SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE



Sex differences in sleep and psychological disturbances among patients admitted for cardiovascular diseases

Yuichi Jono¹ · Takashi Kohno^{1,2} · Shun Kohsaka¹ · Hiroki Kitakata¹ · Yasuyuki Shiraishi¹ · Yoshinori Katsumata³ · Kentaro Hayashida¹ · Shinsuke Yuasa¹ · Seiji Takatsuki¹ · Keiichi Fukuda¹

Received: 11 March 2021 / Revised: 24 November 2021 / Accepted: 30 November 2021 / Published online: 6 January 2022 © The Author(s), under exclusive licence to Springer Nature Switzerland AG 2021

Abstract

Background Understanding sex differences is critical for improving outcomes in patients with cardiovascular conditions. Sleep and psychological disturbances contribute to the development and progression of cardiovascular diseases, and important sex differences persist in their incidence and association with clinical outcomes.

Methods Sex-based variation in sleep and psychological disturbances were assessed in consecutive patients with cardiovascular diseases in a single university hospital. The prevalence of insomnia, sleep disordered breathing (SDB), anxiety, and depression was assessed using the Pittsburgh Sleep Quality Index (PSQI), nocturnal pulse oximeter, and the Hospital Anxiety and Depression Scale (HADS). The effect of sex on the prevalence of sleep and psychological disturbances as well as their associations was quantified using multivariate logistic regression models.

Results Among 1,233 patients (mean age 63.6 years, 25% women), women were significantly less likely than men to experience SDB (17.5% vs 31.5%, p < 0.001), but more likely to report an increased burden of insomnia (54.7% vs 43.3%, p = 0.001) and depression (23.9% vs 16.7%, p = 0.004). Insomnia was associated with depression, which was more remarkable among women (p value for interaction: 0.039). SDB was associated with anxiety among women but not men (p value for interaction: 0.039). There was no significant difference in the prevalence of anxiety between women and men.

Conclusions Among patients with cardiovascular disease, women reported an increased burden of insomnia and depression compared to men. The association between sleep and psychological disturbances may be more pronounced in women, suggesting that cardiologists should increase efforts for identification of such comorbidities and administer corresponding treatment, especially in women.

Keywords Sex · Depression · Anxiety · Sleep disturbances · Cardiovascular diseases

Introduction

Cardiovascular (CV) diseases remain the leading cause of morbidity and mortality for women worldwide [1, 2]. Compared with men, women are less likely to receive preventive care for CV diseases which may be attributable to a

Takashi Kohno kohno-ta@ks.kyorin-u.ac.jp

- ¹ Division of Cardiology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan
- ² Department of Cardiovascular Medicine, Faculty of Medicine, Kyorin University, 6-20-2, Shinkawa, Mitaka, Tokyo 181-8611, Japan
- ³ Institute for Integrated Sports Medicine, Keio University School of Medicine, Tokyo, Japan

lower perceived risk in women by patients and clinicians, even when traditional CV risk factors are present [3]. The 2019 American College of Cardiology/American Heart Association guideline on the primary prevention of CV diseases introduced the concept of risk-enhancing factors that are specific to women. These factors favor intensified lifestyle interventions for primary prevention to mitigate the increased risk [4].

Sleep disturbances (i.e., insomnia and sleep disordered breathing [SDB]) and psychological disturbances (i.e., anxiety and depression) have been identified as modifiable risk factors of various CV diseases [5–7], though their burden remains under-recognized. In general, women are more likely to have sleep or psychological disturbances [8, 9]. A community-based cross-sectional study demonstrated that women reported more depressive symptoms and insomnia

complaints than men in specific age groups, such as elderly adults and adolescents [9, 10]. However, these cohorts contained few patients with CV diseases, and there is lack of evidence regarding sex-dependent variation of sleep or psychological disturbances in patients with CV diseases. Because these comorbidities are largely modifiable, identifying actionable areas for intervention may lead to improved outcomes.

Accordingly, we examined the following among patients hospitalized with various CV diseases: (1) sex differences in the prevalence of sleep and psychological disturbances, and (2) whether or not sex modified this association.

Materials and methods

Study population

The present study is a single-center, cross-sectional study, details of which have been previously described [11]. We recruited 2,110 consecutive patients who were admitted for CV diseases and underwent pulse oximeter testing as a part of SDB screening during hospitalization, between September 2013 and December 2015. All patients registered in this study were requested to complete self-reported, paper-based questionnaires on sleep and psychological disturbances. We excluded 217 patients with completely missing questionnaires (either declined to answer the questionnaire or were in conditions that made it difficult to complete a self-administered written questionnaire [e.g., unconsciousness, delirium, dementia]) and 611 patients who were missing one or more answers in one or more questionnaires. Subsequent assessments of 49 patients who had been admitted to our hospital more than once and had undergone additional screenings during the study period were also excluded. Finally, 877 patients (41.6%) were excluded, and 1,233 patients were analyzed for this study (coronary artery disease [n=384], heart failure [n=83], valvular heart disease [n=130], arrhythmia [n=503], and miscellaneous [n=133]). The study protocol was approved by the Keio University institutional review boards, and informed consent was obtained from all patients.

Patient assessments

Nocturnal pulse oximetry was used to assess the severity of SDB in all study patients, as we have reported previously [12, 13]. A pulse oximeter is a device commonly used to record percutaneous oxyhemoglobin saturation in a peripheral artery using a finger probe. In this study, the sampling efficiency of the pulse oximeter (PULSOX-Me300, Teijin Pharma Ltd., Tokyo, Japan) was 1 Hz during the memory interval, for an average time of 3 s each. An oxygen desaturation index of $\geq 3\%$ (3% ODI), which is the number of episodes per hour in which oxygen saturation decreases $\geq 3\%$ from baseline, was used as a surrogate marker of SDB. Pulse oximetry was validated through its concurrent one-night recordings with polysomnography; its sensitivity and specificity were 85% and 100%, respectively, for detecting an apnea hypopnea index of ≥ 20 by polysomnography using a cutoff threshold of 3% ODI = 15 [12, 14, 15]. Most patients underwent pulse oximetry within a few days after hospital admission, and patients who initially required intensive care underwent pulse oximetry before discharge. Patients who used oxygen inhalation or ventilator therapy were not included in this study.

We assessed the severity of insomnia using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [16]. The PSQI is a self-administered tool to assess sleep quality. Nineteen items constitute seven components (i.e., sleep quality, latency, duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication, and daytime dysfunction). The summed score for these seven components (which each have a range of 0 to 3) generates one global PSQI score (which ranges from 0 to 21). [17] Insomnia was defined as a PSQI score > 5 [17, 18]. The following data obtained from the components of PSQI were also analyzed: poor subjective sleep quality (its component score > 1), reduced sleep efficiency (< 85%), increased sleep latency (its component score > 1), short sleep duration (<6 h of sleep per night), sleep disturbances (its component score > 1), sleep drug usage, and daytime dysfunction (its component score > 1). We evaluated excessive daytime sleepiness (EDS) using the Japanese version of the Epworth sleepiness scale (ESS), a self-administered questionnaire with eight questions that is used to identify the severity of daytime sleepiness [19, 20]. Each component is weighed equally on a four-point scale (0 to 3), and the sum of scores for the eight items ranges from 0 to 24. ESS scores > 10 represent increased EDS levels [21].

Anxiety and depression were evaluated using the Hospital Anxiety and Depression Scale (HADS) [22]. It comprises a self-rated scale of seven components designed to evaluate anxiety and depressive symptoms. Each component is rated from 0 (minimally present) to 3 (maximally present), and the summed score ranges from 0 to 21 [23]. Anxiety and depression were defined as a HADS-anxiety score ≥ 8 and HADS-depression score ≥ 8 , respectively, as originally recommended for identifying clinically significant anxiety and depression, providing the optimal balance between sensitivity and specificity for identifying cases [23].

By means of medical chart abstraction, clinical data, including sex, age, body mass index (BMI), lifestyle (smoking, alcohol intake, and living conditions), laboratory data (albumin level, brain natriuretic peptide [BNP] level, C-reactive protein level, estimated glomerular filtration rate [eGFR], and hemoglobin A1c level), and history of CV risk factors and comorbidities, were collected.

Statistical analyses

Continuous variables are presented as the means \pm standard deviations or medians (interquartile ranges). Categorical variables are presented as absolute values and percentages. Clinical characteristics, laboratory data, and sleep and psychological questionnaires were compared between men and women. Student t-test, Mann-Whitney U test, or chi-square test was used to compare normally distributed variables, non-normally distributed variables, or categorical variables, respectively. Using multiple logistic regression models, we evaluated the association between sex and SDB (3% ODI > 15), insomnia (PSQI score > 5), HADS scores for anxiety (HADS-A ≥ 8), or HADS scores for depression (HADS-D \geq 8), and a series of sequential models were adapted. Model 1 was adjusted for age and obesity $(BMI \ge 25 \text{ kg/m}^2)$. Model 2 was further adjusted for living alone, employment status, and CV comorbidities (coronary artery disease, heart failure, and atrial fibrillation). Model 3 was additionally adjusted for CV risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking) and chronic kidney disease (CKD, eGFR < 45 ml/min/1.73 m²). Obesity was defined as BMI \geq 25 kg/m², as recommended by the WHO Western Pacific Region and Japanese Society for the Study of Obesity [24]. In fact, the prevalence of obesity defined by BMI \geq 30 kg/m² is quite low in Japan, and Japanese people are more likely to have metabolic disorders even with a BMI of 25-30 kg/m² [25]. Before performing multiple logistic regression analyses, we evaluated multicollinearity and eliminated factors indicating serious multicollinearity from the model. We then performed sensitivity analyses to determine the impact of female sex as a determinant of SDB, defined by 4% ODI > 5 and > 15.

Further, multiple logistic regression analyses adjusted by model 2 were used to evaluate the association between sleep disturbances (i.e., SDB and insomnia) and psychological disturbances (anxiety and depression) in men and women. The effect of the interaction between sleep disturbances and sex on psychological disturbances was examined by adding an interaction term to the statistical model. We also assessed sex differences in the association between SDB and insomnia, adjusted by model 2. *p* values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS software (version 25; IBM Corp., Armonk, NY).

Results

Baseline characteristics

The baseline characteristics of the overall cohort has been described previously [11]. Table 1 shows the patients' demographic characteristics of men and women. Women were older than men and had a lower BMI and a lower prevalence of coronary risk factors (hypertension, diabetes mellitus, dyslipidemia, and smoking), coronary artery disease, and atrial fibrillation. However, women had a higher prevalence of heart failure and valvular heart disease compared to men. Plasma BNP levels were higher in women, whereas albumin and hemoglobin A1c levels were lower.

Sex differences in the prevalence of sleep and psychological disturbances

Women had a significantly lower prevalence of SDB (3% $ODI \ge 15$; 17.5% vs 31.5%, p < 0.001; Fig. 1A) and a significantly higher prevalence of insomnia (PSQI score > 5; 54.7% vs 43.3%, p = 0.001; Fig. 1B). Women also had a lower 3% ODI (6.7 [3.7–11.6] vs 9.8 [5.6–17.5], *p* < 0.001) and 4% ODI (4.3 [2.1–7.6] vs 6.4 [3.3–12.8], p < 0.001), as well as a higher PSQI score (6.0 [4.0–9.0] vs 5.0 [3.0–7.0], p < 0.001). According to the analysis of PSQI categories, increased sleep latency, reduced sleep efficiency, sleep disturbances, and use of sleep medications contributed to the higher PSOI scores (insomnia) in women (Table 2). Although women had a slightly higher prevalence of anxiety, there was not a significant difference between women and men (19.7% vs 15.9%, p = 0.119; Fig. 1C). The prevalence of depression was significantly higher in women than in men (23.9% vs 16.7%, p = 0.004; Fig. 1D). Women also had higher subscores of HADS-A (4.0 [2.0–7.0] vs 3.0 [2.0–6.0], p=0.034) and HADS-D (4.0 [2.0–7.0] vs 3.0 [1.0–6.0], p = 0.012) than men.

We assessed the association between women and sleep or psychological disturbances by logistical regression analyses. The odds ratio was estimated comparing women to men (Table 3). In age- and obesity-adjusted models, female sex was a negative determinant of SDB (odds ratio [OR]: 0.35, 95% confidence interval [CI]: 0.25–0.51, p < 0.001) and a positive determinant of insomnia (OR: 1.58, 95% CI: 1.21–2.06, p = 0.001) and depression (OR: 1.49, 95% CI: 1.08–2.05, p = 0.016). Women tended to be associated with anxiety, although this difference was not statistically significant (OR: 1.34, 95% CI: 0.95–1.88, p = 0.092). The association of women with SDB or insomnia remained significant after adjustment for living status, employment status, CV comorbidities, CV risk factors, and CKD (SDB: OR: 0.37, 95% CI: 0.23–0.60, p < 0.001; insomnia: OR: 1.56, 95% CI: Table 1 Clinical characteristics of patients (men and women) included in the study

| | Men | Women | p value |
|--------------------------------------|-------------------|-------------------|---------|
| | n=924 | n=309 | |
| Age (years) | 62.6 ± 13.4 | 66.6±17.5 | < 0.001 |
| Body mass index (kg/m ²) | 24.4 ± 3.5 | 22.3 ± 3.9 | < 0.001 |
| Medical history (%) | | | |
| Coronary artery disease | 43.5 | 27.8 | < 0.001 |
| Heart Failure | 13.8 | 27.6 | < 0.001 |
| Valvular heart disease | 9.5 | 30.2 | < 0.001 |
| Atrial fibrillation | 41.6 | 25.2 | < 0.001 |
| Hypertension | 56.0 | 48.0 | 0.016 |
| Diabetes | 23.8 | 14.7 | 0.001 |
| Dyslipidemia | 47.2 | 40.5 | 0.042 |
| Smoking | 71.5 | 22.9 | < 0.001 |
| Alcohol | 65.6 | 28.8 | < 0.001 |
| Laboratory data | | | |
| C-reactive protein (mg/dl) | 0.06 [0.02-0.19] | 0.06 [0.02-0.21] | 0.484 |
| Albumin (g/dl) | 4.2 [3.9–4.4] | 4.1 [3.8–4.3] | 0.001 |
| BNP (pg/ml) | 50.3 [19.6-131.6] | 77.4 [31.4–214.3] | < 0.001 |
| eGFR (ml/min/1.73 m ²) | 63.0 [53.0-73.0] | 62.0 [48.8–73.5] | 0.169 |
| HbA1c (%) | 5.8 [5.5-6.2] | 5.7 [5.4-6.0] | 0.038 |
| Other | | | |
| Living alone (%) | 14.4 | 19.2 | 0.049 |

Values are % or mean \pm SD, or median [interquartile range]. BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c

1.09-2.24, p = 0.016). The association between women and depression was not statistically significant in the models further adjusted for the full set of covariates (OR: 1.36, 95% CI: 0.87-2.12, p = 0.181 (Table 3).

We defined two exploratory subgroups of patients without (i) insomnia and (ii) use of sleep medications. After fully adjusting for covariates, female sex was a negative determinant of SDB among the CV diseases inpatients without insomnia (OR: 0.33, 95% CI: 0.16–0.69, p = 0.003) and those without use of sleep medications (OR: 0.35, 95% CI: 0.19-0.62, p < 0.001). In sensitivity analyses, female sex was a negative determinant of SDB, defined by 4% ODI > 5 (OR: 0.38, 95% CI: 0.25–0.59, p < 0.001), as well as defined by 4% ODI > 15 (OR: 0.19, 95% CI: 0.10–0.38, *p* < 0.001).

Sex differences in the association between sleep and psychological disturbances

We assessed sex differences in the association between sleep disturbances (i.e., SDB and insomnia) and anxiety or depression (Fig. 2 and Table 4). Sex modified the association between SDB and anxiety (p value for interaction = 0.003), and between insomnia and depression (p value for interaction = 0.039). The association between SDB and anxiety was significant among women (OR: 2.41, 95% CI: 1.10-5.33,

p = 0.029) but not in men (OR: 0.97, 95% CI: 0.60–1.58, p = 0.914). The association between insomnia and depression was more significant among women (OR: 7.06, 95% CI: 3.19–15.64, *p* < 0.001) than among men (OR: 3.06, 95%) CI: 2.01–4.65, p < 0.001), although the association was still significant in men (Table 4). Sex did not modify the association between SDB and insomnia (male: OR: 1.15, 95% CI: 0.82-1.63, p = 0.418; female: OR: 1.60, 95% CI: 0.75-3.42, p = 0.221, p value for interaction = 0.376).

Furthermore, we generated four groups based on the presence of SDB and insomnia, and clarified the prevalence of psychological disturbances in each group. There were 364 men and 121 women who had neither SDB nor insomnia, 160 men and 19 women who had SDB alone, 269 men and 134 women who had insomnia alone, and 131 men and 35 women who had both. Among the no SDB or insomnia, SDB alone, insomnia alone, and both SDB and insomnia groups, the prevalence of anxiety was 8.8%, 6.3%, 26.4%, and 26.0% in men, and 6.6%, 10.5%, 26.9%, and 42.9% in women, respectively (Supplemental Fig. 1A-B). The prevalence of depression was 10.2%, 10.0%, 25.3%, and 25.2% in men, and 11.6%, 10.5%, 32.8%, and 40.0% in women, respectively (Supplemental Fig. 1 C-D).

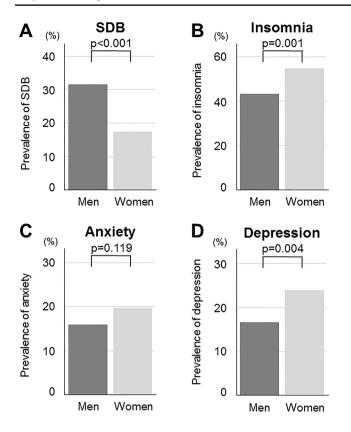


Fig. 1 Comparison of the prevalence of SDB (**A**), insomnia (**B**), anxiety (**C**), and depression (**D**) between male and female patients hospitalized for cardiovascular diseases. SDB, sleep disordered breathing

Table 2Sex-based differencesin the sleep disturbances ofpatients (men and women)

We demonstrated that among hospitalized patients with CV disease, women had symptoms of insomnia and depression more commonly, despite the lower prevalence of SDB. Furthermore, the association between sleep and psychological disturbances was more prominent in women. The association between insomnia and depression, and that between SDB and anxiety, was stronger in women.

Quantifying the burden of sleep and psychological disturbances in patients with a variety of CV conditions facilitates prioritization of interventions. The strength of our study is that we revealed a higher burden of insomnia and depression among women with a variety of CV diseases compared to men through comprehensive screening using validated and reliable tools (i.e., PSQI, HADS, pulse oximeter). Previous reports of disease-specific cohort studies and randomized clinical trials demonstrated that women are more likely to have psychological disturbances [26, 27] or sleep disturbances separately [28-30], which is consistent with our results. In a multicenter prospective cohort study of coronary artery disease (Heart and Soul Study) and a multinational randomized clinical trial involving atrial fibrillation and heart failure patients (Atrial Fibrillation and Congestive Heart Failure trial), depression was more prevalent in women than in men [26, 27]. Insomnia was also more prevalent in women than in men in a single-center prospective cohort study of heart failure [28] and acute myocardial infarction [29], and in a multicenter prospective cohort

| | Men | Women | p value |
|------------------------------------|------------------|------------------|---------|
| | n=924 | n=309 | |
| Pulse oximeter | | | |
| 3% ODI | 9.8 [5.6–17.5] | 6.7 [3.7–11.6] | < 0.001 |
| 4% ODI | 6.4 [3.3–12.8] | 4.3 [2.1–7.6] | < 0.001 |
| Mean SpO2 (%) | 95.7 [94.9–96.5] | 95.8 [94.6–96.7] | 0.653 |
| Minimum SpO2 (%) | 82.6 [77.5-86.1] | 82.7 [77.5-86.2] | 0.667 |
| Sleep-related questionnaire | | | |
| ESS score | 7.0 [4.0–9.0] | 6.0 [3.0–9.5] | 0.142 |
| EDS (ESS score > 10) (%) | 18.8 | 22.0 | 0.224 |
| PSQI score | 5.0 [3.0-7.0] | 6.0 [4.0–9.0] | < 0.001 |
| Poor sleep quality (%) | 27.5 | 32.4 | 0.101 |
| Increased sleep latency (%) | 19.4 | 32.4 | < 0.001 |
| Sleep duration (h) | 390 [360-420] | 390 [360-420] | 0.801 |
| Short sleep duration $(< 6 h)$ (%) | 22.7 | 22.3 | 0.885 |
| Reduced sleep efficiency (%) | 19.0 | 29.1 | < 0.001 |
| Sleep disturbances (%) | 8.2 | 17.5 | < 0.001 |
| Use of sleep medications (%) | 17.0 | 25.9 | 0.001 |
| Daytime dysfunction (%) | 9.3 | 8.1 | 0.518 |

Values are % or median [interquartile range]. ODI, oxygen desaturation index; ESS, Epworth sleepiness scale; EDS, excessive daytime sleepiness; PSQI, Pittsburgh Sleep Quality Index

Table 3 Multiple regression analyses to determine the impact of female sex as a determinant of SDB, insomnia, anxiety, and depression

| | OR | 95% CI | p value |
|------------|------|-----------|---------|
| SDB | | | |
| Model 1 | 0.35 | 0.25-0.51 | < 0.001 |
| Model 2 | 0.33 | 0.21-0.52 | < 0.001 |
| Model 3 | 0.37 | 0.23-0.60 | < 0.001 |
| Insomnia | | | |
| Model 1 | 1.58 | 1.21-2.06 | 0.001 |
| Model 2 | 1.55 | 1.11-2.15 | 0.009 |
| Model 3 | 1.56 | 1.09-2.24 | 0.016 |
| Anxiety | | | |
| Model 1 | 1.34 | 0.95-1.88 | 0.092 |
| Model 2 | 1.33 | 0.87-2.02 | 0.189 |
| Model 3 | 1.26 | 0.79-2.01 | 0.338 |
| Depression | | | |
| Model 1 | 1.49 | 1.08-2.05 | 0.016 |
| Model 2 | 1.34 | 0.90-2.00 | 0.155 |
| Model 3 | 1.36 | 0.87-2.12 | 0.181 |

Mode 1: age and obesity (body mass index $\geq 25 \text{ kg/m}^2$)

Model 2: model 1+living alone, job, cardiovascular comorbidities (coronary artery disease, heart failure, atrial fibrillation)

Model 3: model 2+hypertension, diabetes mellitus, dyslipidemia, smoking, and chronic kidney disease (estimated glomerular filtration rate $< 45 \text{ ml/min}/1.73 \text{ m}^2$)

OR, odds ratio; CI, confidence interval; SDB, sleep disordered breathing

The odds ratio was estimated comparing women to men

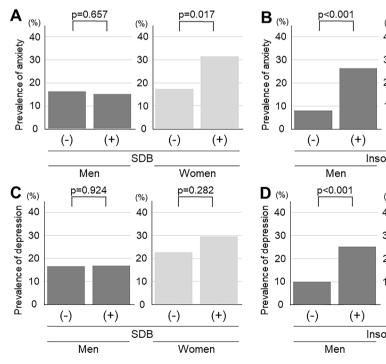
Sleep and Breathing (2022) 26:1693-1701

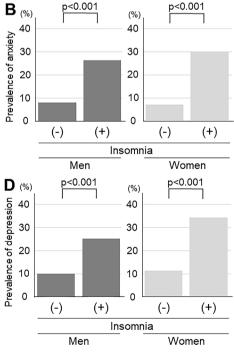
study of coronary artery disease [30]. Given the high incidence of sleep-related disorders, identification of psychological disturbances associated with this condition should be underscored among women with CV diseases, in addition to screening for and managing CV risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and smoking.

In addition to depression and insomnia, sex differences in patients with various CV diseases [31-35] exist with respect to other patient-centered outcomes, such as quality of life (OOL), which was recently emphasized to be a significant outcome in addition to traditional clinical outcomes (e.g., mortality and readmission rate) [36, 37]. For instance, women with coronary artery disease reported a worse OOL in the Canadian registry [33]. Women had a worse QOL in a study analyzing two randomized clinical trials of heart failure with reduced ejection fraction [35]. Patient-centered outcomes could be closely intertwined independently of objective disease severity [38]. Whether management of depression and insomnia can improve QOL also needs to be assessed in the future, especially among women with CV diseases.

Women's health could be optimized by focusing attention on unique sex-specific aspects of background characteristics, risk factors, and the response to non-pharmacological treatments among patients with CV diseases [2, 39]. For instance, women often present with multiple comorbidities and poor cardiorespiratory fitness at an older age [39]. Based on a large database of coronary artery disease, despite a lower enrollment rate for cardiac rehabilitation programs, attendance in the program is related with a significant reduction of mortality in women compared with men [40]. Very

Fig. 2 Comparison of the prevalence of anxiety between male and female patients hospitalized for cardiovascular diseases, divided by SDB (A) or insomnia (B). Comparison of the prevalence of depression between male and female patients hospitalized for cardiovascular diseases, divided by SDB (C) or insomnia (D). SDB, sleep disordered breathing





p value for interaction

95% CI

[able 4 Sex-based differences in the association between sleep disturbances (SDB and insomnia) and psychological disturbances (anxiety or depression)

OR

p value

A: Anxiety

Men

SDB

| $\begin{array}{cccccccccccccccccccccccccccccccccccc$ | 0.60-1.58 0.003 1.10-5.33 2.50-6.12 0.365 2.11-10.01 |
|--|---|
| 2.41 1 3.91 1 4.60 0.92 1.30 | |
| 1 3.91 1 4.60 0.92 1.30 | |
| 1 4.60 0.92 1.30 | 2.11–10.01 |
| 0.92 1.30 | |
| 0.92 1.30 | |
| 1.30 | 0.58–1.45 0.200 |
| | 0.59–2.88 |
| <0.001 3.06 2.01-4.65 | 2.01-4.65 0.039 |
| 7.06 | 3.19–15.64 |

3: Depression

Women

nsomnia

Men

SDB Men Women

Women Insomnia Men Women *OR*, odds ratio; *CI*, confidence interval; *SDB*, sleep disordered breathing

little is known whether the therapeutic impact of sleep and/ or psychological disturbances on these symptoms and CV clinical outcomes could differ depending on the sex. This point needs to be emphasized as an area of high priority in future research.

There are several important clinical implications of our findings. First, medical providers (including cardiologists as well as primary care providers) for patients with CV diseases should comprehensively pay attention to sleep and psychological disturbances. Despite the well-known male predominance in the prevalence of SDB, which is the most examined among sleep disturbances in CV diseases, medical providers should comprehensively assess various sleep and psychological disturbances to ensure their early diagnosis in CV disease patients including women. Although the detailed reasons for the more robust associations between sleep and psychological disturbances in women are unknown, such as in cases of women with both insomnia and SDB, we need to consider the possible coexistence of psychological disturbances. Second, because of the paucity of female-specific clinical trial data, further research will be needed to evaluate whether the identification and intervention of sleep and psychological disturbances can improve outcomes, especially in women with CV diseases.

There are limitations that should be considered when interpreting our results. First, due to our study design (i.e., cross-sectional study), causal associations between sleep and psychological disturbances cannot be concluded. Future prospective longitudinal studies need to be performed to elucidate their cause-effect association and whether or not their association has an impact on long-term CV outcomes. Second, the study participants were derived from a single Japanese university hospital, and the results may not be generalized to other countries. Third, several methodological issues need to be mentioned, such as the lack of a polysomnography study, which did not allow us to address the type of SDB (e.g., obstructive or central), details of respiratory events (e.g., apnea or hypopnea, arousal), and sleep duration. Thus, polysomnography is preferred over pulse oximeter in terms of accurate determination of the type and severity of SDB, details of respiratory events (e.g., hypoxemic burden and degree of arousal), sleep duration, and sleep stages. We assessed anxiety and depression using the HADS, which is a screening tool and is not capable of providing a full clinical diagnosis. Fourth, patients with missing variables were excluded from the analyses, which could result in selection bias. Because of the considerable proportion of the missing data, we reported the complete case analysis [41]. Because of this limitation, our study may be considered as hypothesis-generating. Further research is needed to evaluate the effects of screening and treatment of sleep disorders and its adverse influence on psychological problems among CV diseases patients, especially women. Fifth, we did not collect the data regarding other aspects of comorbidities (e.g., respiratory diseases) and living conditions (e.g., married, number of cohabitors). Sixth, the severity of CV disease may be associated with sleep and psychological disturbances and may affect our results, which needs to be evaluated in the future.

Conclusions

There were significant sex-based differences in sleep and psychological disturbances in patients hospitalized for CV diseases, such as an increased burden of insomnia and depression and a pronounced association between sleep and psychological disturbances in women. Further studies are needed to determine if outcomes can be improved by treating sleep and psychological disturbances in women with CV diseases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11325-021-02544-4.

Acknowledgements The authors would like to thank all the study patients for their time and effort, as well as the nurses and staff for their role in data capture.

Funding This study was funded by Grant-in-Aid for Scientific Research (17K09526 and 18H03087).

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare no competing interests.

References

- Benjamin EJ, Muntner P, Alonso A et al (2019) Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation 139(10):e56–e528. https://doi.org/10. 1161/CIR.00000000000659
- Cho L, Davis M, Elgendy I et al (2020) Summary of updated recommendations for primary prevention of cardiovascular disease in women: JACC state-of-the-art review. J Am Coll Cardiol 75(20):2602–2618. https://doi.org/10.1016/j.jacc.2020.03.060
- Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS (2020) The use of sex-specific factors in the assessment of women's cardiovascular risk. Circulation 141(7):592–599. https://doi. org/10.1161/CIRCULATIONAHA.119.043429

- Arnett DK, Blumenthal RS, Albert MA et al (2019) 2019 ACC/ AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 140(11):e596–e646. https://doi.org/10.1161/CIR. 000000000000678
- Jha MK, Qamar A, Vaduganathan M, Charney DS, Murrough JW (2019) Screening and management of depression in patients with cardiovascular disease: JACC state-of-the-art review. J Am Coll Cardiol 73(14):1827–1845. https://doi.org/10.1016/j.jacc.2019. 01.041
- St-Onge MP, Grandner MA, Brown D et al (2016) Sleep duration and quality: impact on lifestyle behaviors and cardiometabolic health: a scientific statement from the American Heart Association. Circulation 134(18):e367–e386. https://doi.org/10.1161/CIR. 0000000000000444
- Piepoli MF, Hoes AW, Agewall S et al (2016) 2016 European guidelines on cardiovascular disease prevention in clinical practice: the sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 37(29):2315–2381. https://doi.org/ 10.1093/eurheartj/ehw106
- Mallampalli MP, Carter CL (2014) Exploring sex and gender differences in sleep health: a Society for Women's Health Research report. J Womens Health (Larchmt) 23(7):553–562. https://doi. org/10.1089/jwh.2014.4816
- Schechtman KB, Kutner NG, Wallace RB, Buchner DM, Ory MG (1997) Gender, self-reported depressive symptoms, and sleep disturbance among older community-dwelling persons. FICSIT group. Frailty and injuries: cooperative studies of intervention techniques. J Psychosom Res 43(5):513–27.
- Blank M, Zhang J, Lamers F, Taylor AD, Hickie IB, Merikangas KR (2015) Health correlates of insomnia symptoms and comorbid mental disorders in a nationally representative sample of US adolescents. Sleep 38(2):197–204. https://doi.org/10.5665/ sleep.4396
- Horie H, Kohno T, Kohsaka S et al (2021) Frequent nightmares and its associations with psychological and sleep disturbances in hospitalized patients with cardiovascular diseases. Eur J Cardiovasc Nurs 20(5):421–427. https://doi.org/10.1093/eurjcn/ zvaa016
- Kimura T, Kohno T, Nakajima K et al (2015) Effect of nocturnal intermittent hypoxia on left atrial appendage flow velocity in atrial fibrillation. Can J Cardiol 31(7):846–852. https://doi.org/ 10.1016/j.cjca.2014.12.032
- 13. Fukuoka R, Kohno T, Kohsaka S et al (2017) Nocturnal intermittent hypoxia and short sleep duration are independently associated with elevated C-reactive protein levels in patients with coronary artery disease. Sleep Med 29:29–34. https://doi.org/10.1016/j. sleep.2016.09.012
- 14. Muraki I, Tanigawa T, Yamagishi K et al (2010) Nocturnal intermittent hypoxia and the development of type 2 diabetes: the Circulatory Risk in Communities Study (CIRCS). Diabetologia 53(3):481–488. https://doi.org/10.1007/s00125-009-1616-0
- Tanigawa T, Tachibana N, Yamagishi K et al (2004) Usual alcohol consumption and arterial oxygen desaturation during sleep. JAMA 292(8):923–925. https://doi.org/10.1001/jama.292.8.923-b
- 16. Doi Y, Minowa M, Uchiyama M, et al (2000) Psychometric assessment of subjective sleep quality using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI-J) in psychiatric disordered and control subjects. Psychiatry Res. 97(2–3):165–72. https://doi.org/10.1016/s0165-1781(00)00232-8

- Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28(2):193–213. https://doi.org/10.1016/0165-1781(89)90047-4
- Bruno RM, Palagini L, Gemignani A et al (2013) Poor sleep quality and resistant hypertension. Sleep Med 14(11):1157–1163. https://doi.org/10.1016/j.sleep.2013.04.020
- Johns MW (1991) A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14(6):540–545. https:// doi.org/10.1093/sleep/14.6.540
- Takegami M, Suzukamo Y, Wakita T et al (2009) Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. Sleep Med 10(5):556–565. https://doi. org/10.1016/j.sleep.2008.04.015
- Johns MW (1993) Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest 103(1):30–6. doi:https://doi.org/10.1378/chest.103.1.30
- Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67(6):361–370. https://doi.org/ 10.1111/j.1600-0447.1983.tb09716.x
- Bjelland I, Dahl AA, Haug TT, Neckelmann D (2002) The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res 52(2):69–77. https://doi.org/ 10.1016/s0022-3999(01)00296-3
- Examination Committee of Criteria for 'Obesity Disease' in J (2002) Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. Circ J 66(11):987–92 https://doi.org/10.1253/ circj.66.987
- Ota T, Takamura T, Hirai N, Kobayashi K (2002) Preobesity in World Health Organization classification involves the metabolic syndrome in Japanese. Diabetes Care 25(7):1252–1253. https:// doi.org/10.2337/diacare.25.7.1252
- Grenon SM, Hiramoto J, Smolderen KG, Vittinghoff E, Whooley MA, Cohen BE (2012) Association between depression and peripheral artery disease: insights from the heart and soul study. J Am Heart Assoc 1(4):e002667. https://doi.org/10.1161/JAHA. 112.002667
- Frasure-Smith N, Lesperance F, Habra M, et al (2009) Elevated depression symptoms predict long-term cardiovascular mortality in patients with atrial fibrillation and heart failure. Circulation 120(2):134–40, 3p following 140. doi:https://doi.org/10.1161/ CIRCULATIONAHA.109.851675
- Kanno Y, Yoshihisa A, Watanabe S et al (2016) Prognostic significance of insomnia in heart failure. Circ J 80(7):1571–1577. https://doi.org/10.1253/circj.CJ-16-0205
- Conden E, Rosenblad A (2016) Insomnia predicts long-term allcause mortality after acute myocardial infarction: a prospective cohort study. Int J Cardiol 215:217–222. https://doi.org/10.1016/j. ijcard.2016.04.080
- Johansson A, Svanborg E, Swahn E, Ejdeback J, Tygesen H, Edell-Gustafsson U (2011) Sleep, arousal and health-related quality of life in men and women with coronary artery disease. J Clin Nurs 20(19–20):2787–2801. https://doi.org/10.1111/j.1365-2702. 2011.03787.x
- 31. Dewan P, Rorth R, Raparelli V et al (2019) Sex-related differences in heart failure with preserved ejection fraction. Circ Heart Fail

12(12):e006539. https://doi.org/10.1161/CIRCHEARTFAILURE. 119.006539

- 32. Włodarczyk D (2016) [Gender and quality of life and coping over one year after myocardial infarction: do men really have the upper hand?]. Kardiol Pol 74(5):447–53. Plec a jakosc zycia i radzenie sobie w okresie roku po zawale serca: czy rzeczywiscie mezczyzni gora? https://doi.org/10.5603/KP.a2015.0212
- 33. Norris CM, Spertus JA, Jensen L et al (2008) Sex and gender discrepancies in health-related quality of life outcomes among patients with established coronary artery disease. Circ Cardiovasc Qual Outcomes 1(2):123–130. https://doi.org/10.1161/CIRCO UTCOMES.108.793448
- Chapa DW, Akintade B, Schron E, Friedmann E, Thomas SA (2014) Is health-related quality of life a predictor of hospitalization or mortality among women or men with atrial fibrillation? J Cardiovasc Nurs Nov-Dec 29(6):555–564. https://doi.org/10. 1097/JCN.000000000000095
- Dewan P, Rorth R, Jhund PS et al (2019) Differential impact of heart failure with reduced ejection fraction on men and women. J Am Coll Cardiol 73(1):29–40. https://doi.org/10.1016/j.jacc.2018. 09.081
- Rich MW, Chyun DA, Skolnick AH et al (2016) Knowledge gaps in cardiovascular care of the older adult population: a scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. Circulation 133(21):2103–2122. https://doi.org/10.1161/CIR.0000000000 000380
- 37. Forman DE, Arena R, Boxer R et al (2017) Prioritizing functional capacity as a principal end point for therapies oriented to older adults with cardiovascular disease: a scientific statement for healthcare professionals from the American Heart Association. Circulation 135(16):e894–e918. https://doi.org/10.1161/CIR. 0000000000000483
- Gottlieb SS, Kop WJ, Ellis SJ et al (2009) Relation of depression to severity of illness in heart failure (from Heart Failure And a Controlled Trial Investigating Outcomes of Exercise Training [HF-ACTION]). Am J Cardiol 103(9):1285–1289. https://doi.org/10.1016/j.amjcard.2009.01.025
- Lam CSP, Arnott C, Beale AL et al (2019) Sex differences in heart failure. Eur Heart J 40(47):3859–3868c. https://doi.org/10.1093/ eurheartj/ehz835
- Colbert JD, Martin BJ, Haykowsky MJ et al (2015) Cardiac rehabilitation referral, attendance and mortality in women. Eur J Prev Cardiol 22(8):979–986. https://doi.org/10.1177/2047487314 545279
- Jakobsen JC, Gluud C, Wetterslev J, Winkel P (2017) When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. BMC Med Res Methodol 17(1):162 https://doi.org/10.1186/ s12874-017-0442-1

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.