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Risk of Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders: A Nationwide Population-Based Cohort Study

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Abstract

Objective: The association between depression and benign peripheral persistent vertigo (BPPV) remains debated. This study aimed to investigate the risk of BPPV in patients with depressive disorders.

Design: Longitudinal nationwide cohort study

Setting: National health insurance research database in Taiwan

Participants: We enrolled 10,297 patients diagnosed with depressive disorders between 2000 and 2009 and compared them to 41,188 selected control patients who had never been diagnosed with depressive disorders (at a 1:4 ratio matched by age, gender and index year) in relation to the risk of developing BPPV.

Methods: The follow-up period was defined as the time from the initial diagnosis of depressive disorders to the date of BPPV, censoring, or 31 December 2009. Cox proportional hazards regression analysis was used to investigate the risk of BPPV by sex, age and comorbidities, with hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During the 9-year follow-up period, 44 (0.59 per 1,000 person-years) patients with depressive disorders and 99 (0.33 per 1,000 person-years) control patients were diagnosed with BPPV. The incidence risk ratio of BPPV among both cohorts calculating from events of BPPV per 1,000 person-years of observation time was 1.79 (95% CI, 1.23–2.58,p= .002). Following adjustments for age, sex, comorbidities, urbanization, and socioeconomic status, patients with depressive disorders were 1.57 times more likely to develop BPPV (95% CI, 1.09–2.26, p= .014) as compared to control patients. In addition, hyperthyroidism (HR = 3.55, 95% CI,1.58–7.98, p= .002) was an independent risk factor for the development of new-onset BPPV in patients with depressive disorders.

Conclusions: Patients with depressive disorders may have an increased risk of developing BPPV, especially those who have hyperthyroidism.

Keywords: depressive disorders; benign peripheral persistent vertigo; hyperthyroidism; risk factor; cohort study

Strengths and limitations of this study

1. The association between depression and benign peripheral persistent vertigo (BPPV) remains debated. This longitudinal population-based data was conducted to assess the risk of BPPV in patients with depressive disorders.
2. The NHIRD lacks detailed clinical data regarding severity and outcomes of BPPV
3. Results from our study may underestimate the current condition since only patients seeking medical service would be identified in the Registry of NHIRD.

Introduction

Depressive disorders are common mood disorders occurring in all populations and the Global Burden of Disease 2017 had refereed depressive disorders as a leading cause of health burden across the globe.[1] Patients with depressive disorders have been reported with an increased risk of mortality and propose the classification of depressive disorders as life-threatening.[2 3] Furthermore, people with depressive disorders have been reported with many somatic symptoms and result in increased need for clinical services, associated economic costs,[4 5] and considerable loss in quality of life.[6]

Benign paroxysmal positional vertigo (BPPV) have been reported with a lifetime prevalence of 2.4%, is the most common type of peripheral vertigo. Which is characterized by brief spinning sensations, usually induced by a sudden change in head position with respect to gravity, with attacks generally lasting less than 1 minute.[7] The fundamental pathophysiology of BPPV is dislodged calcium carbonate crystals in the utricle of the inner ear entering the semicircular canals.[8] Old age [7] and several co-morbidities, such as hypertension, diabetes mellitus, hypercholesterolemia, cerebrovascular ischemia, and cervical spondylosis result in the degeneration of the posterior labyrinth and otoconia detachment, have been regarded as risk factors of BPPV.

Psychiatric disorders or emotional stress are frequently observed in patients suffering from vertigo.[9 10] The results of most studies have been reported the higher rate of coexistence of depression and vestibular disorders[11-13] will lead to a vicious circle and a serious influence on the quality of life[14] and peripheral vertigo may play an essential role in the pathophysiology of development of subsequent depressive disorder, most of these studies report contradictory or conflicting results. Furthermore, when specified to explore the association between depression and BPPV, only a relatively small-scaled case-control study

indicates that life stressors and related depressive disorder may be seen as a trigger of vestibular dysfunction, that is, a potential precursor of BPPV.[15]

Therefore, considering the debates on the association between the depression and BPPV and no large-scaled study have tried to investigate the issue, we designed a nationwide retrospective cohort study to explore the association between depressive disorder and the subsequent BPPV. In addition, independent risk factors for developing BPPV among patients with depressive disorders were also investigated.

Materials and Methods

Data Sources

Nearly 99% of Taiwan's population utilizes health care services as a consequence of the National Health Insurance (NHI) Program Bold Legislative Act enacted in 1995.[16] The program offers comprehensive medical care coverage regarding outpatient, inpatient, emergency visits, and Chinese medicine to all residents of Taiwan. The NHI research database (NHIRD) contains comprehensive information with regard to clinical practice, including prescription details and diagnostic codes in the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) format. The NHIRD is managed by the National Health Research Institutes (NHRI) and privacy is maintained according to directives from the Bureau of the NHI.[17] The data source for our study was obtained from the Longitudinal Health Insurance Database 2005 (LHID2005), a dataset of the NHIRD. LHID2005 contains the data of 1,000,000 beneficiaries which were sampled from January 1, 2005 to January 1, 2006, that is, collected from those who were available in the Registry of the NHIRD in 2005. In addition, it is worth emphasizing that although the dataset was collected from those available in 2005, the LHID20005 included all original claim data of 1,000,000 individuals from January 1, 1996 to December 31, 2009. Moreover, the NHRI

affirms that there are no statistical differences in the distributions of age, sex, or health care costs between the data in the LHID2005 and that of the NHIRD.[17]

Availability of Data and Materials section

The NHIRD is addressed in publicity by the NHRI and the use of NHIRD is only for research purposes. All applicants must obey the Computer-Processed Personal Data Protection Law[18] and relevant regulations of Bureau of National Health Insurance and NHRI. Moreover, applicants and their supervisor were asking for signing agreements upon application submission. All applications are reviewed for approval of data delivered. Request for the dataset may be sent an e-mail to the NHRI at nhird@nhri.org.tw or call at +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30 (UTC+8).

Study design and subjects

We utilized data from the LHID 2005 and conducted a retrospective cohort study using a dataset collected between January 1, 2000 and December 31, 2004. We enrolled patients ≥ 20 years who were diagnosed with depressive disorders by a psychiatrist according to the ICD-9-CM depressive disorders diagnosis codes: 296.2X-296.3X, 300.4, and 311.X. We defined the date of enrolling an adult patient with depressive disorders as case cohort between 2000 and 2004 as enrolment date. For each patient with depressive disorders included in the final cohort, 4 age- and sex-matched control patients without depressive disorders were randomly selected on the same enrolment date from the LHID 2005. We excluded patients who were previously diagnosed with BPPV (ICD-9-CM code 386.11) before the enrollment date. For each patient with depressive disorders included in the final cohort, 4 age- and sex-matched control patients without depressive disorders were randomly selected from the LHID 2005. The primary clinical outcome assessed was only BPPV diagnosed by neurologists or otorhinolaryngologists. We excluded those who diagnosed

with acoustic neuroma (ICD-9-CM code 225.1), Meniere's disease (ICD-9-CM code 386.0X), vestibular neuritis (ICD-9-CM code 386.12), labyrinthitis (ICD-9-CM code 386.3X), sudden hearing loss (ICD-9-CM code 388.2), and head injury (ICD-9-CM code 310.2, 800.X, 804.X, 850.X–854.×, 870.X–873.X, 907.0, 907.1, 959 .0X, and V15.52) during the follow-up period. The cohort including patients with and without depressive disorders was observed until the development of BPPV, death, withdrawal from the NHI system, or December 31, 2009.

Ethics Statement

This study was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital (No.: VGHKS14-CT7-07). We could not obtain written consent from study patients as the NHI dataset consists of de-identified secondary data for research purposes. The IRB of Kaohsiung Veterans General Hospital issued a formal written waiver for the need for consent.

Statistical analyses

The incidence of newly diagnosed BPPV in patients with depressive disorders and controls during the observational period was calculated and stratified by sex and age (≥ 65 years or < 65 years). Comparisons between continuous variables were conducted with the independent *t*-test. Chi-squared analysis was used to examine the association of two categorical characteristics between the depressive disorders and control cohort. A Cox proportional hazards model was used to evaluate confounding variables and whether depressive disorders increase the risk of developing BPPV. The confounding variables were age, sex, and common comorbidities including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, congestive heart failure, hyperthyroidism, hypothyroidism,

cerebrovascular disease, and malignancy; urbanization; and monthly income (table 3). Another Cox proportional-hazards regression model was performed again to identify variables that predicted BPPV in the patients with depressive disorders (table 4). The cumulative incidences of BPPV were compared between depressive disorder and control cohorts using Kaplan–Meier curves and stratified log rank test was applied to determine the differences in the risk for BPPV in the cohort.

Results

Participant Selection

We analyzed 10,297 patients with depressive disorders and 41,188 control patients. The majority of patients in the cohort were female (61%). The median age was 39 years (interquartile range [IQR], 30–51 years), and the median follow-up period was 7.19 years (IQR = 5.96–8.48 years) for patients with depressive disorders and 7.22 years (IQR = 6.00–8.51 years) for control patients (p=0 .002). Table 1 includes comparisons of demographic, clinical variables, and socioeconomic data between the control and depressive cohorts. In the depressive disorders group, the most common comorbidities were hypertension (2,124 patients, 20.6%), diabetes mellitus (1,236 patients, 12.0%), and dyslipidemia (1,541patients, 14.5%). As compared to the controls, depressive disorders patients had significantly more physical comorbidities. Besides, depressive disorders patients had a significantly higher prevalence in low-income populations (50.4% vs. 44.4%, p<0.001) and in urban areas (64.1% vs. 60.9%, p< 0.001) as compared to non-depressive disorders patients

Incidence Rate of BPPV

During the follow-up period, 44 patients (0.59 per 1,000 person-years) were diagnosed with BPPV in the depressive disorders group, and 99 patients (0.33 per 1,000 person-years) were diagnosed with BPPV in the control group. The incidence risk ratio (IRR) of BPPV between depressive disorders and control patients was 1.79 (95% CI [confidence interval],

1.23–2.58, p=0.002). When stratified by sex and age, the IRR of BPPV remained higher in the depressive disorders than in the control patients. The results are shown in Table 2.

Risks of Newly Diagnosed BPPV among the Patients with and without Depressive Disorders

After adjusting for age, sex, comorbidities, urbanization, and monthly income, there was a higher risk of developing BPPV in patients with depressive disorders than in the control patients (HR = 1.57, 95% CI, 1.09–2.26, p=0.014). Results are summarized in Table 3 and Figure 1.

Risks Factors for BPPV in patients with Depressive Disorders

As shown in Table 4, we predicted the development of BPPV in the depressive disorder cohorts by applying univariate analysis. Univariate logistic regression demonstrated that dyslipidemia (HR = 1.97, 95% CI, 0.99–3.89, p=0.053), hyperthyroidism (HR = 3.74, 95% CI, 1.67–8.38, p<0.001), and cerebrovascular disease (HR =2.31, 95% CI, 0.91–5.85, p=0.079) were possible prognostic factors. Multivariate analysis indicated that only hyperthyroidism (HR =3.55, 95% CI, 1.58–7.98, p=0.002) was an independent risk factor for patients with depressive disorders. All tables were placed at the end of the document text file.

Discussion

The two major findings in our study are as the following. First, patients with depressive disorders presented a 1.57 -fold greater risk of subsequently developing BPPV than did the general population by utilizing a nationwide population-based cohort study. Secondly, only hyperthyroidism (HR =3.55, 95% CI, 1.58–7.98, p=0.002) was an independent risk factor to develop BPPV among patients with depressive disorders.

The strength of this study is using a nationwide population-based data to evaluate BPPV risk in patients with depressive disorders. Advantages of using our NHIRD in medical research have been previously described,[19] which include enormous sample size,

lack of selection and participation bias and long-term comprehensive follow up. Whereas the results of most studies demonstrated the correlation between BPPV and following depressive disorders,[20 21] to the best of our knowledge, this is the first study implying that patients with depressive disorders have higher risk of developing BPPV.

Though depressive disorder have been reported to produce somatic symptoms including symptoms like BPPV,[22] one research indicated that patients with unrecognized BPPV were more likely to have depressive disorder.[23] Another study pointed out that depressive disorders may be an early presentation of neural circuitry alterations involving connections between the vestibular system and anatomical area such as hippocampus, amygdala, and infralimbic cortex.[24] One Asian literature showed that depression symptoms may adversely affect BPPV recurrence.[25] Though there was no strong evidence consistent with our findings, evidence mentioned above may indirectly prove our hypothesis.

The pathophysiology of depressive disorders and subsequent BPPV is unknown. There are several proposed mechanisms to explain this association. First, dysregulation of oxidative and inflammatory processes in depressive disorders may result in subsequent BPPV development. Numerous studies have demonstrated patients with depressive disorders have excessive oxidative stress and elevation in inflammatory responses.[26-29] Evidence supports a role for oxidative stress in otolith dysfunction leading to an increased risk of developing canalolithiasis, an essential step in the pathogenesis of BPPV.[30-33] Additional studies conclude depressive disorders associated with oxidative stress result in vestibular hair cells and neuronal damage in the inner ear,[34] which contributes to vestibular dysfunction and subsequent BPPV development.[35 36] Second, depressive disorders may induce abnormalities of the hypothalamus-pituitary-adrenal axis, which may hinder the inner ear blood flow and influence inner ear fluid balance. These abnormalities lead to dysfunction of the otoconial homeostasis,[15 37] an established risk factor for development of

BPPV.[38] Therefore, alterations to the neuroendocrine system may be the link between depressive disorders and the development of BPPV. Third, BPPV development in depressive disorders may be induced by serotonin dysfunction. The vestibular nucleus complex is composed of a large number of serotonin receptors, and lack of serotonin may result in a substantial impact on the electrophysiological activity of neurons, and dysfunction of the vestibular nucleus complex.[39] Previous studies have hypothesized a role for vestibular nucleus damage in the pathogenesis of BPPV development.[36 40] Finally, the dysregulation of the immune system, frequently observed in depressive disorders,[41 42] has proved to be an essential part of BPPV pathogenesis. Stone and Francis[43] suggest BPPV could develop by immune system's direct attack or indirect attack, resulting in debris within the inner ears. This explanation could be confirmed by the association of several autoimmune diseases, such as systemic sclerosis,[44] systemic lupus erythematosus, ulcerative colitis, Sjogren's syndrome, rheumatoid arthritis,[43] and chronic inflammatory demyelinating polyneuropathy[45] in the development of BPPV.

We conclude patients with depressive disorders are more likely to develop BPPV if they are afflicted with hyperthyroidism. Mechanical movements of thyroid autoantibodies in the inner ear fluid or the development of autoimmune microangiitis in the labyrinth can result in BPPV in the presence of hyperthyroidism or hypothyroidism.[46] Other studies support a role for thyroid hormone fluctuations[47] and circulating anti-thyroid autoantibodies [48] related to vestibular dysfunction in subsequent BPPV development. Therefore, dysregulation of the immune system may play a vital role between hyperthyroidism and BPPV as documented by our study.

There are several limitations in this study. The first limitation relates to the lack of detailed information regarding tobacco use, alcohol consumption, head position in bed, and family history of BPPV in patient data collected from the NHIRD, factors which may

influence risk of BPPV development.[49-51] Thus, we were unable to control for these potentially confounding factors. Second, the NHIRD is an administrative database, which lacks detailed clinical data regarding severity and outcomes of BPPV patients, which interferes with analysis of BPPV prognoses in the cohort. Third, in the claims-based study design, only patients seeking medical service would be identified in the Registry of NHIRD and these identification issues may underestimate the results.

Since profound health burden and extensive health care utilization may be influential with BPPV development.[52 53] Our findings and findings in other literature raised our attention to unrecognized BPPV and inappropriate treatment among patients with depressive disorders may lead to disabling and related poor quality of life.

Conclusions

In the population-based retrospective study, we found that patients with depressive disorders have statistically higher risk of developing BPPV. Furthermore, hyperthyroidism was identified an independent risk factor to develop BPPV for patients with depressive disorders. Future studies are required to clarify the underlying biological mechanisms of these associations. Clinicians are encouraged to provide appropriate medical care for those who diagnosed with BPPV and preexisting depressive disorder. Monitoring and management depressive symptoms for the high-risk patients are also warranted.

List of abbreviations:

BPPV, benign paroxysmal positional vertigo; NHI, National Health Insurance; LHID 2005, Longitudinal Health Insurance Database 2005; NHIRD, National Health Insurance Research Database; ICD-9-CM, the International Classification of Diseases, ninth revision, Clinical Modification; IRRs, incidence rate ratios; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

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Authors Contributions

Chiao-Lin Hsu and Li-Yu, Hu wrote the manuscript. Cheng-Che Shen and Ti, Lu helped with study design and data collection. Cheng-Che Shen, Shih-Jen Tsai and Yao-Min Hung contributed to the revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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Table 1 Baseline Characteristics of Patients with and without Depressive Disorders

Demographic data	Patients with Depressive Disorders *n*= 10,297		Patients without Depressive Disorders *n*= 41,188		*P* value
	n	%	*n*	%	
Age (years)[a]	39 (30–51)		39 (30–51)		
≥65	1,036	10.1	4,143	10.1	.999
<65	9,261	89.9	37,045	89.9	
Sex					
Male	4,012	39.0	16,048	39.0	1.000
Female	6,285	61.0	25,140	61.0	
Comorbidities					
Hypertension	2,124	20.6	5,444	13.2	<.001
Diabetes mellitus	1,236	12.0	3,112	7.5	<.001
Dyslipidemia	1,541	14.5	3,829	9.3	<.001
Coronary artery disease	87	0.8	235	0.6	.002
Congestive heart failure	272	2.6	563	1.4	<.001
Hyperthyroidism	511	5.0	727	1.8	<.001
Hypothyroidism	116	1.1	193	0.5	<.001
Cerebrovascular disease	573	5.6	1,106	2.7	<.001
Malignant neoplasms	181	1.8	415	1.0	<.001
Degree of urbanization					

Urban	6,599	64.1	25,196	60.9	<.001
Suburban	2,680	26.0	12,172	29.4	
Rural	817	7.9	3,205	7.8	
Income group					
Low income	5,189	50.4	18,340	44.4	<.001
Medium income	3,819	37.1	16,426	39.7	
High income	1,289	12.5	6,422	15.5	
Follow-up years[a]	7.19 (5.96–8.48)		7.22 (6.00–8.51)		.002

[a]Median (interquartile range)

Table 2 Person-Time Incidence of Benign Paroxysmal Positional Vertigo in Patients with and without Depressive Disorders

	Patients with Depressive Disorders		Patients without Depressive Disorders		Risk ratio (95% CI)	*P* value
	No. of BPPV	Per 1,000 person-years	No. of BPPV	Per 1,000 person-years		
Total	44	0.59	99	0.33	1.79 (1.23–2.58)	.002
Age						
≥65	7	0.98	15	0.51	1.90 (0.66–4.95)	.153
<65	37	0.55	84	0.31	1.77 (1.17–2.64)	.003
Sex						
Male	16	0.56	31	0.27	2.08 (1.16–3.76)	.023
Female	28	0.62	68	0.37	1.66 (1.07–2.56)	.030

CI, confidence interval

Table 3 Analyses of Risk Factors for Benign Paroxysmal Positional Vertigo in Patients with and without Depressive Disorders

	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Depressive Disorders	1.79 (1.26–2.56)	<.001	1.57 (1.09–2.26)	.014
Age (≥65 = 1, <65= 0)	1.69 (1.07–2.66)	.002	1.20 (0.71–2.02)	.503
Sex (Female = 1, Male = 0)	1.29 (0.91–1.82)	.158		
Comorbidities				
Hypertension	1.91 (1.30–2.81)	<.001	1.23 (0.76–2.00)	.401
Diabetes mellitus	1.36 (0.80–2.32)	.261		
Dyslipidemia	2.15 (1.42–3.27)	<.001	1.70 (1.05–2.76)	.032
Coronary artery disease	5.06 (1.87–13.67)	<.001	3.00 (1.05–8.61)	.041
Congestive heart failure	1.95 (0.72–5.27)	.188		
Hyperthyroidism	2.90 (1.48–5.70)	.002	2.52 (1.26–5.03)	.009
Hypothyroidism	1.26 (0.18–9.02)	.817		
Cerebrovascular disease	3.23 (1.83–5.71)	<.001	2.19 (1.17–4.11)	.014
Malignant neoplasms	2.09 (0.67–6.55)	.207		
Degree of urbanization				
Urban	Reference		Reference	
Suburban	1.10 (0.77–1.57)	.606	1.10 (0.77–1.56)	.618
Rural	4.38 (0.18–1.08)	.072	0.39 (0.16–0.97)	.043
Income group				
Low income	Reference			
Medium income	0.98 (0.69–1.38)	.886		
High income	0.65 (0.37–1.14)	.133		

HR, hazard ratio; CI, confidence interval

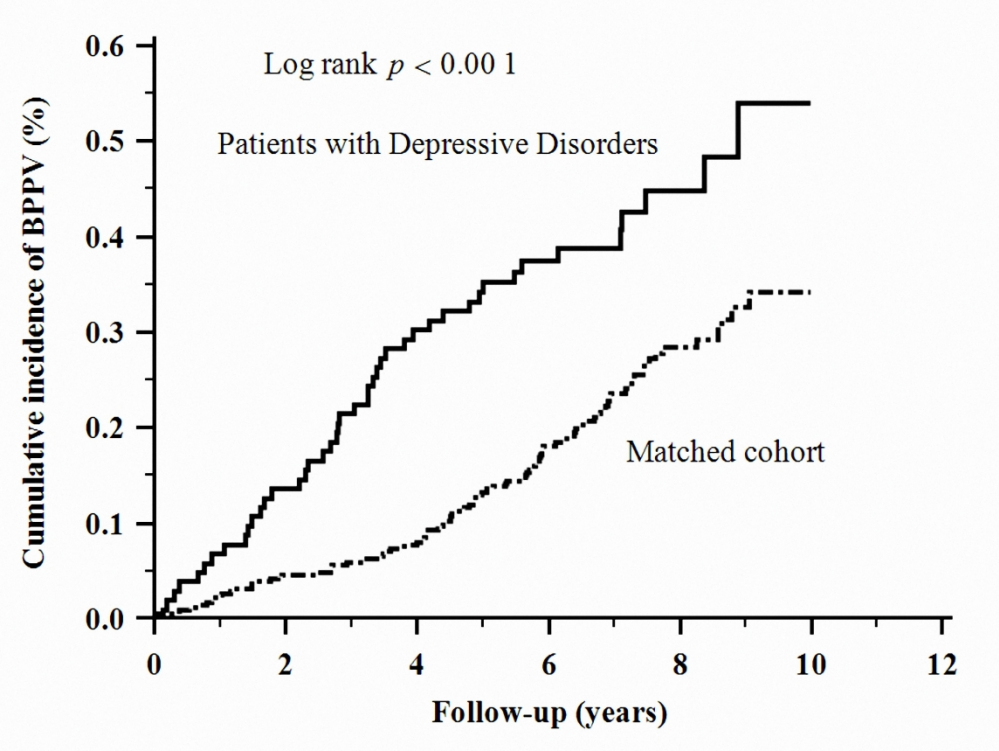
Table 4 Analyses of Risk Factors for Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders

	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≥65 = 1, <65 = 0)	1.75 (0.78–3.93)	.174		
Sex (Female = 1, Male = 0)	1.10 (0.60–2.04)	.752		
Comorbidities				
Hypertension	0.88 (0.41–1.90)	.747		
Diabetes mellitus	0.98 (0.39–2.49)	.969		
Dyslipidemia	1.97 (0.99–3.89)	.053	1.72 (0.86–3.46)	.127
Coronary artery disease	2.93 (0.40–21.26)	.288		
Congestive heart failure	0.92 (0.13–6.68)	.935		
Hyperthyroidism	3.74 (1.67–8.38)	<.001	3.55 (1.58–7.98)	.002
Hypothyroidism	2.17 (0.30–15.75)	.444		
Cerebrovascular disease	2.31 (0.91–5.85)	.079	1.99 (0.77–5.15)	.154
Malignant neoplasms	2.90 (0.70–11.97)	.142		
Degree of urbanization				
Urban	Reference			
Suburban	1.53 (0.82–2.86)	.180		
Rural	0.31 (0.04–2.28)	.249		
Income group				
Low income	Reference			
Medium income	1.33 (0.71–2.52)	.377		
High income	1.24 (0.50–3.11)	.644		

HR, hazard ratio; CI, confidence interval

Figure legend.

Cumulative incidence of benign paroxysmal positional vertigo in patients with and without depressive disorders. The cumulative incidence of BPPV in patients with depressive disorders was significantly higher than that in the matched cohort. (log-rank test, $p < 0.001$)



260x195mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6,7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	8,9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8,9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11,12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk of Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders: A Nationwide Population-Based Cohort Study

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Keywords:	depressive disorder, hyperthyroidism, risk factor, cohort study, systemic lupus erythematosus, benign paroxysmal positional vertigo

Risk of Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders: A Nationwide Population-Based Cohort Study

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Abstract

Objective: The association between depression andbenign paroxysmal positional vertigo (BPPV) remains debated. This study aimed to investigate the risk of BPPV in patients with depressive disorders.

Design: Longitudinal nationwide cohort study

Setting: National health insurance research database in Taiwan

Participants: We enrolled 10,297 patients diagnosed with depressive disorders between 2000 and 2009 and compared them to 41,188 selected control patients who had never been diagnosed with depressive disorders (at a 1:4 ratio matched by age, gender and index date) in relation to the risk of developing BPPV.

Methods: The follow-up period was defined as the time from the initial diagnosis of depressive disorders to the date of BPPV, censoring, or 31 December 2009. Cox proportional hazards regression analysis was used to investigate the risk of BPPV by sex, age, and comorbidities, with hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During the 9-year follow-up period, 44 (0.59 per 1,000 person-years) patients with depressive disorders and 99 (0.33 per 1,000 person-years) control patients were diagnosed with BPPV. The incidence risk ratio of BPPV among both cohorts calculating from events of BPPV per 1,000 person-years of observation time was 1.79 (95% CI, 1.23–2.58,p= .002). Following adjustments for age, sex, and comorbidities, patients with depressive disorders were 1.55 times more likely to develop BPPV (95% CI, 1.08–2.23, p= .019) as compared to control patients. In addition, hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and systemic lupus erythematosus (SLE) (HR = 3.47, 95% CI, 1.07-11.22, p= .038) were potential risk factors for new-onset BPPV in patients with depressive disorders.

Conclusions: Patients with depressive disorders may have an increased risk of developing BPPV, especially those who have hyperthyroidism and SLE.

Keywords: Depressive disorders; benign paroxysmal positional vertigo; hyperthyroidism; systemic lupus erythematosus; risk factor; cohort study

Strengths and limitations of this study

1. The incidence of benign peripheral persistent vertigo (BPPV) among depressive disorders patient remains unclear. This longitudinal population-based data was conducted to assess the risk of BPPV in patients with depressive disorders.
2. The NHIRD lacks detailed clinical data regarding severity and outcomes of BPPV
3. Results from our study may underestimate the current condition since only patients seeking medical service would be identified in the Registry of NHIRD.

Introduction

Depressive disorders are common mood disorders occurring in all populations and the Global Burden of Disease 2017 had refereed depressive disorders as a leading cause of health burden across the globe.[1] Patients with depressive disorders have been reported with an increased risk of mortality and propose the classification of depressive disorders as life-threatening.[2 3] Furthermore, people with depressive disorders have been reported with many somatic symptoms and result in increased need for clinical services, associated economic costs,[4 5] and considerable loss in quality of life.[6]

BPPV have been reported with a lifetime prevalence of 2.4%, is the most common type of peripheral vertigo. Which is characterized by brief spinning sensations, usually induced by a sudden change in head position with respect to gravity, with attacks generally lasting less than 1 minute. The fundamental pathophysiology of BPPV is dislodged calcium carbonate crystals in the utricle of the inner ear entering the semicircular canals.[7] Old age [8] and several co-morbidities, such as hypertension[9], diabetes mellitus[9], hypercholesterolemia[10], pre-existing cardiovascular, thyroid and autoimmune[10] disease have been regarded as risk factors of BPPV. Patients who suffered from BPPV related symptoms and following economic burden have also been reported[11].

Psychiatric disorders or emotional stress are frequently observed in patients suffering from vertigo.[12 13] The results of most studies have been reported the higher rate of coexistence of depression and vestibular disorders[14-16]. Which may lead to a vicious circle and a serious influence on the quality of life[17]. Peripheral vertigo may play an essential role in the pathophysiology of development of subsequent depressive disorder. However, most of these studies report contradictory or conflicting results. Furthermore, when specified to explore the association between depression and BPPV, only a relatively small-scaled case-control study indicates that life stressors and related depressive disorder may be seen as a trigger of vestibular dysfunction, that is, a potential precursor of BPPV.[18]

Therefore, considering the debates on the association between the depression and BPPV and no large-scaled study have tried to investigate the issue, we designed a nationwide retrospective cohort study to explore the association between depressive disorder and the subsequent BPPV development. In addition, independent risk factors for developing BPPV among patients with depressive disorders were also investigated.

Materials and Methods

Data Sources

Nearly 99% of Taiwan's population utilizes health care services as a consequence of the National Health Insurance (NHI) Program Bold Legislative Act enacted in 1995.[19] The

program offers comprehensive medical care coverage regarding outpatient, inpatient, emergency visits, and Chinese medicine to all residents of Taiwan. The NHI research database (NHIRD) contains comprehensive information with regard to clinical practice, including prescription details and diagnostic codes in the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) format. The NHIRD is managed by the National Health Research Institutes (NHRI) and privacy is maintained according to directives from the Bureau of the NHI.[20] The data source for our study was obtained from the Longitudinal Health Insurance Database 2000 (LHID2000), a dataset of the NHIRD. The LHID 2000, which contains all original claims data for 1,000,000 subjects, is a representative database randomly selected from the 2000 Registry of Beneficiaries under the NHI program. Which also maintains the registration data of everyone who was a beneficiary of the National Health Insurance program during the period of 1996–2000. Moreover, the NHRI affirms that there are no statistical differences in the distributions of age, sex, or health care costs between the data in the LHID2000 and that of the NHIRD.[20] For each patient with depressive disorders included in the final cohort

Availability of Data and Materials section

The NHIRD is addressed in publicity by the NHRI and the use of NHIRD is only for research purposes. All applicants must obey the Computer-Processed Personal Data

Protection Law[21] and relevant regulations of Bureau of National Health Insurance and NHRI. Moreover, applicants and their supervisor were asking for signing agreements upon application submission. All applications are reviewed for approval of data delivered. Request for the dataset may be sent an e-mail to the NHRI at nhird@nhri.org.tw or call at +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30 (UTC+8).

The NHIRD, which was open to the researchers in Taiwan, was available from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW) (http://www.mohw.gov.tw/cht/DOS/).The data underlying this study is from the NHIRD. Interested researchers can obtain the data through formal application to the Ministry of Health and Welfare, Taiwan. In the last sentence of the paragraph, which said "Kindly visit MOHW and NHIA on-site services for National Health Insurance Data." The Database was transferred to a higher-level government administration, called the "Health and Welfare Data Science Center (HWDC)" for more efficient health-related data linkage, wider application, and better security management. At present, interested researchers could still obtain the National Health Insurance Data in Taiwan through formal application to the Health and Welfare Data Science Center (HWDC), Department of Statistics, Ministry of Health and Welfare (MOHW). HWDC, MOHW website (Chinese only currently): http://dep.mohw.gov.tw/DOS/np-2497-113.html

Study design and subjects

We utilized data from the LHID 2000 and conducted a retrospective cohort study using a dataset collected between January 1, 2000 and December 31, 2004. We enrolled patients ≥ 20 years and received at least twice diagnosis of depressive disorders by psychiatrists with ICD-9-CM depressive disorders diagnosis codes of 296.2X-296.3X, 300.4, and 311.X. We defined the date of enrolling an adult patient with depressive disorders as case cohort between 2000 and 2004 as enrolment date. We excluded both in depressive disorders and control groups who were previously diagnosed with BPPV (ICD-9-CM code 386.11) before the enrollment date. We also used A-code (A-code: A249) to exclude patients who had vertigo related diagnoses before diagnosed with BPPV between 1996 and 2000. Which included acute myringitis, chronic myringitis, perforation of tympanic membrane, traumatic perforation of tympanic membrane, cholesteatoma of the middle ear, Meniere's disease, peripheral vertigo, vestibulopathy, vertigo of central origin, labyrinthitis, presbycusis, sudden hearing loss, tinnitus, and otalgia

The A-code, a much briefer version of the ICD-9-CM codes, is another disease classification system launched for fulfilling medical claims. The A-code was mainly used for ambulatory care before 2000 in Taiwan and has switched to the ICD-9-CM codes by NHI program since 2000 to perpetuate consistency between different claims records and to truly

reflect the distribution of various diseases. The cohort including patients with and without depressive disorders was observed until the development of BPPV, death, withdrawal from the NHI system, or December 31, 2009. The primary clinical outcome in our study was only BPPV diagnosed by neurologists or otorhinolaryngologists. For each patient with depressive disorders included in the final cohort, 4 age- and sex-matched control patients without depressive disorders were randomly selected on the same enrolment date from the LHID 2000. Finally, we identified 10,297 patients with depressive disorders. To assemble a comparison cohort, we randomly selected 41,188 enrollees without a history of depressive disorders.

Ethics Statement

This study was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital (No.: VGHKS14-CT7-07). We could not obtain written consent from study patients as the NHI dataset consists of de-identified secondary data for research purposes. The IRB of Kaohsiung Veterans General Hospital issued a formal written waiver for the need for consent.

Statistical analyses

The incidence of newly diagnosed BPPV in patients with depressive disorders and controls during the observational period was calculated and stratified by sex and age (≥ 65 years or < 65 years). Comparisons between continuous variables were conducted with the independent *t*-test. Chi-squared analysis was used to examine the association of two

categorical characteristics between the depressive disorders and control cohort. A Cox proportional hazards model was used to evaluate confounding variables and whether depressive disorders increase the risk of developing BPPV. The confounding variables were age, sex, and common comorbidities including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, hyperthyroidism, hypothyroidism, cerebrovascular disease, and systemic lupus erythematosus (SLE). Another Cox proportional-hazards regression model was performed again to identify variables that predicted BPPV in the patients with depressive disorders. The variables that demonstrated a moderately significant statistical relationship with BPPV in the univariate analysis ($P < .1$) were entered through forward selection in a multivariate analysis.

The cumulative incidences of BPPV were compared between depressive disorder and control cohorts using Kaplan–Meier curves. Stratified log rank test was applied to determine the differences in the risk for BPPV in the cohort.

Patient and Public involvement

The data source used for this study was the claims data of Taiwan's NHIRD. We did not involve patients/service users in the research question, the outcome measures, or the design or implementation of the study. There are no plans to disseminate the results of the research to study participants.

Results

Participant Selection

We analyzed 10,297 patients with depressive disorders and 41,188 control patients. The majority of patients in the cohort were female (61%). The median age was 39 years

(interquartile range [IQR], 30–51 years), and the median follow-up period was 7.19 years (IQR = 5.96–8.48 years) for patients with depressive disorders and 7.22 years (IQR = 6.00–8.51 years) for control patients (p= .002). Table 1 includes comparisons of demographic, clinical variables, and socioeconomic data between the control and depressive cohorts. In the depressive disorders group, the most common comorbidities were hypertension (2,124 patients, 20.6%), diabetes mellitus (1,236 patients, 12.0%), and dyslipidemia (1,541patients, 14.5%). As compared to the controls, depressive disorders patients had significantly more physical comorbidities. Besides, depressive disorders patients had a significantly higher prevalence in low-income populations (50.4% vs. 44.4%, p< .001) and in urban areas (64.1% vs. 60.9%, p< .001) as compared to non-depressive disorders patients.

Person-Time Incidence Rate of BPPV

During the follow-up period, 44 patients (0.59 per 1,000 person-years) were diagnosed with BPPV in the depressive disorders group, and 99 patients (0.33 per 1,000 person-years) were diagnosed with BPPV in the control group. The incidence rate ratio (IRR) of BPPV between depressive disorders and control patients was 1.79 (95% CI [confidence interval], 1.23–2.58, p= .002). The IRR of BPPV remained higher in the depressive disorders than in the control patients among both sexes. When stratified with age, only patient younger than 65 years old have higher IRR of BPPV. The results are shown in Table 2.

The cumulative incidence of BPPV in the patients with depressive disorders was significantly higher than that in the control cohort (log-rank test, P < .001, Figure 1).

Risks of Newly Diagnosed BPPV among the Patients with and without Depressive Disorders

After adjusting for age, sex, common comorbidities and SLE there was a higher risk of developing BPPV in patients with depressive disorders than in the control patients (HR =1.55, 95% CI, 1.08–2.23, p= .019). Results are summarized in Table 3.

Risks Factors for BPPV in patients with Depressive Disorders

As shown in Table 4, we predicted the development of BPPV in the depressive disorder cohorts by applying univariate analysis. Univariate analysis demonstrated that dyslipidemia (HR = 1.97, 95% CI, 0.99–3.89, p= .053), hyperthyroidism (HR = 3.74, 95% CI, 1.67–8.38, p< .001), cerebrovascular disease (HR =2.31, 95% CI, 0.91-5.85, p= .079) and SLE (HR =3.58, 95% CI, 1.11-11.56, p= .033) were possible prognostic factors. Multivariate analysis indicated that hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and SLE (HR = 3.47, 95% CI, 1.07-11.22, p= .038) were an independent risk factor for patients with depressive disorders.

Discussion

The two major findings in our study are as the following. First, patients with depressive disorders presented a 1.55 -fold greater risk of subsequently developing BPPV than did the

general population by utilizing a nationwide population-based cohort study. Secondly, only hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and SLE (HR = 3.47, 95% CI, 1.07-11.22, p= .038) were independent risk factors to develop BPPV among patients with depressive disorders.

The strength of this study is using a nationwide population-based data to evaluate BPPV risk in patients with depressive disorders. Advantages of using our NHIRD in medical research have been previously described,[22] which include enormous sample size, lack of selection and participation bias and long term comprehensive follow up. Whereas the results of most studies demonstrated the correlation between BPPV and following depressive disorders,[23 24] to the best of our knowledge, this is the first study implying that patients with depressive disorders have higher risk of developing BPPV.

Though depressive disorder have been reported to produce somatic symptoms including symptoms like BPPV,[25] one research indicated that patients with unrecognized BPPV were more likely to have depressive disorder.[26] Another study pointed out that depressive disorders may be an early presentation of neural circuitry alterations involving connections between the vestibular system and anatomical area such as hippocampus, amygdala, and infralimbic cortex.[27] One Asian literature showed that depression symptoms may adversely affect BPPV

recurrence.[28] Though there was no strong evidence consistent with our findings, evidence mentioned above may indirectly prove our hypothesis.

The pathophysiology of depressive disorders and subsequent BPPV is unknown. There are several proposed mechanisms to explain this association.First, dysregulation of oxidative and inflammatory processes in depressive disorders may result in subsequent BPPV development. Numerous studies have demonstrated patients with depressive disorders have excessive oxidative stress and elevation in inflammatory responses.[29-32] Evidence supports a role for oxidative stress in otolith dysfunction leading to an increased risk of developing canalolithiasis, an essential step in the pathogenesis of BPPV.[33-36] Additional studies conclude depressive disorders associated with oxidative stress result in vestibular hair cells and neuronal damage in the inner ear,[37] which contributes to vestibular dysfunction and subsequent BPPV development.[38 39]Second, depressive disorders may induce abnormalities of the hypothalamus-pituitary-adrenal axis, which may hinder the inner ear blood flow and influence inner ear fluid balance. These abnormalities lead to dysfunction of the otoconial homeostasis,[18 40] an established risk factor for development of BPPV.[41] Therefore, alterations to the neuroendocrine system may be the link between depressive disorders and the development of BPPV. Third, BPPV development in depressive disorders may be induced by serotonin dysfunction. The vestibular nucleus complex is composed of a large number of

serotonin receptors, and lack of serotonin may result in a substantial impact on the electrophysiological activity of neurons, and dysfunction of the vestibular nucleus complex.[42] Previous studies have hypothesized a role for vestibular nucleus damage in the pathogenesis of BPPV development.[39 43]Fourth, the dysregulation of the immune system, frequently observed in depressive disorders,[44 45] has proved to be an essential part of BPPV pathogenesis. Stone and Francis[46] suggest BPPV could develop by immune system's direct attack or indirect attack, resulting in debris within the inner ears. This explanation could be confirmed by studies demonstrated the association of several autoimmune diseases, such as systemic sclerosis,[47]SLE, ulcerative colitis, Sjogren's syndrome, rheumatoid arthritis,[46] and chronic inflammatory demyelinating polyneuropathy[48] in the development of BPPV.The relation between immune system and BPPV was also in keeping with our result that SLE is a potential risk factor for developing BPPV.

We conclude patients with depressive disorders are more likely to develop BPPV if they are afflicted with hyperthyroidism. Mechanical movements of thyroid autoantibodies in the inner ear fluid or the development of autoimmune microangiitis in the labyrinth can result in BPPV in the presence of hyperthyroidism or hypothyroidism.[49] Other studies support a role for thyroid hormone fluctuations[50] and circulating anti-thyroid autoantibodies [51] related to vestibular dysfunction in subsequent BPPV development. Therefore, dysregulation of the

immune system may play a vital role between hyperthyroidism and BPPV as documented by our study. In addition, we inferred that hyperthyroidism altered calcium metabolism and otoconia dissolve impairment may play a role in developing BPPV among depressive disorders patients. Up to 20 percent of thyrotoxic patients have mild hypercalcemia because of thyroid hormone-mediated bone resorption[52]. Otoconia, mainly synthesized from calcium[53], which breaks free and moves into the semicircular canals was the fundamental pathophysiology of BPPV[8]. Therefore, hyperthyroidism with increased calcium might lead to increased concentration of free calcium in the endolymph and reduce its capacity to dissolve the dislodged otoconia[54], this mechanism involved in the pathophysiology of BPPV.

Though there is no direct evidence support the pathophysiology of BPPV occurred in patients co-existence with depressive disorder and hyperthyroidism. Patients suffered from symptoms like palpitation, insomnia, anxiety, and irritability, which symptoms usually belonging to hyperthyroidism and was difficult to discriminate from the psychiatric disorder, have been proposed easily seeking medical treatment[55]. Therefore, we proposed that hyperthyroidism related panic -like symptoms may increase the chance of diagnosis of BPPV through greater medical contact.

There are several limitations in this study. The first limitation relates to the lack of detailed information regarding tobacco use, alcohol consumption, head position in bed, and

family history of BPPV in patient data collected from the NHIRD, factors which may influence risk of BPPV development.[56-58] Thus, we were unable to control for these potentially confounding factors. Second, the NHIRD is an administrative database, which lacks detailed clinical data regarding severity and outcomes of BPPV patients, which interferes with analysis of BPPV prognoses in the cohort. Third, in the claims-based study design, only patients seeking medical service would be identified in the Registry of NHIRD and these identification issues may either overestimate or underestimate the results. Fourth, our study did not provide any information about medications administered for BPPV.

Since profound health burden and extensive health care utilization may be influential with BPPV development.[59 60] Our findings and findings in other literature raised our attention to unrecognized BPPV and inappropriate treatment among patients with depressive disorders may lead to disabling and related poor quality of life.

Conclusions

In the population-based retrospective study, we found that patients with depressive disorders have statistically higher risk of developing BPPV. Furthermore, hyperthyroidism and SLE were identified an independent risk factor to develop BPPV for patients with depressive disorders. Future studies are required to clarify the underlying biological mechanisms of these associations. Clinicians are encouraged to provide appropriate medical

care for those who diagnosed with BPPV and preexisting depressive disorder. Monitoring and management depressive symptoms for the high-risk patients are also warranted.

List of abbreviations:

BPPV, benign paroxysmal positional vertigo; NHI, National Health Insurance; LHID 2000, Longitudinal Health Insurance Database 2000; NHIRD, National Health Insurance Research Database; ICD-9-CM, the International Classification of Diseases, ninth revision, Clinical Modification; IRRs, incidence rate ratios; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

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Author contributions

Chiao-Lin Hsu and Li-Yu, Hu wrote the manuscript. Cheng-Che Shen and Ti, Lu helped with study design and data collection. Cheng-Che Shen, Shih-Jen Tsai and Yao-Min Hung contributed to the revision of the manuscript. All authors read and approved the final

manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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Legend for Figure 1:

Fig.1 Cumulative incidence of benign paroxysmal positional vertigo in depressive disorders and comparison cohort

The cumulative incidence of benign paroxysmal positional vertigo in patients with depressive disorders was significantly higher than that in the comparison cohor

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Table 1 Baseline Characteristics of Patients with and without Depressive Disorders

Demographic data	Patients with Depressive Disorders *n*= 10,297		Patients without Depressive Disorders *n*= 41,188		*P* value
	n	%	*n*	%	
Age (years)[a]	39 (30–51)		39 (30–51)		
≥65	1,036	10.1	4,143	10.1	.999
<65	9,261	89.9	37,045	89.9	
Sex					
Male	4,012	39.0	16,048	39.0	1.000
Female	6,285	61.0	25,140	61.0	
Comorbidities					
Hypertension	2,124	20.6	5,444	13.2	<.001
Diabetes mellitus	1,236	12.0	3,112	7.5	<.001
Dyslipidemia	1,541	14.5	3,829	9.3	<.001
Coronary artery disease	87	0.8	235	0.6	.002
Hyperthyroidism	511	5.0	727	1.8	<.001
Hypothyroidism	116	1.1	193	0.5	<.001
Cerebrovascular disease	573	5.6	1,106	2.7	<.001
Systemic lupus erythematosus	216	2.1	437	1.1	<.001
Degree of urbanization					
Urban	6,599	64.1	25,196	60.9	<.001
Suburban	2,680	26.0	12,172	29.4	
Rural	817	7.9	3,205	7.8	
Income group					
Low income	5,189	50.4	18,340	44.4	<.001
Medium income	3,819	37.1	16,426	39.7	

High income	1,289	12.5	6,422	15.5	
Follow-up years[a]	7.19 (5.96–8.48)		7.22 (6.00–8.51)		.002

[a]Median (interquartile range)

Table 2 Person-Time Incidence of Benign Paroxysmal Positional Vertigo (BPPV) in Patients with and without Depressive Disorders

	Patients with Depressive Disorders		Patients without Depressive Disorders		Rate ratio (95% CI)	*P* value
	No. of BPPV	Per 1,000 person-years	No. of BPPV	Per 1,000 person-years		
Total	44	0.59	99	0.33	1.79 (1.23–2.58)	.002
Age						
≥65	7	0.98	15	0.51	1.90 (0.66–4.95)	.153
<65	37	0.55	84	0.31	1.77 (1.17–2.64)	.003
Sex						
Male	16	0.56	31	0.27	2.08 (1.16–3.76)	.023
Female	28	0.62	68	0.37	1.66 (1.07–2.56)	.030

CI, confidence interval

Table 3 Analyses of Risk Factors for Benign Paroxysmal Positional Vertigo in Patients with and without Depressive Disorders

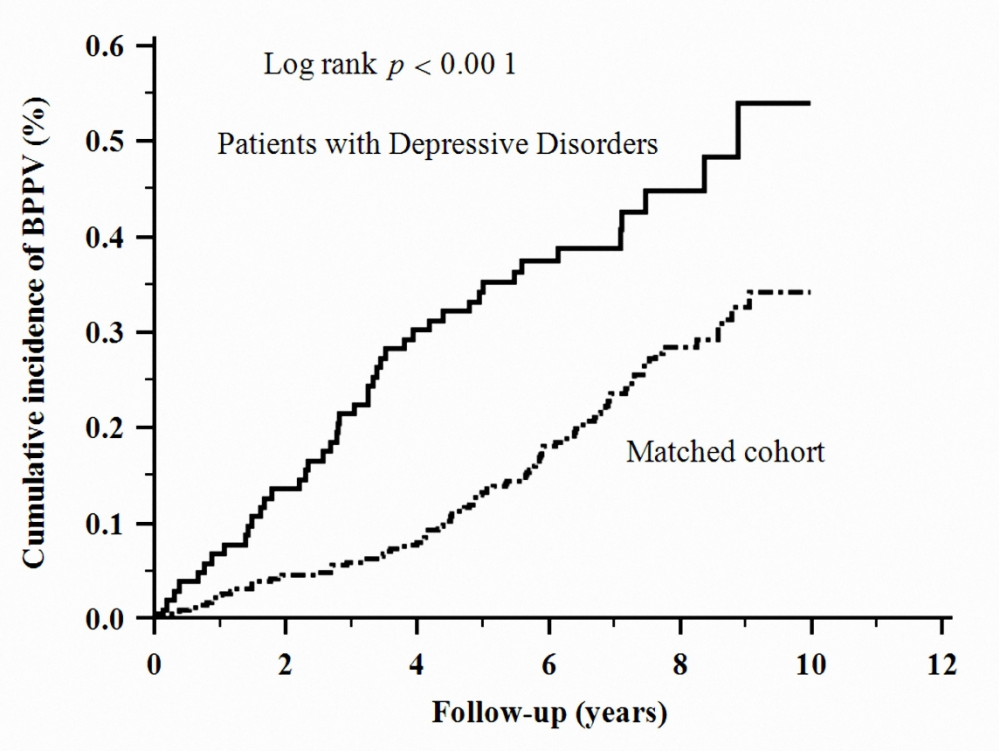
	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Depressive Disorders	1.79 (1.26–2.56)	<.001	1.55 (1.08–2.23)	.019
Age (≥65 = 1, <65= 0)	1.69 (1.07–2.66)	.002		
Sex (Female = 1, Male = 0)	1.29 (0.91–1.82)	.158		
Comorbidities				
Hypertension	1.91 (1.30–2.81)	<.001		
Diabetes mellitus	1.36 (0.80–2.32)	.261		
Dyslipidemia	2.15 (1.42–3.27)	<.001	1.78 (1.15–2.75)	.010
Coronary artery disease	5.06 (1.87–13.67)	<.001	3.29 (1.18–9.17)	.023
Hyperthyroidism	2.90 (1.48–5.70)	.002	2.46 (1.24–4.87)	.010
Hypothyroidism	1.26 (0.18–9.02)	.817		
Cerebrovascular disease	3.23 (1.83–5.71)	<.001	2.24 (1.21–4.15)	.010
Systemic lupus erythematosus	2.44 (0.90-6.60)	.079		
Degree of urbanization				
Urban	Reference			
Suburban	1.10 (0.77–1.57)	.606		
Rural	4.38 (0.18–1.08)	.072		
Income group				
Low income	Reference			
Medium income	0.98 (0.69–1.38)	.886		
High income	0.65 (0.37–1.14)	.133		

HR, hazard ratio; CI, confidence interval

Table 4 Analyses of Risk Factors for Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders

	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≥65 = 1, <65 = 0)	1.75 (0.78–3.93)	.174		
Sex (Female = 1, Male = 0)	1.10 (0.60–2.04)	.752		
Comorbidities				
Hypertension	0.88 (0.41–1.90)	.747		
Diabetes mellitus	0.98 (0.39–2.49)	.969		
Dyslipidemia	1.97 (0.99–3.89)	.053		
Coronary artery disease	2.93 (0.40–21.26)	.288		
Hyperthyroidism	3.74 (1.67–8.38)	<.001	3.75 (1.67–8.42)	.001
Hypothyroidism	2.17 (0.30–15.75)	.444		
Cerebrovascular disease	2.31 (0.91–5.85)	.079		
Systemic lupus Erythematosus	3.58 (1.11-11.56)	.033	3.47(1.07-11.22)	.038
Degree of urbanization				
Urban	Reference			
Suburban	1.53 (0.82–2.86)	.180		
Rural	0.31 (0.04–2.28)	.249		
Income group				
Low income	Reference			
Medium income	1.33 (0.71–2.52)	.377		
High income	1.24 (0.50–3.11)	.644		

HR, hazard ratio; CI, confidence interval



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5.6
Objectives	3	State specific objectives, including any prespecified hypotheses	9,10
Methods			
Study design	4	Present key elements of study design early in the paper	9,10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7,8,10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7,8
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	10
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	Report numbers of outcome events or summary measures over time	13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Risk of Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders: A Nationwide Population-Based Cohort Study

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Risk of Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders: A Nationwide Population-Based Cohort Study

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Abstract

Objective: The association between depression and benign paroxysmal positional vertigo (BPPV) remains debated. This study aimed to investigate the risk of BPPV in patients with depressive disorders.

Design: Longitudinal nationwide cohort study

Setting: National health insurance research database in Taiwan

Participants: We enrolled 10,297 patients diagnosed with depressive disorders between 2000 and 2009 and compared them to 41,188 selected control patients who had never been diagnosed with depressive disorders (at a 1:4 ratio matched by age, sex and index date) in relation to the risk of developing BPPV.

Methods: The follow-up period was defined as the time from the initial diagnosis of depressive disorders to the date of BPPV, censoring, or 31 December 2009. Cox proportional hazard regression analysis was used to investigate the risk of BPPV by sex, age, and comorbidities, with hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During the 9-year follow-up period, 44 (0.59 per 1,000 person-years) patients with depressive disorders and 99 (0.33 per 1,000 person-years) control patients were diagnosed with BPPV. The incidence rate ratio of BPPV among both cohorts calculating from events of BPPV per 1,000 person-years of observation time was 1.79 (95% CI, 1.23–2.58,p= .002). Following adjustments for age, sex, and comorbidities, patients with depressive disorders were 1.55 times more likely to develop BPPV (95% CI, 1.08–2.23, p= .019) as compared to control patients. In addition, hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and systemic lupus erythematosus (SLE) (HR = 3.47, 95% CI, 1.07-11.22, p= .038) were potential risk factors for developing BPPV in patients with depressive disorders.

Conclusions: Patients with depressive disorders may have an increased risk of developing BPPV, especially those who have hyperthyroidism and SLE.

Keywords: Depressive disorders; benign paroxysmal positional vertigo; hyperthyroidism; systemic lupus erythematosus; risk factor; cohort study

Strengths and limitations of this study

1. The incidence of benign peripheral persistent vertigo (BPPV) among depressive disorders patient remains unclear. This longitudinal population-based data was conducted to assess the risk of BPPV in patients with depressive disorders.
2. The NHIRD lacks detailed clinical data regarding severity and outcomes of BPPV
3. Results from our study may underestimate the current condition since only patients seeking medical service would be identified in the Registry of NHIRD.

Introduction

Depressive disorders are common mood disorders occurring in all populations and the Global Burden of Disease 2017 had refereed depressive disorders as a leading cause of health burden across the globe.[1] Patients with depressive disorders have been reported with an increased risk of mortality and propose the classification of depressive disorders as life-threatening.[2 3] Furthermore, people with depressive disorders have been reported with many somatic symptoms and result in increased need for clinical services, associated economic costs,[4 5] and considerable loss in quality of life.[6]

BPPV have been reported with a lifetime prevalence of 2.4%, is the most common type of peripheral vertigo. Which is characterized by brief spinning sensations, usually induced by a sudden change in head position with respect to gravity, with attacks generally lasting less than 1 minute. The fundamental pathophysiology of BPPV is dislodged calcium carbonate crystals in the utricle of the inner ear entering the semicircular canals.[7] Old age [8] and several co-morbidities, such as hypertension[9], diabetes mellitus[9], hypercholesterolemia[10], pre-existing cardiovascular, thyroid and autoimmune[10] disease have been regarded as risk factors of BPPV. Patients who suffered from BPPV related symptoms and following economic burden have also been reported[11].

Psychiatric disorders or emotional stress are frequently observed in patients suffering from vertigo.[12 13] The results of most studies have been reported the higher rate of coexistence of depression and vestibular disorders[14-16]. Which may lead to a vicious circle and a serious influence on the quality of life[17]. Peripheral vertigo may play an essential role in the pathophysiology of development of subsequent depressive disorder. However, most of these studies report contradictory or conflicting results. Furthermore, when specified to explore the association between depression and BPPV, only a relatively small-scaled case-control study

indicates that life stressors and related depressive disorder may be seen as a trigger of vestibular dysfunction, that is, a potential precursor of BPPV.[18]

Therefore, considering the debates on the association between the depression and BPPV and no large-scaled study have tried to investigate the issue, we designed a nationwide retrospective cohort study to explore the association between depressive disorder and the subsequent BPPV development. In addition, independent risk factors for developing BPPV among patients with depressive disorders were also investigated.

Materials and Methods

Data Sources

Nearly 99% of Taiwan's population utilizes health care services as a consequence of the National Health Insurance (NHI) Program Bold Legislative Act enacted in 1995.[19] The program offers comprehensive medical care coverage regarding outpatient, inpatient, emergency visits, and Chinese medicine to all residents of Taiwan. The NHI research database (NHIRD) contains comprehensive information with regard to clinical practice, including prescription details and diagnostic codes in the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) format. The NHIRD is managed by the National Health Research Institutes (NHRI) and privacy is maintained according to directives from the Bureau of the NHI.[20] The data source for our study was obtained from the Longitudinal Health Insurance Database 2000 (LHID2000), a dataset of the NHIRD. The LHID 2000, which contains all original claims data for 1,000,000 subjects, is a representative database randomly selected from the 2000 Registry of Beneficiaries under the NHI program. Which also maintains the registration data of everyone who was a beneficiary of the National Health Insurance program during the period of 1996–2000. Moreover, the NHRI affirms that

there are no statistical differences in the distributions of age, sex, or health care costs between the data in the LHID2000 and that of the NHIRD.[20]

Availability of Data and Materials section

The NHIRD is addressed in publicity by the NHRI and the use of NHIRD is only for research purposes. All applicants must obey the Computer-Processed Personal Data Protection Law and relevant regulations of the Bureau of National Health Insurance and NHRI. Moreover, applicants and their supervisor were asking for signing agreements upon application submission. All applications are required to transmit data for review and approval and send an e-mail to the NHRI at nhird@nhri.org.tw or call at +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30 (UTC+8).

The NHIRD from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW) (http://www.mohw.gov.tw/cht/DOS/) is now available for the researchers in Taiwan. The data is basically from the NHIRD. Researchers in Taiwan who interested in the data can apply to the MOHW. In the last sentence of the paragraph on the website, which said, "Kindly visit MOHW and NHIA on-site services for NHIRD." The Database was delivered to a higher-level government administration, called the "Health and Welfare Data Science Center (HWDC)" for more prompt health-related data linkage, broader application, and better security management. Interested researchers could still apply to the HWDC, Department of Statistics, MOHW for NHI Data at present. HWDC, MOHW website (Chinese only currently): http://dep.mohw.gov.tw/DOS/np-2497-113.html[21]

Study design and subjects

We utilized data from the LHID 2000 and conducted a retrospective cohort study using a dataset collected between January 1, 2000 and December 31, 2004. We enrolled patients ≥ 20 years and received at least twice diagnosis of depressive disorders by psychiatrists with ICD-9-CM depressive disorders diagnosis codes of 296.2X-296.3X, 300.4, and 311.X. We defined the date of enrolling an adult patient with depressive disorders as case cohort between 2000 and 2004 as enrolment date. We excluded both in depressive disorders and control groups who were previously diagnosed with BPPV by ICD-9-CM code and A-code at the same time (ICD-9-CM code 386.11 and A-code: A249) to exclude patients who were diagnosed with BPPV before enrollment date.

The A-code, a much briefer version of the ICD-9-CM codes, is another disease classification system launched for fulfilling medical claims, was mainly used for ambulatory care before 2000 in Taiwan. The A-code had switched to the ICD-9-CM codes by NHI program since 2000 to perpetuate consistency between different claims records and to truly reflect the distribution of various diseases. Consequently, we used these two medical code systems at the same time to reduce the discrepancies during the conversion time of A-code and ICD-9-CM codes. Which included acute myringitis, chronic myringitis, perforation of tympanic membrane, traumatic perforation of tympanic membrane, cholesteatoma of the middle ear, Meniere's disease, peripheral vertigo, vestibulopathy, vertigo of central origin, labyrinthitis, presbycusis, sudden hearing loss, tinnitus, and otalgia

The cohort including patients with and without depressive disorders was observed until the development of BPPV, death, withdrawal from the NHI system, or December 31, 2009. The primary clinical outcome in our study was only BPPV diagnosed by neurologists or otorhinolaryngologists. For each patient with depressive disorders included in the final cohort,

4 age- and sex-matched control patients without depressive disorders were randomly selected on the same enrolment date from the LHID 2000. Finally, we identified 10,297 patients with depressive disorders. To assemble a comparison cohort, we randomly selected 41,188 enrollees without a history of depressive disorders.

Ethics Statement

This study was approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital (No.: VGHKS14-CT7-07). We could not obtain written consent from study patients as the NHI dataset consists of de-identified secondary data for research purposes. The IRB of Kaohsiung Veterans General Hospital issued a formal written waiver for the need for consent.

Statistical analyses

The incidence of newly diagnosed BPPV in patients with depressive disorders and controls during the observational period was calculated and stratified by sex and age (≥ 65 years or < 65 years). Comparisons between continuous variables were conducted with the independent *t*-test. Chi-squared analysis was used to examine the association of two categorical characteristics between the depressive disorders and control cohort. A Cox proportional hazard model was used to evaluate confounding variables and whether depressive disorders increase the risk of developing BPPV. The confounding variables were age, sex, and common comorbidities including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, hyperthyroidism, hypothyroidism, cerebrovascular disease, and systemic lupus erythematosus (SLE). Another Cox proportional-hazards regression model was performed again to identify variables that predicted BPPV in the patients with depressive disorders. The variables that demonstrated a moderately significant statistical relationship

with BPPV in the univariate analysis ($P<.1$) were entered through forward selection in a multivariate analysis.

The cumulative incidences of BPPV were compared between depressive disorder and control cohorts using Kaplan–Meier curves. Stratified log rank test was applied to determine the differences in the risk for BPPV in the cohort.

Patient and Public involvement

The data source used for this study was the claims data of Taiwan's NHIRD. We did not involve patients/service users in the research question, the outcome measures, or the design or implementation of the study. There are no plans to disseminate the results of the research to study participants.

Results

Participant Selection

We analyzed 10,297 patients with depressive disorders and 41,188 control patients. The majority of patients in the cohort were female (61%). The median age was 39 years (interquartile range [IQR], 30–51 years), and the median follow-up period was 7.19 years (IQR = 5.96–8.48 years) for patients with depressive disorders and 7.22 years (IQR = 6.00–8.51 years) for control patients (p= .002). Table 1 includes comparisons of demographic, clinical variables, and socioeconomic data between the control and depressive cohorts. In the depressive disorders group, the most common comorbidities were hypertension (2,124 patients, 20.6%), diabetes mellitus (1,236 patients, 12.0%), and dyslipidemia (1,541patients, 14.5%). As compared to the controls, depressive disorders patients had significantly more physical comorbidities. Besides, depressive disorders patients had a significantly higher prevalence in low-income populations (50.4% vs. 44.4%, p< .001) and in urban areas (64.1% vs. 60.9%, p< .001) as compared to non-depressive disorders patients.

Person-Time Incidence Rate of BPPV

During the follow-up period, 44 patients (0.59 per 1,000 person-years) were diagnosed with BPPV in the depressive disorders group, and 99 patients (0.33 per 1,000 person-years) were diagnosed with BPPV in the control group. The incidence rate ratio (IRR) of BPPV between depressive disorders and control patients was 1.79 (95% CI [confidence interval], 1.23–2.58, p= .002). The IRR of BPPV remained higher in the depressive disorders than in the control patients among both sexes. When stratified with age, only patient younger than 65 years old have higher IRR of BPPV. The results are shown in Table 2.

The cumulative incidence of BPPV in the patients with depressive disorders was significantly higher than that in the control cohort (log-rank test, P < .001, Figure 1).

Risks of Newly Diagnosed BPPV among the Patients with and without Depressive Disorders

After adjusting for age, sex, common comorbidities and SLE, there was a higher risk of developing BPPV in patients with depressive disorders than in the control patients (HR =1.55, 95% CI, 1.08–2.23, p= .019). Results are summarized in Table 3.

Risks Factors for BPPV in patients with Depressive Disorders

As shown in Table 4, we predicted the development of BPPV in the depressive disorder cohorts by applying univariate analysis. Univariate analysis demonstrated that dyslipidemia (HR = 1.97, 95% CI, 0.99–3.89, p= .053), hyperthyroidism (HR = 3.74, 95% CI, 1.67–8.38, p< .001), cerebrovascular disease (HR =2.31, 95% CI, 0.91-5.85, p= .079) and SLE (HR =3.58, 95% CI, 1.11-11.56, p= .033) were possible prognostic factors. Multivariate analysis indicated that hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and SLE (HR = 3.47, 95% CI, 1.07-11.22, p= .038) were an independent risk factor for patients with depressive disorders.

Discussion

The two major findings in our study are as the following. First, patients with depressive disorders presented a 1.55 -fold greater risk of subsequently developing BPPV than did the general population by utilizing a nationwide population-based cohort study. Secondly, only hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and SLE (HR = 3.47, 95% CI, 1.07-11.22, p= .038) were independent risk factors to develop BPPV among patients with depressive disorders.

The strength of this study is using a nationwide population-based data to evaluate BPPV risk in patients with depressive disorders. Advantages of using our NHIRD in medical research have been previously described,[22] which include enormous sample size, lack of selection and participation bias and long term comprehensive follow up. Whereas the results of most studies demonstrated the correlation between BPPV and following depressive disorders,[23 24] to the best of our knowledge, this is the first study implying that patients with depressive disorders have higher risk of developing BPPV.

Though depressive disorder have been reported to produce somatic symptoms including symptoms like BPPV,[25] one research indicated that patients with unrecognized BPPV were more likely to have depressive disorder.[26] Another study pointed out that depressive disorders may be an early presentation of neural circuitry alterations involving connections between the vestibular system and anatomical area such as hippocampus, amygdala, and infralimbic cortex.[27] One Asian literature showed that depression symptoms may adversely affect BPPV recurrence.[28] Though there was no strong evidence consistent with our findings, evidence mentioned above may indirectly prove our hypothesis.

The pathophysiology of depressive disorders and subsequent BPPV is unknown. There are several proposed mechanisms to explain this association.First, dysregulation of oxidative and inflammatory processes in depressive disorders may result in subsequent BPPV

development. Numerous studies have demonstrated patients with depressive disorders have excessive oxidative stress and elevation in inflammatory responses.[29-32] Evidence supports a role for oxidative stress in otolith dysfunction leading to an increased risk of developing canalolithiasis, an essential step in the pathogenesis of BPPV.[33-36] Additional studies conclude depressive disorders associated with oxidative stress result in vestibular hair cells and neuronal damage in the inner ear,[37] which contributes to vestibular dysfunction and subsequent BPPV development.[38 39]Second, depressive disorders may induce abnormalities of the hypothalamus-pituitary-adrenal axis, which may hinder the inner ear blood flow and influence inner ear fluid balance. These abnormalities lead to dysfunction of the otoconial homeostasis,[18 40] an established risk factor for development of BPPV.[41] Therefore, alterations to the neuroendocrine system may be the link between depressive disorders and the development of BPPV. Third, BPPV development in depressive disorders may be induced by serotonin dysfunction. The vestibular nucleus complex is composed of a large number of serotonin receptors, and lack of serotonin may result in a substantial impact on the electrophysiological activity of neurons, and dysfunction of the vestibular nucleus complex.[42] Previous studies have hypothesized a role for vestibular nucleus damage in the pathogenesis of BPPV development.[39 43]Fourth, the dysregulation of the immune system, frequently observed in depressive disorders,[44 45] has proved to be an essential part of BPPV pathogenesis. Stone and Francis[46] suggest BPPV could develop by immune system's direct attack or indirect attack, resulting in debris within the inner ears. This explanation could be confirmed by studies demonstrated the association of several autoimmune diseases, such as systemic sclerosis,[47]SLE, ulcerative colitis, Sjogren's syndrome, and rheumatoid arthritis[46] in the development of BPPV. Consistent with the studies mentioned above, we found that SLE is a risk factor for BPPV among depressive cohort (Table 4) but not for all the participants (Table

3) in this study. Based on the previous studies, several results of the studies could provide the evidence revealing that the comorbidities with depressive disorder and SLE would result in the exacerbation of the SLE disease activities, no matter the possible explanations were psychological or behavioral issues such as lack of insight and poor anti-inflammatory drug compliance.[48-50] The evidence indicated that the severity of inflammatory processes on the differences between the patients with depressive disorder alone and the depressive patients comorbid with SLE.

We conclude patients with depressive disorders are more likely to develop BPPV if they are afflicted with hyperthyroidism. Mechanical movements of thyroid autoantibodies in the inner ear fluid or the development of autoimmune microangiitis in the labyrinth can result in BPPV in the presence of hyperthyroidism or hypothyroidism.[51] Other studies support a role for thyroid hormone fluctuations[52] and circulating anti-thyroid autoantibodies [53] related to vestibular dysfunction in subsequent BPPV development. Therefore, dysregulation of the immune system may play a vital role between hyperthyroidism and BPPV as documented by our study. In addition, we inferred that hyperthyroidism altered calcium metabolism and otoconia dissolve impairment may play a role in developing BPPV among depressive disorders patients. Up to 20 percent of thyrotoxic patients have mild hypercalcemia because of thyroid hormone-mediated bone resorption[54]. Otoconia, mainly synthesized from calcium[55], which breaks free and moves into the semicircular canals was the fundamental pathophysiology of BPPV[8]. Therefore, hyperthyroidism with increased calcium might lead to increased concentration of free calcium in the endolymph and reduce its capacity to dissolve the dislodged otoconia[56], this mechanism involved in the pathophysiology of BPPV.

Though there is no direct evidence support the pathophysiology of BPPV occurred in patients co-existence with depressive disorder and hyperthyroidism. Patients suffered from

symptoms like palpitation, insomnia, anxiety, and irritability, which symptoms usually belonging to hyperthyroidism and was difficult to discriminate from the psychiatric disorder, have been proposed easily seeking medical treatment[57]. Therefore, we proposed that hyperthyroidism related panic-like symptoms may increase the chance of diagnosis of BPPV through greater medical contact.

There are several limitations in this study. The first limitation relates to the lack of detailed information regarding tobacco use, alcohol consumption, head position in bed, and family history of BPPV in patient data collected from the NHIRD, factors which may influence risk of BPPV development.[58-60] Thus, we were unable to control for these potentially confounding factors. Second, the NHIRD is an administrative database, which lacks detailed clinical data regarding severity and outcomes of BPPV patients, which interferes with analysis of BPPV prognoses in the cohort. Third, in the claims-based study design, only patients seeking medical service would be identified in the Registry of NHIRD and these identification issues may either overestimate or underestimate the results. Fourth, our study did not provide any information about medications administered for BPPV.

Since profound health burden and extensive health care utilization may be influential with BPPV development.[61 62] Our findings and findings in other literature raised our attention to unrecognized BPPV and inappropriate treatment among patients with depressive disorders may lead to disabling and related poor quality of life.

Conclusions

In the population-based retrospective study, we found that patients with depressive disorders have statistically higher risk of developing BPPV. Furthermore, hyperthyroidism and SLE were identified an independent risk factor to develop BPPV for patients with depressive disorders. Future studies are required to clarify the underlying biological

mechanisms of these associations. Clinicians are encouraged to provide appropriate medical care for those who diagnosed with BPPV and preexisting depressive disorder. Monitoring and management depressive symptoms for the high-risk patients are also warranted.

List of abbreviations:

BPPV, benign paroxysmal positional vertigo; NHI, National Health Insurance; LHID 2000, Longitudinal Health Insurance Database 2000; HWDC, Health and Welfare Data Science Center; MOHW, Ministry of Health and Welfare; NHIRD, National Health Insurance Research Database; ICD-9-CM, the International Classification of Diseases, ninth revision, Clinical Modification; IRRs, incidence rate ratios; HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval.

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Author contributions

Chiao-Lin Hsu and Li-Yu, Hu wrote the manuscript. Cheng-Che Shen and Ti, Lu helped with study design and data collection. Cheng-Che Shen, Shih-Jen Tsai and Yao-Min Hung contributed to the revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interest.

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Legend for Figure 1:

Fig.1 Cumulative incidence of benign paroxysmal positional vertigo in depressive disorders and comparison cohort

The cumulative incidence of benign paroxysmal positional vertigo in patients with depressive disorders was significantly higher than that in the comparison cohort

Data availability statement

The data that support the findings of this study are available from the Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW) (http://www.mohw.gov.tw/cht/DOS/) for the researchers in Taiwan. Data are available at http://dep.mohw.gov.tw/DOS/np-2497-113.html (Chinese only currently) with the permission of HWDC, Department of Statistics, MOHW.

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Table 1 Baseline Characteristics of Patients with and without Depressive Disorders

Demographic data	Patients with Depressive Disorders *n*= 10,297		Patients without Depressive Disorders *n*= 41,188		*P* value
	n	%	*n*	%	
Age (years)[a]	39 (30–51)		39 (30–51)		
≥65	1,036	10.1	4,143	10.1	.999
<65	9,261	89.9	37,045	89.9	
Sex					
Male	4,012	39.0	16,048	39.0	1.000
Female	6,285	61.0	25,140	61.0	
Comorbidities					
Hypertension	2,124	20.6	5,444	13.2	<.001
Diabetes mellitus	1,236	12.0	3,112	7.5	<.001
Dyslipidemia	1,541	14.5	3,829	9.3	<.001
Coronary artery disease	87	0.8	235	0.6	.002
Hyperthyroidism	511	5.0	727	1.8	<.001
Hypothyroidism	116	1.1	193	0.5	<.001
Cerebrovascular disease	573	5.6	1,106	2.7	<.001
Systemic lupus erythematosus	216	2.1	437	1.1	<.001
Degree of urbanization					
Urban	6,599	64.1	25,196	60.9	<.001
Suburban	2,680	26.0	12,172	29.4	
Rural	817	7.9	3,205	7.8	
Income group					
Low income	5,189	50.4	18,340	44.4	<.001
Medium income	3,819	37.1	16,426	39.7	

High income	1,289	12.5	6,422	15.5	
Follow-up years[a]	7.19 (5.96–8.48)		7.22 (6.00–8.51)		.002

[a]Median (interquartile range)

Table 2 Person-Time Incidence of Benign Paroxysmal Positional Vertigo (BPPV) in Patients with and without Depressive Disorders

	Patients with Depressive Disorders		Patients without Depressive Disorders		Rate ratio (95% CI)	*P* value
	No. of BPPV	Per 1,000 person-years	No. of BPPV	Per 1,000 person-years		
Total	44	0.59	99	0.33	1.79 (1.23–2.58)	.002
Age						
≥65	7	0.98	15	0.51	1.90 (0.66–4.95)	.153
<65	37	0.55	84	0.31	1.77 (1.17–2.64)	.003
Sex						
Male	16	0.56	31	0.27	2.08 (1.16–3.76)	.023
Female	28	0.62	68	0.37	1.66 (1.07–2.56)	.030

CI, confidence interval

Table 3 Analyses of Risk Factors for Benign Paroxysmal Positional Vertigo in Patients with and without Depressive Disorders

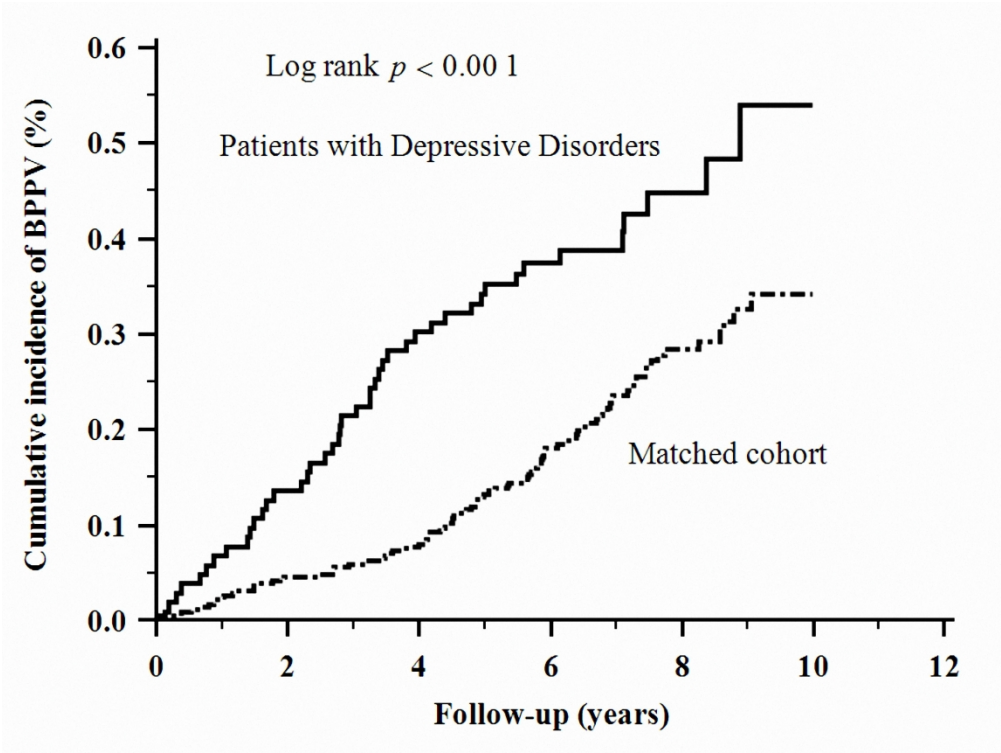
	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Depressive Disorders	1.79 (1.26–2.56)	<.001	1.55 (1.08–2.23)	.019
Age (≥65 = 1, <65= 0)	1.69 (1.07–2.66)	.002		
Sex (Female = 1, Male = 0)	1.29 (0.91–1.82)	.158		
Comorbidities				
Hypertension	1.91 (1.30–2.81)	<.001		
Diabetes mellitus	1.36 (0.80–2.32)	.261		
Dyslipidemia	2.15 (1.42–3.27)	<.001	1.78 (1.15–2.75)	.010
Coronary artery disease	5.06 (1.87–13.67)	<.001	3.29 (1.18–9.17)	.023
Hyperthyroidism	2.90 (1.48–5.70)	.002	2.46 (1.24–4.87)	.010
Hypothyroidism	1.26 (0.18–9.02)	.817		
Cerebrovascular disease	3.23 (1.83–5.71)	<.001	2.24 (1.21–4.15)	.010
Systemic lupus erythematosus	2.44 (0.90-6.60)	.079		
Degree of urbanization				
Urban	Reference			
Suburban	1.10 (0.77–1.57)	.606		
Rural	4.38 (0.18–1.08)	.072		
Income group				
Low income	Reference			
Medium income	0.98 (0.69–1.38)	.886		
High income	0.65 (0.37–1.14)	.133		

HR, hazard ratio; CI, confidence interval

Table 4 Analyses of Risk Factors for Benign Paroxysmal Positional Vertigo in Patients with Depressive Disorders

	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≥65 = 1, <65 = 0)	1.75 (0.78–3.93)	.174		
Sex (Female = 1, Male = 0)	1.10 (0.60–2.04)	.752		
Comorbidities				
Hypertension	0.88 (0.41–1.90)	.747		
Diabetes mellitus	0.98 (0.39–2.49)	.969		
Dyslipidemia	1.97 (0.99–3.89)	.053		
Coronary artery disease	2.93 (0.40–21.26)	.288		
Hyperthyroidism	3.74 (1.67–8.38)	<.001	3.75 (1.67–8.42)	.001
Hypothyroidism	2.17 (0.30–15.75)	.444		
Cerebrovascular disease	2.31 (0.91–5.85)	.079		
Systemic lupus Erythematosus	3.58 (1.11-11.56)	.033	3.47(1.07-11.22)	.038
Degree of urbanization				
Urban	Reference			
Suburban	1.53 (0.82–2.86)	.180		
Rural	0.31 (0.04–2.28)	.249		
Income group				
Low income	Reference			
Medium income	1.33 (0.71–2.52)	.377		
High income	1.24 (0.50–3.11)	.644		

HR, hazard ratio; CI, confidence interval



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