Risk of migraine in iron deficiency anemia patients with or without iron supplementation usage: a nationwide database analysis

Type

Research paper

Keywords

gender difference, iron deficiency anemia, migraine, iron supplementation

Abstract

Introduction
This study evaluated the association between iron deficiency anemia (IDA) and migraine and investigated the effects of iron supplementation, and comorbid conditions, including cardiovascular, respiratory, hepatic, endocrine, metabolic, and other diseases on migraine development.

Material and methods
All study subjects aged ≥20 years with newly diagnosed IDA in the Taiwan National Health Insurance Database during 2000–2012 were enrolled. We matched IDA and non-IDA subjects according to age and sex at a 1:2 ratio. Our primary outcome was diagnosis of migraine, and the patients were monitored until the end of 2013. A Cox proportional hazards regression model was used to evaluate the risk of migraine events in IDA.

Results
The cumulative incidence of migraine in patients with IDA was 5.82 per 1,000 person-years, which was higher than that in the comparison group (3.99 per 1,000 person-years) during the follow-up period (log-rank test, $p < 0.001$). After controlling for potentially confounding factors, the risk of migraine was higher in the IDA group compared with the non-IDA group (the adjusted hazard ratio = 1.68, 95% CI = 1.51−1.87, $p < 0.001$). Female and ≤50 year-old IDA patients with or without iron supplementation use had an increased incidence of migraine ($p < 0.05$).

Conclusions
Our study provided additional evidence of an increased risk of migraine in patients with IDA. We also found that females and ≤50 year-old IDA patients with or without iron supplementation use had an increased risk of migraines.

Risk of migraine in iron deficiency anemia patients with or without iron supplementation usage: a nationwide database analysis

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Key words: iron deficiency anemia, migraine, iron supplementation, gender

difference

Running title

Iron supplementation usage and migraine in IDA patients

Introduction

Migraine is a common chronic, intermittent primary headache disorder characterized by recurrent attacks of moderate-to-severe throbbing or pulsatile sensations on one side of the head lasting 4–72 h [1, 2]. Approximately 1.04 billion adults in the world are affected by migraine [3]. The etiology of migraine is multifactorial, involving genetic, hormonal, and environmental factors [4, 5]. Studies have indicated that many comorbidities are associated with migraine, including cardiovascular disorders, psychiatric disorders, neurological diseases, sleep conditions, and inflammatory conditions [6-9]. Moreover, studies have identified comorbidities associated with specific migraine subgroups, such as iron deficiency anemia (IDA) accompanying menstrually related migraine (MRM) [7, 10].

Iron deficiency anemia (IDA) is the dominant type of anemia accounting for >50% of anemic cases [11]. In the developed world, IDA is prevalent among 2%–5% of adult men and postmenopausal women [12]. IDA can cause various symptoms, such as fatigue, weakness, anxiety, and shortness of breath, and these symptoms may also trigger migraine [13, 14]. Furthermore, IDA has been linked to migraine headaches and an increased predisposition to pain [15, 16]. Recent studies have revealed that iron deficiency (with or without anemia) was associated with

reduced dopamine transporter density and activity, leading to extracellular dopamine

and a decline in the number of dopamine receptors in the striatum [17]. Evidence

suggests that dopamine is involved in migraine pathogenicity [18].

Till date, no large-scale population-based study has evaluated the increased risk

of migraine in patients with IDA. In the present study, we hypothesized that the

incidence of IDA is highly correlated with migraine. The objectives of this study

were to evaluate the association between iron deficiency anemia (IDA) and migraine

and investigate the effects of iron supplementation and comorbid conditions,

including cardiovascular disease, respiratory disease, hepatic disease, endocrine and

metabolic disorders, and other diseases on migraine development.

Materials and Methods

Taiwan's National Health Insurance (NHI) program was launched as a single-payer system on March 1, 1995. As of 2014, the NHI program provides insurance for 99.9% of Taiwan's population. Data for this study were gathered from the Longitudinal Health Insurance Database 2005 (LHID2005), a subset of the National Health Insurance Research Database (NHIRD). The LHID2005 comprises 1 million people randomly selected from the NHIRD, and no statistically significant differences in age, sex, or health care costs between the LHID2005 sample group and all enrollees were found according to a National Health Research Institutes report [19]. The LHID2005 contains the demographic data of enrollees, including service records and expenditure claims for outpatient, inpatient, and ambulatory care and data associated with contracted pharmacies for reimbursement purposes. The International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) is used to define disease in this database. The data underlying this study are from the NHIRD, which has been transferred to the Health and Welfare Data Science Center (HWDC). Interested researchers can obtain the data through formal application to the HWDC, Department of Statistics, Ministry of Health and Welfare, Taiwan. This study was reviewed and approved by the Institutional Review Board of the Ditmanson Medical Foundation, Chia-Yi Christian Hospital

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(CYCH-IRB No: 2018078, November 23, 2018), Taiwan. All patient data from the NHIRD were anonymized; therefore, the board did not require informed consent from the patients for this study.

A retrospective cohort study design and a study cohort comprising patients aged ≥20 years who had received a diagnosis of IDA (ICD-9-CM Code 280) between 2000 and 2012 was conducted. Patients diagnosed as having IDA before 2000 were excluded to increase the likelihood of identifying new cases. The index date was defined as the date of first IDA diagnosis between 2000 and 2012. To ensure accurate diagnoses of IDA, only patients diagnosed with IDA for at least 2 times during the study period were included in this study. The iron supplementary medication (ATC: B03A) data were also collected. Individuals who had missing data and those who were diagnosed without blood tests were excluded. Subjects without IDA were randomly selected from the LHID2005 and designated the non-IDA group. The non-IDA group was frequency matched with the IDA cohort at a 2:1 ratio for age, sex, and the index year that IDA was diagnosed. The study endpoint was development of migraine (ICD-9-CM code 346). Migraine diagnoses were identified according to the International Classification of Headache Disorders, Second Edition criteria (ICHD-II) [20]. The ICHD-II criteria was shown in supplemental Table S1. We included patients in this group only when migraine was diagnosed after the IDA

index date. For those who did not have migraine, the last day of follow-up was defined as the date of insurance withdrawal or the last day of the study period (December 31, 2013). The mean follow-up duration for the IDA and non-IDA groups were 7.03 ± 3.82 and 7.11 ± 3.81 years, respectively. The comorbidities consisted of common medical diseases and disorders that may possibly affect IDA or migraine. We considered the following comorbidities as confounding factors in this study: cardiovascular disease, respiratory disease, hepatic disease, endocrine and metabolic disorders, and other diseases. A comorbidity was defined as having the comorbidity before the IDA index date and included hypertension (ICD-9-CM Code 401–405), diabetes mellitus (DM, ICD-9-CM Code 250), dyslipidemia (ICD-9-CM Code 272), coronary artery disease (CAD, ICD-9-CM Code 410–414), stroke (ICD-9-CM Code 430–438), chronic kidney disease (CKD, ICD-9-CM Code 585), cirrhosis (ICD-9-CM: 571.2, 571.5, and 571.6), hyperthyroidism (ICD-9-CM Code 242), hypothyroidism (ICD-9-CM Code 244), and chronic pulmonary disease (COPD, ICD-9-CM Code 490–496). In addition, sociodemographic factors, including age, sex, urbanization level, and economic status were also considered to be confounding factors. There were four urbanization levels (urban, suburban, rural and remote areas), and economic status was classified into three categories: a monthly insurable wage < new Taiwan dollar (NTD) 19,100 (low-income level),

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NTD 19,100–41,999 (intermediate-income level), and NTD ≥ 42,000 (high-income

level). The current exchange rate is approximately US $0.0316 = NTD 1.00.

The chi-square test and Student's *t* test were used to compare the differences in

the demographic and clinical characteristics between the IDA and non-IDA groups.

The Kaplan–Meier method was used to estimate the cumulative incidence of

migraine between the two groups, and significance was determined using the

log-rank test. The incidence rate was calculated as the number of first diagnoses of

migraine per 1,000 person-years. We calculated the hazard ratio (HR) and the

accompanying 95% CI by Cox proportional regression models and adjusted the

possible covariates that were mentioned above. Subgroup analyses were used to

identify any potential differences in the responses to iron supplementation. All

statistical analyses were performed using SPSS for Windows version 21.0 (IBM

Corporation, Armonk, NY, USA). R software (R Foundation for Statistical

Computing, Vienna, Austria) was used to draw the survival curve. A two-tailed

p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 26,217 patients diagnosed as having IDA and 52,434 sex- and age-matched controls were included (Table 1). Figure 1 depicts the flowchart for selecting the study population.

Incidence rates and HR analysis of migraine in the patients with IDA

The cumulative incidence of migraine was higher in the patients with IDA than in the comparison group (5.82 per 1,000 person-years vs. 3.99 per 1,000 person-years, respectively; log-rank test, $p < 0.001$) during the follow-up period (Figure 2). After adjusting for age, sex, area, income level, iron supplementation, and comorbidities, the risk of migraine was significantly higher in the IDA group than in the comparison group [adjusted HR (aHR) = 1.68, 95% CI = 1.51–1.87, $p < 0.001$]. Multivariate Cox proportional hazards analysis showed that female, rural area, dyslipidemia, and COPD were at a heightened risk of migraine relative to non-IDA group ($p < 0.05$). Moreover, age > 50 years, hypertension, DM, CKD, and iron supplementation were at a lower risk of migraine ($p < 0.05$, Table 2).

Adjusted HRs measured using the multivariate Cox proportional model for patients with migraine associated with IDA and iron supplementation and stratified by sex

Table 3 presents the sex stratification analysis of the risk of IDA-associated migraine. In the comparison group, females without iron supplementation use had a higher risk of migraine than the risk of those with iron supplementation use (aHR = 1.45, 95% CI = 1.12–1.87). Furthermore, females who had IDA with or without iron supplementation use had a higher migraine risk than non-IDA females ($p < 0.001$).

Adjusted HRs measured using the multivariate Cox proportional model for patients with migraine associated with IDA and iron supplementation and stratified by age

Non-IDA controls ≦50 years old without iron supplementation use had a higher risk of migraine than that of non-IDA controls ≦50 years old with iron supplementation use (aHR = 1.63 with 95% CI = 1.20–2.22). In addition, IDA patients ≦50 years old with or without iron supplementation use had a higher risk of migraine than that of the non-IDA controls <50 years old without iron supplementation use ($p < 0.001$, Table 4).

Discussion

This nationwide population-based cohort study demonstrated that the risk of migraine was markedly higher for patients with IDA than for the non-IDA group, with an aHR of 1.68. Furthermore, the IDA patients with or without iron supplementation were associated with significantly higher risks of migraine, especially in females or patients ≤ 50 years old. These results support those of previous reports showing that IDA may be a risk factor for developing migraine. Pamuk et al. stated that IDA patients experienced migraines more frequently, which can be indicative of an underlying relationship between IDA and diseases and central nervous system problems [15]. A similar study was conducted in Iran by Gholamreza-Mirzaee et al. They found that iron supplements might be an effective treatment or prophylaxis in patients with migraine associated with IDA [21]. We also found that migraine was more prevalent in females with IDA than in males with IDA. Previous research has also found that IDA was more common in patients with menstrual migraine and that migraine attacks could be triggered by IDA [10].

In the present study, we revealed that IDA had negative effects on the risk for migraine in patients aged <50 years. Former studies have stated that migraine is most commonly diagnosed in individuals aged between 25 and 55 years and its peak is between 30–39 years of age [22]. A previous study suggested that migraines are a

genetic disorder that runs in the family, which usually occur during childhood near the age of adolescence with a few attacks per year [4]. Then, it progresses into a few attacks per week between the ages of 22 and 55 years, after which the symptoms of migraine may be less intense, milder, or may disappear altogether [5]. Moreover, a 12 year retrospective follow-up study that included 374 patients with migraine from Sweden found that 29% of the patients no longer had the disorder as they aged, and the remaining 71% had fewer attacks that were less frequent and caused milder pain [23]. Previous study was also indicated that female after menopause, the prevalence of migraine falls by approximately one-half, at least partly as a result of hormonal stability [24, 25]. This decrease in migraines with increasing age may be because of altered brain structure and functionality caused by repeated headache episodes [26, 27]. Additionally, during the aging process, the brain begins to lose cells and shrinks and may exhibit a decrease in several neurological functions and signaling pathways [28].

Besides age, our results indicated that females had a higher risk of migraine than males, consistent with previously published results [29, 30]. Significant differences between genders have been found in multiple epidemiological studies of migraine [31]. Migraine is reported to be three times more prevalent in females than in males [32]. A distinction in hormonal balances is the major reason why females

suffer migraines more frequently than males. Estrogen and progesterone can affect

the pain-processing networks and the endothelium involved in the pathophysiology

of migraine [33, 34]. More recent studies have proved that the drop in estrogen may

lead to the vasodilatation of cranial vasculature and a sensitization of trigeminal

nerves, which can trigger migraine [35, 36]. A study also found that women with

migraine experience a faster drop in estrogen levels just before the onset of their

period than non-migraineurs [34]. In addition, the estrogen also influence serotonin

neurotransmission system and calcitonin gene-related peptide (CGRP) levels making

women more predisposed to migraine attacks. Previous research was showed that

the level of CGRP were higher in women of reproductive age than in men [37].

Hormonal fluctuations during the female reproductive life cycle (eg., menstruation,

pregnancy, and menopause) are known to impact the frequency and intensity of

migraine [38]. In addition to hormonal triggers, there are a number of factors

contributing to migraine, such as genetic and epigenetic factors, environmental

stressors, psychosocial factors, and coping strategies in response to stress and pain

[4, 5]. Psychosocial factors (stress, anxiety, and irritability) have a greater effect on

females than on males [39]. These parameters may explain, in part, the differences

in prevalence and presentation of migraine between females and males.

Although there are many causes of migraine, one of these may be iron

deficiency. Several studies have shown an association between iron deficiency and

migraine headache in adults [15, 21, 40]. Keivani et al. showed that iron deficiency

was more frequent in 15 to 45 year-old women with migraines than in women

without migraines [40]. A study in Turkey reported that 36.2% of iron-deficient

patients experienced migraines [15]. Another study in Iran indicated that ferrous

sulfate therapy was effective in reducing the monthly frequency and severity of

migraine headaches in 15 to 45 year-old women with and without iron deficiency

[21]. Previous studies have also indicated that there might be an association between

body iron storage status and the incidence of migraine [15, 41]. Similar to previous

findings, our results found that iron supplementation was beneficial for reducing

migraine risk in IDA patients. A possible explanation may be that iron deficiency

can decrease hemoglobin levels and the blood then is unable to deliver enough

oxygen to the brain, which causes migraines [15]. Therefore, it could be important

for adults with migraine to have their iron status and serum iron and ferritin levels

evaluated.

Studies have also indicated that migraine is associated with comorbidities,

including cardiovascular disorders, stroke, psychiatric disorders, sleep conditions,

inflammatory conditions, and chronic pain [7, 9]. In this research, we found that

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patients with dyslipidemia were at a high risk of migraine. Recent studies have

suggested that the intensity and frequency of migraine attacks may be related to the

level of blood lipids [42, 43]. This may be attributed to the fact that dyslipidemia

induces platelet aggregation and triggers neurogenic inflammation by inducing

changes in serum serotonin and platelet serotonin levels, initiating the cascades of

prostaglandins (mainly PGE2) and leukotrienes (LT) formation [44]. These changes

lead to vasodilatation and migraine headache. Our research also found that patients

with COPD were at a high risk of migraine. In a cross-sectional study, data from the

2013–2015 National Health Interview Survey (n = 104,926 adults) indicated

associations between migraine and COPD [45]. Another study using multivariate

logistic regression analyses suggested that COPD was positively associated with

migraine. Patients with COPD have damaged lungs caused by chronic bronchitis and

emphysema that hampers the normal functioning of the lungs [46]. These problems

along with restricted airflow may cause migraine.

    This study had a number of strengths. First, the data were retrieved from the

NHIRD, which is highly representative of the general Taiwanese population.

Moreover, a large population-based sample size can provide adequate statistical

power to show the significance of any associations between factors and an effect and

avoids selection bias. However, this study had several limitations that should be

addressed. First, the incidence rate of migraine may have been underestimated

because only patients who sought medical help were enrolled in the study. Second,

each patient's clinical information, such as IDA severity, migraine frequency, and the

presence or absence of auras, neuroimaging, or other laboratory results, was not

available in the NHIRD. Therefore, it was difficult to evaluate the effect of IDA

severity on migraines in this study. Finally, detailed information on lifestyle,

individual behavior, psychological status, nutrition status, and environmental effects

were not recorded in the NHIRD, all of which might have been confounding factors.

Hence, more prospective studies are warranted to further investigate the association

between IDA and migraine.

Conclusion

Our study showed that IDA increased the likelihood of experiencing migraines in the

subjects. Moreover, female and ≤50 year-old IDA patients with or without iron

supplementation use were found to have an increased risk of migraines. According

to our results, iron supplementation was beneficial for reducing the risk of migraine

in patients with IDA. It indicates that iron supplements might be an effective

treatment or prophylaxis to reduce the risk of migraine in patients with IDA.

Clinicians should be aware of the high migraine risk in patients with new IDA

diagnosis and implement appropriate monitoring of high-risk groups. Future studies

are needed to clarify the pathogenesis of IDA on the development of migraine.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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Figure legends

Figure 1. Flow diagram of the present study from the NHIRD.

Figure 2. Cumulative incidence of migraine in the IDA and non-IDA groups,

compared with a log-rank test. A statistically significant difference exists between

the IDA and non-IDA groups ($p < 0.001$)

Table 1. Demographic characteristics and comorbidities in groups with and without IDA

	IDA Group N = 26,217	Non-IDA Group N = 52,434	*p*-value
Age, mean ± SD	51.76 ± 18.40	51.76 ± 18.40	0.998
≤50	14698 (56.06)	29424 (56.12)	0.887
>50	11519 (43.94)	23010 (43.88)	
Sex			1.000
Male	6644 (25.34)	13288 (25.34)	
Female	19573 (74.66)	39146 (74.66)	
Area			<0.001
Urban	15201 (57.98)	32028 (61.08)	
Suburban	8167 (31.15)	15491 (29.54)	
Rural	1833 (6.99)	3086 (5.89)	
Remote area	1016 (3.88)	1829 (3.49)	
Income level			<0.001
Low	13332 (50.85)	27296 (52.06)	
Intermediate	11176 (42.63)	21435 (40.88)	
High	1709 (6.52)	3703 (7.06)	
Hypertension	8350 (31.85)	13438 (25.63)	<0.001
DM	4532 (17.29)	6200 (11.82)	<0.001
Dyslipidemia	4805 (18.33)	7849 (14.97)	<0.001
CAD	4538 (17.31)	6785 (12.94)	<0.001
Stroke	3363 (12.83)	4732 (9.02)	<0.001
CKD	1501 (5.73)	844 (1.61)	<0.001
Cirrhosis	999 (3.81)	425 (0.81)	<0.001
Hyperthyroidism	865 (3.30)	1177 (2.24)	<0.001
Hypothyroidism	336 (1.28)	423 (0.81)	<0.001
COPD	6185 (23.59)	9698 (18.50)	<0.001
Iron supplementation	16802 (64.09)	2504 (4.78)	<0.001

Data are presented as the mean ± SD or number (percentage, %); DM = diabetes mellitus; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

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

Variables	IDA			Non-IDA			Adjusted HR
	Event	PY	Rate#	Event	PY	Rate#	(95% CI)
Migraine	1073	184373.67	5.82	1490	373241.22	3.99	1.68 (1.51–1.87)***
Age - ≤50	831	107922.02	7.70	1087	219576.05	4.95	1.00 (ref.)
- >50	242	76451.65	3.17	403	153665.17	2.62	0.59 (0.52–0.66)***
Sex - Male	98	44033.65	2.23	161	88592.38	1.82	1.00 (ref.)
- Female	975	140340.03	6.95	1329	284648.84	4.67	2.30 (2.01–2.63)***
Area - Urban	631	107172.02	5.89	917	227405.87	4.03	1.00 (ref.)
- Suburban	331	57291.88	5.78	421	110426.96	3.81	1.03 (0.95–1.13)
- Rural	73	12805.61	5.70	94	22263.52	4.22	1.25 (1.06–1.47)**
- Remote area	38	7104.16	5.35	58	13144.87	4.41	1.17 (0.95–1.44)
Income level - Low	504	93723.21	5.38	740	196017.5	3.78	1.00 (ref.)
- Intermediate	492	78598.78	6.26	626	151375.19	4.14	1.01 (0.93–1.10)
- High	77	12051.68	6.39	124	25848.53	4.80	1.07 (0.92–1.24)
Hypertension - No	898	131754.42	6.82	1255	289118.45	4.34	1.00 (ref.)
- Yes	175	52619.25	3.33	235	84122.77	2.79	0.84 (0.73–0.97)*
DM - No	986	156457.96	6.30	1396	335417.79	4.16	1.00 (ref.)
- Yes	87	27915.72	3.12	94	37823.43	2.49	0.75 (0.63–0.88)**
Dyslipidemia - No	954	156655.30	6.09	1331	329107.70	4.04	1.00 (ref.)
- Yes	119	27718.37	4.29	159	44133.52	3.60	1.26 (1.10–1.46)**
CAD - No	966	155899.47	6.20	1359	331987.76	4.09	1.00 (ref.)
- Yes	107	28474.21	3.76	131	41253.46	3.18	1.14 (0.97–1.33)
Stroke - No	1014	164226.33	6.17	1421	345445.03	4.11	1.00 (ref.)
- Yes	59	20147.35	2.93	69	27796.19	2.48	0.84 (0.69–1.03)
CKD - No	1051	175040.47	6.00	1482	368683.62	4.02	1.00 (ref.)
- Yes	22	9333.20	2.36	8	4557.59	1.76	0.64 (0.45–0.93)*
Cirrhosis - No	1058	178576.68	5.92	1482	370745.68	4.00	1.00 (ref.)
- Yes	15	5796.99	2.59	8	2495.53	3.21	0.84 (0.55–1.27)
Hyperthyroidism - No	1029	178921.00	5.75	1463	366467.96	3.99	1.00 (ref.)
- Yes	44	5452.67	8.07	27	6773.26	3.99	0.99 (0.78–1.27)
Hypothyroidism - No	1052	182464.64	5.77	1482	371023.02	3.99	1.00 (ref.)
- Yes	21	1909.04	11.00	8	2218.20	3.61	1.33 (0.92–1.93)
COPD - No	870	146049.19	5.96	1255	315021.44	3.98	1.00 (ref.)
- Yes	203	38324.49	5.30	235	58219.78	4.04	1.33 (1.19–1.49)***
Iron supplementation							
- No	343	59456.23	5.77	1424	351321.93	4.05	1.00 (ref.)
- Yes	730	124917.45	5.84	66	21919.29	3.01	0.81 (0.72–0.91)***

DM = diabetes mellitus; CAD = coronary artery disease; PY = person–years; Rate# = incidence rate in per 1,000 person–years; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

Table 3. Adjusted HRs measured using the multivariate Cox proportional model for patients with migraine associated with IDA and iron supplementation and stratified by sex

Male

IDA	Iron supplementation	Event	PY	Rate[#]	IRR (95% CI)	Adjusted HR (95% CI)‡
−	+	6	3564.42	1.68	1.00 (ref.)	1.00 (ref.)
−	−	155	85027.95	1.82	1.08 (0.48–2.45)	0.86 (0.38–1.95)
+	+	44	22739.86	1.93	1.15 (0.49–2.70)	0.97 (0.41–2.29)
+	−	54	21293.79	2.54	1.51 (0.65–3.50)	1.17 (0.50–2.74)

Female

IDA	Iron supplementation	Event	PY	Rate[#]	IRR (95% CI)	Adjusted HR (95% CI)‡
−	+	60	18354.87	3.27	1.00 (ref.)	1.00 (ref.)
−	−	1269	266293.98	4.77	1.46 (1.13–1.89)***	1.45 (1.12–1.87)*
+	+	686	102177.59	6.71	2.05 (1.58–2.67)***	2.00 (1.54–2.61)***
+	−	289	38162.44	7.57	2.32 (1.75–3.06)**	2.37 (1.80–3.13)***

Adjusted hazard ratio (HR)‡: multiple analysis of age, area, income level, and comorbidities; PY = person–years; Rate[#] = incidence rate in per 1,000 person–years; IRR = incidence rate ratio; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$

Table 4. Adjusted HRs measured using the multivariate Cox proportional model for patients with migraine associated with IDA and iron supplementation and stratified by age

≦50

IDA	Iron supplementation	Event	PY	Rate[#]	IRR (95% CI)	Adjusted HR (95% CI)‡
−	+	42	12675.34	3.31	1 (reference)	1 (reference)
−	−	1045	206900.72	5.05	1.52 (1.12–2.08)**	1.63 (1.20–2.22)**
+	+	588	79164.72	7.43	2.24 (1.64–3.07)***	2.24 (1.64–3.07)***
+	−	243	28757.30	8.45	2.55 (1.84–3.54)***	2.93 (2.11–4.07)***

>50

IDA	Iron supplementation	Event	PY	Rate[#]	IRR (95% CI)	Adjusted HR (95% CI)‡
−	+	24	9243.95	2.60	1 (reference)	1 (reference)
−	−	379	144421.21	2.62	1.01 (0.67–1.53)	0.96 (0.63–1.45)
+	+	142	45752.73	3.10	1.20 (0.78–1.84)	1.20 (0.78–1.85)
+	−	100	30698.92	3.26	1.26 (0.80–1.96)	1.29 (0.83–2.02)

Adjusted hazard ratio (HR)‡: multivariable analysis of age, area, income level, and comorbidities; PY = person–years; Rate[#] = incidence rate in per 1,000 person–years; IRR = incidence rate ratio; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Supplemental Table 1. The International Classification of Headache Disorders, Second Edition criteria (ICHD-II).

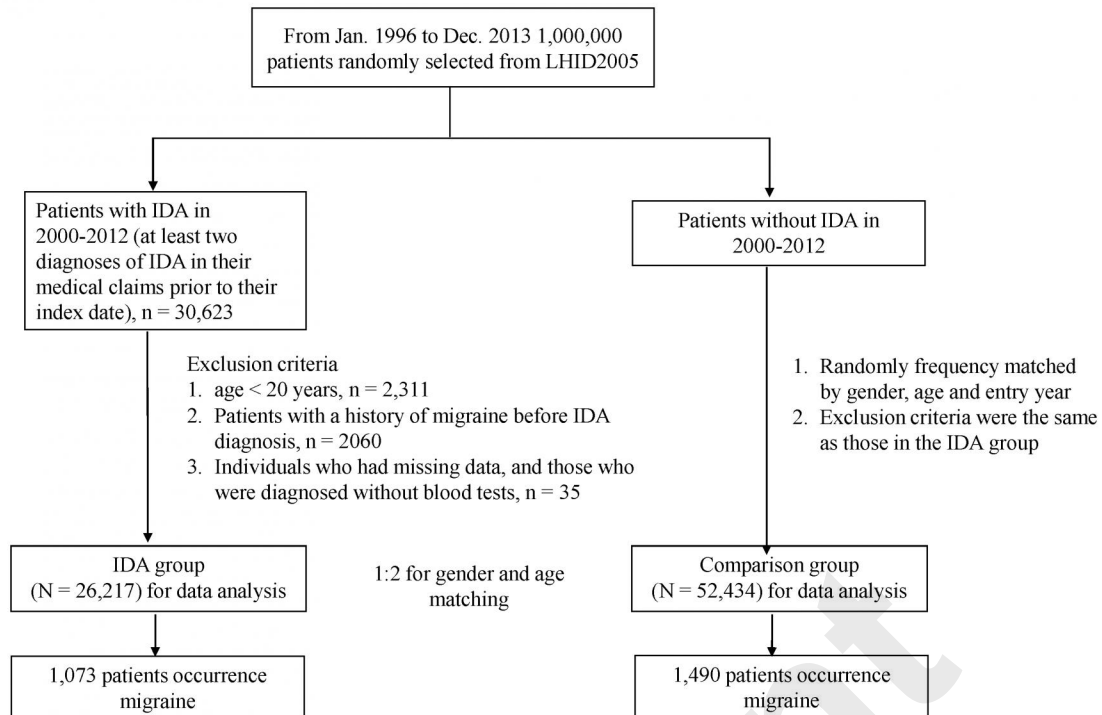| ICHD-II criteria	
	A. Headache present on 15 days/month fulfilling criteria C and D
	B. Regular overuse for >3 months of 1 drugs that can be taken for acute and/or symptomatic treatment of headache
	C. Headache has developed or markedly worsened during medication overuse
	D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication

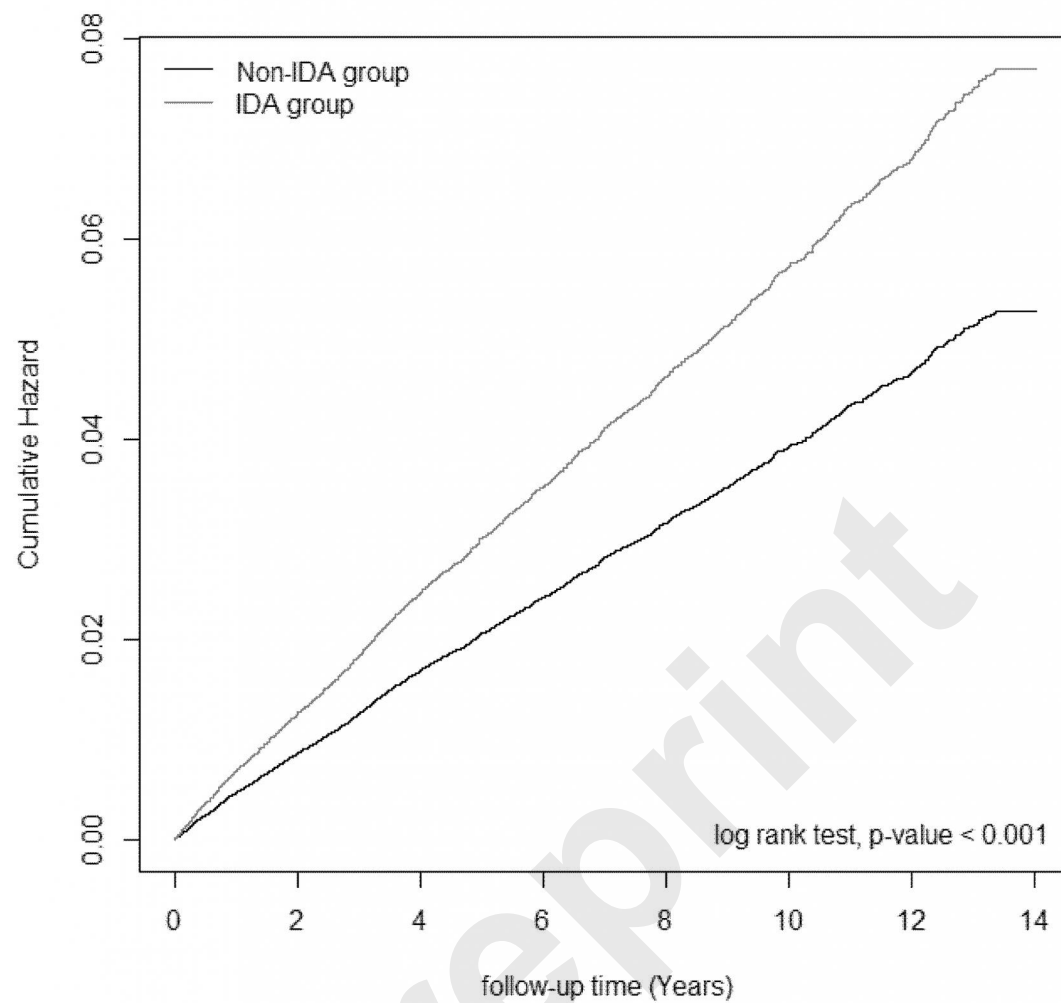Figure 1. Flow diagram of the present study from the NHIRD.

Figure 2. Cumulative incidence of migraine in the IDA and non-IDA groups, compared with a log-rank test. A statistically significant difference exists between the IDA and non-IDA groups (p < 0.001)