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The risk of insomnia after surgical operation: A longitudinal, population-based, case-crossover study

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Abstract

Background: The acute onset of insomnia following surgical operations has long been neglected, and long-term outcomes are not clear. Our aims were (1) to evaluate the risk of postoperative insomnia, (2) to identify which surgeries are related, and (3) to follow patients with postoperative insomnia for the development of major mental and physical disorders.

Methods: We conducted a case-crossover study comprising 9898 participants with new-onset insomnia from the Taiwan National Health Insurance Research Database between 1997 and 2011. We determined the odds of having surgery in the case period (30 days) before the onset of insomnia by logistic regression analysis. Types of surgery that postoperative insomniacs had undergone were compared with age-/gender-/timing-matched controls. Longitudinal follow-up of postoperative and non-postoperative insomniacs was performed.

Results: The odds ratio of surgical exposure vs. nonexposure within 30 days was 12.05 ($p < 0.001$) before new-onset insomnia. Surgery of musculoskeletal and nervous systems predisposed to insomnia. The duration of hypnotic drug use (0.83 years) was shorter and with a nearly 2-fold faster remission rate in postoperative than in non-postoperative insomniacs (1.45 years). Approximately 25% of each insomnia group developed persistent sleep disturbance.

Conclusion: Surgery is associated with subsequent insomnia, which has a shorter duration and a faster remission than non-postoperative insomnia. Our data provide a reference for postoperative care, and warrant future studies.

Keywords: Insomnia; Postoperative care; Surgery

1. INTRODUCTION

Insomnia is a debilitating disorder comprising symptoms of difficulty initiating or maintaining sleep or early morning awakenings with impaired daytime functioning.[1] Insomnia is one of the most commonly encountered sleep disorders, affecting about 6% to 10% of the population.[2,3] The acute onset of insomnia following surgical operations has long been noted, with initial reports published in the 1980s.[4,5] Harrell and Othmer[4] observed that sleep time loss in patients who had undergone cardiotomy peaked at postoperative days 1 and 2. Rosenberg-Adamsen[6] reviewed several studies of postoperative sleep disturbances evaluated by EEG. Major alterations of sleep patterns occurred during the initial six nights and gradually normalized to preoperative levels within the first week.

The complex perioperative stress response influences sleep, levels of hormones and other humoral mediators of the endocrine-metabolic system, immune function, inflammatory responses, and sympathetic nervous system activity.[7] Postoperative pain, medications, starvation, psychological factors, age, usual sleep profile, and environmental factors all affect sleep after surgery.[8]

Most reports have focused on the immediate postoperative period, and few longitudinal studies have been conducted. Whether postoperative insomnia may elicit chronic sleep disturbances and increase the risk of long-term hypnotic drug use compared to insomnia due to other causes are still unknown.

We conducted a case-crossover study using the National Health Insurance Research Database (NHIRD) to determine whether patients with the new onset of insomnia were more likely to have undergone preceding surgery. We further searched all types of surgery in association with postoperative insomnia. By separating patients with new-onset insomnia into postoperative and non-postoperative groups, we compared the duration of insomnia and the risk of long-term hypnotic use.

2. METHODS

2.1. Data sources

The National Health Insurance program was instituted in Taiwan in 1995,[9] and is a mandatory single-payer program, covering >96% of residents of this island. The NHIRD was

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established in 1997, and contains comprehensive data of patients' demographic characteristics, medical expenditures, prescription claims data, surgery codes, treatment codes, and diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The Institutional Review Board of the Taipei Veterans General Hospital (2015-02-007CC) approved this study.

2.2. Study subjects

Data from the NHIRD (n = 1,000,000) in 2011 was used, and 559,199 patients with hypnotic prescriptions were identified. We defined patients (age ≧20 years) with newly diagnosed insomnia by psychiatrists or family physicians between January 1, 1996 and December 31, 2011. The definition of insomnia included: (1) prescription of hypnotic drugs for more than 90 defined daily doses (DDD)[9] in 3 months following the index date; (2) previous history of hypnotic use is excluded (Fig. 1). We used surgery code (01.XX-86.XX) and treatment code (96014C-96022C) to define patients who had been exposed to different surgical operations with general anesthesia. To remove confounding factors of socioeconomic status, we categorized levels of monthly income and urbanization.[10]

2.3. Study 1

To assess if preceding surgery within 1 month might be associated with the new onset of insomnia, we used a case-crossover design to evaluate whether exposure to surgery might increase the risk of subsequent insomnia.

2.4. Case-crossover design

The case-crossover design is used to examine acute effects after transient exposure.[11] To exclude selection bias, each subject serves as his/her own control. We divided the incidence of surgery during the case period (1-30 days before index date) by that during the control period (61-90 days before index date) to calculate odds ratio (OR). Case and control periods were separated by a 30-day washout period to render them distinct and independent. We performed sensitivity analysis by using two different time windows (15 and 60 days).

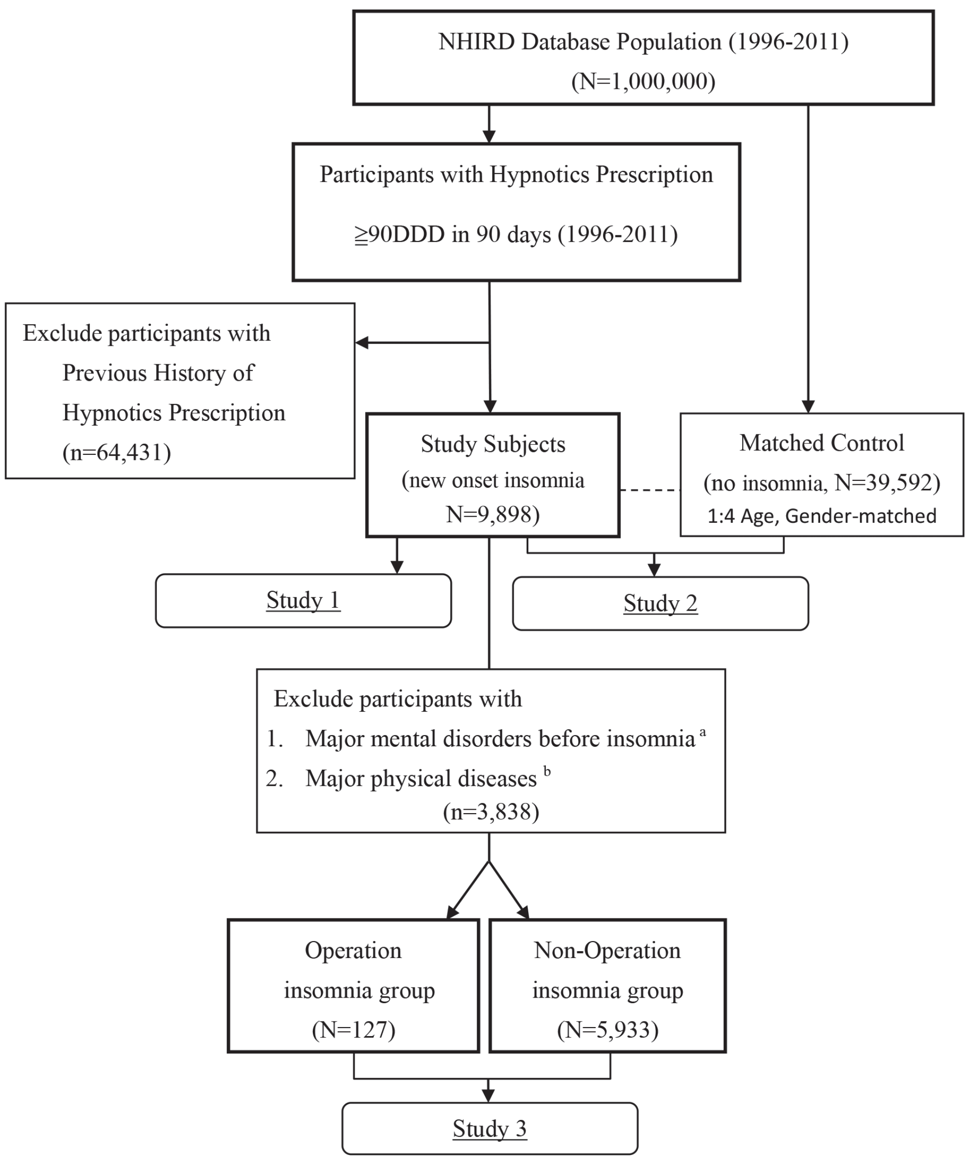

Fig. 1 Flowchart of the study.

2.5. Study 2

To determine which surgical categories might be more likely to be associated with subsequent insomnia, we compared the frequency of all types of surgery in insomnia patients with that of the randomly selected sex-/age-/timing-matched controls (1:4 ratio). By using the incidence rate (IR) per 10,000 persons, we divided the IR of insomniacs by that of controls to calculate the relative ratio (RR).

2.6. Study 3

To determine the duration of hypnotic use and insomnia, we excluded patients with previous histories of major mental disorders (depressive disorder, bipolar disorder, schizophrenia, and anxiety disorder) and major organic diseases (cancer, stroke, coronary heart disease, and all disorders that are listed in the Major Disease Card) before the index date of insomnia (Fig. 1). We followed postoperative and non-postoperative insomnia patients until the year 2011 to determine their durations of hypnotic drug therapy. The date of discontinuation of hypnotics was defined when the patient had no records of hypnotic prescription for 120 days.

2.7. Statistical analyses

The baseline descriptive characteristics were analyzed using the Chi-square test for categorical variables and the independent t-test for continuous variables. A conditional logistic regression was performed to calculate the OR of operation before first diagnoses of insomnia. Subgroup analysis was performed by stratifying age, sex, and medical comorbidities (Charlson Comorbidity Index, CCI).[12] The Log-Rank test was conducted to determine the survival curve of hypnotics use between groups. We calculated IRs (per 1000 person-years) and used Poisson regression to compare differences between groups. Adjusted hazard ratios were analyzed by adjusting for age, gender, level of urbanization, and monthly income. The SAS statistical package, version 9.2 (SAS Institute, Inc., Cary, NC), and SPSS (Version 19.0 for Windows; IBM Corp., New York, NY) were both used for data analysis. The p value less than 0.05 was considered statistically significant.

3. RESULTS

Age at the onset of insomnia within 30 days of surgery clustered at age 20-35 (29.6%), 36-45 (24.1%) and 46-55 years (19.8%), with a mean of 45.7 ± 14.9 years (Table 1). Most subjects had low monthly income (0-500 USD, 53.7%) and resided in highly urbanized areas (62.9%).

3.1. Study 1

Among subjects with the new onset of insomnia (n = 9,898), 229 patients had undergone surgery and general anesthesia in the 30-day case periods compared to 19 patients in the 30-day control periods (OR 12.05 [95% confidence interval, 7.54–20.39, $p < 0.001$]). Subgroup analysis showed the OR was high in all age groups (especially age 20-35, OR 28; age 56-65, OR 18; age ≥66, OR 22; all $p < 0.001$) and gender groups (OR 17.88 for men and 7.82 for women, both $p < 0.001$). The OR was high in the group of CCI = 0 (OR 17, $p < 0.001$). The results of sensitivity analysis were consistent with these findings (15- and 60-day time windows with OR 13.27 and 12.75, respectively) (Table 1).

3.2. Study 2

Fig. 2 illustrates the distributions of surgical categories associated with subsequent insomnia from the most to the least likely, using the IR per 10,000 persons. The surgical categories are listed in decreasing order: musculoskeletal system (92), nervous system (54), integumentary system (47), digestive system (34), cardiovascular system (33), respiratory system (24), and others (≤15). Compared with control subjects, the RRs for subsequent insomnia were found in surgeries of the musculoskeletal system (30.6), nervous system (54), integumentary system (23.5), and digestive system (8.5).

3.3. Study 3

Fig. 3 illustrates the Kaplan-Meier survival curve for the discontinuation of hypnotics. The median duration from insomnia onset to discontinuation of hypnotics was 1.27 years (postoperative, 0.80 year vs. non-postoperative, 1.29 years). Fifty percent

Table 1

Demographic data and the risk of insomnia after exposure to surgery

Measure	Only in Case Period[a]	Only in Control Period[b]	In Both Periods	Not in Both Periods	Crude Odds Ratios	Crude 95% CI	Crude *p* value
All patients (N = 9898, 100%)	229	19	0	9650	12.05	7.54–20.39	<0.001
Subgroup analysis							
Age group (y, mean = 45.7, SD = 14.9)							
20-35 (n = 2933, 29.6%)	56	2	0	2875	28.00	7.40–236.9	<0.001
36-45 (n = 2389, 24.1%)	56	7	0	2326	8.00	3.64–20.81	<0.001
46-55 (n = 1962, 19.8%)	56	7	0	1896	8.43	3.85–21.88	<0.001
56-65 (n = 1505, 15.2%)	36	2	0	1467	18.00	4.63–154.3	<0.001
≥66 (n = 1109, 11.2%)	22	1	0	1086	22.00	3.56–907.96	<0.001
Gender							
Female (n = 4591, 53.7%)	81	11	0	4494	7.82	4.16–16.25	<0.001
Male (n = 5307, 46.3%)	143	8	0	5156	17.88	8.83-42.20	<0.001
CCI[c]							
0 (n = 7685, 77.6%)	153	9	0	7523	17.00	8.72–37.9	<0.001
1-2 (n = 1929, 19.5%)	58	7	0	1864	8.29	3.78–21.52	<0.001
≥3 (n = 284, 2.9%)	18	3	0	263	6.00	1.75–31.80	0.002
Sensitivity analysis							
15-Day window	199	15	0	9684	13.27	7.85–24.15	<0.001
60-Day window	255	20	3	9620	12.75	8.08–21.23	<0.001

[a]Case period is the period between the index date and 30 d before index date.
[b]Control period is the period between 60 d before index date and 90 d before index date.
[c]:CCI = Charlson Comorbidity Index).

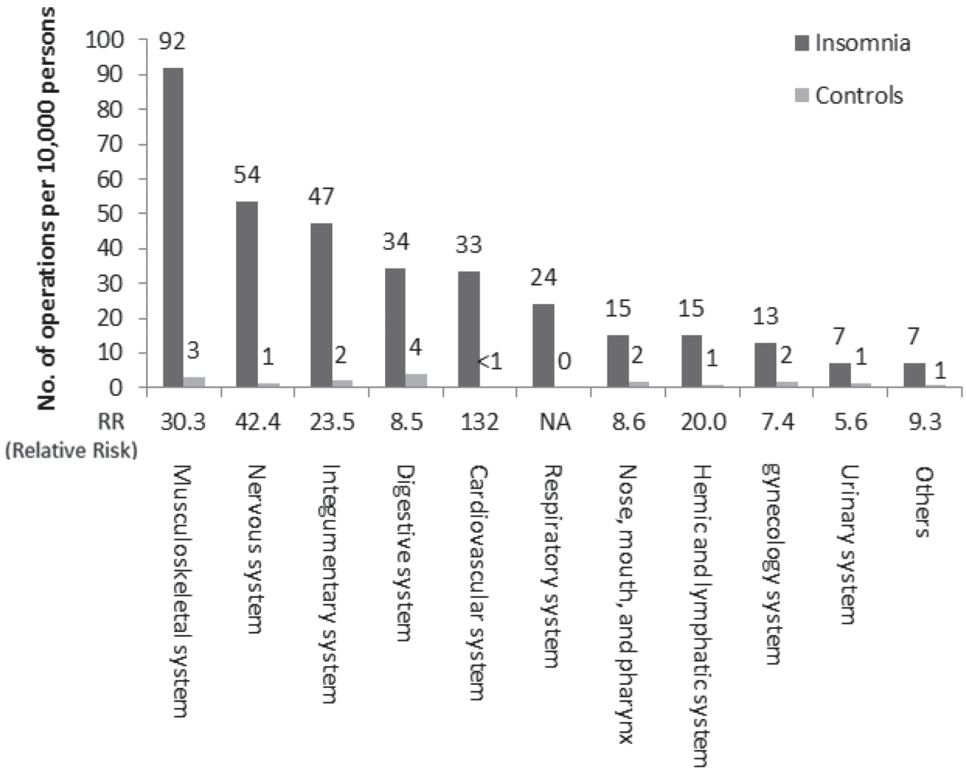

Fig. 2 Comparison of the incidences of different categorical operations per 10,000 persons between insomnia group and 4-fold age-/gender-matched controls during the same period.

of insomnia patients in the postoperative group stopped hypnotic drug therapy at 0.83 years, while 50% of the non-postoperative group ceased hypnotic use at 1.45 years ($\chi^2(1) = 5.81$, $p < 0.05$). The remission rate persisted in the postoperative group until the fourth year after surgery. Between the fourth and eighth years, the remaining 25% of the postoperative insomnia patients continued to use hypnotics. The non-postoperative insomnia patients took 8 years to reach the same prevalence of hypnotic drug use that the postoperative group exhibited by the fourth year.

3.4. Subgroup analyses

After stratifying our data by age and gender, subgroup analyses showed that female patients with postoperative insomnia (n = 41) had an earlier remission than the non-postoperative group (n = 2,866) (50% patients discontinued hypnotics: 0.59 vs. 1.47 years, $p < 0.001$). Male patients exhibited a trend of shorter duration of hypnotic use in the postoperative (n = 86) than in the non-postoperative (n = 3067) group (0.97 vs. 1.40 years, $p = 0.56$). 2) Patients at age 46-55 years in the postoperative group (n = 28) had a shorter duration of hypnotics use than

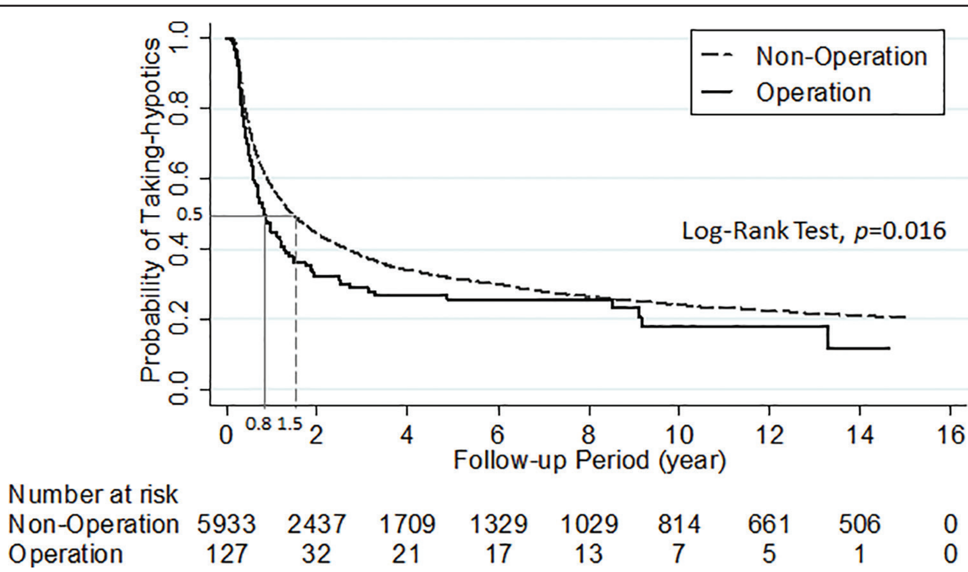

Fig. 3 Survival curve of hypnotics use between operation (N = 127) and nonoperation insomnia (N = 5933) groups.

those in the non-postoperative group (n = 1273) (0.59 vs. 1.50 years, $p = 0.021$). We confirmed that only female patients in the 46- to 55-year age group had a shorter duration of hypnotic use in the postoperative (n = 13) than non-postoperative (n = 648) group (0.46 vs. 1.56 years, $p = 0.018$). Male patients of this age group did not show a significant difference in the duration of hypnotic use (n = 15, 0.82 year vs. n = 625, 1.31 years, $p = 0.3$).

4. DISCUSSION

We report a large-scale case-crossover study of a nationwide population to investigate the relationship between surgery and subsequent acute-onset insomnia. The OR of insomnia was 12.05 times higher after surgery than during the self-control period. Sensitivity analysis of the 15- and 60-day windows also validated the 30-day window results. Male participants had a 2-fold higher probable risk of postoperative insomnia than female participants. High probable risks of postoperative insomnia were also found in the 20-35 and 56-75 year age groups. Musculoskeletal and nervous system surgeries were the most common categories among patients with postoperative insomnia. Longitudinal observation found that 50% of patients with postoperative insomnia used hypnotics for approximately half the duration used by those with non-postoperative insomnia (0.83 years vs. 1.45 years). However, 25% of patients with either type of insomnia continued to use hypnotics for 8 years after onset.

The separation of surgical procedures and general anesthesia related to postoperative sleep disturbances is the first issue to be addressed. Postoperative sleep disturbances were previously attributed to general anesthesia. This hypothesis was disapproved by a study that revealed that general anesthesia of three hours duration in nonsurgical volunteers produced only minimal sleep disturbances.[13] A recent study demonstrated that operations with general anesthesia in the evening are associated with a greater degree of postoperative sleep disturbance than those performed in the morning.[14] Our findings support the conclusion that general anesthesia per se may not be an important pathogenic factor for postoperative insomnia.[6] The use of dexmedetomidine during daytime operations under general anesthesia may improve postoperative sleep quality.[15]

A >12-fold higher incidence of new-onset insomnia was related to preceding surgery. This finding indicates that surgery might be an acute precipitant of insomnia. Postoperative insomnia was particularly prominent in males, young adults, and during the transition period to advanced age. These findings differ from the reported increased prevalence of insomnia related to aging and the 1.5-times higher prevalence in female patients compared to male patients across all age groups in previous studies across countries.[2,16,17] This discrepancy may be possibly explained by considering that young people, particularly males, who are about to become freshmen of society, may experience escalating pressures and attempt to accommodate stress, which might predispose to postoperative insomnia. Maladaptive physiologic responses to stress that promote inflammation and elevate interleukin-6 levels, which may predispose to sleep disturbances, have been previously observed in elderly patients.[18] The reversed gender effect on postoperative insomnia (afflicting males more than female patients) is plausibly explained by higher cortisol levels, which predispose to depression and insomnia, following surgery in male patients than in female patients.[19] We also found that the incidence of postoperative insomnia was much higher in patients without rather than with medical comorbidities. Comorbidities may cause chronic stress and possibly reduce susceptibility to postsurgical stress.

The most common surgeries that induced postoperative insomnia were of the musculoskeletal and nervous systems. Chronic postoperative pain occurs in 10% to 50% of patients[20] and is frequently associated with sleep disturbance as a consequence of arousal from discomfort. In turn, patients suffering from insomnia frequently report daily pain.[21,22] Several studies have reported a correlation between insufficient or disturbed sleep and pain symptoms.[22] Worsened pain following lumbar spine surgery is significantly associated with clinical insomnia.[23] Musculoskeletal procedures such as total knee or hip arthroplasties cause significant levels of postoperative pain for 1 year in 28 to 35%[24] and for 3-4 years in 27% to 44% of patients.[25] Another study disclosed that 55 of 260 (21%) patients reported moderate to severe pain at rest one year after orthopedic foot surgery, which is comparable to outcomes of more aggressive surgical procedures.[20] In neurosurgery, nerve damage-related neuropathic pain, chronic low back pain, and sciatic nerve pain were postulated to result from a cascade initiated by glutamate release from nerve endings that triggers intracellular changes, which further contribute to sustained central sensitization and pain perception.[26]

By conducting longitudinal follow-up, we determined that postoperative insomniacs ceased hypnotic use more rapidly, in approximately half the time required by non-postoperative patients. This finding indicates that postoperative insomnia is an acute or subacute disorder with a shorter duration of sleep disturbances. Although approximately 75% of patients with postoperative insomnia remitted by the fourth postoperative year, the rest 25% continued to take hypnotics until the eighth year. This observation suggests that the sustained sleep disturbance in the remaining 25% of patients of both groups might be due to perpetuating factors in the stress-diathesis model of insomnia.[27] The behavioral model proposed by Spielman to explain the etiology of insomnia consists of predisposing, precipitating, and perpetuating factors.[28] Surgery serves as a prominent precipitating factor. Through the long-term clinical course, mixed factors that include medication use, insomnia conditioning, and possible psychiatric comorbidities may perpetuate insomnia.[29]

Perimenopausal (aged 46-55 years) female patients with postoperative insomnia used hypnotics for shorter durations than male patients and female patients of other age groups. This finding contrasts with those of multiple previous studies that indicate that menopausal women are highly susceptible to insomnia.[30–32] Surgical procedures might be less consequential than natural life changes in the pathogenesis of insomnia during perimenopause.

This study has several limitations. First, the causal relationship of surgery and insomnia could not be demonstrated because we did not include previous/current hypnotic drug users, although we confined these two events in the 30-day time window by using a case-crossover control design instead of using IR estimates. In that regard, the sample size of postoperative insomnia patients would be too small to be investigated. Second, surgery may cause depression or anxiety, which might also induce insomnia, thus confounding the attribution of insomnia to surgery per se. However, we found that the prevalence of major depression was not significantly different between postoperative and non-postoperative insomnia groups during follow-up, whereas postoperative anxiety would be a component of the surgical effects related to insomnia. When insomnia symptoms resolve, anxiety may also decrease. Third, the index subjects of insomnia might be false-negatives. However, we identified patients with hypnotic prescriptions of more than 90 DDD in 90 days to minimize potential misclassification and to further exclude false-negatives. Finally, we did not exclude potential confounding factors that might affect insomnia risks such as obstructive sleep apnea (OSA), restless leg syndrome (RLS), and periodic limb movement disorder (PLMD) in our study subjects. The codings of RLS and PLMD were not available in our database, and the diagnostic rate of OSA in major depressive disorder with insomnia is low in Taiwan.[33]

In conclusion, surgery, as a possible precipitating factor, has a relatively strong temporal association with acute-onset insomnia. Patients with postoperative insomnia may experience remission in half the time duration required in non-postoperative cases. Nearly 25% of patients with either postoperative or non-postoperative insomnia may develop chronic sleep disturbances. Male patients, young adults, and patients approaching advanced age may be predisposed to postoperative insomnia. Musculoskeletal and nervous system procedures may be among the surgeries most highly associated with postoperative insomnia. These data may provide a reference for postsurgical care. Future evidence-based investigations are warranted to explore the causal relationship between surgery and insomnia.

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