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Bidirectional Association Between Depression and Fibromyalgia Syndrome: A Nationwide Longitudinal Study

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Abstract: Several cross-sectional studies have reported a common comorbidity between depression and fibromyalgia syndrome (FMS). However, a bidirectional temporal association between these 2 distinct diseases has rarely been investigated. Using the Taiwan National Health Insurance Research Database, 25,969 patients with FMS and without any psychiatric disorder and 17,142 patients with depression and without FMS between 2000 and 2008 were enrolled and separately compared with age- and sex-matched (1:4) control groups. Patients with FMS who developed a new-onset depression and those with depression who developed new-onset FMS were identified during follow-up (to the end of 2011). The conditional Cox regression analyses, after adjustment for demographic data and medical comorbidities, showed that the patients with FMS were associated with an increased risk (hazard ratio [HR] 7.46, 95% confidence interval [CI] 6.77–8.22) of subsequent depression and that those with depression were associated with an increased risk (HR 6.28, 95% CI 5.67–6.96) of subsequent FMS. Our results supported a bidirectional temporal association between depression and FMS. Each disease occurring first may increase the risk of the other subsequently. Further study may be necessary to determine the underlying mechanism between depression and FMS and to clarify whether a prompt intervention for depression or FMS may decrease the risk of the other later in life.

***Perspective:** Our study supported a bidirectional temporal association between depression and FMS such that each disease occurring first may increase the risk of the other subsequently. This result may imply a shared pathophysiology between FMS and depression, but further investigation is needed.*

***Key words:** Depression, fibromyalgia syndrome, bidirectional association.*

Fibromyalgia syndrome (FMS) is characterized by chronic and widespread musculoskeletal pain, with a prevalence ranging between 2 and 5% and a predominance in middle-aged women.[8,35] Beyond the widespread pain, patients with FMS also display many somatic symptoms, including chronic fatigue, gastrointestinal symptoms, paresthesia, joint stiffness, and headache.[3,8,28,35] Previous studies have further reported that FMS is commonly associated with psychiatric and psychological symptoms such as depression, anxiety, sleep disturbance, and cognitive dysfunction.[3,27,28]

Depression is one of the most common mental health problems and affects more than 10% of the general population.[1] A growing body of evidence suggests comorbidity and symptom overlap between depression and FMS.[11,14] Assessing the psychiatric symptoms in 33,176 patients with FMS and matched controls, Berger et al[2] reported that those with FMS had a higher prevalence of depression (12% vs 3%, $P < .001$) and anxiety (5% vs 1%, $P < .001$) disorders than did those without FMS. Hudson et al[14] reviewed the prevalence of current and lifetime major depressive disorder among patients with

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FMS and concluded that a wide range, between 6 and 35% of the patients with FMS, were comorbid with a current major depressive episode and that from 20 to 86% were comorbid with a lifetime major depressive disorder. Focusing instead on the risk of chronic pain among depressed patients, Gerrits et al[10] surveyed the pain symptoms in 1122 patients with depressive or anxiety disorder and found that more than 30% of the patients had chronic widespread pain over the neck, back, head, chest, and joints and that the pain symptom was associated with an increased risk of exacerbating depression (hazard ratio [HR] 1.51, 95% confidence interval [CI] 1.09–2.08), with a dose-dependent relationship between the number of pain locations and the risk of exacerbation (HR 1.07, 95% CI 1.02–1.12). Vishne et al[29] found that FMS was more prevalent (26% vs 2%, $P = .002$) and had a greater number of tender points (6.1 $\pm$ 5 vs 2.2 $\pm$ 3, $P < .001$) in depressed females than in depressed males.

These studies have supported the frequent comorbidity between FMS and depression.[1,2,10,11,14,29] However, most of them were cross-sectional studies, not longitudinal follow-up studies, and thus it has not been possible to clarify the temporal association between FMS and depression. Which disease comes first and which comes later has remained unknown, although several previous longitudinal studies supported the pain–depression relationship.[13,21] For example, Magni et al[21] tested the hypotheses that depression caused pain and that pain caused depression in a sample of 2,324 patients who were assessed for the presence of musculoskeletal pain and the presence of depression; they found that depression at baseline significantly predicted the development of chronic musculoskeletal pain and that depressive symptoms could predict the persistence of existing pain. Hawker et al[13] found that osteoarthritis pain determined subsequent depressed mood, fatigue, and disability (both short- and long-term). In addition, other limitations in previous studies regarding the association between FMS and depression also included the use of self-report questionnaires defining somatic and psychiatric symptoms rather than certificated physicians' diagnoses.

In our study, using the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal study design, we investigated a bidirectional temporal relationship between depression and FMS. We hypothesized that patients with FMS would have an increased risk of subsequent depression later in life and that, conversely, those with depression would have an increased likelihood of developing FMS later in life.

Methods

Data Source

The National Health Insurance program was implemented in 1995 and covers up to 99% of the 23,000,000 residents of Taiwan. The NHIRD was audited and released by the National Health Research Institute. Comprehensive information on insured patients, such as demographic data, dates of clinical visits, and disease diagnoses, is included in the database. To guarantee privacy, all patients included in the NHIRD are anonymous. The diagnostic codes used were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). The requirement for informed consent was waived because the study was register based and the individuals included were not identifiable at any time. The NHIRD has been used extensively in many epidemiologic studies in Taiwan.[5,6,17,26]

Study 1: FMS → Depression

Patients diagnosed with FMS (ICD-9-CM code 729.1) by neurologists, rheumatologists, rehabilitation doctors, or pain specialists between January 1, 2000, and December 31, 2008, and who had no history of any psychiatric disorder (ICD-9-CM codes 290–319) before enrollment were included as the FMS cohort. The exact age- and sex-matched control cohort (case to control ratio, 1:4) was randomly identified from among the 1,000,000 NHIRD patients after eliminating patients who had been diagnosed with FMS at any time and those with any psychiatric disorder before enrollment. Diagnoses of depression (ICD-9-CM codes 296.2x, 296.3x, 300.4, and 311) by psychiatrists were identified during follow-up (from enrollment until December 31, 2011, or death).

Study 2: Depression → FMS

Patients diagnosed with depression (ICD-9-CM codes 296.2x, 296.3x, 300.4, and 311) by psychiatrists between January 1, 2000, and December 31, 2008, and who had no history of FMS (ICD-9-CM code 729.1) before enrollment were included as the depression cohort. The exact age- and sex-matched (1:4) control cohort was randomly identified from among the 1,000,000 NHIRD patients after eliminating patients who had been diagnosed with any psychiatric disorder at any time and those with FMS before enrollment. Diagnoses of FMS given by neurologists, rheumatologists, rehabilitation doctors, or pain specialists were identified during follow-up (from enrollment until December 31, 2011, or death).

In addition, medical comorbidities that were diagnosed at baseline and during follow-up before the event onset, including hypertension, dyslipidemia, diabetes mellitus, allergic diseases, migraine, and low back pain, were investigated as time-dependent confounding factors in both study 1 and study 2. All diagnoses had been given at least twice by corresponding physicians to achieve diagnostic validity. We also assessed the level of urbanization (level 1 to level 5: level 1, most urbanized region, to level 5, least urbanized region). Both study 1 and study 2 were approved by the Taipei Veterans General Hospital, Taiwan Institutional Review Board.

Statistical Analysis

For between-group comparisons, an independent t-test was used for continuous variables and Pearson's