Association of Migraine and Sleep-Related Breathing Disorder
A Population-Based Cohort Study

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Abstract: In this nationwide population-based cohort study, we aimed to evaluate the effects of sleep-related breathing disorders (SBD) on migraine development.

Patients ages 20 years or more and diagnosed with SBD between 2000 and 2009 were evaluated as the SBD cohort (n = 3411), and compared with comparison cohort (n = 13,644). The adjusted hazard ratio (aHR) for developing migraine was calculated in both cohorts by multivariate Cox proportional hazards model.

The cumulative incidence of migraine was significantly higher in the SBD cohort than in the comparison cohort. In the SBD cohort, the overall aHR for developing migraine was 2.43 (95% confidence interval [CI] 1.72–3.44). The risk of developing migraine was higher in men (aHR 2.71) than in women (aHR 2.29) with SBD. When stratifying by age, we observed increased incidence of migraine in patients ages 20 to 44 years and 45 to 64 years, with a higher aHR of 2.51 (95% CI 1.47–4.30) and 2.68 (95% CI 1.63–4.43), respectively. The risk of developing migraine in the patients with SBD with or without comorbidity exhibited nonsignificant differences. After stratifying by the use of hypnotics, the aHR for developing migraine was 2.39 in the patients with hypnotics use and 3.58 in the patients without hypnotics use.

Our findings indicate increased risk of developing migraine in adults, but not elderly ones, with SBD.

Abbreviations: aHR = adjusted hazard ratio, BZD = benzodiazepines, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, IL = interleukin, LHID = the Longitudinal Health Insurance Database, NHI = national health insurance, NHIRD = the National Health Insurance Research Database, SBD = sleep-related breathing disorder, TNF = tumor necrosis factor.

INTRODUCTION
Insomnia and headache are both common complaints that could affect the quality of our daily lives. In Asia, migraine is the most prevalent type of headache diagnosed at neurology clinics (66.6% of headache patients, ranging from 50.9% to 85.8% in various countries). Worldwide, the estimated annual prevalence of migraine is approximately 15% to 20% in women and 6% to 10% in men. On the other side, insomnia, especially the sleep-related breathing disorders (SBD) can temporarily or chronically happen in a person and would be highly associated with other medical disorders. Higher prevalence of SBD was usually observed in the elderly population, and was thought to threaten their lives with increasing the risk of various vascular diseases.

Migraine is considered as a neurovascular disease and is associated with other vascular diseases, too. Previous studies have reported interacting relationships among migraine, various sleep disorders, anxiety, and depression. However, whether SBD can be considered a trigger or a predisposing factor for migraine development still remains unclear. Therefore, in this study, we used a Taiwanese nationwide population-based database to evaluate the risk of developing subsequent migraine in patients with SBD.

METHODS AND MATERIALS
Data Source
Taiwan launched a national health insurance (NHI) in 1995, operated by a single-buyer, the government. Medical reimbursement specialists and peer review should scrutinize all insurance claims. This retrospective population-based cohort study was conducted using the Longitudinal Health Insurance Database (LHID) of the National Health Insurance Research Database (NHIRD), established by the National Health Research Institutes, Department of Health, Taiwan. The
Statistical Analysis
Risk factors for migraine, including age, sex, comorbidity, and history of drug use, were compared between the SBD and comparison cohorts by using Student t test and Chi-squared test. The incidence rate of migraine (per 1000 person-year) was calculated in the 2 cohorts, according to demographic variables, comorbidity (yes/no), and drug use (yes/no). A Poisson regression model was used to estimate the incidence rate ratios and 95% confidence intervals (CIs) for migraine in the SBD and comparison cohorts according to the various variables. A multivariate Cox proportional hazards model was used to calculate the adjusted hazard ratio (aHR) and 95% CI for migraine in both cohorts, after controlling for potential confounding risk factors. The Cox model was also used to estimate the HR for migraine and SBD with various comorbidities.

RESULTS
In this study, we evaluated 3411 patients with SBD diagnosed between 2000 and 2009 as the SBD cohort, and 13,644 comparison patients as the comparison cohort (Table 1). The distributions of sex and age were similar between the 2 cohorts. However, the majority of the patients were men (67.8%) and were ages <65 years (85.1%). The mean age (± standard deviation) of 2 cohorts was 48.3 ± 15.3 years. During the 12-year follow-up, the incidence of migraine development was 2.17% in the SBD cohort and 0.66% in the comparison cohort, with the mean migraine-onset age of 46.3 and 51.6 years, respectively. The proportion of patients with a comorbidity, such as hypertension (49.7% vs 30.5%), hyperlipidemia (41.2% vs 21.5%), diabetes (24.5% vs 15.1%), stroke (26.4% vs 14.3%), COPD (37.6% vs 16.8%), depression (16.4% vs. 2.61%), and anxiety (28.2% vs. 6.18%), was substantially higher in the SBD cohort than in the comparison cohort. The proportion of patients using zolpidem, BZD, or both was higher in the SBD cohort than in the comparison cohort at the baseline (89.9% vs 68%). Surprisingly, most participants took BZD or both and only very few in the 2 cohorts used zolpidem alone (1.44% vs 0.86%; Table 1).

As shown in Figure 1, the cumulative incidence of developing migraine during the follow-up was higher in the SBD cohort than in the comparison cohort (log-rank test, P < 0.0001). The overall aHR for developing migraine was 2.43 (95% CI = 1.72–3.44), and the incidence rate of migraine was higher in the SBD cohort than in the comparison cohort (3.83 vs 1.17 per 1000 person-year; Table 2). The risk of developing migraine was higher in men (aHR = 2.71, 95% CI = 1.64–4.47) than in women (aHR = 2.29, 95% CI = 1.41–3.72) with SBD. When stratifying by age, the patients ages between 45 and 64 years were associated with the highest risk of developing subsequent migraine, with an aHR of 2.68 (95% CI = 1.63–4.43). The aHR for developing migraine was 2.51 (95% CI = 1.47–4.30) in the patients ages 20 to 44 years and 1.09 in the patients ages ≥65 years. In both the SBD and comparison cohorts, the incidence of developing migraine was greater in patients with ≥1 type comorbidities. After stratifying the patients in the SBD and comparison cohorts by drug use, we identified an aHR of 2.39 (95% CI = 1.68–3.40) in the patients with drug use and 3.58 (95% CI = 0.42–30.7) in the patients without drug use. Table 3 shows the multiplicative risk of developing migraine in the patients with SBD and various comorbidities. The comorbidities having significant interaction with SBD for migraine development included hypertension (P = 0.0146), hyperlipidemia (P = 0.0227), diabetes (P = 0.0497), and stroke (P = 0.0367). But we also observed increased risk of developing migraine in the patients with SBD and COPD (aHR = 3.08, 95% CI = 1.96–4.83), depression (aHR = 4.44, 95% CI = 2.67–7.39), or anxiety (aHR = 5.12, 95% CI = 3.41–7.69).
DISCUSSION

Our results indicate significantly increased risk of developing subsequent migraine in patients with SBD ages between 20 and 64 years, but not in older patients. Migraine is a combining neuronal and vascular disorder, which associates with other vascular events. Murinova et al proposed that migraine would be considered a risk factor for other vascular diseases based on the vascular mechanism and that migraineurs might have different endothelial, structural, and genetic factors of vessels than regular people. Through the vascular mechanism, SBD can possibly result in repeated episodes of hypoxia and hypercapnia during sleep, and altered vascular endothelial function. Tissue hypoxia was also reportedly associated with the upregulated expression of transcription factors such as hypoxia inducible factor, nuclear factor kappa B, tumor necrosis factor (TNF), inducible nitric oxide synthase, and vascular endothelial growth factor. Therefore, migraine could be caused by the changed production of endothelium-derived hyperpolarizing factors, which dilates the meningeal vessels and presents a migraine headache. These changes might also lead to other vascular comorbidities, such as hypertension, atherosclerosis, ischemia, thrombosis, and stroke.

Another study suggested that hypoxia might increase blood–brain barrier permeability, leading to brain edema, neurovascular uncoupling, and neuronal dysfunction and damage, which would be related to the neuronal or cortical mechanism of migraine. Such changes in brain cortices and

| TABLE 1. Comparison of Demographics, Comorbidity, and History of Drug Use Between SBD and Comparison Cohorts |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Gender*                                         | SBD             |                 |                 |                 |
| Women                                           | 4396            | 32.2            | 1099            | 32.2            |
| Men                                             | 9248            | 67.8            | 2312            | 67.8            |
| Age, yr**                                       |                 |                 |                 |                 |
| 20–44                                           | 6068            | 44.5            | 1517            | 44.5            |
| 45–64                                           | 5540            | 40.6            | 1385            | 40.6            |
| ≥65                                             | 2036            | 14.9            | 509             | 14.9            |
| Mean (SD)**                                     | 48.3 (15.3)     |                 | 48.3 (15.3)     |                 |
| Migraine*                                       | 90              | 0.66            | 74              | 2.17            |
| Mean of onset age (SD), yr†                      | 51.6 (15.2)     |                 | 46.3 (12.8)     |                 |
| Comorbidity*                                    |                 |                 |                 |                 |
| Hypertension                                    | 4155            | 30.5            | 1694            | 49.7            |
| Hyperlipidemia                                  | 2936            | 21.5            | 1404            | 41.2            |
| Diabetes                                        | 2062            | 15.1            | 835             | 24.5            |
| Stroke                                          | 1951            | 14.3            | 901             | 26.4            |
| COPD                                            | 2287            | 16.8            | 1283            | 37.6            |
| Depression                                      | 356             | 2.61            | 561             | 16.4            |
| Anxiety                                         | 843             | 6.18            | 961             | 28.2            |
| Drug*                                           |                 |                 |                 | <0.0001         |
| None                                            | 4362            | 32.0            | 345             | 10.1            |
| Zolpidem                                        | 117             | 0.86            | 49              | 1.44            |
| BZD                                             | 7681            | 56.3            | 1418            | 41.6            |
| Both                                            | 1484            | 10.9            | 1599            | 46.9            |

COPD = chronic obstructive pulmonary disease; BZD = benzodiazepines; SBD = sleep-related breathing disorders; SD = standard deviation.
*Chi-squared test.
†Student t test.

FIGURE 1. Comparison of cumulative incidence of developing migraine between participants with (dashed line) and without (solid line) sleep-related breathing disorders.
neurons may lead to various neurological diseases, and a high degree of comorbidity has been observed among Alzheimer’s disease, migraine, and epilepsy. Therefore, SBD might induce hypoxia and cause an unstable neuronal condition, resulting in the symptoms of migraine in patients. Furthermore, there is another possible mechanism causing from the comorbid condition of migraine and epilepsy. A sleep disorder itself can increase the occurrence of interictal spikes and epileptic seizures,\textsuperscript{21,22} and migraine like headache can be preceded to a subtle seizure before the epilepsy diagnosis being made. It is due to the well-known association between migraine and epilepsy in recent studies.\textsuperscript{23} In the future, we would like to study the occurrence of interictal spikes and epileptic seizures due to the well-known association between migraine and epilepsy in recent studies.\textsuperscript{23}

### TABLE 2. Incidence and Adjusted Hazard Ratio of Migraine Stratified by Sex, Age, Comorbidity (Yes/No) and Drug Use (Yes/No) Between SBD and Comparison Cohorts

| Variables | Event | PY | Rate | Event | PY | Rate |
|-----------|-------|----|------|-------|----|------|
| Overall  |       |    |      |       |    |      |
| Gender    |       |    |      |       |    |      |
| Women     |       |    |      |       |    |      |
| Men       |       |    |      |       |    |      |
| Age, yr   |       |    |      |       |    |      |
| 20–44     |       |    |      |       |    |      |
| 45–64     |       |    |      |       |    |      |
| ≥65       |       |    |      |       |    |      |
| Comorbidity |   |    |      |       |    |      |
| No        |       |    |      |       |    |      |
| Yes       |       |    |      |       |    |      |
| Drug      |       |    |      |       |    |      |
| No        |       |    |      |       |    |      |
| Yes       |       |    |      |       |    |      |

Adjusted HR = multiple analysis including age, sex, comorbidities, and drug used; IRR = incidence rate ratio; CI = confidence interval; PY = person-year; Rate = incidence rate (per 1000 person-years); SBD = sleep-related breathing disorders.

As shown in Figure 1, we observed that the risk of developing subsequent migraine increased in the SBD cohort over time. We analyzed the interactions between various comorbidities and SBD, and considered the major confounding factors for migraine development. Vascular-related comorbidities, such as hypertension, hyperlipidemia, diabetes, and stroke, were significantly associated with SBD and migraine development (Table 3). However, nonvascular-related comorbidities, such as COPD, depression, and anxiety, were nonsignificantly associated with SBD and migraine development. As shown in Table 2, comorbidity and drug use exerted nonsignificant effects on the HRs for developing migraine. However, because of limited numbers of SBD patients who had no comorbidity or without drug use, these results could not be considered reliable to us in the interpretation.

The strengths of this study are its nationwide population-based design and representativeness of the 2 cohorts. However, this study also has some limitations. First, information on migraine frequency, presence or absence of aura, smoking habits, alcohol consumption, body mass index or weight, socioeconomic status, and family history were not available in the NHIRD, all of which might represent confounding factors for developing migraine. Second, evidence deriving from a cohort study is subject to several biases related to adjustment for confounders. Although our study design included adequate confounders, such as COPD, depression, and anxiety, were nonsignificantly associated with SBD and migraine development. As shown in Table 2, comorbidity and drug use exerted nonsignificant effects on the HRs for developing migraine. However, because of limited numbers of SBD patients who had no comorbidity or without drug use, these results could not be considered reliable to us in the interpretation.

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### TABLE 3. Adjusted Hazard Ratios of Migraine Associated SBD Interaction With Comorbidity

| Variable | N   | Event | Adjusted HR (95% CI) | P Value |
|----------|-----|-------|----------------------|---------|
| SBD Hypertension | No  | No    | 9489 51              | Ref.    |
|           | No  | Yes   | 4155 39              | 1.53 (0.97–2.43)*** |
|           | Yes | No    | 1717 42              | 4.58 (3.04–6.90)*** |
|           | Yes | Yes   | 1694 32              | 3.23 (2.02–5.16)*** |
| SBD Hyperlipidemia | No  | No    | 10,708 58            | Ref.    |
|           | No  | Yes   | 2936 32              | 1.79 (1.15–2.80)* |
|           | Yes | No    | 2007 45              | 4.17 (2.82–6.16)*** |
|           | Yes | Yes   | 1404 29              | 3.57 (2.26–5.62)*** |
| SBD Diabetes | No  | No    | 11,582 70            | Ref.    |
|           | No  | Yes   | 2062 20              | 1.45 (0.87–2.43) |
|           | Yes | No    | 2576 59              | 3.87 (2.74–5.48)*** |
|           | Yes | Yes   | 835 15               | 2.64 (1.50–4.66)*** |
| SBD Stroke | No  | No    | 11,693 69            | Ref.    |
|           | No  | Yes   | 1951 21              | 1.65 (0.98–2.78) |
|           | Yes | No    | 2510 57              | 3.89 (2.74–5.53)*** |
|           | Yes | Yes   | 901 17               | 2.96 (1.70–5.14)*** |
| SBD COPD  | No  | No    | 11,357 71            | Ref.    |
|           | No  | Yes   | 2287 19              | 1.23 (0.73–2.06) |
|           | Yes | No    | 2128 47              | 3.67 (2.54–5.31)*** |
|           | Yes | Yes   | 1283 27              | 3.08 (1.96–4.83)*** |
| SBD Depression | No  | No    | 13,288 87            | Ref.    |
|           | No  | Yes   | 356 3                | 1.13 (0.36–3.58) |
|           | Yes | No    | 2850 56              | 3.06 (2.19–4.28)*** |
|           | Yes | Yes   | 561 18               | 4.44 (2.67–7.39)*** |
| SBD Anxiety | No  | No    | 12,801 79            | Ref.    |
|           | No  | Yes   | 843 11               | 1.72 (0.91–3.26) |
|           | Yes | No    | 2450 40              | 2.75 (1.86–3.99)*** |
|           | Yes | Yes   | 961 34               | 3.12 (2.41–7.69)*** |

Model adjusted for age and sex; P value for interaction; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; Ref. = reference group; SBD = sleep-related breathing disorders.

* P < 0.05, ** P < 0.01.

high accuracy and validity of diagnoses from ICD-9-CM codes in the NHIRD research,27,28 and those convinced us that some valuable evidences had been shown in this study about the causal correlation between SBD and subsequent migraine development.

### CONCLUSION

The findings from this population-based cohort study indicate increased risk of developing subsequent migraine in adults, but not elderly ones, with SBD, which could be thought as a trigger or a predisposing factor for migraine development. Additional large unbiased population-based studies with further categorization and analysis are required to confirm these findings.

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