



OPEN Germ aversion is a risk factor for chronic low back pain and shoulder pain under the COVID-19 pandemic: an internet-based panel study

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The COVID-19 pandemic has increased germ aversion, an aversive affective response to a high likelihood of pathogen transmission. While psychological factors are associated with chronic pain, the relationship between germ aversion and chronic pain remains unexplored. This study aimed to examine the relationship between germ aversion and new-onset and prognosis of chronic pain using longitudinal data collected during the COVID-19 pandemic. We conducted web-based surveys of full-time workers at baseline and after three months. Data were collected on demographic characteristics, psychological factors, and chronic pain. Germ aversion was assessed using a modified Perceived Vulnerability to Disease scale. We analyzed responses from 1265 panelists who completed the survey twice. The prevalence of chronic low back pain (CLBP) and chronic neck and shoulder pain (CNSP) was associated with sex, short sleep duration, psychological distress, loneliness, and germ aversion. Stratified analyses showed that germ aversion was a risk factor for CLBP at three months in both individuals with and without CLBP at baseline, and for CNSP at three months in those with CNSP at baseline, even after adjustment for confounders. In conclusion, this preliminary study suggests that high germ aversion is a risk factor for CLBP and CNSP in young and middle-aged workers.

Keywords Germ aversion, Behavior immune system, Chronic pain, Coronavirus disease 2019 (COVID-19), Chronic musculoskeletal pain, Fear for infection

Coronavirus disease 2019 (COVID-19) is a serious infectious disease that has spread worldwide. The COVID-19 pandemic has created an enormous fear of infection and restricted social activities to an unprecedented degree. Although the situation is waning, there is always the possibility of a new infectious disease epidemic.

The behavioral immune system, which evolved separately from the physiological immune system, is a psychological mechanism that detects cues of infectious agents in the immediate environment, triggers disease-relevant responses, and facilitates behavioral avoidance or escape¹. Germ aversion, a major component of the behavioral immune system, is defined as an aversive affective response to situations that imply a relatively high likelihood of pathogen transmission². An Australian study found that germ aversion among university students during the lockdown in the spring of 2020 was higher than that before the COVID-19 pandemic³.

Psychological factors, such as depression, anxiety, and negative beliefs, are associated with noncommunicable diseases and chronic pain. Chronic pain, defined as pain that persists or recurs for more than three months, is a common health problem affecting over 30% of the global population according to previous studies^{4,5}. A Japanese national survey conducted in 2019 reported that low back pain, neck and shoulder pain, joint pain, and headaches were the most common subjective symptoms⁶. Chronic pain has been shown to reduce quality of life and cause significant economic losses^{7,8}. Therefore, understanding the pathophysiology of chronic pain and

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developing treatments for it are important. Psychological factors are associated not only with the development of chronic pain but also with a worse prognosis of chronic pain, including chronic musculoskeletal pain^{9–12}. Negative psychological factors increase pain sensitivity and the tendency to limit activities, further exacerbating pain and creating a vicious cycle of chronic musculoskeletal pain¹³.

During the COVID-19 pandemic, germ aversion has the potential to cause activity limitations and negative psychological factors, such as feelings of loneliness¹⁴, suggesting that germ aversion may be associated with chronic pain. However, no study has investigated the relationship between germ aversion and chronic pain, including chronic musculoskeletal pain. In this study, we investigated the relationship between germ aversion, the onset of new chronic musculoskeletal pain, and its prognosis using longitudinal data collected during the COVID-19 pandemic.

Methods

This study was conducted as part of a multi-wave longitudinal research project organized by the Shimazu Laboratory (Faculty of Policy Management, Keio University, <https://hp3.jp/project/study-on-covid-19-and-worker-well-being>) using web-based, self-reported questionnaire surveys. All surveys were supported by a large Internet research agency (Rakuten Insight, Inc.), which had approximately 2.2 million qualified panelists in 2019. The questionnaires were distributed to 1600 full-time workers aged 20–59 years who were stratified by sex (male and female) and age (20–29, 30–39, 40–49, and 50–59 years) to control for selection bias¹⁵. The panelists were selected for each sex and age category using simple random sampling, consented to participate in the survey through the designated website, and responded to the questionnaires with the option of not responding to or withdrawing at any point.

We used data from the third survey (baseline), conducted from December 8 to December 17, 2020, and the fourth survey, conducted from March 8 to March 12, 2021 (three months later), because we began to include the germ aversion questionnaire from the third survey.

We collected data including age, sex, height, weight, highest educational level achieved, marital status, sleep duration, smoking status (current smoker or not), teleworking opportunity, frequency of low back, neck, and shoulder pain (rarely, sometimes, often, and always), and psychological status (germ aversion, loneliness, and psychological distress). Chronic pain is generally defined as pain that persists for more than three months. However, due to the absence of specific items assessing the duration of pain in the questionnaire, chronic pain was defined as “always” in the pain frequency category.

Ethics

This study was approved by the Institutional Ethics Committee of the SFC Research Ethics Committee of the Keio University School (approval number: 336). The protocol was registered in the UMIN Clinical Trials Registry (UMIN-CTR ID: UMIN000040683). This study was performed in accordance with the relevant guidelines/regulations and the Declaration of Helsinki, and informed consent was obtained from all participants.

Germ aversion

Germ aversion refers to beliefs about personal susceptibility to infectious diseases and the emotional discomfort associated with potential disease transmission². The Perceived Vulnerability to Disease (PVD) scale, consisting of 15 items, measures vulnerability to infectious diseases from two aspects: perceived infectiousness, which pertains to susceptibility to colds and flu, and germ aversion, which is the discomfort experienced when pathogens are likely to be present, such as when touching unhygienic objects². The two-factor structure and internal consistency of the scale have been confirmed by analyzing survey data from college students of various ethnic backgrounds¹⁶.

We modified the germ aversion portion of the PVD to fit the current context of our society. The original version included items about situations that are rare today, such as “I do not like to write with a pencil someone else has obviously chewed on” and “I avoid using public telephones because of the risk that I may catch something from the previous user.” These items were excluded from the questionnaire used in this study. Additionally, an item with the lowest factor loading (0.38)¹⁶ in the original scale, “It does not make me anxious to be around sick people,” was rephrased to “It makes me anxious to be around people without masks.”

The germ aversion questionnaire in this study consisted of six items scored on a 7-point Likert scale, ranging from 0 (“strongly disagree”) to 6 (“strongly agree”), with two items scored in reverse for a total of 36 points (Table 1). We calculated factor loadings for validity using a confirmatory factor analysis and assessed internal consistency using Cronbach’s alpha to evaluate the reliability of the modified germ aversion questionnaire.

No.	Item description	Loading
1	It really bothers me when people sneeze without covering their mouths	0.65
2*	I am comfortable sharing a water bottle with a friend	0.25
3	I prefer to wash my hands pretty soon after shaking someone’s hand	0.61
4	I dislike wearing used clothes because you do not know what the last person who wore it was like	0.47
5*	My hands do not feel dirty after touching money	0.18
6	It makes me anxious to be around people with no mask	0.84

Table 1. List and loadings of items of the germ aversion questionnaire. *Reverse-scored items.

Assessment of loneliness

Loneliness was assessed using the Japanese version of the University of California, Los Angeles Loneliness Scale (Version 3) and the Short Form 3-item scale (UCLA-LS3-SF3) to assess loneliness. Although this scale was originally developed in English, both the English and Japanese versions have been previously found to be valid and reliable^{17,18}. The items were as follows: (1) “How often do you feel that you lack companionship?”, (2) “How often do you feel left out?”, and (3) “How often do you feel isolated from others?”. Participants rated the frequency with which they experienced these feelings on a 3-point scale [1 (hardly ever), 2 (some of the time), 3 (often)] of 1 to 3. The Cronbach's alpha for the internal consistency of the loneliness scale was 0.93.

Assessment of psychological distress

Psychological distress was assessed using the Japanese version of the Kessler Psychological Distress Scale (K6), which was well validated in the previous study (Cronbach's $\alpha = 0.85$)^{19–21}. Participants rated their psychological distress over the past 30 days on a 5-point scale, with frequencies ranging from 0 (never) to 4 (always) for the six K6 items (e.g., nervousness, worthlessness). Higher scores indicate greater psychological distress. Consistent with previous studies, participants who scored 13 or more points were classified as having severe psychological distress^{21,22}.

Statistical analysis

First, we compared the demographic characteristics at baseline between people with and without chronic low back pain (CLBP) three months later. The t-test was used for continuous data, and the chi-square test was used for categorical data. Second, multivariable logistic regression analyses including age, sex, body mass index (BMI), highest educational level achieved, marital status, sleep duration, smoking status, teleworking opportunities, loneliness, and psychological distress as confounding factors, were performed to identify the relationship between germ aversion and the prevalence of CLBP at baseline.

Finally, we stratified people based on the presence of CLBP at baseline and performed the same regression analysis to identify the associations of germ aversion with new-onset CLBP and recovery from CLBP at three months.

Furthermore, similar analyses were performed for people with chronic neck and shoulder pain (CNSP).

All statistical analyses were performed by the JMP[®] Version 16.0.0 (SAS Institute) software package. Statistical significance was determined using two-tailed p-values < 0.05.

Results

Of the 1600 people who received the questionnaire, 1386 panelists (86.6%) responded at baseline and 1345 panelists (84.1%) responded three months later; 1265 panelists (79.1%) completed the survey twice (Fig. 1).

In the reliability analysis, Cronbach's alpha of the modified germ aversion questionnaire was 0.67. Table 1 presents the factor loadings of the items.

Table 2 shows demographic characteristics at baseline between people with and without CLBP, and between those with and without CNSP. People with CLBP or CNSP had a significantly higher prevalence among females, people with short sleep duration (< 5 h), and people with psychological distress (K6 \geq 13), as well as greater feelings of loneliness and the germ aversion.

Multivariable logistic regression analyses for people with CLBP and CNSP after three months (Table 3) showed significant associations of the germ aversion with prevalence of the CLBP (odds ratio [OR] = 1.34; 95% confidence interval [CI] 1.14–1.57; $p < 0.001$) and the CNSP (OR = 1.35; 95% CI 1.17–1.54; $p < 0.001$), even under adjustment of confounding factors. Sex, short sleep duration, and psychological distress were significantly associated with CLBP and CNSP.

In the stratified analyses of people without CLBP at baseline, the odds ratio of germ aversion with the prevalence of CLBP three months later was significantly high (OR = 1.35; 95% CI 1.03–1.76; $p = 0.031$, Table 4). Similarly, the stratified logistic regression analysis among people with the CLBP at baseline identified a significantly high odds ratio of the germ aversion with the prevalence of the CLBP at three months (OR = 1.50; 95% CI 1.09–2.07; $p = 0.010$, Table 4).

According to another stratified analysis by the prevalence of the CNSP at baseline (Table 5), there was no statistical significance of association between the germ aversion and the prevalence of the CNSP at three months alter among people without the CNSP at baseline (OR 1.16; 95% CI 0.92–1.47; $p = 0.206$). On the other hand, the odds ratio of the germ aversion with the prevalence of the CNSP at three months was significantly high in people with the CNSP at baseline (O = 1.36; 95% CI 1.05–1.77; $p = 0.020$).

Discussion

This longitudinal study conducted during the COVID-19 pandemic suggests that germ aversion is a risk factor for new-onset CLBP and inhibits recovery from CLBP and CNSP in young and middle-aged workers.

We assessed the internal consistency of the modified germ aversion questionnaire using Cronbach's alpha, a measure of reliability. Typically, values in the range of 0.7 to 0.9 indicate good reliability. However, Cronbach's alpha of the Japanese version of the PVD (15 items) was 0.73, and that of the Japanese germ aversion (8 items) was 0.67¹⁶. The result of this study (Cronbach's $\alpha = 0.67$) was less than 0.7, which is not ideal, but not less than that of the previous validation study, indicating that the modified germ aversion scale has reasonable internal consistency. The low loading of the items “I feel comfortable sharing a water bottle with a friend” and “My hands do not feel dirty after touching money” in the germ aversion questionnaire may be because the custom of sharing a bottle with a friend is not common, and cashless payment is becoming more common, and touching money is decreasing.

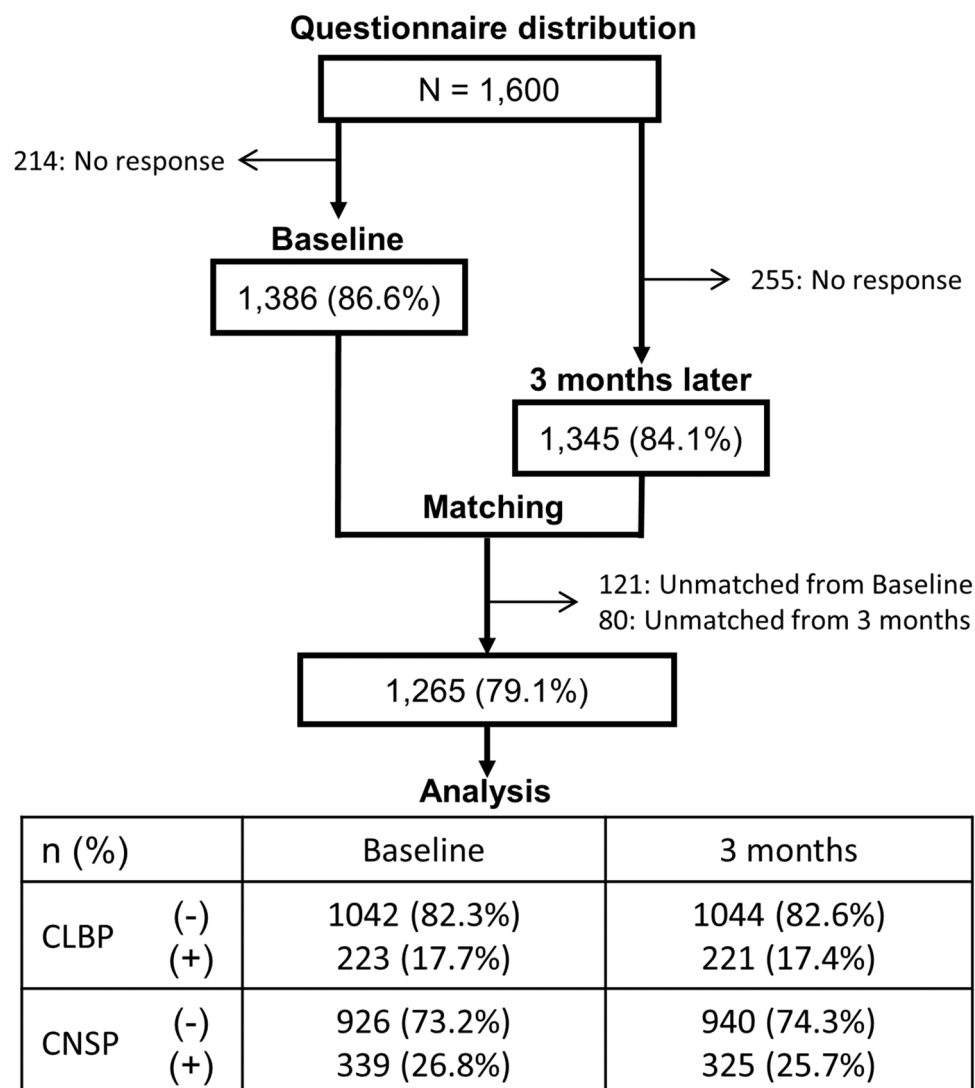


Fig. 1. Flowchart of study participants and prevalence of chronic musculoskeletal pain. *CLBP* Chronic low back pain, *CNSP* chronic neck and shoulder pain.

The results of the demographic characteristics at baseline suggested that females, people with germ aversion, people with psychological distress, and people with less sleep were more likely to have CLBP and CNSP. The finding that CLBP is more common in females is consistent with the results of a previous study that examined the global prevalence of CLBP²³. Previous systematic reviews have concluded that psychological distress prolongs CLBP²⁴. A prospective study reported that short sleep duration is a risk factor for chronic musculoskeletal pain, similar to the findings of this study²⁵. Thus, the population in this study had shown a general trend toward chronic musculoskeletal pain.

In the multivariable logistic regression analyses, germ aversion was associated with the prevalence of CLBP and CNSP, even after adjusting for confounding factors, including psychological distress. General mechanisms of psychological factors working for chronic musculoskeletal pain includes both biological processes such as neuromechanisms^{26,27} and behavioral processes such as sedentary behavior resulting from fear of movement^{13,28,29}. Given that germ aversion is associated with COVID-19 concern as shown in a previous study³⁰, we can consider a similar mechanism to general psychological factors in the effect of germ aversion on musculoskeletal pain. In the COVID-19 pandemic, it has been reported that higher levels of germ aversion are associated with greater disease-avoidance behaviors^{31,32} and social distancing adherence³³. Similarly, sedentary behavior associated with germ aversion may have led to CLBP and CNSP in this study. Although most people during the COVID-19 pandemic lived at a low activity level, those with high germ aversion may have had more sedentary behavior, which may have led to CLBP and CNSP. On the other hand, telework opportunity was not associated with CLBP and CNSP in this study. Although telework drives staying at home, sedentary behaviors other than work-related aspects may have contributed to our findings.

Stratified analyses showed that germ aversion was a risk factor for new-onset CLBP. Even among people without pain at baseline, chronicity is likely to occur after acute low back pain if germ aversion is high. Since

		Without CLBP	With CLBP	p value	Without CNSP	With CNSP	p value
N (%)		1044 (82.5)	221 (17.5)		940 (74.3)	325 (25.7)	
Germ aversion	Mean (SD)	22.4 (6.1)	24.6 (6.0)	<0.001	22.2 (6.0)	24.6 (6.2)	<0.001
Age (years)	Mean (SD)	41.2 (10.3)	41.9 (10.4)	0.40	41.2 (10.5)	41.6 (10.0)	0.53
Female	n (%)	474 (45.4)	135 (61.1)	<0.001	393 (41.8)	216 (66.5)	<0.001
BMI (kg/m ²)	Mean (SD)	22.0 (3.5)	22.0 (4.2)	0.92	22.2 (3.6)	21.6 (3.8)	0.016
Low education	n (%)	427 (40.9)	107 (48.4)	0.04	389 (41.4)	145 (44.6)	0.31
Marital status							
Single	n (%)	445 (42.6)	101 (45.7)	0.32	388 (41.3)	158 (48.6)	0.048
Married		502 (48.1)	92 (41.6)		463 (49.3)	131 (40.3)	
Short sleep (< 5 h)	n (%)	95 (9.1)	42 (19.0)	<0.001	89 (9.5)	48 (14.8)	0.01
Smoking habit	n (%)	226 (21.7)	45 (20.4)	0.67	211 (22.5)	60 (18.5)	0.13
Telework opportunity	n (%)	210 (20.5)	40 (18.5)	0.50	182 (19.9)	68 (21.1)	0.64
Psychological distress (K6 ≥ 13)	n (%)	124 (11.9)	73 (33.0)	<0.001	118 (12.6)	79 (24.3)	<0.001
Loneliness	Mean (SD)	4.7 (1.6)	5.2 (1.8)	<0.001	4.7 (1.6)	5.0 (1.7)	<0.001
CLBP at baseline	n (%)	74 (7.1)	149 (67.4)	<0.001	192 (18.4)	147 (66.5)	<0.001
CNSP at baseline	n (%)	81 (8.6)	142 (43.7)	<0.001	98 (10.4)	241 (74.2)	<0.001

Table 2. Demographic characteristics at baseline between people with and without CLBP, and between those with and without CNSP after three months. *CLBP* chronic low back pain, *CNSP* chronic neck and shoulder pain, *BMI* body mass index, *K6* Kessler psychological distress scale, *SD* standard deviation.

	CLBP after three months			CNSP after three months		
	OR	95%CI (LL, UL)	p value	OR	95%CI (LL, UL)	p value
Germ aversion	1.34	(1.14, 1.57)	<0.001	1.35	(1.17, 1.54)	<0.001
Age	1.00	(0.84, 1.20)	0.972	1.02	(0.87, 1.19)	0.835
Female	1.98	(1.38, 2.84)	<0.001	2.70	(1.98, 3.68)	<0.001
BMI	1.34	(1.14, 1.57)	0.094	1.01	(0.88, 1.17)	0.880
Low education	1.29	(0.93, 1.80)	0.130	1.08	(0.81, 1.45)	0.583
Marital status (married)	1.02	(0.72, 1.45)	0.922	0.94	(0.70, 1.27)	0.692
Short sleep (< 5 h)	2.10	(1.36, 3.25)	<0.001	1.54	(1.03, 2.32)	0.037
Smoking habit	1.11	(0.74, 1.66)	0.602	1.04	(0.73, 1.49)	0.814
Telework opportunity	1.00	(0.67, 1.50)	0.995	1.20	(0.86, 1.68)	0.292
Psychological distress (K6 ≥ 13)	3.43	(2.31, 5.09)	<0.001	1.99	(1.37, 2.88)	<0.001
Loneliness	1.09	(0.93, 1.29)	0.295	1.12	(0.97, 1.29)	0.139

Table 3. Multivariable logistic regression analyses for people with CLBP and CNSP after three months. Continuous variables were standardized. In marital status, married status was compared to single one. *CLBP* chronic low back pain, *CNSP* chronic neck and shoulder pain, *OR* odds ratio, *CI* confidential intervals, *LL* lower limit, *UL* upper limit, *BMI* body mass index, *K6* Kessler psychological distress scale.

higher germ aversion is also associated with a higher prevalence of CLBP at three months among individuals with CLBP at baseline, recovery from CLBP is likely to be difficult under conditions of high germ aversion. These longitudinal results suggest that germ aversion is a risk factor for CLBP, implying the aforementioned biological and behavioral mechanisms. In individuals with CNSP, germ aversion contributes to delayed recovery, with similar mechanisms thought to be responsible. Although there was no significant association with new-onset CNSP, a similar trend was observed. The lack of statistical significance may be due to the small sample size and observation period, which, if increased, may have revealed significant differences.

The behavioral immune system is likely to be more activated in individuals with higher germ aversion when the threat of an infectious disease arises¹. The association between germ aversion and chronic musculoskeletal pain may involve excessive behavioral restriction due to activation of the behavioral immune system. Indeed, behavioral restriction increases the likelihood of protection from infection; however, the results of this study suggest that noninfectious diseases such as chronic musculoskeletal pain may increase. Overall, we need to avoid excessive behavioral restrictions and provide psychological reassurance against infections and epidemics. To achieve this, we need to provide accurate information about infectious diseases and encourage appropriate behaviors from multiple perspectives, including both communicable and noncommunicable diseases.

The present study had several limitations. First, the target population was limited to those aged 20 to 59 years who were employed full-time; therefore, it is unclear whether the same conclusions can be applied to the rest

	Without CLBP (n = 1042)			With CLBP (n = 223)		
	OR	95%CI (LL, UL)	p value	OR	95%CI (LL, UL)	p value
Germ aversion	1.35	(1.03, 1.76)	0.031	1.50	(1.09, 2.07)	0.010
Age	0.82	(0.60, 1.11)	0.205	1.21	(0.84, 1.74)	0.312
Female	1.62	(0.90, 2.91)	0.108	1.33	(0.65, 2.71)	0.437
BMI	1.44	(1.13, 1.84)	0.003	0.81	(0.61, 1.07)	0.143
Low education	1.00	(0.57, 1.76)	0.992	1.25	(0.65, 2.39)	0.500
Marital status (married)	0.67	(0.37, 1.22)	0.192	1.19	(0.59, 2.39)	0.633
Short sleep (< 5 h)	2.36	(1.17, 4.75)	0.016	1.43	(0.62, 3.31)	0.401
Smoking habit	0.96	(0.48, 1.93)	0.916	0.99	(0.46, 2.13)	0.986
Telework opportunity	1.25	(0.66, 2.36)	0.492	1.03	(0.46, 2.30)	0.948
Psychological distress (K6 ≥ 13)	3.25	(1.70, 6.20)	< 0.001	1.78	(0.84, 3.80)	0.133
Loneliness	1.13	(0.84, 1.50)	0.418	0.79	(0.59, 1.07)	0.123

Table 4. Multivariable logistic regression analyses for people with CLBP after three months in people with and without CLBP at baseline. Continuous variables were standardized. In marital status, married status was compared to single one. *CLBP* chronic low back pain, *OR* odds ratio, *CI* confidential intervals, *LL* lower limit, *UL* upper limit, *BMI* body mass index, *K6* Kessler psychological distress scale.

	Without CNSP (n = 926)			With CNSP (n = 339)		
	OR	95%CI (LL, UL)	p value	OR	95%CI (LL, UL)	p value
Germ aversion	1.16	(0.92, 1.47)	0.206	1.36	(1.05, 1.77)	0.019
Age	0.74	(0.57, 0.97)	0.027	1.31	(0.98, 1.76)	0.072
Female	1.79	(1.07, 3.00)	0.026	1.33	(0.73, 2.45)	0.355
BMI	1.05	(0.82, 1.34)	0.709	0.76	(0.60, 0.98)	0.034
Low education	1.21	(0.74, 1.98)	0.455	0.89	(0.51, 1.52)	0.660
Marital status (married)	1.23	(0.74, 2.05)	0.428	0.83	(0.46, 1.50)	0.538
Short sleep (< 5 h)	1.38	(0.67, 2.87)	0.381	1.80	(0.81, 4.03)	0.152
Smoking habit	0.98	(0.54, 1.78)	0.938	0.94	(0.49, 1.83)	0.865
Telework opportunity	1.10	(0.61, 1.97)	0.751	1.37	(0.71, 2.65)	0.348
Psychological distress (K6 ≥ 13)	1.39	(0.71, 2.75)	0.336	1.24	(0.65, 2.35)	0.518
Loneliness	1.15	(0.90, 1.47)	0.265	0.90	(0.69, 1.16)	0.417

Table 5. Multivariable logistic regression analyses for people with CNSP after three months in people with and without CNSP at baseline. Continuous variables were standardized. In marital status, married status was compared to single one. *CNSP* chronic neck and shoulder pain, *OR* odds ratio, *CI* confidential intervals, *LL* lower limit, *UL* upper limit, *BMI* body mass index, *K6* Kessler psychological distress scale.

of the population. Second, we did not assess the external validity or reliability of the modified germ aversion questionnaire, so our results are preliminary, and further studies are needed to confirm its scientific usefulness. Third, as we did not adhere to the common definition of chronic pain, which is pain persisting for three months or more, there is a possibility that the chronic pain identified in this study cannot be generalized. Additionally, we could not clarify the relationship between germ aversion and pain intensity, as the intensity of chronic musculoskeletal pain was not assessed in this survey. Fourth, pain-specific psychological factors, such as pain catastrophizing, were not assessed. Therefore, further studies are needed to identify the actual psychological mechanisms underlying the development of chronic musculoskeletal pain due to germ aversion. Fifth, the individuals' history of COVID-19 infection or vaccination was unknown, although these experiences should be associated with the intensity of germ aversion. Moreover, the relationship between chronic musculoskeletal pain and these experiences remains unclear. Sixth, the results of the present study may be specific to a situation in which COVID-19 was prevalent, and it is not clear whether our findings would be replicated in other situations. In conclusion, this preliminary study suggested that high germ aversion is a risk factor for the new onset of CLBP and delayed recovery from CLBP and CNSP in young and middle-aged workers. Our findings provide important evidence for making clinical suggestions to prevent the development of chronic musculoskeletal pain in people with low back pain or neck and shoulder pain. Additionally, given that chronic musculoskeletal pain corresponding to greater germ aversion is also a socioeconomic burden, our findings suggest that there will be a greater social cost–benefit in managing physical and psychological safety against emerging infectious diseases. Even after the COVID-19 pandemic subsides, the present study will be helpful for our lives and activities during the next pandemic situation of a new infectious disease.

Data availability

The data are available upon request. The data analyzed in this study are available with permission from the Shimazu Laboratory (Faculty of Policy Management, Keio University, <https://hp3.jp/project/study-on-covid-19-and-worker-well-being>) and the Institutional Review Board of Keio University School of Medicine corresponding to each request (<https://www.ctr.med.keio.ac.jp/rinri/>).

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Author contributions

Yuki Mashima contributed to interpretation and drafting of the manuscript. Morihiko Kawate, Yihuan Wu, Yuta Shinohara, Reiko Hoshino, Saki Takaoka, and Chisato Tanaka contributed to study conception and manuscript editing. Masahito Tokita and Akihito Shimazu collected the data. Kenta Wakaizumi designed the study, analyzed the data, edited the first draft, and supervised the study. Morihiko Kawate, Yihuan Wu, Chisato Tanaka, Masahito Tokita, Akihito Shimazu and Kenta Wakaizumi critically revised the manuscript for important intellectual content. All the authors have read and agreed to the published version of the manuscript.

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Competing interests

The authors declare no competing interests.

Additional information

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