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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, benign peripheral persistent vertigo, hyperthyroidism, risk factor, 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 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.<sup>1</sup> Patients with depressive disorders have been reported with an increased risk of mortality and propose the classification of depressive disorders as life-threatening.<sup>2,3</sup> Furthermore, people with depressive disorders have been reported with many somatic symptoms and result in increased need for clinical services, associated economic costs,<sup>4,5</sup> and considerable loss in quality of life.<sup>6</sup>

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.<sup>7</sup> The fundamental pathophysiology of BPPV is dislodged calcium carbonate crystals in the utricle of the inner ear entering the semicircular canals.<sup>8</sup> Old age<sup>7</sup> 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.<sup>9,10</sup> The results of most studies have been reported the higher rate of coexistence of depression and vestibular disorders<sup>11-13</sup> will lead to a vicious circle and a serious influence on the quality of life<sup>14</sup> 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

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3 indicates that life stressors and related depressive disorder may be seen as a trigger of  
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5 vestibular dysfunction, that is, a potential precursor of BPPV.<sup>15</sup>  
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8 Therefore, considering the debates on the association between the depression and  
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10 BPPV and no large-scaled study have tried to investigate the issue, we designed a  
11  
12 nationwide retrospective cohort study to explore the association between depressive  
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14 disorder and the subsequent BPPV. In addition, independent risk factors for developing  
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16 BPPV among patients with depressive disorders were also investigated.  
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## 18 **Materials and Methods**

### 19 *Data Sources*

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22 Nearly 99% of Taiwan's population utilizes health care services as a consequence of the  
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24 National Health Insurance (NHI) Program Bold Legislative Act enacted in 1995.<sup>16</sup> The  
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26 program offers comprehensive medical care coverage regarding outpatient, inpatient,  
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28 emergency visits, and Chinese medicine to all residents of Taiwan. The NHI research  
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30 database (NHIRD) contains comprehensive information with regard to clinical practice,  
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32 including prescription details and diagnostic codes in the International Classification of  
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34 Diseases, Ninth revision, Clinical Modification (ICD-9-CM) format. The NHIRD is managed  
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36 by the National Health Research Institutes (NHRI) and privacy is maintained according to  
37  
38 directives from the Bureau of the NHI.<sup>17</sup> The data source for our study was obtained from the  
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40 Longitudinal Health Insurance Database 2005 (LHID2005), a dataset of the NHIRD.  
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42 LHID2005 contains the data of 1,000,000 beneficiaries which were sampled from January 1,  
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44 2005 to January 1, 2006, that is, collected from those who were available in the Registry of  
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46 the NHIRD in 2005. In addition, it is worth emphasizing that although the dataset was  
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48 collected from those available in 2005, the LHID20005 included all original claim data of  
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50 1,000,000 individuals from January 1, 1996 to December 31, 2009. Moreover, the NHRI  
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3 affirms that there are no statistical differences in the distributions of age, sex, or health care  
4 costs between the data in the LHID2005 and that of the NHIRD.<sup>17</sup>  
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#### 7 *Availability of Data and Materials section*

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9 The NHIRD is addressed in publicity by the NHRI and the use of NHIRD is only for  
10 research purposes. All applicants must obey the Computer-Processed Personal Data  
11 Protection Law<sup>18</sup> and relevant regulations of Bureau of National Health Insurance and NHRI.  
12  
13 Moreover, applicants and their supervisor were asking for signing agreements upon  
14 application submission. All applications are reviewed for approval of data delivered. Request  
15 for the dataset may be sent an e-mail to the NHRI at [nhird@nhri.org.tw](mailto:nhird@nhri.org.tw) or call at  
16 +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30  
17 (UTC+8).  
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19

#### 20 *Study design and subjects*

21  
22 We utilized data from the LHID 2005 and conducted a retrospective cohort study using  
23 a dataset collected between January 1, 2000 and December 31, 2004. We enrolled patients  $\geq$   
24 20 years who were diagnosed with depressive disorders by a psychiatrist according to the  
25 ICD-9-CM depressive disorders diagnosis codes: 296.2X-296.3X, 300.4, and 311.X. We  
26 defined the date of enrolling an adult patient with depressive disorders as case cohort  
27 between 2000 and 2004 as enrolment date. For each patient with depressive disorders  
28 included in the final cohort, 4 age- and sex-matched control patients without depressive  
29 disorders were randomly selected on the same enrolment date from the LHID 2005. We  
30 excluded patients who were previously diagnosed with BPPV (ICD-9-CM code 386.11)  
31 before the enrollment date. For each patient with depressive disorders included in the final  
32 cohort, 4 age- and sex-matched control patients without depressive disorders were randomly  
33 selected from the LHID 2005. The primary clinical outcome assessed was only BPPV  
34 diagnosed by neurologists or otorhinolaryngologists. We excluded those who diagnosed  
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3 with acoustic neuroma (ICD-9-CM code 225.1), Meniere's disease (ICD-9-CM code  
4 386.0X), vestibular neuritis (ICD-9-CM code 386.12), labyrinthitis (ICD-9-CM code  
5 386.3X), sudden hearing loss (ICD-9-CM code 388.2), and head injury (ICD-9-CM code  
6 310.2, 800.X, 804.X, 850.X–854.×, 870.X–873.X, 907.0, 907.1, 959 .0X, and V15.52)  
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8 during the follow-up period. The cohort including patients with and without depressive  
9 disorders was observed until the development of BPPV, death, withdrawal from the NHI  
10 system, or December 31, 2009.  
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### 18 *Ethics Statement*

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

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37 The incidence of newly diagnosed BPPV in patients with depressive disorders and  
38 controls during the observational period was calculated and stratified by sex and age ( $\geq 65$   
39 years or  $< 65$  years). Comparisons between continuous variables were conducted with the  
40 independent *t*-test. Chi-squared analysis was used to examine the association of two  
41 categorical characteristics between the depressive disorders and control cohort. A Cox  
42 proportional hazards model was used to evaluate confounding variables and whether  
43 depressive disorders increase the risk of developing BPPV. The confounding variables were  
44 age, sex, and common comorbidities including hypertension, diabetes mellitus, dyslipidemia,  
45 coronary artery disease, congestive heart failure, hyperthyroidism, hypothyroidism,  
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3 cerebrovascular disease, and malignancy; urbanization; and monthly income (table 3).

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5 Another Cox proportional-hazards regression model was performed again to identify variables  
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7 that predicted BPPV in the patients with depressive disorders (table 4). The cumulative  
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9 incidences of BPPV were compared between depressive disorder and control cohorts using  
10  
11 Kaplan–Meier curves and stratified log rank test was applied to determine the differences in  
12  
13 the risk for BPPV in the cohort.  
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## 15 **Results**

### 16 *Participant Selection*

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18 We analyzed 10,297 patients with depressive disorders and 41,188 control patients. The  
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20 majority of patients in the cohort were female (61%). The median age was 39 years  
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22 (interquartile range [IQR], 30–51 years), and the median follow-up period was 7.19 years  
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24 (IQR = 5.96–8.48 years) for patients with depressive disorders and 7.22 years (IQR =  
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26 6.00–8.51 years) for control patients (p=0 .002). Table 1 includes comparisons of  
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28 demographic, clinical variables, and socioeconomic data between the control and depressive  
29  
30 cohorts. In the depressive disorders group, the most common comorbidities were hypertension  
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32 (2,124 patients, 20.6%), diabetes mellitus (1,236 patients, 12.0%), and dyslipidemia  
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34 (1,541 patients, 14.5%). As compared to the controls, depressive disorders patients had  
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36 significantly more physical comorbidities. Besides, depressive disorders patients had a  
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38 significantly higher prevalence in low-income populations (50.4% vs. 44.4%, p<0.001) and in  
39  
40 urban areas (64.1% vs. 60.9%, p< 0.001) as compared to non-depressive disorders patients  
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### 45 *Incidence Rate of BPPV*

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47 During the follow-up period, 44 patients (0.59 per 1,000 person-years) were diagnosed  
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49 with BPPV in the depressive disorders group, and 99 patients (0.33 per 1,000 person-years)  
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51 were diagnosed with BPPV in the control group. The incidence risk ratio (IRR) of BPPV  
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53 between depressive disorders and control patients was 1.79 (95% CI [confidence interval],  
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3 1.23–2.58,  $p=0.002$ ). When stratified by sex and age, the IRR of BPPV remained higher in the  
4 depressive disorders than in the control patients. The results are shown in Table 2.  
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### 6 ***Risks of Newly Diagnosed BPPV among the Patients with and without Depressive***

#### 7 ***Disorders***

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

## 4 **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,<sup>19</sup> which include enormous sample size,

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2  
3 lack of selection and participation bias and long-term comprehensive follow up. Whereas  
4 the results of most studies demonstrated the correlation between BPPV and following  
5 depressive disorders,<sup>20 21</sup> to the best of our knowledge, this is the first study implying that  
6 patients with depressive disorders have higher risk of developing BPPV.  
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Though depressive disorder have been reported to produce somatic symptoms including symptoms like BPPV,<sup>22</sup> one research indicated that patients with unrecognized BPPV were more likely to have depressive disorder.<sup>23</sup> 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.<sup>24</sup> One Asian literature showed that depression symptoms may adversely affect BPPV recurrence.<sup>25</sup> 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.<sup>26-29</sup> 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.<sup>30-33</sup> Additional studies conclude depressive disorders associated with oxidative stress result in vestibular hair cells and neuronal damage in the inner ear,<sup>34</sup> which contributes to vestibular dysfunction and subsequent BPPV development.<sup>35 36</sup> 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,<sup>15 37</sup> an established risk factor for development of

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

17  
18 We conclude patients with depressive disorders are more likely to develop BPPV if they  
19 are afflicted with hyperthyroidism. Mechanical movements of thyroid autoantibodies in the  
20 inner ear fluid or the development of autoimmune microangiitis in the labyrinth can result in  
21 BPPV in the presence of hyperthyroidism or hypothyroidism.<sup>46</sup> Other studies support a role  
22 for thyroid hormone fluctuations<sup>47</sup> and circulating anti-thyroid autoantibodies<sup>48</sup> related to  
23 vestibular dysfunction in subsequent BPPV development. Therefore, dysregulation of the  
24 immune system may play a vital role between hyperthyroidism and BPPV as documented  
25 by our study.

26  
27 There are several limitations in this study. The first limitation relates to the lack of  
28 detailed information regarding tobacco use, alcohol consumption, head position in bed, and  
29 family history of BPPV in patient data collected from the NHIRD, factors which may

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2  
3 influence risk of BPPV development.<sup>49-51</sup> Thus, we were unable to control for these  
4  
5 potentially confounding factors. Second, the NHIRD is an administrative database, which  
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7 lacks detailed clinical data regarding severity and outcomes of BPPV patients, which  
8  
9 interferes with analysis of BPPV prognoses in the cohort. Third, in the claims-based study  
10  
11 design, only patients seeking medical service would be identified in the Registry of NHIRD  
12  
13 and these identification issues may underestimate the results.  
14

15  
16 Since profound health burden and extensive health care utilization may be influential  
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18 with BPPV development.<sup>52-53</sup> Our findings and findings in other literature raised our  
19  
20 attention to unrecognized BPPV and inappropriate treatment among patients with  
21  
22 depressive disorders may lead to disabling and related poor quality of life.  
23

## 24 **Conclusions**

25  
26 In the population-based retrospective study, we found that patients with depressive  
27  
28 disorders have statistically higher risk of developing BPPV. Furthermore, hyperthyroidism  
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30 was identified an independent risk factor to develop BPPV for patients with depressive  
31  
32 disorders. Future studies are required to clarify the underlying biological mechanisms of these  
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34 associations. Clinicians are encouraged to provide appropriate medical care for those who  
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36 diagnosed with BPPV and preexisting depressive disorder. Monitoring and management  
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38 depressive symptoms for the high-risk patients are also warranted.  
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## 41 **List of abbreviations:**

42  
43 BPPV, benign paroxysmal positional vertigo; NHI, National Health Insurance; LHID  
44  
45 2005, Longitudinal Health Insurance Database 2005; NHIRD, National Health Insurance  
46  
47 Research Database; ICD-9-CM, the International Classification of Diseases, ninth revision,  
48  
49 Clinical Modification; IRRs, incidence rate ratios; HR, hazard ratio; aHR, adjusted hazard  
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51 ratio; CI, confidence interval.  
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4  
5 comments and fruitful discussion on the manuscript.  
6

### 7 **Authors Contributions**

8  
9 Chiao-Lin Hsu and Li-Yu, Hu wrote the manuscript. Cheng-Che Shen and Ti, Lu helped  
10  
11 with study design and data collection. Cheng-Che Shen, Shih-Jen Tsai and Yao-Min Hung  
12  
13 contributed to the revision of the manuscript. All authors read and approved the final  
14  
15 manuscript.  
16

### 17 **Competing interests**

18  
19 The authors declare that they have no conflict of interest.  
20  
21

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25  
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27  
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30 for publication.  
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**Table 1 Baseline Characteristics of Patients with and without Depressive Disorders**

Demographic data	Patients with Depressive Disorders		Patients without Depressive Disorders		<i>P</i> value
	<i>n</i>	%	<i>n</i>	%	
Age (years) <sup>a</sup>	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					

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3	Urban	6,599	64.1	25,196	60.9	<.001
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5	Suburban	2,680	26.0	12,172	29.4	
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7	Rural	817	7.9	3,205	7.8	
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10	Income group					
11						
12	Low income	5,189	50.4	18,340	44.4	<.001
13						
14	Medium income	3,819	37.1	16,426	39.7	
15						
16	High income	1,289	12.5	6,422	15.5	
17						
18	Follow-up years <sup>a</sup>	7.19 (5.96–8.48)		7.22 (6.00–8.51)		.002
19						

<sup>a</sup>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**

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Depressive Disorders	1.79 (1.26–2.56)	<.001	1.57 (1.09–2.26)	.014
Age ( $\geq 65 = 1$ , $<65 = 0$ )	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		

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

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age ( $\geq 65 = 1$ , $< 65 = 0$ )	1.75 (0.78–3.93)	.174		
Sex (Female = 1, Male = 0)	1.10 (0.60–2.04)	.752		
<b>Comorbidities</b>				
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		
<b>Degree of urbanization</b>				
Urban	Reference			
Suburban	1.53 (0.82–2.86)	.180		
Rural	0.31 (0.04–2.28)	.249		
<b>Income group</b>				
Low income	Reference			
Medium income	1.33 (0.71–2.52)	.377		
High income	1.24 (0.50–3.11)	.644		

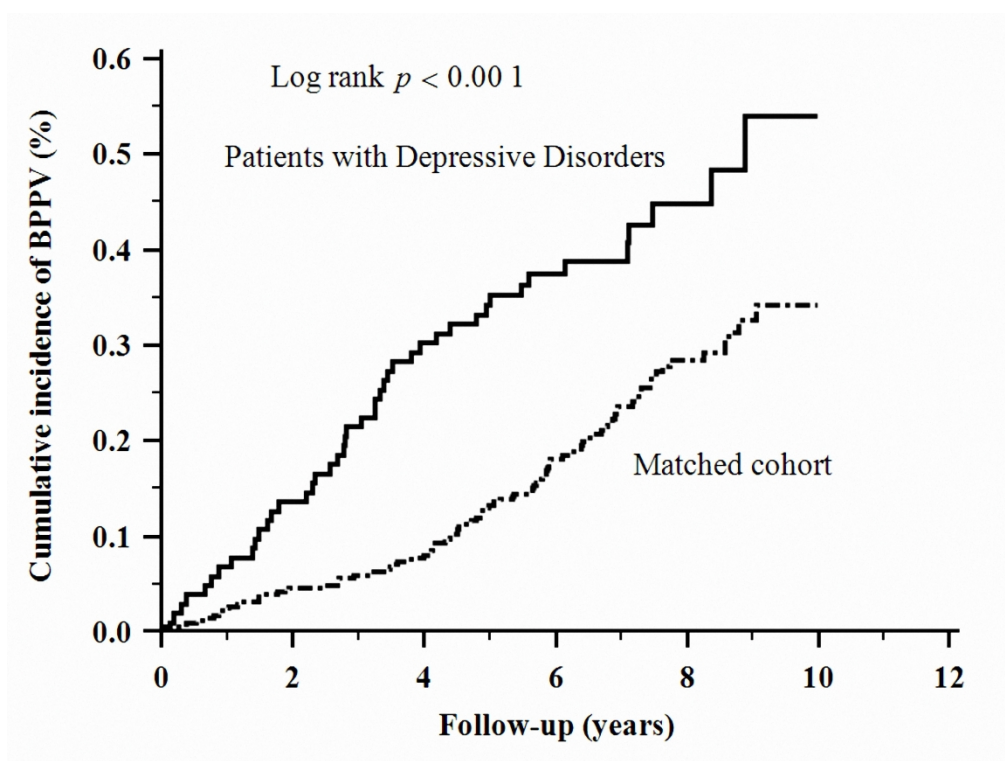
HR, hazard ratio; CI, confidence interval

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5 Cumulative incidence of benign paroxysmal positional vertigo in patients with and without  
6 depressive disorders. The cumulative incidence of BPPV in patients with depressive disorders  
7 was significantly higher than that in the matched cohort. (log-rank test,  $p < 0.001$ )  
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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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

1	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	8,9
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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8	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
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10	<b>Discussion</b>			
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12	Key results	18	Summarise key results with reference to study objectives	9
13	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
14				
15	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
16				
17				
18	Generalisability	21	Discuss the generalisability (external validity) of the study results	11,12
19				
20	<b>Other information</b>			
21	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
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\*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>.

# BMJ Open

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

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<b>Primary Subject Heading</b>:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Epidemiology, General practice / Family practice, Mental health, Rehabilitation medicine
Keywords:	depressive disorder, hyperthyroidism, risk factor, cohort study, systemic lupus erythematosus, benign paroxysmal positional vertigo

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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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## 1 Abstract

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

5 **Design:** Longitudinal nationwide cohort study

6 **Setting:** National health insurance research database in Taiwan

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

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

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



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3 24 **Conclusions:** Patients with depressive disorders may have an increased risk of developing  
4  
5 25 BPPV, especially those who have hyperthyroidism and SLE.  
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8 26

9  
10 27 **Keywords:** Depressive disorders; benign paroxysmal positional vertigo; hyperthyroidism;  
11  
12 28 systemic lupus erythematosus; risk factor; cohort study  
13

### 14 29 **Strengths and limitations of this study**

- 15  
16  
17 30 1. The incidence of benign peripheral persistent vertigo (BPPV) among depressive disorders  
18  
19 31 patient remains unclear. This longitudinal population-based data was conducted to assess the  
20  
21 32 risk of BPPV in patients with depressive disorders.  
22  
23  
24 33 2. The NHIRD lacks detailed clinical data regarding severity and outcomes of BPPV  
25  
26 34 3. Results from our study may underestimate the current condition since only patients  
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28 35 seeking medical service would be identified in the Registry of NHIRD.  
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## 37 **Introduction**

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

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

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4 54 Psychiatric disorders or emotional stress are frequently observed in patients suffering  
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6  
7 55 from vertigo.<sup>12 13</sup> The results of most studies have been reported the higher rate of coexistence  
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10 56 of depression and vestibular disorders<sup>14-16</sup>. Which may lead to a vicious circle and a serious  
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13 57 influence on the quality of life<sup>17</sup>. Peripheral vertigo may play an essential role in the  
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16 58 pathophysiology of development of subsequent depressive disorder. However, most of these  
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19 59 studies report contradictory or conflicting results. Furthermore, when specified to explore the  
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22 60 association between depression and BPPV, only a relatively small-scaled case-control study  
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25 61 indicates that life stressors and related depressive disorder may be seen as a trigger of  
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27  
28 62 vestibular dysfunction, that is, a potential precursor of BPPV.<sup>18</sup>

31 63 Therefore, considering the debates on the association between the depression and  
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34 64 BPPV and no large-scaled study have tried to investigate the issue, we designed a nationwide  
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36  
37 65 retrospective cohort study to explore the association between depressive disorder and the  
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40 66 subsequent BPPV development. In addition, independent risk factors for developing BPPV  
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43 67 among patients with depressive disorders were also investigated.

## 46 68 **Materials and Methods**

### 49 69 *Data Sources*

52 70 Nearly 99% of Taiwan's population utilizes health care services as a consequence of the  
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54  
55 71 National Health Insurance (NHI) Program Bold Legislative Act enacted in 1995.<sup>19</sup> The

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4 72 program offers comprehensive medical care coverage regarding outpatient, inpatient,  
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7 73 emergency visits, and Chinese medicine to all residents of Taiwan. The NHI research  
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10 74 database (NHIRD) contains comprehensive information with regard to clinical practice,  
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13 75 including prescription details and diagnostic codes in the International Classification of  
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15  
16 76 Diseases, Ninth revision, Clinical Modification (ICD-9-CM) format. The NHIRD is managed  
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18  
19 77 by the National Health Research Institutes (NHRI) and privacy is maintained according to  
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21  
22 78 directives from the Bureau of the NHI.<sup>20</sup> The data source for our study was obtained from the  
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25 79 Longitudinal Health Insurance Database 2000 (LHID2000), a dataset of the NHIRD. The  
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28 80 LHID 2000, which contains all original claims data for 1,000,000 subjects, is a representative  
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31 81 database randomly selected from the 2000 Registry of Beneficiaries under the NHI program.  
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34 82 Which also maintains the registration data of everyone who was a beneficiary of the National  
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37 83 Health Insurance program during the period of 1996–2000. Moreover, the NHRI affirms that  
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39  
40 84 there are no statistical differences in the distributions of age, sex, or health care costs between  
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42  
43 85 the data in the LHID2000 and that of the NHIRD.<sup>20</sup> For each patient with depressive  
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45  
46 86 disorders included in the final cohort

#### 47 48 49 87 *Availability of Data and Materials section*

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51  
52 88 The NHIRD is addressed in publicity by the NHRI and the use of NHIRD is only for  
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55 89 research purposes. All applicants must obey the Computer-Processed Personal Data  
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4 90 Protection Law<sup>21</sup> and relevant regulations of Bureau of National Health Insurance and NHRI.

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6  
7 91 Moreover, applicants and their supervisor were asking for signing agreements upon

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10 92 application submission. All applications are reviewed for approval of data delivered. Request

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12  
13 93 for the dataset may be sent an e-mail to the NHRI at [nhird@nhri.org.tw](mailto:nhird@nhri.org.tw) or call at

14  
15  
16 94 +886-037-246166 ext. 33603 for immediate service. Office Hour: Monday-Friday 8:00-17:30

17  
18  
19 95 (UTC+8).

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21  
22 96 The NHIRD, which was open to the researchers in Taiwan, was available from the

23  
24  
25 97 Health and Welfare Data Science Center (HWDC), Ministry of Health and Welfare (MOHW)

26  
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28 98 (<http://www.mohw.gov.tw/cht/DOS/>). The data underlying this study is from the NHIRD.

29  
30  
31 99 Interested researchers can obtain the data through formal application to the Ministry of Health

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34 100 and Welfare, Taiwan. In the last sentence of the paragraph, which said "Kindly visit MOHW

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36  
37 101 and NHIA on-site services for National Health Insurance Data." The Database was transferred

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39  
40 102 to a higher-level government administration, called the "Health and Welfare Data Science

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43 103 Center (HWDC)" for more efficient health-related data linkage, wider application, and better

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46 104 security management. At present, interested researchers could still obtain the National Health

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49 105 Insurance Data in Taiwan through formal application to the Health and Welfare Data Science

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52 106 Center (HWDC), Department of Statistics, Ministry of Health and Welfare (MOHW). HWDC,

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54  
55 107 MOHW website (Chinese only currently): <http://dep.mohw.gov.tw/DOS/np-2497-113.html>

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4 108 *Study design and subjects*  
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7 109 We utilized data from the LHID 2000 and conducted a retrospective cohort study using a  
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10 110 dataset collected between January 1, 2000 and December 31, 2004. We enrolled patients  $\geq 20$   
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13 111 years and received at least twice diagnosis of depressive disorders by psychiatrists with  
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16 112 ICD-9-CM depressive disorders diagnosis codes of 296.2X-296.3X, 300.4, and 311.X. We  
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18  
19 113 defined the date of enrolling an adult patient with depressive disorders as case cohort between  
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21  
22 114 2000 and 2004 as enrolment date. We excluded both in depressive disorders and control  
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24  
25 115 groups who were previously diagnosed with BPPV (ICD-9-CM code 386.11) before the  
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27  
28 116 enrollment date. We also used A-code (A-code: A249) to exclude patients who had vertigo  
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30  
31 117 related diagnoses before diagnosed with BPPV between 1996 and 2000. Which included  
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34 118 acute myringitis, chronic myringitis, perforation of tympanic membrane, traumatic perforation  
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37 119 of tympanic membrane, cholesteatoma of the middle ear, Meniere's disease, peripheral vertigo,  
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39  
40 120 vestibulopathy, vertigo of central origin, labyrinthitis, presbycusis, sudden hearing loss,  
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43 121 tinnitus, and otalgia  
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46 122 The A-code, a much briefer version of the ICD-9-CM codes, is another disease  
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49 123 classification system launched for fulfilling medical claims. The A-code was mainly used for  
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52 124 ambulatory care before 2000 in Taiwan and has switched to the ICD-9-CM codes by NHI  
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55 125 program since 2000 to perpetuate consistency between different claims records and to truly  
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4 126 reflect the distribution of various diseases. The cohort including patients with and without  
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7 127 depressive disorders was observed until the development of BPPV, death, withdrawal from  
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10 128 the NHI system, or December 31, 2009. The primary clinical outcome in our study was only  
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13 129 BPPV diagnosed by neurologists or otorhinolaryngologists. For each patient with depressive  
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16 130 disorders included in the final cohort, 4 age- and sex-matched control patients without  
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19 131 depressive disorders were randomly selected on the same enrolment date from the LHID 2000.  
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22 132 Finally, we identified 10,297 patients with depressive disorders. To assemble a comparison  
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25 133 cohort, we randomly selected 41,188 enrollees without a history of depressive disorders.  
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#### 28 134 *Ethics Statement*

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31 135 This study was approved by the Institutional Review Board of the Kaohsiung Veterans  
32  
33  
34 136 General Hospital (No.: VGHKS14-CT7-07). We could not obtain written consent from study  
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36  
37 137 patients as the NHI dataset consists of de-identified secondary data for research purposes. The  
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40 138 IRB of Kaohsiung Veterans General Hospital issued a formal written waiver for the need for  
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43 139 consent.  
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#### 46 140 *Statistical analyses*

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48  
49 141 The incidence of newly diagnosed BPPV in patients with depressive disorders and  
50  
51 142 controls during the observational period was calculated and stratified by sex and age ( $\geq 65$   
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53 143 years or  $< 65$  years). Comparisons between continuous variables were conducted with the  
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56 144 independent *t*-test. Chi-squared analysis was used to examine the association of two  
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3 145 categorical characteristics between the depressive disorders and control cohort. A Cox  
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5 146 proportional hazards model was used to evaluate confounding variables and whether  
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7 147 depressive disorders increase the risk of developing BPPV. The confounding variables were  
8  
9 148 age, sex, and common comorbidities including hypertension, diabetes mellitus, dyslipidemia,  
10  
11 149 coronary artery disease, hyperthyroidism, hypothyroidism, cerebrovascular disease, and  
12  
13 150 systemic lupus erythematosus (SLE). Another Cox proportional-hazards regression model  
14  
15 151 was performed again to identify variables that predicted BPPV in the patients with depressive  
16  
17 152 disorders. The variables that demonstrated a moderately significant statistical relationship  
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19 153 with BPPV in the univariate analysis ( $P < .1$ ) were entered through forward selection in a  
20  
21 154 multivariate analysis.  
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25  
26 155 The cumulative incidences of BPPV were compared between depressive disorder and  
27  
28 156 control cohorts using Kaplan–Meier curves. Stratified log rank test was applied to determine  
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30 157 the differences in the risk for BPPV in the cohort.  
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#### 34 158 *Patient and Public involvement*

35  
36 159 The data source used for this study was the claims data of Taiwan's NHIRD. We did not  
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38 160 involve patients/service users in the research question, the outcome measures, or the design or  
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40 161 implementation of the study. There are no plans to disseminate the results of the research to  
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42 162 study participants.  
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## 46 163 **Results**

### 47 48 49 164 *Participant Selection*

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52 165 We analyzed 10,297 patients with depressive disorders and 41,188 control patients. The  
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55 166 majority of patients in the cohort were female (61%). The median age was 39 years  
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4 167 (interquartile range [IQR], 30–51 years), and the median follow-up period was 7.19 years  
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6  
7 168 (IQR = 5.96–8.48 years) for patients with depressive disorders and 7.22 years (IQR =  
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9  
10 169 6.00–8.51 years) for control patients ( $p = .002$ ). Table 1 includes comparisons of demographic,  
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12  
13 170 clinical variables, and socioeconomic data between the control and depressive cohorts. In the  
14  
15  
16 171 depressive disorders group, the most common comorbidities were hypertension (2,124  
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19 172 patients, 20.6%), diabetes mellitus (1,236 patients, 12.0%), and dyslipidemia (1,541 patients,  
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21  
22 173 14.5%). As compared to the controls, depressive disorders patients had significantly more  
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24  
25 174 physical comorbidities. Besides, depressive disorders patients had a significantly higher  
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27  
28 175 prevalence in low-income populations (50.4% vs. 44.4%,  $p < .001$ ) and in urban areas (64.1%  
29  
30  
31 176 vs. 60.9%,  $p < .001$ ) as compared to non-depressive disorders patients.

### 34 177 ***Person-Time Incidence Rate of BPPV***

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37 178 During the follow-up period, 44 patients (0.59 per 1,000 person-years) were diagnosed  
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39  
40 179 with BPPV in the depressive disorders group, and 99 patients (0.33 per 1,000 person-years)  
41  
42  
43 180 were diagnosed with BPPV in the control group. The incidence rate ratio (IRR) of BPPV  
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45  
46 181 between depressive disorders and control patients was 1.79 (95% CI [confidence interval],  
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48  
49 182 1.23–2.58,  $p = .002$ ). The IRR of BPPV remained higher in the depressive disorders than in the  
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51  
52 183 control patients among both sexes. When stratified with age, only patient younger than 65  
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55 184 years old have higher IRR of BPPV. The results are shown in Table 2.

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4 185 The cumulative incidence of BPPV in the patients with depressive disorders was  
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7 186 significantly higher than that in the control cohort (log-rank test,  $P < .001$ , Figure 1).  
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10 187 ***Risks of Newly Diagnosed BPPV among the Patients with and without Depressive***  
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12  
13 188 ***Disorders***  
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16 189 After adjusting for age, sex, common comorbidities and SLE there was a higher risk of  
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19 190 developing BPPV in patients with depressive disorders than in the control patients (HR =1.55,  
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21  
22 191 95% CI, 1.08–2.23,  $p = .019$ ). Results are summarized in Table 3.  
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25 192 ***Risks Factors for BPPV in patients with Depressive Disorders***  
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28 193 As shown in Table 4, we predicted the development of BPPV in the depressive disorder  
29  
30  
31 194 cohorts by applying univariate analysis. Univariate analysis demonstrated that dyslipidemia  
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34 195 (HR = 1.97, 95% CI, 0.99–3.89,  $p = .053$ ), hyperthyroidism (HR = 3.74, 95% CI, 1.67–8.38,  
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36  
37 196  $p < .001$ ), cerebrovascular disease (HR =2.31, 95% CI, 0.91-5.85,  $p = .079$ ) and SLE (HR =3.58,  
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39  
40 197 95% CI, 1.11-11.56,  $p = .033$ ) were possible prognostic factors. Multivariate analysis indicated  
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42  
43 198 that hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42,  $p = .001$ ) and SLE (HR = 3.47, 95% CI,  
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45  
46 199 1.07-11.22,  $p = .038$ ) were an independent risk factor for patients with depressive disorders.  
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49 200 **Discussion**  
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52 201 The two major findings in our study are as the following. First, patients with depressive  
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55 202 disorders presented a 1.55 -fold greater risk of subsequently developing BPPV than did the  
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4 203 general population by utilizing a nationwide population-based cohort study. Secondly, only  
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7 204 hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and SLE (HR = 3.47, 95% CI,  
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10 205 1.07-11.22, p= .038) were independent risk factors to develop BPPV among patients with  
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12  
13 206 depressive disorders.

16 207 The strength of this study is using a nationwide population-based data to evaluate BPPV  
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19 208 risk in patients with depressive disorders. Advantages of using our NHIRD in medical  
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22 209 research have been previously described,<sup>22</sup> which include enormous sample size, lack of  
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24  
25 210 selection and participation bias and long term comprehensive follow up. Whereas the results  
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28 211 of most studies demonstrated the correlation between BPPV and following depressive  
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30  
31 212 disorders,<sup>23 24</sup> to the best of our knowledge, this is the first study implying that patients with  
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33  
34 213 depressive disorders have higher risk of developing BPPV.

37 214 Though depressive disorder have been reported to produce somatic symptoms including  
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39  
40 215 symptoms like BPPV,<sup>25</sup> one research indicated that patients with unrecognized BPPV were  
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42  
43 216 more likely to have depressive disorder.<sup>26</sup> Another study pointed out that depressive disorders  
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45  
46 217 may be an early presentation of neural circuitry alterations involving connections between the  
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49 218 vestibular system and anatomical area such as hippocampus, amygdala, and infralimbic  
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52 219 cortex.<sup>27</sup> One Asian literature showed that depression symptoms may adversely affect BPPV  
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4 220 recurrence.<sup>28</sup> Though there was no strong evidence consistent with our findings, evidence  
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6  
7 221 mentioned above may indirectly prove our hypothesis.  
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10 222 The pathophysiology of depressive disorders and subsequent BPPV is unknown. There  
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12  
13 223 are several proposed mechanisms to explain this association. First, dysregulation of oxidative  
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15  
16 224 and inflammatory processes in depressive disorders may result in subsequent BPPV  
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19 225 development. Numerous studies have demonstrated patients with depressive disorders have  
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21  
22 226 excessive oxidative stress and elevation in inflammatory responses.<sup>29-32</sup> Evidence supports a  
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24  
25 227 role for oxidative stress in otolith dysfunction leading to an increased risk of developing  
26  
27  
28 228 canalolithiasis, an essential step in the pathogenesis of BPPV.<sup>33-36</sup> Additional studies conclude  
29  
30  
31 229 depressive disorders associated with oxidative stress result in vestibular hair cells and  
32  
33  
34 230 neuronal damage in the inner ear,<sup>37</sup> which contributes to vestibular dysfunction and  
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36  
37 231 subsequent BPPV development.<sup>38 39</sup> Second, depressive disorders may induce abnormalities of  
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40 232 the hypothalamus-pituitary-adrenal axis, which may hinder the inner ear blood flow and  
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42  
43 233 influence inner ear fluid balance. These abnormalities lead to dysfunction of the otoconial  
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46 234 homeostasis,<sup>18 40</sup> an established risk factor for development of BPPV.<sup>41</sup> Therefore, alterations  
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48  
49 235 to the neuroendocrine system may be the link between depressive disorders and the  
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52 236 development of BPPV. Third, BPPV development in depressive disorders may be induced by  
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55 237 serotonin dysfunction. The vestibular nucleus complex is composed of a large number of  
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4 238 serotonin receptors, and lack of serotonin may result in a substantial impact on the  
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7 239 electrophysiological activity of neurons, and dysfunction of the vestibular nucleus complex.<sup>42</sup>  
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10 240 Previous studies have hypothesized a role for vestibular nucleus damage in the pathogenesis  
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12  
13 241 of BPPV development.<sup>39 43</sup>Fourth, the dysregulation of the immune system, frequently  
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15  
16 242 observed in depressive disorders,<sup>44 45</sup> has proved to be an essential part of BPPV pathogenesis.  
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19 243 Stone and Francis<sup>46</sup> suggest BPPV could develop by immune system's direct attack or  
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21  
22 244 indirect attack, resulting in debris within the inner ears. This explanation could be confirmed  
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24  
25 245 by studies demonstrated the association of several autoimmune diseases, such as systemic  
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28 246 sclerosis,<sup>47</sup>SLE, ulcerative colitis, Sjogren's syndrome, rheumatoid arthritis,<sup>46</sup> and chronic  
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31 247 inflammatory demyelinating polyneuropathy<sup>48</sup> in the development of BPPV. The relation  
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34 248 between immune system and BPPV was also in keeping with our result that SLE is a potential  
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37 249 risk factor for developing BPPV.

40 250 We conclude patients with depressive disorders are more likely to develop BPPV if they  
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43 251 are afflicted with hyperthyroidism. Mechanical movements of thyroid autoantibodies in the  
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46 252 inner ear fluid or the development of autoimmune microangiitis in the labyrinth can result in  
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49 253 BPPV in the presence of hyperthyroidism or hypothyroidism.<sup>49</sup> Other studies support a role  
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52 254 for thyroid hormone fluctuations<sup>50</sup> and circulating anti-thyroid autoantibodies<sup>51</sup> related to  
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55 255 vestibular dysfunction in subsequent BPPV development. Therefore, dysregulation of the

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4 256 immune system may play a vital role between hyperthyroidism and BPPV as documented by  
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6  
7 257 our study. In addition, we inferred that hyperthyroidism altered calcium metabolism and  
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10 258 otoconia dissolve impairment may play a role in developing BPPV among depressive  
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13 259 disorders patients. Up to 20 percent of thyrotoxic patients have mild hypercalcemia because  
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16 260 of thyroid hormone-mediated bone resorption<sup>52</sup>. Otoconia, mainly synthesized from calcium<sup>53</sup>,  
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18  
19 261 which breaks free and moves into the semicircular canals was the fundamental  
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22 262 pathophysiology of BPPV<sup>8</sup>. Therefore, hyperthyroidism with increased calcium might lead to  
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25 263 increased concentration of free calcium in the endolymph and reduce its capacity to dissolve  
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27  
28 264 the dislodged otoconia<sup>54</sup>, this mechanism involved in the pathophysiology of BPPV.

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31 265       Though there is no direct evidence support the pathophysiology of BPPV occurred in  
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34 266 patients co-existence with depressive disorder and hyperthyroidism. Patients suffered from  
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37 267 symptoms like palpitation, insomnia, anxiety, and irritability, which symptoms usually  
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40 268 belonging to hyperthyroidism and was difficult to discriminate from the psychiatric disorder,  
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43 269 have been proposed easily seeking medical treatment<sup>55</sup>. Therefore, we proposed that  
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46 270 hyperthyroidism related panic -like symptoms may increase the chance of diagnosis of BPPV  
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48  
49 271 through greater medical contact.

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51  
52 272       There are several limitations in this study. The first limitation relates to the lack of  
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55 273 detailed information regarding tobacco use, alcohol consumption, head position in bed, and

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4 274 family history of BPPV in patient data collected from the NHIRD, factors which may  
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6  
7 275 influence risk of BPPV development.<sup>56-58</sup> Thus, we were unable to control for these  
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9  
10 276 potentially confounding factors. Second, the NHIRD is an administrative database, which  
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12  
13 277 lacks detailed clinical data regarding severity and outcomes of BPPV patients, which  
14  
15  
16 278 interferes with analysis of BPPV prognoses in the cohort. Third, in the claims-based study  
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19 279 design, only patients seeking medical service would be identified in the Registry of NHIRD  
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22 280 and these identification issues may either overestimate or underestimate the results. Fourth,  
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25 281 our study did not provide any information about medications administered for BPPV.

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28 282 Since profound health burden and extensive health care utilization may be influential  
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31 283 with BPPV development.<sup>59 60</sup> Our findings and findings in other literature raised our attention  
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34 284 to unrecognized BPPV and inappropriate treatment among patients with depressive disorders  
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37 285 may lead to disabling and related poor quality of life.

## 38 39 40 286 **Conclusions**

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43 287 In the population-based retrospective study, we found that patients with depressive  
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46 288 disorders have statistically higher risk of developing BPPV. Furthermore, hyperthyroidism  
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49 289 and SLE were identified an independent risk factor to develop BPPV for patients with  
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52 290 depressive disorders. Future studies are required to clarify the underlying biological  
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55 291 mechanisms of these associations. Clinicians are encouraged to provide appropriate medical  
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4 292 care for those who diagnosed with BPPV and preexisting depressive disorder. Monitoring and  
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7 293 management depressive symptoms for the high-risk patients are also warranted.  
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### 10 294 **List of abbreviations:**

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13 295 BPPV, benign paroxysmal positional vertigo; NHI, National Health Insurance; LHID  
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16 296 2000, Longitudinal Health Insurance Database 2000; NHIRD, National Health Insurance  
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19 297 Research Database; ICD-9-CM, the International Classification of Diseases, ninth revision,  
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21  
22 298 Clinical Modification; IRRs, incidence rate ratios; HR, hazard ratio; aHR, adjusted hazard  
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25 299 ratio; CI, confidence interval.  
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41  
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45

### 46 306 **Author contributions**

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48  
49 307 Chiao-Lin Hsu and Li-Yu, Hu wrote the manuscript. Cheng-Che Shen and Ti, Lu helped  
50  
51  
52 308 with study design and data collection. Cheng-Che Shen, Shih-Jen Tsai and Yao-Min Hung  
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54  
55 309 contributed to the revision of the manuscript. All authors read and approved the final  
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4 310 manuscript.  
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7 311 **Competing interests**  
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10 312 The authors declare that they have no conflict of interest.  
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21  
22 316 funding sources had no role in the study design or conduct, or in the decision to submit for  
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25 317 publication.  
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28 318 **Legend for Figure 1:**  
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31 319 Fig.1 Cumulative incidence of benign paroxysmal positional vertigo in depressive disorders  
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34 320 and comparison cohort  
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37 321 The cumulative incidence of benign paroxysmal positional vertigo in patients with depressive  
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40 322 disorders was significantly higher than that in the comparison cohort  
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**Table 1 Baseline Characteristics of Patients with and without Depressive Disorders**

Demographic data	Patients with Depressive Disorders		Patients without Depressive Disorders		<i>P</i> value
	<i>n</i> = 10,297		<i>n</i> = 41,188		
	<i>n</i>	%	<i>n</i>	%	
Age (years) <sup>a</sup>	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	

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3	High income	1,289	12.5	6,422	15.5
4					
5	Follow-up years <sup>a</sup>	7.19 (5.96–8.48)		7.22 (6.00–8.51)	.002
6	<hr/>				

<sup>a</sup>Median (interquartile range)

For peer review only



**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)	<i>P</i> 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**

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Depressive Disorders	1.79 (1.26–2.56)	<.001	1.55 (1.08–2.23)	.019
Age ( $\geq 65 = 1$ , $< 65 = 0$ )	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		

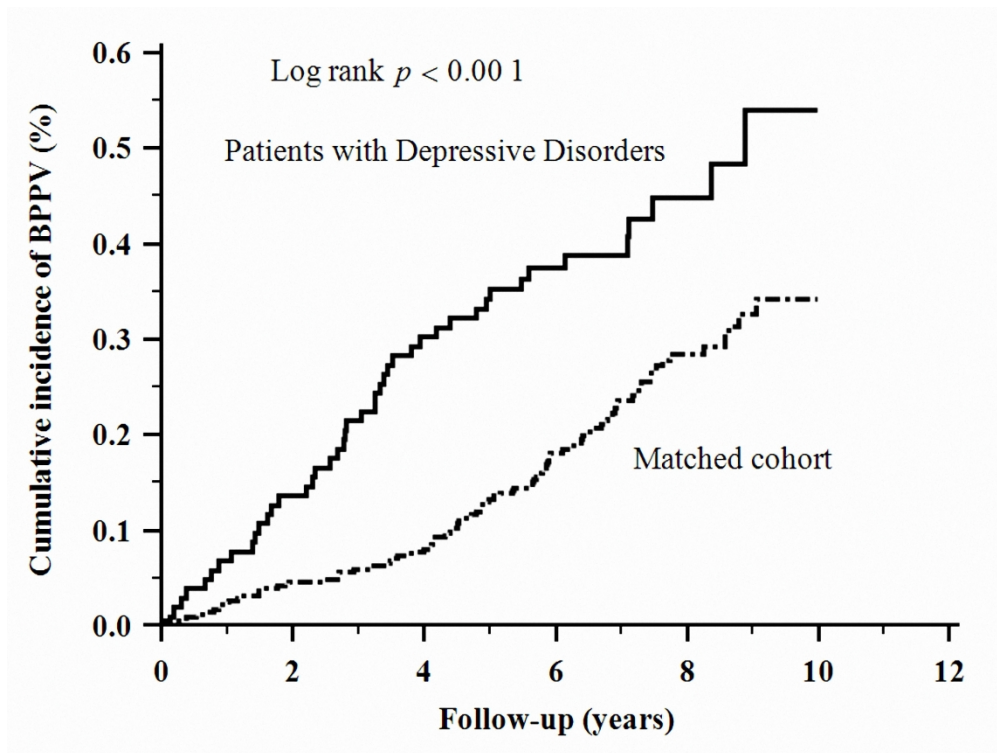
HR, hazard ratio; CI, confidence interval

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

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age ( $\geq 65 = 1$ , $< 65 = 0$ )	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	3.58 (1.11–11.56)	.033	3.47(1.07–11.22)	.038
Erythematosus				
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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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
<b>Results</b>			
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

1	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	13
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10
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11	<b>Discussion</b>			
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13	Key results	18	Summarise key results with reference to study objectives	14
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
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
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18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	19
20				
21	<b>Other information</b>			
22	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
23				
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\*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>.

# BMJ Open

## 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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For peer review only

## 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.

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2  
3 **Conclusions:** Patients with depressive disorders may have an increased risk of developing  
4 BPPV, especially those who have hyperthyroidism and SLE.  
5  
6

7 **Keywords:** Depressive disorders; benign paroxysmal positional vertigo; hyperthyroidism;  
8  
9 systemic lupus erythematosus; risk factor; cohort study  
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11

### 12 **Strengths and limitations of this study**

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- 14
- 15 1. The incidence of benign peripheral persistent vertigo (BPPV) among depressive disorders  
16 patient remains unclear. This longitudinal population-based data was conducted to assess the  
17 risk of BPPV in patients with depressive disorders.  
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19
  - 20 2. The NHIRD lacks detailed clinical data regarding severity and outcomes of BPPV  
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  - 23 3. Results from our study may underestimate the current condition since only patients  
24 seeking medical service would be identified in the Registry of NHIRD.  
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## 1 Introduction

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

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

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

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3 25 indicates that life stressors and related depressive disorder may be seen as a trigger of  
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5 26 vestibular dysfunction, that is, a potential precursor of BPPV.<sup>18</sup>  
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8 27 Therefore, considering the debates on the association between the depression and  
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10 28 BPPV and no large-scaled study have tried to investigate the issue, we designed a nationwide  
11  
12 29 retrospective cohort study to explore the association between depressive disorder and the  
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14 30 subsequent BPPV development. In addition, independent risk factors for developing BPPV  
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16 31 among patients with depressive disorders were also investigated.  
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## 19 32 **Materials and Methods**

### 20 33 *Data Sources*

21  
22 34 Nearly 99% of Taiwan's population utilizes health care services as a consequence of the  
23  
24 35 National Health Insurance (NHI) Program Bold Legislative Act enacted in 1995.<sup>19</sup> The  
25  
26 36 program offers comprehensive medical care coverage regarding outpatient, inpatient,  
27  
28 37 emergency visits, and Chinese medicine to all residents of Taiwan. The NHI research  
29  
30 38 database (NHIRD) contains comprehensive information with regard to clinical practice,  
31  
32 39 including prescription details and diagnostic codes in the International Classification of  
33  
34 40 Diseases, Ninth revision, Clinical Modification (ICD-9-CM) format. The NHIRD is managed  
35  
36 41 by the National Health Research Institutes (NHRI) and privacy is maintained according to  
37  
38 42 directives from the Bureau of the NHI.<sup>20</sup> The data source for our study was obtained from the  
39  
40 43 Longitudinal Health Insurance Database 2000 (LHID2000), a dataset of the NHIRD. The  
41  
42 44 LHID 2000, which contains all original claims data for 1,000,000 subjects, is a representative  
43  
44 45 database randomly selected from the 2000 Registry of Beneficiaries under the NHI program.  
45  
46 46 Which also maintains the registration data of everyone who was a beneficiary of the National  
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48 47 Health Insurance program during the period of 1996–2000. Moreover, the NHRI affirms that  
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3 48 there are no statistical differences in the distributions of age, sex, or health care costs between  
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5 49 the data in the LHID2000 and that of the NHIRD.<sup>20</sup>  
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7  
8 50 *Availability of Data and Materials section*  
9

10 51 The NHIRD is addressed in publicity by the NHRI and the use of NHIRD is only for  
11  
12 52 research purposes. All applicants must obey the Computer-Processed Personal Data  
13  
14 53 Protection Law and relevant regulations of the Bureau of National Health Insurance and  
15  
16 54 NHRI. Moreover, applicants and their supervisor were asking for signing agreements upon  
17  
18 55 application submission. All applications are required to transmit data for review and approval  
19  
20 56 and send an e-mail to the NHRI at [nhird@nhri.org.tw](mailto:nhird@nhri.org.tw) or call at +886-037-246166 ext. 33603  
21  
22 57 for immediate service. Office Hour: Monday-Friday 8:00-17:30 (UTC+8).  
23  
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25  
26 58 The NHIRD from the Health and Welfare Data Science Center (HWDC), Ministry of  
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28 59 Health and Welfare (MOHW) (<http://www.mohw.gov.tw/cht/DOS/>) is now available for the  
29  
30 60 researchers in Taiwan. The data is basically from the NHIRD. Researchers in Taiwan who  
31  
32 61 interested in the data can apply to the MOHW. In the last sentence of the paragraph on the  
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34 62 website, which said, "Kindly visit MOHW and NHIA on-site services for NHIRD." The  
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36 63 Database was delivered to a higher-level government administration, called the "Health and  
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38 64 Welfare Data Science Center (HWDC)" for more prompt health-related data linkage, broader  
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40 65 application, and better security management. Interested researchers could still apply to the  
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42 66 HWDC, Department of Statistics, MOHW for NHI Data at present. HWDC, MOHW website  
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44 67 (Chinese only currently): <http://dep.mohw.gov.tw/DOS/np-2497-113.html><sup>21</sup>  
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3 68 *Study design and subjects*  
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5 69 We utilized data from the LHID 2000 and conducted a retrospective cohort study using a  
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7 70 dataset collected between January 1, 2000 and December 31, 2004. We enrolled patients  $\geq 20$   
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9 71 years and received at least twice diagnosis of depressive disorders by psychiatrists with  
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11 72 ICD-9-CM depressive disorders diagnosis codes of 296.2X-296.3X, 300.4, and 311.X. We  
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13 73 defined the date of enrolling an adult patient with depressive disorders as case cohort between  
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15 74 2000 and 2004 as enrolment date. We excluded both in depressive disorders and control  
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17 75 groups who were previously diagnosed with BPPV by ICD-9-CM code and A-code at the  
18  
19 76 same time (ICD-9-CM code 386.11 and A-code: A249) to exclude patients who were  
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21 77 diagnosed with BPPV before enrollment date.  
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24  
25 78 The A-code, a much briefer version of the ICD-9-CM codes, is another disease  
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27 79 classification system launched for fulfilling medical claims, was mainly used for ambulatory  
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29 80 care before 2000 in Taiwan. The A-code had switched to the ICD-9-CM codes by NHI  
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31 81 program since 2000 to perpetuate consistency between different claims records and to truly  
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33 82 reflect the distribution of various diseases. Consequently, we used these two medical code  
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35 83 systems at the same time to reduce the discrepancies during the conversion time of A-code  
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37 84 and ICD-9-CM codes. Which included acute myringitis, chronic myringitis, perforation of  
38  
39 85 tympanic membrane, traumatic perforation of tympanic membrane, cholesteatoma of the  
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41 86 middle ear, Meniere's disease, peripheral vertigo, vestibulopathy, vertigo of central origin,  
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43 87 labyrinthitis, presbycusis, sudden hearing loss, tinnitus, and otalgia  
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47  
48 88 The cohort including patients with and without depressive disorders was observed until  
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50 89 the development of BPPV, death, withdrawal from the NHI system, or December 31, 2009.  
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52 90 The primary clinical outcome in our study was only BPPV diagnosed by neurologists or  
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54 91 otorhinolaryngologists. For each patient with depressive disorders included in the final cohort,  
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3 92 4 age- and sex-matched control patients without depressive disorders were randomly selected  
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5 93 on the same enrolment date from the LHID 2000. Finally, we identified 10,297 patients with  
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7 94 depressive disorders. To assemble a comparison cohort, we randomly selected 41,188  
8  
9 95 enrollees without a history of depressive disorders.

### 12 96 *Ethics Statement*

14 97 This study was approved by the Institutional Review Board of the Kaohsiung Veterans  
15  
16 98 General Hospital (No.: VGHKS14-CT7-07). We could not obtain written consent from study  
17  
18 99 patients as the NHI dataset consists of de-identified secondary data for research purposes. The  
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20 100 IRB of Kaohsiung Veterans General Hospital issued a formal written waiver for the need for  
21  
22 101 consent.

### 26 102 *Statistical analyses*

29 103 The incidence of newly diagnosed BPPV in patients with depressive disorders and  
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31 104 controls during the observational period was calculated and stratified by sex and age ( $\geq 65$   
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33 105 years or  $< 65$  years). Comparisons between continuous variables were conducted with the  
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35 106 independent *t*-test. Chi-squared analysis was used to examine the association of two  
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37 107 categorical characteristics between the depressive disorders and control cohort. A Cox  
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39 108 proportional hazard model was used to evaluate confounding variables and whether  
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41 109 depressive disorders increase the risk of developing BPPV. The confounding variables were  
42  
43 110 age, sex, and common comorbidities including hypertension, diabetes mellitus, dyslipidemia,  
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45 111 coronary artery disease, hyperthyroidism, hypothyroidism, cerebrovascular disease, and  
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47 112 systemic lupus erythematosus (SLE). Another Cox proportional-hazards regression model  
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49 113 was performed again to identify variables that predicted BPPV in the patients with depressive  
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51 114 disorders. The variables that demonstrated a moderately significant statistical relationship  
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3 115 with BPPV in the univariate analysis ( $P < .1$ ) were entered through forward selection in a  
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5 116 multivariate analysis.

7 117 The cumulative incidences of BPPV were compared between depressive disorder and  
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10 118 control cohorts using Kaplan–Meier curves. Stratified log rank test was applied to determine  
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12 119 the differences in the risk for BPPV in the cohort.

#### 14 120 *Patient and Public involvement*

16  
17 121 The data source used for this study was the claims data of Taiwan’s NHIRD. We did not  
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19 122 involve patients/service users in the research question, the outcome measures, or the design or  
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21 123 implementation of the study. There are no plans to disseminate the results of the research to  
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24 124 study participants.

## 26 125 **Results**

### 28 126 *Participant Selection*

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31 127 We analyzed 10,297 patients with depressive disorders and 41,188 control patients. The  
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33 128 majority of patients in the cohort were female (61%). The median age was 39 years  
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35 129 (interquartile range [IQR], 30–51 years), and the median follow-up period was 7.19 years  
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37 130 (IQR = 5.96–8.48 years) for patients with depressive disorders and 7.22 years (IQR =  
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39 131 6.00–8.51 years) for control patients ( $p = .002$ ). Table 1 includes comparisons of demographic,  
40  
41  
42 132 clinical variables, and socioeconomic data between the control and depressive cohorts. In the  
43  
44 133 depressive disorders group, the most common comorbidities were hypertension (2,124  
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46 134 patients, 20.6%), diabetes mellitus (1,236 patients, 12.0%), and dyslipidemia (1,541 patients,  
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48 135 14.5%). As compared to the controls, depressive disorders patients had significantly more  
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50  
51 136 physical comorbidities. Besides, depressive disorders patients had a significantly higher  
52  
53 137 prevalence in low-income populations (50.4% vs. 44.4%,  $p < .001$ ) and in urban areas (64.1%  
54  
55 138 vs. 60.9%,  $p < .001$ ) as compared to non-depressive disorders patients.

### 139 *Person-Time Incidence Rate of BPPV*

140 During the follow-up period, 44 patients (0.59 per 1,000 person-years) were diagnosed  
141 with BPPV in the depressive disorders group, and 99 patients (0.33 per 1,000 person-years)  
142 were diagnosed with BPPV in the control group. The incidence rate ratio (IRR) of BPPV  
143 between depressive disorders and control patients was 1.79 (95% CI [confidence interval],  
144 1.23–2.58,  $p = .002$ ). The IRR of BPPV remained higher in the depressive disorders than in the  
145 control patients among both sexes. When stratified with age, only patient younger than 65  
146 years old have higher IRR of BPPV. The results are shown in Table 2.

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

### 149 *Risks of Newly Diagnosed BPPV among the Patients with and without Depressive* 150 *Disorders*

151 After adjusting for age, sex, common comorbidities and SLE, there was a higher risk of  
152 developing BPPV in patients with depressive disorders than in the control patients (HR = 1.55,  
153 95% CI, 1.08–2.23,  $p = .019$ ). Results are summarized in Table 3.

### 154 *Risks Factors for BPPV in patients with Depressive Disorders*

155 As shown in Table 4, we predicted the development of BPPV in the depressive disorder  
156 cohorts by applying univariate analysis. Univariate analysis demonstrated that dyslipidemia  
157 (HR = 1.97, 95% CI, 0.99–3.89,  $p = .053$ ), hyperthyroidism (HR = 3.74, 95% CI, 1.67–8.38,  
158  $p < .001$ ), cerebrovascular disease (HR = 2.31, 95% CI, 0.91–5.85,  $p = .079$ ) and SLE (HR = 3.58,  
159 95% CI, 1.11–11.56,  $p = .033$ ) were possible prognostic factors. Multivariate analysis indicated  
160 that hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42,  $p = .001$ ) and SLE (HR = 3.47, 95% CI,  
161 1.07–11.22,  $p = .038$ ) were an independent risk factor for patients with depressive disorders.

### 162 **Discussion**

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3 163 The two major findings in our study are as the following. First, patients with depressive  
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5 164 disorders presented a 1.55 -fold greater risk of subsequently developing BPPV than did the  
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8 165 general population by utilizing a nationwide population-based cohort study. Secondly, only  
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10 166 hyperthyroidism (HR = 3.75, 95% CI, 1.67–8.42, p= .001) and SLE (HR = 3.47, 95% CI,  
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12 167 1.07-11.22, p= .038) were independent risk factors to develop BPPV among patients with  
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14 168 depressive disorders.

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17 169 The strength of this study is using a nationwide population-based data to evaluate BPPV  
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19 170 risk in patients with depressive disorders. Advantages of using our NHIRD in medical  
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21 171 research have been previously described,<sup>22</sup> which include enormous sample size, lack of  
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23 172 selection and participation bias and long term comprehensive follow up. Whereas the results  
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25 173 of most studies demonstrated the correlation between BPPV and following depressive  
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27 174 disorders,<sup>23 24</sup> to the best of our knowledge, this is the first study implying that patients with  
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29 175 depressive disorders have higher risk of developing BPPV.

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33 176 Though depressive disorder have been reported to produce somatic symptoms including  
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35 177 symptoms like BPPV,<sup>25</sup> one research indicated that patients with unrecognized BPPV were  
36  
37 178 more likely to have depressive disorder.<sup>26</sup> Another study pointed out that depressive disorders  
38  
39 179 may be an early presentation of neural circuitry alterations involving connections between the  
40  
41 180 vestibular system and anatomical area such as hippocampus, amygdala, and infralimbic  
42  
43 181 cortex.<sup>27</sup> One Asian literature showed that depression symptoms may adversely affect BPPV  
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45 182 recurrence.<sup>28</sup> Though there was no strong evidence consistent with our findings, evidence  
46  
47 183 mentioned above may indirectly prove our hypothesis.

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51 184 The pathophysiology of depressive disorders and subsequent BPPV is unknown. There  
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53 185 are several proposed mechanisms to explain this association. First, dysregulation of oxidative  
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55 186 and inflammatory processes in depressive disorders may result in subsequent BPPV

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3 187 development. Numerous studies have demonstrated patients with depressive disorders have  
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5 188 excessive oxidative stress and elevation in inflammatory responses.<sup>29-32</sup> Evidence supports a  
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7 189 role for oxidative stress in otolith dysfunction leading to an increased risk of developing  
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9  
10 190 canalolithiasis, an essential step in the pathogenesis of BPPV.<sup>33-36</sup> Additional studies conclude  
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12 191 depressive disorders associated with oxidative stress result in vestibular hair cells and  
13  
14 192 neuronal damage in the inner ear,<sup>37</sup> which contributes to vestibular dysfunction and  
15  
16 193 subsequent BPPV development.<sup>38 39</sup> Second, depressive disorders may induce abnormalities of  
17  
18 194 the hypothalamus-pituitary-adrenal axis, which may hinder the inner ear blood flow and  
19  
20 195 influence inner ear fluid balance. These abnormalities lead to dysfunction of the otoconial  
21  
22 196 homeostasis,<sup>18 40</sup> an established risk factor for development of BPPV.<sup>41</sup> Therefore, alterations  
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24 197 to the neuroendocrine system may be the link between depressive disorders and the  
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26 198 development of BPPV. Third, BPPV development in depressive disorders may be induced by  
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28 199 serotonin dysfunction. The vestibular nucleus complex is composed of a large number of  
29  
30 200 serotonin receptors, and lack of serotonin may result in a substantial impact on the  
31  
32 201 electrophysiological activity of neurons, and dysfunction of the vestibular nucleus complex.<sup>42</sup>  
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34 202 Previous studies have hypothesized a role for vestibular nucleus damage in the pathogenesis  
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36 203 of BPPV development.<sup>39 43</sup> Fourth, the dysregulation of the immune system, frequently  
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38 204 observed in depressive disorders,<sup>44 45</sup> has proved to be an essential part of BPPV pathogenesis.  
39  
40 205 Stone and Francis<sup>46</sup> suggest BPPV could develop by immune system's direct attack or  
41  
42 206 indirect attack, resulting in debris within the inner ears. This explanation could be confirmed  
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44 207 by studies demonstrated the association of several autoimmune diseases, such as systemic  
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46 208 sclerosis,<sup>47</sup> SLE, ulcerative colitis, Sjogren's syndrome, and rheumatoid arthritis<sup>46</sup> in the  
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48 209 development of BPPV. Consistent with the studies mentioned above, we found that SLE is a  
49  
50 210 risk factor for BPPV among depressive cohort (Table 4) but not for all the participants (Table  
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3 211 3) in this study. Based on the previous studies, several results of the studies could provide the  
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5 212 evidence revealing that the comorbidities with depressive disorder and SLE would result in  
6  
7 213 the exacerbation of the SLE disease activities, no matter the possible explanations were  
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9 214 psychological or behavioral issues such as lack of insight and poor anti-inflammatory drug  
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11 215 compliance.<sup>48-50</sup> The evidence indicated that the severity of inflammatory processes on the  
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13 216 differences between the patients with depressive disorder alone and the depressive patients  
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15 217 comorbid with SLE.

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19 218 We conclude patients with depressive disorders are more likely to develop BPPV if they  
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21 219 are afflicted with hyperthyroidism. Mechanical movements of thyroid autoantibodies in the  
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23 220 inner ear fluid or the development of autoimmune microangiitis in the labyrinth can result in  
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25 221 BPPV in the presence of hyperthyroidism or hypothyroidism.<sup>51</sup> Other studies support a role  
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27 222 for thyroid hormone fluctuations<sup>52</sup> and circulating anti-thyroid autoantibodies<sup>53</sup> related to  
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29 223 vestibular dysfunction in subsequent BPPV development. Therefore, dysregulation of the  
30  
31 224 immune system may play a vital role between hyperthyroidism and BPPV as documented by  
32  
33 225 our study. In addition, we inferred that hyperthyroidism altered calcium metabolism and  
34  
35 226 otoconia dissolve impairment may play a role in developing BPPV among depressive  
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37 227 disorders patients. Up to 20 percent of thyrotoxic patients have mild hypercalcemia because  
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39 228 of thyroid hormone-mediated bone resorption<sup>54</sup>. Otoconia, mainly synthesized from calcium<sup>55</sup>,  
40  
41 229 which breaks free and moves into the semicircular canals was the fundamental  
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43 230 pathophysiology of BPPV<sup>8</sup>. Therefore, hyperthyroidism with increased calcium might lead to  
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45 231 increased concentration of free calcium in the endolymph and reduce its capacity to dissolve  
46  
47 232 the dislodged otoconia<sup>56</sup>, this mechanism involved in the pathophysiology of BPPV.

48  
49 233 Though there is no direct evidence support the pathophysiology of BPPV occurred in  
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51 234 patients co-existence with depressive disorder and hyperthyroidism. Patients suffered from  
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3 235 symptoms like palpitation, insomnia, anxiety, and irritability, which symptoms usually  
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5 236 belonging to hyperthyroidism and was difficult to discriminate from the psychiatric disorder,  
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7 237 have been proposed easily seeking medical treatment<sup>57</sup>. Therefore, we proposed that  
8  
9 238 hyperthyroidism related panic-like symptoms may increase the chance of diagnosis of BPPV  
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11 239 through greater medical contact.  
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14 240 There are several limitations in this study. The first limitation relates to the lack of  
15  
16 241 detailed information regarding tobacco use, alcohol consumption, head position in bed, and  
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18 242 family history of BPPV in patient data collected from the NHIRD, factors which may  
19  
20 243 influence risk of BPPV development.<sup>58-60</sup> Thus, we were unable to control for these  
21  
22 244 potentially confounding factors. Second, the NHIRD is an administrative database, which  
23  
24 245 lacks detailed clinical data regarding severity and outcomes of BPPV patients, which  
25  
26 246 interferes with analysis of BPPV prognoses in the cohort. Third, in the claims-based study  
27  
28 247 design, only patients seeking medical service would be identified in the Registry of NHIRD  
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30 248 and these identification issues may either overestimate or underestimate the results. Fourth,  
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32 249 our study did not provide any information about medications administered for BPPV.  
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37 250 Since profound health burden and extensive health care utilization may be influential  
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39 251 with BPPV development.<sup>61 62</sup> Our findings and findings in other literature raised our attention  
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41 252 to unrecognized BPPV and inappropriate treatment among patients with depressive disorders  
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43 253 may lead to disabling and related poor quality of life.  
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## 47 254 **Conclusions**

48  
49 255 In the population-based retrospective study, we found that patients with depressive  
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51 256 disorders have statistically higher risk of developing BPPV. Furthermore, hyperthyroidism  
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53 257 and SLE were identified an independent risk factor to develop BPPV for patients with  
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55 258 depressive disorders. Future studies are required to clarify the underlying biological  
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3 259 mechanisms of these associations. Clinicians are encouraged to provide appropriate medical  
4  
5 260 care for those who diagnosed with BPPV and preexisting depressive disorder. Monitoring and  
6  
7 261 management depressive symptoms for the high-risk patients are also warranted.  
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## 10 262 **List of abbreviations:**

11  
12 263 BPPV, benign paroxysmal positional vertigo; NHI, National Health Insurance; LHID  
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14 264 2000, Longitudinal Health Insurance Database 2000; HWDC, Health and Welfare Data  
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16 265 Science Center; MOHW, Ministry of Health and Welfare; NHIRD, National Health Insurance  
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18 266 Research Database; ICD-9-CM, the International Classification of Diseases, ninth revision,  
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20 267 Clinical Modification; IRRs, incidence rate ratios; HR, hazard ratio; aHR, adjusted hazard  
21  
22 268 ratio; CI, confidence interval.  
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36  
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## 41 275 **Author contributions**

42  
43 276 Chiao-Lin Hsu and Li-Yu, Hu wrote the manuscript. Cheng-Che Shen and Ti, Lu helped  
44  
45 277 with study design and data collection. Cheng-Che Shen, Shih-Jen Tsai and Yao-Min Hung  
46  
47 278 contributed to the revision of the manuscript. All authors read and approved the final  
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49 279 manuscript.  
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## 52 280 **Competing interests**

53  
54  
55 281 The authors declare that they have no conflict of interest.  
56

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9  
10 286 publication.

### 11 12 287 **Legend for Figure 1:**

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14  
15 288 Fig.1 Cumulative incidence of benign paroxysmal positional vertigo in depressive disorders  
16  
17 289 and comparison cohort  
18  
19 290 The cumulative incidence of benign paroxysmal positional vertigo in patients with depressive  
20  
21 291 disorders was significantly higher than that in the comparison cohort

### 22 23 24 292 **Data availability statement**

25  
26  
27 293 The data that support the findings of this study are available from the Health and Welfare  
28  
29 294 Data Science Center (HWDC), Ministry of Health and Welfare (MOHW)  
30  
31 295 (<http://www.mohw.gov.tw/cht/DOS/>) for the researchers in Taiwan. Data are available at  
32  
33 296 <http://dep.mohw.gov.tw/DOS/np-2497-113.html> (Chinese only currently) with the permission  
34  
35 297 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		Patients without Depressive Disorders		<i>P</i> value
	<i>n</i> = 10,297		<i>n</i> = 41,188		
	<i>n</i>	%	<i>n</i>	%	
Age (years) <sup>a</sup>	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	

1					
2					
3	High income	1,289	12.5	6,422	15.5
4					
5	Follow-up years <sup>a</sup>	7.19 (5.96–8.48)		7.22 (6.00–8.51)	.002
6	<hr/>				

<sup>a</sup>Median (interquartile range)

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**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)	<i>P</i> 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**

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Depressive Disorders	1.79 (1.26–2.56)	<.001	1.55 (1.08–2.23)	.019
Age ( $\geq 65 = 1$ , $<65 = 0$ )	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		

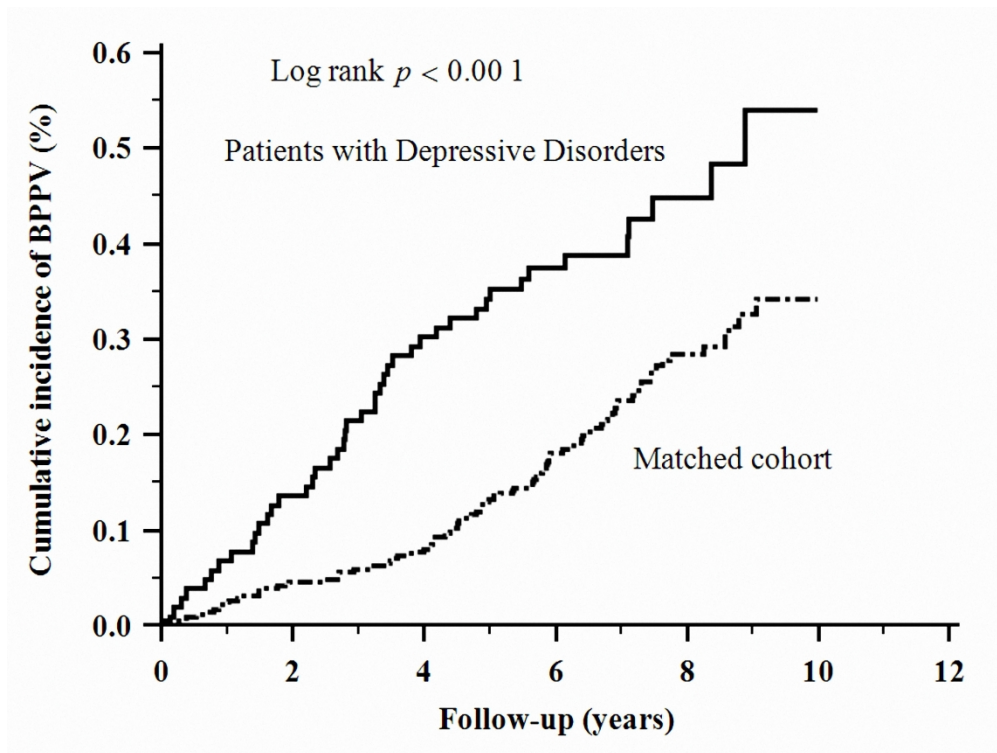
HR, hazard ratio; CI, confidence interval

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

Predictive variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age ( $\geq 65 = 1$ , $< 65 = 0$ )	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	3.58 (1.11–11.56)	.033	3.47(1.07–11.22)	.038
Erythematosus				
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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