

# A large-scale population-based epidemiological study on the prevalence of central sensitization syndromes in Japan

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## Research Article

**Keywords:** Central sensitization, Prevalence, Community surveys, Epidemiological studies

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**A large-scale population-based epidemiological study on the prevalence of central sensitization syndromes in Japan**

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**Abstract:** To investigate the prevalence of CSS in a general population. A large-scale cross-sectional study on 21,661 residents (7,531 men, 14,130 women) in a community in Japan was performed. CSS were assessed using Central Sensitization Inventory (CSI-A, B). Participants with a CSI-A score  $\geq 40$  was defined as having CSS. Age, sex, district, CSI-B (10 CSS-related diseases), lifestyle, and mental health factors were rated in a self-reported survey. The prevalence of CSS and its relationship with potential factors were examined by sex using descriptive and logistic regression models. The prevalence of CSS was 5.4% (95% Confidence Interval (CI) 5.1 to 5.7) in all participants. It significantly differed between men (3.6%, 95% CI 3.2 to 4.1) and women (6.3%, 95% CI 5.6 to 6.7). A CSI-A score  $\geq 40$  correlated with more than one CSI-B disease, exercise habits, sleeping hours per day, perceived stress, and resilience in both men and women. In women, age, ex-smokers, coffee intake ( $\geq 1$  day per week), and alcohol intake correlated with CSS. The prevalence of CSS was 5.4% in the community examined and was higher in women than in men. CSS-related diseases and many factors correlated with CSS. The present results provide important information for future research on CSS.

**Keywords:** Central sensitization; Prevalence; Community surveys; Epidemiological studies

## Introduction

In clinical medicine, central sensitization syndromes (CSS) are overlapping disorders of multiple psycho-neurological, musculoskeletal, and chronic pain-related diseases<sup>1-3</sup>. CSS mainly include fibromyalgia (FM), restless leg syndrome (RLS), chronic fatigue syndrome (CFS), temporomandibular joint disorder (TJD), migraine or tension-type headaches (M/TTH), irritable bowel syndrome (IBS), multiple chemical sensitivity (MCS), and posttraumatic stress disorder (PTSD)<sup>1,2,4,5</sup>. CSS are characterized by complex physical and mental symptoms, with the main symptoms of disproportionate pain and diffuse pain distribution manifested by hypersensitivity of the central neurons, which have a negative impact on the quality of life of patients<sup>1,2,6</sup>. CSS are intractable and there are currently no established medical interventions due to the lack of a clinically obvious pathology<sup>4,7</sup>.

In 2012, Mayer et al. initially developed Central Sensitization Inventory (CSI) part A, comprising 25 symptoms, and part B, consisting of 10 diseases, to evaluate CSS<sup>8</sup>. The 40-point cut-off score of CSI part A was recommended to classify the presence of CSS in patients with chronic pain<sup>6,8</sup>. Many clinical studies have since reported the rates of a CSI score  $\geq 40$  in patients with CSS-related diseases: 11.0% in 290 orthopedic patients with musculoskeletal pain, including the neck, shoulders, hips, knees, or ankles<sup>9</sup>, 13% in 238 patients with low back pain<sup>10</sup>, 34.9% in 66 patients with pelvic floor muscle tenderness<sup>11</sup>, 48.4% in 91 patients with osteoarthritis<sup>12</sup>, 68.2% in 763 patients with chronic spinal pain disorder<sup>13</sup>, and 84% in 32 patients with hereditary neuropathy<sup>14</sup>. These findings demonstrated that the prevalence of CSS varied in a CSS-related disease-dependent manner; however, data on the general population is lacking.

Neblett et al. previously reported that the rate of a CSI score  $\geq 40$  was 24.8% in 129 non-patients, with an average CSI score (SD) of 30.9 (12.3)<sup>15,16</sup>. Other studies found average CSI scores (SD) of 37.1 (15.0) in 63 healthy individuals,<sup>17</sup> 28.9 (13.5) in 40 university students<sup>8</sup>, and

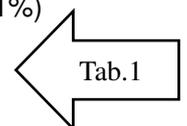
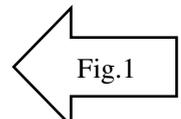
16.2 (11.8) in 20 healthy individuals<sup>18</sup>. Only a few studies have examined healthy individuals as a non-patient comparison sample; however, these sample sizes were small and did not avoid selection bias. To the best of our knowledge, an epidemiological study has not yet been conducted, and, thus, the rate of a CSI score  $\geq 40$  in the general population remains unclear. Therefore, we herein investigated the prevalence of CSS using a large-scale general population-based survey.

## Results

### 1. Descriptive statistics of CSS and each variable

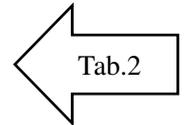
Following the exclusion of participants with missing values, including age and sex ( $n=1,719$ ) and CSI ( $n=809$ ), 21,661 were ultimately analyzed in the present study. The effective response rate was 55.3% (Figure 1). Table 1 shows the characteristics of participants. The average age (SD) of participants was 63.4 yr. (11.7) for all, 66.6 yr. (10.8) for men, and 61.7 yr. (11.8) for women. The rate of depression was the highest among the 10 CSS-related diseases in CSI-B, while none of the participants reported TJD or MCS. In total, 3,764 (17.4%) and 1,531 (7.1%) participants were missing values on coffee and alcohol intake, respectively.

Cronbach's coefficient alpha of CSI-A was 0.892 overall, 0.889 for men, and 0.893 for women. Minimum and maximum CSI-A scores ranged between 1 and 92 points. The average CSI-A score (SD) overall was 17.5 (11.9) and was significantly higher in women (18.6 (12.2)) than in men (15.3 (10.9)) ( $P<0.001$ ). Among the 4 age groups examined, the average CSI-A score in the 60-79 yr. age group was the lowest (Figure 2). The prevalence of CSS with CSI-A  $\geq 40$  points in all participants was 5.4% (95% CI 5.1 to 5.7) (Figure 3). The prevalence of CSS significantly differed between men (3.6%, 95% CI 3.2 to 4.1) and women (6.3%, 95% CI 5.6 to 6.7) ( $P<0.001$ ). A significant sex difference was observed between the 40-59 yr. and 60-79 yr. groups.

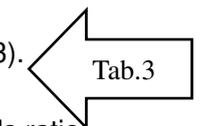


## 2. Relationships between CSS and related factors

CSS with CSI-A  $\geq 40$  points correlated with age groups, CSI-B-related diseases, alcohol intake, exercise habits, perceived stress, sleeping hours per day, and resilience in men and women. In women, smoking and coffee intake correlated with CSS (Table 2).



Age (20-39 yr. and 40-59 yr. vs 60-79 yr.), CSI-B-related diseases (1 or 2 vs 0 disease), perceived stress (high vs low), sleeping hours per day ( $\leq 5$  hr. vs 6-9 hr.), and resilience (low vs medium) showed significantly higher crude odds ratio (cOR), while exercise habits (yes vs no) and resilience (high vs medium) had significantly lower cOR in both men and women. Alcohol intake ( $>1$  day per week vs non-drinker) in men and coffee intake ( $>1$  day per week vs non-drinker) in women showed significantly lower cOR, while age (80-97 yr. vs 60-79 yr.) and smoking (ex-smokers and smokers vs non-smokers) had significantly lower cOR in women (Table 3).



In the multivariable logistic regression model, CSS showed a significantly adjusted odds ratio (aOR) (95%CI) for 1 or 2 CSI-B-related diseases of 3.51 (1.78 to 6.92) for men and 3.07 (2.10 to 4.48) for women and identified several significant factors in both men and women, such as fewer sleeping hours per day, high perceived stress, low and high resilience, and exercise habits. Furthermore, the 20-39, 40-59, and 80-97 yr. age groups and ex-smokers showed higher aOR, while coffee intake ( $>1$  day per week) showed lower aOR in women. Alcohol intake showed lower aOR in men (Table 3).

## Discussion

In the present study, the prevalence of CSS (CSI-A  $\geq 40$ ) in all participants was 5.4% (95% CI 5.1 to 5.7). Its prevalence was significantly higher in women than in men (6.3% vs 3.6%,  $P < 0.001$ ). To the best of our knowledge, this is the first study to report the prevalence of CSS in a general population.

In the present study, the prevalence of CSS was 5.4% and differed with sex. The CSI-A Japanese version had higher Cronbach's alpha and test-retest reliability than the English version: 0.879 and 0.817, and 0.89 and 0.85, respectively<sup>8,9</sup>. We confirmed that CSI-A in the present study was stable with Cronbach's alpha for all participants, men, and women of 0.892, 0.889, and 0.893, respectively. Furthermore, the accuracy and specificity of a cut-off CSI-A score of 40 points were 81 and 75%, respectively, and the area under the curve (AUC) was 0.86<sup>15</sup>. The prevalence of CSS in Japanese patients with musculoskeletal disorder was previously reported to be 11%, and the average CSI-A score was 21.9 (SD13.3)<sup>9</sup>. These patients with chronic pain had a higher CSS prevalence and mean CSI scores than our health population, so our results showed 5.4% in the general population, which should be considered appropriate. A previous study reported that the prevalence of CSS was 24.8% in healthy individuals; however, the sample size was very small. We compared Japanese patients to those in other countries and found a lower mean CSI-A score in the former, suggesting racial differences.

The present results demonstrated that the prevalence of CSS was higher in healthy women than in men. In patients with musculoskeletal disorders, the prevalence of CSS (CSI-A  $\geq$ 40) was also higher in women than in men<sup>19-21</sup>. Therefore, sex may be an independent factor in the pathology of CSS.

Although rare CSI-B-related diseases were included in the present study, the main diseases associated with CSS were depression (0.79%), anxiety or panic attacks (0.24%), M/TTH (0.08%), and IBS (0.06%), which is consistent with previous findings showing high CSI-A scores in individuals with more than one CSI-B-related disease<sup>9,16</sup>.

The pathology of CSS has not yet been elucidated in detail; however, the mechanisms underlying pain hypersensitivity syndrome after peripheral tissue injury have been shown to involve the central sensitization of high-threshold primary afferents and increased spinal

excitability<sup>1,22,23</sup>. The present results also indicated that participants with exercise habits and high resilience have lower CSS. Conversely, participants with perceived stress and fewer sleeping hours per day, and low resilience have higher CSS. Furthermore, although alcohol intake in men and ex-smokers and coffee intake in women correlated with CSS, their causal relationship currently remains unknown.

The present results clarified the prevalence of CSS and provided basic data on CSI-A and -B based on sex and age groups in a general population using a large sample size. CSI-A is a useful tool for assessing CSS according to an international consensus. Several limitations need to be addressed. The present study included an information bias and participants may have underestimated CSI-B-related diseases because of the self-reported survey. However, agreement between self-reported CSI-B-related diseases and their diagnoses by physicians was previously reported to be high<sup>15</sup>, and it is a commonly used method in large-scale epidemiological studies. Furthermore, since this was a cross-sectional study, the causal relationship between the prevalence of CS and significant factors currently remains unclear; therefore, future longitudinal studies are needed. Another limitation is that the average age in Japanese communities is older, with fewer younger men, which needs to be considered when interpreting the present results.

In conclusion, the prevalence of CSS in the present study was 5.4% and was higher in women than in men. CSS-related diseases and a few other factors correlated with CSS. The present results provide important information for future epidemiological research on CSS.

## **Methods**

### **Study design and participants**

A large-scale cross-sectional survey was performed in Japan in the fiscal year of 2019. All participants were recruited from Utsunomiya city and Nasu town located approximately 100 and

150 km, respectively, northeast of Tokyo, in Tochigi prefecture. In total, 39,152 residents were invited to complete this survey using an anonymous self-reported questionnaire when they underwent annual health check-ups. Written informed consent was agreed from residents to participate according to the Declaration of Helsinki, and the Institutional Review Boards of Dokkyo Medical University approved the study protocol (No: R-7-3). A total of 24,189 out of 39,152 residents (61.8%) agreed to participate in the present study and responded to the questionnaire (Figure 1).

### **Questionnaire**

Participants were instructed to complete the questionnaire, which included questions on age, sex, smoking (non-smoker, ex-smoker, and smoker), caffeine and alcohol intakes (non-drinker,  $\leq$  or  $>$  one day per week), exercise habits (walking more than one hr. per day or similar physical activity, yes, no), perceived stress (high or low), sleeping hours per day ( $\leq 5$  hr., 6-9 hr., and  $\geq 10$  hr.), and resilience (low, medium, and high). CSS were assessed using the CSI Japanese version, comprising parts A (CSI-A) and B (CSI-B)<sup>9</sup>. CSI-A addresses 25 items on 5-point Likert scale for CS-related somatic symptoms (score, 0-100). Participants with a CSI-A score  $\geq 40$  was defined as having CSS<sup>6,8,9</sup>. CSI-B was evaluated according to 10 self-reported CSS-related diseases: RLS, CFS, FM, TJD, M/TTH, IBS, MCS, neck injury (including whiplash) (NIW), anxiety or panic attacks, and depression.

### **Statistical analysis**

Each variable was described by sex. Age was divided into 4 groups (20-39, 40-59, 60-79, and 80-97 yr.). The reliability of CSI-A in the present study was discussed using Cronbach's coefficient alpha. The average CSI score and prevalence of CSS (CSI-A  $\geq 40$  points) were analyzed using descriptive statistics by sex and age groups. The Mann-Whitney test or Kruskal-Wallis test with the Bonferroni post-hoc test was performed to assess differences in CSI scores in the sex or age

groups. The 10 diseases in CSI-B were re-categorized as 0 diseases and 1 or 2 diseases. The relationships between CSS and lifestyle and mental factors were examined using the chi-squared test or Fisher's exact test. Univariate and multivariable analyses using logistic regression models were performed to identify factors contributing to CSS in the general population.

All statistical analyses were conducted using an assumed type I error rate of 0.05 with SPSS Statistics 26.0 (IBM SPSS, Inc., Tokyo, Japan).

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and Intractable Diseases Program [Grant Number H29-I-G-061,20FC1056] in Japan.

### **Author contributions statement**

Y.H. and G.K. conceived and designed the study. T.S. and K.U. recruited participants. Y.H. performed the data analysis and drafted the manuscript. Y.H., K.S., T.S., K.U., K.H., and G.K. contributed to the interpretation of data and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

### **Competing interests**

The authors declare no competing interests.

### **Data availability**

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

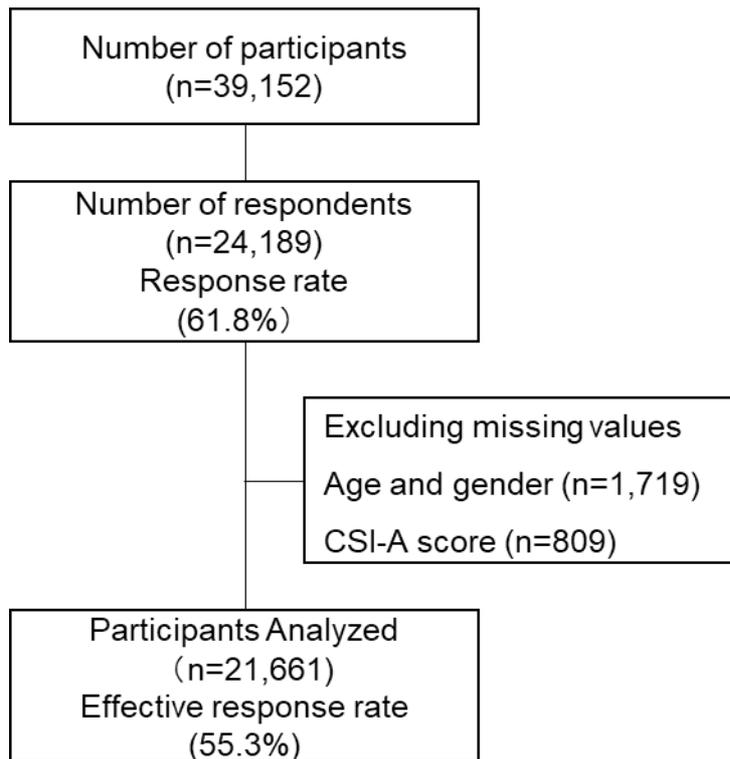


Figure 1 . Chart of the epidemiological survey

CSI: Central Sensitization Inventory

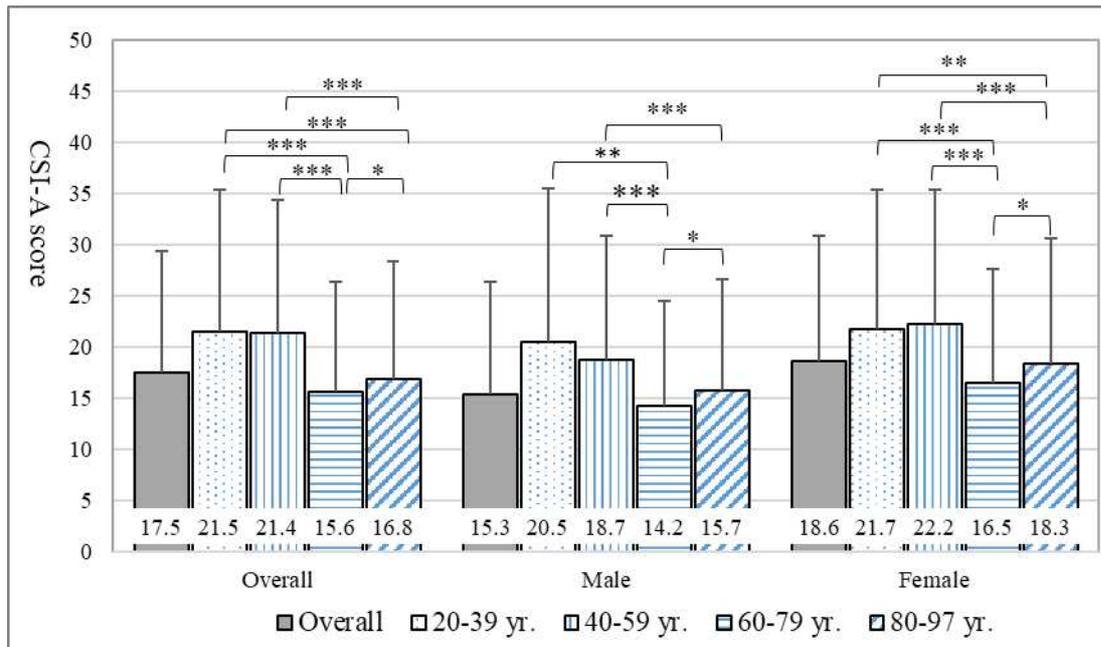


Figure 2. Average CSI-A score by sex and age groups

CSS: central sensitization syndromes; CSI: Central Sensitization Inventory.

A Kruskal-Wallis test with the Bonferroni post-hoc test was performed among age groups

Error bars indicate the standard deviation; \*:  $P < .05$ , \*\*:  $P < .01$  \*\*\*:  $P < .001$

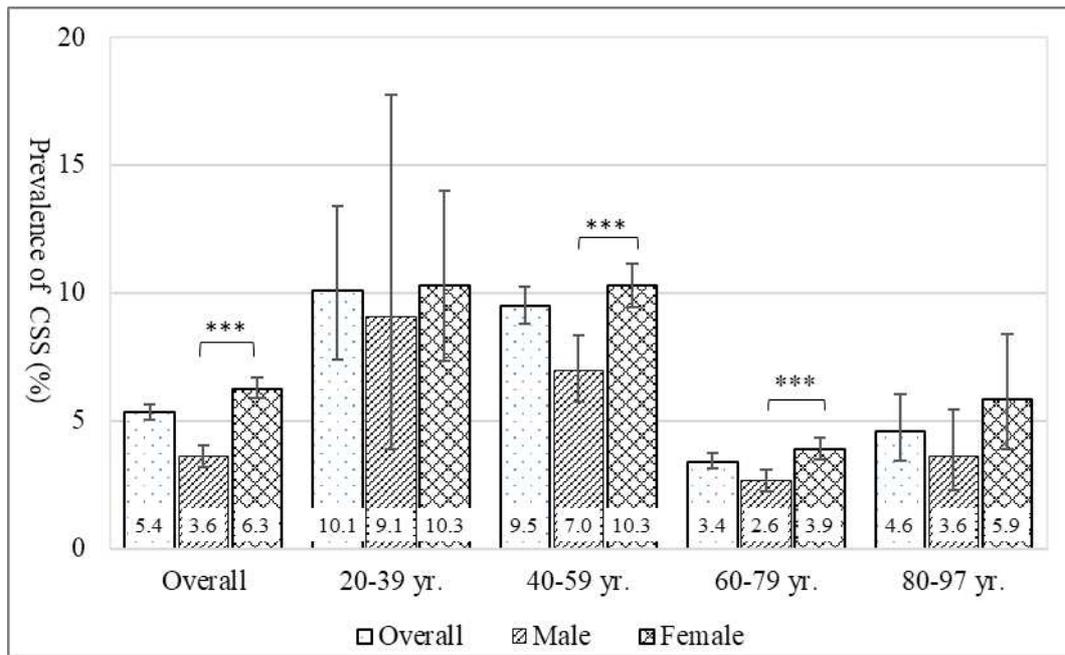


Figure 3. Prevalence of CSS with CSI-A  $\geq$ 40 points by sex and age groups

CSS: central sensitization syndromes; CSI: Central Sensitization Inventory.

A Chi-squared test was performed between men and women

Error bars indicate the 95% confidence interval; \*\*\*:  $P < .001$

Table 1 Characteristics of participants by sex

|                                     |                 | Overall (n=21,661) |        | Men (n=7,531) |        | Women (n=14,130) |        |
|-------------------------------------|-----------------|--------------------|--------|---------------|--------|------------------|--------|
|                                     |                 | n                  | %      | n             | %      | n                | %      |
| Age, mean (SD), min, max yr.        |                 | 63.4(11.7)         | 20, 97 | 66.6(10.8)    | 25, 96 | 61.7(11.8)       | 20, 97 |
| Age groups, yr.                     | 20-39           | 386                | 1.8    | 66            | 0.9    | 320              | 2.3    |
|                                     | 40-59           | 6,275              | 29.0   | 1,478         | 19.6   | 4,797            | 33.9   |
|                                     | 60-79           | 14,023             | 64.7   | 5,437         | 72.2   | 8,586            | 60.8   |
|                                     | 80-97           | 977                | 4.5    | 550           | 7.3    | 427              | 3.0    |
| District                            | Rural area      | 2,603              | 12.0   | 1,210         | 16.1   | 1,393            | 9.9    |
|                                     | Urban area      | 19,058             | 88.0   | 6,321         | 83.9   | 12,737           | 90.1   |
| CSI-B-related diseases, yes         |                 |                    |        |               |        |                  |        |
| Migraine or tension headaches       |                 | 18                 | 0.08   | 4             | 0.05   | 14               | 0.10   |
| Restless legs syndrome              |                 | 3                  | 0.01   | 1             | 0.01   | 2                | 0.01   |
| Chronic fatigue syndrome            |                 | 2                  | 0.01   | 0             | 0.00   | 2                | 0.01   |
| Fibromyalgia                        |                 | 2                  | 0.01   | 0             | 0.00   | 2                | 0.01   |
| Temporomandibular joint disorder    |                 | 0                  | 0.00   | 0             | 0.00   | 0                | 0.00   |
| Irritable bowel syndrome            |                 | 14                 | 0.06   | 5             | 0.07   | 9                | 0.06   |
| Multiple chemical sensitivities     |                 | 0                  | 0.00   | 0             | 0.00   | 0                | 0.00   |
| Neck injury (including whiplash)    |                 | 3                  | 0.01   | 1             | 0.01   | 2                | 0.01   |
| Anxiety or panic attacks            |                 | 53                 | 0.24   | 7             | 0.09   | 46               | 0.33   |
| Depression                          |                 | 170                | 0.79   | 57            | 0.76   | 113              | 0.80   |
| Smoking <sup>a</sup>                | Non-smoker      | 14,778             | 69.8   | 2,736         | 37.9   | 12,042           | 86.3   |
|                                     | Ex-smoker       | 4,861              | 23.0   | 3,495         | 48.4   | 1,366            | 9.8    |
|                                     | Smoker          | 1,527              | 7.2    | 985           | 13.7   | 542              | 3.9    |
| Alcohol intake <sup>a</sup>         | Non-drinker     | 11,509             | 57.2   | 2,431         | 37.3   | 9,078            | 66.7   |
|                                     | ≤1 day per week | 2,964              | 14.7   | 903           | 13.9   | 2,061            | 15.1   |
|                                     | >1 day per week | 5,657              | 28.1   | 3,177         | 48.8   | 2,480            | 18.2   |
| Coffee intake <sup>a</sup>          | Non-drinker     | 2,507              | 14.0   | 996           | 16.0   | 1,511            | 12.9   |
|                                     | ≤1 day per week | 2,686              | 15.0   | 939           | 15.1   | 1,747            | 15.0   |
|                                     | >1 day per week | 12,704             | 71.0   | 4,279         | 68.9   | 8,425            | 72.1   |
| Exercise habits <sup>a</sup>        | No              | 10,130             | 47.8   | 3,314         | 44.7   | 6,816            | 49.4   |
|                                     | Yes             | 11,067             | 52.2   | 4,092         | 55.3   | 6,975            | 50.6   |
| Sleeping hours per day <sup>a</sup> | ≤5 hr.          | 4,467              | 20.7   | 1,228         | 16.3   | 3,239            | 23.0   |
|                                     | 6-9 hr.         | 17,067             | 79.0   | 6,252         | 83.2   | 10,815           | 76.8   |
|                                     | ≥10 hr.         | 57                 | 0.3    | 38            | 0.5    | 19               | 0.1    |
| Perceived stress <sup>a</sup>       | Low             | 12,725             | 59.3   | 5,376         | 71.9   | 7,349            | 52.6   |
|                                     | High            | 8,739              | 40.7   | 2,104         | 28.1   | 6,635            | 47.4   |
| Resilience <sup>b</sup>             | Low             | 3,858              | 17.9   | 1,183         | 15.8   | 2,675            | 19.0   |
|                                     | Medium          | 8,582              | 39.8   | 3,163         | 42.2   | 5,419            | 38.6   |
|                                     | High            | 9,098              | 42.2   | 3,141         | 42.0   | 5,957            | 42.4   |

CSI:Central Sensitization Inventory

a: Participants with missing values for smoking (n=495), alcohol intake (n=1,531), coffee intake (n=3,764), exercise habits (n=464), sleeping hours per day (n=70), perceived stress (n=197), and resilience (n=123) were excluded.

Table 2 Prevalence of CSS with CSI-A  $\geq 40$  points in each variable by sex

|                                     |                       | CSS with CSI-A $\geq 40$ points |      |                             |       |      |                             |
|-------------------------------------|-----------------------|---------------------------------|------|-----------------------------|-------|------|-----------------------------|
|                                     |                       | Men                             |      | <i>P</i> value <sup>a</sup> | Women |      | <i>P</i> value <sup>a</sup> |
|                                     |                       | n                               | %    |                             | n     | %    |                             |
| Age, yr.                            | 20-39                 | 6                               | 9.1  | <0.001                      | 33    | 10.3 | <0.001                      |
|                                     | 40-59                 | 103                             | 7.0  |                             | 493   | 10.3 |                             |
|                                     | 60-79                 | 144                             | 2.6  |                             | 335   | 3.9  |                             |
|                                     | 80-97                 | 20                              | 3.6  |                             | 25    | 5.9  |                             |
| District                            | Rural area            | 45                              | 3.7  | 0.849                       | 73    | 5.2  | 0.095                       |
|                                     | Urban area            | 228                             | 3.6  |                             | 913   | 6.4  |                             |
| CIS-B-related diseases              | 0 diseases            | 254                             | 3.4  | <0.001                      | 828   | 5.9  | <0.001                      |
|                                     | 1 disease             | 19                              | 26.8 |                             | 58    | 32.0 |                             |
|                                     | 2 diseases            | 0                               | 0.0  |                             | 1     | 16.7 |                             |
| Smoking <sup>b</sup>                | Non-smoker            | 104                             | 3.8  | 0.290                       | 686   | 5.7  | <0.001                      |
|                                     | Ex-smoker             | 112                             | 3.2  |                             | 129   | 9.4  |                             |
|                                     | Smoker                | 40                              | 4.1  |                             | 55    | 10.1 |                             |
| Alcohol intake <sup>b</sup>         | Non-drinker           | 120                             | 4.9  | 0.001                       | 564   | 6.2  | <0.001                      |
|                                     | $\leq 1$ day per week | 31                              | 3.4  |                             | 164   | 8.0  |                             |
|                                     | >1 day per week       | 94                              | 3.0  |                             | 136   | 5.5  |                             |
| Coffee intake <sup>b</sup>          | Non-drinker           | 32                              | 3.2  | 0.386                       | 126   | 8.3  | 0.002                       |
|                                     | $\leq 1$ day per week | 41                              | 4.4  |                             | 116   | 6.6  |                             |
|                                     | >1 day per week       | 155                             | 3.6  |                             | 510   | 6.1  |                             |
| Exercise habits <sup>b</sup>        | No                    | 171                             | 5.2  | <0.001                      | 599   | 8.8  | 0.004                       |
|                                     | Yes                   | 99                              | 2.4  |                             | 272   | 3.9  |                             |
| Sleeping hours per day <sup>b</sup> | $\leq 5$ hr.          | 98                              | 8.0  | <0.001                      | 359   | 11.1 | <0.001                      |
|                                     | 6-9 hr.               | 172                             | 2.8  |                             | 520   | 4.8  |                             |
|                                     | $\geq 10$ hr.         | 2                               | 5.3  |                             | 1     | 5.3  |                             |
| Perceived stress <sup>b</sup>       | Low                   | 68                              | 1.3  | <0.001                      | 125   | 1.7  | <0.001                      |
|                                     | High                  | 204                             | 9.7  |                             | 754   | 11.4 |                             |
| Resilience <sup>b</sup>             | Low                   | 125                             | 10.6 | <0.001                      | 411   | 15.4 | <0.001                      |
|                                     | Medium                | 99                              | 3.1  |                             | 272   | 5.0  |                             |
|                                     | High                  | 47                              | 1.5  |                             | 201   | 3.4  |                             |

CSS: Central sensitization syndrome; CSI: Central sensitization inventory

a: Using the chi-squared test or Fisher's exact test

b: Participants with missing values for smoking (n=495), alcohol intake (n=1,531), coffee intake (n=3,764), exercise habits (n=464), perceived stress (n=197), sleeping hours per day (n=70), and resilience (n=123) were excluded.

Table 3 Relationships between the prevalence of CSS with CSI-A  $\geq$ 40 points and factors by sex

|                                     |                       | Men              |                   |                  |                  | Women            |                   |                  |                   |
|-------------------------------------|-----------------------|------------------|-------------------|------------------|------------------|------------------|-------------------|------------------|-------------------|
|                                     |                       | cOR <sup>a</sup> | 95%CI             | aOR <sup>a</sup> | 95%CI            | cOR <sup>a</sup> | 95%CI             | aOR <sup>a</sup> | 95%CI             |
| Age, yr.                            | 20-39                 | <b>3.68</b>      | <b>1.56-8.65</b>  | 1.99             | 0.69-5.78        | <b>2.82</b>      | <b>2.44-3.26</b>  | <b>1.65</b>      | <b>1.07-2.54</b>  |
|                                     | 40-59                 | <b>2.75</b>      | <b>2.12-3.57</b>  | 1.09             | 0.77-1.53        | <b>2.83</b>      | <b>1.94-4.13</b>  | <b>1.86</b>      | <b>1.56-2.22</b>  |
|                                     | 60-79                 | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | 80-97                 | 1.39             | 0.86-2.23         | 1.72             | 0.93-3.17        | <b>1.53</b>      | <b>1.01- 2.33</b> | <b>2.40</b>      | <b>1.46-3.93</b>  |
| District                            | Rural area            | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | Urban area            | 0.97             | 0.70-1.34         | 0.82             | 0.55-1.22        | 1.23             | 0.96-1.58         | 0.98             | 0.73-1.31         |
| CSI-B-related diseases              | 0 diseases            | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | 1 or 2 diseases       | <b>9.98</b>      | <b>5.83-17.03</b> | <b>3.51</b>      | <b>1.78-6.92</b> | <b>7.29</b>      | <b>5.30-10.03</b> | <b>3.07</b>      | <b>2.10-4.48</b>  |
| Smoking <sup>b</sup>                | Non-smoker            | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | Ex-smoker             | 0.84             | 0.64-1.10         | 0.75             | 0.54-1.05        | <b>1.73</b>      | <b>1.42-2.10</b>  | <b>1.30</b>      | <b>1.03-1.65</b>  |
|                                     | Smoker                | 1.07             | 0.74-1.55         | 0.84             | 0.54-1.30        | <b>1.87</b>      | <b>1.40-2.50</b>  | 1.35             | 0.96-1.89         |
| Alcohol intake <sup>b</sup>         | Non-drinker           | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | $\leq$ 1 day per week | 0.69             | 0.46-1.02         | <b>0.57</b>      | <b>0.35-0.91</b> | <b>1.31</b>      | <b>1.09-1.56</b>  | 1.21             | 0.98-1.49         |
|                                     | $>$ 1 day per week    | <b>0.59</b>      | <b>0.45-0.77</b>  | <b>0.65</b>      | <b>0.47-0.91</b> | 0.88             | 0.72-1.06         | 0.88             | 0.71-1.10         |
| Coffee intake <sup>b</sup>          | Non-drinker           | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | $\leq$ 1 day per week | 1.38             | 0.86-2.20         | 1.54             | 0.89-2.67        | 0.78             | 0.60-1.02         | 0.81             | 0.61-1.09         |
|                                     | $>$ 1 day per week    | 1.13             | 0.77-1.67         | 1.27             | 0.80-2.01        | <b>0.71</b>      | <b>0.58-0.87</b>  | <b>0.68</b>      | <b>0.54-0.85</b>  |
| Exercise habits <sup>b</sup>        | No                    | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | Yes                   | <b>0.46</b>      | <b>0.35-0.59</b>  | <b>0.66</b>      | <b>0.48-0.89</b> | <b>0.42</b>      | <b>0.36-0.49</b>  | <b>0.53</b>      | <b>0.44-0.62</b>  |
| Sleeping hours per day <sup>b</sup> | $\leq$ 5 hr.          | <b>3.07</b>      | <b>2.37-3.96</b>  | <b>2.18</b>      | <b>1.59-3.00</b> | <b>2.47</b>      | <b>2.14-2.84</b>  | <b>1.94</b>      | <b>1.64-2.29</b>  |
|                                     | 6-9 hr.               | <b>1.00</b>      |                   | <b>1.00</b>      |                  | <b>1.00</b>      |                   | <b>1.00</b>      |                   |
|                                     | $\geq$ 10 hr.         | <b>1.96</b>      | <b>0.47-8.22</b>  | <b>3.13</b>      | <b>0.63-3.82</b> | <b>1.10</b>      | <b>0.15-8.26</b>  | <b>1.40</b>      | <b>0.16-12.39</b> |
| Perceived stress <sup>b</sup>       | Low                   | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | High                  | <b>8.38</b>      | <b>6.34-11.08</b> | <b>5.34</b>      | <b>3.76-7.58</b> | <b>7.41</b>      | <b>6.11-8.98</b>  | <b>4.38</b>      | <b>3.53-5.43</b>  |
| Resilience <sup>b</sup>             | Low                   | <b>3.66</b>      | <b>2.78-4.80</b>  | <b>2.73</b>      | <b>1.95-3.82</b> | <b>3.44</b>      | <b>2.92-4.04</b>  | <b>2.68</b>      | <b>2.22-3.23</b>  |
|                                     | Medium                | 1.00             |                   | 1.00             |                  | 1.00             |                   | 1.00             |                   |
|                                     | High                  | <b>0.47</b>      | <b>0.33-0.67</b>  | <b>0.43</b>      | <b>0.28-0.67</b> | <b>0.66</b>      | <b>0.55-0.80</b>  | <b>0.70</b>      | <b>0.56-0.86</b>  |

a: cOR and aOR mean crude and adjusted odds ratios analyzed with univariate and multivariable logistic regression models.

b: Participants with missing values for smoking (n=495), alcohol intake (n=1,531), coffee intake (n=3,764), exercise habits (n=464), perceived stress (n=197), sleeping hours per day (n=70), and resilience (n=123) were excluded.

## Figures

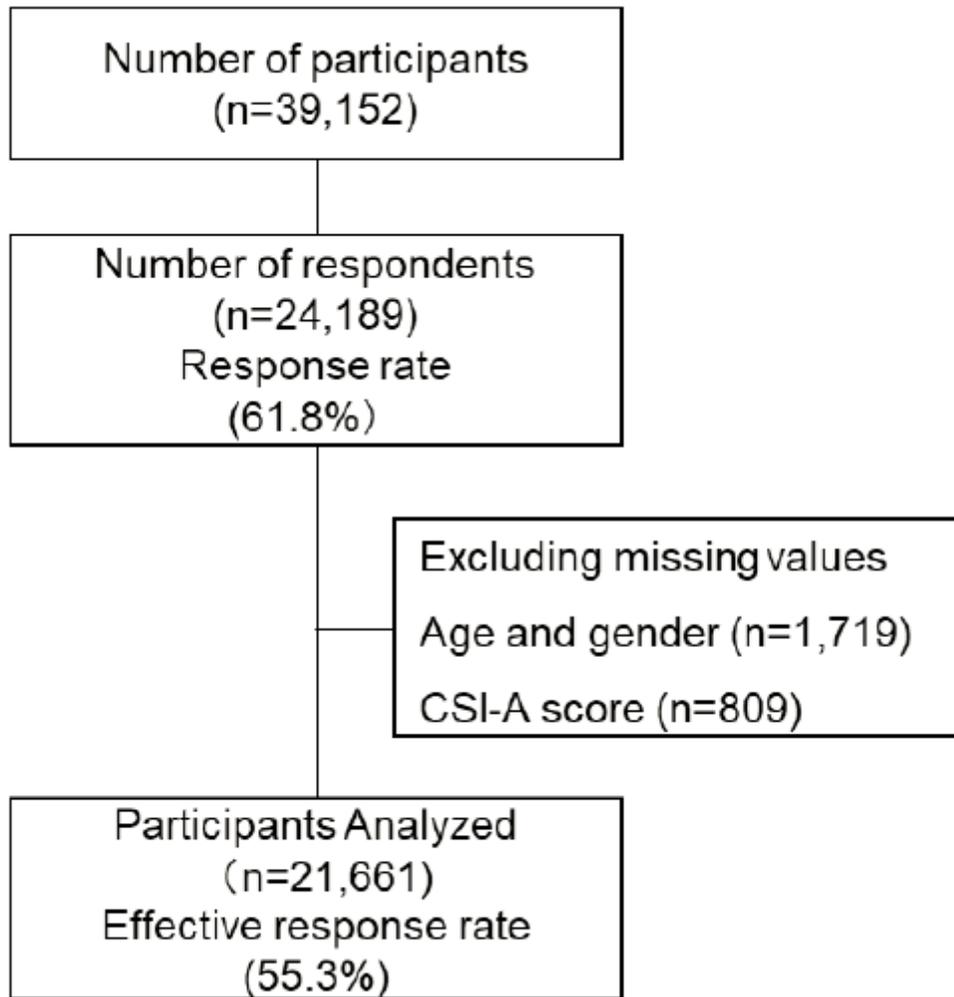
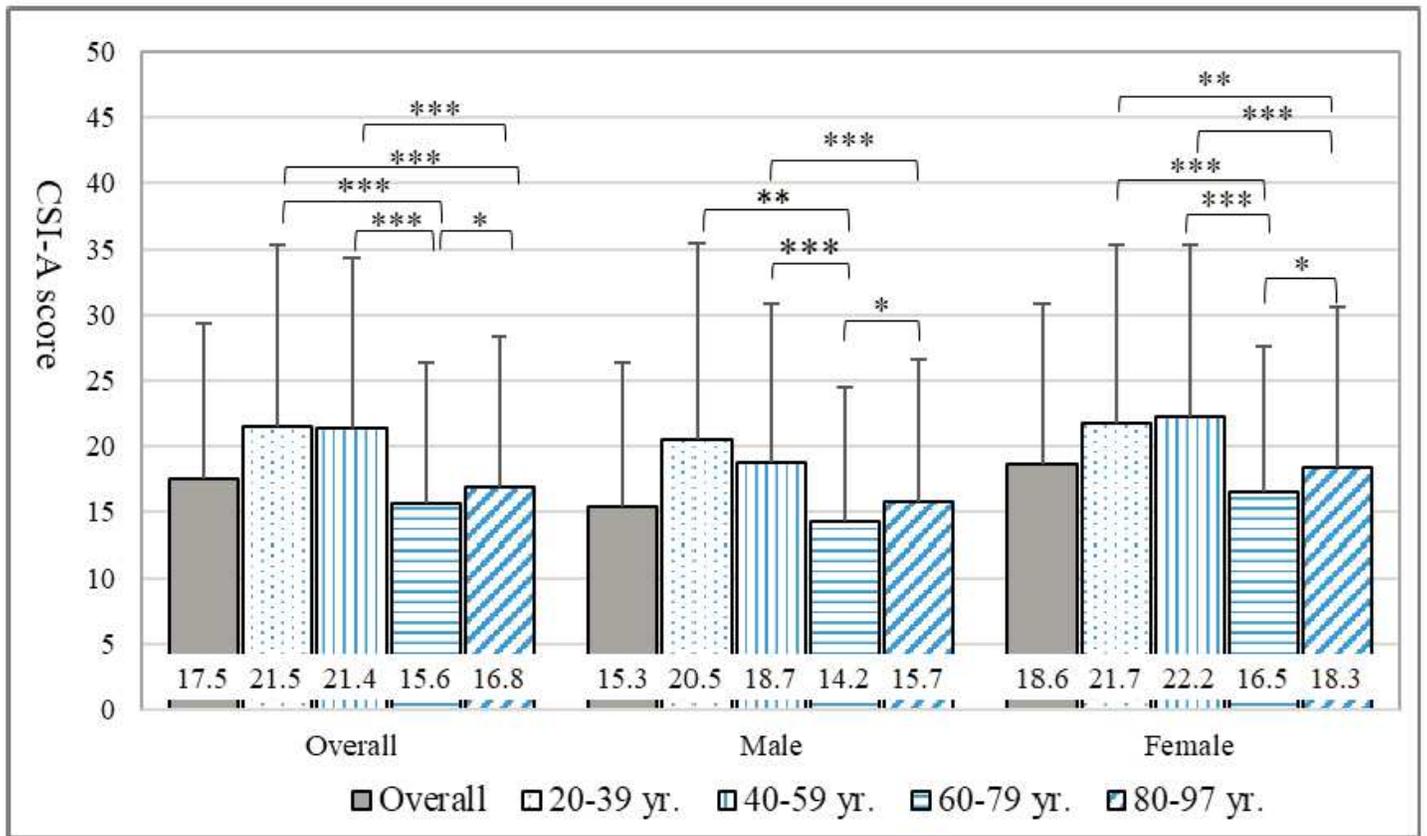


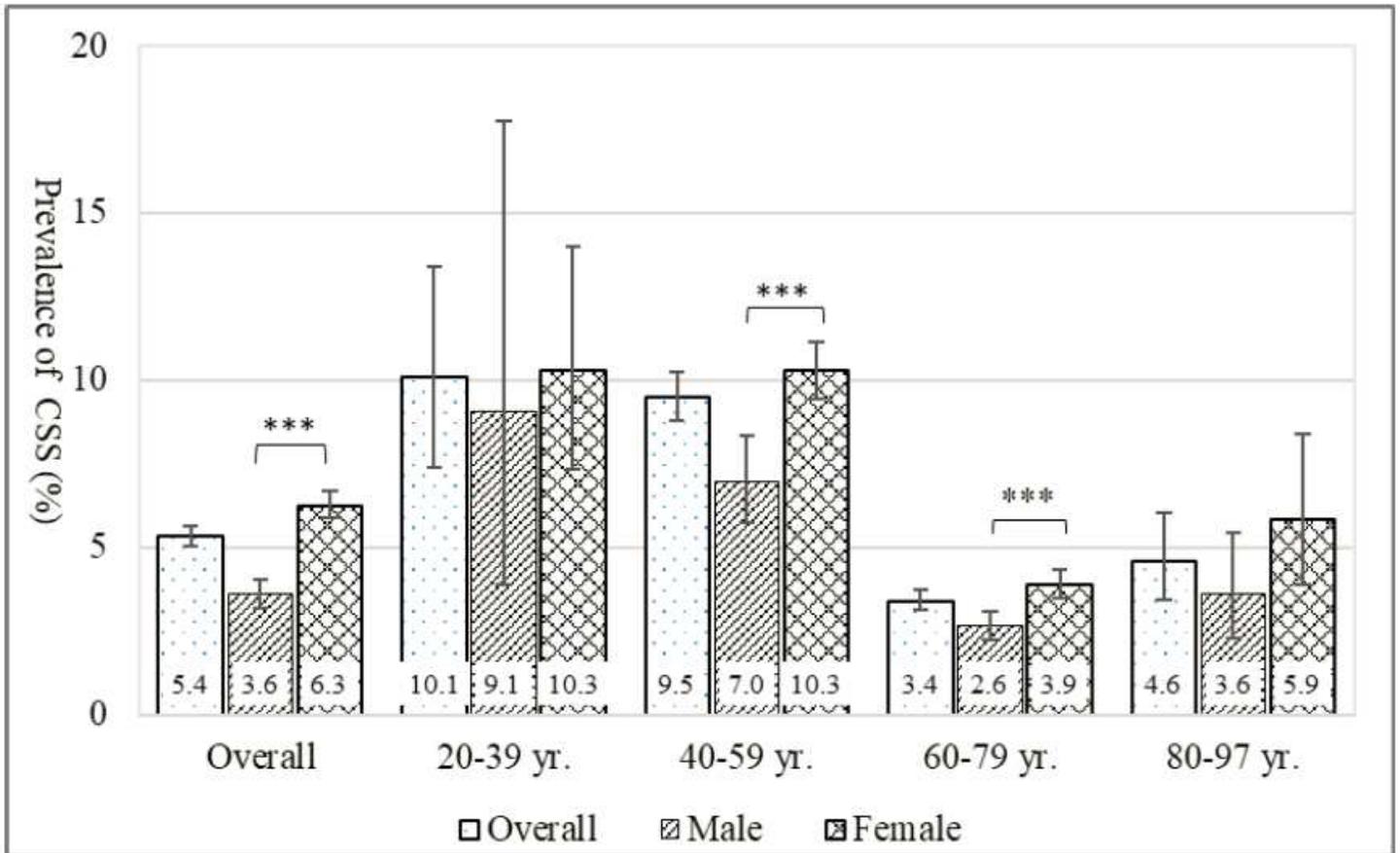
Figure 1

Chart of the epidemiological survey. CSI: Central Sensitization Inventory



**Figure 2**

Average CSI-A score by sex and age groups CSS: central sensitization syndromes; CSI: Central Sensitization Inventory. A Kruskal-Wallis test with the Bonferroni post-hoc test was performed among age groups Error bars indicate the standard deviation; \*: P<.05, \*\*: P<.01 \*\*\*: P<.001



**Figure 3**

Prevalence of CSS with CSI-A  $\geq 40$  points by sex and age groups CSS: central sensitization syndromes; CSI: Central Sensitization Inventory. A Chi-squared test was performed between men and women Error bars indicate the 95% confidence interval; \*\*\*:  $P < .001$