

Association of migraine with asthma risk: A retrospective population-based cohort study

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Original Article

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Abbreviations

CI: confidence interval

COPD: chronic obstructive pulmonary disease

HR: hazard ratio

ICD-9-CM: International Classification of Disease, Ninth Revision, Clinical

Modification

LABA: long-acting beta-2 agonists

LHID2000: Longitudinal Health Insurance Database

NHI: National Health Insurance

NHIRD: National Health Insurance Research Database

OPD: outpatient department

PAF: platelet-activating factor

SD: standard deviation

TRPV1: transient receptor potential cation channel subfamily V member 1

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Abstract

Background: Both migraine and asthma are common health problems in the general population. However, the association between these two disorders is yet to be fully explored.

Objective: We examined whether adult patients with migraine are at a higher risk of asthma development.

Methods: We used data retrieved from the National Health Insurance Research Database in Taiwan to conduct this nationwide population-based cohort study. We identified 6647 patients aged 20 – 60 years who were newly diagnosed with migraine between 2000 and 2005 for the migraine group and identified 26 588 patients without migraine for the nonmigraine group. Both groups were followed up until the end of 2011 to examine the incidence of asthma. Cox proportional hazards regression analysis was used to measure the hazard ratio (HR) of asthma in the migraine group compared with the nonmigraine group.

Results: The HR of asthma development was 1.37 (95% confidence interval = 1.21–1.56) for the migraine group compared with the nonmigraine group after adjustment for age, sex, occupational status, insurance premium, urbanization, comorbidities, and annual outpatient department visits. Further stratified analysis revealed that this risk was also significantly higher for both sexes and in the 40–60-year age group. The

main limitation of this study was that some relevant data were unavailable, such as pain medication prescriptions and family history of migraine and asthma.

Conclusion: Adult patients with migraine are at a higher future risk of asthma development.

Keywords: migraine, asthma, comorbidity, cohort study, epidemiology, National Health Insurance Research Database

Accepted Article

Introduction

Migraine is one of the most prevalent disorders, with an estimated lifetime incidence of 43% in women and 18% in men (1). It is characterized by episodic unilateral headache, which usually coexists with nausea, vomiting, photophobia, and phonophobia. Migraine causes substantial levels of disability, and has been reported to be comorbid with various illnesses such as stroke (2), coronary artery disease (3), and anxiety disorder (4). The disease not only affects those with it but also the people around them, causing a substantial societal burden (5).

Asthma is also a widespread disorder, with reports estimating that nearly 300 million people have asthma worldwide (6). Individuals with asthma generally experience recurrent episodes of coughing, shortness of breath, and chest tightness. Although the interaction of environmental, genetic, and socioeconomic factors has been reported to be associated with asthma risk (7), much remains to be explored in the pathogenesis of asthma.

Becker et al reported that patients with migraine are not at an increased risk of asthma (8). By contrast, Peng et al recently concluded from a nationwide cohort study that adult-onset asthma is associated with a higher risk of migraine (9). However, whether a bidirectional association exists between migraine and asthma is unclear. Moreover, no study to date has investigated the longitudinal frequency of asthma in

patients with migraine. This nationwide cohort study used the National Health Insurance Research Database (NHIRD) to examine whether patients with migraine have a higher risk of asthma than do those without migraine.

Methods

Data sources

The NHIRD was used for this retrospective population-based cohort study. The National Health Insurance (NHI) program was implemented in 1995 and covered more than 99.9% of the Taiwan population as of 2014. In this study, we used the Longitudinal Health Insurance Database (LHID2000), which contains medical reimbursement claims of the NHI program for 1 million enrollees from the period 1996–2011. The National Health Research Institutes reported no significant difference in the distribution of age or sex between the patients in the LHID2000 and all those in the NHIRD. The LHID2000 contains medical information including sex, date of birth, dates of clinical visits, details of prescriptions, and diagnoses coded using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). All personal identification was encrypted for privacy protection before being released for research. This study was approved by the institutional review board of China Medical University Hospital (CMUH104-REC2-115).

Study population

We conducted a nationwide population-based cohort study that comprised two groups, namely a migraine group and a nonmigraine group. We identified patients newly diagnosed with migraine (ICD-9-CM 346) between 2000 and 2005. The date of migraine diagnosis was defined as the “index date.” To ensure the accuracy of the migraine diagnosis, we selected patients who had records of at least three outpatient or inpatient visits within the most recent 3 years of their medical history. For each patient with migraine, four patients without a diagnosis of migraine in the LHID2000 were randomly selected and frequency-matched according to sex, age (every 5-year span) and the year of index date. The index date for the nonmigraine group was randomly assigned by day and month, and the index year was set to be the same year as that of the matched migraine patient. For both groups, we excluded those aged less than 20 or more than 60 years, with a diagnosis of asthma (ICD-9-CM 493) before the index date, or with missing sex or age information. Overall, 6647 patients were included in the migraine group and 26 588 patients were included in the nonmigraine group.

The variables of relevance were sex, age (20–39 and 40–60 years), occupational status, insurance premium, urbanization, comorbidities, and annual number of outpatient department (OPD) visits. We classified occupational status into three levels: white-collar workers, blue-collar workers, and other. The insurance premium of an

individual was determined by his/her work salary. Insurance premium amounts were categorized into three levels: NTD<15 000, 15 000-29 999, and $\geq 30\,000$ per month.

Urbanization level was defined according to the NHRI report. City districts and townships in which participants were registered for insurance purposes were grouped into four levels of urbanization based on population density (persons/km²); population ratios of people with an educational level of college or above, of people aged over 65 years, and of agricultural workers; and number of physicians per 100,000 people (10).

Level 1 indicates the most urbanized areas, and level 4 indicates the least urbanized areas. The records of comorbidities were determined for each study participant before the index date; these comorbidities including rhinitis (ICD-9-CM 472.0 and 477), chronic sinusitis (ICD-9-CM 473), atopic dermatitis (ICD-9-CM 691), and chronic obstructive pulmonary disease (COPD; ICD-9-CM 496).

The primary outcome of this study was to identify new cases of asthma, which were coded in the database as “ICD-9-CM 493.” To increase the validity of asthma diagnoses, we included only patients who were diagnosed with asthma and treated with relevant medication including inhaled corticosteroids, systemic corticosteroids (oral or intravenous), inhaled short-acting beta-2 agonists, or inhaled long-acting beta-2 agonists. Both the migraine and nonmigraine groups were followed up from the index date to the development of asthma, censoring because of removal from the

NHI program, death, or the end of 2011.

Statistical analysis

The descriptive statistics of the two groups were presented as mean and standard deviation (SD) for continuous variables and as number and percentage for categorical variables. We used the Pearson Chi-square test and Student *t* test to compare sex, age, and comorbidity differences between the two groups. The incidence density (per 1000 person-years) was estimated for the two groups according to sex, age, occupational status, insurance premium, urbanization, and comorbidity. The cumulative incidence of asthma was calculated using the Kaplan–Meier method and the difference between the nonmigraine and migraine groups was tested using the log-rank test. We used univariate and multivariate Cox proportional hazards regression models to examine asthma-associated risk factors and the risk of asthma. We also evaluated the association between migraine and the risk of asthma in various subgroups according to sex, age, and comorbidities. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the risk of asthma after adjustment for sex, age, occupational status, insurance premium, urbanization, rhinitis, chronic sinusitis, atopic dermatitis, COPD, and annual number of OPD visits.

All the aforementioned analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC, USA). A two-tailed P value of 0.05 was

considered significant.

Results

Between 2000 and 2005, 6647 patients with migraine and 26 588 patients without migraine were enrolled. Both groups exhibited similar sex and age distributions. The mean age of the patients with migraine was 40.1 years (SD = 10.2 years), with a mild predominance of women (approximately 74.9%). Patients with migraine were more likely to have white-collar occupations (55.7%), insurance premium of NTD15 000-29 999 per month (65.4%), and live in urban areas (59.5%). In addition, the migraine group had a higher prevalence of comorbidities, namely rhinitis, chronic sinusitis, atopic dermatitis, and COPD, than did the nonmigraine group. The mean annual OPD visits of the migraine and nonmigraine groups were 26.9 (SD = 18.8) and 14.3 (SD = 12.0), respectively (Table 1).

The cumulative incidence curves of asthma in the migraine and nonmigraine groups are shown in Figure 1. We found the cumulative incidence of asthma to be significantly higher in the migraine group than in the nonmigraine group (log-rank test, $P < .001$).

During the mean follow-up period of 8.57 years, 383 patients in the migraine group were diagnosed with asthma, with an incidence density of 6.76/1000 person-years, compared with 919 patients in the nonmigraine group (incidence density = 3.27/1000

person-years). After adjustment for sex, age, occupational status, insurance premium, urbanization, comorbidities, and annual number of OPD visits, a Cox proportional hazard regression analysis showed that the migraine group had a higher risk of asthma (adjusted HR = 1.37, 95% CI = 1.21–1.56) than the nonmigraine group did (Table 2). According to the results of multivariate Cox regression analysis, female sex, older age (aged 40–60 years), blue-collar work, rhinitis, COPD, and more than 15 OPD visits annually were associated with a higher risk of asthma.

When the study population was stratified by sex, we found that both the women and men in the migraine group had a significantly higher risk of asthma than did those in the nonmigraine group (adjusted HR = 1.29, 95% CI = 1.11–1.49; and adjusted HR = 1.46, 95% CI = 1.07–2.00, respectively). When stratified by age, we found that patients aged 40–60 years with migraine had a higher risk of asthma than did those without migraine (adjusted HR = 1.43, 95 % CI = 1.21 – 1.70). In study participants without comorbidity, patients with migraine had a higher risk of asthma than that of the patients without migraine (adjusted HR = 1.37, 95% CI = 1.16 – 1.60) (Table 3).

Discussion

In this large retrospective cohort study, we observed that patients with migraine were 1.43-fold more likely to develop asthma than those without migraine in the subsequent 12 years. Although migraineurs exhibit a higher prevalence of rhinitis,

chronic sinusitis, atopic dermatitis, COPD, and have more annual OPD visits than those without migraine, migraine remained an independent risk factor after adjusting for these covariates. Additional stratified analysis revealed that the increased risk of asthma remained significantly higher in both sexes and in those between 40 and 60 years of age.

The associations between migraine and asthma have been reported in several observational studies. Gurkan et al reported that a parental history of migraine was more prevalent in children with asthma than in those without asthma (11). A case–control study in the United Kingdom reported that the relative risk of asthma in patients with migraine was 1.59 (95% CI = 1.54–1.65), compared with those without migraine (12). Ozge et al found that among the 186 patients with migraine, 77 (41.4%) reported at least one atopic disorder including asthma (13). A questionnaire-based cross-sectional study in Norway indicated that migraine was 1.5 times more likely in patients with asthma, and the association increased with headache frequency (14). Our findings were consistent with those of these studies. According to the literature, patients with asthma also had a higher risk of migraine (9, 15), implying that the relationship between migraine and asthma may be bidirectional. However, a population-based follow-up study and a nested case–control analysis conducted in the United Kingdom by Becker et al indicated that the risk of newly diagnosed asthma

was not increased in patients with migraine (8). We do not know exactly what contributed to the differences between Becker and co-workers' study and our study. Obviously, the databases used in these studies (Becker et al vs. the present study) represent quite different ethnic groups. Accordingly, further research must be conducted to determine whether ethnic differences play a role in defining the relationship between migraine and asthma.

Currently, the underlying pathophysiology regarding the association between migraine and asthma is unknown. However, several lines of evidence may offer plausible explanations. First, migraine and asthma are considered inflammatory disorders of the trigeminovascular system and airway, respectively (16, 17). Studies have observed that in asthmatic patients, mast cells can infiltrate the airway smooth muscle, release various inflammatory mediators, and induce airway remodeling (18, 19). Similarly, in patients with migraine, mast cells are located perivascularly in association with neurons in the dura mater, and when activated by various neuropeptides, they secrete proinflammatory and vasodilatory molecules, which lead to the activation of the trigeminal pain pathway that underlies migraine pathogenesis (20, 21).

Second, the platelet-activating factors, the proinflammatory mediator involved in hyperresponsiveness and inflammation of the airway, were also demonstrated to be

increased during migraine crises (22). Thus, it is hypothesized that platelet-activating factors are responsible for persistent platelet activation and hyperfunction in the cerebral circulation during migraine attacks (22).

Third, a nonselective cation channel primarily expressed in the cell membrane of sensory afferent fibers named transient receptor potential cation channel subfamily V member 1 (TRPV1) reportedly plays a crucial role in the pathophysiology of both migraine and asthma (23, 24). TRPV1 expressed on the nociceptors of trigeminal ganglion can be directly activated by acid, heat, and various chemical substances, which results in the release of neuropeptides that exert a vasodilatory effect and cause neurogenic inflammation, both of which are crucial events in migraine pathogenesis (23, 25, 26). Moreover, it is well documented that TRPV1 is also expressed in airway C-fiber afferent neurons, which can be activated by endogenous TRPV1 activators or inhaled irritants (24, 27). Increased activation of these sensory nerves by endogenous TRPV1 activators or inhaled irritants has been observed in patients with asthma. Consequently, afferent fibers can release various neuropeptides upon activation. These processes are believed to contribute to the pathophysiological effects of asthma, such as reflex bronchoconstriction and coughing (28, 29).

Finally, autoimmune disorder was reported to be associated with the pathogenesis of both migraine and asthma (30, 31). For example, Nahm et al reported that

circulating immunoglobulin G autoantibodies to human bronchial epithelial cell antigen were detected in 43% of patients with nonallergic asthma (32). Arumugam and Parthasarathy observed a significant reduction in the autoimmunity marker CD4⁺CD25⁺ regulatory T cells in patients with migraine, implying that immunodysregulation could be involved in the pathophysiology of migraine (30).

In the age-stratified analysis, only the patients with migraine aged 40 – 60 years exhibited a significantly higher risk of asthma. Because this study is observational, whether age has an influence on the risk of asthma in patients with migraine still requires further research.

The strength of this study is that the database we used was derived from NHI data, which is a compulsory program for Taiwan residents. Therefore, its coverage rate is as high as 99.9%, making our study sample highly representative of the general population, and all claims from different institutions can be obtained for analysis. This enabled us to minimize recall bias which are common in many longitudinal studies.

However, our study also has several limitations that should be considered when interpreting the results. First, because each patient's identification was encrypted in the NHIRD to protect personal information, detailed lifestyle information such as alcohol consumption, smoking, body mass index, and asthma-related environmental exposure was unavailable. Therefore, we could not include these as confounding

factors for analysis. Second, because data on each patient's clinical variables, such as lung function tests, migraine frequency, psychiatric illness, pain medications prescriptions, family history of migraine and asthma, and presence or absence of aura were unavailable, distinguishing different types of migraine as well as different types of asthma was difficult. Finally, although we designed this retrospective cohort study meticulously, potential bias related to the adjustment of confounding factors might still exist. Nevertheless, we believed that the relationship between migraine and asthma observed in this study is still reliable because of the validity of the database, large sample size, and long follow-up periods.

In summary, this retrospective nationwide cohort study found that, after adjustment for rhinitis, chronic sinusitis, atopic dermatitis, and COPD, migraine is associated with a significantly increased risk of asthma. This increased risk remained significantly higher in both sexes and in the 40–60-year age group. Thus, clinicians should consider migraine as a predisposing factor for asthma in the adult population. However, additional studies exploring the underlying association between migraine and asthma are warranted.

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Table 1. Baseline demographic factors and comorbidities of patients according to migraine status

Variable	Nonmigraine group N = 26 588		Migraine group N = 6647		P-value
	n	%	n	%	
Sex					> 0.99
Women	19 908	74.9	4977	74.9	
Men	6680	25.1	1670	25.1	
Age, years					> 0.99
20-39	12 864	48.4	3216	48.4	
40-60	13 724	51.6	3431	51.6	
Mean (SD)	39.8	(10.4)	40.1	(10.2)	0.10
Occupational status					<0.001
White-collar workers	15 551	58.5	3703	55.7	
Blue-collar workers	7971	30.0	2206	33.2	
Other	3066	11.5	738	11.1	
Insurance premium (NTD/ month)					<0.001
<15000	5167	19.4	1189	17.9	
15000-29999	16 736	63.0	4350	65.4	
≥30000	4685	17.6	1108	16.7	
Urbanization					<0.001
Level 1 (highest)	8769	33.0	1920	28.9	
Level 2	7902	29.7	2032	30.6	
Level 3	4954	18.6	1158	17.4	
Level 4 (lowest)	4963	18.7	1537	23.1	
Comorbidity					
Rhinitis	2484	9.34	1287	19.4	< 0.001
Chronic sinusitis	312	1.17	187	2.81	< 0.001
Atopic dermatitis	213	0.80	99	1.49	< 0.001
COPD	46	0.17	26	0.39	0.001
Annual OPD visits					< 0.001
< 15	16 876	63.5	1837	27.6	
≥ 15	9712	36.5	4810	72.4	
Mean (SD)	14.3	(12.0)	26.9	(18.8)	< 0.001

Abbreviation: COPD, chronic obstructive pulmonary disease; NTD: New Taiwan Dollars (1 USD ≐ 32 NTD as of October 2016); OPD, outpatient department; SD, standard deviation;

Table 2. Cox model-measured hazard ratios and 95% confidence interval of asthma associated with migraine and covariates

Variable	Event no.	Person-years	Incidence density	HR (95% CI)	
				Univariate	Multivariate [†]
Migraine					
No	745	228 144	3.27	1.00	1.00
Yes	383	56 658	6.76	2.07 (1.83-2.34)***	1.37 (1.21-1.56)***
Sex					
Women	916	214 027	4.28	1.44 (1.24-1.67)***	1.26 (1.08-1.47)**
Men	212	70 776	3.00	1.00	1.00
Age, years					
20-39	406	137 188	2.96	1.00	1.00
40-60	722	147 614	4.89	1.66 (1.47-1.88)***	1.43 (1.26-1.62)***
Occupational status					
White-collar workers	585	165 525	3.53	1.00	1.00
Blue-collar workers	423	86 974	4.86	1.38 (1.22-1.56)***	1.16 (1.01-1.33)*
Other	120	32 304	3.71	1.05 (0.86-1.27)	1.04 (0.84-1.28)
Insurance premium (NT\$/ month)					
<15000	203	53 845	3.77	1.00	1.00
15000-29999	740	180 528	4.10	1.09 (0.94-1.28)	0.93 (0.98-1.10)
≥30000	185	50 429	3.67	0.98 (0.84-1.20)	0.95 (0.77-1.18)
Urbanization					
Level 1 (highest)	333	92 066	3.62	1.00	1.00
Level 2	347	84 912	4.09	1.13 (0.97-1.31)	1.06 (0.91-1.23)
Level 3	188	52 343	3.59	0.99 (0.83-1.19)	0.99 (0.83-1.18)
Level 4 (lowest)	260	55 482	4.69	1.29 (1.10-1.52)**	1.15 (0.97-1.36)
Comorbidity					
Rhinitis					
No	864	254 768	3.39	1.00	1.00
Yes	264	30 035	8.79	2.51 (2.19-2.88)***	1.90 (1.65-2.20)***
Chronic sinusitis					
No	1092	280 742	3.89	1.00	1.00
Yes	36	4061	8.87	2.23 (1.60-3.11)***	1.24 (0.89-1.75)
Atopic dermatitis					
No	1119	282 327	3.96	1.00	1.00
Yes	9	2475	3.64	0.88 (0.46-1.70)	0.64 (0.33-1.24)

COPD					
No	1115	284 279	3.92	1.00	1.00
Yes	13	523	24.9	6.08 (3.52-10.5)***	3.54 (2.04-6.14)***
Annual OPD visits					
< 15	289	160 475	1.80	1.00	1.00
≥ 15	839	124 327	6.75	3.77 (3.29-4.30)***	2.90 (2.51-3.34)***

Abbreviation: HR, hazard ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

[†] Multivariate Cox proportional hazards regression model including migraine, sex, age (categorical), occupational status (categorical), insurance premium (categorical), urbanization (categorical), rhinitis, chronic sinusitis, atopic dermatitis, chronic obstructive pulmonary disease, and number of annual OPD visits (categorical).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 3. Incidence density and hazard ratios of asthma according to migraine status stratified by sex, age, and comorbidities

Variable	Nonmigraine group			Migraine group			Compared to nonmigraine group HR (95% CI)	
	Event no.	Person-years	Incidence density	Event no.	Person-years	Incidence density	Crude	Adjusted [‡]
Sex								
Women	615	171 545	3.59	301	42 482	7.09	1.98 (1.72-2.27)***	1.29 (1.11-1.49)**
Men	130	56 600	2.30	82	14 176	5.78	2.52 (1.91-3.32)***	1.46 (1.07-2.00)*
Age, years								
20-39	277	109 616	2.53	129	27 572	4.68	1.86 (1.51-2.29)***	1.09 (0.86-1.37)
40-60	468	118 528	3.95	254	29 086	8.73	2.21 (1.89-2.57)***	1.43 (1.21-1.70)***
Comorbidity status [†]								
No	577	205 567	2.81	255	44 972	5.67	2.02 (1.75-2.35)***	1.37 (1.16-1.60)***
Yes	168	22 577	7.44	128	11 686	11.0	1.49 (1.18-1.87)***	1.18 (0.92-1.51)

Abbreviation: HR, hazard ratio; CI, confidence interval.

[†] Patients with any one of rhinitis, chronic sinusitis, atopic dermatitis, and chronic obstructive pulmonary disease were classified as the comorbidity group.

[‡] Model mutually adjusting for sex, age (continuous), occupational status (categorical), insurance premium (categorical), urbanization (categorical), rhinitis, chronic sinusitis, atopic dermatitis, chronic obstructive pulmonary disease, and number of annual OPD visits (continuous).

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Accepted Article

Figure 1. Cumulative incidence curves of asthma for the migraine and nonmigraine groups.

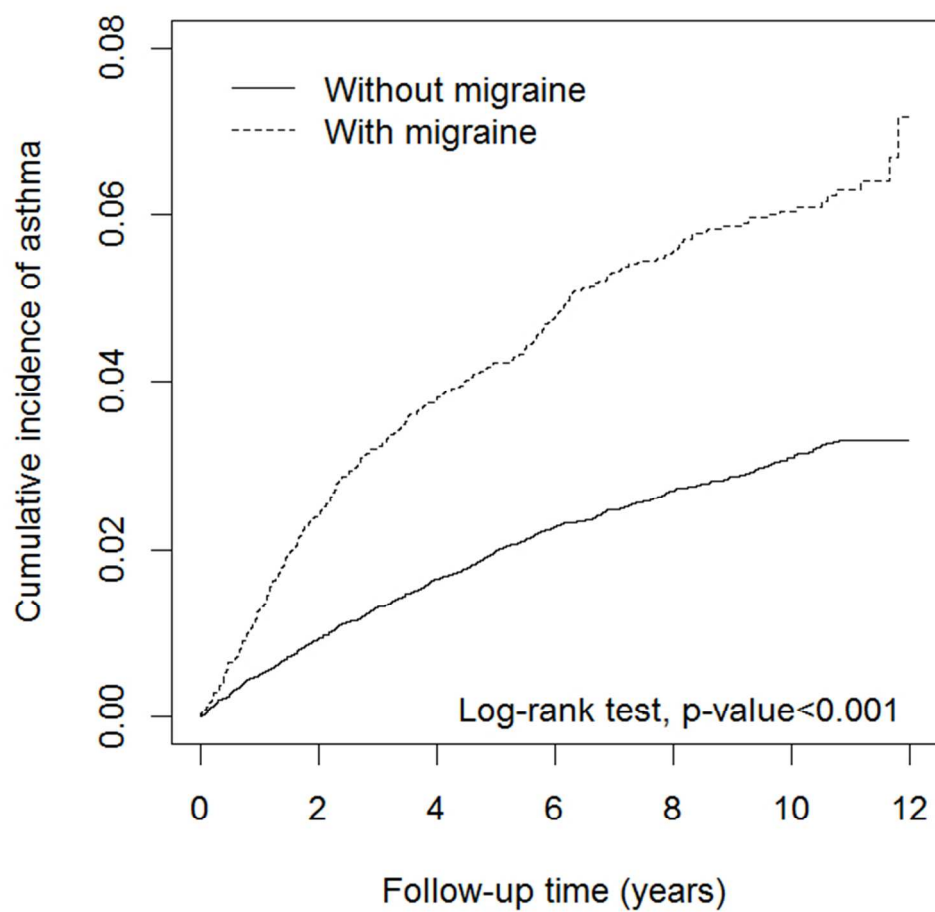


Figure 1. Cumulative incidence curves of asthma for the migraine and nonmigraine groups.

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