Psychiatric Disorders in Female Psychosexual Disorders—A Nationwide, Cohort Study in Taiwan

Iau-Jin Lin
Graduate Institute of Life Sciences, National Defense Medical Center

Nian-Sheng Tzeng
Tri-Service General Hospital, National Defense Medical Center

Chi-Hsiang Chung
Tri-Service General Hospital

Chien Wu-chien (chienwu@ndmctsgh.edu.tw)
National Defense Medical Center  https://orcid.org/0000-0002-3286-0780

Research article

Keywords: Psychosexual disorders, affective disorders, females, National Health Insurance Research Database, cohort study

DOI: https://doi.org/10.21203/rs.3.rs-49580/v2

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

We aimed to investigate as to whether females with psychosexual disorders were associated with the risk of affective and other psychiatric disorders. A total of 2,240 enrolled individuals, with 560 patients with psychosexual disorders and 1,680 subjects without psychosexual disorders (1:3) matched for age and index year, from the Longitudinal Health Insurance Database, retrieved from the National Health Insurance Research Database (NHIRD), between 2000-2015 in Taiwan. The multivariate Cox regression model was used to compare the risk of developing psychiatric disorders during the 15 years of follow-up. There were 98 in the cohort with psychosexual disorders (736.07 per 100,000 person-year) and 119 in the cohort without psychosexual disorders (736.07 per 100,000 person-year) that developed psychiatric disorders. The multivariate Cox regression model revealed that the adjusted hazard ratio (HR) was 9.848 (95% CI= 7.298 — 13.291, p < 0.001), after the adjustment of age, monthly income, urbanization level, geographic region, and comorbidities. Female patients with psychosexual disorders were associated with the risk of psychiatric disorders. This finding could be a reminder for clinicians about the mental health problems in the patients with psychosexual disorders.

Background

Psychosexual disorders could be classified into sexual dysfunctions, paraphilias, and gender identity disorders [1, 2], and these psychosexual disorders are regarded as part of the psychiatric disorders [3]. Previous studies have shown that female patients with psychosexual disorders, such as sexual dysfunctions, paraphilias, and gender identity disorders, would suffer from emotional distress, social embarrassment, and even stigmatization [4, 5].

Several researchers have shown the neurodevelopmental interlinks between the psychosexual and psychiatric disorders: Sex differences in the microglial function might partially explain the differences observed in susceptibilities and outcomes of the neuropsychiatric disorders in men and women [6]. Rajkumar (2014) pointed out that both gender identity disorders and schizophrenia are associated with altered cerebral sexual dimorphism and changes in cerebral lateralization [7]. Previous studies have also found that endocrine factors are related to female psychosexual disorders. For examples, sex steroid, such as estrogen or progesterin, insufficiency may adversely affect central sexual thought processes, and contribute to the female sexual dysfunctions, such as hypoactive sexual desire disorder [8]. In addition, gender dysphoria may have several genes involved in the sex hormone–signaling in the brains [9]. Sex hormones such as estrogen have many effects on anxiety and depression [10]. Several studies have found mutual relations between the psychiatric comorbidity and the psychosexual disorders [11-16]. For the clinicians, it is essential to better understand the mutual relationship between female patients with psychosexual disorders and their psychiatric morbidity. And these psychiatric disorders might well contribute to the distress, disability, or an increased risk of suffering death, pain, or disability, and consequent behavioral, psychological, or biological dysfunctions [3, 17]. Therefore, several neurodevelopmental, endocrine, and the psychological factors could be the linkage between psychosexual and psychiatric disorders.

Previous studies have found that depressive disorders are frequently associated with sexual dysfunction, across all the phases of sexual responses [18], and the attention problems related to anxiety might impair the sexual motivation even with adequate stimuli [19]. In addition, sexual dysfunction is frequent in patients with posttraumatic stress disorder [20, 21]. However, some researchers have revealed that no psychiatric comorbidity was found in the female patients with gender identity disorder [22, 23]. Furthermore, the relationship between female paraphilia and psychiatric disorders remains unclear, since patients with female paraphilia are rare [24, 25]. Therefore, depression, anxiety, and trauma-related disorders are associated with sexual dysfunctions, and also with the association between psychiatric disorders and paraphilia and gender identity disorder. In addition, there is a gap in the literature that no previous cohort studies have been conducted to examine the risk of psychiatric disorders in the female patients with psychosexual disorders. We hypothesize that these psychosexual disorders are associated with the risk of psychiatric disorders in a long-term follow up. We therefore conduct the present study, using Taiwan’s National Health Insurance Research Database (NHIRD), to investigate the association between psychosexual disorders and psychiatric disorders, in a 15-year follow-up.

Methods
Data sources

The National Health Insurance (NHI) Program was launched in Taiwan in 1995, and as of June 2009, included contracts with 97% of the medical providers, with approximately 23 million beneficiaries, or more than 99% of the entire population [26]. The National Health Insurance Research Database (NHIRD) uses the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to record the diagnoses [27]. The present study has used the NHIRD to identify the inpatients with a discharge diagnosis of psychosexual disorders based on the ICD-9-CM codes, including sexual dysfunctions, paraphilia, and gender identity disorders, during 2000–2015. The paraphilias included the diagnoses as exhibitionism, fetishism, frotteurism, pedophilia, sexual masochism, sexual sadism, transvestic fetishism, voyeurism, other paraphilia, and paraphilia, not otherwise specified [3]. All the ICD-9-CM codes of psychosexual disorders are as listed in Table S1. In this database, all the personal identification data were enciphered, for the protection of the privacy of the patients. The records of ambulatory care visits and inpatient claims periodically were reviewed randomly by the NHI Administration to verify the accuracy of the diagnoses [28]. Several previous studies have documented the details of the program [29-33].

Study design and sampled participants

Patients with newly diagnosed psychosexual disorders were selected from the from the two million Longitudinal Health Insurance Database (LHID), randomized retrieved from the NHIRD, which covers 99% of the entire population of Taiwan, between January 1, 2000 and December 31, 2015. The patients with psychosexual disorders before 2000 were excluded. In addition, the patients diagnosed with psychiatric disorders before 2000, or before their first visit for any psychosexual disorder, were also excluded. In Taiwan, the legal age of full civil competency is 20 years of age, according to Taiwan’s Civil Code [34], therefore, all patients aged <20, were excluded as well. In this study, 560 patients with psychosexual disorder and 1,680 subjects without psychosexual disorders, were 1:3 matched, for age, and index-year control, with a statistic power of 0.72 [35], and little power improvement resulted from increasing the number of controls while the ratio beyond 1:3 or 1:4 [36]. Therefore, the present study is a population-based, matched-cohort study.

Covariates

The covariates included age groups (20-49, ≥50 years), geographical area of residence (north, center, south, and east of Taiwan), urbanization level of residence (levels 1 to 4), and monthly income (in New Taiwan Dollars [NT$]; <18,000, 18,000-34,999, ≥35,000). The urbanization level of residence was defined according to the population and various indicators of the level of development. Level 1 was defined as a population of >1,250,000, and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500,000 and 1,249,999, and as playing an important role in the politics, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, and <149,999, respectively.

Comorbidity

We assessed the comorbidities by using the Charlson Comorbidity Index (CCI), which categorizes comorbidities using the ICD-9-CM codes and scores each comorbidity category [37-39]. The CCI is used for comorbidity adjustment as a useful measure and substitutes for the usage of the individual comorbidity variables in health services research [41]. In CCI, the comorbidities includes the myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, dementia, paralysis, diabetes mellitus, diabetes with sequelae, chronic renal failure, cirrhosis of liver, moderate-severe liver disease, peptic ulcers, rheumatoid arthritis, and AIDS [42]. The combination of all the scores were regarded as a single comorbidity score. A score of zero indicates that no comorbidities were found, and higher scores indicate higher comorbidity burdens [40].

Outcome measures

Enrolled individuals in these two cohorts were tracked for 15 years, starting from the index date, to identify those who developed psychiatric disorders, including dementia, anxiety disorders, depressive disorders, bipolar disorders, eating disorders, sleep
disorders, and psychotic disorders, withdrew from the NHI program, or reached the end of 2015. All the ICD-9-CM codes of psychiatric disorders are as listed in Table S1.

Statistical analysis

All statistical analyses were performed using the SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY). $\chi^2$ and t tests were used to appraise the distributions of the categorical and continuous variables, respectively. The multivariate regression model was used to determine the risk of psychiatric disorders since death can act as a competing risk factor for psychiatric disorders [41, 42]. The results were presented as a hazard ratio (HR) with a 95% confidence interval (CI). Differences in the risk of psychiatric disorders between the study and control groups were estimated using the Kaplan-Meier method with the log-rank test. A 2-tailed $p$ value <0.001 was considered to indicate a statistical significance, to minimize the type I error as possible.

Ethics

This study was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of the Tri-Service General Hospital approved this study and waived the need of individual consents since all the identification data were encrypted in the NHIRD (No. 1-106-05-055).

Results

Sample characteristics

There was no significant difference between these two cohorts in age, marital status, education, insured monthly premiums, and the CCI scores. The cohort with psychosexual disorders tended to search for medical help in the seasons of summer, autumn, and winter. Furthermore, the cohort with psychosexual disorders tended to live in the north, and the offshore islands, resided more in the region of urbanization level 2 and received their medical treatments in the medical centers (Table 1).
| Variables                  | Total   | With     | Without | P    |
|----------------------------|---------|----------|---------|------|
| n                          | 2,240   | 560      | 1,680   |      |
| Total                      |         | 25.00    | 75.00   |      |
| Age (years)                | 35.08 ± 12.99 | 34.70 ± 11.46 | 35.21 ± 13.46 | 0.421 |
| Age group (years)          |         | 0.999    |         |      |
| 20–49                      | 2,016   | 90.00    | 1,512   | 90.00|
| ≧ 50                       | 224     | 10.00    | 168     | 10.00|
| Married                    |         | 0.692    |         |      |
| Yes                        | 936     | 41.79    | 706     | 42.02|
| No                         | 1,304   | 58.21    | 974     | 57.98|
| Education (years)          |         | 0.823    |         |      |
| < 12                       | 568     | 25.36    | 424     | 25.24|
| ≧ 12                       | 1,672   | 74.64    | 1,256   | 74.76|
| Insured premium (NT$)      |         | 0.663    |         |      |
| < 18,000                   | 1,974   | 88.13    | 1,475   | 87.80|
| 18,000–34,999              | 184     | 8.21     | 143     | 8.51 |
| ≧ 35,000                   | 82      | 3.66     | 62      | 3.69 |
| CCLR                       | 0.39 ± 1.37 | 0.30 ± 0.94 | 0.42 ± 1.48 | 0.081|
| Season                     |         | < 0.001  |         |      |
| Spring (March-May)         | 581     | 25.94    | 490     | 29.17|
| Summer (June-August)       | 602     | 26.88    | 448     | 26.67|
| Autumn (September-November)| 476     | 21.25    | 329     | 19.58|
| Winter (December-February) | 581     | 25.94    | 413     | 24.58|
| Location                   |         | < 0.001  |         |      |
| Northern Taiwan            | 945     | 42.19    | 637     | 37.92|
| Middle Taiwan              | 581     | 25.94    | 469     | 27.92|
| Southern Taiwan            | 574     | 25.63    | 462     | 27.50|
| Eastern Taiwan             | 126     | 5.63     | 105     | 6.25 |
| Outlets islands            | 14      | 0.63     | 7       | 0.42 |
| Urbanization level         |         | < 0.001  |         |      |
| 1 (The highest)            | 784     | 35.00    | 658     | 39.17|
| 2                          | 1,029   | 45.94    | 672     | 40.00|
| 3                          | 112     | 5.00     | 91      | 5.42 |
| 4 (The lowest)             | 315     | 14.06    | 259     | 15.42|
Psychosexual disorders

| Variables       | Total |     | With |     | Without |     | P         |
|-----------------|-------|-----|------|-----|---------|-----|-----------|
|                 | n    | %   | n    | %   | n       | %   |          |
| Level of care   |       |     |      |     |         |     | < 0.001  |
| Medical center  | 798   | 35.63 | 357  | 63.75 | 441     | 26.25 |          |
| Regional hospital | 595  | 26.56 | 147  | 26.25 | 448     | 26.67 |          |
| Local hospital  | 847   | 37.81 | 56   | 10.00 | 791     | 47.08 |          |

P: Chi-square / Fisher exact test on category variables and t-test on continue variables

Without married: un-married, divorce, spouse death, and unknown

Education years < 12: elementary school, junior high school, (vocational) high school, and unknown; Education years ≥ 12: university, college, and graduate

CCI_R: Charlson comorbidity index removed dementia

The cumulative incidence of psychiatric disorders

There were 98 in the cohort with psychosexual disorders and 119 in the comparison cohort that developed psychiatric disorders (3444.66 vs 736.07 per 100,000 person-year). Figure 1 depicts that the difference was statistically significant in the Kaplan-Meier survival analysis (log-rank, p < 0.001).

Changes of psychosexual disorders in the follow up period, 2000-2015

Figure 2 reveals that there was no significant difference between the beginning and the end-point of the follow-up in all these psychosexual disorders, between 2000 and 2015. In addition, the treatment prevalence of the female psychosexual disorders was 0.007% of the sexual dysfunctions, paraphilias were around 0.004%, and the female-to-male (FTM) gender identity disorder was 0.017%, during the 15-year follow-up.

HR analysis of psychiatric disorders in the patients with psychosexual disorders

The multivariate Cox regression model showed that the adjusted HR of the cohort with psychosexual disorders in the development of psychiatric disorders was 9.848 (95% CI= 7.298 – 13.291, p < 0.001), after adjustment for age, marital status, education, comorbidity (CCI scores), urbanizations/areas of residence, insurance premiums, seasons of visits, and levels of medical facilities, as compared to the control group (Table 2).
| Table 2. Factors of psychiatric disorders stratified by variables listed in the table by using Cox regression model |
|-----------------------------------------------------|
| Psychosexual disorders (With vs. Without)          |
| Stratified | Event | PYS   | Rate (per 10^5 PYS) | Event | PYS   | Rate (per 10^5 PYS) | Adjusted HR | 95% CI | 95% CI | P     |
| Total      | 98    | 2,844.99 | 3,444.66       | 119   | 16,167.03 | 736.07          | 9.848       | 7.298  | 13.291 | <0.001 |
| Age group (years) |  |       |               |       |          |               |             |       |       |       |
| 20-49      | 70    | 1,823.05 | 3,839.71 | 91    | 9,797.14 | 928.84         | 8.699       | 6.447  | 11.740 | <0.001 |
| ≥50        | 28    | 1,021.93 | 2,739.91 | 28    | 6,369.89 | 439.57         | 13.117      | 9.720  | 17.703 | <0.001 |
| Married    |  |       |               |       |          |               |             |       |       |       |
| Yes        | 38    | 1,400.98 | 2,712.38 | 48    | 7,754.07 | 619.03         | 9.221       | 6.833  | 12.444 | <0.001 |
| No         | 60    | 1,444.00 | 4,155.12 | 71    | 8,412.96 | 843.94         | 10.361      | 7.678  | 13.983 | <0.001 |
| Education (years) |  |       |               |       |          |               |             |       |       |       |
| <12        | 27    | 1,034.02 | 2,611.17 | 20    | 8,026.18 | 249.18         | 22.051      | 16.341 | 29.761 | <0.001 |
| ≥12        | 71    | 1,810.97 | 3,920.56 | 99    | 8,140.85 | 1,216.09       | 6.784       | 5.028  | 9.156  | <0.001 |
| Insured premium (NT$) |  |       |               |       |          |               |             |       |       |       |
| <18,000    | 67    | 1,512.44 | 4,429.93 | 73    | 7,558.18 | 965.84         | 9.652       | 7.153  | 13.026 | <0.001 |
| 18,000-34,999 | 24   | 851.67  | 2,818.01 | 38    | 4,311.00 | 881.47         | 6.728       | 4.986  | 9.080  | <0.001 |
| ≥35,000    | 7     | 480.88  | 1,455.66 | 8     | 4,297.85 | 186.14         | 16.457      | 12.195 | 22.210 | <0.001 |
| Season     |  |       |               |       |          |               |             |       |       |       |
| Spring     | 21    | 535.28  | 3,923.14 | 28    | 3,746.20 | 747.42         | 11.046      | 8.185  | 14.907 | <0.001 |
| Summer     | 28    | 1,081.07| 2,590.02 | 35    | 4,793.88 | 730.10         | 7.465       | 5.332  | 10.075 | <0.001 |
| Autumn     | 21    | 205.32  | 10,228.13 | 28    | 3,561.62 | 786.16         | 27.378      | 20.289 | 36.950 | <0.001 |
| Winter     | 28    | 1,023.31| 2,736.22 | 28    | 4,065.33 | 688.75         | 8.360       | 6.195  | 11.283 | <0.001 |
| Urbanization level |  |       |               |       |          |               |             |       |       |       |
| 1 (The highest) | 42   | 1,173.26 | 3,579.77 | 42    | 5,526.97 | 759.91         | 9.913       | 7.346  | 13.379 | <0.001 |
| 2          | 35    | 1,081.95| 3,234.89 | 42    | 5,927.50 | 708.56         | 9.607       | 7.120  | 12.966 | <0.001 |
| 3          | 0     | 267.33  | 0.00     | 21    | 1,360.70 | 1,543.33       | 0.000       | -      | -      | 0.781 |
| 4 (The lowest) | 21   | 322.44  | 6,512.77 | 14    | 3,351.86 | 417.68         | 32.813      | 24.316 | 44.285 | <0.001 |
| Level of care |  |       |               |       |          |               |             |       |       |       |
| Medical    | 21    | 932.95  | 2,250.93 | 21    | 5,334.73 | 393.65         | 12.033      | 8.917  | 16.240 | <0.001 |
### Types of psychiatric disorders in female patients with psychosexual disorders

Table 3 depicts that the cohort with psychosexual disorders was associated with the risk of dementia, anxiety, depressive, sleep, and psychotic disorders. Sexual dysfunctions were associated with dementia, anxiety, depressive disorders, and sleep disorders. Gender identity disorder was associated with anxiety, depressive, sleep, and psychotic disorders. Paraphilias were associated with dementia and depression.

#### Table 3. Factors of psychiatric disorders subgroup stratified by psychosexual disorders subgroup by using Cox regression model

| Psychosexual disorders | Psychiatric disorders | Adjusted HR | 95% CI      | 95% CI      | P      |
|------------------------|-----------------------|-------------|-------------|-------------|--------|
| Overall (N=98)         | Overall               | 9.848       | 7.298       | 13.291      | <0.001 |
|                        | Dementia (N=14)       | 11.958      | 8.862       | 16.139      | <0.001 |
|                        | Anxiety (N=14)        | 7.972       | 5.908       | 10.759      | <0.001 |
|                        | Depression (N=63)     | 21.525      | 15.951      | 29.050      | <0.001 |
|                        | Sleep disorders (N=14)| 7.972       | 5.908       | 10.759      | <0.001 |
|                        | Psychotic disorders (N=7) | 3.986 | 2.954       | 5.380       | <0.001 |
| Sexual dysfunctions (N=42) | Overall             | 6.488       | 4.808       | 8.757       | <0.001 |
|                        | Dementia (N=7)        | 9.192       | 6.812       | 12.406      | <0.001 |
|                        | Anxiety (N=7)         | 6.128       | 4.541       | 8.270       | <0.001 |
|                        | Depression (N=28)     | 14.707      | 10.899      | 19.849      | <0.001 |
|                        | Sleep disorders (N=7) | 6.128       | 4.541       | 8.270       | <0.001 |
| Paraphilias (N=21)     | Overall               | 33.366      | 24.726      | 45.031      | <0.001 |
|                        | Dementia (N=7)        | 94.537      | 70.058      | 127.589     | <0.001 |
|                        | Depression (N=14)     | 75.630      | 56.047      | 102.071     | <0.001 |
| Gender identity disorders (N=35) | Overall            | 12.286      | 9.105       | 16.581      | <0.001 |
|                        | Anxiety (N=7)         | 13.924      | 10.318      | 18.792      | <0.001 |
|                        | Depression (N=21)     | 25.063      | 18.573      | 33.825      | <0.001 |
|                        | Sleep disorders (N=7) | 13.924      | 10.318      | 18.792      | <0.001 |
|                        | Psychotic disorders (N=7) | 13.924 | 10.318  | 18.792      | <0.001 |

*PYs = Person-years; Adjusted HR = Adjusted Hazard ratio: Adjusted for the variables listed in Table 1.; CI = confidence interval*

In addition, there were no significant differences in the times of the psychiatric visits between the two cohorts, even though the cohort with psychosexual disorders had more psychiatric visits than the comparison cohort (3.82 [standard deviation (SD) ± 4.06] vs 3.15 [SD ± 3.97]), without statistical difference ($p = 0.001$) (Table S2)
Discussion

Association between psychosexual disorders and the risk of psychiatric disorders

The adjusted HR was 9.848 (95% CI = 7.298 – 13.291, \( p < 0.001 \)) in the association between the psychosexual disorders and psychiatric disorders, and the female patients with psychosexual disorders had a 9.8-fold increase in the risk of psychiatric disorders, after the adjustment of age, monthly income, urbanization level, geographic region, and comorbidities. The Kaplan-Meier analysis demonstrated that the cohort with psychosexual disorders had a significantly higher 15-year psychiatric disorders cumulative incidence than the comparison cohort. To the best of our knowledge, this is the first study on the topic of an association between the female patients with psychosexual disorders and the risk of psychiatric morbidity. This finding could serve as a reminder for the clinicians to pay much more attention to these patients because of the issues about the psychiatric disorders.

Comparison of this study to previous literatures

Previous studies have shown the association between psychosexual disorders and psychiatric disorders that included antidepressant-related sexual dysfunctions patients with depressive or anxiety disorders [16, 43-45], female paraphilia focused and the personality disorders on the forensic psychiatric topics [14, 15], and the FTM gender disorders and depression, post-traumatic stress disorder, anxiety disorders and suicides [12, 13, 46]. However, these studies were mostly conducted in cross-section methods, and our study is unique for the retrospective cohort design, from a larger population-based database. In addition, the male patients with psychosexual disorders has been associated with the increased risk in anxiety disorders, depressive disorders, bipolar disorders, sleep disorders, and psychotic disorders, respectively [33]. There were several differences in the risk of different psychiatric disorders in these two studies. The underlying reasons for the difference of risk for the psychiatric disorders, between the female patients with psychosexual disorders, needs further studies.

Treatment prevalence of psychosexual disorders in this study

Previous studies revealed that the prevalence of female sexual dysfunctions was 30–60%, in different countries [47-50], but we found that there was 0.007% of the sexual dysfunctions in this sample of 15-year of follow-up. In the present study, there were 70 paraphilia patients from the database, and the treatment prevalence of female paraphilias were around 0.004% in this LHID. The prevalence of the female paraphilias were 2% in exhibitionist behaviors in previous studies [25, 51], 4% in voyeuristic behaviors [25, 51], 0.4% in transvestic fetishism [52], and 1% in sadomasochistic activity [53], from surveys in the population of Sweden [25, 51], and Australia [53]. Previous reports have shown that there were 0.003% in Belgium [54], 0.82% in Japan [55], and 0.023% 0.058% in the United States veteran's populations [12, 56] of FTM gender identity disorder. Furthermore, the present study found that the treatment prevalence of FTM gender identity disorder, was 0.017%, in the duration of the 15 years of follow-up. The discrepancy of the prevalence might be the difference of studies from a claims database or the survey. Cultural differences might also contribute to this difference: previous studies have shown that females have more difficulties in their help-seeking for sex-related problems in Asian countries [57, 58]. However, the present study is the first one for the females with psychosexual disorders and the risk of the psychiatric disorders in an Asian country.

Possible mechanisms for the increased risk of psychiatric disorders in patients with psychosexual disorders

In the present study, female patients with sexual dysfunctions were associated with dementia, anxiety, depressive disorders, and sleep disorders, and female patients with paraphilias were associated with dementia and psychotic disorders. There are several neurodevelopmental, endocrine and psychological factors related to the linkage between these two groups of disorders. The stress from the suffering of sexual dysfunction [59, 60], paraphilias [61, 62], and gender identity disorders [63-65], might well contribute to the association between these psychosexual disorders and the risk of anxiety, depressive, or sleep disorders. One study has found that hyperprolactinemia seems to play a role to the pathogenesis of hypoactive sexual desire disorder, one of the female sexual dysfunctions [66], and hyperprolactinemia might induced depression and anxiety [67-70].

Evidence suggests that female and male brains are different in the mean volumes of the hippocampus, amygdala and thalamus [71], the concentration of estrogen or androgen receptors [72], and the total brain, cerebrum, and cerebellum volumes [73]. Thus,
the difference in the brain anatomy and neuronal signaling pathways are more closely aligned with a person's perceived gender identity, and individuals with discordant gonadal and brain developments might experience psychological challenges for the generalized dissatisfaction with their biological sex [74]. In addition, paraphilias and depression might share a common dysregulation of this monoaminergic pathway in these patients [11, 75].

Psychological, social, and cultural factors might also contribute to both the psychosexual disorders and psychiatric disorders. Previous studies have shown that the patients with paraphilias might suffer emotional distress, social embarrassment [4], and stigma [5]. For example, a study from Turkey has found that patients with vaginismus have higher levels of depression and anxiety [76]. Phobic defense mechanism [77], the rejection of the female role, and religious orthodoxy which regards sex as dirty or shameful[78], are the psychosocial factors that contribute to vaginismus, depression, and anxiety [76].

However, the mechanisms underlying the association between female paraphilias and dementia are unknown, and we speculate that this finding might well be related to the sexually inappropriate behaviors before the apparent cognitive deterioration, in the early stages of frontotemporal Alzheimer or early-stage dementia .[79] The association between the FTM gender identity disorders and psychotic disorders also remain unknown and are in the need of further studies.

Limitations

The present study has several limitations that warrant consideration. First, similar to previous studies using the NHIRD on psychosexual disorders [32, 80-82], we were unable to evaluate the severity, weakness severity, laboratory parameters, or psychological assessments in the patients with psychosexual disorders, since the data were not recorded in the NHIRD. Second, the genetic, psychosocial, and environmental factors, were not included in the dataset. Third, even though we have excluded the patients diagnosed with dementia, depressive, anxiety, bipolar, sleep, and psychotic disorders before 2000, or before their first visit for any psychosexual disorders, there is the possibility of the protopathic bias, in which some patients could have been introduced into this study by subjects who have an undiagnosed disease. Fourth, although paraphilias and gender dysphoria are distinct categories, there is some evidence for an overlap between paraphilias and gender dysphoria [83]. The combination of distinct entities, in a single heterogeneous category of psychosexual disorders, is a limitation when discussing the results of the data analysis. Fifth, there is a possibility that the high prevalence of psychiatric disorders, among female patients with psychosexual disorders, is due to the high utilization of psychiatric services. However, as shown in Table S2, there were no significant differences in the times of psychiatric visits between the two cohorts.

Conclusions

Female patients who suffer from psychosexual disorders have a 9.8-fold increase in risk of psychiatric disorders, and this finding should serve as a timely reminder for the clinicians to pay much more attention towards these patients because of their mental health issues.

Abbreviations

CCI: Charlson Comorbidity Index
CI: confidence interval
FTM: female-to-male
HR: hazard ratio
ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification
LHID: Longitudinal Health Insurance Database
NHIRD: National Health Insurance Research Database
Declarations

Acknowledgments

We appreciate the support from the Tri-Service General Hospital Research Foundation and the Medical Affairs Bureau, Ministry of Defense, Taiwan, ROC. We also appreciate the database provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW).

Authorship contribution statement

Iau-Jin Lin: Conceptualization, Investigation, Writing-original draft. Nian-Sheng Tzeng: Data curation, Funding acquisition, Investigation, Methodology, Resources. Chi-Hsiang Chung: Formal analysis, Investigation, Methodology, Software, Visualization. Wu-Chien Chien: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing-review & editing.

Competing Interests

None

Role of funding sources

This study was supported by The Program for Promoting Teaching Excellence Universities, Ministry of Education (NDMC 104-106: I2-4), the Medical Affairs Bureau, Ministry of Defense (MAB-107-084), and the Tri-Service General Hospital Foundation (TSGH-C107-004, TSGH-C107-106, TSGH-C108-003, TSGH-C108-151, TSGH-B-109-010, TSGH-B-110005), and the sponsor has no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. However, all authors declare no financial interests nor conflict of interest or the appearance of a conflict of interest with regard to the work.

Data Availability

Data are available from the National Health Insurance Research Database (NHIRD) published by Taiwan National Health Insurance (NHI) Administration. Due to legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act", data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (http://www.mohw.gov.tw/cht/DOS/DM1.aspx?f_list_no=812).

References

1. Friedman JM, Czekala JE: Psychosexual Disorders. In: Medical Factors and Psychological Disorders. edn. Edited by R.L. M, A.S. B. Boston, MA: Springer; 1987.
2. Crépault C: [Classification of psychosexual disorders]. Contracept Fertil Sex 1993, 21(2):177-183.
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders 4th Edition, 4 edn. USA: American Psychiatric Association; 1994.
4. Saleh FM, Berlin FS: Sex hormones, neurotransmitters, and psychopharmacological treatments in men with paraphilic disorders. Journal of child sexual abuse 2003, 12(3-4):233-253.
5. Jahnke S, Schmidt AF, Geradt M, Hoyer J: Stigma-Related Stress and Its Correlates Among Men with Pedophilic Sexual Interests. Archives of sexual behavior 2015, 44(8):2173-2187.
6. Hanamsagar R, Bilbo SD: Sex differences in neurodevelopmental and neurodegenerative disorders: Focus on microglial function and neuroinflammation during development. J Steroid Biochem Mol Biol 2016, 160:127-133.
7. Rajkumar RP: Gender identity disorder and schizophrenia: neurodevelopmental disorders with common causal mechanisms? Schizophr Res Treatment 2014, 2014:463757.
8. Davis SR, Guay AT, Shifren JL, Mazer NA: Endocrine aspects of female sexual dysfunction. *The journal of sexual medicine* 2004, 1(1):82-86.

9. Foreman M, Hare L, York K, Balakrishnan K, Sanchez FJ, Harte F, Erasmus J, Vilain E, Harley VR: Genetic Link Between Gender Dysphoria and Sex Hormone Signaling. *J Clin Endocrinol Metab* 2019, 104(2):390-396.

10. Walf AA, Frye CA: A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. *Neuropsychopharmacology* 2006, 31(6):1097-1111.

11. Bradford JM: The paraphilias, obsessive compulsive spectrum disorder, and the treatment of sexually deviant behavior. *The Psychiatric quarterly* 1999, 70(3):209-219.

12. Brown GR, Jones KT: Mental Health and Medical Health Disparities in 5135 Transgender Veterans Receiving Healthcare in the Veterans Health Administration: A Case-Control Study. *LGBT health* 2016, 3(2):122-131.

13. Dhejne C, Van Vlerken R, Heylens G, Arcelus J: Mental health and gender dysphoria: A review of the literature. *International review of psychiatry (Abingdon, England)* 2016, 28(1):44-57.

14. Segal DL, Gottschling J, Marty M, Meyer WJ, Coolidge FL: Relationships among depressive, passive-aggressive, sadistic and self-defeating personality disorder features with suicidal ideation and reasons for living among older adults. *Aging & mental health* 2015, 19(12):1071-1077.

15. Turner D, Briken P: Treatment of Paraphilic Disorders in Sexual Offenders or Men With a Risk of Sexual Offending With Lueteinizing Hormone-Releasing Hormone Agonists: An Updated Systematic Review. *The journal of sexual medicine* 2018, 15(1):77-93.

16. Duke SR, Jayaram SD, Chittaranjan A: Sexual Dysfunction in Patients with Antidepressant-treated Anxiety or Depressive Disorders: a Pragmatic Multivariable Longitudinal Study. *East Asian archives of psychiatry : official journal of the Hong Kong College of Psychiatrists = Dong Ya jing shen ke xue zhi : Xianggang jing shen ke yi xue yuan qi kan* 2018, 28(1):9-16.

17. Stein DJ, Phillips KA, Bolton D, Fulford KW, Sadler JZ, Kendler KS: What is a mental/psychiatric disorder? From DSM-IV to DSM-V. *Psychological medicine* 2010, 40(11):1759-1765.

18. Atlantis E, Sullivan T: Bidirectional association between depression and sexual dysfunction: a systematic review and meta-analysis. *The journal of sexual medicine* 2012, 9(6):1497-1507.

19. Bhasin S, Basson R: Sexual dysfunction in men and women. In: editors. In: *Williams Textbook of Endocrinology*. 13th edn. Edited by Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Philadelphia Elsevier, Inc; 2016: 785–830.

20. Yehuda R, Lehrer A, Rosenbaum TY: PTSD and Sexual Dysfunction in Men and Women. *The journal of sexual medicine* 2015, 12(5):1107-1119.

21. Ho Chan WS: Taiwan's healthcare report 2010. *The EPMA journal* 2010, 1(4):563-585.

22. Chinese Hospital Association: ICD-9-CM English-Chinese Dictionary. Taipei, Taiwan.: Chinese Hospital Association Press; 2000.

23. National Health Insurance Reimbursement Regulations. [http://law.moj.gov.tw/LawClass/LawAllff.aspx?PCode=L0060006]
30. Chien WC, Chung CH, Lin FH, Chang HA, Kao YC, Tzeng NS: Is weight control surgery associated with increased risk of newly onset psychiatric disorders? A population-based, matched cohort study in Taiwan. J Med Sci 2017, 37(4):137-149.

31. Tzeng NS, Chung CH, Lin FH, Yeh CB, Huang SY, Lu RB, Chang HA, Kao YC, Chiang WS, Chou YC et al.: Headaches and Risk of Dementia. Am J Med Sci 2017, 353(3):197-206.

32. Yang YJ, Chien WC, Chung CH, Hong KT, Yu YL, Hueng DY, Chen YH, Ma HI, Chang HA, Kao YC et al.: Risk of Erectile Dysfunction After Traumatic Brain Injury: A Nationwide Population-Based Cohort study in Taiwan. American journal of men's health 2018:1557988317750970.

33. Yang YJ, Chien WC, Chung CH, Hong KT, Yu YL, Hueng DY, Chen YH, Ma HI, Chang HA, Kao YC et al.: Risk of Erectile Dysfunction After Traumatic Brain Injury: A Nationwide Population-Based Cohort study in Taiwan. American journal of men's health 2018:1557988317750970.

34. Tzeng NS, Yeh HW, Chung CH, Chang HA, Kao YC, Chiang WS, Chien WC: Risk of Psychiatric Morbidity in Psychosexual Disorders in Male Patients: A Nationwide, Cohort Study in Taiwan. American journal of men's health 2019, 13(2):1557988319842985.

35. Civil Code [https://law.moj.gov.tw/ENG/LawClass/LawAll.aspx?pcode=B0000001]

36. Kang MS, Choi SH, Koh IS: The Effect of Increasing Control-to-case Ratio on Statistical Power in a Simulated Case-control SNP Association Study. Genomics & Informatics 2009, 7(3):148-151.

37. Grimes DA, Schulz KF: Compared to what? Finding controls for case-control studies. Lancet (London, England) 2005, 365(9468):1429-1433.

38. McGrogan A, Madle GC, Seaman HE, de Vries CS: The Epidemiology of Guillain-Barré Syndrome Worldwide. Neuroepidemiology 2009, 32(2):150-163.

39. van den Berg B, Walgaard C, Drenthen J, Fokke C, van Doorn PA: Guillain-Barre syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol 2014, 10(8):469-482.

40. Sandoglobulin Guillain-Barre Syndrome Trial Group: Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barre syndrome. Plasma Exchange. Lancet (London, England) 1997, 349(9047):225-230.

41. Needham DM, Scales DC, Laupacis A, Pronovost PJ: A systematic review of the Charlson comorbidity index using Canadian administrative databases: a perspective on risk adjustment in critical care research. Journal of Critical Care 2005, 20(1):12-19.

42. Blanche P, Proust-Lima C, Loubere L, Berr C, Dartigues JF, Jacqmin-Gadda H: Quantifying and comparing dynamic predictive accuracy of joint models for longitudinal marker and time-to-event in presence of censoring and competing risks. Biometrics 2015, 71(1):102-113.

43. Clayton AH, Gommoll C, Chen D, Nunez R, Mathews M: Sexual dysfunction during treatment of major depressive disorder with vilazodone, citalopram, or placebo: results from a phase IV clinical trial. International clinical psychopharmacology 2015, 30(4):216-223.

44. Jacobsen PL, Mahaheshwarkar AR, Palo WA, Chen Y, Dragheim M, Clayton AH: Treatment-emergent sexual dysfunction in randomized trials of vortioxetine for major depressive disorder or generalized anxiety disorder: a pooled analysis. CNS spectrums 2016, 21(5):367-378.

45. Olisah VO, Sheikh TL, Abah ER, Mahmud-Ajeigbe AF: Sociodemographic and clinical correlates of sexual dysfunction among psychiatric outpatients receiving common psychotropic medications in a Neuropsychiatric Hospital in Northern Nigeria. Nigerian journal of clinical practice 2016, 19(6):799-806.

46. Ibrahim C, Haddad R, Richa S: [Psychiatric comorbidities in transsexualism: Study of a Lebanese transgender population]. L'Encephale 2016, 42(6):517-522.

47. Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E: Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). Maturitas 2016, 94:87-91.

48. Zhang C, Tong J, Zhu L, Zhang L, Xu T, Lang J, Xie Y: A Population-Based Epidemiologic Study of Female Sexual Dysfunction Risk in Mainland China: Prevalence and Predictors. The journal of sexual medicine 2017, 14(11):1348-1356.
49. Lou WJ, Chen B, Zhu L, Han SM, Xu T, Lang JH, Zhang L: Prevalence and Factors Associated with Female Sexual Dysfunction in Beijing, China. *Chinese medical journal* 2017, 130(12):1389-1394.

50. Singh JC, Tharyan P, Kekre NS, Singh G, Gopalakrishnan G: Prevalence and risk factors for female sexual dysfunction in women attending a medical clinic in south India. *Journal of postgraduate medicine* 2009, 55(2):113-120.

51. Langstrom N, Seto MC: Exhibitionistic and voyeuristic behavior in a Swedish national population survey. *Archives of sexual behavior* 2006, 35(4):427-435.

52. Langstrom N, Zucker KJ: Transvestic fetishism in the general population: prevalence and correlates. *Journal of sex & marital therapy* 2005, 31(2):87-95.

53. Richters J, de Visser RO, Rissel CE, Grulich AE, Smith AM: Demographic and psychosocial features of participants in bondage and discipline, “sadomasochism” or dominance and submission (BDSM): data from a national survey. *The journal of sexual medicine* 2008, 5(7):1660-1668.

54. De Cuypere G, Van Hemelrijck M, Michel A, Caraël B, Heylens G, Rubens R, Hoebek P, Monstrey S: Prevalence and demography of transsexualism in Belgium. *European psychiatry : the journal of the Association of European Psychiatrists* 2007, 22(3):137-141.

55. Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T et al: Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *The journal of sexual medicine* 2011, 8(6):1686-1693.

56. Blosnich JR, Brown GR, Shiperd Phd JC, Kauth M, Piegari RI, Bossarte RM: Prevalence of gender identity disorder and suicide risk among transgender veterans utilizing veterans health administration care. *American journal of public health* 2013, 103(10):e27-32.

57. Vahdaninia M, Montazeri A, Goshtasebi A: Help-seeking behaviors for female sexual dysfunction: a cross sectional study from Iran. *BMC women's health* 2009, 9:3.

58. Moreira ED, Jr., Kim SC, Glasser D, Gingell C: Sexual activity, prevalence of sexual problems, and associated help-seeking patterns in men and women aged 40-80 years in Korea: data from the Global Study of Sexual Attitudes and Behaviors (GSSAB). *The journal of sexual medicine* 2006, 3(2):201-211.

59. Hamilton LD, Meston CM: Chronic stress and sexual function in women. *The journal of sexual medicine* 2013, 10(10):2443-2454.

60. Yazdanpanahi Z, Nikkhonlgh M, Akbarzadeh M, Pourrahmad S: Stress, anxiety, depression, and sexual dysfunction among postmenopausal women in Shiraz, Iran, 2015. *Journal of family & community medicine* 2018, 25(2):82-87.

61. Bradford JM, Ahmed AG: The natural history of the paraphilias. *The Psychiatric clinics of North America* 2014, 37(2):xi-xxv.

62. Kuzma JM, Black DW: Epidemiology, prevalence, and natural history of compulsive sexual behavior. *The Psychiatric clinics of North America* 2008, 31(4):603-611.

63. Colizzi M, Costa R, Pace V, Todarello O: Hormonal treatment reduces psychobiological distress in gender identity disorder, independently of the attachment style. *The journal of sexual medicine* 2013, 10(12):3049-3058.

64. Matsumoto Y, Sato T, Ohnishi M, Kishimoto Y, Terada S, Kuroda S: Stress-coping strategies of patients with gender identity disorder. *Psychiatry and clinical neurosciences* 2009, 63(6):715-720.

65. Wallien MS, van Goozen SH, Cohen-Kettenis PT: Physiological correlates of anxiety in children with gender identity disorder. *European child & adolescent psychiatry* 2007, 16(5):309-315.

66. Corona G, Petrone L, Mannucci E, Ricca V, Balercia G, Giommi R, Forti G, Maggi M: The impotent couple: low desire. *Int J Androl* 2005, 28 Suppl 2:46-52.

67. Hinojosa-Amaya JM, Johnson N, González-Torres C, Varlamov EV, Yedinak CG, McCartney S, Fleseriu M: Depression and Impulsivity Self-Assessment Tools to Identify Dopamine Agonist Side Effects in Patients With Pituitary Adenomas. *Front Endocrinol (Lausanne)* 2020, 11:579606.

68. Ioachimescu AG, Fleseriu M, Hoffman AR, Vaughan lii TB, Katznelson L: Psychological effects of dopamine agonist treatment in patients with hyperprolactinemia and prolactin-secreting adenomas. *Eur J Endocrinol* 2019, 180(1):31-40.
69. Krysiak R, Szkróbka W, Okopień B: The effect of bromocriptine treatment on sexual functioning and depressive symptoms in women with mild hyperprolactinemia. *Pharmacol Rep* 2018, 70(2):227-232.

70. Liao WT, Bai YM: Major depressive disorder induced by prolactinoma--a case report. *Gen Hosp Psychiatry* 2014, 36(1):125.e121-122.

71. Ritchie SJ, Cox SR, Shen X, Lombardo MV, Reus LM, Alloza C, Harris MA, Alderson HL, Hunter S, Neilson E *et al*: Sex Differences in the Adult Human Brain: Evidence from 5216 UK Biobank Participants. *Cereb Cortex* 2018, 28(8):2959-2975.

72. Halpern D: Sex Differences in Cognitive Abilities. New York: Psychology Press; 2012.

73. Ruigrok AN, Salimi-Khorshidi G, Lai MC, Baron-Cohen S, Lombardo MV, Tait RJ, Suckling J: A meta-analysis of sex differences in human brain structure. *Neurosci Biobehav Rev* 2014, 39(100):34-50.

74. Boucher FJO, Chinnah TI: Gender Dysphoria: A Review Investigating the Relationship Between Genetic Influences and Brain Development. *Adolesc Health Med Ther* 2020, 11:89-99.

75. Garcia FD, Thibaut F: Current concepts in the pharmacotherapy of paraphilias. *Drugs* 2011, 71(6):771-790.

76. Karaguzel E, Arslan F, Tiryaki A, Osmanagaoglu M, Kaygusuz E: Sociodemographic features, depression and anxiety in women with life-long vaginismus. *Anatolian Journal of Psychiatry* 2016, 17(6):1.

77. Fugl-Meyer KS, Bohm-Starke N, Damsted Petersen C, Fugl-Meyer A, Parish S, Giraldi A: Standard operating procedures for female genital sexual pain. *The journal of sexual medicine* 2013, 10(1):83-93.

78. Rao TS, Nagaraj AK: Female sexuality. *Indian J Psychiatry* 2015, 57(Suppl 2):S296-302.

79. Mendez MF, Shapiro JS: Hypersexual behavior in frontotemporal dementia: a comparison with early-onset Alzheimer's disease. *Archives of sexual behavior* 2013, 42(3):501-509.

80. Chen KF, Liang SJ, Lin CL, Liao WC, Kao CH: Sleep disorders increase risk of subsequent erectile dysfunction in individuals without sleep apnea: a nationwide population-base cohort study. *Sleep medicine* 2016, 17:64-68.

81. Hou PH, Mao FC, Chang GR, Huang MW, Wang YT, Huang SS: Newly Diagnosed Bipolar Disorder and the Subsequent Risk of Erectile Dysfunction: A Nationwide Cohort Study. *The journal of sexual medicine* 2018, 15(2):183-191.

82. Liu HL, Lee HM, Chung YC: Dyspareunia and its comorbidities among Taiwanese women: analysis of the 2004-2010 Nationwide Health Insurance Database. *The journal of sexual medicine* 2015, 12(4):1012-1018.

83. Zucker K, Seto M: Gender dysphoria and paraphilic sexual disorders. In., edn.; 2015: 983-998.