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Bidirectional association between migraine and fibromyalgia: retrospective cohort analyses of two populations

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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 healthcare 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 (PY)); crude HR=2.12, 95% CI=1.96 to 2.30; adjusted HR (aHR)=1.89, 95% CI=1.75 to 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 PY; aHR=1.52, 95% CI=1.39 to 1.65).

Conclusions The present study revealed a bidirectional link between FM and migraine.

Strengths and limitations of this study

- Our study contained a large sample size because of its population-based design.
- We based our study solely on information from diagnoses in patient files and included no information on patients whose cases were unidentified.
- This study was naturally highly prone to observational bias because patients with migraine and those with fibromyalgia are generally more likely to seek medical attention for other conditions than are those with neither.
- 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.
- 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.

INTRODUCTION

A major symptom of fibromyalgia (FM) is headache. Migraine is a type of headache 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

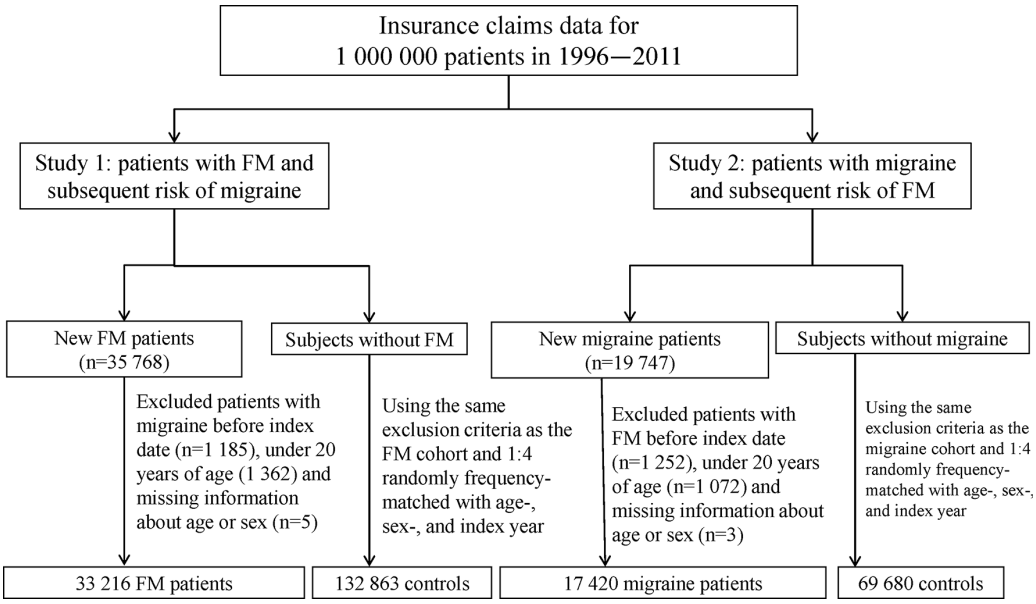

Figure 1 Flow chart illustrating the selection of study subjects. FM, fibromyalgia.

to as '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 sensitisation, 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 non-nociceptive 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 sensitisation 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 that regulate certain chemical messengers in the brain, including serotonin and epinephrine (epinephrine).[1] These defects may be reflected in the similar psychological comorbidities of the two conditions, including depression, anxiety, interpersonal sensitivity and somatisation.[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 centres. 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

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) programme, 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 programme exist with respect to demographic characteristics. The health claims information in the LHID includes general patient information (eg, 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.

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 to 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 to 2010.

Subjects in both arms were followed until diagnosis of migraine or FM, withdrawal from the NHI programme, death or 31 December 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), hyperlipidaemia (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 SD 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 χ^2 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, HRs and corresponding 95% CIs were estimated using single-variable and multivariable Cox proportional hazard models. Data management and all statistical analyses were performed using SAS for Windows V.9.4 (SAS Institute) 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-matched 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 1 Demographic characteristics and comorbidities in patients with and without FM

	FM		
	No	Yes	
Variable	n=132 863	n=33 216	P value
Sex	n (%)	n (%)	0.99
Female	71 880 (54.1)	17 970 (54.1)	
Male	60 983 (45.9)	15 246 (45.9)	
Age, mean (SD)	50.9 (16.9)	51.4 (16.7)	<0.001*
Stratify age			0.99
≤49	64 292 (48.4)	10 673 (48.4)	
50–65	36 820 (27.7)	9205 (27.7)	
65+	31 751 (23.9)	7938 (23.9)	
Comorbidity			
Diabetes	10 485 (7.89)	3193 (9.61)	<0.001
Hypertension	37 284 (28.1)	11 287 (34.0)	<0.001
Hyperlipidaemia	22 446 (16.9)	7301 (22.0)	<0.001
Depression	4690 (3.53)	1804 (5.43)	<0.001
Anxiety	10 494 (7.90)	4214 (12.7)	<0.001
Sleep disorder	21 095 (15.9)	8121 (24.5)	<0.001
CAD	17 918 (13.5)	5821 (17.5)	<0.001
CFS	199 (0.15)	93 (0.28)	<0.001
IBS	5125 (3.86)	1870 (5.63)	<0.001

X^2 test; *two-sample t-test.
CAD, coronary artery disease; CFS, chronic fatigue syndrome; FM, fibromyalgia; IBS, irritable bowel syndrome.

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 to 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 to 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 to 2.67). Regarding age, the HRs for migraine in the FM cohort were 2.06 (95% CI=1.85 to 2.29), 1.66 (95% CI=1.43 to 1.92) and 1.69 (95% CI=1.39 to 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, hyperlipidaemia, 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 the non-migraine cohort.

Table 2 Comparison of the incidence and HRs of migraine stratified by sex and age between patients with and without FM

	Without FM					With FM				
Variable	Event	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)	Event	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
All	1810	876 077	2.07	1(Reference)	1(Reference)	954	217 386	4.39	2.12 (1.96 to 2.30)***	1.89 (1.75 to 2.05)***
Sex										
Female	1373	487 506	2.82	1(Reference)	1(Reference)	669	120 773	5.54	1.97 (1.79 to 2.16)***	1.76 (1.60 to 1.93)***
Male	437	388 571	1.12	1(Reference)	1(Reference)	285	96 613	2.95	2.62 (2.26 to 3.05)***	2.29 (1.97 to 2.67)***
Stratify age										
≤50	922	444 710	2.07	1(Reference)	1(Reference)	548	110 557	4.96	2.39 (2.15 to 2.66)***	2.06 (1.85 to 2.29)***
50–65	564	245 579	2.30	1(Reference)	1(Reference)	258	60 603	4.26	1.85 (1.60 to 2.15)***	1.66 (1.43 to 1.92)***
65+	324	185 788	1.74	1(Reference)	1(Reference)	148	46 226	3.20	1.83 (1.51 to 2.23)***	1.69 (1.39 to 2.05)***
Comorbidity§										
No	774	508 879	1.52	1(Reference)	1(Reference)	311	95 605	3.25	2.14 (1.88 to 2.44)***	2.13 (1.87 to 2.43)***
Yes	1036	367 197	2.82	1(Reference)	1(Reference)	643	121 780	5.28	1.88 (1.71 to 2.08)***	1.80 (1.63 to 1.98)***

***P<0.001.
†Incidence rate per 1000 PY.
‡Multivariable analysis including sex, age, and the comorbidities of diabetes, hypertension, hyperlipidaemia, depression, anxiety, sleep disorder, coronary artery disease (CAD), chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS).
§Patients with any of the comorbidities of diabetes, hypertension, hyperlipidaemia, depression, anxiety, sleep disorder, CAD, CFS or IBS were classified as the comorbidity group.
FM, fibromyalgia; PY, person-years.

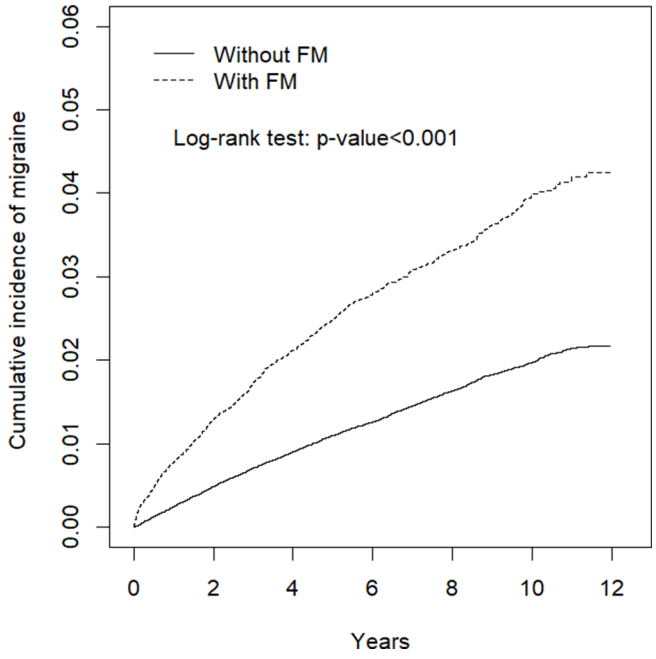

Figure 2 Comparison of cumulative incidence of migraine between patients with and without fibromyalgia using the Kaplan-Meier method.

Table 5 and figure 3 reveals 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 to 1.65). Among female patients, those with migraine exhibited a 1.43-times higher risk of FM compared with non-migraine subjects (HR=1.43, 95% CI=1.29 to 1.59), whereas among male patients, those with migraine exhibited a 1.78-times higher risk of FM compared with non-migraine subjects (95% CI=1.50 to 2.11). Regarding age, the

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

	Migraine		
	No	Yes	
Variable	n=69 680	n=17 420	P value
Sex	n (%)	n (%)	0.99
Female	51 176 (73.4)	12 794 (73.4)	
Male	18 504 (26.6)	4626 (26.6)	
Age, mean (SD)	44.2 (15.6)	44.5 (15.3)	0.04*
Stratify age			0.99
≤49	46 768 (67.1)	11 692 (67.1)	
50–65	14 940 (21.4)	3735 (21.4)	
65+	7972 (11.4)	1993 (11.4)	
Comorbidity			
Diabetes	3567 (5.12)	975 (5.60)	0.01
Hypertension	12 563 (18.0)	4551 (26.1)	<0.001
Hyperlipidaemia	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
CFS	71 (0.10)	41 (0.24)	<0.001
IBS	2106 (3.02)	1224 (7.03)	<0.001

X^2 test. *two-sample t-test.
CAD, coronary artery disease; CFS, chronic fatigue syndrome; IBS, irritable bowel syndrome.

Table 3 Cox model with HRs and 95% CIs for migraine associated with FM and covariates

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

*P<0.05; **P<0.01; ***P<0.001.
†Multivariable analysis including sex, age and the comorbidities of diabetes, hyperlipidaemia, depression, anxiety, sleep disorder, CAD, CFS and IBS.
CAD, coronary artery disease; CFS, chronic fatigue syndrome; FM, fibromyalgia ; IBS, irritable bowel syndrome.

Table 5 Comparison of the incidence and HRs 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	453 130	4.49	1(Reference)	1(Reference)	800	114 070	7.01	1.57 (1.44 to 1.70)***	1.52 (1.39 to 1.65)***
Sex										
Female	1556	335 328	4.64	1(Reference)	1(Reference)	568	84 606	6.71	1.45 (1.32 to 1.60)***	1.43 (1.29 to 1.59)***
Male	478	117 802	4.06	1(Reference)	1(Reference)	232	29 464	7.87	1.94 (1.66 to 2.27)***	1.78 (1.50 to 2.11)***
Stratify age										
≤50	1060	310 621	3.41	1(Reference)	1(Reference)	470	78 131	6.02	1.77 (1.58 to 1.97)***	1.64 (1.46 to 1.84)***
50–65	608	96 607	6.29	1(Reference)	1(Reference)	207	24 189	8.56	1.36 (1.16 to 1.59)***	1.30 (1.09 to 1.53)**
65+	366	45 902	7.97	1(Reference)	1(Reference)	123	11 751	10.5	1.3291.07 to 1.61)**	1.28 (1.03 to 1.58)*
Comorbidity§										
No	1082	309 229	3.50	1(Reference)	1(Reference)	255	43 664	5.84	1.67 (1.46 to 1.92)***	1.79 (1.56 to 2.06)***
Yes	952	143 901	6.62	1(Reference)	1(Reference)	545	70 406	7.74	1.18 (1.06 to 1.31)**	1.2991.16 to 1.44)***

*P<0.05; **P<0.01; ***P<0.001.
†Incidence rate per 1000 PY.
‡Multivariable analysis including sex, age, and the comorbidities of diabetes, hypertension, hyperlipidaemia, depression, anxiety, sleep disorder, CAD, IBS.
§Patients with any of the comorbidities of diabetes, hypertension, hyperlipidaemia, depression, anxiety, sleep disorder, CAD, chronic fatigue syndrome or IBS were classified as the comorbidity group.
PY, person years.

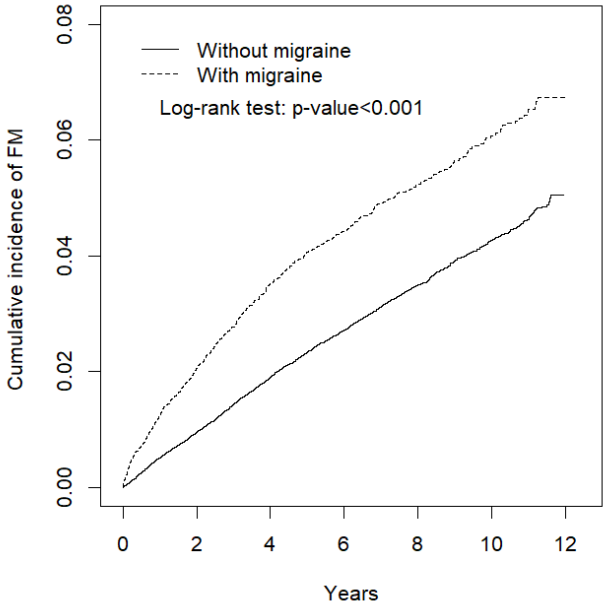

Figure 3 Comparison of the cumulative incidence of fibromyalgia between patients with and without migraine, using the Kaplan-Meier method.

HRs for FM were 1.64 (95% CI=1.46 to 1.84), 1.30 (95% CI=1.09 to 1.53) and 1.28 (95% CI=1.03 to 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, hyperlipidaemia, 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 to 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 to 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

Table 6 Cox model with HRs and 95% CIs for fibromyalgia associated with migraine and covariates

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

*P<0.05; **P<0.01; ***P<0.001.
†Multivariable analysis including age and the comorbidities of diabetes, hypertension, hyperlipidaemia, anxiety, sleep disorders, stroke, and peptic ulcer disease and use of non-steroidal anti-inflammatory drugs.
CAD, coronary artery disease; CFS, chronic fatigue syndrome; IBS, irritable bowel syndrome.

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 hypothesised that patients with FM are more likely to be treated for migraine than are patients with migraine 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 <49 years), diabetes, hyperlipidaemia, depression, anxiety, sleep disorder and IBS continued to demonstrate statistically significant effects.

Because "high frequency and chronic migraine increase sensitivity to pain in patients with FM,[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 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 sensitisation phenomena play a role in the pathogenesis of FM and that of migraine. Central sensitisation 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 sensitisation 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 hyperlipidaemia 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.

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 sensitisation 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 sensitisation 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 minimise 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 categorisation 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.

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