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Brief report

Increased risk of depressive disorder following the diagnosis of benign prostatic enlargement: One-year follow-up study

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ABSTRACT

Purpose: In previous studies, benign prostatic enlargement (BPE) and urinary tract symptoms were demonstrated to be associated with depressive symptoms. However, no longitudinal follow-up study to date has evaluated the relationship between BPE and the subsequent risk of developing depressive disorder. This nationwide, population-based study aimed to prospectively examine the relationship between a history of BPE and the risk of developing depressive disorder.
Materials and methods: A total of 16,130 adult patients diagnosed with BPE for the first time between 2005 and 2007 were recruited along with a comparison cohort of 48,390 matched enrollees without a history of BPE. All the subjects were tracked for a one-year period following their index date to identify those who subsequently developed a depressive disorder. The Cox proportional hazards model was utilized to compute the risk difference for depressive disorder between cohorts.
Results: Of 64,520 sampled patients, 325 (2.01%) from the BPE cohort, and 531 (1.10%) from the comparison cohort were subsequently diagnosed with depressive disorder during the follow-up period. The risk of developing depressive disorder within one-year following diagnosis with BPE was found to be 1.87 (95% CI = 1.63–2.16, $p<0.001$) times the risk in absence of BPE after adjusting for the patients' monthly income, and the geographical location and urbanization level of their place of residence.
Conclusions: Our results suggest that patients with BPE are at an increased risk for contracting depressive disorder.

1. Introduction

Benign prostatic enlargement (BPE) and lower urinary tract symptoms (LUTS) both affect a significant number of older men worldwide (Copeland et al., 1999; Garraway et al., 1991; Katona et al., 1997; Parsons and Kashefi, 2008). The overall prevalence of LUTS was 18.7% and increased with age (Kupelian et al., 2006). In addition, LUTS and depressive symptoms are strongly associated, and exhibit reciprocal relationships (Laumann et al., 2008). Previous studies demonstrated LUTS increased the odds of presenting with depressive symptoms (Litman et al., 2007; Wong et al., 2006). It is also worth noting that some studies confirmed that patients with depression suffer from more

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severe LUTS. Johnson et al. (2010) recently reported that depressed patients are three times more likely to present with severe symptoms of LUTS.

However, most previous studies that concurrently investigated BPE/LUTS and depressive symptoms were cross-sectional in design. No study to date has directly examined the relationship between BPE and depression. It remains unclear whether this relationship represents unidirectional or bidirectional causality. Furthermore, previous studies focused on the relationship between BPE and the presentation of depressive symptoms, rather than focusing on a diagnosis for depressive disorder (DD). To the best of our knowledge, there is still no longitudinal follow-up study to date evaluating the relationship between BPE and the subsequent risk of developing DD. Therefore, we conducted this study by using a nationwide population-based data set from Taiwan. This study's aim was to investigate the relationship between BPE and the risk of subsequently developing DD during a one-year period follow-up period.

2. Methods

2.1. Database

This study utilized the "Longitudinal Health Insurance Database (LHID2000)," derived from the Taiwan National Health Insurance (NHI) program. The LHID2000 largely consists of the following three domains: patients, health care professionals, and the health care services for 1,000,000 enrollees who were systematically and randomly selected from all the enrollees (N = 23.72 million) listed in the 2000 Registry of Beneficiaries under the NHI program. These three domains are linked by the patient's individual identity. The LHID2000 has been utilized by numerous researchers (Chen and Lin, 2011; Chung et al., 2011; Kang et al., 2011).

The LHID2000 consists of de-identified secondary data released to the public for research purposes, and this study was therefore exempted from full review by an Institutional Review Board.

2.2. Study sample

This study included a study cohort and a comparison cohort. We first selected 25,340 patients who received a principal diagnosis of BPE (ICD-9-CM code 600.0, enlargement (benign) of prostate) in their ambulatory care visits from January 1, 2005 to December 31, 2007. According to the reimbursement policy of the NHI Bureau, the diagnosis of BPE must meet the following criteria: enlargement of the prostate gland of equivalent weight >20 g in the presence of symptoms of urinary dysfunction and/or a urinary peak flow rate <15 ml/s, without evidence of malignancy. In order to increase the accuracy of diagnostic coding in medical claims, the NHI Bureau audits claims regularly by using comprehensive chart reviews by clinical specialists. Fines for fraud are 100 times the amount of the false claim charged to the NHI Bureau. A previous study has also documented the high validity of this coding system (Lin et al., 2008). Additionally, we only included patients whose diagnosis of BPE was made by an urologist in order to increase the diagnostic validity of the study. The first ambulatory care visits of the selected patients for receiving a diagnosis of BPE during the 2005 and 2007 were designated as the index date. We also excluded patients who had ever been diagnosed with BPE prior to their index date (N = 8235) in order to increase the possibility of only including newly diagnosed cases. We also excluded patients aged less than 40 years (N = 270). In addition, we further excluded those patients who had received a diagnosis of schizophrenia (ICD-9-CM code 295.XX) or affective disorder (ICD-9-CM code 296.XX) (N = 705). Ultimately, 16,130 patients with BPE were included in the study cohort.

The comparison cohort included subjects remaining in the registry of beneficiaries of the LHID2000 that were matched to the study cohort. We first excluded all patients aged less than 40 years. Then we used SAS statistical software (SAS System for Windows, Version 8.2, SAS Institute Inc, Cary, NC) to randomly extract 48,390 subjects (three for every patient with BPE) matched in terms of age group (<50, 50–59, 60–69, 70–79, and >79) and the year of index ambulatory care visits. The first use of ambulatory care in the index year was assigned as the index date. We also assured that no selected subjects had ever received a diagnosis of schizophrenia or affective disorder prior to their index ambulatory care visit in accordance with the selection criteria of the study cohort. Furthermore, we also ensured that none of the selected comparison subjects had ever been diagnosed with BPE since 1996.

As a result of the selection process, 64,520 subjects were included in this study. We individually followed each subject for a one-year period starting from their index date and identified those patients who had subsequently been diagnosed with DD (ICD-9-CM codes 296.2, 296.3, 300.4, and 311) during the follow-up period.

2.3. Statistical analysis

All statistical analyses were performed with SAS statistical software (version 9.1 for Windows; SAS Institute, Inc., Cary, NC, USA), and the significance level was set to be 0.05 for this study. We described and compared the differences in monthly income (NT$0–NT15,840, NT15,841–NT25,000, ≥NT25,001) and the geographical location (Northern, Central, Eastern, and Southern Taiwan) and urbanization level of the patient's residence (5 levels, 1 being the most urbanized and 5 being the least) between patients with and without BPE by Pearson χ^2 tests. We also used log-rank analysis to compare the difference in one-year DD-free survival rates between these two cohorts. In addition, we performed a stratified Cox proportional hazards regression (stratified by age group and the year of index ambulatory care visits) to investigate the risk of developing DD between these two cohorts. We used hazard ratios (HR) along with 95% confidence intervals (95% CI) to report the risk of DD.

3. Results

The study cohort included 16,130 subjects, whose mean age was 66.6 years with a standard deviation of 12.0 years at the time of the first diagnosis of BPE. After being matched by age group and the year of index ambulatory care visit, there were significant differences in monthly incomes, the geographic locations, and urbanization levels of the patients' residences between cohorts (Table 1). Patients with BPE had a significantly greater tendency to have monthly incomes >NT$25,000

Table 1
Demographic characteristics for the sampled patients in Taiwan, stratified by the presence/absence of benign prostatic enlargement, 2001–2007 (N = 64,520).

Variable	Patients with benign prostatic enlargement N = 16,130		Comparison patients N = 48,390		*p* value
	Total no.	Column %	Total no.	Column %	
Geographic region					<0.001
Northern	7447	46.2	22,074	45.6	
Central	4113	25.5	11,391	23.5	
Southern	4164	25.8	13,518	29.9	
Eastern	406	2.5	1407	2.9	
Age group					1.000
<50	1285	8.0	3855	8.0	
50–59	3431	21.3	10,293	21.3	
60–69	4206	26.1	12,618	26.1	
70–79	4752	29.5	14,256	29.5	
>79	2456	15.2	7368	15.2	
Urbanization level					0.004
1	4639	28.8	13,878	28.7	
2	4458	27.6	12,915	26.7	
3	2600	16.1	7713	15.9	
4	2442	15.1	7377	15.1	
5	1991	12.3	6507	13.4	
Monthly income					<0.001
NT$ 0–15,840	5007	31.0	16,062	33.2	
NT$15,841–25,000	6596	40.9	23,466	49.5	
≥NT$25,001	4527	28.1	8862	18.3	

($p<0.001$) and to reside in central part of Taiwan ($p<0.001$) than those without BPE.

Table 2 shows the incidence of DD within the one-year period after the first diagnosis of BPE. We found that 856 of the 64,520 (1.33%) sampled patients had been diagnosed with DD during the one-year follow-up period. They included 325 (2.01% of patients with benign prostatic enlargement) from the study cohort and 531 (1.10% of patients without benign prostatic enlargement) from the comparison cohort. The log-rank test demonstrated that there was a statistically significant difference in one-year DD-free accumulated survival rates between these two cohorts (Chi-square value = 78.28, $p<0.001$). This suggests that patients with BPE were significantly more likely to have lower one-year DD-free accumulated survival rates than comparison patients.

Table 2 presents the crude and adjusted HR for DD during the one-year follow-up period by cohort. The results of the stratified Cox proportional analysis (stratified by age group and the year of index ambulatory care visit) indicated that when compared to patients without BPE, the HR of DD during the one-year follow-up period was 1.85 (95% CI = 1.61–2.13) for patients with BPE. After adjusting for the patients' monthly income, and the geographical location and urbanization level, the results suggested that the hazard of DD within the one-year period following the first diagnosis of BPE was 1.87 (95% CI = 1.63–2.16, $p<0.001$) times greater for patients with BPE than comparison patients.

4. Discussion

To the best of our knowledge, this study is the first longitudinal, population-based investigation of the risk of DD in one year following a BPE diagnosis. In age-matched patients, our study demonstrated that the likelihood of being diagnosed with DD was 1.87 times greater among patients with BPE than with matched controls during a one-year follow-up period,

Table 2
Crude and covariate-adjusted hazard ratios for depressive disorder among the sampled patients during the one-year follow-up starting from the index ambulatory care visit.

Presence of depressive disorder	Total sample N = 64,520		Patients with benign prostatic enlargement N = 16,130		Comparison patients N = 48,390	
	No.	%	No.	%	No.	%
One-year follow-up period						
Yes	856	1.33	325	2.01	531	1.10
No	63,664	98.67	15,805	97.99	47,859	98.90
Crude HR (95% CI)	–		1.85* (1.61–2.13)		1.00	
Adjusted[a] HR (95% CI)			1.87* (1.63–2.16)		1.00	

Notes: HR = hazard ratio; HR was calculated by stratified Cox proportional hazard regression which was stratified by age group and the year of index ambulatory care visits.
[a] Adjustments are made for patient's geographical location, urbanization level and monthly income.
* Indicates $p<0.001$.

after adjusting for socio-demographic characteristics and region and urbanization of residence.

Many epidemiological studies have previously been conducted that explored the link between BPE and depression. Previous studies demonstrated that the presence of LUTS increased the odds of presenting with depressive symptoms (Laumann et al., 2008; Litman et al., 2007; Wong et al., 2006). This finding is intuitive because LUTS are often associated with embarrassment, impaired physical and sexual health, and interference with daily activities (Robertson et al., 2007; Trueman et al., 1999). LUTS can also affect one's quality of sleep. Marschall-Kehrel et al. (2004) suggested that nocturia could cause sleep deprivation and poor-quality sleep has been shown to cause depression. These findings demonstrate that LUTS have a significant impact on men's mental functioning and may require medical attention. This area of research is important as clinical depression is associated with a significant increase in mortality, and early detection of clinically relevant depressive symptoms may prevent death from suicide (Brittain and Castleden, 1998).

It is worth noting that depressive symptoms can also be a risk factor for having moderate to severe LUTS (Asplund et al., 2004; Johnson et al., 2010). While the true mechanisms remain uncertain, Johnson et al. (2010) indirectly inferred that chronic inflammation may be a possible common cause of these two diseases. However, it could not be excluded if depressed patients might report subjective suffering or, greater symptom scores, than represents their true pathologic state (Kaplan, 2006; Madersbacher et al., 2004). Further longitudinal studies are needed to verify this relationship.

Multiple study designs were utilized to conduct studies investigating the connection at hand (concurrent investigation of BPE/LUTS and depressive symptom). These included community- or hospital-based, cross-sectional, and placebo-controlled studies. Cross-sectional studies cannot delineate the cause–result relationship between depressive symptoms and LUTS. Furthermore, the diagnosis of BPE/LUTS and depressive symptoms in previous studies was based on a self-reported questionnaires interview. In these studies no clinical specialists validated either the diagnosis of LUTS/BPE or that of DD. In contrast to previous studies investigating this issue, our study was based on a nationwide dataset with a longitudinal follow-up. Only patients whose BPE was newly diagnosed by an urologist during the study period were included in order to increase the validity of diagnosis. In addition, we believe that the diagnosis of DD has very high validity since mental illness is still culturally taboo in Taiwan. A physician would not make a diagnosis of DD unless he is relatively certain about his diagnosis. In addition, this study only counted DD diagnosis which was made by a psychiatrist.

Nevertheless, this study suffers from a few limitations. First, some clinically relevant patient and lifestyle information, such as smoking status, alcohol consumption, dietary habits, body mass index, and pharmaceutical use, all of which may contribute to these two conditions, was not available through the administrative dataset. Thus, the association between BPE and DD may be partially explained by the residual confounding of these factors. Second, since patients with BPE are more likely to have frequent outpatient clinic visiting, which may lead to an early detection of DD, there may be a possible surveillance bias. Third, the risk of DD may vary with BPE severity; however, this information was not available for this study.

Despite these limitations, our study demonstrated that there is a significant association between BPE and the subsequent risk of developing DD in a one-year follow-up period after adjusting for socio-demographic characteristics. Health care workers in both primary and urologic settings should be alert to the increased prevalence of clinically depressive symptoms in this population. BPE could be best managed using a multidisciplinary approach, including routine psychological assessment.

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Conflict of interest
None.

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