Depression and anxiety among nursing students during the COVID-19 pandemic in Tohoku region, Japan: A cross-sectional survey

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Abstract
Aim: Restrictions such as physical distancing and online learning for college students were implemented due to the COVID-19 pandemic. Owing to this, students may experience psychological distress from social isolation and loneliness. Nursing students are subjected to an exacerbated level of distress during the pandemic due to their role as health professionals. Therefore, the present study aimed to investigate the level of anxiety and depression among Japanese nursing students, according to their perceived vulnerability to COVID-19.

Methods: A total of 281 college students (104 nursing students and 177 other college students) responded to a web-based anonymous questionnaire survey from 18 August to 31 October 2020. The Hospital Anxiety and Depression Scale was used to evaluate anxiety (HADS-A) and depression (HADS-D). Perceived vulnerability to COVID-19 was assessed using the Perceived Vulnerability to Disease Scale.

Results: In both groups of students, the prevalence of both anxiety (30.5% in nursing students; 69.5% in others) and depressive symptoms (31.1% in nursing students; 68.9% in others) were remarkably high. There were no significant differences in anxiety and depression between nursing and other students after adjusting for perceived vulnerability to COVID-19 plus socio-demographic characteristics and stress coping styles. Perceived vulnerability and its interactions with nursing did not show a significant association with either depression or anxiety.

Conclusion: This study highlights the need for greater support and preventive strategies for mental health problems for college students during the COVID-19 pandemic regardless of perceived vulnerability.

Keywords
anxiety, COVID-19, depression, epidemiology, nursing students
1 | INTRODUCTION

Due to the coronavirus disease (COVID-19) pandemic, universities in many countries were made to close presentational teaching activities and adapt an online or virtual format for classes (Zhai & Du, 2020). The psychological well-being of college students may be particularly vulnerable during this time, since they are still undergoing psychological development at this stage in their lives (Kilgo et al., 2016). Studies have also found that social distancing, as an effect of the COVID-19 pandemic, can lead to negative psychological consequences among college students. In particular, increased symptoms of anxiety and depression were observed in college students as an immediate impact of confinement (Huckins et al., 2020; Li et al., 2021).

Compared with non-medical disciplines, nursing studies are characterized by full-time courses, stringent tests (Chernomas & Shapiro, 2013), formation of complex interpersonal relationships, and practice in a clinical environment (Chen et al., 2015). During nursing education, most nursing students experience moderate to high levels of stress during clinical training (John & Al-Sawad, 2015; Labrague, 2013). With this, there is a high prevalence of anxiety and depressive symptoms among nursing students (Tung et al., 2018). Furthermore, nurses are the leading active partners in primary and secondary infectious disease prevention efforts. During the COVID-19 pandemic, frontline nurses generally work under stress and even put their lives at risk in the course of performing their duties (Catton, 2020; Mo et al., 2020). This is reflected in several studies which reported that nursing students experienced anxiety and depression in the early months of the COVID-19 pandemic (Mechili et al., 2021; Savitsky et al., 2020; Zhu et al., 2021). Moreover, nursing students are likely to be fearful of being infected by COVID-19.

Perceived vulnerability to diseases may play a crucial role in calibrating threat perception among nursing students during a pandemic. Humans perceive themselves as being more likely to be infected with COVID-19 and display threat reactivity (Safra et al., 2021). The fear of contacting individuals who are possibly infected with COVID-19 has been reported (Lin, 2020). Boyraz et al. suggested that the fear of COVID-19 can generate specific negative psychological responses such as maladaptive behaviors, traumatic stress, and avoidance reactions in both general and patient populations (Boyraz et al., 2020). Lovrić et al. reported that most nursing students are afraid of infection and that they worried about the well-being of their families; thus, they constantly applied protective measures during the COVID-19 pandemic (Lovrić et al., 2020). During the COVID-19 pandemic, nursing students showed high anxiety associated with fear of infection and a lack of personal protection equipment (Savitsky et al., 2020). Perceived vulnerability can exist several months after the peak of the COVID-19 pandemic among nursing students. However, studies of psychological well-being in nursing students were mainly focused on the early months of the COVID-19 pandemic and were without a reference group (e.g., other college students). Furthermore, there has been no examination of the role that perceived vulnerability to COVID-19 plays in anxiety and depression among nursing students and how it differs from other college students.

Japan issued its first emergency declaration on 7 April 2020. Although the emergency declaration did not impose a hard lockdown over its population, college students were forced to switch to online learning methods. Despite the easing of COVID-19 related restrictions from 25 May 2020, online education initiatives were continued for college students. The purpose of the present study was to investigate the relationship between mental health issues (i.e., depression and anxiety) and perceived vulnerability to COVID-19 in Japanese college students, and to determine whether nursing students showed anxiety and depressive symptoms according to perceived vulnerability.

2 | METHOD

2.1 | Study design

A web-based cross-sectional survey was conducted. The questionnaire was created using Google Forms, and a request to participate in the study was sent to students. No financial incentive was offered for participation. The questionnaire was anonymous (demographic questions were asked, but the identification details were not included).

2.2 | Setting

This study was conducted between 18 August and 31 October 2020. The two junior colleges, four universities, and two professional training colleges in Japan’s Tohoku region participated in this survey (Table S1 in the Supporting Information). The survey link was distributed to teachers at the participating schools; it contained a detailed explanation of the purpose and significance of the study, as well as its directions. The students then received an email invitation to complete the survey on a secure website. After reading a description of the study, students indicated their consent by clicking on the link to
begin the investigation. Our email addresses and phone numbers were also included on the first page of the questionnaire so that participants could contact us at any time. The “Limit to 1 response” function was used in the Google Form to bar respondents from completing the form more than once.

2.3 | Participants

Convenience sampling was used to recruit the following participants: (1) nursing students who underwent on-the-job training in hospitals; and (2) college students from other departments. Other departments were selected to have similar gender ratios to students in nursing departments. A total of 281 students participated in this study: 43 men and 238 women. The participants were undergraduate students who were at least 20 years old.

2.4 | Variables

The dependent variables were depression and anxiety, which were evaluated using the Hospital Anxiety and Depression Scale (HADS) – a scale used to screen for emotional disorders, such as adjustment disorders, major depression, and anxiety disorders (Zigmond & Snaith, 1983). We selected the HADS to measure depression and anxiety as it has been validated in Japanese, does not burden respondents with too many questions, and has been used with general populations including college students (Matsudaira et al., 2009). The original version of the HADS was translated to Japanese by Kitamura (1993). The HADS is a four-point, 14-item self-assessment scale that measures psychological distress through two factors: depression and anxiety. Of the 14 items, seven evaluate depressive symptoms (HADS-D) and seven evaluate anxiety symptoms (HADS-A). For the HADS-D, a total score of 0–7 points represents no depressive symptoms, while 8–10 points represent a suspected diagnosis and 11–21 points represent a specific diagnosis of depressive symptoms (Hayashi et al., 2011). A total HADS-A score of 0–7 points indicates no anxiety, while 8–21 points represent borderline (8) or severe anxiety (>8) (Fukui et al., 2001). The Japanese versions of the HADS-A and HADS-D are reported to have good reliability in female students, with Cronbach’s alpha coefficients of 0.80 and 0.61, respectively (Matsudaira et al., 2009). Furthermore, the HADS-A has shown high validity in female students, with criterion-related validity reported to be 0.61 for state anxiety and 0.65 for trait anxiety (Matsudaira et al., 2009). In the current study, Cronbach’s alpha coefficient was 0.821 for the HADS-A and 0.722 for the HADS-D.

The main independent variables were the perceived vulnerability to the transmission of infectious diseases, and whether the student was in the nursing discipline. Perceived vulnerability was measured by the Japanese version of the Perceived Vulnerability to Disease (PVD) scale (Duncan et al., 2009; Fukukawa et al., 2014). The PVD consists of 15 items, including a two-factor structure: perceived infectability (seven items) and germ aversion (eight items). The participants rated each item on a seven-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). The total scores of each factor ranged from 7–49 (perceived infectability), and 8–56 (germ aversion), with higher scores indicating greater perceived vulnerability. The average scoring of each factor was used to evaluate PVD (Fukukawa et al., 2014). A previous study reported an acceptable internal consistency of the individual and total scores of the PVD factors (α = 0.87, 0.67, and 0.79 for perceived infectability, germ aversion, and total score, respectively; Fukukawa et al., 2014). Furthermore, a Short Health Anxiety Inventory for correlation evaluated the validities of perceived infectability and germ aversion in the PVD; the scores were 0.4 and 0.22, respectively (Fukukawa et al., 2014). The Fear of COVID-19 Scale, which was developed specifically to measure the fear of infection with COVID-19, correlates significantly with the PVD (Ahorsu et al., 2020). In this study, the Cronbach’s alpha coefficients for perceived infectability, germ aversion, and the total score were 0.777, 0.651, and 0.642, respectively.

All other variables selected were classified according to sociodemographic status or related to health status. These variables have been associated with depressive symptoms and/or anxiety in previous studies (Table S2; Huckins et al., 2020; Li et al., 2021; Mechili et al., 2021; Patelarou et al., 2021; Savitsky et al., 2020; Tung et al., 2018; Zhu et al., 2021). The variables, by group, were as follows:

- Sociodemographic variables were gender, age, number of living family members, and finances.
- Health status variables were exercise, sleep, time spent online, game, alcohol consumption, and stress coping. In the questionnaire, response options (problems) were presented for each health status, and respondents were asked to check if the problem was present. Respondents were categorized into “no trouble” if all problems were absent, or “trouble” if any problems were present.

Stress coping style was measured using the Coping Inventory for Stressful Situations (CISS). The CISS is composed of 48 items and is a reliable measure of coping strategies (Endler & Parker, 1990). Respondents were asked to indicate how often they engaged in various
activities when they encountered stressful situations, on a scale from 1 (not at all) to 5 (very often). The CISS contains three 16-item scales assessing task-oriented coping (task scale), emotion-oriented coping (emotion scale), and avoidance-oriented coping (avoidance scale). The Japanese version of the CISS was obtained from Kanekoshobo (Tokyo, Japan). This instrument was previously reported to have acceptable internal consistency ($\alpha = 0.75$–$0.89$) for all scales (Watanabe et al., 2015). The internal consistency and concurrent validity for each type of stress coping in the Japanese version of the CISS were 0.854 and 0.790 (task-oriented), 0.854 and 0.790 (emotion-oriented), and 0.854 and 0.790 (avoidance-oriented), respectively (Watanabe et al., 2015). In this study, the Cronbach’s alpha coefficient for the task scale, emotion scale, and avoidance scale was 0.918, 0.893, and 0.847, respectively.

2.5 | Sample size

The required sample size was calculated using G*Power 3.1.9.7 (Faul et al., 2007; Faul et al., 2009). Assuming an alpha level of 0.05%, 95% power, a medium effect size (Cohen’s $f = 0.25$), 2 × 2 groups (nursing and PVD), and 17 covariates, the desired sample size was 211. Therefore, this study was able to meet the sample size needed to test this hypothesis with 281 participants.

2.6 | Statistical method

Data analysis was performed using SPSS statistical software version 24 (IBM Corp., Armonk, NY, USA). In addition to descriptive statistics and frequency analyses of demographic characteristics and health status information, $t$ tests were used to analyze differences in the nursing discipline. Multiple linear regression analyses were used to assess the associations between outcome variables (i.e. anxiety and depression) and potential predictors (i.e. nursing students, PVD, and their interaction) while adjusting for other identified explanatory variables. When running the process model, the forced method selection algorithm was used, and variables were screened based on the significance levels of the Wald inclusion test statistic being less than 0.05.

2.7 | Ethics statement

This survey was conducted following approval by the Ethics Committee of Tohoku University Graduate School of Medicine and with permission from the head of the research institution (2021–1-733).

### 3 | RESULTS

#### 3.1 | Sample characteristics

A total of 281 students were included in the study, and their demographic and lifestyle characteristics are shown in Table 1.

| All participants ($n = 281$) |
|-------------------------------|
| **Sex**                      |                          |
| Male                          | 43 (15.3%)               |
| Female                        | 238 (84.7%)              |
| **Age (years)**               |                          |
| 20                            | 86 (30.6%)               |
| 21                            | 143 (50.9%)              |
| 22                            | 52 (18.5%)               |
| **Department**                |                          |
| Nursing                       | 104 (37.0%)              |
| Others                        | 177 (63.0%)              |
| **Living**                    |                          |
| Alone                         | 149 (53.0%)              |
| With others                   | 132 (47.0%)              |
| **Online (hours)**            |                          |
| 0-3                           | 129 (45.9%)              |
| 3-6                           | 109 (38.8%)              |
| 6                             | 43 (15.3%)               |
| **Game (hours)**              |                          |
| 0                             | 138 (49.1%)              |
| <1                            | 86 (30.6%)               |
| 1                             | 57 (20.3%)               |
| **Exercise (hours)**          |                          |
| 0                             | 59 (21.0%)               |
| <1                            | 147 (52.3%)              |
| 1                             | 75 (26.7%)               |
| **Sleep**                     |                          |
| No trouble                    | 127 (45.2%)              |
| Trouble                       | 154 (54.8%)              |
| **Appetite**                  |                          |
| No trouble                    | 177 (60.6%)              |
| Trouble                       | 104 (35.6%)              |
| **Alcohol consumption**       |                          |
| No trouble                    | 119 (42.3%)              |
| Trouble                       | 162 (57.7%)              |
| **Finance**                   |                          |
| No trouble                    | 156 (55.5%)              |
| Trouble                       | 125 (44.5%)              |
in Table 1. Most of the respondents were women (n = 238), accounting for 84.7% of the sample. Overall, 104 (37.0%) students majored in nursing. The remaining

177 students majored in rehabilitation (n = 70, 24.0%), psychology (n = 63, 21.6%), home economics (n = 29, 9.9%), acupuncture and moxibustion (n = 6, 2.1%), literature and others (n = 6, 2.1%), and education (n = 3, 1.0%).

The 281 students had an average HADS-A score of 6.8 (standard deviation [SD] = 4.2). A total of 118 students (42.0%) exceeded the cut-off value of 7 (Fukui et al., 2001); 30.5% (n = 36) of nursing students and 69.5% (n = 82) from other disciplines. The average HADS-D score was 6.7 (SD = 3.8). A total of 61 (21.7%) students exceeded the cut-off value of 10 (Table 2) (Kugaya et al., 1998); 31.1% (n = 19) of nursing students and 68.9% (n = 42) others. No gender differences in anxiety (HADS-A; t = −1.66, p = 0.099) and depressive symptoms (HADS-D; t = −0.98, P = 0.389) were observed.

The subscale scores of stress coping styles measured by the CISS are presented in Table 2. The average scores for the task, emotion, and avoidance scales were 49.5 (SD = 10.8), 40.9 (SD = 11.5), and 45.8 (SD = 10.6), respectively (Table 2). The average total score for perceived vulnerability, measured by the PVD, was 8.0 (SD = 1.4), and the average subscale scores were

### Table 2: Scores for each assessment tool for all respondents during the outbreak of COVID-19 (N = 281)

| Variables                      | Mean | SD  |
|-------------------------------|------|-----|
| **Stress coping**             |      |     |
| Task-oriented                 | 49.5 | 10.8|
| Emotion-oriented              | 40.9 | 11.5|
| Avoidance-oriented            | 45.8 | 10.6|
| **Perceived vulnerability to disease** |      |     |
| Total score                   | 8.0  | 1.4 |
| Perceived infectability       | 3.8  | 1.0 |
| Germ aversion                 | 4.2  | 0.9 |

Abbreviation: SD, standard deviation.

Note: Stress coping was evaluated using the Japanese version of the Coping Inventory for Stressful Situations (CISS). The CISS contains three subscales which assess task-oriented, emotion-oriented and avoidance-oriented coping. Perceived vulnerability to disease was evaluated using the Japanese version of the Perceived Vulnerability to Disease Scale (PVDS). The PVDS consists of a two-factor structure: perceived infectability and germ aversion.

### Table 3: Results for Student’s t test analysis of nursing students’ mental health during the COVID-19 pandemic (N = 281)

| Outcome (range) | Nursing (n = 104) Mean (SD) | Other (n = 177) Mean (SD) | t(df) | P-value |
|-----------------|-------------------------------|--------------------------|-------|---------|
| Anxiety (0-21)  | 6.0 (4.1)                     | 7.2 (4.3)                | 2.41 (279) | 0.002   |
| Depression (0-21)| 6.7 (3.7)                    | 6.8 (3.9)                | 0.27 (279) | 0.788   |

Abbreviations: SD, standard deviation.

Note: Anxiety was evaluated using the Japanese version of the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Depression was evaluated using the Japanese version of the Hospital Anxiety and Depression Scale-Depression (HADS-D). Psychiatric symptoms and lifestyle measures during the pandemic were divided according to nursing versus other students, and the levels of significance of the observed differences (Student's t test analysis). The mean difference is significant at the level of 0.05.

### Table 4: Factors associated with respondents’ mental health during the COVID-19 pandemic (N = 281)

|                  | Anxiety Coefficient | 95% CI       | P-value | Depression Coefficient | 95% CI       | P-value |
|------------------|---------------------|--------------|---------|------------------------|--------------|---------|
| Nursing          | -0.089              | -1.98, 0.43  | 0.207   | -0.009                 | -1.17, 1.03  | 0.90    |
| Perceived vulnerability (PVD) | 0.05               | -0.58, 1.43  | 0.403   | -0.027                 | -1.12, 0.71  | 0.656   |
| Nursing × PVD    | -0.035              | -1.99, 1.24  | 0.648   | 0.094                  | -0.57, 2.39  | 0.227   |
| Adjusted R-square| 0.416              |              | 0.405   |                        |              |         |

Abbreviation: CI, confidence interval.

Note: Anxiety was evaluated using Japanese version of Hospital Anxiety and Depression Scale-Anxiety. Depression was evaluated using Japanese version of Hospital Anxiety and Depression Scale-Depression. Perceived vulnerability was evaluated using Japanese version of Perceived Vulnerability to Disease Scale. Covariates of the linear regression models included age, sex, lifestyle (appetite, exercise, sleep, gaming, internet, and alcohol), social support (finance and family), and coping style of emotion-oriented, task-oriented, avoidance-oriented, as measured by the Japanese version of the Coping Inventory for Stressful Situations. Anxiety: F = 10.964, P < 0.01, R² < 0.458, Adjusted R² < 0.416. The forced entry procedure was employed to select the model based on age, appetite, exercise, finance, game, family, internet, PVD, alcohol, nursing, sex, sleep, emotion-oriented (CISS), task-oriented (CISS), and avoidance-oriented (CISS), which showed statistical differences in levels of anxiety (total score of HADS-A). Depression: F = 10.515, P < 0.01, R² = 0.447, Adjusted R² = 0.405. The forced entry procedure was employed to select the model based on age, appetite, exercise, finance, game, family, internet, PVD, alcohol, nursing, sex, sleep, emotion-oriented (CISS), task-oriented (CISS), and avoidance-oriented (CISS), which showed statistical differences in levels of depression (total score of HADS-D).
perceived infectability as 3.8 (SD = 1.0) and germ aversion as 4.2 (SD = 0.9) (Table 2).

3.2 Difference between nursing students and other students

When compared to students from other departments, nursing students showed a significantly lower level of anxiety ($t = 2.41, P = 0.002$; Table 3). However, the level of depression did not differ between nursing students and other students (Student’s t test; $t = 0.27, P = 0.788$).

The results of the multiple linear regression analyses are shown in Table 4 (all covariates are shown in Table S3). After adjusting for sociodemographic characteristics and stress coping styles, there was no significant difference in anxiety (Table 4, left side) and depressive symptoms (Table 4, right side) between nursing students and those from other departments. Perceived vulnerability, or the interaction between perceived vulnerability and nursing, was not significantly associated with anxiety and depressive symptoms (Table 4). Non-significant interactions between nursing students and perceived vulnerability are shown in Figure 1. When students were divided into four groups by nursing or other and high or low perceived vulnerability using a median score (7.95), the slope of anxiety and depression according to perceived vulnerability did not differ between nursing and other students (Figure 1).

4 DISCUSSION

This study is the first to determine whether the anxiety and depression symptoms several months after the onset of the COVID-19 pandemic differed between nursing students and other college students. Contrary to our hypothesis, PVD did not affect anxiety and depressive symptoms in nursing students. In the bivariate analysis, nursing students exhibited significantly lower anxiety than other college students. However, the association did not remain significant in the final multiple linear regression analyses, including perceived vulnerability to disease, lifestyle, and stress coping style.

The COVID-19 pandemic specifically caused anxiety and depression among college students, due to the fear of infection as reported by a study conducted in April 2020 (Khan et al., 2020). Many nursing students were also worried about being infected by the COVID-19 virus in the early months of the COVID-19 pandemic (Aslan & Pekince, 2021). According to a study in March 2020, PVD is associated with increased anxiety in the general adult population. (Makhanova & Shepherd, 2020). However, in our study, the PVD or PVD-nursing interaction did not affect depression or anxiety. Since our data collection was performed several months after the easing of the first COVID-19 related measures, participating nursing students’ mental distress may have represented long-term distress rather than an immediate response to the fear of COVID-19 infection. Among college students, nursing students are required to follow more long-term and stricter behavioral restrictions during the COVID-19 pandemic. While nursing education moved online during the COVID-19 pandemic, nursing students could still come in contact with vulnerable populations, such as hospital patients and nursing home residents, during clinical training. Therefore, such restrictions and the closure of physical campuses may have placed nursing students in a persistently stressful environment. Furthermore, nursing students were afraid that there would be a delay in their graduation and a discontinuation of clinical practice because of the COVID-19 pandemic (Deo et al., 2020). In light of these results, future nursing education should develop strategies to encourage students to adjust to mental health emergencies during the COVID-19 pandemic. Remote delivery of peer support

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FIGURE 1 Interactions between nursing and perceived vulnerability to anxiety (upper panel) and depression (lower panel). High/low perceived vulnerability is divided into groups by a median score (7.95)
(Arenas et al., 2021) and stress management interventions (Khademian et al., 2020) are suggested for college students in the context of the pandemic. Such psychosocial interventions should be adapted to nursing students. The long-term restrictions on college life owing to COVID-19 might have elevated the level of anxiety among college students regardless of discipline.

The prevalence rates of anxiety (34.6%) and depression (18.3%) among nursing students appeared to be even higher than those previously reported among medical students in Japan (Arima et al., 2020; Nishimura et al., 2021). Medical students are also known to have a high prevalence of depressive symptoms compared to students in non-medical disciplines (Rottenstein et al., 2016). During the COVID-19 pandemic between May and June 2020, 28.5% of medical students in Japan showed signs of psychological distress (Arima et al., 2020). Another survey from June 2020 reported that 7.0% of Japanese medical students had anxiety and 16.0% had depression (Nishimura et al., 2021). The difference in reported prevalence rates could be attributed to the anticipated working styles and high frequency of human contact. However, as our study did not include medical students, direct comparisons of nursing and medical students should be undertaken with caution. The highly prevalent anxiety and depressive symptoms in both nursing and other students may have reflected long-term distress owing to the behavioral restrictions imposed in response to the COVID-19 pandemic. Future studies comparing nursing and medical students would be helpful for identifying the different risk factors for anxiety and depression in these groups during the pandemic.

A strength of our study lies in the inclusion of other college students to compare levels of anxiety and depression. Another strength lies in the measurement of psychological distress several months after the peak of the COVID-19 pandemic. However, this study had some limitations. This study was based on a cross-sectional design, so that observed anxiety and depression could not also represent the usual level of psychological distress among nursing students before the COVID-19 pandemic. Additionally, information on other possible causes of distress may have been lacking, such as stress and burden due to the online transformation of nursing education, distance learning, and academic workloads (Majrashi et al., 2021). Also, most participants in our study were women. Females were more likely to report higher depression scores than men before the COVID-19 pandemic (Konno et al., 2010). Therefore, women would also show more severe psychological distress in response to the COVID-19 pandemic, as suggested by the rise in suicide rates during the COVID-19 pandemic in Japanese women (Nomura et al., 2021).

5 | CONCLUSION

The COVID-19 pandemic caused a global and long-term education crisis, which had a negative impact on the psychological well-being of college students, including nursing students. This study revealed that anxiety and depression were prevalent (more than 30%) in nursing students several months after the onset of the COVID-19 pandemic, though the prevalence of anxiety was lower than for other college students. The results imply that long-term strategies are needed to address mental health problems in nursing students, while they adjust to the current online learning setup, until the reopening of schools. Remote delivery of psychosocial interventions for college students, such as peer support and stress management programs, should be developed, with customizations for nursing students.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Hatsumi Yoshii contributed to the conception and design of this study; Keita Toshi carried out the data collection, data analyses, and interpreted data; Zhiqian Yu, Miharu Nakanishi, Gen Takagi, and Koubun Wakashima critically reviewed the manuscript and supervised the whole study process. Mai Sakai performed the statistical analysis and wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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