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The bidirectional relationship between anxiety, depression, and lower urinary track symptoms: A nationwide population-based cohort study

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ABSTRACT

Background: Evidence has shown a positive correlation between lower urinary tract symptoms (LUTS) and anxiety/depression, but the direction and strength of the association are still unclear. We aimed to test the bidirectional association between LUTS and anxiety/depression using a longitudinal population database.

Methods: Using claims data obtained from the Taiwan National Health Insurance Research Database, 17,489 patients with LUTS and 34,978 non-LUTS matched controls (cohort 1); and 45,707 patients with anxiety, 19,306 patients with depression, 91,414 non-anxiety, and 38,720 non-depression matched controls (cohort 2) were enrolled between 1999 and 2008. All subjects were followed at least three years or until the date of death or the end of 2011 to estimate the risk of developing anxiety/depression (cohort 1) or LUTS (cohort 2).

Results: After controlling for age, gender, and medical comorbidities, LUTS patients were 2.12 (95%CI: 1.95–2.30) and 2.03 (95%CI: 1.76–2.33) times more likely to develop anxiety and depression, respectively. After controlling for age, gender, and medical comorbidities, patients with anxiety and depression were 2.01 (95%CI: 1.88–2.14) and 2.37 (95%CI: 2.13–2.65) times more likely to develop LUTS, respectively.

Limitations: The incidence of anxiety, depression, and LUTS may be under-estimated because only healthcare-seeking subjects were enrolled in our study.

Conclusions: Our findings suggested a bidirectional relationship between administrated anxiety/depression and LUTS in the cohorts. Further studies are warranted to clarify the underlying mechanisms.

1. Introduction

It has long been observed that depression and anxiety are highly correlated with chronic medical illnesses [1], and even early manifestations of medical illness [2]. Depression and anxiety are stress-related common mental disorders and are caused by a combination of multiple environmental and genetic factors affecting certain brain circuits [3]. Lower urinary tract symptoms (LUTS), including voiding, storage, and post-micturition, are highly prevalent in all communities worldwide and are known to have a negative influence on sleep, mental health, and health-related quality of life (HRQL) as well as healthcare burden of patients [4–5]. Data showed that a total of 53.7% of Taiwanese women suffered from LUTS and the prevalence increases with age [6]. There is accumulating evidence that psychological factors may play a significant role in the manifestation of LUTS, in addition to interplays between the vascular, nervous, immune, and endocrine systems [7]. A number of recent studies have suggested a correlation between LUTS and anxiety/depression [8–14], although some studies have reported contradictory results [15–16]. Among these studies, one study in Japan found that LUTS are not related to depression [15]; another study in UK suggested that anxious patients present with a lesser degree of incontinence than nonanxious patients [16]. Furthermore, the association of anxiety, depression, and LUTS appears to be an additive effect on both mental and physical health, as well as HRQL [13,17].

The contradictory results in previous studies might be due to small sample sizes, cross-sectional study designs and ambiguous definitions of

Abbreviations: CI, confidence interval; HR, hazard ratio; aHR, adjusted hazard ratio; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Diseases 9th Revision Clinical Modification; PY, person-years; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; PSC, physical symptom checklist; HPA axis, hypothalamic–pituitary–adrenal axis

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the diagnosis. Most studies have used self-reported rating scales concerning LUTS and anxiety/depression symptoms rather than diagnoses confirmed by physicians [8–11,14,16]. In addition, only a few studies have explored the relationship of LUTS with depression and anxiety simultaneously [8–10,13]. For example, the Norwegian cross-section study used questionnaire survey and focused on middle-aged women with urinary incontinence only [9]; the EpiLUTS cross-section study used questionnaire survey and focused on overactive bladder symptoms [10]. In the recent data from the Florey Adelaide Male Ageing Study (FAMAS) in Australia [8], authors found that there is a bidirectional relationship between storage, but not voiding, LUTS and both depression and anxiety. A recent review concluded that although the literature suggests an association between LUTS, depression and anxiety, longitudinal follow-up studies are limited in number and most studies failed to demonstrate temporal changes and lacked evidence of causality [18].

In our previous nationwide population-based association study [13], we revealed a significant association between LUTS and anxiety as well as depression, even after controlling for possible confounding factors. Although this finding suggests that anxiety/depression may play a role in the pathogenesis of LUTS and vice versa, causal interpretations can be inferred only plausibly due to the cross-sectional design of the study. In this study we aimed to further examine the direction and strength of the temporal association between LUTS and anxiety/depression using a representative data set from the Taiwan's National Health Insurance program and using a longitudinal follow-up study design.

2. Methods

A nationwide population database was used in this bidirectional cohort study to estimate the risk probability of LUTS patients developing anxiety and depression (cohort study 1); and anxiety and depression, respectively, patients developing LUTS (cohort study 2).

2.1. Database

Data from the National Health Insurance Research Database (NHIRD), which includes approximately 99% of the population of Taiwan, was used in this study. The validity of the database has been confirmed with hundreds of published papers [19]. The Longitudinal Health Insurance Database 2000 (LHID2000) which consists of a random sample of 1,000,000 persons (approximately 5% of Taiwan's population) selected from the total NHI-insured population enrolled in the system in 2000, was analyzed in this study. The NHIRD was provided by the Bureau of National Health Insurance (BNHI) and released by the National Health Research Institute. The diseases recorded in the NHIRD were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The privacy of each individual's information was protected using encrypted personal identification to avoid the potential for ethical violations related to the data, so informed consent was not required. Exemption was obtained from the institutional review board of Chi Mei Medical Center (IRB No. 10202-E70).

2.2. Study design and subjects

Two cohort analyses were performed in this study to examine the bidirectional relationship between LUTS and anxiety as well as LUTS and depression. Patients who had LUTS, anxiety, and depression were defined as having at least three outpatient service claims in one year or at least one inpatient hospitalization claim during the period 1999–2008. As in our previous study using ICD-9-CM criteria [13], LUTS was defined as hypertonicity of the bladder (596.51); frequency and polyuria (788.4); stress urinary incontinence in females (625.6) and males (788.32); urge incontinence (788.31); nocturnal enuresis (788.36); nocturia (788.43); mixed incontinence (788.33); retention of urine (788.2); splitting and slowing of the urine stream (788.6); postvoid dribbling (788.35); and benign prostatic hyperplasia (enlargement) (600). In addition, the definition of anxiety was: anxiety states (300.0); phobic disorders (300.2); obsessive-compulsive disorders (300.3); and adjustment disorder with anxiety (309.24). Depression was defined using ICD-9-CM codes, as major depressive disorder, single episode (296.2); major depressive disorder, recurrent episode (296.3); bipolar I disorder, most recent (or current) episode of depression (296.5); depressive disorder, not elsewhere classified (311); dysthymic disorder (300.4); atypical depressive disorder (296.82); adjustment disorder with depressed mood (309.0); and prolonged depressive reaction (309.1).The aim of cohort study 1 was to determine the risk of anxiety and depression between LUTS patients and matched individual controls without LUTS. The control subjects were randomly selected and matched to two LUTS individuals by age, gender, hypertension (HTN), diabetes mellitus (DM), and coronary artery disease (CAD). Subjects with a diagnosis of anxiety or depression before the first date of diagnosis of LUTS or the index date of the controls were excluded. The index date of the controls was set as the date closest to the first diagnosis date of LUTS.

For cohort study 2, we wanted to estimate the risk of LUTS between anxiety patients and compared cohorts (individuals without anxiety or depression) as well as depression patients and compared cohorts. One anxiety or depression subject was matched to two individuals without anxiety or depression by age, gender, HTN, DM, and CAD. Subjects who were diagnosed as having LUTS before the first date of diagnosis of anxiety or depression or the index date of the controls were excluded. The index date of the controls was set as the date closest to the first date of diagnosis of anxiety or depression. To estimate the incidence of anxiety and depression (for the first cohort) or LUTS (for the second cohort), all subjects were followed at least three years or to the date of death or the end of 2011.

2.3. Risk variables

Age, gender, and comorbidities such as HTN (ICD-9-CM: 401–405, 437.2, 362.11), DM (ICD-9-CM: 250, 357.2, 362.0, 366.41), and CAD (ICD-9-CM: 410–414), overweight and obesity (ICD-9-CM: 278), urinary tract infection (ICD-9-CM:599.0), Parkinson's disease (ICD-9-CM: 332), multiple sclerosis (ICD-9-CM: 340), spinal cord injury (ICD-9-CM: 806 and 952), multiple system atrophy (other degenerative diseases of the basal ganglia) (ICD-9-CM:333.0), and cerebral degeneration, unspecified (ICD-9-CM:331.9) were estimated in this study. Age was categorized as $< =35$, 36–50, 51–65, 66–80, and > 80. Comorbidities were determined by medical records within one year before the diagnosis of LUTS or anxiety and depression.

2.4. Statistical methods

Student's *t*-test or Wilcoxon rank-sum test for continuous variables and Pearson's Chi-square or Fisher's exact test for categorical variables were used to compare the difference between cases and controls. The incidence rate was calculated by the number of cases divided by the total person-years (PY) as the denominator. Cox proportional hazards regression model was used to estimate the new-onset risk (hazard ratio, HR) of anxiety and depression (for the first cohort) or LUTS (for the second cohort) with age, gender, and comorbidities in the model. Statistical significance was set as a p-value of < 0.05, and Statistical Analysis System (SAS) software (version 9.4; SAS Institute, Inc., Cary, NC) was used to perform all statistical analyses.

3. Results

3.1. Cohort study 1: LUTS and subsequent risk of anxiety/depression

During the study period (1999–2008), we identified 17,489 patients