



Original Article

Reducing Parkinson's disease incidence in patients with insomnia through acupuncture: A cohort study



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ABSTRACT

Background: Parkinson's disease (PD) is a prevalent neurodegenerative condition characterized primarily by motor symptoms, often accompanied by non-motor manifestations such as insomnia. Acupuncture, an increasingly popular alternative therapy, has shown promise in the prevention and alleviation of PD motor symptoms. However, the specific impact of acupuncture on the risk of developing PD in insomnia patients remains uncertain.

Methods: In this retrospective study, we identified and matched 152,585 newly diagnosed insomnia patients from Taiwan's National Health Insurance Research Database (NHIRD) from 2000 to 2010. Using a 1:1 propensity score matching method, we ensured the comparability of two groups: patients who received acupuncture treatment and those who did not. It resulted in a final cohort of 20,112 patients in both the acupuncture and non-acupuncture groups.

Results: Our analysis revealed that insomnia patients who underwent acupuncture treatment exhibited a significantly reduced risk of developing PD. The adjusted hazard ratio (aHR) was 0.44 (95% confidence interval = 0.39–0.50) compared to those who did not receive acupuncture. Furthermore, the cumulative incidence of PD in the acupuncture group was significantly lower, as evidenced by the log-rank test ($p < 0.001$).

Conclusion: In conclusion, our study provides evidence suggesting that acupuncture treatment is associated with a decreased risk of PD in patients with insomnia. However, further research is warranted to strengthen the evidence supporting these findings.

1. Introduction

Insomnia, the most prevalent type of sleep disorder, is characterized by difficulties initiating or maintaining sleep, accompanied by symptoms like irritability or fatigue during wakefulness.¹ Insomnia's prevalence ranges from 10% to 20%, with approximately 50% of individuals experiencing a chronic course.¹ The etiology and pathophysiology of insomnia involve a combination of genetic, environmental, behavioral, and physiological factors. Insomnia can occur independently or co-occur with other medical conditions or mental health disorders; if left untreated, it poses a risk for the onset and worsening of these comorbid conditions.² Insomnia is strongly associated with an increased mortality rate, cardiovascular diseases, and depression, along with other

somatic and mental health problems.³ Moreover, insomnia serves as a risk factor for impaired functioning, the development of other medical and mental disorders, and elevated healthcare costs.¹ Chronic insomnia is recognized as a significant contributing factor to neurodegenerative diseases, including Parkinson's disease (PD).⁴

PD causes by dopaminergic neuronal death in the substantia nigra, resulting in a deficiency of dopamine in the striatum, leading to classical motor symptoms such as tremor, rigidity, and bradykinesia.^{5, 6} The prevalence of PD is estimated at 1–2 cases per 1000 people within the general population at any given time.⁶ This prevalence increases with age, affecting approximately 1% of individuals over 60.⁶ Notably, the highest incidence rates of PD occur in individuals aged over 65, with the most significant percentage increase observed in those over 80 years

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old.⁷ PD diagnosis primarily relies on brain imaging, neurological assessments, and clinical symptomatology.⁸ However, PD's clinical presentation is acknowledged to be heterogeneous, encompassing significant non-motor manifestations.⁵ PD progression is marked by the worsening of motor symptoms, which can initially be managed by dopamine replacement therapy.^{5, 9} Non-motor features are frequently present in PD patients before the onset of the classical motor symptoms,⁵ and insomnia ranks among the most common PD non-motor features.¹⁰

Previous research has underscored the potential efficacy of acupuncture in managing late-life insomnia and improving sleep quality. Wang et al. (2020) demonstrated that multi-point acupuncture for primary insomnia yielded better clinical outcomes compared to single acupoint or sham acupuncture.¹¹ Their study utilized the Pittsburgh Sleep Quality Index, Athens Insomnia Scale, polysomnography, and resting-state functional MRI, revealing that acupuncture not only improved sleep quality but also modulated brain activity in sleep-related regions.¹¹ Chen et al. (2023) further explored acupuncture's modulation of functional connectivity in insomnia disorder.¹² Their study showed significant improvements in sleep quality with real acupuncture compared to sham acupuncture.¹² They also found that acupuncture modulated functional connectivity between the locus coeruleus and various brain regions, including the inferior frontal gyrus and supramarginal gyrus.¹² These changes correlated with improved sleep quality, suggesting that acupuncture's effects may be mediated through alterations in brain connectivity.¹² Fang et al. (2021) delved into the influence of acupuncture on sleep architecture among individuals with insomnia. Their systematic review and meta-analysis indicated that acupuncture interventions were associated with positive alterations in sleep stages, notably an increase in deep sleep stages and enhanced sleep efficiency.¹³ Hu et al. (2023) conducted a comprehensive meta-analysis of 20 studies involving 1677 patients with senile insomnia. Their collective findings suggest that acupuncture, either as a standalone treatment or in conjunction with other therapies, exhibits notable clinical efficacy in addressing sleep quality and alleviating insomnia symptoms.¹⁴ These results show that acupuncture effectively manages insomnia by improving sleep quality, modulating brain activity, and enhancing sleep stages.

Acupuncture has demonstrated benefits in ameliorating non-motor symptoms in patients with PD, including insomnia, depression, and overall quality of life. Li et al. (2022) undertook an extensive meta-analysis involving 27 randomized controlled trials to assess the impact of acupuncture on non-motor symptoms in PD patients. Their results suggest that acupuncture, particularly when administered alongside medication, may confer benefits related to PD-related insomnia, depression, cognition, and overall quality of life.¹⁵ Kluger et al. (2016) conducted a randomized controlled trial in PD patients experiencing fatigue. Their investigation revealed that both real and sham acupuncture groups experienced improvements in fatigue, implying that acupuncture may alleviate PD-related fatigue primarily through non-specific or placebo effects.¹⁶ Zhao et al. (2021) reviewed the efficacy of acupuncture in PD treatment, highlighting its potential to ameliorate symptoms and reduce medication use.¹⁷ This review emphasized acupuncture's neuroprotective effects, including anti-oxidative, anti-inflammatory, and anti-apoptotic mechanisms, which may slow PD progression by preserving dopaminergic neurons in the substantia nigra.¹⁷ Supporting the potential of acupuncture in PD treatment, Tamtaji et al. (2019) examined its impact on molecular mechanisms in PD.¹⁸ They found that acupuncture influenced apoptosis pathways, inflammatory cytokines, oxidative stress, and neurotransmitter regulation, suggesting a comprehensive effect on PD pathophysiology.¹⁸ The existing literature prompts the hypothesis that acupuncture may play a role in reducing the risk of individuals with insomnia transitioning to PD.

In the present study, we hypothesized that using acupuncture to treat insomnia patients could affect the prevalence of PD. Therefore, in this population-based cohort study, the association between acupuncture treatment and the risk of PD was evaluated in 40,224 patients with insomnia between 2000 and 2010 who were identified in the NHIRD.

2. Methods

2.1. Data sources

The National Health Insurance Research Database (NHIRD) from the Taiwan National Health Insurance (NHI) contains comprehensive records, including hospital visits, outpatient visits, hospitalizations, medication treatments, prescriptions, surgeries, and various other medical services received during hospital visits. NHIRD also includes outpatient records such as Chinese herbal medicine and acupuncture. For our current study, we utilized data from the Longitudinal Health Insurance Database (LHID 2000), a dataset that comprises a randomly selected sample of 1 million patients drawn from the NHIRD. To safeguard the privacy of study subjects, identifying information is encrypted before the database is made available for research purposes. The diagnoses within the Taiwan NHI system adhere to the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), with each diagnosis assigned a code based on the ICD-9-CM framework. This study received approval from the research ethics committee at China Medical University Hospital in Taiwan (CMUH104-REC2-115-CR8) and was conducted in accordance with the Declaration of Helsinki.

2.2. Study population

In order to investigate the relationship between acupuncture treatment and the incidence of PD in patients with insomnia, we conducted a retrospective cohort study. Initially, we identified patients with insomnia based on the following criteria: they had either at least two outpatient visits or one hospitalization specifically for insomnia (identified using ICD-9-CM codes 307.41, 307.42, 780.50, and 780.52) between 2000 and 2010. We applied specific exclusion criteria in this study. Patients with a diagnosis of PD (ICD-9-CM code 332) before the index date were excluded to ensure that the extracted insomnia cohort had no previous history of PD. Additionally, we excluded patients younger than 20 or older than 100 years, those with a follow-up period of less than one year, and those who received fewer than six acupuncture sessions. Subsequently, we divided these insomnia patients into two cohorts: those who had received acupuncture treatment (the acupuncture cohort) and those who had not received acupuncture treatment (the non-acupuncture cohort). In this study, we identified acupuncture treatments using the following National Health Insurance procedure codes B41, B42, B45, B46, B80-B84, B90-B94, P27041, P31103, P32103, P33031, and electroacupuncture treatments B43, B44, B86-B89, and P33032.

The primary endpoint we focused on in this study was the occurrence of PD in patients with insomnia. PD was defined as being diagnosed with it (using ICD-9-CM code 332) through at least two outpatient visits or one hospitalization. For the purposes of this study, we established the index date as the first date when acupuncture treatment was administered. For insomnia patients who did not receive acupuncture treatment, we randomly assigned a reasonable index date during their period of insurance coverage. The follow-up period extended from the index date to the earliest of the following events: a diagnosis of PD, withdrawal from the NHIRD, or December 31, 2013. For each patient who received acupuncture treatment, we selected a matching patient who had never undergone acupuncture treatment using propensity score matching. The variables used for matching included age, gender, index year, insurance amount, urbanization level, comorbidities, and related medications (as illustrated in Fig. 1).

2.3. Main outcome and comorbidities

We defined individuals as having a history of comorbidity if it was documented before their index date and if they had undergone at least two outpatient visits or one hospitalization for each specific condition. The average index year for the entire cohort was 2006. Since our data

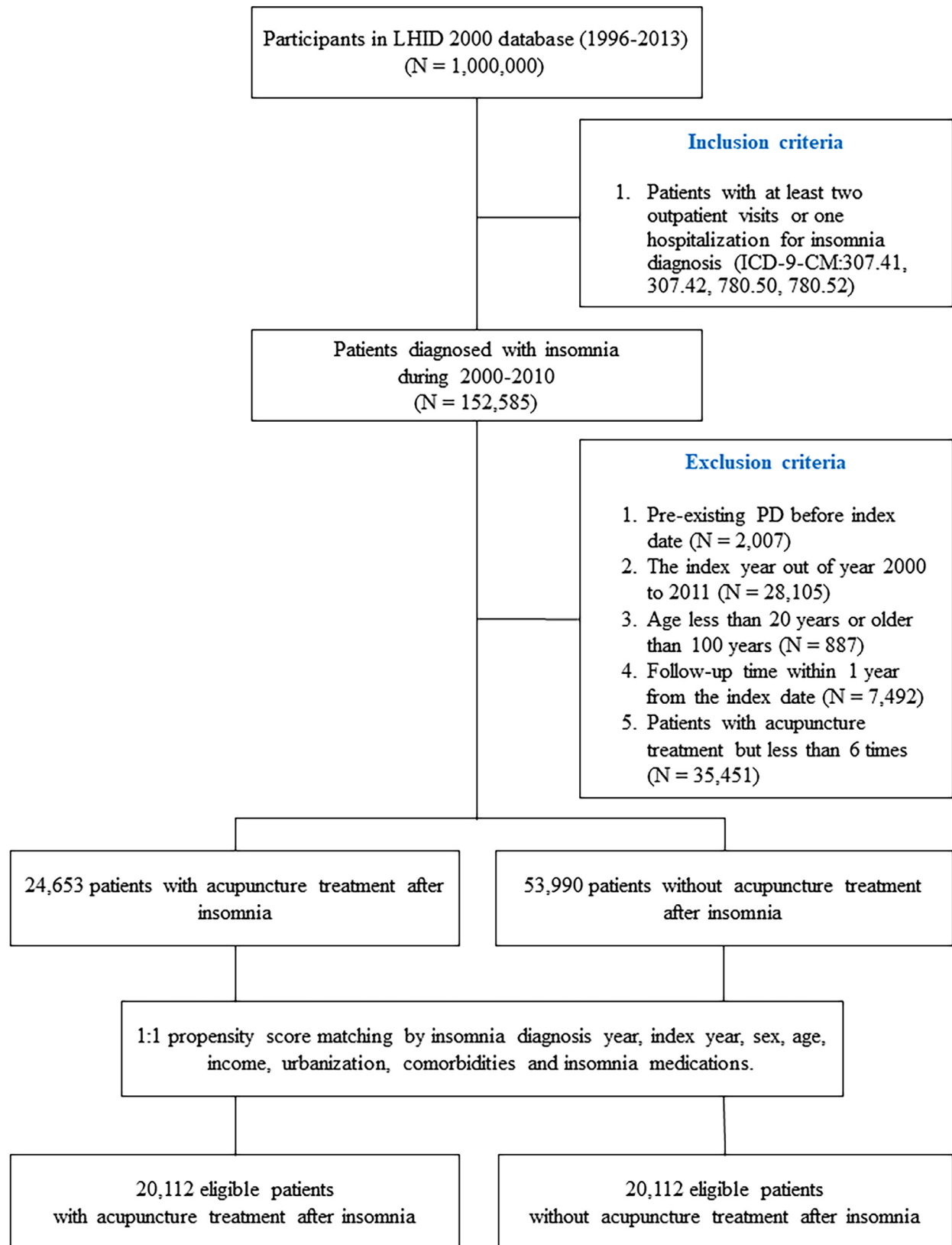


Fig. 1. Selection process for the study population. This flowchart illustrates the selection process for our study population. We initially identified 152,585 individuals newly diagnosed with insomnia between 2000 and 2010 from the Longitudinal Health Insurance Database 2000 (LHID 2000). After applying predefined exclusion criteria, we retained 24,653 individuals who had undergone acupuncture treatment and 53,990 individuals who had not. Using a 1:1 propensity score matching method based on insomnia diagnosis, index year, sex, age, income, urbanization, comorbidities, and insomnia medications, we created matched cohorts of 20,112 individuals each for both the acupuncture and non-acupuncture groups.

collection began in 2000, we had a sufficient follow-up period to thoroughly track and identify comorbidities, ensuring accurate and comprehensive data collection. These comorbidities included diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), coronary artery disease (ICD-9-CM codes 410–414), congestive heart failure with or without renal disease (ICD-9-CM codes 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, and 428.0), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 308.91), alcoholism (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3, and V11.3), tobacco use (ICD-9-CM code 305.1), obesity (ICD-9-CM codes 278 and A183), stroke (ICD-9-CM codes 430–438), and depression (ICD-9-CM codes 296.2, 296.3, 296.82, 300.4, 309.0, 309.1, 309.28, 311). Medication use was defined as the first prescription received after the diagnosis of insomnia and included nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, statins, benzodiazepines (BZDs), non-BZDs, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, heterocyclic antidepressants, and other antidepressant drugs.

2.4. Statistical analysis

We presented categorical variable distributions using both counts and percentages, while continuous variables were depicted by their mean and standard deviation. In our analysis, we employed the chi-square test and *t*-test to assess differences between the acupuncture-treated and non-acupuncture-treated cohorts for categorical and continuous variables, respectively. We measured the difference in each variable between the two cohorts by calculating the standardized mean difference (SMD). An SMD equal to or < 0.1 indicated a negligible difference between the two groups. To elucidate the relationship between acupuncture treatment and the risk of PD among patients with insomnia, we employed a Cox proportional hazard model. We reported hazard ratios (HR), adjusted hazard ratios (aHR), and their corresponding 95 % confidence intervals (CIs) as measures of PD risk. For graphical representation, we utilized the Kaplan-Meier method to create cumulative incidence curves for both the acupuncture-treated and non-acupuncture-treated groups. All statistical analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC), and the cumulative incidence curve was plotted using R software. The significance level was set at < 0.05 for two-sided *p*-value testing.

3. Results

3.1. No significant differences in demographic and clinical characteristics between the acupuncture-treated and non-treated cohorts

Following our inclusion criteria, we initially identified 152,585 patients in the LHID 2000 database who had received a new diagnosis of insomnia from 2000 to 2010. After a thorough exclusion process based on predefined criteria (as detailed in Fig. 1), we ended up with a total of 24,653 subjects who had undergone acupuncture treatment and 53,990 subjects who had not received acupuncture treatment. We then applied a 1:1 propensity score matching technique, aligning the two groups based on parameters including the diagnosis of insomnia, index year, gender, age, income, urbanization, comorbidities, and medication. Post-matching, both the acupuncture treatment and non-acupuncture groups each comprised 20,112 subjects (as shown in Table 1). Table 1 reveals that after propensity score matching, there were no significant differences between the two cohorts in terms of gender, age, insurance amount, urbanization levels, baseline comorbidities, and medication (SMD < 0.1). Among all subjects, approximately 66 % were female, and the mean age ranged from 50.9 to 50.6 years in the non-acupuncture and acupuncture cohorts, respectively (Table 1). The largest age group in the acupuncture cohort was under 50 years old (49.2 %). A majority of patients in the acupuncture cohort received manual acupuncture (78.3 %),

while 1.1 % received electroacupuncture, and 20.6 % received a combination of manual acupuncture and electroacupuncture (Table 1). On average, patients in the acupuncture cohort had around 20.3 acupuncture visits during the study period (Table 1).

3.2. A significantly lower cumulative incidence of PD among insomnia patients receiving acupuncture treatment compared to those without acupuncture treatment

The Kaplan-Meier plot (Fig. 2) demonstrated that insomnia patients who received acupuncture treatment had a significantly lower cumulative incidence of PD compared to those in the non-acupuncture treatment cohort ($p < 0.001$). Several stratified analyses were carried out to confirm the associations. The patients in the entire cohort were followed for an average of 6.93 years (mean \pm SD: 6.93 \pm 2.77).

Table 2 displays the relationships between potential risk factors and the occurrence of PD among patients with insomnia. Notably, insomnia patients who underwent acupuncture treatment exhibited a significantly lower risk of PD (aHR = 0.44, 95 % CI: 0.39–0.50). This reduced risk was also observed in patients with higher insurance amounts and those prescribed statins (aHR = 0.67, 95 % CI: 0.56–0.79) and tricyclic antidepressants (aHR = 0.73, 95 % CI: 0.61–0.87). Conversely, male patients (aHR = 1.18, 95 % CI: 1.03–1.35), those of increasing age, patients with diabetes (aHR = 1.30, 95 % CI: 1.13–1.49), anxiety (aHR = 1.25, 95 % CI: 1.10–1.43), alcoholism (aHR = 2.23, 95 % CI: 1.39–3.59), a history of stroke (aHR = 1.22, 95 % CI: 1.06–1.42), depression (aHR = 1.56, 95 % CI: 1.34–1.82), those prescribed with monoamine oxidase inhibitors (MAOIs) (aHR = 10.05, 95 % CI: 6.89–14.66), and selective serotonin reuptake inhibitors (SSRIs) (aHR = 1.44, 95 % CI: 1.22–1.70) demonstrated a higher risk of PD.

3.2.1. Acupuncture treatment is associated with a significantly reduced risk of PD across all stratified groups, except for patients with specific insurance amounts, alcoholism, and those prescribed tricyclic antidepressants

The data from Table 3 reveals significant findings in the stratified incidence rates of PD for insomnia patients who did and did not receive acupuncture. Among female patients, those who received acupuncture had a notably lower adjusted hazard ratio (aHR = 0.42, 95 % CI: 0.36–0.50) compared to those who did not (Table 3). Similarly, male patients who received acupuncture also exhibited a lower aHR (0.47, 95 % CI: 0.38–0.58) compared to their counterparts (Table 3). When examining age groups, the protective effect of acupuncture was observed across all categories, with an aHR of 0.32 (95 % CI: 0.25–0.42) for patients aged 50–65 and 0.48 (95 % CI: 0.41–0.56) for those aged 65 or older (Table 3). Additionally, patients with lower insurance amounts benefited more from acupuncture, as indicated by an aHR of 0.39 (95 % CI: 0.32–0.48) for the 0–15,840 New Taiwan dollars (NT\$) category (Table 3). In summary, acupuncture treatment was associated with a reduced risk of PD in all stratified groups ($p < 0.001$), except for patients with an insurance amount of NT\$28,801–45,800, those with alcoholism, and those prescribed tricyclic antidepressants.

3.3. Patients with insomnia receiving acupuncture show a reduced risk of PD regardless of the number of acupuncture sessions

Table 4 investigated the association between the number of acupuncture sessions and the risk of PD in patients with insomnia. Patients who received 6–11 acupuncture sessions had a significantly reduced risk of PD compared to those who did not receive acupuncture (aHR = 0.41, 95 % CI: 0.34–0.50). Similarly, patients who received 12–17 acupuncture sessions also exhibited a significantly reduced risk of PD (aHR = 0.39, 95 % CI: 0.30–0.51). Those who underwent 18–23 acupuncture sessions had a reduced risk as well (aHR = 0.46, 95 % CI: 0.33–0.64). Patients receiving 24 or more acupuncture sessions demonstrated a reduced risk of PD (aHR = 0.46, 95 % CI: 0.37–0.56). These findings indicate that

Table 1
Characteristics of newly diagnosed insomnia patients with and without acupuncture treatment.

Variable	Acupuncture treatment		SMD*
	No (N = 20,112) n (%) / Mean (SD)	Yes (N = 20,112) n (%) / Mean (SD)	
Gender			0.004
Women	13,267 (66.0)	13,307 (66.2)	
Men	6,845 (34.0)	6,805 (33.8)	
Age at baseline			0.095
<50	10,150 (50.5)	9,905 (49.2)	
50–65	5,440 (27.0)	6,228 (31.0)	
>65	4,522 (22.5)	3,979 (19.8)	
Mean (SD), years [†]	50.9 (16.6)	50.6 (15.1)	0.015
Insurance amount (NT\$)			0.045
0–15,840	8,360 (41.6)	8,313 (41.3)	
15,841–28,800	8,664 (43.1)	8,573 (42.6)	
28,801–45,800	2,182 (10.8)	2,428 (12.1)	
>45,800	906 (4.5)	798 (4.0)	
Urbanization [‡]			0.072
1 (highest)	6,416 (31.9)	6,492 (32.3)	
2	6,081 (30.2)	5,865 (29.2)	
3	3,140 (15.6)	3,621 (18.0)	
4 (lowest)	4,475 (22.3)	4,134 (20.6)	
Baseline comorbidity			
Diabetes mellitus	4,047 (20.1)	4,031 (20.0)	0.002
Hypertension	7,710 (38.3)	7,706 (38.3)	0.000
Hyperlipidemia	6,519 (32.4)	6,475 (32.2)	0.005
Coronary artery disease	4,907 (24.4)	4,876 (24.2)	0.004
Congestive heart failure	893 (4.4)	899 (4.5)	0.001
Anxiety	6,548 (32.6)	6,490 (32.3)	0.006
Alcoholism	287 (1.4)	263 (1.3)	0.010
Tobacco used	166 (0.8)	167 (0.8)	0.001
Obesity	276 (1.4)	295 (1.5)	0.008
Stroke	2,448 (6.1)	2,585 (6.4)	0.021
Depression	3,290 (16.4)	3,268 (16.2)	0.003
Medications [§]			
NSAID	80 (0.4)	83 (0.4)	0.002
Oral steroid	1,672 (8.3)	1,726 (8.6)	0.010
Statin	3,130 (15.6)	3,106 (15.4)	0.003
BZD	711 (3.5)	752 (3.7)	0.011
Non-BZD	3,452 (17.2)	3,448 (17.1)	0.001
MAOI	24 (0.1)	29 (0.1)	0.007
SSRI	2,296 (11.4)	2,251 (11.2)	0.007
Tricyclic antidepressants	2,694 (13.4)	2,662 (13.2)	0.005
Heterocyclic antidepressants	2,227 (11.1)	2,196 (10.9)	0.005
Other antidepressant drugs	1,263 (6.3)	1,263 (6.3)	0.000
Duration between insomnia date and index date, days	737	677	0.086
Types of acupuncture, n (%)			
Manual acupuncture of TCM type	–	15,752 (78.3)	
Electroacupuncture	–	224 (1.1)	
Combination of manual acupuncture and electroacupuncture	–	4136 (20.6)	
Acupuncture visits, times		20.3 (27.8)	

* A standardized mean difference (SMD) of ≤ 0.1 indicates a negligible difference between the two cohorts.

[†] *t*-test.

[‡] Urbanization was categorized into four levels according to the population density of the residential areas, with level 1 being the most urbanized and level 4 being the least urbanized.

[§] Medications included the following: nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, statins, benzodiazepines (BZD), non-BZD hypnotic drugs, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, heterocyclic antidepressants, and other antidepressants.

there was not a significant dose-dependent decrease of PD risk with increasing use of acupuncture treatment. Table 5 displays the distribution of acupuncture utilization among patients with insomnia categorized by disease diagnoses (ICD-9-CM codes). Musculoskeletal systems and connective tissue disorders (ICD-9-CM 710–739) and injury and poisoning (ICD-9-CM 800–999) had the highest acupuncture utilization, accounting for 83.3 % of acupuncture users among insomnia patients. Symptoms, signs, and ill-defined conditions (ICD-9-CM 780–799) were the second most prevalent category, with 21.5 % of acupuncture users falling into this group. Acupuncture usage was notable in patients with respiratory system disorders (ICD-9-CM 460–519) at 7.5 % and digestive system disorders (ICD-9-CM 520–579) at 8.5 %. On the contrary,

acupuncture utilization was less common in categories like infectious and parasitic diseases, neoplasms (both malignant and benign), and complications of pregnancy, childbirth, and the puerperium. In summary, musculoskeletal disorders dominated acupuncture use among insomnia patients, followed by symptoms and signs-related conditions. Acupuncture was less frequently employed for infectious, neoplastic, and pregnancy-related conditions in this cohort.

4. Discussion

Our study, based on an analysis of the LHID 2000 database, reveals that patients with insomnia who underwent acupuncture treatment had

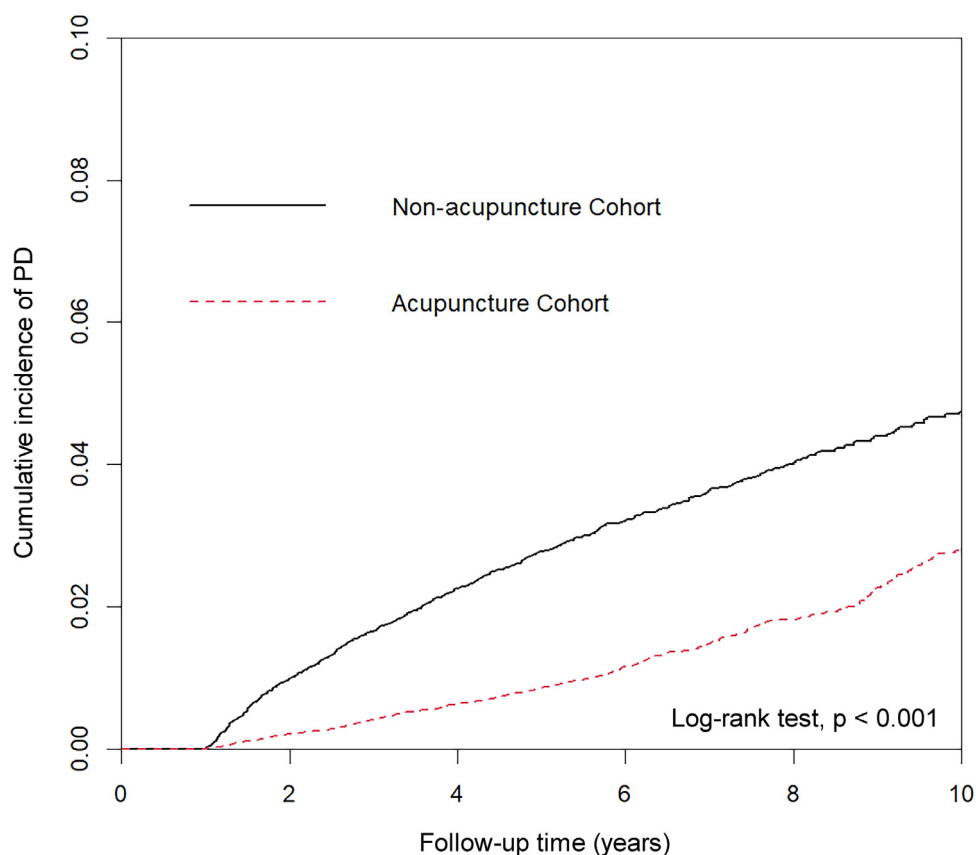


Fig. 2. Cumulative incidence of Parkinson's disease (PD) in insomnia patients: acupuncture vs. non-acupuncture cohorts. The cumulative incidence of PD in patients with insomnia was significantly lower in the acupuncture cohort compared to the non-acupuncture cohort ($p < 0.001$, assessed by the log-rank test).

a significantly reduced risk of PD. This reduced PD risk is also observed in patients with higher income levels, those taking statins, and those prescribed tricyclic antidepressants. On the other hand, male patients, older individuals, residents of less urban areas, diabetics, individuals with anxiety, alcoholism, a history of stroke, depression, and users of MAOIs or SSRIs face a higher risk of PD. Additionally, we find that the majority of insomnia patients sought acupuncture treatment for issues related to injury, poisoning, or musculoskeletal disorders. Importantly, the number of acupuncture sessions does not influence this risk reduction. In summary, our study provides evidence supporting the association between acupuncture and a lower risk of PD in insomnia patients, regardless of session frequency, while also highlighting the diverse health issues for which insomnia patients seek acupuncture as a treatment option.

Acupuncture is gaining recognition as a valuable therapeutic approach. Its effectiveness in treating insomnia has been substantiated by a comprehensive meta-analysis involving 46 clinical trials and 3811 patients.¹⁹ Insomnia is a highly prevalent sleep disorder affecting 40 % of adults, with 10 %–15 % experiencing chronic insomnia and an additional 25 %–35 % grappling with transient or occasional insomnia.²⁰ This underscores that insomnia is a significant health concern. Research has shown that poor sleep quality and insufficient sleep duration increase the risk of developing Parkinsonism and PD, especially within the two years following baseline measurements.²¹ Moreover, acupuncture not only effectively treats insomnia but also holds promise in managing neurodegenerative disorders like PD. Clinical trials have demonstrated that acupuncture can significantly improve motor symptoms in PD patients.^{22–24} Furthermore, our meta-analysis of 13 clinical trials indicates that acupuncture can enhance sleep quality in PD patients.²⁵ These studies collectively highlight that acupuncture's potential benefits extend beyond the management of insomnia. Given that PD is a

progressive neurodegenerative disorder with no cure, any intervention capable of reducing its risk factors is invaluable. Consequently, incorporating acupuncture into insomnia management not only promises to improve sleep but also to mitigate the risk of developing PD. Thus, the integrative medicine technique of acupuncture presents a multifaceted and non-invasive therapeutic strategy with far-reaching benefits for both sleep and neurological health.

The pathological hallmarks of PD include mitochondrial dysfunction, microglial activation, increased oxidative stress, dopaminergic neuronal death, impaired protein clearance, accumulation of α -synuclein and Lewy bodies, dopamine deficiency in the striatum, and neuroinflammation.²⁶ Studies have reported that acupuncture regulates various molecular mechanisms to reduce the pathological hallmarks of PD. Tamtaji et al. (2019) reported that acupuncture treatments decreased levels of inflammatory cytokines and oxidative markers in PD patients.¹⁸ In addition, neuroinflammation and gut-brain axis play crucial roles in PD pathogenesis. Jang et al. (2020) demonstrated that acupuncture inhibited neuroinflammation and corrected gut microbial dysbiosis in a mouse model of PD.²⁷ They also found that acupuncture improved motor functions, reduced anxiety, increased dopaminergic neurons and fibers, and decreased microglia and astrocyte overexpression, suggesting that acupuncture reduces neuroinflammation and neuronal apoptosis in PD mice.²⁷ Proper regulation/balance of neurotransmitters is crucial for maintaining sleep quality and preventing neurodegenerative diseases. Li et al. (2023) reviewed the role of neurotransmitters in insomnia treatment with acupuncture.²⁸ They found acupuncture regulated neurotransmitters such as serotonin, norepinephrine, dopamine, γ -aminobutyric acid, acetylcholine, and orexin, thereby improving sleep architecture.²⁸ They also suggested that acupuncture's effect on increasing deep sleep and rapid-eye-movement sleep supported brain detoxification processes and neuronal repair, potentially offering neuroprotec-

Table 2

Cox model with hazard ratios and 95 % confidence intervals of PD associated with accepted acupuncture and covariates among insomnia patients.

Variable	No. of events (N = 989)	Crude		Adjusted	
		HR* (95 % CI)	p value	HR† (95 % CI)	p value
Received acupuncture					
No	650	Ref.		Ref.	
Yes	339	0.46 (0.40–0.52)	< 0.0001	0.44 (0.39–0.50)	< 0.0001
Gender					
Women	623	Ref.		Ref.	
Men	366	1.16 (1.02–1.32)	0.0220	1.18 (1.03–1.35)	0.0147
Age group					
< 50	103	Ref.		Ref.	
50–65	248	4.17 (3.31–5.25)	< 0.0001	4.08 (3.19–5.22)	< 0.0001
> 65	638	16.27 (13.21–20.03)	< 0.0001	11.73 (9.19–14.97)	< 0.0001
Insurance amount (NT\$)					
0–15,840	447	Ref.		Ref.	
15,841–28,800	469	0.96 (0.84–1.09)	0.5050	0.89 (0.77–1.02)	0.0916
28,801–45,800	54	0.41 (0.31–0.55)	< 0.0001	0.57 (0.42–0.76)	0.0001
> 45,800	19	0.40 (0.26–0.64)	0.0001	0.53 (0.33–0.84)	0.0070
Urbanization					
1 (highest)	283	Ref.		Ref.	
2	287	1.07 (0.91–1.26)	0.4198	1.05 (0.89–1.24)	0.5312
3	151	0.96 (0.79–1.17)	0.6906	1.04 (0.85–1.26)	0.7306
4 (lowest)	268	1.33 (1.12–1.57)	0.0010	1.13 (0.94–1.34)	0.1936
Baseline Comorbidity (ref = nonsite comorbidity)					
Diabetes mellitus	385	2.67 (2.35–3.04)	< 0.0001	1.3 (1.13–1.49)	0.0003
Hypertension	714	4.29 (3.73–4.93)	< 0.0001	1.24 (1.04–1.47)	0.0140
Hyperlipidemia	495	2.25 (1.99–2.55)	< 0.0001	1.05 (0.91–1.20)	0.5125
Coronary artery disease	508	3.40 (3.01–3.86)	< 0.0001	1.09 (0.94–1.26)	0.2688
Congestive heart failure	115	3.32 (2.73–4.03)	< 0.0001	1.06 (0.87–1.30)	0.5601
Anxiety	431	1.68 (1.48–1.90)	< 0.0001	1.25 (1.1–1.43)	0.0009
Alcoholism	18	1.53 (0.96–2.44)	0.0740	2.23 (1.39–3.59)	0.0009
Tobacco used	5	0.78 (0.32–1.87)	0.5690	1.04 (0.43–2.51)	0.9337
Obesity	10	0.80 (0.43–1.50)	0.4910	0.99 (0.53–1.85)	0.9782
Stroke	322	3.74 (3.27–4.27)	< 0.0001	1.22 (1.06–1.42)	0.0073
Depression	248	1.80 (1.56–2.08)	< 0.0001	1.56 (1.34–1.82)	< 0.0001
Medications [‡]					
NSAID	3	0.55 (0.18–1.72)	0.3080	1.02 (0.33–3.17)	0.9783
Oral steroid	69	0.66 (0.51–0.84)	0.0010	0.73 (0.57–0.93)	0.0122
Statin	167	0.91 (0.77–1.08)	0.2820	0.67 (0.56–0.79)	< 0.0001
BZD	14	0.35 (0.21–0.60)	0.0000	0.87 (0.51–1.47)	0.5951
Non-BZD	203	0.98 (0.84–1.15)	0.8100	0.95 (0.81–1.11)	0.4845
MAOI	29	27.22 (18.81–39.38)	< 0.0001	10.05 (6.89–14.66)	< 0.0001
SSRI	193	1.65 (1.41–1.93)	< 0.0001	1.44 (1.22–1.70)	< 0.0001
Tricyclic antidepressants	153	1.02 (0.86–1.21)	0.8350	0.73 (0.61–0.87)	0.0003
Heterocyclic antidepressants	145	1.17 (0.98–1.40)	0.0761	0.97 (0.81–1.16)	0.7136
Other antidepressant drugs	97	1.42 (1.15–1.75)	0.0011	1.21 (0.97–1.51)	0.0983

Crude HR* represents relative hazard ratio.

Adjusted HR† represents the adjusted hazard ratio, which is mutually adjusted for accepted acupuncture, age, sex, insurance amount, urbanization level, all comorbidities, and medication usage using Cox proportional hazard regression.

[‡]Medications included the following: nonsteroidal anti-inflammatory drugs (NSAIDs), oral steroids, statins, benzodiazepines (BZD), non-BZD hypnotic drugs, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, heterocyclic antidepressants, and other antidepressants.

tion against PD.²⁸ In addition, enhancing sleep quality through acupuncture could mitigate chronic stress and inflammatory responses, known contributors to PD pathogenesis. Chen et al. (2023) found that acupuncture modulated functional connectivity between brain regions implicated in sleep regulation, such as the locus coeruleus and the supra-marginal gyrus.¹² Their data suggests that improved sleep quality and reduced hyperarousal states from acupuncture might lower the risk of neurodegenerative processes associated with PD.¹² These findings suggest the possible molecular mechanisms of acupuncture for preventing PD in insomnia patients might be via inhibiting neuroinflammation, regulating gut microbiota, modulating/balancing neurotransmitter levels, and enhancing sleep quality, thus contributing to acupuncture-reduced PD risk in insomnia patients observed in our cohort. However, further research is needed to confirm our hypothesis.

Our team had previously published related studies, including "Acupuncture is associated with reduced dementia risk in patients with insomnia: A propensity-score-matched cohort study of real-world data" and "Acupuncture treatment reduces incidence of Parkinson's disease in

patients with depression: A population-based retrospective cohort study in Taiwan".^{29,30} The research progress and experience from these studies provided a foundation and led us to conduct the present study on the impact of acupuncture on PD incidence in insomnia patients. Insomnia patients suffer from chronic sleep disturbances, leading to fatigue, irritability, and cognitive impairment, whereas depression patients experience persistent sadness, hopelessness, and physical symptoms like fatigue and changes in appetite. The physiological mechanisms underlying these conditions differ significantly: insomnia involves hyperarousal of the central nervous system and circadian rhythm dysregulation, while depression involves neurotransmitter imbalances, hormonal changes, and inflammation. These distinct mechanisms result in different pathways leading to PD, with insomnia potentially increasing PD risk through chronic sleep deprivation, oxidative stress, and inflammation, and depression-related PD risk linked to chronic stress and neuroinflammation affecting dopamine pathways. These differences made it essential to conduct an independent study on the benefits of acupuncture for preventing PD in insomnia patients. Additionally, acupuncture pro-

Table 3

Incidence rates, hazard ratio and confidence intervals of PD for insomnia patients who accepted and non-accepted acupuncture in the stratification of sex, age, comorbidities and drug used.

Variables	Received acupuncture			Compared with non-acupuncture users			Crude HR (95 % CI)	Adjusted HR [†] (95 % CI)
	No (N = 20,112)			Yes (N = 20,112)				
	Event	Person years	IR	Event	Person years	IR		
Gender								
Women	423	84,229	5.02	200	94,069	2.13	0.42 (0.35–0.50)***	0.42 (0.36–0.50)***
Men	227	42,121	5.39	139	48,041	2.89	0.53 (0.43–0.65)***	0.47 (0.38–0.58)***
Age group								
< 50	73	66,477	1.10	30	70,326	0.43	0.39 (0.25–0.60)***	0.36 (0.24–0.56)***
50–65	170	34,693	4.90	78	44,368	1.76	0.35 (0.27–0.46)***	0.32 (0.25–0.42)***
> 65	407	25,180	16.16	231	27,417	8.43	0.51 (0.43–0.60)***	0.48 (0.41–0.56)***
Insurance amount (NT\$)								
0–15,840	300	50,630	5.93	147	57,259	2.57	0.43 (0.35–0.52)***	0.39 (0.32–0.48)***
15,841–28,800	308	55,624	5.54	161	62,055	2.59	0.46 (0.38–0.56)***	0.48 (0.39–0.58)***
28,801–45,800	28	14,282	1.96	26	17,275	1.51	0.76 (0.44–1.29)	0.62 (0.36–1.07)
> 45,800	14	5812	2.41	5	5521	0.91	0.38 (0.14–1.05)	0.29 (0.10–0.84)*
Urbanization								
1 (highest)	192	39,433	4.87	91	44,257	2.06	0.42 (0.33–0.54)***	0.37 (0.29–0.48)***
2	186	38,164	4.87	101	40,952	2.47	0.50 (0.39–0.64)***	0.48 (0.38–0.61)***
3	96	20,049	4.79	55	26,166	2.10	0.44 (0.31–0.61)***	0.44 (0.31–0.61)***
4 (lowest)	176	28,704	6.13	92	30,735	2.99	0.48 (0.38–0.62)***	0.46 (0.36–0.60)***
Baseline Comorbidity (ref = nonsite comorbidity)								
Diabetes mellitus	251	23,742	10.57	134	28,146	4.76	0.44 (0.36–0.54)***	0.43 (0.35–0.53)***
Hypertension	459	16,729	27.44	255	54,681	4.66	0.47 (0.40–0.55)***	0.47 (0.40–0.55)***
Hyperlipidemia	316	39,094	8.08	179	44,047	4.06	0.50 (0.41–0.60)***	0.47 (0.39–0.56)***
Coronary artery disease	323	29,240	11.05	185	34,497	5.36	0.48 (0.40–0.57)***	0.48 (0.40–0.58)***
Congestive heart failure	71	4519	15.71	44	5871	7.49	0.47 (0.32–0.69)***	0.48 (0.33–0.70)**
Anxiety	280	40,336	6.94	151	44,493	3.39	0.48 (0.40–0.59)***	0.44 (0.36–0.53)***
Alcoholism	11	1509	7.29	7	1747	4.01	0.54 (0.21–1.40)	0.52 (0.19–1.41)
Tobacco used	4	844	4.74	1	948	1.05	0.23 (0.03–2.03)	–
Obesity	8	1533	5.22	2	1876	1.07	0.20 (0.04–0.94)*	–
Stroke	198	13,585	14.58	124	17,397	7.13	0.48 (0.39–0.61)***	0.49 (0.39–0.61)***
Depression	167	19,777	8.44	81	22,457	3.61	0.42 (0.32–0.55)***	0.37 (0.28–0.48)***
Medications								
NSAID	3	653	4.59	0	773	0.00	–	–
Oral steroid	49	12,772	3.84	20	14,316	1.40	0.36 (0.22–0.61)**	0.35 (0.20–0.59)***
Statin	111	23,345	4.75	56	24,906	2.25	0.46 (0.34–0.64)***	0.45 (0.32–0.62)***
BZD	10	4769	2.10	4	5714	0.70	0.32 (0.10–1.02)	0.17 (0.04–0.74)*
Non-BZD	146	26,322	5.55	57	28,709	1.99	0.35 (0.26–0.48)***	0.36 (0.27–0.50)***
MAOI	18	108	166.70	11	196	56.10	0.33 (0.16–0.70)**	0.11 (0.03–0.43)*
SSRI	116	16,439	7.06	77	17,667	4.36	0.60 (0.45–0.80)**	0.54 (0.40–0.73)***
Tricyclics	81	19,479	4.16	72	20,987	3.43	0.81 (0.59–1.11)	0.78 (0.57–1.08)
Heterocyclic	89	16,317	5.45	56	17,582	3.19	0.57 (0.41–0.80)**	0.52 (0.37–0.72)**
Other antidepressant drugs	61	9007	6.77	36	9949	3.62	0.52 (0.34–0.78)**	0.43 (0.28–0.66)**

Abbreviations: IR, incidence rates, per 1000 person-years; HR, hazard ratio; CI, confidence interval.

Adjusted HR[†] represents the adjusted hazard ratio, which is mutually adjusted for accepted acupuncture, age, sex, insurance amount, urbanization level, all comorbidities, and medication usage using Cox proportional hazard regression.

p* < 0.05; *p* < 0.01; ****p* < 0.001.

Table 4

Risk of PD and number of acupuncture in insomnia patients.

Number of acupuncture	N	Event	Crude HR	<i>p</i> value	Adjusted HR*	<i>p</i> value
0	20,112	650	ref.		ref.	
6–11	9742	133	0.40 (0.33–0.48)	< 0.0001	0.41 (0.34–0.50)	< 0.0001
12–17	3937	58	0.41 (0.31–0.53)	< 0.0001	0.39 (0.30–0.51)	< 0.0001
18–23	2021	39	0.49 (0.36–0.68)	< 0.0001	0.46 (0.33–0.64)	< 0.0001
≥ 24	4412	109	0.59 (0.48–0.72)	< 0.0001	0.46 (0.37–0.56)	< 0.0001

Adjusted HR* represented adjusted hazard ratio: mutually adjusted for accepted acupuncture, age, gender, income, area, urban, diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, head injury, depression, stroke, chronic kidney disease, and drug use in Cox proportional hazard regression.

tools effective for depression might not apply to insomnia, necessitating specific investigation into its effects on insomnia-related PD risk. Furthermore, insomnia patients might respond differently to acupuncture treatments, and studying these responses could help optimize treatment strategies. We believe that independent research can provide comprehensive evidence and support integrative medicine practices by developing tailored treatments for different patient populations. Conducting the

present study generated targeted evidence, improved patient outcomes, and expanded the therapeutic applications of acupuncture in integrative medicine.

In this study, we did not limit acupuncture sessions to specific diagnostic indications; instead, we included all acupuncture treatments received by insomnia patients. This approach had two main advantages. First, it allowed for comprehensive data collection, capturing a more

Table 5
The distribution of acupuncture cohort by disease categories /diagnosis in patients with insomnia.

Disease (ICD-9-CM)	Acupuncture users	
	N	%
Infectious and parasitic disease (001–139)	81	0.4
Neoplasms (140–239)	113	0.6
Malignant(140–208)	80	0.4
Benign (210–229)	32	0.2
Endocrine, nutritional and metabolic disease and immunity disorder (240–279)	270	1.3
Blood and blood-forming organs (280–289)	37	0.2
Mental disorder (290–319)	373	1.9
Nervous system (320–389)	2311	11.5
Circulatory system (390–459)	1004	5.0
Respiratory system (460–519)	1500	7.5
Digestive system (520–579)	1705	8.5
Genitourinary system (580–629)	662	3.3
Complications of pregnancy, childbirth and the puerperium (630–676)	10	0.0
Skin and subcutaneous tissue (680–709)	303	1.5
Musculoskeletal system and connective tissue (710–739)	16,757	83.3
Congenital anomalies (740–759)	150	0.7
Certain conditions originating in the perinatal period (760–779)	1	0.0
Symptoms, signs and ill-defined conditions (780–799)	4329	21.5
Injury and poisoning (800–999)	16,758	83.3

complete and holistic picture of patients' acupuncture usage. This enabled a thorough analysis of the overall effect of acupuncture on insomnia and its potential role in preventing PD. Second, it enhanced the generalizability of the findings. Including all acupuncture sessions, regardless of specific diagnostic indications, made the results more applicable to real-world clinical settings where patients often receive acupuncture for multiple health issues simultaneously. This broadened the relevance of the study results to a wider patient population. We also excluded patients who received fewer than six acupuncture sessions, ensuring that all participants in the acupuncture group received more than six treatments. Ensuring a minimum number of treatment sessions helped maintain the study's internal validity, as patients who received insufficient treatment might not have experienced the potential benefits, leading to an underestimation of the treatment effect. By setting this threshold, we more accurately captured the true impact of acupuncture.

The present study has several study limitations that need consideration. First, the data file we used was provided by the Taiwan National Health Research Institutes (NHRI), which had been authorized by the Ministry of Health and Welfare to manage the claims data of the national health insurance. The latest updated database by NHRI is not available now. Second, it relies on data from the LHID 2000 database, which may not capture all relevant variables or account for unrecorded confounding factors that could influence the results. Additionally, the database only contained data from 2000 to 2013, limiting the follow-up years and the opportunity to include new treatment methods. Third, despite propensity score matching, there may still be residual confounding factors that were not adequately addressed, potentially affecting the validity of the findings. Fourth, the study primarily focused on the Taiwanese population, limiting the generalizability of the results to other demographic groups. Fifth, the present study defined comorbidities and medications based on the earliest available data rather than a specific period before the diagnosis of insomnia. While this approach aimed to include a comprehensive history of relevant medical conditions, it may only partially capture the patient's health status immediately preceding the diagnosis. This limitation could introduce variability in the temporal relationship between comorbidities, acupuncture, and PD risk. Future studies should use a more defined time frame for assessing comorbidities to understand these relationships better. These study limitations leave room for further exploration in future research.

In summary, our study reveals that acupuncture treatment can lower the risk of PD in people with insomnia. It suggests that incorporating acupuncture into public health programs aimed at managing insomnia could also help reduce the risk of PD in those at risk. However, we still

need to explore how exactly acupuncture achieves this effect in individuals with insomnia.

Author contributions

Cheng-Hao Huang: Conception and design of study, Analysis and interpretation of data, Writing - review & editing; Shun-Ku Lin: Conception and design of study, Investigation, Writing - review & editing; Mei-Chen Lin: Conception and design of study, Writing - original draft; Shih-Ya Hung: Conception and design of study, Acquisition of data, Funding acquisition, Writing - review & editing.

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Ethics statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. The Research Ethics Committee of China Medical University Hospital in Taiwan approved the study (CMUH104-REC2-115-CR8).

Data availability

Data used in this study are available from the National Health Insurance Research Database (NHIRD), published by the Taiwan National Health Insurance (NHI) Bureau, and are restricted exclusively to research purposes. Adhering to the legal constraints mandated by the Taiwanese government under the Personal Information Protection Act, those seeking access to this data may submit a formal proposal through the following link: <http://nhird.nhri.org.tw>.

Declaration of competing interest

The authors confirm that they conducted the research without commercial or financial associations that might be interpreted as potential conflicts of interest.

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