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Bidirectional Association between Migraine and Fibromyalgia: Two Population-Based Retrospective Cohort Analyses

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Bidirectional Association between Migraine and Fibromyalgia: Two Population-Based Retrospective Cohort Analyses

Running title: Bidirectional Association between Fibromyalgia and Migraine

I-Wen Penn[1], Eric Chuang[2], Tien-Yow Chuang[3], Cheng-Li Lin[4,5], Chia-Hung Kao[6,7,8]

[1]Department of Physical Medicine and Rehabilitation, School of Medicine, Fu Jen Catholic University and Affiliated Hospital, New Taipei City, Taiwan

[2]UC Berkeley Mishler Lab Undergraduate Researcher, Intended B.S. Molecular and Cell Biology, University of CA, Berkeley, USA

[3]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

[4]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[5]College of Medicine, China Medical University, Taichung, Taiwan

[6]Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

[7]Department of Nuclear Medicine and PET Center, China Medical University Hospital, Taichung, Taiwan

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[8]Department of Bioinformatics and Medical Engineering, Asia University, Taichung,

Taiwan.

* Tien-Yow Chuang and Chun-Hung Tseng contribute equally to this work

*Corresponding author: Chia-Hung Kao, MD, Graduate Institute of Biomedical

Sciences and School of Medicine, College of Medicine, China Medical University,

No. 2, Yuh-Der Road, Taichung 404, Taiwan. E-mail: d10040@mail.cmuh.org.tw;

dr.kaochiahung@gmail.com

Author contributions:

Conceptualization: IWP, CHK.

Methodology: CLL, CHK.

Software: CLL, CHK.

Validation: IWP, EC, TYC, CLL, CHK

Formal analysis: IWP, EC, TYC, CLL, CHK

Investigation: CLL, CHK.

Resources: CLL, CHK.

Data curation: IWP, EC, TYC, CLL, CHK

Writing (original draft preparation): IWP, EC, TYC, CLL, CHK

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Writing (review and editing): IWP, EC, TYC, CLL, CHK

Visualization: IWP, EC, TYC, CLL, CHK

Supervision: CHK.

Project administration: CHK.

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All authors report no conflicts of interest.

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List of abbreviations

FM: Fibromyalgia; HR: hazard ratio; CI: confidence interval; ICD-9-CM:

International Classification of Diseases, Ninth Revision, Clinical Modification; NHI:

National Health Insurance; LHID: Longitudinal Health Insurance Database

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Abstract

Objective: Fibromyalgia (FM) and migraine are common pain disorders and tend to coexist. This study determined whether these two conditions exhibited any mutual influences.

Setting: Cohort Study.

Participants: A retrospective, longitudinal cohort study was conducted by using the data from a nationwide healthcare database. This study has two separate arms. Arm 1 included 33,216 FM patients, and Arm 2 contained 7420 migraine patients; all of these patients were diagnosed between 2000 and 2010. Using the same database, control subjects who had neither FM nor migraine and who were matched with the FM and migraine patients by sex, age, and index date of diagnosis were recruited. Each control cohort was four times the size of the relevant study cohort. Both the control and study cohorts were followed until the end of 2011.

Results: The incidence rates of migraine and FM were calculated in Arm 1 and Arm 2, respectively. The overall incidence of migraine was greater in the FM cohort than in the control cohort [4.39 vs. 2.07 per 1000 person-years; crude hazard ratio (HR) = 2.12, 95% confidence interval (CI) =1.96–2.30; adjusted hazard ratio (aHR) = 1.89, 95% CI = 1.75–2.05], after adjustment for sex, age, and comorbidities. The overall

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incidence of FM in the migraine cohort was 1.57 times greater than in the control

cohort (7.01 vs. 4.49 per 1000 person-years; aHR = 1.52, 95% CI = 1.39−1.65).

Conclusions: The present study demonstrates the presence of a bidirectional link

between FM and migraine.

Key words: fibromyalgia, migraine, bidirectional analysis, retrospective cohort

Strengths and limitations of this study

1. Our study contained a large sample size because of our population-based design

approach.

2. We based our study solely on the information from diagnoses in patient files, so we

did not include any patients whose cases were unidentified.

3. This study is naturally more prone to observational bias since patients with

migraines and FM are generally more likely to seek medical attention for another

condition.

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Introduction

One of the major symptoms of fibromyalgia (FM) is a headache. Among those different types of headaches, there are migraines—some bad enough to debilitate a person. Interestingly, similarities exist between migraines and fibromyalgia, and as we consider the two conditions in the same context, many instances of overlapping symptoms, causes, and treatments are noted [1]. Several studies have reported that a high proportion (20%–36%) of patients with migraine have FM [2-5]. By contrast, the frequency of migraine in patients with FM is approximately 45%–80%, suggesting that migraine is common in patients with FM [6, 7]. Despite that episodic migraine, chronic headaches and FM could be sourced to the same cause [8-10], explanations for this high degree of co-occurrence between migraine and FM are unknown.

Migraine is a complex, recurrent disorder that manifests as a throbbing headache, which is frequently associated with nausea, allodynia, and sound or light sensitivity, and may develop into a chronic condition and disability [11,12]. The pain is considered to occur due to the nociceptive activation of the trigeminovascular system, including the sensory neurons from the trigeminal ganglion and upper cervical nerve roots, which modulate central signals to numerous subcortical sites [13]. The combination of tonic nociceptive input and central disinhibition may also play a role in the development of FM. Many migraineurs experience a condition termed

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"allodynia" during migraine attacks. Usually, allodynia is confined to the head and neck but may involve other areas of the body [14]. Increasing evidence indicates that the peripheral tissues are relevant contributors to painful impulse input, which might either initiate or maintain central sensitization, thus contributing to the progression of FM [15]. Migraine is also supposed to be a trigger factor for FM. The repeated headaches in migraine patients might increase the neuronal response to both nociceptive and non-nociceptive stimulation and induce spontaneous neuronal activity, which might concurrently heighten the sensitivity of the patient to FM [16]. Several studies have highlighted the role of the hypothalamus in migraines [14]. Evidence indicates its direct and indirect anatomical connections to the thalamus and autonomic brainstem nuclei, supporting its role in nociceptive and autonomic modulation among migraine patients [17]. However, the brain mechanisms also common to FM suffers result in central sensitization of pain neurons leading to the evolution of a complex syndrome [18].

Early in the course of disease, the widespread musculoskeletal pain of FM patients often appears in the neck or shoulder region [19]. Neck pain may activate local nociceptors and transmit painful impulses through the upper cervical spinal nerves, such as the greater occipital nerve, to the trigeminal nucleus caudalis, thus inducing a migraine attack [20]. Some experts believe that FM and migraine

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headaches both involve defects in the systems that regulate certain chemical messengers in the brain, including serotonin and epinephrine (adrenaline) [1]. which might reflect in their similar psychological comorbidities: depression, anxiety, interpersonal sensitivity, somatization, etc [9]. Psychosocial distress and psychological abnormality are common to occur in patients suffering from migraine as well as patients suffering from FM.

Although previous research has demonstrated a high comorbidity rate for migraines and FM, several vital issues must be highlighted. (1) Most of these studies were performed at tertiary care centers. Patients are often referred to tertiary clinics due to high pain complaints, disability, or medication overuse. Hence, the sample populations may differ from patients treated in general practice. (2) Most of these studies used a cross-sectional design for investigating the prevalence instead of the incidence of migraine or FM. (3) If there is a significant association, whether people with migraine are more likely than the general population to develop FM or vice versa remains unknown. Therefore, our population-based longitudinal cohort study is trying to investigate the links between migraine and FM.

Methods

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Data source

The data for this research were sourced from the Longitudinal Health Insurance

Database (LHID). The LHID comprises the data of 1 million insurants' health claims

from the Taiwan National Health Insurance (NHI) program, which covers 99% of 23

million Taiwan citizens with single-payer health insurance. According to the

government's report, no differences were noted in the demographic features between

the LHID and Taiwan NHI program. The health claims information in the LHID

includes general information regarding the insurants (such as birthdate, sex, and

occupation), disease documents (recorded according to the International Classification

of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM), and other medical

service-related data.

Data Availability Statement

The dataset used in this study is held by the Taiwan Ministry of Health and

Welfare (MOHW). The Ministry of Health and Welfare must approve our application

to access this data. Any researcher interested in accessing this dataset can submit an

application form to the Ministry of Health and Welfare requesting access. Please

contact the staff of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance.

Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd.,

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Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848.   All

relevant data are within the paper.

Ethics Statement

The National Health Insurance Research Databank (NHIRD) encrypts patient

personal information to protect privacy and provides researchers with anonymous

identification numbers associated with relevant claims information, including sex,

date of birth, medical services received, and prescriptions. Therefore, patient consent

is not required to access the NHIRD. This study was approved to fulfill the condition

for exemption by the Institutional Review Board (IRB) of China Medical University

(CMUH104-REC2-115-CR2). The IRB also specifically waived the consent

requirement.

Study Cohorts

A bidirectional cohort study design was used to interpret the longitudinal

association between FM and migraine.

Figure 1 shows the procedure for establishing the two study Arms. For study

Arm 1, we identified patients with FM (ICD-9-CM code 729.1) who were aged ≥ 20

years and were newly diagnosed consecutively ≥ 3 times within 3 months in

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2000–2010. The first diagnosis date was designated as the index date for entry into the FM cohort. Patients with a history of migraine (ICD-9-CM codes 346) were excluded from the cohort. For each FM patient, we randomly selected four persons free of FM and migraine from the population of the LHID2000, who were frequency-matched by sex, age (in 5-year increments), and entry date of the FM patient; these subjects were recruited to the non-FM (control) cohort.

For study Arm 2, a similar procedure to that for study Arm 1 was used to establish a migraine cohort of patients who did not have a history of FM, were aged ≥20 years, and were newly diagnosed consecutively ≥3 times within 3 months in 2000–2010.

Subjects in the study Arms 1 and 2 were followed until the diagnosis of migraine or FM, withdrawal from the NHI program, death, or December 31, 2011. The patients in two cohorts contained some baseline comorbidities: diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2, 296.3, 296.5, 300.4, 309, and 311), anxiety (ICD-9-CM code 300.0, 300.2, 300.3, 308.3, and 309.81), sleep disorder (ICD-9-CM codes 307.4 and 780.5), coronary artery disease (CAD; ICD-9-CM codes 410–414), chronic fatigue syndrome (CFS; ICD-9-CM code 780.71), and irritable bowel syndrome (IBS; ICD-9-CM code 564.1).

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Statistical analyses

The characteristics of the study cohorts are expressed as the mean and corresponding standard deviation for age and as number and percentage for sex and comorbidities. Age difference was assessed using the t-test, and sex and comorbidity distributions were tested using the chi-square test. The incidence density for each cohort was calculated as the total event number divided by the sum of follow-ups [per 1000 person-years (PY)]. The cumulative incidence curve for each cohort was measured using the Kaplan–Meier method, with the curve difference being calculated using the log-rank test. To determine the migraine and fibromyalgia risks in Arms 1 and 2, respectively, the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using single-variable and multivariable Cox proportional hazard models. Data management and all statistical analyses were performed using SAS software for Windows (Version 9.4, SAS Institute, Cary, NC, USA), and incidence curves was plotted using R software. All significance levels were set at two-sided $p < 0.05$.

Results

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Table 1 shows the demographic characteristics of the FM and non-FM cohorts. The age- and sex-matched cohorts demonstrated differences in the comorbidity distribution. The prevalence of comorbidities was significantly higher in the FM cohort than in non-FM cohort (p < 0.001).

Table 2 shows the migraine incidence was 4.39 and 2.07 per 1000 PY in the FM and non-FM cohorts, respectively. Figure 2 shows a higher incidence curve for the FM cohort and a lower curve for the non-FM cohort (log rank test=371.4, p < 0.001). After adjustment for age, sex, and comorbidities, the FM patients exhibited a 1.89-fold higher risk of migraine than did the non-FM subjects (HR = 1.89, 95% CI = 1.75–2.05). Among females, the relative risk of migraine was 1.76-fold higher in the FM patients than in the non-FM subjects (HR = 1.76, 95% CI 1.60–1.93), whereas the risk among males was 2.29-fold higher in the FM patients than in the non-FM subjects (HR = 2.29, 95% CI = 1.97–2.67). Regarding the age effect, the HRs for migraine in the FM cohort were 2.06 (95% CI = 1.85–2.29), 1.66 (95% CI = 1.43–1.92), and 1.69 (95% CI = 1.39–2.05) for age ≤ 50, 51–65, and ≥ 65 years, respectively.

Table 3 shows the influence of factors associated with the occurrence of migraine in the FM cohort. Male sex, hyperlipidemia, depression, anxiety, sleep disorder, CAD, CFS, and IBS were associated with a higher risk of migraine (all p-value <0.05).

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Table 4 lists the comorbidities as well as the age- and sex-matched comparisons in the migraine cohort. The migraine cohort showed higher prevalent comorbidities than non-migraine cohort.

Table 5 and Figure 3 show the significantly higher incidence of FM in migraine patients than that in non-migraine subjects (7.01 vs. 4.49 per 1000 PY; log-rank test=116.7, p < 0.001). After adjustment for age, sex, and comorbidities, the migraine patients exhibited a 1.52-fold higher risk of FM than did non-migraine subjects (HR = 1.52, 95% CI = 1.39–1.65). The female migraine patients displayed a 1.43-fold higher risk of FM than did the non-migraine subjects (HR = 1.43, 95% CI = 1.29–1.59), whereas the male migraine patients exhibited a 1.78-fold higher risk of FM (95% CI = 1.50–2.11). Regarding the age effect, the HRs for FM were 1.64 (95% CI = 1.46–1.84), 1.30 (95% CI = 1.09–1.53), and 1.28 (95% CI = 1.03–1.58) in migraine patients aged <50, 50–64, and ≥65 years, respectively.

Table 6 shows the associations of sex, age, and comorbidities with the risk of FM. The variables, including age, migraine, hypertension, hyperlipidemia, depression, sleep disorder, and CAD, were all associated with a lower risk of FM.

Discussion

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The results of the two cohort arms suggested a bidirectional risk of migraine and FM in patients with FM and migraine, respectively. In the Arm 1 analysis, the incidence rates for migraine were 4.39 and 2.07 per 1000 PY in FM patients and non-FM subjects, respectively [adjusted hazard ratio (aHR) = 1.89 and 95% CI = 1.75–2.05 in FM patients]. In the Arm 2 analysis, the incidence rates for FM were 7.01 and 4.49 per 1000 PY in migraine patients and non-migraine subjects, respectively (aHR = 1.52 and 95% CI = 1.39–1.65 in migraine patients). This indicated that FM has a stronger predictive power for the onset of migraine than does migraine for the onset of FM.

The Kaplan–Meier plots demonstrated that the incidence of migraine in the FM cohort and the incidence of FM in the migraine cohort increased steadily during the 12-year follow-up period. Moreover, similar patterns were observed in the two corresponding comparison cohorts. The cumulative incidence measured by the Kaplan–Meier plots revealed a greater risk of migraine among FM patients than that of FM among migraine patients.

Our predictive analytics could potentially dictate diagnosis and treatment. For example, a subsequent diagnosis of FM could come from the failure of anti-migraine treatment to alleviate fatigue [21]. Since migraine is often better managed, the authors would hypothesize that FM patients are more likely to be treated for migraine than

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vice versa. Therefore, clinical trials of migraine patients in the future have the potential to evaluate the effects of FM on health outcomes and its treatment efficacy [10].

Cohort analysis for the association between FM and the risk of new-onset migraine

This study revealed a positive association between the diagnosis of FM and the risk of migraine. Adjustment for factors, including hypertension, CAD, and CFS, had no strong influence on this association. However, sex, age (particularly in patients under 49 years of age), diabetes, hyperlipidemia, depression, anxiety, sleep disorder, and IBS remained statistically significant.

Several hypotheses have been proposed to explain the development of chronic widespread pain and/or episodic throbbing or pulsing pain over the head and neck regions as the possible effects of comorbidities, including depression and anxiety. Depression and anxiety disorders have been identified as important secondary symptoms of FM [22, 23]. The pain of FM may initiate the development of mood disorders as a result of the stress created on the body. In addition, depression and anxiety might also induce the onset or present as a prodrome of migraine, according to several evidence-based studies [24, 25]. Research has indicated that serotonin

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levels might be related to the interconnections between anxiety and migraine [26]. A lower level of serotonin may be central to the dysregulation of descending antinociceptive systems, leading to the occurrence of FM and migraine [26, 27].

Nonrefreshing sleep or sleep deprivation in healthy persons can induce symptoms of fibromyalgia [28], implying that sleep abnormalities might be a pathology and not only a result of pain [29]. To date, the literature has documented the advantage of targeting sleep conditions to possibly relieve the symptoms of migraine [30]. As the prevalence of sleep disorders soars in both FM and migraine patients, appreciation of the close links between FM and migraine increases.

IBS frequently coexists with both FM and migraine [31, 32]. The underlying mechanisms for the association of FM with an increasing risk of IBS and migraine are unclear. FM, migraine, and IBS may be three distinct manifestations of a common pathophysiologic process affecting the gastrointestinal tract. These disorders are known as "central sensitivity syndrome" and are mutually associated [33]. A growing body of evidence indicates that central sensitization phenomena play a role in the pathogenesis of both FM and migraine. Central sensitization at the levels of the spinal dorsal horn and trigeminal nucleus may also be involved in the progression of migraine attacks, and the prolonged nociceptive inputs may result in the maintenance of supraspinal sensitization and central neuroplastic changes, leading to the

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conversion of episodic headaches into chronic [34]. Interestingly, increased intestinal

permeability (IP) may be observed in IBS [35]. Altered IP with intestinal bacteria

overgrowth may trigger the development of FM [36] and migraine [37]. The

microbiome–gut–brain axis, a bidirectional communication between the central and

enteric nervous systems with microbiome via the neural, humoral, endocrine, and

immune pathways [31, 32, 38] was proposed as one of the multidisciplinary

pathophysiologic mechanisms underlying IBS [38], FM [39, 40] and migraine [37,

41]. The gut microbiota interacts with the central, autonomic, and enteric nervous

systems and hypothalamic–pituitary–adrenal axis and vice versa [38].

Cohort analysis for the association between migraine and the risk of new-onset

FM

This study also revealed a higher risk of FM in migraine patients than in

non-migraine subjects in every factor-based subset of the cohorts. One interesting

feature was that patients with hyperlipidemia had a higher risk of FM. Adverse lipid

profiles occurred more frequently in migraine patients with a higher body mass index

[42, 43]. Lack of exercise may precipitate the development of an adverse lipid profile;

however, exercise may trigger acute migraine attacks [44], and some patients might

avoid exercise in the hope of preventing migraines. This hypothesis could be

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supported by a study which revealed that headache patients have less aerobic endurance and flexibility than do healthy controls [45]. Aerobic exercise could relieve depression and anxiety and avoid the harmful consequences of stress [46]. Avoiding exercise may worsen mood distress and is thus possibly related to the development of FM.

Increased migraine frequency—with the transformation of migraine to chronic migraine—intensifies the sensitivity to pain in somatic areas outside the cephalic region and may predispose to FM [6]. Hypothalamic neuroendocrine dysfunction has been proposed as a brain mechanism common to both FM and migraine [47]. Both conditions also share the mechanism of central sensitization of pain neurons. Magnesium, which is often used as an agent for relieving migraine headaches, is also beneficial for treating FM. Low magnesium levels can exacerbate FM symptoms, and they are implicated in migraines [48]. Researchers have discovered that people who do not respond to standard migraine treatments are often affected with FM [14]. Given the high comorbidity rate of migraine and FM, many professionals still assume the role of central nervous system pain-processing abnormalities, including central sensitization and inadequate pain inhibition with repeated headache episodes, and beyond that, tonic peripheral nociceptive input to be associated with the augmented windup in the responses to neurotransmitters, immunomodulation, vascular changes,

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and hormonal influence, which may predispose to the development of FM [1, 6, 31, 32, 38, 47].

Our study contained a large sample size because of our population-based design approach. Additionally, we were careful in our analyses to reduce selection bias, and our vast documents of medical profiles allowed for minimal effect from our confounding factors in the subjects. However, there are still certain limitations in our study. We based our study solely on the information from diagnoses in patient files, so we did not include any patients whose cases were unidentified. In the event of poor categorization of a patient's symptoms, it is possible that it may affect the discernibility between migraine and fibromyalgia. Since many crucial variables are not retrievable and there are multitudes of ways to diagnose fibromyalgia as well as the numerous subtypes of migraines, our data provides merely a glimpse of these two conditions. It is also impossible to assess treatment response from our large database analysis, so it's hard to sort out "diagnosis by exclusion" in this study. Future studies are needed to better delineate "diagnosis by exclusion". Furthermore, this study did not take into account the severity of FM and migraines in patients, therefore, no definitive statement can be made in regards to the intensity of FM and subsequent risk of developing migraine conditions, and vice versa. Moreover, this study is naturally more prone to observational bias since patients with migraines and FM are generally

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more likely to seek medical attention for another condition.

Conclusion

This study is the first to reveal a population-based bidirectional association between the onsets of FM and migraine in patients with migraine and FM, respectively. The risk of developing migraine is greater than the risk of developing FM. The incidence rates of FM in the migraine cohort and of migraine in the FM cohort increased with age in both directions. However, the HRs relative to the corresponding comparison cohorts were attenuated with the increase in age.

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Figure Legend:

Figure 1. Flow chart showing selection of study subjects.

Figure 2. Cummulative incidence of migraine compared between patients with and without fibromyalgia using the Kaplan-Meier method.

Figure 3. Cummulative incidence of fibromyalgia compared between patients with and without migraine using the Kaplan-Meier method.

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Table 1. Demographic characteristics and comorbidity in patient with and without fibromyalgia.

| Variable | Fibromyalgia | | |
	No N =132863	Yes N =33216	*p*-value
Sex	n(%)	n(%)	0.99
Female	71880(54.1)	17970(54.1)	
Male	60983(45.9)	15246(45.9)	
Age, mean(SD)	50.9(16.9)	51.4(16.7)	<0.001[#]
Stratify age			0.99
≤49	64292(48.4)	10673(48.4)	
50-65	36820(27.7)	9205(27.7)	
65+	31751(23.9)	7938(23.9)	
Comorbidity			
Diabetes	10485(7.89)	3193(9.61)	<0.001
Hypertension	37284(28.1)	11287(34.0)	<0.001
Hyperlipidemia	22446(16.9)	7301(22.0)	<0.001
Depression	4690(3.53)	1804(5.43)	<0.001
Anxiety	10494(7.90)	4214(12.7)	<0.001
Sleep disorder	21095(15.9)	8121(24.5)	<0.001
CAD	17918(13.5)	5821(17.5)	<0.001
Chronic fatigue syndrome	199(0.15)	93(0.28)	<0.001
Irritable bowel syndrome	5125(3.86)	1870(5.63)	<0.001

Chi-Square Test; [#]: Two sample T-test

Table 2. Comparison of incidence and hazard ratio of migraine stratified by sex, and age between patients with and without fibromyalgia.

Variable	Without fibromyalgia					With fibromyalgia				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	1810	876077	2.07	1(Reference)	1(Reference)	954	217386	4.39	2.12(1.96, 2.30)***	1.89(1.75, 2.05)***
Sex										
Female	1373	487506	2.82	1(Reference)	1(Reference)	669	120773	5.54	1.97(1.79, 2.16)***	1.76(1.60, 1.93)***
Male	437	388571	1.12	1(Reference)	1(Reference)	285	96613	2.95	2.62(2.26, 3.05)***	2.29(1.97, 2.67)***
Stratify age										
≤50	922	444710	2.07	1(Reference)	1(Reference)	548	110557	4.96	2.39(2.15, 2.66)***	2.06(1.85, 2.29)***
50-65	564	245579	2.30	1(Reference)	1(Reference)	258	60603	4.26	1.85(1.60, 2.15)***	1.66(1.43, 1.92)***
65+	324	185788	1.74	1(Reference)	1(Reference)	148	46226	3.20	1.83(1.51, 2.23)***	1.69(1.39, 2.05)***
Comorbidity[‡]										
No	774	508879	1.52	1(Reference)	1(Reference)	311	95605	3.25	2.14(1.88, 2.44)***	2.13(1.87, 2.43)***
Yes	1036	367197	2.82	1(Reference)	1(Reference)	643	121780	5.28	1.88(1.71, 2.08)***	1.80(1.63, 1.98)***

Rate[#], incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome

***p<0.001

Comorbidity[‡]: Patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome were classified as the comorbidity group

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Table 3. Cox model with hazard ratios and 95% confidence intervals of migraine associated with fibromyalgia and covariates.

Variable	Crude		Adjusted[†]	
	HR	(95% CI)	HR	(95% CI)
Fibromyalgia	2.12	(1.96, 2.30)***	1.89	(1.74, 2.04)***
Sex(Women vs. Men)	2.28	(2.09, 2.48)***	2.08	(1.91, 2.27)***
Age, years	1.00	(0.99, 1.00)**	0.99	(0.99, 1.00)***
Baseline comorbidities (yes vs. no)				
Diabetes	0.82	(0.70, 0.96)*	0.73	(0.61, 0.860***
Hypertension	1.06	(0.97, 1.15)	-	-
Hyperlipidemia	1.30	(1.19, 1.43)***	1.14	(1.03, 1.27)*
Depression	2.37	(2.06, 2.72)***	1.20	(1.03, 1.39)*
Anxiety	2.68	(2.44, 2.95)***	1.64	(1.47, 1.84)***
Sleep disorder	2.63	(2.43, 2.85)***	1.97	(1.80, 2.15)***
CAD	1.30	(1.18, 1.44)***	1.10	(0.98, 1.23)
Chronic fatigue syndrome	2.24	(1.01, 4.99)*	1.45	(0.65, 3.22)
Irritable bowel syndrome	1.98	(1.71, 2.29)***	1.36	(1.17, 1.58)***

Crude HR, relative hazard ratio; Adjusted[†] : multivariable analysis including sex, age, and comorbidities of diabetes, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome;

*p<0.05, **p<0.01, ***p<0.001

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Table 4. Demographic characteristics and comorbidity in patient with and without migraine.

| Variable | migraine | | *p*-value |
	No N =69680	Yes N =17420	
Sex	n(%)	n(%)	0.99
Female	51176(73.4)	12794(73.4)	
Male	18504(26.6)	4626(26.6)	
Age, mean(SD)	44.2(15.6)	44.5(15.3)	0.04[#]
Stratify age			0.99
≤49	46768(67.1)	11692(67.1)	
50-65	14940(21.4)	3735(21.4)	
65+	7972(11.4)	1993(11.4)	
Comorbidity			
Diabetes	3567(5.12)	975(5.60)	0.01
Hypertension	12563(18.0)	4551(26.1)	<0.001
Hyperlipidemia	8278(11.9)	3187(18.3)	<0.001
Depression	2019(2.90)	1851(10.6)	<0.001
Anxiety	4366(6.27)	3724(21.4)	<0.001
Sleep disorder	9469(13.6)	6976(40.1)	<0.001
CAD	5560(7.98)	2449(14.1)	<0.001
Chronic fatigue syndrome	71(0.10)	41(0.24)	<0.001
Irritable bowel syndrome	2106(3.02)	1224(7.03)	<0.001

Chi-Square Test; [#]: Two sample T-test

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Table 5. Comparison of incidence and hazard ratio of fibromyalgia stratified by sex, and age between patients with and without migraine

Variable	Without migraine					With migraine				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	2034	453130	4.49	1(Reference)	1(Reference)	800	114070	7.01	1.57(1.44, 1.70)***	1.52(1.39, 1.65)***
Sex										
Female	1556	335328	4.64	1(Reference)	1(Reference)	568	84606	6.71	1.45(1.32, 1.60)***	1.43(1.29, 1.59)***
Male	478	117802	4.06	1(Reference)	1(Reference)	232	29464	7.87	1.94(1.66, 2.27)***	1.78(1.50, 2.11)***
Stratify age										
≤50	1060	310621	3.41	1(Reference)	1(Reference)	470	78131	6.02	1.77(1.58, 1.97)***	1.64(1.46, 1.84)***
50-65	608	96607	6.29	1(Reference)	1(Reference)	207	24189	8.56	1.36(1.16, 1.59)***	1.30(1.09, 1.53)**
65+	366	45902	7.97	1(Reference)	1(Reference)	123	11751	10.5	1.329(1.07, 1.61)**	1.28(1.03, 1.58)*
Comorbidity[‡]										
No	1082	309229	3.50	1(Reference)	1(Reference)	255	43664	5.84	1.67(1.46, 1.92)***	1.79(1.56, 2.06)***
Yes	952	143901	6.62	1(Reference)	1(Reference)	545	70406	7.74	1.18(1.06, 1.31)**	1.299(1.16, 1.44)***

Rate[#], incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, and irritable bowel syndrome
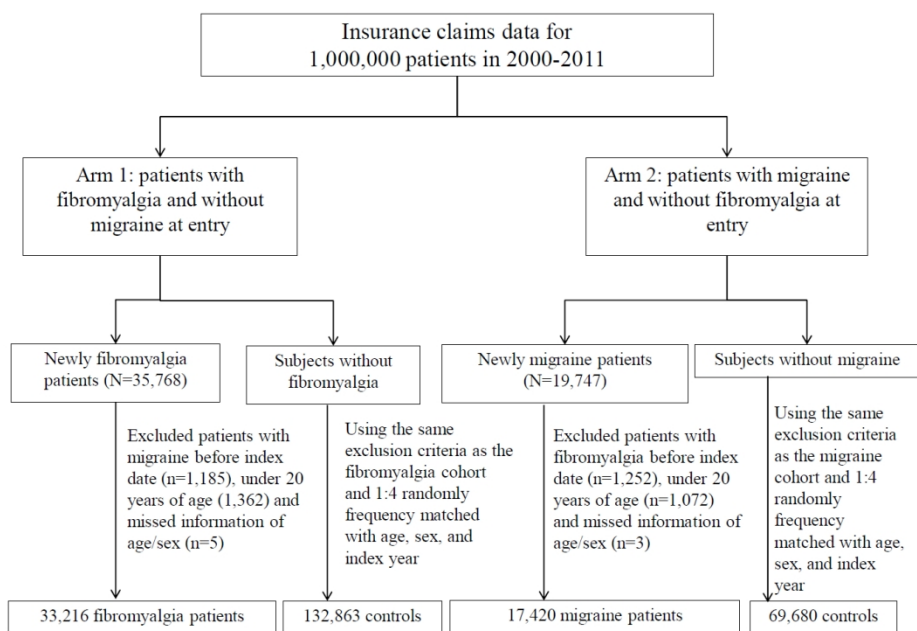
*p<0.05, **p<0.01, ***p<0.001

Comorbidity[‡]: Patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome were classified as the comorbidity group

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Table 6. Cox model with hazard ratios and 95% confidence intervals of fibromyalgia associated with migraine and covariates

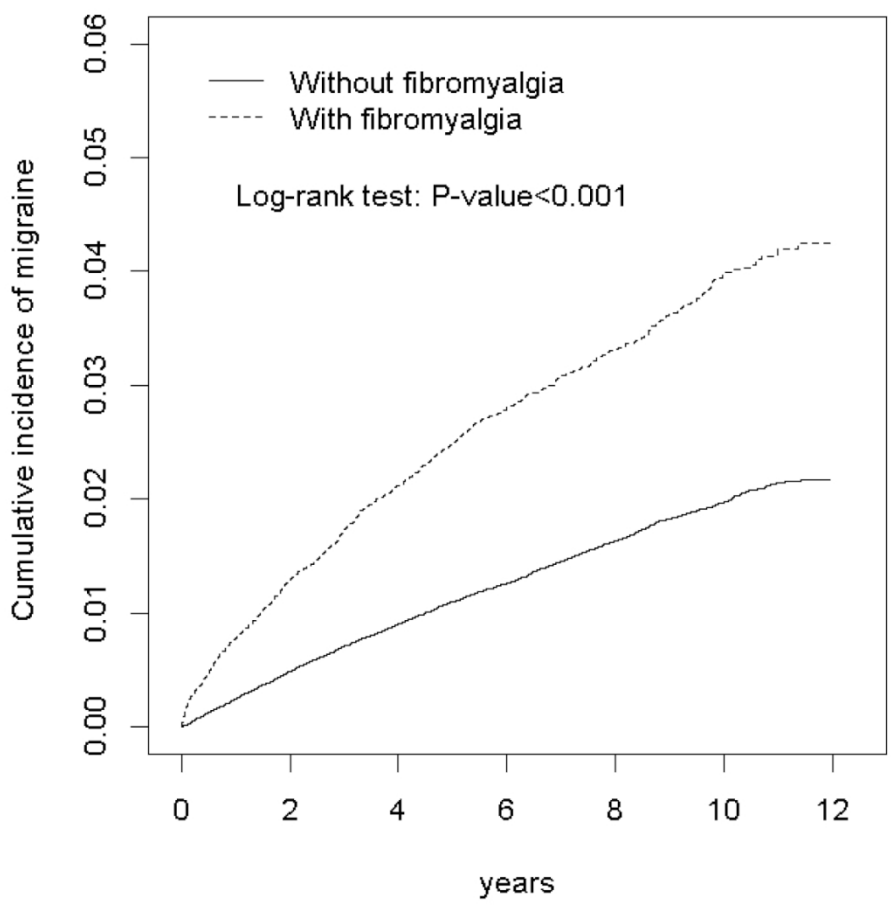| Variable	Crude		Adjusted[†]	
	HR	(95% CI)	HR	(95% CI)
Migraine	1.57	(1.44, 1.70)***	1.51	(1.38, 1.65)***
Sex(Women vs. Men)	1.05	(0.97, 1.15)	-	-
Age, years	1.02	(1.02, 1.03)***	1.02	(1.01, 1.02)***
Baseline comorbidities (yes vs. no)				
Diabetes	1.58	(1.36, 1.82)***	0.99	(0.85, 1.16)
Hypertension	1.81	(1.67, 1.96)***	1.10	(0.99, 1.22)
Hyperlipidemia	1.69	(1.54, 1.85)***	1.15	(1.03, 1.28)*
Depression	1.38	(1.17, 1.63)***	1.06	(0.89, 1.26)
Anxiety	1.34	(1.19, 1.51)***	0.92	(0.80, 1.05)
Sleep disorder	1.45	(1.33, 1.58)***	1.09	(0.98, 1.20)
CAD	1.74	(1.57, 1.94)***	1.01	(0.89, 1.14)
Chronic fatigue syndrome	2.11	(0.79, 5.62)	-	-
Irritable bowel syndrome	1.28	(1.06, 1.53)**	0.94	(0.78, 1.13)

Crude HR, relative hazard ratio; Adjusted[†]: multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, anxiety, sleep disorder, stroke, and peptic ulcer disease, and medication of NSAID;

*p<0.05, **p<0.01, ***p<0.001

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Insurance claims data for
1,000,000 patients in 2000-2011

Arm 1: patients with fibromyalgia and without migraine at entry

Arm 2: patients with migraine and without fibromyalgia at entry

Newly fibromyalgia patients (N=35,768)

Subjects without fibromyalgia

Newly migraine patients (N=19,747)

Subjects without migraine

Excluded patients with migraine before index date (n=1,185), under 20 years of age (1,362) and missed information of age/sex (n=5)

Using the same exclusion criteria as the fibromyalgia cohort and 1:4 randomly frequency matched with age, sex, and index year

Excluded patients with fibromyalgia before index date (n=1,252), under 20 years of age (n=1,072) and missed information of age/sex (n=3)

Using the same exclusion criteria as the migraine cohort and 1:4 randomly frequency matched with age, sex, and index year

33,216 fibromyalgia patients

132,863 controls

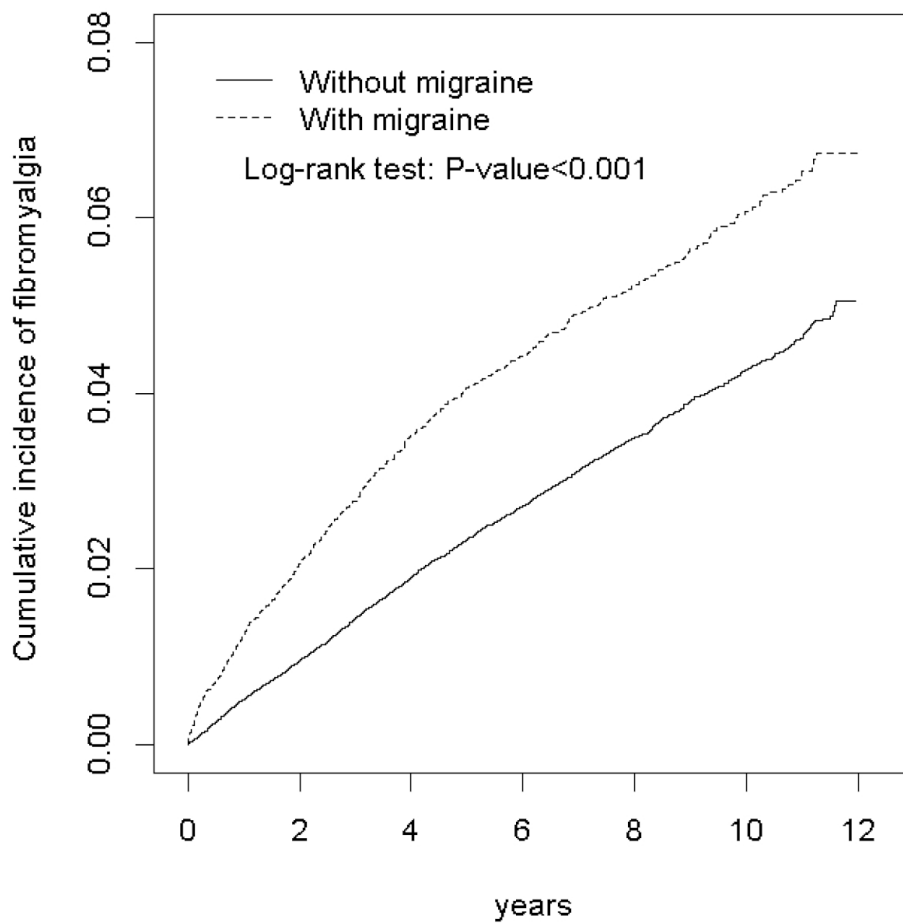17,420 migraine patients

69,680 controls

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8-10
Objectives	3	State specific objectives, including any pre-specified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	11-14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11-14
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	11-14
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	11-14
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	11-14
		Case-control study—For matched studies, give matching criteria and the number of controls per case	11-14
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-14
Bias	9	Describe any efforts to address potential sources of bias	11-14
Study size	10	Explain how the study size was arrived at	11-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-14
		(*b*) Describe any methods used to examine subgroups and interactions	11-14

		(*c*) Explain how missing data were addressed	11-14
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	11-14
		Case-control study—If applicable, explain how matching of cases and controls was addressed	11-14
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	11-14
		(*e*) Describe any sensitivity analyses	11-14
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	15,16
		(b) Give reasons for non-participation at each stage	15,16
		(c) Consider use of a flow diagram	15,16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15,16
		(b) Indicate number of participants with missing data for each variable of interest	15,16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	15,16
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15,16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	15,16
		Cross-sectional study—Report numbers of outcome events or summary measures	15,16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15,16
		(*b*) Report category boundaries when continuous variables were categorized	15,16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15,16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2, 3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Bidirectional Association between Migraine and Fibromyalgia: Two Population-Based Retrospective Cohort Analyses

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	General practice / Family practice, Neurology, Rehabilitation medicine, Rheumatology
Keywords:	fibromyalgia, Migraine < NEUROLOGY, bidirectional analysis, retrospective cohort

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Bidirectional Association between Migraine and Fibromyalgia: Two Population-Based Retrospective Cohort Analyses

Running title: Bidirectional Association between Fibromyalgia and Migraine

I-Wen Penn[1,2], Eric Chuang[3], Tien-Yow Chuang[4], Cheng-Li Lin[5,6], Chia-Hung Kao[7,8,9]

[1]School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan

[2]Department of Physical Medicine and Rehabilitation, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan

[3]UC Berkeley Mishler Lab Undergraduate Researcher, Intended B.S. Molecular and Cell Biology, University of CA, Berkeley, USA

[4]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

[5]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[6]College of Medicine, China Medical University, Taichung, Taiwan

[7]Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

[8]Department of Nuclear Medicine and PET Center, China Medical University Hospital,

Taichung, Taiwan

[9]Department of Bioinformatics and Medical Engineering, Asia University, Taichung,

Taiwan.

*Corresponding author: Chia-Hung Kao, MD, Graduate Institute of Biomedical

Sciences and School of Medicine, College of Medicine, China Medical University, No.

2, Yuh-Der Road, Taichung 404, Taiwan. E-mail: d10040@mail.cmuh.org.tw;

dr.kaochiahung@gmail.com

List of abbreviations

FM: Fibromyalgia; HR: hazard ratio; CI: confidence interval; ICD-9-CM: International

Classification of Diseases, Ninth Revision, Clinical Modification; NHI: National

Health Insurance; LHID: Longitudinal Health Insurance Database

2

Abstract

Objective: Fibromyalgia (FM) and migraine are common pain disorders and tend to coexist. This study determined whether these two conditions exhibited any mutual influences.

Setting: Cohort Study.

Participants: A retrospective, longitudinal cohort study was conducted by using the data from a nationwide healthcare database. This study has two separate arms. Arm 1 included 33,216 FM patients, and Arm 2 contained 7420 migraine patients; all of these patients were diagnosed between 2000 and 2010. Using the same database, control subjects who had neither FM nor migraine and who were matched with the FM and migraine patients by sex, age, and index date of diagnosis were recruited. Each control cohort was four times the size of the relevant study cohort. Both the control and study cohorts were followed until the end of 2011.

Results: The incidence rates of migraine and FM were calculated in Arm 1 and Arm 2, respectively. The overall incidence of migraine was greater in the FM cohort than in the control cohort [4.39 vs. 2.07 per 1000 person-years; crude hazard ratio (HR) = 2.12, 95% confidence interval (CI) =1.96–2.30; adjusted hazard ratio (aHR) = 1.89, 95% CI = 1.75–2.05], after adjustment for sex, age, and comorbidities. The overall incidence of

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FM in the migraine cohort was 1.57 times greater than in the control cohort (7.01 vs.

4.49 per 1000 person-years; aHR = 1.52, 95% CI = 1.39−1.65).

Conclusions: The present study demonstrates the presence of a bidirectional link

between FM and migraine.

Key words: fibromyalgia, migraine, bidirectional analysis, retrospective cohort

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Strengths and limitations of this study:

1. Our study contained a large sample size because of our population-based design approach.

2. We based our study solely on the information from diagnoses in patient files, so we did not include any patients whose cases were unidentified.

3. This study is naturally more prone to observational bias since patients with migraines and FM are generally more likely to seek medical attention for another condition.

4. The health claims information in the LHID includes mainly disease documents recorded according to ICD-9-CM, but lack descriptions on clinical subsets of disease manifestation or progression, such as episodic or chronic migraine, with or without aura, etc.

5. The selections of two study and control cohorts were based on the inclusion and exclusion criteria only. There is no subjective patient omission in the process.

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Introduction

One of the major symptoms of fibromyalgia (FM) is a headache. Among those

different types of headaches, there are migraines—some bad enough to debilitate a

person. Interestingly, similarities exist between migraines and fibromyalgia, and as we

consider the two conditions in the same context, many instances of overlapping

symptoms, causes, and treatments are noted [1]. Several studies have reported that a

high proportion (20%–36%) of patients with migraine have FM [2-5]. By contrast, the

frequency of migraine in patients with FM is approximately 45%–80%, suggesting that

migraine is common in patients with FM [6, 7]. Despite previous reports demonstrated

that the prevalence of fibromyalgia was higher among migraine patients, and vice versa

[8-13], explanations for this high degree of co-occurrence are unknown.

Migraine is a complex, recurrent disorder that manifests as a throbbing headache,

which is frequently associated with nausea, allodynia, and sound or light sensitivity,

and may develop into a chronic condition and disability [14,15]. The pain is considered

to occur due to the nociceptive activation of the trigeminovascular system, including

the sensory neurons from the trigeminal ganglion and upper cervical nerve roots, which

modulate central signals to numerous subcortical sites [16]. The combination of tonic

nociceptive input and central disinhibition may also play a role in the development of

FM. Many migraineurs experience a condition termed "allodynia" during migraine

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attacks. Usually, allodynia is confined to the head and neck but may involve other areas

of the body [17]. Increasing evidence indicates that the peripheral tissues are relevant

contributors to painful impulse input, which might either initiate or maintain central

sensitization, thus contributing to the progression of FM [18]. Migraine is also supposed

to be a trigger factor for FM. The repeated headaches in migraine patients might

increase the neuronal response to both nociceptive and non-nociceptive stimulation and

induce spontaneous neuronal activity, which might concurrently heighten the

sensitivity of the patient to FM [19]. Several studies have highlighted the role of the

hypothalamus in migraines [17]. Evidence indicates its direct and indirect anatomical

connections to the thalamus and autonomic brainstem nuclei, supporting its role in

nociceptive and autonomic modulation among migraine patients [20]. However, the

brain mechanisms also common to FM suffers result in central sensitization of pain

neurons leading to the evolution of a complex syndrome [21].

Early in the course of disease, the widespread musculoskeletal pain of FM patients

often appears in the neck or shoulder region [22]. Neck pain may activate local

nociceptors and transmit painful impulses through the upper cervical spinal nerves,

such as the greater occipital nerve, to the trigeminal nucleus caudalis, thus inducing a

migraine attack [23]. Some experts believe that FM and migraine headaches both

involve defects in the systems that regulate certain chemical messengers in the brain,

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including serotonin and epinephrine (adrenaline) [1]. which might reflect in their

similar psychological comorbidities: depression, anxiety, interpersonal sensitivity,

somatization, etc [9]. Psychosocial distress and psychological abnormality are common

to occur in patients suffering from migraine as well as patients suffering from FM.

Although previous research has demonstrated a high comorbidity rate for

migraines and FM, several vital issues must be highlighted. (1) Most of these studies

were performed at tertiary care centers. Patients are often referred to tertiary clinics due

to high pain complaints, disability, or medication overuse. Hence, the sample

populations may differ from patients treated in general practice. (2) Most of these

studies used a cross-sectional design for investigating the prevalence instead of the

incidence of migraine or FM. (3) If there is a significant association, whether people

with migraine are more likely than the general population to develop FM or vice versa

remains unknown. Therefore, our population-based longitudinal cohort study is trying

to investigate the links between migraine and FM.

Methods

Patient and Public Involvement

The data for this research were sourced from the Longitudinal Health Insurance

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Database (LHID). The LHID comprises the data of 1 million insurants' health claims

from the Taiwan National Health Insurance (NHI) program, which covers 99% of 23

million Taiwan citizens with single-payer health insurance. According to the

government's report, no differences were noted in the demographic features between

the LHID and Taiwan NHI program. The health claims information in the LHID

includes general information regarding the insurants (such as birthdate, sex, and

occupation), disease documents (recorded according to the International Classification

of Diseases, Ninth Revision, Clinical Modification; ICD-9-CM), and other medical

service-related data.

Data Availability Statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare

(MOHW). The Ministry of Health and Welfare must approve our application to access

this data. Any researcher interested in accessing this dataset can submit an application

form to the Ministry of Health and Welfare requesting access. Please contact the staff

of MOHW (Email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan Ministry

of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist.,

Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848.   All relevant data are

within the paper.

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Ethics Statement

The National Health Insurance Research Databank (NHIRD) encrypts patient

personal information to protect privacy and provides researchers with anonymous

identification numbers associated with relevant claims information, including sex, date

of birth, medical services received, and prescriptions. Therefore, patient consent is not

required to access the NHIRD. This study was approved to fulfill the condition for

exemption by the Institutional Review Board (IRB) of China Medical University

(CMUH104-REC2-115-CR3). The IRB also specifically waived the consent

requirement.

Study Cohorts

A bidirectional cohort study design was used to interpret the longitudinal

association between FM and migraine.

Figure 1 shows the procedure for establishing the two study Arms. For study Arm

1, we identified patients with FM (ICD-9-CM code 729.1) who were aged ≥20 years

and were newly diagnosed consecutively ≥3 times within 3 months in 2000–2010. The

first diagnosis date was designated as the index date for entry into the FM cohort.

Patients with a history of migraine (ICD-9-CM codes 346) were excluded from the

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cohort. For each FM patient, we randomly selected four persons free of FM and migraine from the population of the LHID2000, who were frequency-matched by sex, age (in 5-year increments), and entry date of the FM patient; these subjects were recruited to the non-FM (control) cohort.

For study Arm 2, a similar procedure to that for study Arm 1 was used to establish a migraine cohort of patients who did not have a history of FM, were aged ≥20 years, and were newly diagnosed consecutively ≥3 times within 3 months in 2000–2010.

Subjects in the study Arms 1 and 2 were followed until the diagnosis of migraine or FM, withdrawal from the NHI program, death, or December 31, 2011. The patients in two cohorts contained some baseline comorbidities: diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2, 296.3, 296.5, 300.4, 309, and 311), anxiety (ICD-9-CM code 300.0, 300.2, 300.3, 308.3, and 309.81), sleep disorder (ICD-9-CM codes 307.4 and 780.5), coronary artery disease (CAD; ICD-9-CM codes 410–414), chronic fatigue syndrome (CFS; ICD-9-CM code 780.71), and irritable bowel syndrome (IBS; ICD-9-CM code 564.1).

Statistical analyses

The characteristics of the study cohorts are expressed as the mean and

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corresponding standard deviation for age and as number and percentage for sex and comorbidities. Age difference was assessed using the t-test, and sex and comorbidity distributions were tested using the chi-square test. The incidence density for each cohort was calculated as the total event number divided by the sum of follow-ups [per 1000 person-years (PY)]. The cumulative incidence curve for each cohort was measured using the Kaplan–Meier method, with the curve difference being calculated using the log-rank test. To determine the migraine and fibromyalgia risks in Arms 1 and 2, respectively, the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated using single-variable and multivariable Cox proportional hazard models. Data management and all statistical analyses were performed using SAS software for Windows (Version 9.4, SAS Institute, Cary, NC, USA), and incidence curves was plotted using R software. All significance levels were set at two-sided $p < 0.05$.

Results

Table 1 shows the demographic characteristics of the FM and non-FM cohorts. The age- and sex-matched cohorts demonstrated differences in the comorbidity distribution. The prevalence of comorbidities was significantly higher in the FM cohort than in non-FM cohort ($p < 0.001$).

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Table 2 shows the migraine incidence was 4.39 and 2.07 per 1000 PY in the FM

and non-FM cohorts, respectively. Figure 2 shows a higher incidence curve for the FM

cohort and a lower curve for the non-FM cohort (log rank test=371.4, p < 0.001). After

adjustment for age, sex, and comorbidities, the FM patients exhibited a 1.89-fold higher

risk of migraine than did the non-FM subjects (HR = 1.89, 95% CI = 1.75–2.05).

Among females, the relative risk of migraine was 1.76-fold higher in the FM patients

than in the non-FM subjects (HR = 1.76, 95% CI 1.60–1.93), whereas the risk among

males was 2.29-fold higher in the FM patients than in the non-FM subjects (HR = 2.29,

95% CI = 1.97–2.67). Regarding the age effect, the HRs for migraine in the FM cohort

were 2.06 (95% CI = 1.85–2.29), 1.66 (95% CI = 1.43–1.92), and 1.69 (95% CI = 1.39–

2.05) for age ≤ 50, 51–65, and ≥ 65 years, respectively.

Table 3 shows the influence of factors associated with the occurrence of migraine

in the FM cohort. Male sex, hyperlipidemia, depression, anxiety, sleep disorder, CAD,

CFS, and IBS were associated with a higher risk of migraine (all p-value <0.05).

Table 4 lists the comorbidities as well as the age- and sex-matched comparisons

in the migraine cohort. The migraine cohort showed higher prevalent comorbidities

than non-migraine cohort.

Table 5 and Figure 3 show the significantly higher incidence of FM in migraine

patients than that in non-migraine subjects (7.01 vs. 4.49 per 1000 PY; log-rank

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test=116.7, p < 0.001). After adjustment for age, sex, and comorbidities, the migraine

patients exhibited a 1.52-fold higher risk of FM than did non-migraine subjects (HR =

1.52, 95% CI = 1.39–1.65). The female migraine patients displayed a 1.43-fold higher

risk of FM than did the non-migraine subjects (HR = 1.43, 95% CI = 1.29–1.59),

whereas the male migraine patients exhibited a 1.78-fold higher risk of FM (95% CI =

1.50–2.11). Regarding the age effect, the HRs for FM were 1.64 (95% CI = 1.46–1.84),

1.30 (95% CI = 1.09–1.53), and 1.28 (95% CI = 1.03–1.58) in migraine patients aged

<50, 50–64, and ≥65 years, respectively.

Table 6 shows the associations of sex, age, and comorbidities with the risk of FM.

The variables, including age, migraine, hypertension, hyperlipidemia, depression, sleep

disorder, and CAD, were all associated with a lower risk of FM.

Discussion

The results of the two cohort arms suggested a bidirectional risk of migraine and

FM in patients with FM and migraine, respectively. In the Arm 1 analysis, the incidence

rates for migraine were 4.39 and 2.07 per 1000 PY in FM patients and non-FM subjects,

respectively [adjusted hazard ratio (aHR) = 1.89 and 95% CI = 1.75–2.05 in FM

patients]. In the Arm 2 analysis, the incidence rates for FM were 7.01 and 4.49 per 1000

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PY in migraine patients and non-migraine subjects, respectively (aHR = 1.52 and 95%

CI = 1.39–1.65 in migraine patients). This indicated that FM has a stronger predictive

power for the onset of migraine than does migraine for the onset of FM.

The Kaplan–Meier plots demonstrated that the incidence of migraine in the FM

cohort and the incidence of FM in the migraine cohort increased steadily during the 12-

year follow-up period. Moreover, similar patterns were observed in the two

corresponding comparison cohorts. The cumulative incidence measured by the Kaplan–

Meier plots revealed a greater risk of migraine among FM patients than that of FM

among migraine patients.

Our predictive analytics could potentially dictate diagnosis and treatment. For

example, a subsequent diagnosis of FM could come from the failure of anti-migraine

treatment to alleviate fatigue [24]. Since migraine is often better managed, the authors

would hypothesize that FM patients are more likely to be treated for migraine than vice

versa. Therefore, clinical trials of migraine patients in the future have the potential to

evaluate the effects of FM on health outcomes and its treatment efficacy [10].

Cohort analysis for the association between FM and the risk of new-onset migraine

This study revealed a positive association between the diagnosis of FM and the

risk of migraine. Adjustment for factors, including hypertension, CAD, and CFS, had

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no strong influence on this association. However, sex, age (particularly in patients under

49 years of age), diabetes, hyperlipidemia, depression, anxiety, sleep disorder, and IBS

remained statistically significant.

"High frequency and chronic migraine increase the sensitivity to pain in

fibromyalgia (FM) patients [25], such heightened pain sensitivity may be attenuated by

comorbid diabetes. There is also a documented report showing a significant positive

association between migraine frequency and intensity with total and LDL cholesterol,

independent of diet and lifestyle [26]." Several hypotheses have been proposed to

explain the development of chronic widespread pain and/or episodic throbbing or

pulsing pain over the head and neck regions as the possible effects of comorbidities,

including depression and anxiety. Depression and anxiety disorders have been

identified as important secondary symptoms of FM [11, 27, 28]. The pain of FM may

initiate the development of mood disorders as a result of the stress created on the body.

In addition, depression and anxiety might also induce the onset or present as a prodrome

of migraine, according to several evidence-based studies [29, 30]. Research has

indicated that serotonin levels might be related to the interconnections between anxiety

and migraine [31]. A lower level of serotonin may be central to the dysregulation of

descending antinociceptive systems, leading to the occurrence of FM and migraine [31,

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Nonrefreshing sleep or sleep deprivation in healthy persons can induce symptoms of fibromyalgia [33], implying that sleep abnormalities might be a pathology and not only a result of pain [34]. To date, the literature has documented the advantage of targeting sleep conditions to possibly relieve the symptoms of migraine [35]. As the prevalence of sleep disorders soars in both FM and migraine patients, appreciation of the close links between FM and migraine increases.

IBS frequently coexists with both FM and migraine [36, 37]. The underlying mechanisms for the association of FM with an increasing risk of IBS and migraine are unclear. FM, migraine, and IBS may be three distinct manifestations of a common pathophysiologic process affecting the gastrointestinal tract. These disorders are known as "central sensitivity syndrome" and are mutually associated [38]. A growing body of evidence indicates that central sensitization phenomena play a role in the pathogenesis of both FM and migraine. Central sensitization at the levels of the spinal dorsal horn and trigeminal nucleus may also be involved in the progression of migraine attacks, and the prolonged nociceptive inputs may result in the maintenance of supraspinal sensitization and central neuroplastic changes, leading to the conversion of episodic headaches into chronic [39]. Interestingly, increased intestinal permeability (IP) may be observed in IBS [40]. Altered IP with intestinal bacteria overgrowth may trigger the development of FM [41] and migraine [42]. The microbiome–gut–brain axis, a

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bidirectional communication between the central and enteric nervous systems with

microbiome via the neural, humoral, endocrine, and immune pathways [36, 37, 43] was

proposed as one of the multidisciplinary pathophysiologic mechanisms underlying IBS

[43], FM [44, 45] and migraine [42, 46]. The gut microbiota interacts with the central,

autonomic, and enteric nervous systems and hypothalamic–pituitary–adrenal axis and

vice versa [43].

Cohort analysis for the association between migraine and the risk of new-onset

FM

This study also revealed a higher risk of FM in migraine patients than in non-

migraine subjects in every factor-based subset of the cohorts. One interesting feature

was that patients with hyperlipidemia had a higher risk of FM. Adverse lipid profiles

occurred more frequently in migraine patients with a higher body mass index [47, 48].

Lack of exercise may precipitate the development of an adverse lipid profile; however,

exercise may trigger acute migraine attacks [49], and some patients might avoid

exercise in the hope of preventing migraines. This hypothesis could be supported by a

study which revealed that headache patients have less aerobic endurance and flexibility

than do healthy controls [50]. Aerobic exercise could relieve depression and anxiety

and avoid the harmful consequences of stress [51]. Avoiding exercise may worsen

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mood distress and is thus possibly related to the development of FM.

Increased migraine frequency—with the transformation of migraine to chronic migraine—intensifies the sensitivity to pain in somatic areas outside the cephalic region and may predispose to FM [6]. Hypothalamic neuroendocrine dysfunction has been proposed as a brain mechanism common to both FM and migraine [52]. Both conditions also share the mechanism of central sensitization of pain neurons. Magnesium, which is often used as an agent for relieving migraine headaches, is also beneficial for treating FM. Low magnesium levels can exacerbate FM symptoms, and they are implicated in migraines [53]. Researchers have discovered that people who do not respond to standard migraine treatments are often affected with FM [17]. Given the high comorbidity rate of migraine and FM, many professionals still assume the role of central nervous system pain-processing abnormalities, including central sensitization and inadequate pain inhibition with repeated headache episodes, and beyond that, tonic peripheral nociceptive input to be associated with the augmented windup in the responses to neurotransmitters, immunomodulation, vascular changes, and hormonal influence, which may predispose to the development of FM [1, 6, 36, 37, 43, 52].

Our study contained a large sample size because of our population-based design approach. Additionally, we were careful in our analyses to reduce selection bias, and our vast documents of medical profiles allowed for minimal effect from our

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confounding factors in the subjects. However, there are still certain limitations in our study. We based our study solely on the information from diagnoses in patient files, so we did not include any patients whose cases were unidentified. In the event of poor categorization of a patient's symptoms, it is possible that it may affect the discernibility between migraine and fibromyalgia. Since many crucial variables are not retrievable and there are multitudes of ways to diagnose fibromyalgia as well as the numerous subtypes of migraines, our data provides merely a glimpse of these two conditions. It is also impossible to assess treatment response from our large database analysis, so it's hard to sort out "diagnosis by exclusion" in this study. Future studies are needed to better delineate "diagnosis by exclusion". Furthermore, this study did not take into account the severity of FM and migraines in patients, therefore, no definitive statement can be made in regards to the intensity of FM and subsequent risk of developing migraine conditions, and vice versa. Moreover, this study is naturally more prone to observational bias since patients with migraines and FM are generally more likely to seek medical attention for another condition.

Conclusion

This study is the first to reveal a population-based bidirectional association between the onsets of FM and migraine in patients with migraine and FM, respectively.

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The risk of developing migraine is greater than the risk of developing FM. The incidence rates of FM in the migraine cohort and of migraine in the FM cohort increased with age in both directions. However, the HRs relative to the corresponding comparison cohorts were attenuated with the increase in age.

Author contributions:

Conceptualization: I-Wen Penn, Chia-Hung Kao.

Methodology: Cheng-Li Lin, Chia-Hung Kao.

Software: Cheng-Li Lin, Chia-Hung Kao.

Validation: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin, Chia-Hung Kao.

Formal analysis: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin, Chia-Hung Kao.

Investigation: Cheng-Li Lin, Chia-Hung Kao.

Resources: Cheng-Li Lin, Chia-Hung Kao.

Data curation: IWP, EC, TYC, CLL, CHK.

Writing (original draft preparation): I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin, Chia-Hung Kao.

Writing (review and editing): I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-

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Li Lin, Chia-Hung Kao.

Visualization: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin, Chia-Hung Kao.

Supervision: Chia-Hung Kao.

Project administration: Chia-Hung Kao.

Funding acquisition: Chia-Hung Kao.

Conflict of Interest:

All authors report no conflicts of interest.

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Figure Legend:

Figure 1. Flow chart showing selection of study subjects.

Figure 2. Cummulative incidence of migraine compared between patients with and without fibromyalgia using the Kaplan-Meier method.

Figure 3. Cummulative incidence of fibromyalgia compared between patients with and without migraine using the Kaplan-Meier method.

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Table 1. Demographic characteristics and comorbidity in patient with and without fibromyalgia.

| Variable | Fibromyalgia | | |
	No N =132863	Yes N =33216	*p*-value
Sex	n(%)	n(%)	0.99
Female	71880(54.1)	17970(54.1)	
Male	60983(45.9)	15246(45.9)	
Age, mean(SD)	50.9(16.9)	51.4(16.7)	<0.001[#]
Stratify age			0.99
≤49	64292(48.4)	10673(48.4)	
50-65	36820(27.7)	9205(27.7)	
65+	31751(23.9)	7938(23.9)	
Comorbidity			
Diabetes	10485(7.89)	3193(9.61)	<0.001
Hypertension	37284(28.1)	11287(34.0)	<0.001
Hyperlipidemia	22446(16.9)	7301(22.0)	<0.001
Depression	4690(3.53)	1804(5.43)	<0.001
Anxiety	10494(7.90)	4214(12.7)	<0.001
Sleep disorder	21095(15.9)	8121(24.5)	<0.001
CAD	17918(13.5)	5821(17.5)	<0.001
Chronic fatigue syndrome	199(0.15)	93(0.28)	<0.001
Irritable bowel syndrome	5125(3.86)	1870(5.63)	<0.001

Chi-Square Test; [#]: Two sample T-test

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Table 2. Comparison of incidence and hazard ratio of migraine stratified by sex, and age between patients with and without fibromyalgia.

Variable	Without fibromyalgia					With fibromyalgia				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	1810	876077	2.07	1(Reference)	1(Reference)	954	217386	4.39	2.12(1.96, 2.30)***	1.89(1.75, 2.05)***
Sex										
Female	1373	487506	2.82	1(Reference)	1(Reference)	669	120773	5.54	1.97(1.79, 2.16)***	1.76(1.60, 1.93)***
Male	437	388571	1.12	1(Reference)	1(Reference)	285	96613	2.95	2.62(2.26, 3.05)***	2.29(1.97, 2.67)***
Stratify age										
≤50	922	444710	2.07	1(Reference)	1(Reference)	548	110557	4.96	2.39(2.15, 2.66)***	2.06(1.85, 2.29)***
50-65	564	245579	2.30	1(Reference)	1(Reference)	258	60603	4.26	1.85(1.60, 2.15)***	1.66(1.43, 1.92)***
65+	324	185788	1.74	1(Reference)	1(Reference)	148	46226	3.20	1.83(1.51, 2.23)***	1.69(1.39, 2.05)***
Comorbidity[‡]										
No	774	508879	1.52	1(Reference)	1(Reference)	311	95605	3.25	2.14(1.88, 2.44)***	2.13(1.87, 2.43)***
Yes	1036	367197	2.82	1(Reference)	1(Reference)	643	121780	5.28	1.88(1.71, 2.08)***	1.80(1.63, 1.98)***

Rate[#], incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome

***p<0.001

Comorbidity[‡]: Patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome were classified as the comorbidity group

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Table 3. Cox model with hazard ratios and 95% confidence intervals of migraine associated with fibromyalgia and covariates.

Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Fibromyalgia	2.12	(1.96, 2.30)***	1.89	(1.74, 2.04)***
Sex(Women vs. Men)	2.28	(2.09, 2.48)***	2.08	(1.91, 2.27)***
Age, years	1.00	(0.99, 1.00)**	0.99	(0.99, 1.00)***
Baseline comorbidities (yes vs. no)				
Diabetes	0.82	(0.70, 0.96)*	0.73	(0.61, 0.860***
Hypertension	1.06	(0.97, 1.15)	-	-
Hyperlipidemia	1.30	(1.19, 1.43)***	1.14	(1.03, 1.27)*
Depression	2.37	(2.06, 2.72)***	1.20	(1.03, 1.39)*
Anxiety	2.68	(2.44, 2.95)***	1.64	(1.47, 1.84)***
Sleep disorder	2.63	(2.43, 2.85)***	1.97	(1.80, 2.15)***
CAD	1.30	(1.18, 1.44)***	1.10	(0.98, 1.23)
Chronic fatigue syndrome	2.24	(1.01, 4.99)*	1.45	(0.65, 3.22)
Irritable bowel syndrome	1.98	(1.71, 2.29)***	1.36	(1.17, 1.58)***

Crude HR, relative hazard ratio; Adjusted† : multivariable analysis including sex, age, and comorbidities of diabetes, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome;

*p<0.05, **p<0.01, ***p<0.001

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Table 4. Demographic characteristics and comorbidity in patient with and without migraine.

Variable	migraine		
	No N =69680	Yes N =17420	*p*-value
Sex	n(%)	n(%)	0.99
Female	51176(73.4)	12794(73.4)	
Male	18504(26.6)	4626(26.6)	
Age, mean(SD)	44.2(15.6)	44.5(15.3)	0.04[#]
Stratify age			0.99
≤49	46768(67.1)	11692(67.1)	
50-65	14940(21.4)	3735(21.4)	
65+	7972(11.4)	1993(11.4)	
Comorbidity			
Diabetes	3567(5.12)	975(5.60)	0.01
Hypertension	12563(18.0)	4551(26.1)	<0.001
Hyperlipidemia	8278(11.9)	3187(18.3)	<0.001
Depression	2019(2.90)	1851(10.6)	<0.001
Anxiety	4366(6.27)	3724(21.4)	<0.001
Sleep disorder	9469(13.6)	6976(40.1)	<0.001
CAD	5560(7.98)	2449(14.1)	<0.001
Chronic fatigue syndrome	71(0.10)	41(0.24)	<0.001
Irritable bowel syndrome	2106(3.02)	1224(7.03)	<0.001

Chi-Square Test; [#]: Two sample T-test

Table 5. Comparison of incidence and hazard ratio of fibromyalgia stratified by sex, and age between patients with and without migraine

Variable	Without migraine					With migraine				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	2034	453130	4.49	1(Reference)	1(Reference)	800	114070	7.01	1.57(1.44, 1.70)***	1.52(1.39, 1.65)***
Sex										
Female	1556	335328	4.64	1(Reference)	1(Reference)	568	84606	6.71	1.45(1.32, 1.60)***	1.43(1.29, 1.59)***
Male	478	117802	4.06	1(Reference)	1(Reference)	232	29464	7.87	1.94(1.66, 2.27)***	1.78(1.50, 2.11)***
Stratify age										
≤50	1060	310621	3.41	1(Reference)	1(Reference)	470	78131	6.02	1.77(1.58, 1.97)***	1.64(1.46, 1.84)***
50-65	608	96607	6.29	1(Reference)	1(Reference)	207	24189	8.56	1.36(1.16, 1.59)***	1.30(1.09, 1.53)**
65+	366	45902	7.97	1(Reference)	1(Reference)	123	11751	10.5	1.32(1.07, 1.61)**	1.28(1.03, 1.58)*
Comorbidity[‡]										
No	1082	309229	3.50	1(Reference)	1(Reference)	255	43664	5.84	1.67(1.46, 1.92)***	1.79(1.56, 2.06)***
Yes	952	143901	6.62	1(Reference)	1(Reference)	545	70406	7.74	1.18(1.06, 1.31)**	1.29(1.16, 1.44)***

Rate[#], incidence rate, per 1,000 person-years; Crude HR, crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, and irritable bowel syndrome
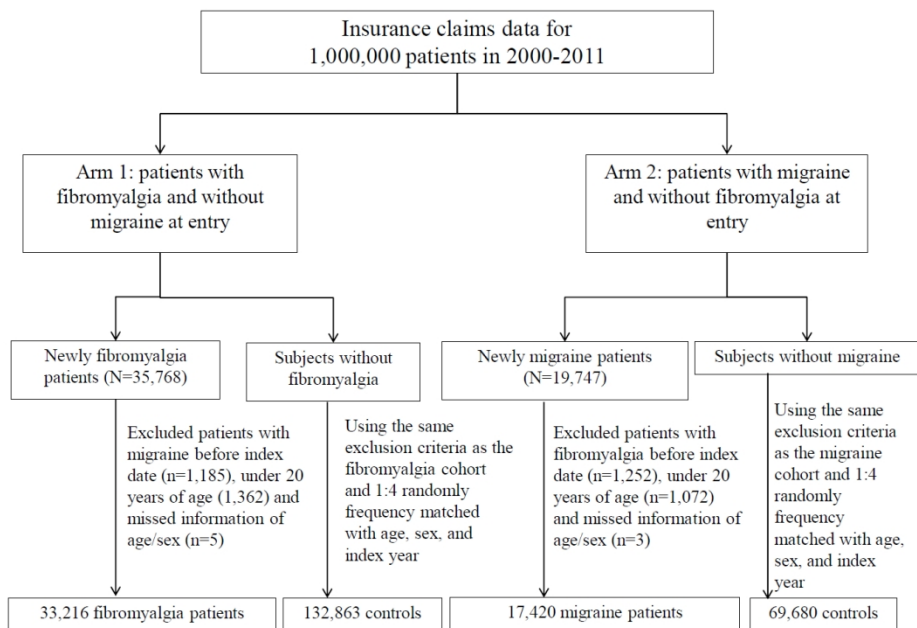
*p<0.05, **p<0.01, ***p<0.001

Comorbidity[‡]: Patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome, and irritable bowel syndrome were classified as the comorbidity group

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Table 6. Cox model with hazard ratios and 95% confidence intervals of fibromyalgia associated with migraine and covariates
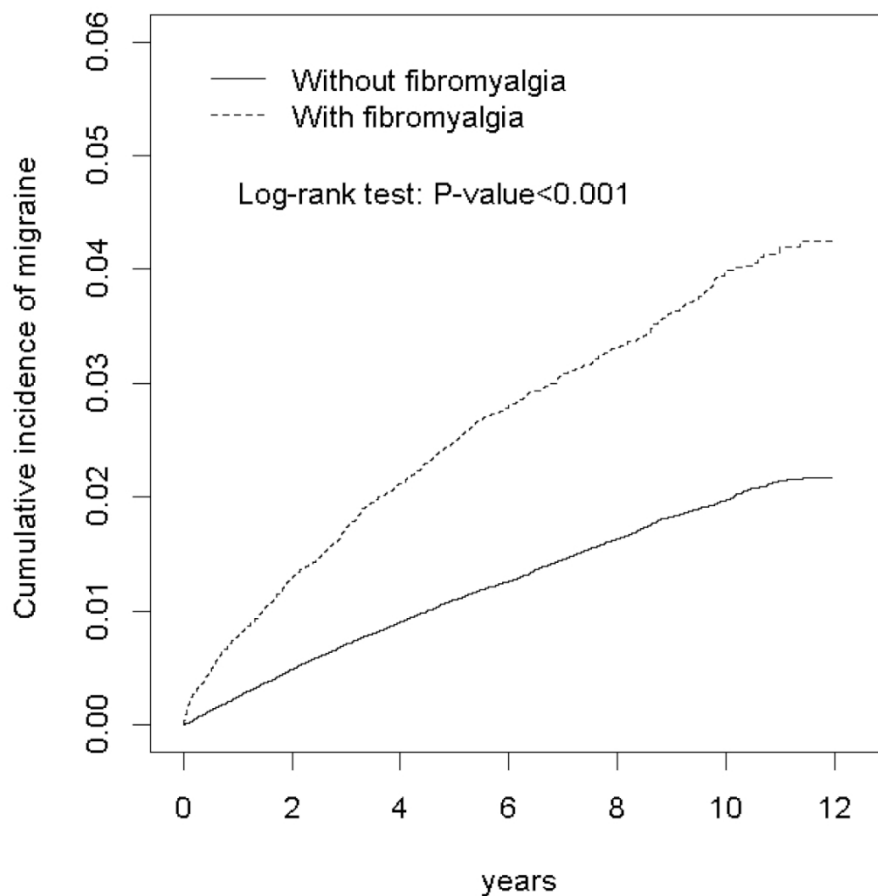
Variable	Crude		Adjusted[†]	
	HR	(95% CI)	HR	(95% CI)
Migraine	1.57	(1.44, 1.70)***	1.51	(1.38, 1.65)***
Sex(Women vs. Men)	1.05	(0.97, 1.15)	-	-
Age, years	1.02	(1.02, 1.03)***	1.02	(1.01, 1.02)***
Baseline comorbidities (yes vs. no)				
Diabetes	1.58	(1.36, 1.82)***	0.99	(0.85, 1.16)
Hypertension	1.81	(1.67, 1.96)***	1.10	(0.99, 1.22)
Hyperlipidemia	1.69	(1.54, 1.85)***	1.15	(1.03, 1.28)*
Depression	1.38	(1.17, 1.63)***	1.06	(0.89, 1.26)
Anxiety	1.34	(1.19, 1.51)***	0.92	(0.80, 1.05)
Sleep disorder	1.45	(1.33, 1.58)***	1.09	(0.98, 1.20)
CAD	1.74	(1.57, 1.94)***	1.01	(0.89, 1.14)
Chronic fatigue syndrome	2.11	(0.79, 5.62)	-	-
Irritable bowel syndrome	1.28	(1.06, 1.53)**	0.94	(0.78, 1.13)

Crude HR, relative hazard ratio; Adjusted[†] : multivariable analysis including age, and comorbidities of diabetes, hypertension, hyperlipidemia, anxiety, sleep disorder, stroke, and peptic ulcer disease, and medication of NSAID;
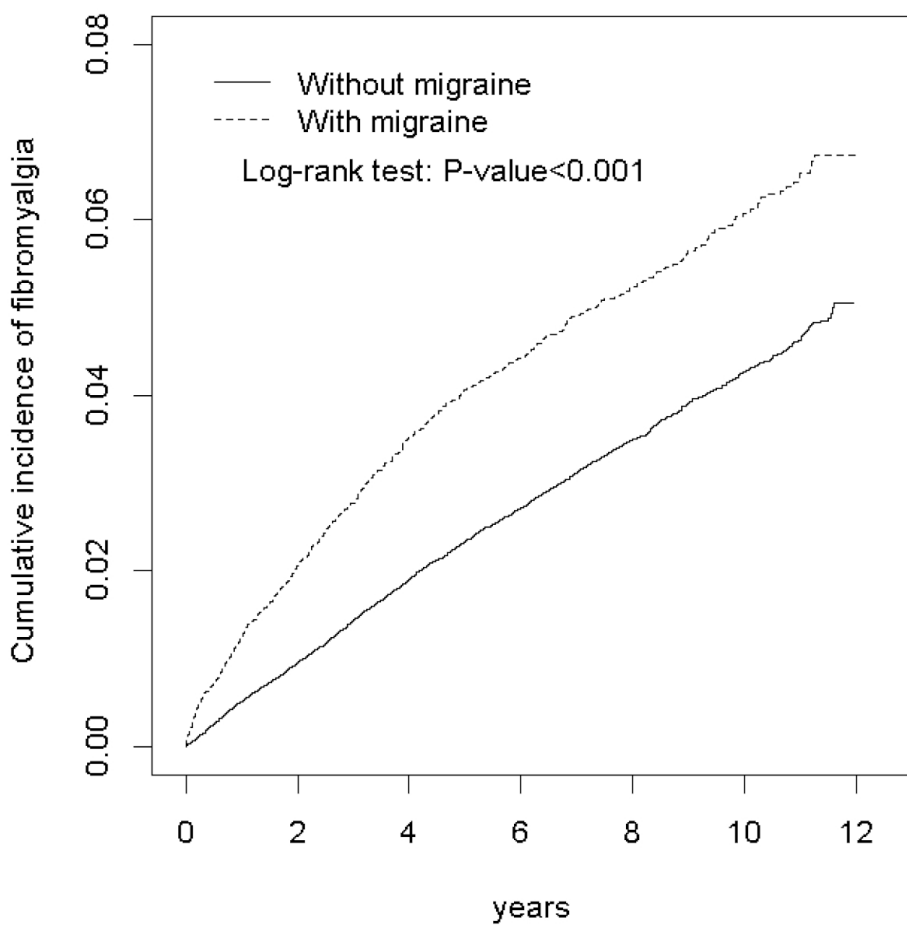
*p<0.05, **p<0.01, ***p<0.001

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Insurance claims data for 1,000,000 patients in 2000-2011

Arm 1: patients with fibromyalgia and without migraine at entry

Arm 2: patients with migraine and without fibromyalgia at entry

Newly fibromyalgia patients (N=35,768)

Subjects without fibromyalgia

Newly migraine patients (N=19,747)

Subjects without migraine

Excluded patients with migraine before index date (n=1,185), under 20 years of age (1,362) and missed information of age/sex (n=5)

Using the same exclusion criteria as the fibromyalgia cohort and 1:4 randomly frequency matched with age, sex, and index year

Excluded patients with fibromyalgia before index date (n=1,252), under 20 years of age (n=1,072) and missed information of age/sex (n=3)

Using the same exclusion criteria as the migraine cohort and 1:4 randomly frequency matched with age, sex, and index year

33,216 fibromyalgia patients

132,863 controls

17,420 migraine patients

69,680 controls

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8-10
Objectives	3	State specific objectives, including any pre-specified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	11-14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11-14
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	11-14
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	11-14
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	11-14
		Case-control study—For matched studies, give matching criteria and the number of controls per case	11-14
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-14
Bias	9	Describe any efforts to address potential sources of bias	11-14
Study size	10	Explain how the study size was arrived at	11-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-14
		(*b*) Describe any methods used to examine subgroups and interactions	11-14

		(*c*) Explain how missing data were addressed	11-14
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	11-14
		Case-control study—If applicable, explain how matching of cases and controls was addressed	11-14
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	11-14
		(*e*) Describe any sensitivity analyses	11-14
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	15,16
		(b) Give reasons for non-participation at each stage	15,16
		(c) Consider use of a flow diagram	15,16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15,16
		(b) Indicate number of participants with missing data for each variable of interest	15,16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	15,16
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15,16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	15,16
		Cross-sectional study—Report numbers of outcome events or summary measures	15,16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15,16
		(*b*) Report category boundaries when continuous variables were categorized	15,16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15,16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2, 3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Bidirectional Association between Migraine and Fibromyalgia: Retrospective Cohort Analyses of Two Populations

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Manuscripts

Bidirectional Association between Migraine and Fibromyalgia: Retrospective

Cohort Analyses of Two Populations

Running title: Bidirectional Association between Fibromyalgia and Migraine

I-Wen Penn[1,2], Eric Chuang[3], Tien-Yow Chuang[4], Cheng-Li Lin[5,6], Chia-Hung Kao[7,8,9]

[1]School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan

[2]Department of Physical Medicine and Rehabilitation, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan

[3]UC Berkeley Mishler Lab Undergraduate Researcher, Intended B.S. Molecular and Cell Biology, University of CA, Berkeley, USA

[4]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

[5]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[6]College of Medicine, China Medical University, Taichung, Taiwan

[7]Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

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[8]Department of Nuclear Medicine and PET Center, China Medical University

Hospital, Taichung, Taiwan

[9]Department of Bioinformatics and Medical Engineering, Asia University, Taichung,

Taiwan.

*Corresponding author: Chia-Hung Kao, MD, Graduate Institute of Biomedical

Sciences and School of Medicine, College of Medicine, China Medical University,

No. 2, Yuh-Der Road, Taichung 404, Taiwan. E-mail: d10040@mail.cmuh.org.tw;

dr.kaochiahung@gmail.com

List of abbreviations

FM: Fibromyalgia; HR: hazard ratio; CI: confidence interval; ICD-9-CM:

International Classification of Diseases, Ninth Revision, Clinical Modification; NHI:

National Health Insurance; LHID: Longitudinal Health Insurance Database

2

Abstract

Objective: Fibromyalgia (FM) and migraine are common pain disorders that tend to coexist. This study determined whether these two conditions exhibited any mutual influences.

Setting: Cohort study

Participants: A retrospective, longitudinal cohort study was conducted using data obtained from a nationwide health care database. This study had two arms. Arm 1 comprised 33,216 patients with FM, and Arm 2 consisted of 7420 patients with migraine; all of these patients were diagnosed between 2000 and 2010. Using the aforementioned database, control subjects who had neither FM nor migraine and were matched with the FM and migraine patients by sex, age, and index date of diagnosis were recruited. Each control cohort was four times the size of the corresponding study cohort. Follow-up for the control and study cohorts was conducted until the end of 2011.

Results: The incidence rates of FM and migraine were calculated in Arms 1 and 2, respectively. The overall incidence of migraine was greater in the FM cohort than in the corresponding control cohort [4.39 vs. 2.07 per 1000 person-years; crude hazard ratio (HR) = 2.12, 95% confidence interval (CI) = 1.96–2.30; adjusted HR (aHR) = 1.89, 95% CI = 1.75–2.05]. After adjustment for sex, age, and comorbidities, the

overall incidence of FM in the migraine cohort was 1.57 times greater than that in the

corresponding control cohort (7.01 vs. 4.49 per 1000 person-years; aHR = 1.52, 95%

CI = 1.39−1.65).

Conclusions: The present study revealed a bidirectional link between FM and

migraine.

Keywords: fibromyalgia, migraine, bidirectional analysis, retrospective cohort

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Strengths and limitations of this study

1. Our study contained a large sample size because of its population-based design.

2. We based our study solely on information from diagnoses in patient files and included no information on patients whose cases were unidentified.

3. This study was naturally highly prone to observational bias because patients with migraine and those with FM are generally more likely to seek medical attention for other conditions than are those with neither.

4. Health claims information in the Longitudinal Health Insurance Database mainly comprises documentation on diseases recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification but lacks descriptions of clinical subsets for disease manifestation or progression such as episodic or chronic migraine and migraine with or without aura.

5. The selection process of two study cohorts and two control cohorts was based solely on inclusion and exclusion criteria and did not involve subjective patient omission.

5

Introduction

A major symptom of fibromyalgia (FM) is headache. Migraine is a type of headaches, and some migraines are severe enough to be debilitating. Notably, similarities have been observed between migraines and FM, and many instances of overlapping symptoms, causes, and treatments were noted in the present study, where the two conditions were considered in the same context [1]. Several studies have reported that high proportions (20%–36%) of patients with migraine also have FM [2-5]. Similarly, the frequency of migraine occurrence in patients with FM is 45%–80%, suggesting that migraine is common in patients with FM [6, 7]. Despite reports that the prevalence of FM is higher among migraine patients and vice versa [8-13], no explanations have been provided for this high rate of co-occurrence.

Migraine is a complex, recurrent disorder that manifests as a throbbing headache and is frequently associated with nausea, allodynia, and sensitivity to sound or light. Migraines may develop into a chronic condition or disability [14, 15]. Migraine pain is believed to be caused by the nociceptive activation of the trigeminovascular system, including sensory neurons from the trigeminal ganglion and upper cervical nerve roots, which modulate central signals to numerous subcortical sites [16]. The combination of tonic nociceptive input and central disinhibition may also play a role in the development of FM. Many migraineurs experience a condition referred to as

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"allodynia" during migraine attacks. Typically, allodynia is confined to the head and neck but may involve other areas of the body [17]. Increasing evidence indicates that peripheral tissues are relevant contributors to painful impulse input and can initiate or maintain central sensitization, thereby contributing to the progression of FM [18]. Migraine is believed to trigger FM. Repeated headaches in patients with migraine may increase the neuronal response to both nociceptive and nonnociceptive stimulation and induce spontaneous neuronal activity, which may concurrently increase patient sensitivity to FM [19]. Several studies have highlighted the role of the hypothalamus in migraines [17]. Evidence indicates the direct and indirect anatomical connections of the hypothalamus to the thalamus and autonomic brainstem nuclei, thereby supporting the role of the hypothalamus in nociceptive and autonomic modulation in patients with migraine [20]. However, brain mechanisms common in patients with FM result in the central sensitization of pain neurons, leading to the evolution of a complex syndrome [21].

Early in the course of FM, widespread musculoskeletal pain often appears in the neck or shoulder region [22]. Neck pain may activate local nociceptors and transmit pain impulses through upper cervical spinal nerves such as the greater occipital nerve to the trigeminal nucleus caudalis, thereby inducing a migraine attack [23]. Some experts believe that FM and migraine headaches both involve defects in the systems

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that regulate certain chemical messengers in the brain, including serotonin and epinephrine (adrenaline) [1]. These defects may be reflected in the similar psychological comorbidities of the two conditions, including depression, anxiety, interpersonal sensitivity, and somatization [9]. Psychosocial distress or abnormalities commonly occur in patients with migraine and those with FM.

Although studies have reported high comorbidity rates for migraine and FM, the following crucial concerns must be addressed. (1) Most such studies were conducted at tertiary care centers. Patients are often referred to tertiary clinics when they present with extreme pain, disability, or medication overuse. Therefore, such sample populations may differ from patients treated in general practice. (2) Most such studies used a cross-sectional design to investigate prevalence rather than incidence of migraine or FM. (3) Whether a significant association exists, suggesting that people with migraine are more likely to develop FM than the general population or vice versa, remains unknown. Therefore, our population-based longitudinal cohort was employed to investigate the link between migraine and FM.

Methods

Patient and public involvement

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Data for this research were obtained from the Longitudinal Health Insurance Database (LHID). The LHID comprises data of insurance claims filed by 1 million patients under Taiwan's National Health Insurance (NHI) program, which covers 99% of Taiwan's 23 million citizens with single-payer health insurance. According to a government report, no differences between the LHID and Taiwan's NHI program exist with respect to demographic characteristics. The health claims information in the LHID includes general patient information (e.g., birthdate, sex, occupation), documentation of diseases [recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)], and other data related to medical services.

Data availability statement

The dataset used in this study was obtained from Taiwan's Ministry of Health and Welfare (MOHW), from which we were required to obtain approval to access the data. Any researcher interested in accessing this dataset can submit an application form to the MOHW requesting access. Please contact the staff of the MOHW (email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan MOHW Address: No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (ROC). Phone: +886-2-8590-6848. All relevant data are provided in this manuscript.

Ethics statement

The NHI Research Databank encrypts patients' personal information to protect

privacy and provides researchers with anonymous identification numbers associated

with relevant claims information, including sex, birthdate, medical services received,

and prescriptions. Therefore, patient consent is not required to access the NHI

Research Databank. This study was approved for exemption by the Institutional

Review Board of China Medical University (CMUH104-REC2-115-CR3). In

addition, the Institutional Review Board waived the requirement for patient consent.

Study cohorts

A bidirectional cohort study design was used to interpret the longitudinal

association between FM and migraine.

Figure 1 displays the procedure for establishing the two arms of this study. For

Arm 1, we identified patients with FM (ICD-9-CM code 729.1) aged ≥20 years and

newly diagnosed ≥3 times consecutively within 3 months from 2000–2010. The first

diagnosis date was designated as the index date for entry into the FM cohort. Patients

with a history of migraine (ICD-9-CM code 346) were excluded from this arm. For

each patient with FM, we randomly selected four individuals without FM or migraine

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from the population of the LHID2000 who were frequency-matched by sex, age (in 5-year increments), and entry date of the patient with FM; these subjects were recruited into the non-FM (control) cohort.

A similar procedure was used for Arm 2 to establish a cohort of patients with migraine who had no history of FM, were aged ≥20 years, and were newly diagnosed ≥3 times consecutively within 3 months from 2000–2010.

Subjects in both arms were followed until diagnosis of migraine or FM, withdrawal from the NHI program, death, or December 31, 2011. The patients in the two cohorts presented with some baseline comorbidities: diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2, 296.3, 296.5, 300.4, 309, and 311), anxiety (ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 309.81), sleep disorder (ICD-9-CM codes 307.4 and 780.5), coronary artery disease (CAD; ICD-9-CM codes 410–414), chronic fatigue syndrome (CFS; ICD-9-CM code 780.71), and irritable bowel syndrome (IBS; ICD-9-CM code 564.1).

Statistical analyses

The characteristics of the study cohorts are expressed as means and corresponding standard deviations for age and as numbers and percentages for sex and

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comorbidities. Age difference was assessed using a t test, and sex and comorbidity

distributions were tested using a chi-square test. The incidence density for each cohort

was calculated as the total event number divided by the sum of follow-ups [per 1000

person-years (PY)]. The cumulative incidence curve for each cohort was measured

using the Kaplan–Meier method, and the curve difference was calculated using the

log-rank test. To determine the risks of migraine and FM in Arms 1 and 2,

respectively, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs)

were estimated using single-variable and multivariable Cox proportional hazard

models. Data management and all statistical analyses were performed using SAS for

Windows (Version 9.4, SAS Institute, Cary, NC, USA), and incidence curves was

plotted using R software. All significance levels were set as two-sided p < 0.05.

Results

Table 1 presents the demographic characteristics of the FM and non-FM cohorts.

The age- and sex-matched cohorts exhibited differences in comorbidity distribution.

The prevalence of comorbidities was significantly higher in the FM cohort than in the

non-FM cohort (p < 0.001).

Table 2 indicates that the migraine incidences were 4.39 and 2.07 per 1000 PY in

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the FM and non-FM cohorts, respectively. Figure 2 reveals a higher incidence curve

for the FM cohort than for the non-FM cohort (log-rank test = 371.4, p < 0.001). After

adjustment for age, sex, and comorbidities, the patients with FM exhibited a

1.89-times higher risk of migraine compared with the non-FM subjects (HR = 1.89,

95% CI = 1.75–2.05). Among women, the relative risk of migraine was 1.76-times

higher in patients with FM compared with non-FM subjects (HR = 1.76, 95% CI

1.60–1.93), whereas among men, the risk was 2.29-times higher in patients with FM

than in non-FM subjects (HR = 2.29, 95% CI = 1.97–2.67). Regarding age, the HRs

for migraine in the FM cohort were 2.06 (95% CI = 1.85–2.29), 1.66 (95% CI =

1.43–1.92), and 1.69 (95% CI = 1.39–2.05) for ≤50, 51–65, and ≥65 years,

respectively.

Table 3 presents the influence of factors associated with migraine occurrence in

the FM cohort. Male sex, hyperlipidemia, depression, anxiety, sleep disorder, CAD,

CFS, and IBS were all associated with higher risk of migraine (all p < 0.05).

Table 4 lists the comorbidities as well as the age- and sex-matched comparisons

in the migraine cohort, which exhibited a higher prevalence of comorbidities than did

the nonmigraine cohort.

Table 5 and Figure 3 reveal that the incidence of FM was significantly higher in

patients with migraine than in those without (7.01 vs. 4.49 per 1000 PY; log-rank test

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= 116.7, p < 0.001). After adjustment for age, sex, and comorbidities, patients with

migraine exhibited a 1.52-times higher risk of FM compared with those without

migraine (HR = 1.52, 95% CI = 1.39–1.65). Among female patients, those with

migraine exhibited a 1.43-times higher risk of FM compared with nonmigraine

subjects (HR = 1.43, 95% CI = 1.29–1.59), whereas among male patients, those with

migraine exhibited a 1.78-times higher risk of FM compared with nonmigraine

subjects (95% CI = 1.50–2.11). Regarding age, the HRs for FM were 1.64 (95% CI =

1.46–1.84), 1.30 (95% CI = 1.09–1.53), and 1.28 (95% CI = 1.03–1.58) in patients

with migraine aged <50, 50–64, and ≥65 years, respectively.

Table 6 presents the associations of sex, age, and comorbidities with risk of FM.

The variables, including age, migraine, hypertension, hyperlipidemia, depression,

sleep disorder, and CAD, were all associated with lower risk of FM.

Discussion

The results of comparing the two cohort arms suggested a bidirectional risk of

migraine and FM in patients with FM and those with migraine, respectively. The

analysis of Arm 1 revealed incidence rates for migraine of 4.39 and 2.07 per 1000 PY

in patients with and without FM, respectively [adjusted HR (aHR) = 1.89, 95% CI =

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1.75–2.05 in patients with FM]. The analysis of Arm 2 revealed incidence rates for FM of 7.01 and 4.49 per 1000 PY in patients with and without migraine, respectively (aHR = 1.52, 95% CI = 1.39–1.65 in patients with migraine). These results indicated that FM had stronger predictive power for the onset of migraine than did migraine for the onset of FM.

The Kaplan–Meier plots demonstrated that incidence of migraine in the FM cohort and that of FM in the migraine cohort increased steadily during the 12-year follow-up period. Moreover, similar patterns were observed in the two corresponding comparison cohorts. The cumulative incidence measured by the Kaplan–Meier plots revealed greater risk of migraine among patients with FM than risk of FM among patients with migraine.

Our predictive analytics have the potential to guide diagnosis and treatment. For example, a subsequent diagnosis of FM may result from failure of antimigraine treatment to alleviate fatigue [24]. Because migraine is often more effectively managed than FM, the authors hypothesized that patients with FM are more likely to be treated for migraine than are patients with migraine to be treated for FM. Therefore, clinical trials of patients with migraine in the future have the potential to evaluate the effects of FM on health outcomes and the efficacy of FM treatment [10].

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Cohort analysis for the association between FM and risk of new-onset migraine

This study revealed a positive association between FM diagnosis and the risk of

migraine. Adjusting for hypertension, CAD, and CFS had no strong influence on this

association. However, sex, age (particularly in patients aged less than 49 years),

diabetes, hyperlipidemia, depression, anxiety, sleep disorder, and IBS continued to

demonstrate statistically significant effects.

Because "high frequency and chronic migraine increase sensitivity to pain

in fibromyalgia (FM) patients [25], such heightened pain sensitivity may be

attenuated by comorbid diabetes. There is also a documented report showing a

significant positive association between migraine frequency and intensity with

total and [low-density lipoprotein] cholesterol, independent of diet and lifestyle

[26]." Several hypotheses have been proposed to explain the development of

chronic widespread pain and episodic throbbing or pulsating pain across the head

and neck regions as possible effects of comorbidities such as depression and

anxiety. Depression and anxiety disorders have been identified as crucial

secondary symptoms of FM [11, 27, 28]. The pain associated with FM may

initiate the development of mood disorders as a result of stress imposed on the

body. Furthermore, according to multiple evidence-based studies, depression and

anxiety may induce the onset or present as a prodrome of migraine [29, 30].

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Research has indicated that serotonin levels might be related to interconnections between anxiety and migraine [31]. A lower level of serotonin may be central to the dysregulation of descending antinociceptive systems, leading to FM and migraine [31, 32].

Poor sleep quality or sleep deprivation in healthy individuals can induce symptoms of FM [33], suggesting that sleep abnormalities may be a pathological characteristic of FM rather than merely a result of pain [34]. Relevant literature has reported the advantages of targeting sleep conditions to relieve the symptoms of migraine [35]. As the prevalence of sleep disorders increases in both patients with FM and those with migraine, appreciation of the strong links between FM and migraine also increases.

IBS frequently coexists with both FM and migraine [36, 37]; however, the underlying mechanisms for the association of FM with increased risks of IBS and migraine are unclear. FM, migraine, and IBS may be distinct manifestations of a common pathophysiological process affecting the gastrointestinal tract. These disorders are referred to as "central sensitivity syndrome" and are mutually associated [38]. A growing amount of evidence indicates that central sensitization phenomena play a role in the pathogenesis of FM and that of migraine. Central sensitization at the levels of the spinal dorsal horn and trigeminal nucleus may also be involved in the

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progression of migraine attacks, and prolonged nociceptive inputs may result in the maintenance of supraspinal sensitization and central neuroplastic changes, causing episodic headaches to become chronic [39]. Notably, increased intestinal permeability may be observed in IBS [40]. Altered intestinal permeability with overgrowth of intestinal bacteria may trigger the development of FM [41] and that of migraine [42]. The microbiome–gut–brain axis—a bidirectional communication route of the central and enteric nervous systems with microbiome through the neural, humoral, endocrine, and immune pathways [36, 37, 43]—has been proposed as a multifaceted pathophysiological mechanism underlying IBS [43], FM [44, 45], and migraine [42, 46]. In addition, mutual interaction has been established between gut microbiota and the central, autonomic, and enteric nervous systems through the hypothalamic–pituitary–adrenal axis [43].

Cohort analysis for the association between migraine and risk of new-onset FM

This study revealed higher risk of FM in patients with migraine than in those without in every factor-based subset of the cohorts. Notably, patients with hyperlipidemia had higher risk of FM. Moreover, adverse lipid profiles occurred more frequently in patients with migraine who had a higher body mass index [47, 48]. Although lack of exercise may precipitate the development of an adverse lipid profile,

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exercise may trigger acute migraine attacks [49], and some patients may avoid

exercise to prevent migraines. This hypothesis could be supported by the results of

one study that revealed that patients with headache had lower aerobic endurance and

flexibility than did healthy controls [50]. Aerobic exercise could relieve depression

and anxiety and prevent the negative effects of stress [51]. Furthermore, avoiding

exercise may exacerbate mood distress, and thus could be related to the development

of FM.

Increased migraine frequency as a result of migraines becoming chronic

intensifies the sensitivity to pain in somatic areas outside of the cephalic region and

may predispose patients to FM [6]. Hypothalamic neuroendocrine dysfunction has

been proposed as a brain mechanism common to both FM and migraine [52]. Both

conditions also share the mechanism of central sensitization of pain neurons.

Magnesium, which is often used as an agent for relieving migraine headaches, is also

beneficial for treating FM. Low magnesium levels can exacerbate symptoms of FM

and are also implicated in migraines [53]. Researchers have discovered that people

who do not respond to standard migraine treatments often also have FM [17].

Considering the high comorbidity rates of migraine and FM, many professionals

assume that the central nervous system is responsible for pain-processing

abnormalities, including central sensitization and inadequate pain inhibition alongside

repeated headache episodes. Moreover, tonic peripheral nociceptive input is associated with augmented windup in response to neurotransmitters, immunomodulation, vascular changes, and hormone influence, which may increase the risk of FM [1, 6, 36, 37, 43, 52].

Our study contained a large sample because of our population-based design. Moreover, we were careful to minimize selection bias during analysis, and our ample documentation of medical profiles allowed for minimal effects from confounding factors among the subjects. However, this study had limitations. We based our study solely on information from diagnoses in patient files and included no information from patients whose cases were unidentified. Poor categorization of a patient's symptoms may have affected the discernibility between migraine and FM. Because many crucial variables are not retrievable and various methods are used to diagnose FM and the numerous subtypes of migraines, our data provides merely a glimpse of these two conditions. Furthermore, assessing treatment responses in our large database analysis was impossible, rendering the identification of "diagnosis by exclusion" difficult in this study. Future studies are recommended to further delineate "diagnosis by exclusion." Furthermore, this study did not consider the severity of FM and migraines in patients; therefore, no definitive statement can be made regarding the intensity of FM and subsequent risk of developing migraine conditions, or vice

versa. Moreover, this study was naturally highly prone to observational bias because patients with migraine and those with FM are generally more likely to seek medical attention for other conditions than are those with neither.

Conclusion

This study was the first to reveal a population-based bidirectional association between onset of FM and that of migraine in patients with migraine and those with FM, respectively. The risk of migraine was reportedly greater than that of FM. The incidence rates of FM in the migraine cohort and migraine in the FM cohort increased with age in both directions. However, the HRs relative to the corresponding comparison cohorts were attenuated with increases in age.

Author contributions:

Conceptualization: I-Wen Penn, Chia-Hung Kao.

Methodology: Cheng-Li Lin, Chia-Hung Kao.

Software: Cheng-Li Lin, Chia-Hung Kao.

Validation: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin, Chia-Hung Kao.

Formal analysis: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin,

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Chia-Hung Kao.

Investigation: Cheng-Li Lin, Chia-Hung Kao.

Resources: Cheng-Li Lin, Chia-Hung Kao.

Data curation: IWP, EC, TYC, CLL, CHK.

Writing (original draft preparation): I-Wen Penn, Eric Chuang, Tien-Yow Chuang,

Cheng-Li Lin, Chia-Hung Kao.

Writing (review and editing): I-Wen Penn, Eric Chuang, Tien-Yow Chuang,

Cheng-Li Lin, Chia-Hung Kao.

Visualization: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin,

Chia-Hung Kao.

Supervision: Chia-Hung Kao.

Project administration: Chia-Hung Kao.

Funding acquisition: Chia-Hung Kao.

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Conflicts of Interest

All authors report no conflicts of interest.

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Figure Legends:

Figure 1. Flow chart illustrating the selection of study subjects.

Figure 2. Comparison of cumulative incidence of migraine between patients with and

without fibromyalgia using the Kaplan–Meier method.

Figure 3. Comparison of the cumulative incidence of fibromyalgia between patients

with and without migraine using the Kaplan–Meier method.

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Table 1. Demographic characteristics and comorbidities in patients with and without fibromyalgia.

| Variable | Fibromyalgia | | |
	No N =132863	Yes N =33216	*p*-value
Sex	n(%)	n(%)	0.99
Female	71880(54.1)	17970(54.1)	
Male	60983(45.9)	15246(45.9)	
Age, mean(SD)	50.9(16.9)	51.4(16.7)	<0.001#
Stratify age			0.99
≤49	64292(48.4)	10673(48.4)	
50-65	36820(27.7)	9205(27.7)	
65+	31751(23.9)	7938(23.9)	
Comorbidity			
Diabetes	10485(7.89)	3193(9.61)	<0.001
Hypertension	37284(28.1)	11287(34.0)	<0.001
Hyperlipidemia	22446(16.9)	7301(22.0)	<0.001
Depression	4690(3.53)	1804(5.43)	<0.001
Anxiety	10494(7.90)	4214(12.7)	<0.001
Sleep disorder	21095(15.9)	8121(24.5)	<0.001
CAD	17918(13.5)	5821(17.5)	<0.001
Chronic fatigue syndrome	199(0.15)	93(0.28)	<0.001
Irritable bowel syndrome	5125(3.86)	1870(5.63)	<0.001

Chi-square test; #: two-sample t test

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Table 2. Comparison of the incidence and hazard ratios of migraine stratified by sex and age between patients with and without fibromyalgia.

Variable	Without fibromyalgia					With fibromyalgia				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	1810	876077	2.07	1(Reference)	1(Reference)	954	217386	4.39	2.12(1.96, 2.30)***	1.89(1.75, 2.05)***
Sex										
Female	1373	487506	2.82	1(Reference)	1(Reference)	669	120773	5.54	1.97(1.79, 2.16)***	1.76(1.60, 1.93)***
Male	437	388571	1.12	1(Reference)	1(Reference)	285	96613	2.95	2.62(2.26, 3.05)***	2.29(1.97, 2.67)***
Stratify age										
≤50	922	444710	2.07	1(Reference)	1(Reference)	548	110557	4.96	2.39(2.15, 2.66)***	2.06(1.85, 2.29)***
50-65	564	245579	2.30	1(Reference)	1(Reference)	258	60603	4.26	1.85(1.60, 2.15)***	1.66(1.43, 1.92)***
65+	324	185788	1.74	1(Reference)	1(Reference)	148	46226	3.20	1.83(1.51, 2.23)***	1.69(1.39, 2.05)***
Comorbidity[‡]										
No	774	508879	1.52	1(Reference)	1(Reference)	311	95605	3.25	2.14(1.88, 2.44)***	2.13(1.87, 2.43)***
Yes	1036	367197	2.82	1(Reference)	1(Reference)	643	121780	5.28	1.88(1.71, 2.08)***	1.80(1.63, 1.98)***

Rate[#]: incidence rate per 1000 person-years; crude HR: crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, and irritable bowel syndrome

***p < 0.001

Comorbidity[‡]: patients with any of the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, or irritable bowel syndrome were classified as the comorbidity group

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Table 3. Cox model with hazard ratios and 95% confidence intervals for migraine associated with fibromyalgia and covariates.

Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Fibromyalgia	2.12	(1.96, 2.30)***	1.89	(1.74, 2.04)***
Sex(Women vs. Men)	2.28	(2.09, 2.48)***	2.08	(1.91, 2.27)***
Age, years	1.00	(0.99, 1.00)**	0.99	(0.99, 1.00)***
Baseline comorbidities (yes vs. no)				
Diabetes	0.82	(0.70, 0.96)*	0.73	(0.61, 0.860)***
Hypertension	1.06	(0.97, 1.15)	-	-
Hyperlipidemia	1.30	(1.19, 1.43)***	1.14	(1.03, 1.27)*
Depression	2.37	(2.06, 2.72)***	1.20	(1.03, 1.39)*
Anxiety	2.68	(2.44, 2.95)***	1.64	(1.47, 1.84)***
Sleep disorder	2.63	(2.43, 2.85)***	1.97	(1.80, 2.15)***
CAD	1.30	(1.18, 1.44)***	1.10	(0.98, 1.23)
Chronic fatigue syndrome	2.24	(1.01, 4.99)*	1.45	(0.65, 3.22)
Irritable bowel syndrome	1.98	(1.71, 2.29)***	1.36	(1.17, 1.58)***

Crude HR: crude hazard ratio; adjusted†: multivariable analysis including sex, age, and the comorbidities of diabetes, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, and irritable bowel syndrome

*p < 0.05, **p < 0.01, and ***p < 0.001

Table 4. Demographic characteristics and comorbidities in patients with and without migraine.

| Variable | migraine | | *p*-value |
	No N =69680	Yes N =17420	
Sex	n(%)	n(%)	0.99
Female	51176(73.4)	12794(73.4)	
Male	18504(26.6)	4626(26.6)	
Age, mean(SD)	44.2(15.6)	44.5(15.3)	0.04[#]
Stratify age			0.99
≤49	46768(67.1)	11692(67.1)	
50-65	14940(21.4)	3735(21.4)	
65+	7972(11.4)	1993(11.4)	
Comorbidity			
Diabetes	3567(5.12)	975(5.60)	0.01
Hypertension	12563(18.0)	4551(26.1)	<0.001
Hyperlipidemia	8278(11.9)	3187(18.3)	<0.001
Depression	2019(2.90)	1851(10.6)	<0.001
Anxiety	4366(6.27)	3724(21.4)	<0.001
Sleep disorder	9469(13.6)	6976(40.1)	<0.001
CAD	5560(7.98)	2449(14.1)	<0.001
Chronic fatigue syndrome	71(0.10)	41(0.24)	<0.001
Irritable bowel syndrome	2106(3.02)	1224(7.03)	<0.001

Chi-square test; [#]: two-sample t test

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Table 5. Comparison of the incidence and hazard ratios of fibromyalgia stratified by sex and age between patients with and without migraine.

	Without migraine					With migraine				
Variable	Event	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)	Event	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
All	2034	453130	4.49	1(Reference)	1(Reference)	800	114070	7.01	1.57(1.44, 1.70)***	1.52(1.39, 1.65)***
Sex										
Female	1556	335328	4.64	1(Reference)	1(Reference)	568	84606	6.71	1.45(1.32, 1.60)***	1.43(1.29, 1.59)***
Male	478	117802	4.06	1(Reference)	1(Reference)	232	29464	7.87	1.94(1.66, 2.27)***	1.78(1.50, 2.11)***
Stratify age										
≤50	1060	310621	3.41	1(Reference)	1(Reference)	470	78131	6.02	1.77(1.58, 1.97)***	1.64(1.46, 1.84)***
50-65	608	96607	6.29	1(Reference)	1(Reference)	207	24189	8.56	1.36(1.16, 1.59)***	1.30(1.09, 1.53)**
65+	366	45902	7.97	1(Reference)	1(Reference)	123	11751	10.5	1.32(1.07, 1.61)**	1.28(1.03, 1.58)*
Comorbidity‡										
No	1082	309229	3.50	1(Reference)	1(Reference)	255	43664	5.84	1.67(1.46, 1.92)***	1.79(1.56, 2.06)***
Yes	952	143901	6.62	1(Reference)	1(Reference)	545	70406	7.74	1.18(1.06, 1.31)**	1.29(1.16, 1.44)***

Rate#: incidence rate per 1000 person-years; crude HR: crude hazard ratio

Adjusted HR†: multivariable analysis including sex, age, and the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, and irritable bowel syndrome
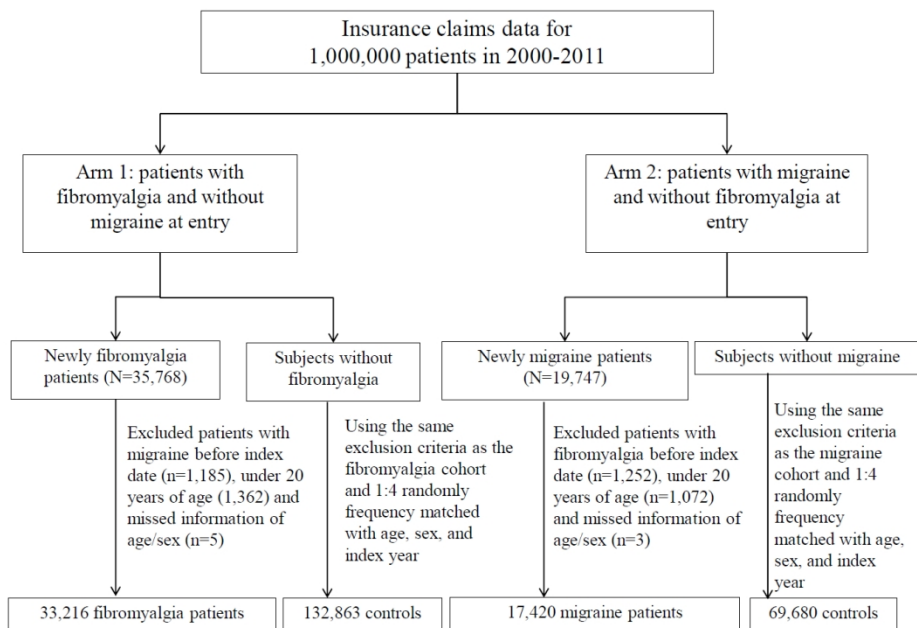
*p < 0.05, **p < 0.01, and ***p < 0.001

Comorbidity‡: patients with any of the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, or irritable bowel syndrome were classified as the comorbidity group
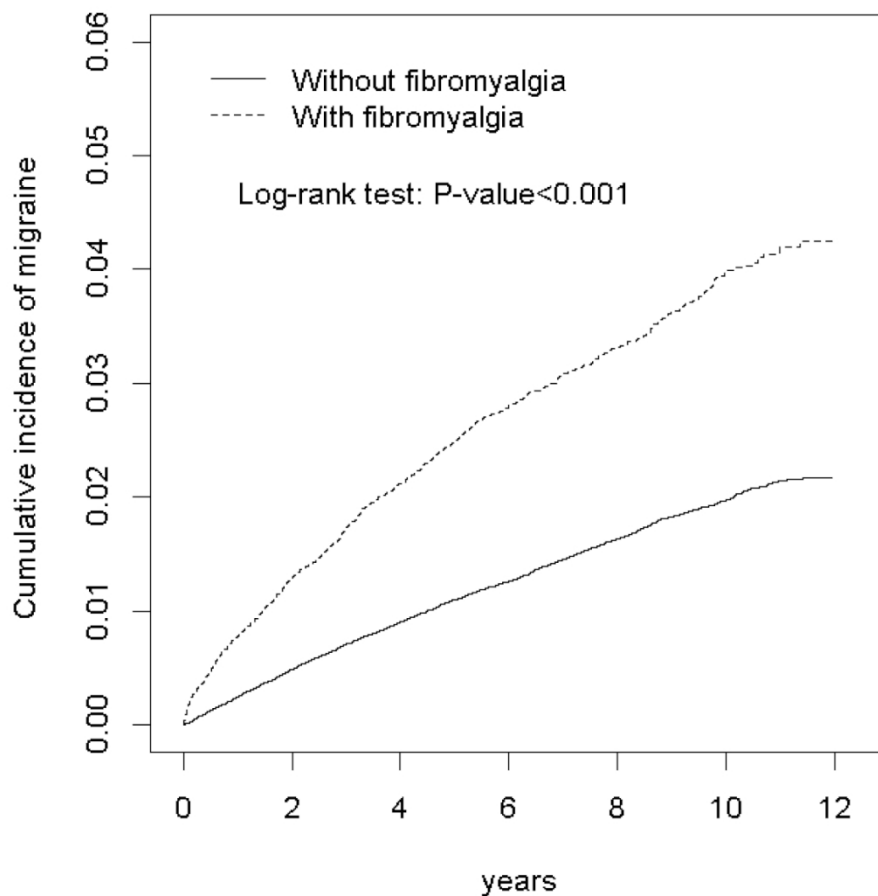
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Table 6. Cox model with hazard ratios and 95% confidence intervals for fibromyalgia associated with migraine and covariates.

Variable	Crude		Adjusted[†]	
	HR	(95% CI)	HR	(95% CI)
Migraine	1.57	(1.44, 1.70)***	1.51	(1.38, 1.65)***
Sex(Women vs. Men)	1.05	(0.97, 1.15)	-	-
Age, years	1.02	(1.02, 1.03)***	1.02	(1.01, 1.02)***
Baseline comorbidities (yes vs. no)				
Diabetes	1.58	(1.36, 1.82)***	0.99	(0.85, 1.16)
Hypertension	1.81	(1.67, 1.96)***	1.10	(0.99, 1.22)
Hyperlipidemia	1.69	(1.54, 1.85)***	1.15	(1.03, 1.28)*
Depression	1.38	(1.17, 1.63)***	1.06	(0.89, 1.26)
Anxiety	1.34	(1.19, 1.51)***	0.92	(0.80, 1.05)
Sleep disorder	1.45	(1.33, 1.58)***	1.09	(0.98, 1.20)
CAD	1.74	(1.57, 1.94)***	1.01	(0.89, 1.14)
Chronic fatigue syndrome	2.11	(0.79, 5.62)	-	-
Irritable bowel syndrome	1.28	(1.06, 1.53)**	0.94	(0.78, 1.13)

Crude HR: crude hazard ratio; adjusted[†]: multivariable analysis including age and the comorbidities of diabetes, hypertension, hyperlipidemia, anxiety, sleep disorders, stroke, and peptic ulcer disease, and use of nonsteroidal anti-inflammatory drugs

$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

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Insurance claims data for
1,000,000 patients in 2000-2011

Arm 1: patients with fibromyalgia and without migraine at entry

Arm 2: patients with migraine and without fibromyalgia at entry

Newly fibromyalgia patients (N=35,768)

Subjects without fibromyalgia

Newly migraine patients (N=19,747)

Subjects without migraine

Excluded patients with migraine before index date (n=1,185), under 20 years of age (1,362) and missed information of age/sex (n=5)

Using the same exclusion criteria as the fibromyalgia cohort and 1:4 randomly frequency matched with age, sex, and index year

Excluded patients with fibromyalgia before index date (n=1,252), under 20 years of age (n=1,072) and missed information of age/sex (n=3)

Using the same exclusion criteria as the migraine cohort and 1:4 randomly frequency matched with age, sex, and index year

33,216 fibromyalgia patients

132,863 controls

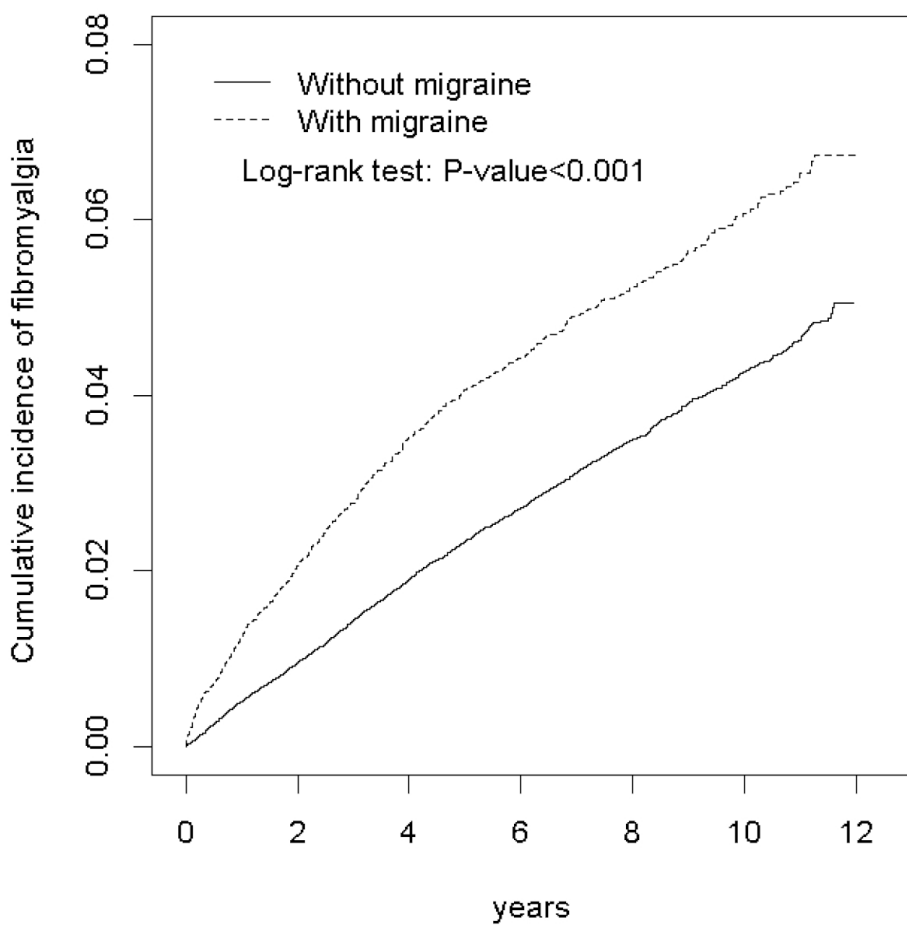17,420 migraine patients

69,680 controls

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8-10
Objectives	3	State specific objectives, including any pre-specified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	11-14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11-14
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	11-14
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	11-14
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	11-14
		Case-control study—For matched studies, give matching criteria and the number of controls per case	11-14
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-14
Bias	9	Describe any efforts to address potential sources of bias	11-14
Study size	10	Explain how the study size was arrived at	11-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-14
		(*b*) Describe any methods used to examine subgroups and interactions	11-14

		(c) Explain how missing data were addressed	11-14
		(d) *Cohort study*—If applicable, explain how loss to follow-up was addressed	11-14
		Case-control study—If applicable, explain how matching of cases and controls was addressed	11-14
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	11-14
		(e) Describe any sensitivity analyses	11-14
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study— eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	15,16
		(b) Give reasons for non-participation at each stage	15,16
		(c) Consider use of a flow diagram	15,16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15,16
		(b) Indicate number of participants with missing data for each variable of interest	15,16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	15,16
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15,16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	15,16
		Cross-sectional study—Report numbers of outcome events or summary measures	15,16
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15,16
		(b) Report category boundaries when continuous variables were categorized	15,16
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15,16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2, 3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Bidirectional Association between Migraine and Fibromyalgia: Retrospective Cohort Analyses of Two Populations

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Manuscripts

Bidirectional Association between Migraine and Fibromyalgia: Retrospective Cohort Analyses of Two Populations

Running title: Bidirectional Association between Fibromyalgia and Migraine

I-Wen Penn[1,2], Eric Chuang[3], Tien-Yow Chuang[4], Cheng-Li Lin[5,6], Chia-Hung Kao[7,8,9]

[1]School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan

[2]Department of Physical Medicine and Rehabilitation, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan

[3]UC Berkeley Mishler Lab Undergraduate Researcher, Intended B.S. Molecular and Cell Biology, University of CA, Berkeley, USA

[4]Department of Physical Medicine and Rehabilitation, Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan

[5]Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan

[6]College of Medicine, China Medical University, Taichung, Taiwan

[7]Graduate Institute of Biomedical Sciences and School of Medicine, College of Medicine, China Medical University, Taichung, Taiwan

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8Department of Nuclear Medicine and PET Center, China Medical University

Hospital, Taichung, Taiwan

9Department of Bioinformatics and Medical Engineering, Asia University, Taichung,

Taiwan.

*Corresponding author: Chia-Hung Kao, MD, Graduate Institute of Biomedical

Sciences and School of Medicine, College of Medicine, China Medical University,

No. 2, Yuh-Der Road, Taichung 404, Taiwan. E-mail: d10040@mail.cmuh.org.tw;

dr.kaochiahung@gmail.com

List of abbreviations

FM: Fibromyalgia; HR: hazard ratio; CI: confidence interval; ICD-9-CM:

International Classification of Diseases, Ninth Revision, Clinical Modification; NHI:

National Health Insurance; LHID: Longitudinal Health Insurance Database

2

Abstract

Objective: Fibromyalgia (FM) and migraine are common pain disorders that tend to coexist. This study determined whether these two conditions exhibited any mutual influences.

Setting: Cohort study

Participants: A retrospective, longitudinal cohort study was conducted using data obtained from a nationwide health care database. This study had two arms. Arm 1 comprised 33,216 patients with FM, and Arm 2 consisted of 7420 patients with migraine; all of these patients were diagnosed between 2000 and 2010. Using the aforementioned database, control subjects who had neither FM nor migraine and were matched with the FM and migraine patients by sex, age, and index date of diagnosis were recruited. Each control cohort was four times the size of the corresponding study cohort. Follow-up for the control and study cohorts was conducted until the end of 2011.

Results: The incidence rates of FM and migraine were calculated in Arms 1 and 2, respectively. The overall incidence of migraine was greater in the FM cohort than in the corresponding control cohort [4.39 vs. 2.07 per 1000 person-years; crude hazard ratio (HR) = 2.12, 95% confidence interval (CI) = 1.96–2.30; adjusted HR (aHR) = 1.89, 95% CI = 1.75–2.05]. After adjustment for sex, age, and comorbidities, the

overall incidence of FM in the migraine cohort was 1.57 times greater than that in the

corresponding control cohort (7.01 vs. 4.49 per 1000 person-years; aHR = 1.52, 95%

CI = 1.39−1.65).

Conclusions: The present study revealed a bidirectional link between FM and

migraine.

Keywords: fibromyalgia, migraine, bidirectional analysis, retrospective cohort

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Strengths and limitations of this study

1. Our study contained a large sample size because of its population-based design.

2. We based our study solely on information from diagnoses in patient files and included no information on patients whose cases were unidentified.

3. This study was naturally highly prone to observational bias because patients with migraine and those with FM are generally more likely to seek medical attention for other conditions than are those with neither.

4. Health claims information in the Longitudinal Health Insurance Database mainly comprises documentation on diseases recorded according to the International Classification of Diseases, Ninth Revision, Clinical Modification but lacks descriptions of clinical subsets for disease manifestation or progression such as episodic or chronic migraine and migraine with or without aura.

5. The selection process of two study cohorts and two control cohorts was based solely on inclusion and exclusion criteria and did not involve subjective patient omission.

5

Introduction

A major symptom of fibromyalgia (FM) is headache. Migraine is a type of headaches, and some migraines are severe enough to be debilitating. Notably, similarities have been observed between migraines and FM, and many instances of overlapping symptoms, causes, and treatments were noted in the present study, where the two conditions were considered in the same context [1]. Several studies have reported that high proportions (20%–36%) of patients with migraine also have FM [2-5]. Similarly, the frequency of migraine occurrence in patients with FM is 45%–80%, suggesting that migraine is common in patients with FM [6, 7]. Despite reports that the prevalence of FM is higher among migraine patients and vice versa [8-13], no explanations have been provided for this high rate of co-occurrence.

Migraine is a complex, recurrent disorder that manifests as a throbbing headache and is frequently associated with nausea, allodynia, and sensitivity to sound or light. Migraines may develop into a chronic condition or disability [14, 15]. Migraine pain is believed to be caused by the nociceptive activation of the trigeminovascular system, including sensory neurons from the trigeminal ganglion and upper cervical nerve roots, which modulate central signals to numerous subcortical sites [16]. The combination of tonic nociceptive input and central disinhibition may also play a role in the development of FM. Many migraineurs experience a condition referred to as

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"allodynia" during migraine attacks. Typically, allodynia is confined to the head and

neck but may involve other areas of the body [17]. Increasing evidence indicates that

peripheral tissues are relevant contributors to painful impulse input and can initiate or

maintain central sensitization, thereby contributing to the progression of FM [18].

Migraine is believed to trigger FM. Repeated headaches in patients with migraine

may increase the neuronal response to both nociceptive and nonnociceptive

stimulation and induce spontaneous neuronal activity, which may concurrently

increase patient sensitivity to FM [19]. Several studies have highlighted the role of the

hypothalamus in migraines [17]. Evidence indicates the direct and indirect anatomical

connections of the hypothalamus to the thalamus and autonomic brainstem nuclei,

thereby supporting the role of the hypothalamus in nociceptive and autonomic

modulation in patients with migraine [20]. However, brain mechanisms common in

patients with FM result in the central sensitization of pain neurons, leading to the

evolution of a complex syndrome [21].

Early in the course of FM, widespread musculoskeletal pain often appears in the

neck or shoulder region [22]. Neck pain may activate local nociceptors and transmit

pain impulses through upper cervical spinal nerves such as the greater occipital nerve

to the trigeminal nucleus caudalis, thereby inducing a migraine attack [23]. Some

experts believe that FM and migraine headaches both involve defects in the systems

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that regulate certain chemical messengers in the brain, including serotonin and

epinephrine (adrenaline) [1]. These defects may be reflected in the similar

psychological comorbidities of the two conditions, including depression, anxiety,

interpersonal sensitivity, and somatization [9]. Psychosocial distress or abnormalities

commonly occur in patients with migraine and those with FM.

Although studies have reported high comorbidity rates for migraine and FM, the

following crucial concerns must be addressed. (1) Most such studies were conducted

at tertiary care centers. Patients are often referred to tertiary clinics when they present

with extreme pain, disability, or medication overuse. Therefore, such sample

populations may differ from patients treated in general practice. (2) Most such studies

used a cross-sectional design to investigate prevalence rather than incidence of

migraine or FM. (3) Whether a significant association exists, suggesting that people

with migraine are more likely to develop FM than the general population or vice versa,

remains unknown. Therefore, our population-based longitudinal cohort was employed

to investigate the link between migraine and FM.

Methods

Data Source

8

Data for this research were obtained from the Longitudinal Health Insurance

Database (LHID). The LHID comprises data of insurance claims filed by 1 million

patients under Taiwan's National Health Insurance (NHI) program, which covers 99%

of Taiwan's 23 million citizens with single-payer health insurance. According to a

government report, no differences between the LHID and Taiwan's NHI program

exist with respect to demographic characteristics. The health claims information in the

LHID includes general patient information (e.g., birthdate, sex, occupation),

documentation of diseases [recorded according to the International Classification of

Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)], and other data related

to medical services.

Ethics statement

The NHI Research Databank encrypts patients' personal information to protect

privacy and provides researchers with anonymous identification numbers associated

with relevant claims information, including sex, birthdate, medical services received,

and prescriptions. Therefore, patient consent is not required to access the NHI

Research Databank. This study was approved for exemption by the Institutional

Review Board of China Medical University (CMUH104-REC2-115-CR3). In

addition, the Institutional Review Board waived the requirement for patient consent.

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Study Cohorts

A bidirectional cohort study design was used to interpret the longitudinal

association between FM and migraine.

Figure 1 displays the procedure for establishing the two arms of this study. For

Arm 1, we identified patients with FM (ICD-9-CM code 729.1) aged ≥20 years and

newly diagnosed ≥3 times consecutively within 3 months from 2000–2010. The first

diagnosis date was designated as the index date for entry into the FM cohort. Patients

with a history of migraine (ICD-9-CM code 346) were excluded from this arm. For

each patient with FM, we randomly selected four individuals without FM or migraine

from the population of the LHID2000 who were frequency-matched by sex, age (in

5-year increments), and entry date of the patient with FM; these subjects were

recruited into the non-FM (control) cohort.

A similar procedure was used for Arm 2 to establish a cohort of patients with

migraine who had no history of FM, were aged ≥20 years, and were newly diagnosed

≥3 times consecutively within 3 months from 2000–2010.

Subjects in both arms were followed until diagnosis of migraine or FM,

withdrawal from the NHI program, death, or December 31, 2011. The patients in the

two cohorts presented with some baseline comorbidities: diabetes (ICD-9-CM code

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250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code

272), depression (ICD-9-CM codes 296.2, 296.3, 296.5, 300.4, 309, and 311), anxiety

(ICD-9-CM codes 300.0, 300.2, 300.3, 308.3, and 309.81), sleep disorder (ICD-9-CM

codes 307.4 and 780.5), coronary artery disease (CAD; ICD-9-CM codes 410–414),

chronic fatigue syndrome (CFS; ICD-9-CM code 780.71), and irritable bowel

syndrome (IBS; ICD-9-CM code 564.1).

Statistical analyses

The characteristics of the study cohorts are expressed as means and

corresponding standard deviations for age and as numbers and percentages for sex and

comorbidities. Age difference was assessed using a t test, and sex and comorbidity

distributions were tested using a chi-square test. The incidence density for each cohort

was calculated as the total event number divided by the sum of follow-ups [per 1000

person-years (PY)]. The cumulative incidence curve for each cohort was measured

using the Kaplan–Meier method, and the curve difference was calculated using the

log-rank test. To determine the risks of migraine and FM in Arms 1 and 2,

respectively, hazard ratios (HRs) and corresponding 95% confidence intervals (CIs)

were estimated using single-variable and multivariable Cox proportional hazard

models. Data management and all statistical analyses were performed using SAS for

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Windows (Version 9.4, SAS Institute, Cary, NC, USA), and incidence curves was

plotted using R software. All significance levels were set as two-sided p < 0.05.

Public and Patient Involvement

None

Results

Table 1 presents the demographic characteristics of the FM and non-FM cohorts.

The age- and sex-matched cohorts exhibited differences in comorbidity distribution.

The prevalence of comorbidities was significantly higher in the FM cohort than in the

non-FM cohort (p < 0.001).

Table 2 indicates that the migraine incidences were 4.39 and 2.07 per 1000 PY in

the FM and non-FM cohorts, respectively. Figure 2 reveals a higher incidence curve

for the FM cohort than for the non-FM cohort (log-rank test = 371.4, p < 0.001). After

adjustment for age, sex, and comorbidities, the patients with FM exhibited a

1.89-times higher risk of migraine compared with the non-FM subjects (HR = 1.89,

95% CI = 1.75–2.05). Among women, the relative risk of migraine was 1.76-times

higher in patients with FM compared with non-FM subjects (HR = 1.76, 95% CI

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1.60–1.93), whereas among men, the risk was 2.29-times higher in patients with FM

than in non-FM subjects (HR = 2.29, 95% CI = 1.97–2.67). Regarding age, the HRs

for migraine in the FM cohort were 2.06 (95% CI = 1.85–2.29), 1.66 (95% CI =

1.43–1.92), and 1.69 (95% CI = 1.39–2.05) for ≤50, 51–65, and ≥65 years,

respectively.

Table 3 presents the influence of factors associated with migraine occurrence in

the FM cohort. Male sex, hyperlipidemia, depression, anxiety, sleep disorder, CAD,

CFS, and IBS were all associated with higher risk of migraine (all p < 0.05).

Table 4 lists the comorbidities as well as the age- and sex-matched comparisons

in the migraine cohort, which exhibited a higher prevalence of comorbidities than did

the nonmigraine cohort.

Table 5 and Figure 3 reveal that the incidence of FM was significantly higher in

patients with migraine than in those without (7.01 vs. 4.49 per 1000 PY; log-rank test

= 116.7, p < 0.001). After adjustment for age, sex, and comorbidities, patients with

migraine exhibited a 1.52-times higher risk of FM compared with those without

migraine (HR = 1.52, 95% CI = 1.39–1.65). Among female patients, those with

migraine exhibited a 1.43-times higher risk of FM compared with nonmigraine

subjects (HR = 1.43, 95% CI = 1.29–1.59), whereas among male patients, those with

migraine exhibited a 1.78-times higher risk of FM compared with nonmigraine

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subjects (95% CI = 1.50–2.11). Regarding age, the HRs for FM were 1.64 (95% CI = 1.46–1.84), 1.30 (95% CI = 1.09–1.53), and 1.28 (95% CI = 1.03–1.58) in patients with migraine aged <50, 50–64, and ≥65 years, respectively.

Table 6 presents the associations of sex, age, and comorbidities with risk of FM. The variables, including age, migraine, hypertension, hyperlipidemia, depression, sleep disorder, and CAD, were all associated with lower risk of FM.

Discussion

The results of comparing the two cohort arms suggested a bidirectional risk of migraine and FM in patients with FM and those with migraine, respectively. The analysis of Arm 1 revealed incidence rates for migraine of 4.39 and 2.07 per 1000 PY in patients with and without FM, respectively [adjusted HR (aHR) = 1.89, 95% CI = 1.75–2.05 in patients with FM]. The analysis of Arm 2 revealed incidence rates for FM of 7.01 and 4.49 per 1000 PY in patients with and without migraine, respectively (aHR = 1.52, 95% CI = 1.39–1.65 in patients with migraine). These results indicated that FM had stronger predictive power for the onset of migraine than did migraine for the onset of FM.

The Kaplan–Meier plots demonstrated that incidence of migraine in the FM

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cohort and that of FM in the migraine cohort increased steadily during the 12-year follow-up period. Moreover, similar patterns were observed in the two corresponding comparison cohorts. The cumulative incidence measured by the Kaplan–Meier plots revealed greater risk of migraine among patients with FM than risk of FM among patients with migraine.

Our predictive analytics have the potential to guide diagnosis and treatment. For example, a subsequent diagnosis of FM may result from failure of antimigraine treatment to alleviate fatigue [24]. Because migraine is often more effectively managed than FM, the authors hypothesized that patients with FM are more likely to be treated for migraine than are patients with migraine to be treated for FM. Therefore, clinical trials of patients with migraine in the future have the potential to evaluate the effects of FM on health outcomes and the efficacy of FM treatment [10].

Cohort analysis for the association between FM and risk of new-onset migraine

This study revealed a positive association between FM diagnosis and the risk of migraine. Adjusting for hypertension, CAD, and CFS had no strong influence on this association. However, sex, age (particularly in patients aged less than 49 years), diabetes, hyperlipidemia, depression, anxiety, sleep disorder, and IBS continued to demonstrate statistically significant effects.

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Because "high frequency and chronic migraine increase sensitivity to pain in fibromyalgia (FM) patients [25], such heightened pain sensitivity may be attenuated by comorbid diabetes. There is also a documented report showing a significant positive association between migraine frequency and intensity with total and [low-density lipoprotein] cholesterol, independent of diet and lifestyle [26]." Several hypotheses have been proposed to explain the development of chronic widespread pain and episodic throbbing or pulsating pain across the head and neck regions as possible effects of comorbidities such as depression and anxiety. Depression and anxiety disorders have been identified as crucial secondary symptoms of FM [11, 27, 28]. The pain associated with FM may initiate the development of mood disorders as a result of stress imposed on the body. Furthermore, according to multiple evidence-based studies, depression and anxiety may induce the onset or present as a prodrome of migraine [29, 30]. Research has indicated that serotonin levels might be related to interconnections between anxiety and migraine [31]. A lower level of serotonin may be central to the dysregulation of descending antinociceptive systems, leading to FM and migraine [31, 32].

Poor sleep quality or sleep deprivation in healthy individuals can induce symptoms of FM [33], suggesting that sleep abnormalities may be a pathological characteristic of FM rather than merely a result of pain [34]. Relevant literature has

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reported the advantages of targeting sleep conditions to relieve the symptoms of

migraine [35]. As the prevalence of sleep disorders increases in both patients with FM

and those with migraine, appreciation of the strong links between FM and migraine

also increases.

IBS frequently coexists with both FM and migraine [36, 37]; however, the

underlying mechanisms for the association of FM with increased risks of IBS and

migraine are unclear. FM, migraine, and IBS may be distinct manifestations of a

common pathophysiological process affecting the gastrointestinal tract. These

disorders are referred to as "central sensitivity syndrome" and are mutually associated

[38]. A growing amount of evidence indicates that central sensitization phenomena

play a role in the pathogenesis of FM and that of migraine. Central sensitization at the

levels of the spinal dorsal horn and trigeminal nucleus may also be involved in the

progression of migraine attacks, and prolonged nociceptive inputs may result in the

maintenance of supraspinal sensitization and central neuroplastic changes, causing

episodic headaches to become chronic [39]. Notably, increased intestinal permeability

may be observed in IBS [40]. Altered intestinal permeability with overgrowth of

intestinal bacteria may trigger the development of FM [41] and that of migraine [42].

The microbiome–gut–brain axis—a bidirectional communication route of the central

and enteric nervous systems with microbiome through the neural, humoral, endocrine,

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and immune pathways [36, 37, 43]—has been proposed as a multifaceted pathophysiological mechanism underlying IBS [43], FM [44, 45], and migraine [42, 46]. In addition, mutual interaction has been established between gut microbiota and the central, autonomic, and enteric nervous systems through the hypothalamic–pituitary–adrenal axis [43].

Cohort analysis for the association between migraine and risk of new-onset FM

This study revealed higher risk of FM in patients with migraine than in those without in every factor-based subset of the cohorts. Notably, patients with hyperlipidemia had higher risk of FM. Moreover, adverse lipid profiles occurred more frequently in patients with migraine who had a higher body mass index [47, 48]. Although lack of exercise may precipitate the development of an adverse lipid profile, exercise may trigger acute migraine attacks [49], and some patients may avoid exercise to prevent migraines. This hypothesis could be supported by the results of one study that revealed that patients with headache had lower aerobic endurance and flexibility than did healthy controls [50]. Aerobic exercise could relieve depression and anxiety and prevent the negative effects of stress [51]. Furthermore, avoiding exercise may exacerbate mood distress, and thus could be related to the development of FM.

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Increased migraine frequency as a result of migraines becoming chronic intensifies the sensitivity to pain in somatic areas outside of the cephalic region and may predispose patients to FM [6]. Hypothalamic neuroendocrine dysfunction has been proposed as a brain mechanism common to both FM and migraine [52]. Both conditions also share the mechanism of central sensitization of pain neurons. Magnesium, which is often used as an agent for relieving migraine headaches, is also beneficial for treating FM. Low magnesium levels can exacerbate symptoms of FM and are also implicated in migraines [53]. Researchers have discovered that people who do not respond to standard migraine treatments often also have FM [17]. Considering the high comorbidity rates of migraine and FM, many professionals assume that the central nervous system is responsible for pain-processing abnormalities, including central sensitization and inadequate pain inhibition alongside repeated headache episodes. Moreover, tonic peripheral nociceptive input is associated with augmented windup in response to neurotransmitters, immunomodulation, vascular changes, and hormone influence, which may increase the risk of FM [1, 6, 36, 37, 43, 52].

Our study contained a large sample because of our population-based design. Moreover, we were careful to minimize selection bias during analysis, and our ample documentation of medical profiles allowed for minimal effects from confounding

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factors among the subjects. However, this study had limitations. We based our study solely on information from diagnoses in patient files and included no information from patients whose cases were unidentified. Poor categorization of a patient's symptoms may have affected the discernibility between migraine and FM. Because many crucial variables are not retrievable and various methods are used to diagnose FM and the numerous subtypes of migraines, our data provides merely a glimpse of these two conditions. Furthermore, assessing treatment responses in our large database analysis was impossible, rendering the identification of "diagnosis by exclusion" difficult in this study. Future studies are recommended to further delineate "diagnosis by exclusion." Furthermore, this study did not consider the severity of FM and migraines in patients; therefore, no definitive statement can be made regarding the intensity of FM and subsequent risk of developing migraine conditions, or vice versa. Moreover, this study was naturally highly prone to observational bias because patients with migraine and those with FM are generally more likely to seek medical attention for other conditions than are those with neither.

Conclusion

This study was the first to reveal a population-based bidirectional association between onset of FM and that of migraine in patients with migraine and those with

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FM, respectively. The risk of migraine was reportedly greater than that of FM. The incidence rates of FM in the migraine cohort and migraine in the FM cohort increased with age in both directions. However, the HRs relative to the corresponding comparison cohorts were attenuated with increases in age.

Data availability statement

The dataset used in this study was obtained from Taiwan's Ministry of Health and Welfare (MOHW), from which we were required to obtain approval to access the data. Any researcher interested in accessing this dataset can submit an application form to the MOHW requesting access. Please contact the staff of the MOHW (email: stcarolwu@mohw.gov.tw) for further assistance. Taiwan MOHW Address: No. 488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (ROC). Phone: +886-2-8590-6848. All relevant data are provided in this manuscript.

Author contributions:

Conceptualization: I-Wen Penn, Chia-Hung Kao.

Methodology: Cheng-Li Lin, Chia-Hung Kao.

Software: Cheng-Li Lin, Chia-Hung Kao.

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Validation: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin, Chia-Hung

Kao.

Formal analysis: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin,

Chia-Hung Kao.

Investigation: Cheng-Li Lin, Chia-Hung Kao.

Resources: Cheng-Li Lin, Chia-Hung Kao.

Data curation: IWP, EC, TYC, CLL, CHK.

Writing (original draft preparation): I-Wen Penn, Eric Chuang, Tien-Yow Chuang,

Cheng-Li Lin, Chia-Hung Kao.

Writing (review and editing): I-Wen Penn, Eric Chuang, Tien-Yow Chuang,

Cheng-Li Lin, Chia-Hung Kao.

Visualization: I-Wen Penn, Eric Chuang, Tien-Yow Chuang, Cheng-Li Lin,

Chia-Hung Kao.

Supervision: Chia-Hung Kao.

Project administration: Chia-Hung Kao.

Funding acquisition: Chia-Hung Kao.

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Conflicts of Interest

All authors report no conflicts of interest.

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Figure Legends:

Figure 1. Flow chart illustrating the selection of study subjects.

Figure 2. Comparison of cumulative incidence of migraine between patients with and

without fibromyalgia using the Kaplan–Meier method.

Figure 3. Comparison of the cumulative incidence of fibromyalgia between patients

with and without migraine using the Kaplan–Meier method.

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Table 1. Demographic characteristics and comorbidities in patients with and without fibromyalgia.

Variable	Fibromyalgia		
	No N =132863	Yes N =33216	*p*-value
Sex	n(%)	n(%)	0.99
Female	71880(54.1)	17970(54.1)	
Male	60983(45.9)	15246(45.9)	
Age, mean(SD)	50.9(16.9)	51.4(16.7)	<0.001#
Stratify age			0.99
≤49	64292(48.4)	10673(48.4)	
50-65	36820(27.7)	9205(27.7)	
65+	31751(23.9)	7938(23.9)	
Comorbidity			
Diabetes	10485(7.89)	3193(9.61)	<0.001
Hypertension	37284(28.1)	11287(34.0)	<0.001
Hyperlipidemia	22446(16.9)	7301(22.0)	<0.001
Depression	4690(3.53)	1804(5.43)	<0.001
Anxiety	10494(7.90)	4214(12.7)	<0.001
Sleep disorder	21095(15.9)	8121(24.5)	<0.001
CAD	17918(13.5)	5821(17.5)	<0.001
Chronic fatigue syndrome	199(0.15)	93(0.28)	<0.001
Irritable bowel syndrome	5125(3.86)	1870(5.63)	<0.001

Chi-square test; #: two-sample t test

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Table 2. Comparison of the incidence and hazard ratios of migraine stratified by sex and age between patients with and without fibromyalgia.

Variable	Without fibromyalgia					With fibromyalgia				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	1810	876077	2.07	1(Reference)	1(Reference)	954	217386	4.39	2.12(1.96, 2.30)***	1.89(1.75, 2.05)***
Sex										
Female	1373	487506	2.82	1(Reference)	1(Reference)	669	120773	5.54	1.97(1.79, 2.16)***	1.76(1.60, 1.93)***
Male	437	388571	1.12	1(Reference)	1(Reference)	285	96613	2.95	2.62(2.26, 3.05)***	2.29(1.97, 2.67)***
Stratify age										
≤50	922	444710	2.07	1(Reference)	1(Reference)	548	110557	4.96	2.39(2.15, 2.66)***	2.06(1.85, 2.29)***
50-65	564	245579	2.30	1(Reference)	1(Reference)	258	60603	4.26	1.85(1.60, 2.15)***	1.66(1.43, 1.92)***
65+	324	185788	1.74	1(Reference)	1(Reference)	148	46226	3.20	1.83(1.51, 2.23)***	1.69(1.39, 2.05)***
Comorbidity[‡]										
No	774	508879	1.52	1(Reference)	1(Reference)	311	95605	3.25	2.14(1.88, 2.44)***	2.13(1.87, 2.43)***
Yes	1036	367197	2.82	1(Reference)	1(Reference)	643	121780	5.28	1.88(1.71, 2.08)***	1.80(1.63, 1.98)***

Rate[#]: incidence rate per 1000 person-years; crude HR: crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, and irritable bowel syndrome

***p < 0.001

Comorbidity[‡]: patients with any of the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, or irritable bowel syndrome were classified as the comorbidity group

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Table 3. Cox model with hazard ratios and 95% confidence intervals for migraine associated with fibromyalgia and covariates.

Variable	Crude		Adjusted†	
	HR	(95% CI)	HR	(95% CI)
Fibromyalgia	2.12	(1.96, 2.30)***	1.89	(1.74, 2.04)***
Sex(Women vs. Men)	2.28	(2.09, 2.48)***	2.08	(1.91, 2.27)***
Age, years	1.00	(0.99, 1.00)**	0.99	(0.99, 1.00)***
Baseline comorbidities (yes vs. no)				
Diabetes	0.82	(0.70, 0.96)*	0.73	(0.61, 0.860***
Hypertension	1.06	(0.97, 1.15)	-	-
Hyperlipidemia	1.30	(1.19, 1.43)***	1.14	(1.03, 1.27)*
Depression	2.37	(2.06, 2.72)***	1.20	(1.03, 1.39)*
Anxiety	2.68	(2.44, 2.95)***	1.64	(1.47, 1.84)***
Sleep disorder	2.63	(2.43, 2.85)***	1.97	(1.80, 2.15)***
CAD	1.30	(1.18, 1.44)***	1.10	(0.98, 1.23)
Chronic fatigue syndrome	2.24	(1.01, 4.99)*	1.45	(0.65, 3.22)
Irritable bowel syndrome	1.98	(1.71, 2.29)***	1.36	(1.17, 1.58)***

Crude HR: crude hazard ratio; adjusted†: multivariable analysis including sex, age, and the comorbidities of diabetes, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, and irritable bowel syndrome

*p < 0.05, **p < 0.01, and ***p < 0.001

Table 4. Demographic characteristics and comorbidities in patients with and without migraine.

Variable	migraine		
	No **N =69680**	**Yes** **N =17420**	*p*-value
Sex	n(%)	n(%)	0.99
Female	51176(73.4)	12794(73.4)	
Male	18504(26.6)	4626(26.6)	
Age, mean(SD)	44.2(15.6)	44.5(15.3)	0.04[#]
Stratify age			0.99
≤49	46768(67.1)	11692(67.1)	
50-65	14940(21.4)	3735(21.4)	
65+	7972(11.4)	1993(11.4)	
Comorbidity			
Diabetes	3567(5.12)	975(5.60)	0.01
Hypertension	12563(18.0)	4551(26.1)	<0.001
Hyperlipidemia	8278(11.9)	3187(18.3)	<0.001
Depression	2019(2.90)	1851(10.6)	<0.001
Anxiety	4366(6.27)	3724(21.4)	<0.001
Sleep disorder	9469(13.6)	6976(40.1)	<0.001
CAD	5560(7.98)	2449(14.1)	<0.001
Chronic fatigue syndrome	71(0.10)	41(0.24)	<0.001
Irritable bowel syndrome	2106(3.02)	1224(7.03)	<0.001

Chi-square test; [#]: two-sample t test

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Table 5. Comparison of the incidence and hazard ratios of fibromyalgia stratified by sex and age between patients with and without migraine.

Variable	Without migraine					With migraine				
	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)	Event	PY	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
All	2034	453130	4.49	1(Reference)	1(Reference)	800	114070	7.01	1.57(1.44, 1.70)***	1.52(1.39, 1.65)***
Sex										
Female	1556	335328	4.64	1(Reference)	1(Reference)	568	84606	6.71	1.45(1.32, 1.60)***	1.43(1.29, 1.59)***
Male	478	117802	4.06	1(Reference)	1(Reference)	232	29464	7.87	1.94(1.66, 2.27)***	1.78(1.50, 2.11)***
Stratify age										
≤50	1060	310621	3.41	1(Reference)	1(Reference)	470	78131	6.02	1.77(1.58, 1.97)***	1.64(1.46, 1.84)***
50-65	608	96607	6.29	1(Reference)	1(Reference)	207	24189	8.56	1.36(1.16, 1.59)***	1.30(1.09, 1.53)**
65+	366	45902	7.97	1(Reference)	1(Reference)	123	11751	10.5	1.32(1.07, 1.61)**	1.28(1.03, 1.58)*
Comorbidity[‡]										
No	1082	309229	3.50	1(Reference)	1(Reference)	255	43664	5.84	1.67(1.46, 1.92)***	1.79(1.56, 2.06)***
Yes	952	143901	6.62	1(Reference)	1(Reference)	545	70406	7.74	1.18(1.06, 1.31)**	1.29(1.16, 1.44)***

Rate[#]: incidence rate per 1000 person-years; crude HR: crude hazard ratio

Adjusted HR[†]: multivariable analysis including sex, age, and the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, and irritable bowel syndrome
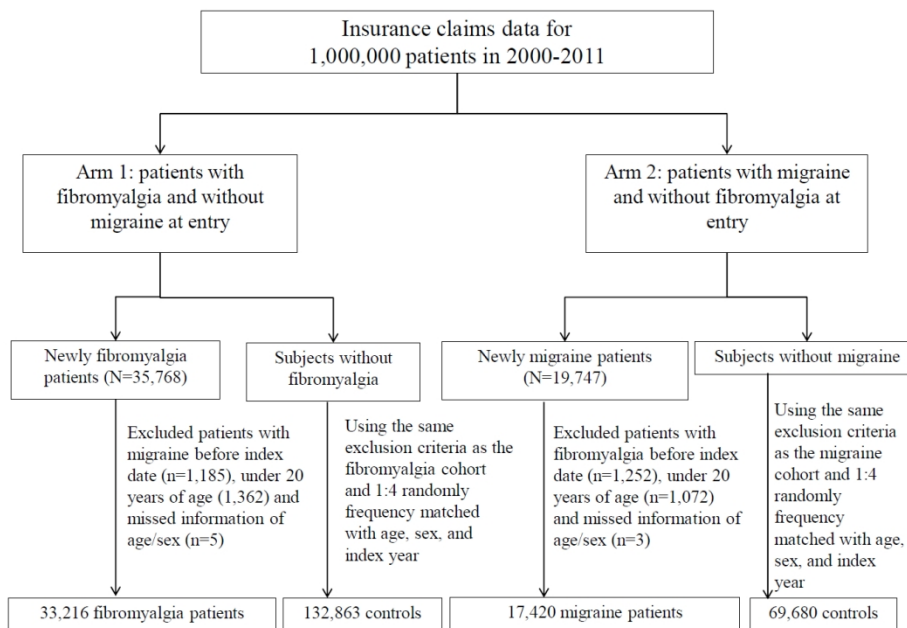
*p < 0.05, **p < 0.01, and ***p < 0.001

Comorbidity[‡]: patients with any of the comorbidities of diabetes, hypertension, hyperlipidemia, depression, anxiety, sleep disorder, coronary artery disease, chronic fatigue syndrome, or irritable bowel syndrome were classified as the comorbidity group

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Table 6. Cox model with hazard ratios and 95% confidence intervals for fibromyalgia associated with migraine and covariates.

Variable	Crude		Adjusted[†]	
	HR	(95% CI)	HR	(95% CI)
Migraine	1.57	(1.44, 1.70)***	1.51	(1.38, 1.65)***
Sex(Women vs. Men)	1.05	(0.97, 1.15)	-	-
Age, years	1.02	(1.02, 1.03)***	1.02	(1.01, 1.02)***
Baseline comorbidities (yes vs. no)				
Diabetes	1.58	(1.36, 1.82)***	0.99	(0.85, 1.16)
Hypertension	1.81	(1.67, 1.96)***	1.10	(0.99, 1.22)
Hyperlipidemia	1.69	(1.54, 1.85)***	1.15	(1.03, 1.28)*
Depression	1.38	(1.17, 1.63)***	1.06	(0.89, 1.26)
Anxiety	1.34	(1.19, 1.51)***	0.92	(0.80, 1.05)
Sleep disorder	1.45	(1.33, 1.58)***	1.09	(0.98, 1.20)
CAD	1.74	(1.57, 1.94)***	1.01	(0.89, 1.14)
Chronic fatigue syndrome	2.11	(0.79, 5.62)	-	-
Irritable bowel syndrome	1.28	(1.06, 1.53)**	0.94	(0.78, 1.13)

Crude HR: crude hazard ratio; adjusted[†]: multivariable analysis including age and the comorbidities of diabetes, hypertension, hyperlipidemia, anxiety, sleep disorders, stroke, and peptic ulcer disease, and use of nonsteroidal anti-inflammatory drugs

*p < 0.05, **p < 0.01, and ***p < 0.001

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Insurance claims data for
1,000,000 patients in 2000-2011

Arm 1: patients with fibromyalgia and without migraine at entry

Arm 2: patients with migraine and without fibromyalgia at entry

Newly fibromyalgia patients (N=35,768)

Subjects without fibromyalgia

Newly migraine patients (N=19,747)

Subjects without migraine

Excluded patients with migraine before index date (n=1,185), under 20 years of age (1,362) and missed information of age/sex (n=5)

Using the same exclusion criteria as the fibromyalgia cohort and 1:4 randomly frequency matched with age, sex, and index year

Excluded patients with fibromyalgia before index date (n=1,252), under 20 years of age (n=1,072) and missed information of age/sex (n=3)

Using the same exclusion criteria as the migraine cohort and 1:4 randomly frequency matched with age, sex, and index year

33,216 fibromyalgia patients

132,863 controls

17,420 migraine patients

69,680 controls

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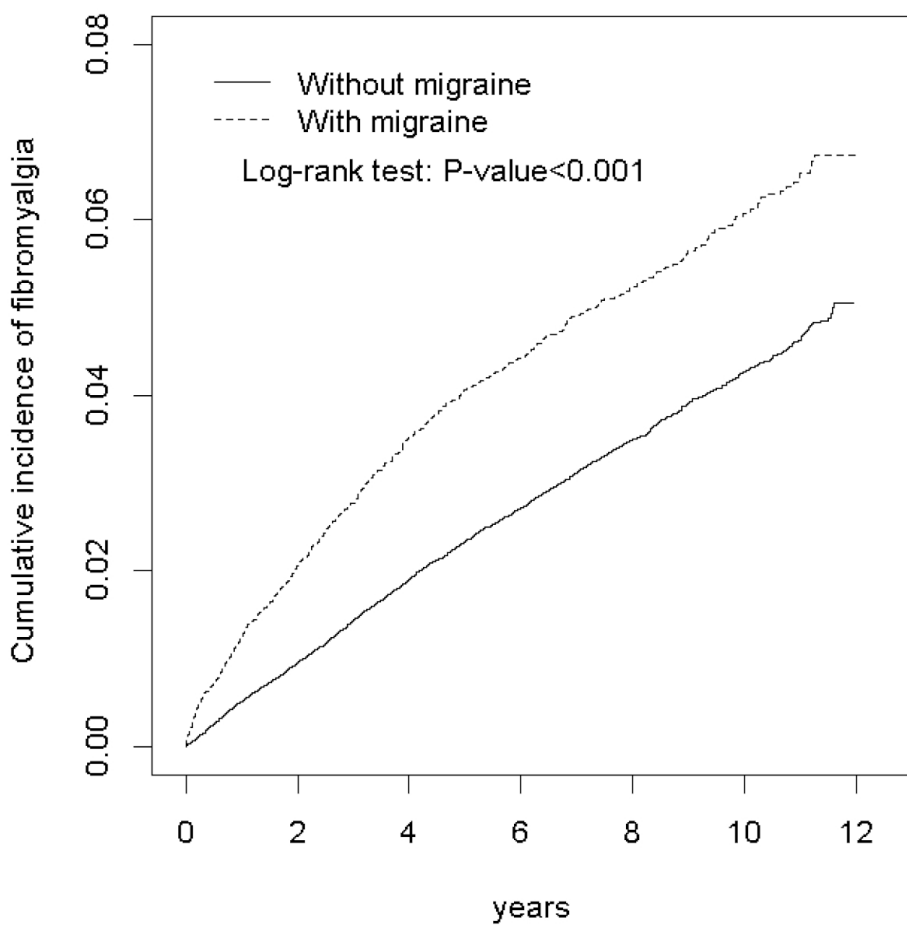33
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Included on page:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,5,6
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	5,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8-10
Objectives	3	State specific objectives, including any pre-specified hypotheses	10
Methods			
Study design	4	Present key elements of study design early in the paper	11-14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	11-14
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-14
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	11-14
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	11-14
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	11-14
		Case-control study—For matched studies, give matching criteria and the number of controls per case	11-14
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-14
Bias	9	Describe any efforts to address potential sources of bias	11-14
Study size	10	Explain how the study size was arrived at	11-14
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-14
		(*b*) Describe any methods used to examine subgroups and interactions	11-14

		(*c*) Explain how missing data were addressed	11-14
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	11-14
		Case-control study—If applicable, explain how matching of cases and controls was addressed	11-14
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	11-14
		(*e*) Describe any sensitivity analyses	11-14
Continued on next page			
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	15,16
		(b) Give reasons for non-participation at each stage	15,16
		(c) Consider use of a flow diagram	15,16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15,16
		(b) Indicate number of participants with missing data for each variable of interest	15,16
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	15,16
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	15,16
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	15,16
		Cross-sectional study—Report numbers of outcome events or summary measures	15,16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15,16
		(*b*) Report category boundaries when continuous variables were categorized	15,16
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15,16
Discussion			
Key results	18	Summarise key results with reference to study objectives	17-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-23
Generalisability	21	Discuss the generalisability (external validity) of the study results	17-23
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2, 3

Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.