43.7	76.1	2.0	Peach	27.7	0	1.21	16.63	NA
									Tomato	1.73	0	2.62	13.76	NA
10	12/M	+	+	+	1192	100	92.9	1.47	Peach	59.1	2	1.33	18.03	NA

PFAS, pollen-food allergy syndrome; AD, atopic dermatitis; BA, bronchial asthma; AR, allergic rhinitis; T-IgE, total IgE; sIgE, specific IgE; PPT, prick-to-prick test; BAT, basophil activation test; SI, stimulation index; and NA, not available.

Table 2. Results and sensitivities of tests in PFAS patients

Test	Median (range)	Sensitivity
Specific IgE (U_A/mL)		
Peach	27.7 (0.1-84.4)	85.7%
Watermelon	1.63 (0-5.8)	83.3%
Tomato	7.52 (1.73-13.3)	100%
Total	5.8 (0-84.4)	86.7%
PPT (+)		
Peach	2 (0-4)	71.4%
Watermelon	1 (0-3)	50%
Tomato	1.5 (0-3)	50%
Total	2 (0-4)	60%
BAT-CD203c SI (extract at 10 μg/mL)		
Peach	1.21 (0.56-3.13)	14.3%
Watermelon	1.54 (0.44-13.24)	33.3%
Tomato	4.47 (2.62-6.32)	100%
Total	1.40 (0.44-13.24)	33.3%
BAT-CD203c SI (extract at 100 μg/mL)		
Peach	18.03 (1.31-39.84)	85.7%
Watermelon	78.67 (17.65-157.86)	100%
Tomato	43.62 (13.76-73.48)	100%
Total	39.36 (1.31-157.86)	93.3%

PPT, prick-to-prick test; BAT, basophil activation test; and SI, stimulation index.

(33.3%).

Correlation between BAT-CD203c SI and threshold dose

OFC was performed on four patients who consented to the test (peach: n=2, watermelon: n=1,

both peach and watermelon: n=1), and the correlation between threshold doses and BAT-CD203c SI was examined (Fig. 1). There was a significant negative correlation between threshold doses and BAT-CD203c SI in the extract at 10 μg/mL (r_s=−0.975, p=0.005). The correlation between threshold doses and BAT-CD203c SI in the extract at 100 μg/mL tended to be negative, although not significant (r_s=−0.718, p=0.172).

Difference in laboratory results between systemic and oral symptoms in peach allergy

The laboratory results of seven patients who had oral allergy symptoms (OAS) (OAS patients) after eating raw peach were compared with those of a patient who had systemic symptoms [systemic reaction (SR) patient] (Table 3). Total IgE was normal in the SR patient, but it was high in OAS patients. Peach-specific IgE was negative in the SR patient; in contrast, it was positive in six of the seven OAS patients. Specific IgEs against Pru p 1, 3, 4, and 7, which are peach allergen components, was measured in the SR and OAS patients. In the SR patient, Pru p 1-, 3-, and 4-specific IgE levels were negative, and the Pru p 7-specific IgE level increased to 0.67 U_A/mL (CAP class 1). Pru p 7 as peach gibberellin-regulated protein (GRP) has been identified[8], and GRP has been reported as food antigens that result in systemic symptoms[10]. Therefore, we diagnosed the SR patient as having peach GRP allergy. In contrast, among the OAS patients, Pru p 1-specific IgE was positive in six of the seven patients, Pru p 4-specific IgE was positive in two of the seven patients, and Pru p 3- and 7-specific IgE were negative in all patients. Alder-specific IgE was negative in the SR patient and positive in all OAS patients. PPT was positive in the SR patient and in five of the seven OAS patients. BAT-CD203c was performed on the SR patient, the seven OAS patients, and six healthy controls (Fig. 2). In healthy controls, BAT-CD203c SI in the extracts at both 10 and 100 μg/mL was negative. In the OAS patients, BAT-CD203c SI in the extract at 10 μg/mL was positive in one of the seven patients and in the extract at 100 μg/mL was positive in six of the seven patients. BAT-CD203c

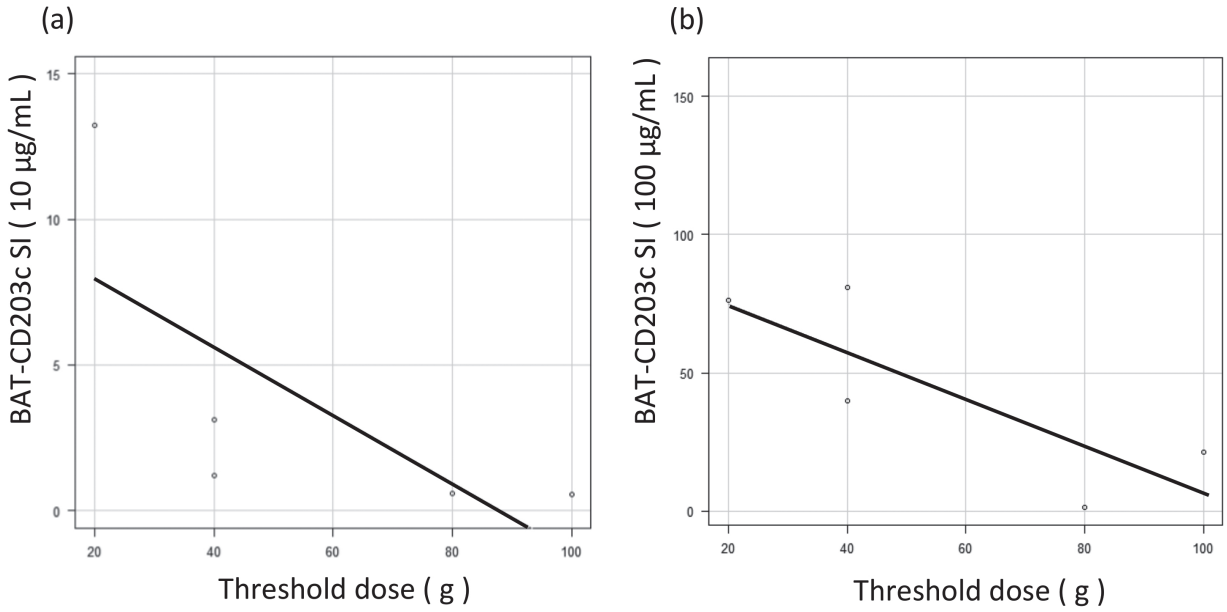


Figure 1. Correlation between BAT-CD203c SI and threshold dose in patients with PFAS. There was a significant negative correlation between threshold doses and BAT-CD203c SI in the extract at (a) 10 μg/mL (n=5, r_s=−0.975, p=0.005). The correlation between threshold doses and BAT-CD203c SI in the extract at (b) 100 μg/mL tended to be negative, although not significant (n=5, r_s=−0.718, p=0.172). BAT, basophil activation test; SI, stimulation index; and PFAS, pollen-food allergy syndrome.

SI in the extract at 100 μg/mL was significantly higher in the OAS patients than in healthy controls. In the SR patient, BAT-CD203c SI in the extract at both 10 and 100 μg/mL was positive, and BAT-CD203c SI in the extract at 10 μg/mL was markedly higher than that in the OAS patients and healthy controls.

Table 3. Demographics and sensitization of patients with peach allergy

	Peach allergy	
	SR (n=1)	OAS (n=7)
Age (y)	24	12 (8-18)
Female	1	3 (43)
Total IgE (IU/mL)	35	1192 (360-2700)
Specific IgE (U_A/mL)		
Peach	0	27.7 (0.1-84.4)
Pru p 1	0	44.8 (0-100)
Pru p 3	0	0 (0-0.34)
Pru p 4	0	0 (0-46)
Pru p 7	0.67	0 (0-0.29)
Japanese cedar	6.38	75.3 (0.14-100)
Alder	0	76.1 (8.07-100)
PPT (+)	2	2 (0-4)

Values in OAS are expressed as median (range) or numbers (percentages). SR, systemic reaction; and OAS, oral allergy syndrome.

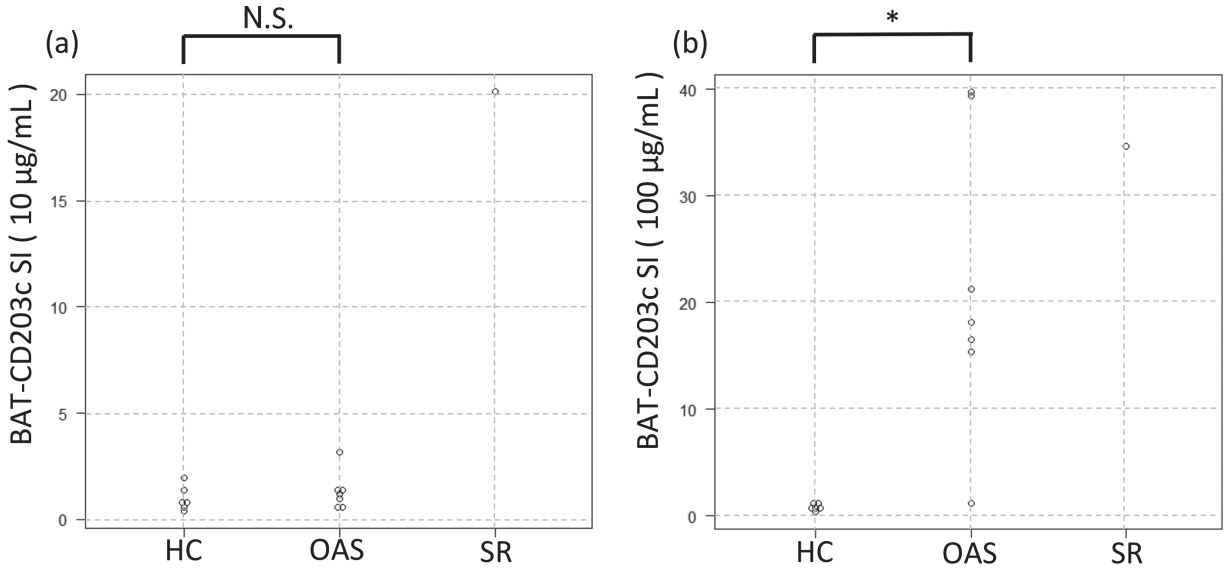


Figure 2. Comparison of BAT-CD203c SI in peach allergy and healthy control. BAT-CD203c was performed on the SR patient, the seven OAS patients, and six healthy controls. BAT-CD203c SI in the extract at (b) 100 μg/mL was significantly higher in the OAS patients than in healthy controls. In the SR patient, BAT-CD203c SI in the extract at both (a) 10 and (b) 100 μg/mL was positive, and BAT-CD203c SI in the extract at (a) 10 μg/mL was markedly higher than that in the OAS patients and healthy controls. *$p<0.05$. BAT, basophil activation test; SI, stimulation index; SR, systemic reaction; OAS, oral allergy syndrome; HC, healthy control; and N.S., not significant.

Discussion

In this study, we found that BAT-CD203c using crude antigen extracts showed high sensitivity in the diagnosis of PFAS. Moreover, the higher the BAT-CD203c SI, the lower the threshold dose. We suggest that BAT-CD203c using peach extracts may distinguish between systemic and oral symptoms in peach allergy.

It has been reported that BAT has a high sensitivity and specificity in the diagnosis of peanut, milk, egg, and wheat allergies[15-17] and has a high diagnostic accuracy for PFAS[18-21]. In this study, we showed that BAT has a high sensitivity for the diagnosis of PFAS, a result consistent with those of previous studies. There have been no reports examining the correlation between threshold doses and BAT-CD203c. In this study, we reported for the first time that there was a significant negative correlation between threshold doses on the basis of the results of OFC and BAT-CD203c SI for PFAS. Therefore, BAT may be useful for predicting the threshold doses of food allergens for PFAS. There have been some reports examining the difference in BAT between systemic and oral symptoms for PFAS[20,21]. However, there has been no consensus on this topic. In fruit and vegetable allergies, lipid transfer protein (LTP) and GRP have been reported as food antigens that result in systemic symptoms and sometimes anaphylaxis[9,10]. Pru p 3 as peach LTP and Pru p 7 as peach GRP have been identified[8,23]. Fruit peels contain more LTP, whereas fruit pulp contains more GRP. It has been suspected that the causative antigen of severe peach allergy in Japan is mainly Pru p 7 because most Japanese people eat peeled peaches[10]. In recent years, it has been reported that cypmaclein, a cypress GRP, is cross-reactive with Pru p 7[24]. In this study, the patient who had systemic symptoms after eating raw peaches was diagnosed as having GRP allergy because of an increase in the Pru p 7-specific IgE level. In this patient, BAT-CD203c in the peach extract at 10 μg/mL was markedly higher than that in the patients who had only oral symptoms and healthy controls. This suggests that BAT-CD203c may be useful in predicting the risk of systemic symptoms in PFAS.

Currently, there is no unified standard for the concentration of antigen extracts used in BAT. In this study, BAT was performed in extracts at two concentrations (10 and 100 μg/mL), and the results at each concentration were analyzed. As a result, there were some differences in the results between the two concentrations. First, the sensitivity of BAT in diagnosing PFAS was high at 100 μg/mL, whereas it was low at 10 μg/mL, except for tomatoes. Second, BAT-CD203c SI in peach OAS was significantly higher only at 100 μg/mL than in healthy controls. Third, there was a significant negative correlation between threshold doses and BAT-CD203c SI in the extract at 10 μg/mL. Fourth, BAT-CD203c SI in the peach extract at 10 μg/mL was markedly higher in the SR patient than in the OAS patients and healthy controls; however, the SI at 100 μg/mL did not differ between the SR patient and the OAS patients. Therefore, we suggest that BAT in extracts at a higher concentration (100 μg/mL) and a lower concentration (10 μg/mL) may be useful for diagnosing PFAS and for predicting the severity of PFAS, respectively. BAT should be performed simultaneously at multiple antigen concentrations for one causative food. In contrary, PPT, which was reported to have high sensitivity in the diagnosis of PFAS, was less sensitive than BAT and the crude antigen-specific IgE test in this study. This result is possibly attributed to the fact that some patients did not comply with discontinuation of antihistamines before PPT and that the doctor who performed PPT was not the same person at the two medical institutions.

This study has several limitations. First, in this study, the sensitivity of each test could be obtained, but the specificity could not be obtained, which was insufficient to evaluate the diagnostic

accuracy. However, by comparing the sensitivities of the tests in this study, it was found that BAT is a useful test for the exclusion diagnosis of PFAS. Second, the number of patients in this study was small, and only one patient had systemic symptoms due to the ingestion of a raw peach. Therefore, it was insufficient to compare BAT-CD203c SI in SR patients with that in OAS patients. Long-term prospective studies are required in the future. Third, in this study, open OFCs were performed instead of DBPCFC. This may have affected the results because PFAS mainly causes subjective symptoms such as itching and tingling in the oropharyngeal area. The medical institutions where DBPCFC can be performed are limited; therefore, large multicenter studies will be needed in the future.

In conclusion, BAT-CD203c has high sensitivity for the diagnosis of PFAS and may be useful for predicting the severity of PFAS. We suggest that BAT is a reliable tool for predicting PFAS.

Acknowledgements

All authors have no COI to declare regarding the present study.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The authors thank Shinichi Takeda, Tomoko Fujisaka, Aya Ikemoto, and Shigeyoshi Imai for their analysis of the samples using a flow cytometer and Reiko Tokuda, Mizuho Nagao, and Takao Fujisawa of the Department of Pediatrics, Mie National Hospital for their technical guidance in BAT. We would like to thank Editage (www.editage.com) for English language editing.

References

1. Ma S, Sicherer SH, Nowak-Wegrzyn A. A survey on the management of pollen-food allergy syndrome in allergy practices. J Allergy Clin Immunol 2003;112:784-788.
2. Carlson G, Coop C. Pollen food allergy syndrome (PFAS): a review of current available literature. Ann Allergy Asthma Immunol 2019;123:359-365.
3. Mastrorilli C, Cardinale F, Giannetti A, et al. Pollen-food allergy syndrome: a not so rare disease in childhood. Medicina (Kaunas) 2019;55:641.
4. Osterballe M, Hansen TK, Mortz CG, et al. The clinical relevance of sensitization to pollen-related fruits and vegetables in unselected pollen-sensitized adults. Allergy 2005;60:218-225.
5. Skypala IJ, Calderon MA, Leeds AR, et al. Development and validation of a structured questionnaire for the diagnosis of oral allergy syndrome in subjects with seasonal allergic rhinitis during the UK birch pollen season. Clin Exp Allergy 2011;41:1001-1011.
6. Ortolani C, Ispano M, Pastorello E, et al. The oral allergy syndrome. Ann Allergy 1988;61:47-52.
7. Ortolani C, Ispano M, Pastorello EA, et al. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. J Allergy Clin Immunol 1989; 83:683-690.
8. Tuppo L, Alessandri C, Pomponi D, et al. Peamaclein - A new peach allergenic protein: similarities, differences and misleading features compared to Pru p 3. Clin Exp Allergy 2013;43:128-140.
9. Pascal M, Muñoz-Cano R, Reina Z, et al. Lipid transfer protein syndrome: clinical pattern, cofactor effect and profile of molecular sensitization to plant-foods and pollens. Clin Exp Allergy 2012;42:1529-1539.
10. Inomata N. Gibberellin-regulated protein allergy: clinical features and cross-reactivity. Allergol Int 2020;69:11-18.
11. Rodriguez J, Crespo JF, Burks W, et al. Randomized, double-blind, crossover challenge study in 53 subjects reporting adverse reactions to melon (Cucumis melo). J Allergy Clin Immunol 2000;106:968-972.
12. Shirao K, Inoue M, Tokuda R, et al. "Bitter sweet": a child case of erythritol-induced anaphylaxis. Allergol Int 2013;62:269-271.
13. Falcone FH, Haas H, Gibbs BF. The human basophil: a new appreciation of its role in immune responses. Blood 2000;96:4028-4038.
14. Boumiza R, Debard AL, Monneret G. The basophil activation test by flow cytometry: recent developments in clinical studies, standardization and emerging perspectives. Clin Mol Allergy 2005;3:9.

15. Santos AF, Douiri A, Bécares N, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol 2014;134:645-652.
16. Sato S, Tachimoto H, Shukuya A, et al. Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children. Int Arch Allergy Immunol 2010;152 (Suppl 1):54-61.
17. Tokuda R, Nagao M, Hiraguchi Y, et al. Antigen-induced expression of CD203c on basophils predicts IgE-mediated wheat allergy. Allergol Int 2009;58:193-199.
18. Ebo DG, Hagendorens MM, Bridts CH, et al. Flow cytometric analysis of in vitro activated basophils, specific IgE and skin tests in the diagnosis of pollen-associated food allergy. Cytometry B Clin Cytom 2005;64:28-33.
19. Erdmann SM, Heussen N, Moll-Slodowy S, et al. CD63 expression on basophils as a tool for the diagnosis of pollen-associated food allergy: sensitivity and specificity. Clin Exp Allergy 2003;33:607-614.
20. Gamboa PM, Cáceres O, Antepara I, et al. Two different profiles of peach allergy in the north of Spain. Allergy 2007;62:408-414.
21. Deng S, Yin J. Clinical utility of basophil activation test in diagnosis and predicting severity of mugwort pollen-related peach allergy. World Allergy Organ J 2019;12:100043.
22. Malling HJ. Skin prick testing and the use of histamine references. Allergy 1984;39:596-601.
23. Carnés J, Fernández-Caldas E, Gallego MT, et al. Pru p 3 (LTP) content in peach extracts. Allergy 2002;57:1071-1075.
24. Tuppo L, Alessandri C, Giangrieco I, et al. Isolation of cypress gibberellin-regulated protein: analysis of its structural features and IgE binding competition with homologous allergens. Mol Immunol 2019;114:189-195.

Osaka City Med. J. Vol. 68, 39-49, 2022

Association between Job Stressors and Extended Long-term Sickness Absence due to Mental Disorders among Public Servants in Japan

Yoshiki Shirahama, Shinichi Iwasaki, Yasuhiko Deguchi, Aya Kadowaki, Akihiro Niki, Tomoyuki Hirota, Yoko Nakamichi, and Koki Inoue

Department of Neuropsychiatry, Osaka City University Graduate School of Medicine

Abstract

Background

Long-term sickness absence due to mental disorders in the workplace is a public health concern. The period of sickness absence due to mental disorders tends to be much longer relative to other diagnoses. Few studies have investigated the period of an extended long-term sickness absence due to mental disorders and the job factors associated with it.

Methods

This study examined differences in job stressors, stress responses, and social support between workers who took extended (≧8 months) and the usual (3-8 months) long-term sickness absence due to mental disorders. Data from responses to the last Brief Job Stress Questionnaire by municipal workers in the Kinki region of Japan before their sickness absence were analyzed for the period between 2011 and 2015. Workers who took long-term sickness absence due to mental disorders were divided into two cohorts (usual or extended long-term sickness absence; 123 individuals each): leave of longer or shorter than eight months (the median leave period). The Brief Job Stress Questionnaire subscales for propensity between the two cohorts were compared using the Mann-Whitney U test.

Results

Workers with extended long-term sickness absence had higher quantitative workloads, poorer physical environments, and less job control, than workers with usual long-term sickness absence.

Conclusions

To reduce long-term sickness absence due to mental disorders, it is necessary to pay particular attention to job stressors and implement appropriate improvements, such as increasing freedom of discretion and reducing the workload.

Key Words: Job stressors; Sickness absence; Mental disorder; Brief Job Stress Questionnaire; Public servant

Received September 15, 2021; accepted November 30, 2021.

Correspondence to: Yoshiki Shirahama, MD.
Department of Neuropsychiatry, Osaka City University Graduate School of Medicine,
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan
Tel: +81-6-6645-3821; Fax: +81-6-6636-0439
E-mail: skybluegreen.2112@gmail.com

Introduction

Sickness absence is a significant public health and economic concern. It not only has a considerable social impact, but also reduces individuals' quality of life. Sickness absence results in a substantial loss of productivity and insurance costs among the working population, and is a critical risk factor for permanent exclusion from the labor market and for disability retirement[1,2]. Reducing and preventing sickness absence is crucial, as it exerts a considerable economic burden on individuals, employers, and society[3].

Mental disorders (MD) among workers are a global concern. In Japan, over 60% of workers have reportedly experienced intense occupational worry or stress[4], and 32% of Japanese companies have shown a growing number of employees who exhibit mental health problems[5]. The Japanese Ministry of Health, Labour and Welfare reported that in approximately 10% of all companies, employees are taking a sickness absence of over a month or quitting their jobs due to MD[6]. It has been the second largest cause of sickness absence in Japan. In Finland, an increase in sickness absence due to MD was observed between 2016 and 2019 in all age groups of both genders[7,8]. Both changing and persistent common mental disorders at the two time points, which were separated by five years, elevated the risk of sickness absence due to MD, as well as all-cause sickness absence[9]. Additionally, sickness absence due to MD has increased in a number of countries in recent times[10,11].

The period of sickness absence due to MD tends to be longer concerning other diagnoses resulting in absence, such as musculoskeletal diseases[12-15]. In Japan, MD are the most common causes of long-term sickness absence (LTSA), followed by cancer, with both accounting for more than half of all LTSAs[16]. A study in the UK found that MD, largely neurosis and neurosis ill-defined, was the second largest cause of long periods of sickness absence (>21 days), accounting for 16% of absences among men and 18% among women[17]. On the other hand, study of employees in a Japanese manufacturing company reported on their sickness absence days due to MD[18]; the mean sickness absence period was 330.2 days for major depressive disorder, 237.8 days for adjustment disorder, and 506.2 days for anxiety disorders. In the Japanese workforce, as of 1997, the average length of absence due to MD and non-MD were 119.5 and 47.3 days, respectively[12]. As shown above, MD tend to have longer periods of sickness absence from work than non-MD in Japan.

Public service jobs, including typical jobs in various fields such as general affairs, accounting, personnel affairs, and taxes, are among the most popular in Japan. We presumed these to represent typical work in the country. Japanese public servants with sickness absence are provided sufficient welfare benefits, such as being paid a part of their wages. This may permit ease of taking sickness absence. Additionally, in comparison to private sector workers, public servants often work under uniform conditions, including having high education levels, stable wages, and guaranteed job stability with no threat of unemployment until retirement[19,20]. Because of these benefits, public servants may tend to take long sickness absences without being able to return to work early. The Japan National Personnel Authority[21] in 2017 reported that the most frequent reason given (65.5%) for sickness absence lasting over one month was "Mental and behavioral disorders" among public servants. Another survey by the Japan Local Government Employee Safety and Health Association[22], examined 760000 local public servants in 2018 and found that 2551 per 100000 public servants took more than one month of sickness absence; the most frequent reason given for sickness absence was "Mental and behavioral disorders" accounting for 57.7% of the absence lasting more than one month. This rate is continually increasing.

Several studies have reported factors associated with prolonged periods of sickness absence. A longitudinal study in Germany demonstrated a prospective association between high job strain and LTSA (>6 weeks)[23]. A longitudinal cohort study in Norway among 543 sick listed employees revealed that low decision control as well as psychologically demanding jobs were independent predictors of delayed return to work[24]. In Japan, diagnosis and employee rank were factors predicting the duration of sickness absence due to MD[25].

A meta-analysis has shown that exposure to psychosocial stressors at work was associated with an increased risk of a varied duration of sickness absence due to mental disorders[26]. However, few studies have investigated the association between an extended LTSA due to MD and job stressors and focused on very long-term sickness absences among public servants. According to the job stress model proposed by the National Institute for Occupational Safety and Health, job stressors bring acute stress responses, or strains, to workers. Such short-term strains, in turn, are presumed to have an impact on longer-term indicators of mental and physical health, such as sickness absences[27]. Therefore, we hypothesize that workers with extended LTSA due to MD experience much higher job stressors than the workers with usual LTSA-MD among public servants. We conducted a study on the differences in job stressors between the shorter and longer leave periods among LTSA-MD workers.

Methods

Participants

Public servants working for the municipal or ward office of City A in the Kinki region of Japan answered the Brief Job Stress Questionnaire (BJSQ) as a part of the annual Stress Check Program[28]. The Japanese government launched this occupational health policy with approximately 50 employees in 2015, to screen workers with high psychosocial stress in the workplace. We requested the municipal office of City A for a list of workers who took a sickness absence of 90 days or more between 2011 and 2015 in the city, and for the BJSQ data collected immediately before their leave. Both absence data and BJSQ data were anonymized by the office staff before the acquisition. Figure 1 shows an inclusion-exclusion flowchart. Of the 810 workers who took long-term leave of 90 days or more, the following employees were excluded: 216 who provided incomplete responses, 161 who took leave for reasons other than MD, and 99 who retired whilst on leave. A total of 334 workers who had MD and provided complete answers on their last BJSQ before taking sickness absence, were analyzed in this study.

The median sickness absence period for all participants was eight months. Participants were divided into two cohorts based on their sickness absence period: eight months or longer (extended LTSA) and less than eight months (usual LTSA). The presence of overcontrol bias due to common method variance was tested using Harman's single-factor test.

Ethics statement

The Human Subjects Review Committee at Osaka City University approved the protocol of this study (authorization number: 3337). As the data already existed, the review committee did not require written informed consent. We obtained the BJSQ data of the workers anonymously (with encrypted ID). The health care center of City "A" provided a list of workers who took LTSA annually for a mental health checkup and evaluated and improved the psychological work environment.

Long-term sickness absence due to mental disorders

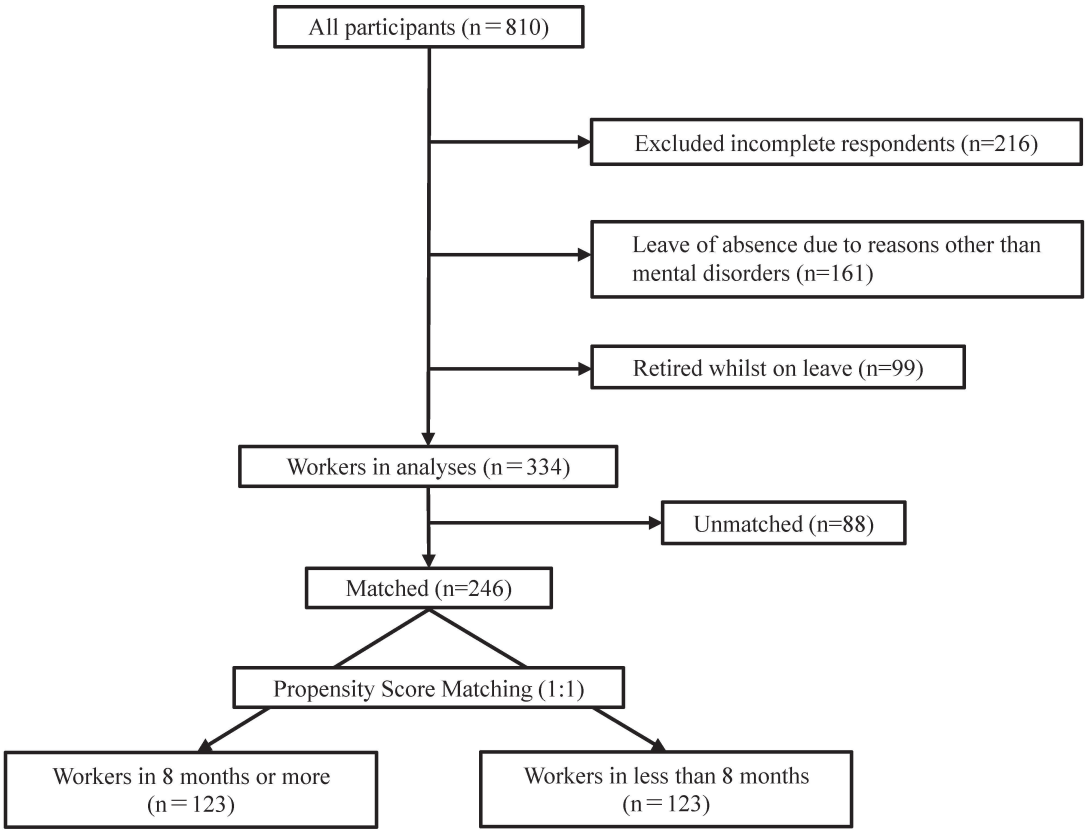


Figure 1. Flow chart for the selected study population.

LTSA-MD is defined as MD related sickness absence for greater than 90 days. The reason for LTSA-MD was confirmed using a medical certificate issued by a doctor. The diagnoses on these certificates are not necessarily based on the International Classification of Diseases, Tenth Revision (ICD-10)[29]. The medical certificate for each LTSA in this study was confirmed by the researchers/issuing doctors with over 10 years' experience, who diagnosed and classified MD (F code) that resulted in the LTSA-MD. The medical certificates occasionally had two or more diagnoses. In such cases, if the multiple diagnoses were from a single ICD-10 category, they were classified into that category. If the multiple diagnoses belonged to different categories, we classified them into the category of causal disease (Priority order; F0, F1, F7, F8, and F9>F6>F2 and F3>F4 and F5).

Brief Job Stress Questionnaire

The BJSQ utilized questions from the Job Content Questionnaire and Generic Job Stress Questionnaire, which were developed by the National Institute for Occupational Safety and Health. A large-scale investigation among Japanese workers confirmed the questionnaire's validity and reliability[30]. The BJSQ evaluated 57 items on a four-point Likert scale, ranging from 1 (disagree) to 4 (agree). The items were grouped into scales of: job stressors (17 items), stress responses (29 items), social support (9 items), and work and life satisfaction (2 items). Job stressors represented psychological stressors related to work, and comprise quantitative workload, qualitative workload, physical demands, interpersonal conflict, poor physical environment, job control, skill utilization, suitable jobs, and meaningfulness of work subscales. Stress responses represented psychological and physiological stress reactions and consist of vigor, irritability, fatigue, anxiety, depression, and

physical stress response subscales. Social support represented social support in the workplace and comprised support from supervisors, from coworkers, and from family/friends subscales. Higher scores on each BJSQ subscale indicated higher levels of stress. Average scores were calculated for each subscale by dividing the total scores by the number of items for each subscale.

Demographic and occupational variables

Gender and age were the demographic variables, whereas job rank (manager/chief/staff) and job categories (clerical, technical, professional) were the occupational variables.

Statistical analysis

Propensity score matching was used for the two groups to minimize bias due to confounding factors, such as the diagnosis that led to the leave, the period from the administration of BJSQ to the start of the sickness absence, and background factors. The propensity score was calculated by logistic regression analysis using the period in which the participants took LTSA. Extended and usual LTSA were the dependent variables, whereas age, gender, position, occupation type, diagnosis resulting in sickness absence, and the period from the time they answered BJSQ to the start of LTSA, were independent variables.

Matching was performed by nearest-neighbor, with one non-restoration extraction with the caliper of $\times 0.2$ as the standard deviation of the propensity score. Chi-square tests were performed to compare the number of participants classified before and after propensity score matching for each subscale of the BJSQ in the two groups.

Between-group comparisons were performed using the Mann-Whitney U test, as the data were not normally distributed. A value of $p < 0.05$ was regarded as a statistically significant difference between groups. The data were analyzed using IBM SPSS version 26 (IBM, USA).

Results

Participant characteristics

Of the 334 study participants, 237 were men (71%) and 97 were women (29%). The mean age ± standard deviation (SD) was 41.9±7.8 years. A total of 136 employees were in the usual LTSA group and 198 were in the extended LTSA group before propensity score matching. Among all participants, the most frequent ICD-10 codes diagnosed for LTSA-MD were F3 (mood disorders; N=226, 67.7%), followed by F4 (stress-related and somatoform disorders; N=86, 25.7%). The remaining workers in the cohort (6.6%) were diagnosed under codes F0 (organic, including symptomatic, mental disorders), F1 (mental and behavioral disorders due to psychoactive substance use), F2 (schizophrenia, schizotypal and delusional disorders), F8 (disorders of psychological development), or F9 (behavioral and emotional disorders with onset usually occurring in childhood and adolescence). The demographic and occupational characteristics of the pre-matched and matched participants in the usual and extended LTSA groups are summarized in Table 1, respectively. In the cohort with usual LTSA, after matching, there were 101 men and 22 women, with a mean age±SD of 42.4±7.7. In the cohort with extended LTSA, there were 103 men and 20 women, with a mean age±SD of 42.8±7.0. After propensity score matching, no significant differences were found for diagnosis, gender, age, position, and job category between the two LTSA groups.

Comparison of BJSQ subscales between shorter and longer LTSA

For Harman's single-factor test, the largest factor did not account for a majority of the variance (26.6%), indicating that overcontrol bias due to common method variance was not of great concern.

Table 1. Demographic and occupational characteristics before and after propensity score matching

	Before matching (n=334)		After matching (n=246)	
	Usual LTSA	Extended LTSA	Usual LTSA	Extended LTSA
Period of sickness absence (months), mean±SD	5.9±1.6	17.5±8.6	5.9±1.6	17.7±8.7
N	136	198	123	123
ICD-10 code				
F3	106 (77.9%)	120 (60.6%)	93 (75.6%)	92 (74.8%)
F4	24 (17.7%)	62 (31.3%)	24 (19.5%)	24 (19.5%)
Other mental disorders	6 (4.4%)	16 (8.1%)	6 (4.9%)	7 (5.7%)
Gender (men:women)	114:22	123:75	101:22	103:20
Age	42.4±8.0	41.7±7.6	42.4±7.7	42.8±7.0
Position (job title)				
Manager	15	25	13	16
Chief	13	34	13	14
Staff	108	139	97	93
Job category				
Clerical worker	97	137	89	92
Technical worker	26	35	23	21
Professional worker	13	26	11	10

LTSA, Long-term sickness absence; and ICD-10, The International Classification of Diseases, Tenth Revision.

The BJSQ subscale scores in the usual and extended LTSA groups are summarized in Table 2. Workers in the extended LTSA group showed a more significant quantitative workload, poorer physical environment, and less job control among job stressors compared with workers with usual LTSA. No significant differences were found for the remaining subscales. In addition, there were no significant differences for the subscales of the stress response, social support, and satisfaction.

Discussion

This study divided the participants into two groups (usual and extended LTSA-MD) based on the period of their sickness absence and compared the scores of the scales of job stressors, stress response, and social support. The results revealed that workers with extended LTSA-MD had a more significant quantitative workload, poorer physical environments, and less job control. There were no significant differences for other job stressors, stress response, social support, and satisfaction with the length of sickness absence.

This study hypothesized that greater job stressors prolonged the period of sickness absence, which was partly supported by our findings. It demonstrated that a greater quantitative workload and lower job control were correlated with a longer period of sickness absence, which followed the job demand control model developed by Karasek[31]. According to this model, a combination of high job demands and low job control, referred to as high job strain, predicts adverse health effects. The findings of this study were largely consistent with the model in terms of workload and job control. The meta-analysis on the risk of sickness absences due to mental disorders (not limited to long-term) showed that exposure to job strain elevated the risk of sickness absences by 47%[26]. Some aforementioned longitudinal studies reported the association between high job strain and LTSA[23,24]. Particularly, Norwegian employees who report high levels of job strain are at an increased risk of

Table 2. Subscale scores on the Brief Job Stress Questionnaire

	Range	Usual LTSA	Extended LTSA	p-value
Job stressor				
Quantitative workload	3-12	7.8±2.4	8.8±2.3	0.01*
Qualitative workload	3-12	8.6±2.2	9.0±2.1	0.20
Physical demands	1-4	1.9±1.0	2.1±1.1	0.07
Interpersonal conflict	3-12	6.4±1.8	6.5±2.0	0.55
Poor physical environment	1-4	2.4±1.0	2.7±1.0	0.03*
Lack of job control	3-12	8.0±2.2	8.5±2.0	0.03*
Skill utilization	1-4	2.6±0.8	2.5±0.9	0.45
Suitable jobs	1-4	2.8±0.9	2.8±0.9	0.72
Meaningfulness of work	1-4	2.6±0.9	2.6±0.9	0.62
Stress response				
Vigor	3-12	9.8±2.0	9.8±2.3	0.84
Irritability	3-12	6.5±2.7	6.5±2.5	0.95
Fatigue	3-12	7.8±2.7	8.3±2.9	0.11
Anxiety	3-12	7.3±2.9	7.8±2.9	0.23
Depression	6–24	12.8±5.0	13.4±5.0	0.36
Physical stress response	11-44	22.0±6.9	23.0±6.9	0.25
Social support				
Support from supervisor	3-12	7.8±2.3	7.8±2.0	0.77
Support from coworker	3-12	7.7±2.3	7.8±2.2	0.69
Support from family/friends	3-12	5.8±2.6	5.8±2.5	0.55
Other factors				
Job satisfaction	2-8	5.0±1.5	4.9±1.5	0.53

Each score is expressed as mean±standard deviation. *Denotes a significant difference in scores between the usual and extended LTSA cohorts ($p<0.05$). LTSA, Long-term sickness absence.

LTSA (>16 days)[32]. Several studies also focused on the association between the period of LTSA and job factors. A one-year follow-up study in Belgium reported a significant indirect association between job strain-mediated bullying and LTSA (>15 consecutive days)[33]. Our results were consistent with the findings of these studies on the association between job strain and LTSA. Milner et al found contemporaneous associations between various work stressors and mental health, while only job demands (consistent with quantitative workload, qualitative workload, physical demands, interpersonal conflict, and poor physical environment in the BJSQ) had a lagged effect on mental health one year later[34]. This lagged effect may explain the reason for the extended LTSA-MD.

However, there was no significant difference between usual and extended LTSA with regard to social support. The demand-control-support model states that social support acts as a buffer against the negative impact of a more significant strain on workers[35]. Furthermore, according to the National Institute for Occupational Safety and Health in Japan, social support acts as a buffer to control stress responses in the workplace and illness caused by stress[36]. Interestingly, not only physical workload but also social support from colleagues have been associated with the length of sickness absence[37]. Moreover, low psychological job demands, high social support from coworkers, supervisor support (Odds Raito; OR=3.4, 95% Confidence Interval; CI: 1.6-7.3), and low strain (low job demands and high control) were predictive of shorter periods before returning to work after absence[38]. A comparative study showed that the combination of high job strain and low social support at work was

associated with sickness absences due to mental disorders for more than 15 days[39]. Our results are not consistent with these findings. Some studies have reported that social support has little correlation with long-term leave. For instance, a study in Belgium in 2004 did not find any effect of social support on LTSA due to mental health problems[40]. The meta-analysis mentioned above showed that the association between low social support at work and a risk of sickness absence was found; however, it is not statistically significant[26]. Similarly, a study in the Republic of Slovenia indicated that workplace support from coworkers and leaders was not associated with the period of sickness absence in understanding the influencing factors of LTSA-MD[41]; therefore, the associations of social support with LTSA remain unclear.

In contrast to this study, previous studies focused on LTSA not only due to MD but also somatic disorders (not LTSA-MD); moreover, the boundary between short- and long-term absences varied in each study, ranging between six weeks and three months[42]. This boundary range is remarkably shorter than that considered in this study (eight months). To date, no research has attempted to examine LTSA-MD of such length.

We used job stressors data before the workers' sickness absence. The data included prolonged stressful periods experienced by workers before extended LTSA-MD. These factors are predicted to be higher in extended LTSA-MD (quantitative workload, poor physical environment, and low job control) than the usual LTSA-MD and have extended long-lasting effects. We assumed that the factors that were not different between extended and usual LTSA-MD (social support) do not have major long-lasting effects. Our results also showed that almost all other BJSQ subscales did not show the differences between extended and usual LTSA. We assume these factors similarly do not have major long-lasting effects. Kristel et al reported that workers with subjective health complaints do not differ from the reference group concerning return-to-work predictors from long-term sickness absences[43]. This is in line with the results of stress responses, which did not differ between usual and extended LTSA in this study. By contrast, a Hordaland study reported that anxiety and depression were stronger predictors of a longer duration of sickness absences[44]. However, the longest sickness absence duration used in the study was more than 90 days. It is significantly shorter than the duration we used in our study. The results of the present study are significant for understanding extended LTSA-MD, as MD often induces long periods of sickness absences.

Our study also showed that workers with extended LTSA-MD worked in a significantly poorer physical environment than usual LTSA-MD workers. In the BJSQ, a poor physical environment means, "The environment of your workplace (noise, light, humidity, and ventilation) is not so good"[30]. We found no studies focusing on the association between poor work environment and the period of sickness absence. Fletcher et al found effects for lagged environmental work stressors on health over a five-year period, with these stressors contributing to a sustained decline in worker health[45]. These findings are consistent with our results. We presume that the workers in the poor physical environmental workplace are demotivated to return to work earlier. Our results can explain the long-lasting effect of poor physical environment in the workplace and hesitation to return to work. As mentioned above, Japanese public servants are provided with sufficient financial support and benefits during leaves of absence. These may be contributing factors as to why a worker may maintain a long leave of absence.

Meta-analysis revealed that, compared to the control group, clinical or work-focused interventions aimed at improving return to work reduced the number of sickness absence days in the intervention

group[46].

This study had several strengths. First, the defined period of sickness absence was much longer than in most other studies. To the best of our knowledge, few studies have focused on sickness absence for more than eight months. Second, this investigation was a nested case-control study, allowing the evaluation of temporal causal relationships with a control cohort to increase the robustness of our evaluations. Third, participants were selected from about 20000 employees ×5 years, who belong to a single large workplace. Therefore, compared to other studies that gathered participants from multiple companies, there is less variation in work content and occupations; it is thought that the bias by company unit is also less. Fourth, we used propensity score matching method to reduce the bias from the time separation between the period participants answered BJSQ and the end of sickness absence. Because it is difficult to require answering questionnaire, such as job stressors, during sickness absence in general, we could obtain data before the sickness absence. Further, no other study used propensity scores to compare sickness absence periods. Fifth, the diagnosis, which constituted the reason for the employees' absence, were objectively confirmed mental disorders by psychiatrists rather than being subjectively measured (e.g., through a mental health questionnaire).

On the other hand, this study encountered the following limitations. First, data were obtained only from public servants from a single city in Japan, making it difficult to generalize the findings to other jobs and locations. Second, the BJSQ was collected before their period of absence. However, their responses may have altered during the leave; because such information could not be obtained, these possibilities remain ambiguous. Third, past MD or comorbidities could not be determined, as participants' medical certificates identified only the present disease. Fourth, differences in specific roles within a worker's occupation were not considered; work atmosphere and content may further affect workers' job stressors. Fifth, the frequency of sickness absence could not be considered. Sixth, in this study, it is difficult to predict the period of sickness absence for those who retired whilst on leave. Therefore, we excluded them, but it is possible that this underestimates or overestimates the impact of job stressors on extended LTSA. Finally, all data were self-reported; as such, personality differences or response tendencies may have influenced the results. Further research using methods to measure workers' stress through objective investigations, such as semi-structured interviews, is required.

Conclusions

Our findings showed that workers who took extended LTSA-MD for more than eight months had a more significant quantitative workload, poorer physical environments, and less job control. Mitigating lost time and productivity by monitoring workers' stress levels, and identifying and intervening when workplace stress is exceptionally high, could serve as a possible solution to mitigate LTSA-MD.

Acknowledgements

All authors have no COI to declare regarding the present study.

We would like to thank all participants for their cooperation.

References

1. Kivimäki M, Forma P, Wikström J, et al. Sickness absence as a risk marker of future disability pension: the 10-

town study. J Epidemiol Community Health 2004;58:710-711.
2. Alexanderson K, Kivimäki M, Ferrie JE, et al. Diagnosis-specific sick leave as a long-term predictor of disability pension: a 13-year follow-up of the GAZEL cohort study. J Epidemiol Community Health 2012;66: 155-159.
3. Organisation for Economic Cooperation and Development (OECD); European Union. Health at a glance: Europe 2018: state of health in the EU cycle. Paris: OECD Publishing; 2018.
4. Ministry of Health, Labour and Welfare. Annual health, labour and welfare report 2009-2010, Section 7. Tokyo: Ministry of Health, Labour and Welfare; 2010. (In Japanese)
5. Japan Productivity Center. Nineth survey about efforts to mental health problems among Japanese enterprises [Internet]. Tokyo: Japan Productivity Center; 2019 [cited 2021 Oct 28]. Available from: https://www.jpc-net.jp/research/assets/pdf/R4attached.pdf. (In Japanese)
6. Ministry of Health, Labour and Welfare. Survey on state of employees' health [Internet]. Tokyo: Ministry of Health, Labour and Welfare; 2013 [cited 2021 Oct 28]. Available from: http://www.mhlw.go.jp/toukei/list/dl/h25-46-50_01.pdf. (In Japanese)
7. Kela. Statistical yearbook of the Social Insurance Institution [Internet]. Helsinki: Kela; DATE [cited 2021 Oct 28]. Available from: https://www.kela.fi/web/en/statistical-publications_statistical-yearbook.
8. Blomgren J, Perhoniemi R. Increase in sickness absence due to mental disorders in Finland: trends by gender, age and diagnostic group in 2005-2019. Scand J Public Health 2021 Feb 20;1403494821993705. doi: 10.1177/1403494821993705.
9. Mauramo E, Lallukka T, Mänty M, et al. Diagnosis-specific sickness absence and subsequent common mental disorders: a register-linkage cohort study among Finnish public sector employees. Int J Environ Res Public Health 2020;17:782.
10. Järvisalo J, Andersson B, Boedeker W, et al, editors. Mental disorders as a major challenge in prevention of work disability: experiences in Finland, Germany, the Netherlands and Sweden. Helsinki: Kela; 2005.
11. Swedish Council on Technology Assessment in Health Care. Sickness absence: causes, consequences, and physicians' sickness certification practice. A systematic literature review by the Swedish Council on Technology Assessment in Health Care (SBU). Scand J Public Health Suppl 2004;63:3-263.
12. Muto T, Sumiyoshi Y, Sawada S, et al. Sickness absence due to mental disorders in Japanese workforce. Ind Health 1999;37:243-252.
13. Gabbay M, Shiels C, Hillage J. Factors associated with the length of fit note-certified sickness episodes in the UK. Occup Environ Med 2015;72:467-475.
14. Kausto J, Pentti J, Oksanen T, et al. Length of sickness absence and sustained return-to-work in mental disorders and musculoskeletal diseases: a cohort study of public sector employees. Scand J Work Environ Health 2017;43:358-366.
15. van Hoffen MFA, Norder G, Twisk JWR, et al. External validation of a prediction model and decision tree for sickness absence due to mental disorders. Int Arch Occup Environ Health 2020;93:1007-1012.
16. Tsutsumi A, Shimazu A, Eguchi H, et al. A Japanese Stress Check Program screening tool predicts employee long-term sickness absence: a prospective study. J Occup Health 2018;60:55-63.
17. Stansfeld S, Feeney A, Head J, et al. Sickness absence for psychiatric illness: the Whitehall Ⅱ Study. Soc Sci Med 1995;40:189-197.
18. Sakakibara S, Sado M, Ninomiya A, et al. Predictive factors of the duration of sick leave due to mental disorders. Int J Ment Health Syst 2019;13:19.
19. Moncada S. Working conditions and social inequalities in health. J Epidemiol Community Health 1999;53:390-391.
20. Kawasaki Y, Nagashima S. What effects do the high salaries for local public employment have on the regional economy in Japan? [Internet]. 2007 [cited 2021 Oct 28]. Available from: https://www.jbaudit.go.jp/koryu/study/mag/pdf/j36d08.pdf. (In Japanese)
21. National Personnel Authority. Annual report 2017 [Internet]. Tokyo: National Personnel Authority; 2017 [cited 2021 Oct 28]. Available from: https://www.jinji.go.jp/hakusho/h29/1-3-05-2-1.html. (In Japanese)
22. Japan Local Government Employee Safety & Health Association. Survey on industrial safety and health of local government employees 2018 [Internet]. Tokyo: Japan Local Government Employee Safety & Health Association; 2018 [cited 2021 Oct 28]. Available from: https://www.jinji.go.jp/hakusho/h30/1-3-05-2-1.html. (In Japanese)
23. Mutambudzi M, Theorell T, Li J. Job strain and long-term sickness absence from work: a ten-year prospective study in German working population. J Occup Environ Med 2019;61:278-284.
24. Haveraaen LA, Skarpaas LS, Aas RW. Job demands and decision control predicted return to work: the rapid-RTW cohort study. BMC Public Health 2017;17:154.

25. Sakakibara S, Sado M, Ninomiya A, et al. Predictive factors of the duration of sick leave due to mental disorders. Int J Ment Health Syst 2019;13:19.
26. Duchaine CS, Aubé K, Gilbert-Ouimet M, et al. Psychosocial stressors at work and the risk of sickness absence due to a diagnosed mental disorder: a systematic review and meta-analysis. JAMA Psychiatry 2020;77:842-851.
27. Hurrell JJ Jr, McLaney MA. Exposure to job stress--a new psychometric instrument. Scand J Work Environ Health 1988;14 Suppl 1:27-28.
28. Kawakami N, Tsutsumi A. The Stress Check Program: a new national policy for monitoring and screening psychosocial stress in the workplace in Japan. J Occup Health 2016;58:1-6.
29. World Health Organization. ICD-10: International statistical classification of diseases and related health problems – 10th revision. Geneva: World Health Organization; 2011.
30. Shimomitsu T, Haratani T, Nakamura K, et al. The final development of the Brief Job Stress Questionnaire mainly used for assessment of the individuals. In: Kato M, editor. The Ministry of Labor sponsored grant for the prevention of work-related illness, FY 1999 report. Tokyo: Tokyo Medical University, 2000;126-164. (In Japanese)
31. Karasek RA Jr. Job demands, job decision latitude, and mental strain: implications for job redesign. Adm Sci Q 1979;24:285-308.
32. Wang MJ, Mykletun A, Møyner EI, et al. Job strain, health and sickness absence: results from the Hordaland Health Study. PLoS One 2014;9:e96025.
33. Janssens H, Braeckman L, De Clercq B, et al. The indirect association of job strain with long-term sickness absence through bullying: a mediation analysis using structural equation modeling. BMC Public Health 2016; 16:851.
34. Milner A, Aitken Z, Kavanagh A, et al. Persistent and contemporaneous effects of job stressors on mental health: a study testing multiple analytic approaches across 13 waves of annually collected cohort data. Occup Environ Med 2016;73:787-793.
35. Johnson JV, Hall EM. Job strain, work place social support, and cardiovascular disease: a cross-sectional study of a random sample of the Swedish working population. Am J Public Health 1988;78:1336-1342.
36. Harada H, Suwazono Y, Sakata K, et al. Three-shift system increases job-related stress in Japanese workers. J Occup Health 2005;47:397-404.
37. Goorts K, Boets I, Decuman S, et al. Psychosocial determinants predicting long-term sickness absence: a register-based cohort study. J Epidemiol Community Health 2020;74:913-918.
38. Haveraaen LA, Skarpaas LS, Berg JE, et al. Do psychological job demands, decision control and social support predict return to work three months after a return-to-work (RTW) programme? The rapid-RTW cohort study. Work 2015;53:61-71.
39. da Silva-Junior JS, Fischer FM. Long-term sickness absence due to mental disorders is associated with individual features and psychosocial work conditions. PLoS One 2014;9:e115885.
40. Janssens H, Clays E, De Clercq B, et al. The relation between psychosocial risk factors and cause-specific long-term sickness absence. Eur J Public Health 2014;24:428-433.
41. Boštjančič E, Galič K. Returning to work after sick leave – the role of work demands and resources, self-efficacy, and social support. Front Psychol 2020;11:661.
42. Cornelius LR, van der Klink JJL, Groothoff JW, et al. Prognostic factors of long term disability due to mental disorders: a systematic review. J Occup Rehabil 2011;21:259-274.
43. Weerdesteijn KHN, Schaafsma F, Bonefaas-Groenewoud K, et al. Predicting return to work after long-term sickness absence with subjective health complaints: a prospective cohort study. BMC Public Health 2020;20: 1095.
44. Knudsen AK, Harvey SB, Mykletun A, et al. Common mental disorders and long-term sickness absence in a general working population. The Hordaland Health Study. Acta Psychiatr Scand 2013;127:287-297.
45. Fletcher JM, Sindelar JL, Yamaguchi S. Cumulative effects of job characteristics on health. Health Econ 2011; 20:553-570.
46. Nigatu YT, Liu Y, Uppal M, et al. Prognostic factors for return to work of employees with common mental disorders: a meta-analysis of cohort studies. Soc Psychiatry Psychiatr Epidemiol 2017;52:1205-1215.

Instructions for Authors

The Osaka City Medical Journal will consider the publication of any original manuscript, review, case report, or short communication. Articles should be in English.

Manuscript submission. Manuscripts should be sent to the Editor, Osaka City Medical Journal, Osaka City Medical Association, Graduate School of Medicine, Osaka Metropolitan University, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan; phone and fax 06-6645-3782; e-mail shiigakukai@med.osaka-cu.ac.jp

The Journal accepts only manuscripts that contain material that has not been and will not be published elsewhere. Duplicate publication of scientific data is not permitted. If closely related papers might be considered to be duplicate publications, the possible duplicate should be submitted with the manuscript and the authors should explain in their covering letter what is original in the submitted paper. Submit three copies of the manuscript (two of which may be photocopies) together with CD-R or DVD-R containing the body text, tables and figures. The manuscript should be prepared by Microsoft Word or its compatible software (doc or docx). Acceptable formats for figures are JPG or TIF. Use only 12-point font size and a standard serif font. Double-space throughout the manuscript and use standard-sized (ISO A4, 212×297 mm) white bond paper. Make margins at least 25 mm wide on all sides. Number pages consecutively starting with the title page and ending with the reference list. Begin each of these sections on a separate page: title page, abstract, text, acknowledgements, references, tables (each one separate), and figure legends. Do not use abbreviations in the title or abstract and limit their use in the text, defining each when it first appears. Manuscripts should meet the requirements outlined below to avoid delay in review and publication. Authors whose native language is not English must seek the assistance of a native English speaker who is familiar with medical sciences. Please attach the certificate from the person(s) who edit the manuscript. Some minor editorial revision of the manuscript will be made when the editorial committee considers it necessary.

Title page. All submissions must include a title page. The full title of the paper, should be concise, specific, and informative, and should contain the message of the paper without being in sentence form. Next, include the full names and academic affiliations of all authors, and indicate the corresponding author, address, phone, fax, and e-mail address. Give a running title (not to exceed 50 characters including spaces), and three to five key words. Last, give the word count for text only, exclusive of title, abstract, references, tables, and figure legends.

Structured abstract. The abstract of 250 words or less should consist of four paragraphs headed **Background, Methods, Results,** and **Conclusions.**

Text. Full papers about experiments or observations may be divided into sections headed **Introduction, Methods, Results,** and **Discussion.**

Tables. Each table should be typed on a separate sheet in characters of ordinary size, double-spaced (with at least 6 mm of white space between lines). Each table must have a title and should be assigned an Arabic numeral ('Table 3'). Vertical rules should not be used.

Figures. For black-and-white figures, submit three original glossy prints or laser-quality proofs and three photocopies of each. One transparency and three color prints should be submitted of each color figure. Label the front of figures with the figure number. Indicate on the back of each figure the first author, the first few words of the manuscript title, and the direction of the top of the figure (if needed). Photomicrographs should have scale markers that indicate the magnification. Provide figure legends on a separate page, double-spaced, immediately after the tables. All illustrations and graphs, to be referred to as figures, should be numbered in Arabic numerals ('Fig. 2' etc.). The approximate position of each figure in the text should be indicated in the right margin of the manuscript. Illustrations in full color are accepted for publication if the editors judge that color is necessary, with the cost paid by the author.

References. Reference must be double-spaced and numbered consecutively in the order cited in the text. When listing references, follow the style of the Uniform Requirements (http://www.icmje.org/) and abbreviate names of journals according to PubMed (http://www.ncbi.nlm.nih.gov/sites/netrez). List all authors up to three; when there are four or more, list the first three and use et al.

Examples of reference style

1. Priori SG, Schwartz PJ, Napolitano C, et al. Risk stratification in the long-QT syndrome. N Engl J Med 2003;348:1866-1874.
2. Schwartz PJ, Priori SG, Napolitano C. The long-QT syndrome. In: Zipes DP, Jalife J, editors. Cardiac electrophysiology: from cell to bedside. 3rd ed. Philadelphia: W.B. Saunders; 2000. pp. 597-615.

Proofs. One set of proofs together with the original manuscript will be sent to the author, to be carefully checked for any essential changes or printer's errors. The author is requested to return the corrected proofs within 48 h of their receipt.

Short communications and case reports.

1. A short communication should have between 1500 and 2000 words, including the abstract. This word count is equivalent to about four double-spaced manuscript pages.
2. The original and two copies including three sets of figures and tables should be sent to the Editorial Office.

Manuscript submission fee. A nonrefundable fee of 10,000 JPY is due on submission of original manuscripts, case reports, and short communications. A manuscript returned beyond six months of the date of the initial decision will be considered a new submission.

Page charges. A standard publication fee of 100,000 JPY will be applied for each accepted paper. Authors are also required to pay page charge of 10,000 JPY per printed page.
Ex) If your article has 10 pages, the amount of fee is 100,000 JPY+10 pages×10,000 JPY=200,000 JPY.

Reprints. If you were interested in ordering reprints of your article, we accept at least 50 full-color copies. Authors are required to pay page charge of 100 JPY per printed page. Ex) If you request 60 copies for 10-page article, the amount of fee is 100 JPY×10 pages×60 copies=60,000 JPY.

Studies of human subjects. It is the responsibility of the authors to ensure that any clinical investigation they did and report in manuscripts submitted to the Osaka City Medical Journal are in accordance with the Declaration of Helsinki (http://www.wma.net).

Animal studies. It is the responsibility of the authors to ensure that their experimental procedures are in compliance with the "Guiding Principles in the Care and Use of Animals" (http://www.the-aps.org/pub_affairs/humane/pa_aps_guiding.htm) published each month in the information for authors of the American Journal of Physiology.

Conflict of Interest (COI) Disclosure.

1. It is the responsibility of the authors to disclose any COI by signing the form.
2. If the authors have no conflicts, please state "All authors have no COI to declare regarding the present study" in the Acknowledgements.
   Authors are required to disclose any relationships with company or organization (such as funds, consultancy fee, grant, fee for speaking, stock or shares). At the time of initial submission, the corresponding author is responsible for obtaining conflict of interest information from all authors.

[Revised: June 8, 2021]

COPYRIGHT TRANSFER AND STATEMENT OF ORIGINALITY

We approve the submission of this paper to the Osaka City Medical Association for publication and have taken to ensure the integrity of this work. We confirm that the manuscript is original and does not in whole or part infringe any copyright, violate any right of privacy or other personal or priority right whatever, or falsely designate the source of authorship, and that it has not been published in whole or in part and is not being submitted or considered for publication in whole or in part elsewhere (abstracts excluded).
We agree to transfer copyright the manuscript entitled

_____

_____

to the Osaka City Medical Association upon its acceptance for publication.

Write clearly and signature

(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____
(Author: print or type)	(Signature)	(Date)
_____	_____	_____

OCMJ for Conflict of Interest (COI) Disclosure Statement

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed and stored electronically. Each author should submit this form and is responsible for the accuracy and completeness of the submitted information.

1. 1) Have you accepted from a sponsor or any company or organization (More than 1,000,000 JPY per year from a specific organization) ? (Please circle below)
   (1) Funds ? ····· Yes / No
   (2) Consultancy fee ? ····· Yes / No
   (3) Any grant ? ····· Yes / No
   (4) Fee for speaking ? ····· Yes / No

   2) Do you hold any stock or shares related to the manuscript ?
   (1) Directly ? ····· Yes / No
   (2) Indirectly, via family members or relatives ? ····· Yes / No

   3) If any of above items are “yes”, please provide detailed information below.

2. If none of the above apply and there is no COI please clearly state “All authors have no COI to declare regarding the present study”.

Manuscript Title:

Name / Signature_____ **Date**_____

Manuscript Identifying Number (if you know it):

The volumes and issues published in 1954-2018 were as follows: Vol 1 (one issue), Vols 2-5 (2 issues, each), Vols 6-7 (one issue, each), Vols 8-9 (2 issues, each), Vol 10 (one issue), Vol 11 (2 issues), Vol 12 (one issue), Vol 13 (2 issues), Vols 14-20 (one issue, each), Vol 21 (2 issues), Vol 22 (one issue), Vols 23-65 (2 issues, each), Vol 66 (one issue), Vol 67 (2 issues)

Publisher : Osaka City Medical Association,
Graduate School of Medicine, Osaka Metropolitan University
1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585, Japan