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Research paper

# Risk of stroke among patients with borderline personality disorder: A nationwide longitudinal study

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ABSTRACT

*Background:* Previous studies suggested that patients with borderline personality disorder (BPD) had a higher prevalence of stroke-related risk factors, such as hypertension, dyslipidemia, and diabetes mellitus. But, the association between BPD and subsequent stroke has been rarely investigated.

*Methods:* Using the Taiwan National Health Insurance Research Database, 5969 borderline patients aged 18 years and older and 23,876 age-and sex-matched controls were enrolled between 2002 and 2009, and followed up to the end of 2011 to identify the development of stroke.

*Results:* The Cox regression model after adjusting for demographic data, psychiatric comorbidities, and medical comorbidities showed that BPD was associated with an increased risk of developing any stroke (HR: 4.82, 95% CI: 2.77–8.40) and ischemic stroke (HR: 5.67, 95% CI: 2.49–12.93). The findings of sensitivity analysis after excluding the first year of observation were consistent: any stroke (HR: 3.44, 95% CI: 1.83–6.47) and ischemic stroke (HR: 4.75, 95% CI: 1.91–11.77).

*Discussion:* Patients with BPD had an elevated vulnerability to subsequent stroke and ischemic stroke compared to those without BPD. Further studies would be required to investigate the underlying mechanisms.

## 1. Introduction

Borderline personality disorder (BPD) is a severe form of psychopathology with a characteristic pervasive pattern of instability in emotional regulation, interpersonal relationships, self-esteem, and impulse control (Kernberg and Michels, 2009; Leichsenring et al., 2011; Lieb et al., 2004). Major clinical symptoms of the disorder include persistent irritability, impulsive aggression, repeated self-mutilation, and chronic suicidal tendencies, which make these patients frequent users of mental health resources (Kernberg and Michels, 2009; Leichsenring et al., 2011; Lieb et al., 2004). BPD is estimated to affect about 4% of the general population and up to 20% of individuals seen in clinical settings, with a peak onset of disease in late adolescence and early adulthood and a progressive decline in symptomology over time (Kernberg and Michels, 2009; Leichsenring et al., 2011; Lieb et al., 2004). Previous studies reported that BPD is more common in women than men (about 70% and 30%, respectively), and that it carries an increased risk of psychiatric comorbidities, especially major depressive disorder and post-traumatic stress disorder (PTSD), and a high mortality rate due to suicide (Kernberg and Michels, 2009; Leichsenring et al., 2011; Lieb et al., 2004).

A growing body of evidence suggests that patients with BPD have a higher prevalence of medical comorbidities, especially metabolic disorders, than the general population (Douzenis et al., 2012; El-Gabalawy et al., 2010; Frankenburg and Zanarini, 2006a, b). Frankenburg and Zanarini (2006a) followed 264 patients with BPD for six years, and found that 28% developed obesity, as indicated by a body mass index (BMI) $\geq 30\ kg/m^2$, during the follow-up. Patients with BPD and obesity had a higher prevalence of hypertension (12.2% vs. 4.2%, $p = 0.023$) and diabetes mellitus (10.8% vs. 1.1%, $p = 0.003$) than those with BPD alone (Frankenburg and Zanarini, 2006a). In an assessment of more than 30,000 adults aged 20 and older in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), El-Gabalawy et al. reported that the presence of BPD was significantly associated with an elevated risk of obesity (odds ratio [OR]: 1.29, 95% confidence interval [CI]: 1.14–1.46), arteriosclerosis or hypertension (OR: 1.86,

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95% CI: 1.60–2.16), diabetes mellitus (OR: 1.55, 95% CI: 1.26–1.91), and cardiovascular disease (OR: 2.78, 95% CI: 2.35–3.29) (El-Gabalawy et al., 2010). Douzenis et al. (2012) further indicated that the poor lifestyle and health behaviors related to BPD (i.e., lack of exercise and smoking) made these patients more prone to an elevated risk of developing metabolic disorders in later life. However, the association between BPD and stroke has been rarely investigated, and with inconsistent findings (El-Gabalawy et al., 2010; Moran et al., 2007). In a cross-sectional study using the screening questionnaire of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders and the self-reported history of stroke of 8580 adults aged 16–74 years, Moran et al. (2007) found that BPD was significantly associated with stroke (OR: 8.2, 95% CI: 2.6–25.8) after adjusting for demographic data, hypertension, and diabetes mellitus. However, the NESARC study cited above failed to validate this association (El-Gabalawy et al., 2010). It reported that patients with BPD had a significant increase in the risk of stroke (OR: 1.89, 95% CI: 1.08–3.31) in the unadjusted regression model, but this significance disappeared (OR: 1.42, 95% CI: 0.63–3.17) after controlling demographic data and other psychiatric comorbidities (El-Gabalawy et al., 2010). The major limitations in the above studies included the use of self-reported questionnaires instead of physician-given diagnoses and the cross-sectional study design rather than a longitudinal study design. In addition, biopsychosocial risks, including the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, chronic and altered inflammatory reactions to psychosocial stresses, more stroke-related metabolic comorbidities, and vicious and repetitive stressful life events, of BPD may also be associated with the risk of the elevated risk of subsequent stroke (Carvalho Fernando et al., 2012; Craft and Devries, 2009; Rinne et al., 2002).

In the present study, we used the Taiwan National Health Insurance Research Database with a large sample size and a longitudinal study design in an attempt to investigate the temporal association between BPD and stroke. We hypothesized that patients with BPD had an increased risk of developing stroke in later life.

## 2. Methods

### 2.1. Data source

Taiwan's National Health Insurance (NHI) is a mandatory universal health insurance program that was implemented in 1995 and offers comprehensive medical care coverage to all Taiwanese residents. The National Health Research Institute (NHRI) is in charge of the entire insurance claims database, namely the National Health Insurance Research Database (NHIRD), which consists of healthcare data from > 97% of the entire Taiwan population (http://www.nhi.gov.tw/). The NHRI audits and releases the NHIRD for scientific and study purposes. Individual medical records included in the NHIRD are anonymous to protect patient privacy. Comprehensive information on insured individuals is included in the database, including demographic data, dates of clinical visits, and disease diagnoses. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Chen et al., 2013; Li et al., 2012; Shen et al., 2013; Wu et al., 2012).

### 2.2. Inclusion criteria for individuals with BPD and the control group

Subjects aged ≥18 years who were identified as having a diagnosis BPD (ICD-9-CM codes: 301.83) by board-certificated psychiatrists between January 1, 2002 and December 31, 2009, and who had no history of any stroke (ICD-9-CM codes: 430–438) before enrollment, were included as the BPD cohort. The time of BPD diagnosis was defined as the time of enrollment. The age- and gender-matched (1:4) control cohort was randomly identified after eliminating the study subjects, those who had been given a diagnosis of BPD at any time, and those with any stroke before enrollment. Diagnoses of any stroke (ICD-9-CM code: 430–438), ischemic stroke (ICD-9-CM code: 433, 434, 435), and hemorrhagic stroke (ICD-9-CM code: 430, 431, 432) given by neurologists, neurosurgeons, internal medicine physicians, and emergency room physicians after brain image examinations (brain computed tomography or brain magnetic resonance imaging) were identified during the follow-up (from enrollment to December 31, 2011 or patient death). Stroke-related medical comorbidities during the whole follow-up (from enrollment to stroke onset or study end), including major depression, PTSD, bipolar disorder, alcohol-related disorders, substance use disorder, hypertension, dyslipidemia, diabetes mellitus, renal diseases, ischemic heart diseases, arrhythmia, and head injury, were also assessed in our study. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed for our study (Liu et al., 2006).

### 2.3. Statistical analysis

For between-group comparisons, the independent *t*-test was used for continuous variables and Pearson's $X^2$ test for nominal variables, where appropriate. The Cox regression model was used to investigate the hazard ratio (HR) with a 95% CI of any stroke, ischemic stroke, and hemorrhagic stroke after adjusting for demographic data and medical comorbidities among subjects with BPD and the control group. Sensitivity analysis was performed to investigate the above associations after excluding the first year of observation. We also performed a sub-analysis of the risk of any stroke, ischemic stroke, and hemorrhagic stroke with BPD stratified by age groups: young adults (< 40 years), mid-adults (40–59 years), and the elderly (≧60 years). A 2-tailed *P*-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc.) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

## 3. Results

A total of 5969 patients with BPD and 23,876 age-and sex-matched controls were enrolled in our study. They had an average age of 28.55 ± 8.42 years and were female-predominant (69.7%); 89.1% of patients with BPD were aged less than 40 years and 10.6% were aged between 40 and 59 years. Very few (0.2%) patients with BPD were aged 60 years or older (Table 1). Patients with BPD had a higher incidence of developing any stroke (2.32 vs. 0.38 1000 person-years, $p < 0.001$), ischemic stroke (0.88 vs. 0.18 1000 person-years, $p < 0.001$), and hemorrhagic stroke (0.55 vs. 0.12 1000 person-years, $p < 0.001$) and an earlier age at onset of any stroke (38.96 ± 10.82 vs. 46.34 ± 14.71 years, $p = 0.001$) and ischemic stroke (41.92 ± 9.01 vs. 51.68 ± 13.59 years, $p = 0.002$) than the controls (Table 1). Furthermore, patients with BPD had a higher prevalence of major depression (41.6% vs. 1.5%, $p < 0.001$), PTSD (3.3% vs. 0%, $p < 0.001$), bipolar disorder (33.4% vs. 0.5%, $p < 0.001$), alcohol related disorders (12.2% vs. 0.2%, $p < 0.001$), substance use disorders (12.2% vs. 0.1%, $p < 0.001$), hypertension (6.4% vs. 3.7%, $p < 0.001$), dyslipidemia (6.2% vs. 3.5%, $p < 0.001$), diabetes mellitus (4.2% vs. 1.9%, $p < 0.001$), renal diseases (1.0% vs. 0.5%, $p < 0.001$), ischemic heart diseases (2.0% vs. 0.5%, $p < 0.001$), arrhythmia (3.8% vs. 1.1%, $p < 0.001$), and head injury (13.6% vs. 2.2%, $p < 0.001$) than the control group (Table 1). Patients with BPD resided less in urbanized regions ($p < 0.001$) and had lower income ($p < 0.001$) (Table 1).(Fig. 1).

The Cox regression model showed that patients with BPD were associated with an increased risk of developing any stroke (HR: 4.82, 95% CI: 2.77–8.40) and ischemic stroke (HR: 5.67, 95% CI: 2.49–12.93) after adjusting for demographic data and medical comorbidities (Table 2). In addition, the unadjusted Cox regression model found a significant association (HR: 4.72, 95% CI: 2.47–9.01) between BPD and hemorrhagic stroke, but this significance disappeared (HR: 2.75, 95%