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Increased risk of ischemic stroke in patients with migraine: A longitudinal follow-up study using a national sample cohort in Korea

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Abstract

Objective: Growing evidence has supported the association between migraine and stroke, but the causative association remains unclear at present. According to stroke type, we aimed to investigate the risk of stroke in patients with migraine using a national sample cohort from Korea.

Design: A longitudinal follow-up study

Setting: Data from 2002 to 2013 national cohort collected by Korean Health Insurance Review and Assessment were used.

Participants: We extracted the data from patients with migraine (n = 41,585) and 1:4-matched controls (n = 166,340) and analyzed the occurrence of ischemic and hemorrhagic strokes. The migraine group included participants diagnosed with migraine (ICD-10: G43) ≥ 2 times. Hemorrhagic stroke (I60-I62) and ischemic stroke (I63) were determined using admission histories. The crude and adjusted hazard ratios (HRs) were calculated using Cox proportional hazard models, and the 95% confidence intervals (CIs) were determined. Subgroup analyses based on age and sex were also performed.

Results: The rates of ischemic stroke were higher in the migraine group (2.3% [964/41, 585]) than in the control group (2.0% [3,294/163,046], P < 0.001). The adjusted HR of ischemic stroke was 1.18 (95% CI = 1.10-1.26) in the migraine group (P < 0.001). The strongest association between migraine and ischemic stroke was found in young women. The contribution of migraine to the occurrence of ischemic stroke was also observed in middle aged women, old women, and young men (each P < 0.05). The risk of hemorrhagic stroke did not reach statistical significance.

Conclusion: Migraine is associated with an increased risk of ischemic stroke but not hemorrhagic stroke.

Keywords: migraine, stroke, cohort study, Korea

STRENGHTS AND LIMITATIONS OF THIS STUDY

* Migraine is associated with the increased risk of developing ischemic stroke.

* The strongest association between migraine and ischemic stroke was found in young women (20-39 years old).

* A higher risk of hemorrhagic stroke in patients with migraine did not reach statistical significance, but it awaits further confirmation.

Introduction

Migraine is a common neurovascular disorder characterized by recurrent disabling episodes of headache, most often unilateral headache. The headache is partly accompanied with visual or sensory symptoms, namely, aura.[1] The annual prevalence of migraine is approximately 8%–15% worldwide,[2 3] and in Korea, the estimated incidence is 6.1%.[4] Migraine appears to present at a relatively young age (< 45 years); it is more prevalent in women than men, with a prevalence of > 25% in the 35–39-year-old female population worldwide.[1] The use of migraine as an independent risk factor for cardiovascular events has been debated for many years, but it is an established risk factor for ischemic stroke.[5]

Stroke is a cerebrovascular condition involving limitation of blood flow to the brain due to blockage or rupture in the cerebrovascular system.[6] Stroke is responsible for approximately 700,000 deaths annually in the Western world.[7] In Korea, the estimated stroke incidence is approximately 795,000 in people aged ≥ 30 years.[8] More than 80% of stroke cases are ischemic, and the rest are hemorrhagic; ischemic and hemorrhagic strokes differ with regard to risk factors, genetic predisposition, and mortality rates.[9 10]

To date, several underlying physiological mechanisms have been suggested to explain the association between migraine and stroke. The risk factors for stroke in migraineurs have been widely evaluated; the common comorbidities, including hypertension, obesity, dyslipidemia, and smoking, were validated.[11] In addition, specific genetic etiologies associated with vasculopathy can manifest in both migraine and stroke.[12] A recent investigation employing a migraine mutant mouse model also indicated that shared genetic risk factors rendered the brain more vulnerable to ischemic stroke.[13]

Moreover, migraine itself carries an increased risk of ischemic stroke. Recently, a population-based case-control study in Taiwan demonstrated an association between

migraine and ischemic stroke (adjusted hazard ratio [HR]: 1.24, confidence interval [CI]: 1.12–1.38).[3] Similarly, an increased risk of ischemic stroke has been consistently found in migraineurs, especially in those with migraine with aura.[3 14-17] Furthermore, growing evidence has supported the association between migraine and hemorrhagic stroke,[18 19] but the causative association remains unclear at present. Given that stroke is a leading cause of mortality, validation of the association between migraine and stroke may facilitate treatment and prognosis in such cases.

Herein, by using a national Korean population-based sample cohort, we examined the association between migraine and stroke. We extracted data for patients with migraine and a 1:4-matched control group and analyzed the occurrence of ischemic stroke and hemorrhagic stroke in this cohort. Subgroup analyses according to age and sex were also performed.

Materials and Methods

Study Population and Data Collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The Institutional Review Board exempted the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly from the entire population database to prevent non-sampling errors. Approximately 2% of the samples (one million) were selected from the entire Korean population (50 million). The selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized stratified systematic sampling methods via proportional allocation to represent the entire population. A previous study verified the appropriateness of the sample after data selection.[20] The National Health Insurance Sharing

Service provides a detailed description of the methods used to perform these procedures.[21] This cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes using the International Classification of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using the Korean Standard Classification of disease), (v) socio-economic data (residence and income), and (vi) medical examination data for each participant from 2002 to 2013.

All Korean citizens are recognized by a 13-digit resident registration number from birth to death. Therefore, exact population statistics have been determined using this database. All Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit resident registration number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. All medical treatments in Korea are tracked without exception using the Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice of death must be provided to an administrative entity before a funeral can be held. Medical doctors record the date and cause of death on a death certificate.

Participant Selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, participants who were diagnosed with migraine (ICD-10: G43) were included. Among them, participants who were treated ≥ 2 times (n = 45,587) were selected. The participants were followed up for 12 years.

The history of admission for hemorrhagic stroke (I60: Subarachnoid hemorrhage, I61: Intracerebral hemorrhage, and I62: Other nontraumatic intracranial hemorrhage) and ischemic stroke (I63: Cerebral infarction) was identified using ICD-10 codes. We selected the

participants who were treated ≥ 1 times. These methods were used in other studies evaluating the incidence of stoke in Korea.[8 22]

The migraine participants were matched 1:4 with participants (control group) who were never diagnosed with a migraine from 2002 through 2013 in this cohort. The control groups were selected from the mother population (n = 1,080,104). The matches were processed for age, group, sex, income group, region of residence, and past medical histories (hypertension, diabetes, and dyslipidemia). To prevent selection bias when selecting the matched participants, we sorted the control group participants using a random number order, and they were then selected from top to bottom. It was assumed that the matched control participants were involved at the same time as each matched migraine participant (index date). Therefore, control group members who died before the index date were excluded. In both the migraine and control groups, participants with histories of hemorrhagic or ischemic stroke before the index date were excluded. In the migraine group, 438 participants were excluded. The migraine participants for whom we could not identify sufficient numbers of matching participants were excluded (n = 185). We excluded participants under 20 years old (n = 3,379). Finally, 1:4 matching resulted in the inclusion of 41,585 migraine participants and 166,340 control participants (Fig.1).

Variables

The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34…, and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were re-categorized into 11 classes (class 1 [lowest income]–class 11 [highest income]). Region of residence was divided into 16

areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of the participants were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were assessed if the participants were treated ≥ 2 times.

Statistical Analyses

Chi-square tests were used to compare the general characteristics between the migraine and control groups. For analysis of the HRs of migraine on hemorrhagic stroke and ischemic stroke, Cox proportional hazard models were used, and 95% CIs were calculated. In these analyses, crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia) models were used. For the subgroup analysis, we divided the participants by age and sex (20–39 years old, 40–59 years old, 60+ years old; men and women). Two-tailed analyses were conducted, and P values less than 0.05 were considered significant. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY, USA).

Results

The mean follow-up was 80.9 (standard deviation [SD] = 41.6) months in migraine patients and 80.9 (SD = 41.6) months in controls. The rates of hemorrhagic stroke were not higher in the migraine group (0.7% [295/41,585]) than the control group (0.7% [1,113/166,340], P = 0.370, Table 1). The rates of ischemic stroke were higher in the migraine group (2.3%

[964/41,585]) than the control group (2.0% [3,294/163,046]. P < 0.001). The general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories) of participants were the same due to the matching protocol (P = 1.000).

Table 1 General Characteristics of Participants

Characteristics	Total participants		
	Psoriasis (n, %)	Control (n, %)	P-value
Age (years old)			1.000
20-24	1,994 (4.8)	7,976 (4.8)	
25-29	2,649 (6.4)	10,596 (6.4)	
30-34	3,640 (8.8)	14,560 (8.8)	
35-39	4,309 (10.4)	17,236 (10.4)	
40-44	4,859 (11.7)	19,436 (11.7)	
45-49	5,187 (12.5)	20,748 (12.5)	
50-54	4,512 (10.9)	18,048 (10.9)	
55-59	3,508 (8.4)	14,032 (8.4)	
60-64	3,209 (7.7)	12,836 (7.7)	
65-69	3,049 (7.3)	12,196 (7.3)	
70-74	2,328 (5.6)	9,312 (5.6)	
75-79	1,423 (3.4)	5,692 (3.4)	
80-84	651 (1.6)	2,604 (1.6)	
85+	267 (0.6)	1,068 (0.6)	
Sex			1.000

Male	10,476 (25.2)	41,904 (25.2)	
Female	31,109 (74.8)	124,436 (74.8)	
Income			1.000
1 (lowest)	837 (2.0)	3,348 (2.0)	
2	3,170 (7.6)	12,680 (7.6)	
3	3,004 (7.2)	12,016 (7.2)	
4	3,131 (7.5)	12,524 (7.5)	
5	3,345 (8.0)	13,380 (8.0)	
6	3,615 (8.7)	14,460 (8.7)	
7	3,908 (9.4)	15,632 (9.4)	
8	4,411 (10.6)	17,644 (10.6)	
9	4,908 (11.8)	19,632 (11.8)	
10	5,456 (13.1)	21,824 (13.1)	
11 (highest)	5,800 (13.9)	23,200 (13.9)	
Region of residence			1.000
Urban	17,959 (43.2)	71,836 (43.2)	
Rural	23,626 (56.8)	94,504 (56.8)	
Hypertension			1.000
Yes	16,209 (39.0)	64,836 (39.0)	
No	25,376 (61.0)	101,504 (61.0)	
Diabetes			1.000
Yes	7,261 (17.5)	29,044 (17.5)	
No	34,324 (82.5)	137,296 (82.5)	
Dyslipidemia			1.000

Yes	12,837 (30.9)	51,348 (30.9)	
No	28,748 (69.1)	114,992 (69.1)	
Hemorrhagic stroke			0.370
Yes	295 (0.7)	1,113 (0.7)	
No	41,290 (99.3)	165,227 (99.3)	
Ischemic stroke			<0.001*
Yes	964 (2.3)	3,294 (2.0)	
No	40,621 (97.7)	163,046 (98.0)	

*Chi-square test. Significance at P < 0.05

The crude and adjusted HRs of hemorrhagic stroke were 1.06 (95% CI = 0.93–1.21, P = 0.369) and 1.06 (95% CI = 0.93–1.21, P = 0.371), respectively, in the migraine group (Table 2). The crude and adjusted HRs of ischemic stroke were 1.17 (95% CI = 1.09–1.26) and 1.18 (95% CI = 1.10–1.26), respectively, in the migraine group (each P < 0.001).

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine		0.369		0.371		<0.001*		<0.001*
Yes	1.06 (0.93-1.21)		1.06 (0.93-1.21)		1.17 (1.09-1.26)		1.18 (1.10-1.26)	
No	1.00		1.00		1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories

In the subgroup analyses, all crude and adjusted HRs of hemorrhagic stroke did not reach statistical significance (Table 3). For patients with ischemic stroke, young men, young women, middle aged men, old men, and old women showed statistical significance (each $P < 0.05$). The significant adjusted HRs were 2.15 (95% CI = 1.15–4.02) in < 40-year-old men; 2.54 (95% CI = 1.55–4.15) in < 40-year-old women; 1.36 (95% CI = 1.36–1.64) in 40–59-year-old women; and 1.17 (95% CI = 1.06–1.29) in ≥ 60-year-old women.

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Young men (20-39 years old, n = 15,550)								
Migraine		0.158		0.158		0.017*		0.017*
Yes	1.56 (0.84-2.89)		1.56 (0.84-2.89)		2.15 (1.15-4.02)		2.15 (1.15-4.02)	
No	1.00		1.00		1.00		1.00	
Young women (20-39 years old, n = 47,410)								
Migraine		0.726		0.726		<0.001*		<0.001*
Yes	1.10 (0.64-1.92)		1.10 (0.64-1.92)		2.54 (1.55-4.15)		2.54 (1.55-4.15)	
No	1.00		1.00		1.00		1.00	
Middle aged men (40-59 years old, n = 22,090)								
Migraine		0.721		0.725		0.565		0.565
Yes	1.07 (0.73-1.56)		1.07 (0.73-1.56)		0.93 (0.71-1.21)		0.93 (0.71-1.21)	

No	1.00	1.00	1.00	1.00	
Middle aged women (40-59 years old, n = 68,240)					
Migraine		0.582	0.583	0.002*	0.002*
Yes	1.07 (0.84-1.38)	1.07 (0.84-1.38)	1.35 (1.12-1.64)	1.36 (1.12-1.64)	
No	1.00	1.00	1.00	1.00	
Old men (60+ years old, n = 14,740)					
Migraine		0.115	0.116	0.275	0.279
Yes	1.29 (0.94-1.78)	1.29 (0.94-1.78)	1.09 (0.93-1.27)	1.09 (0.93-1.27)	
No	1.00	1.00	1.00	1.00	
Old women (60+ years old, n = 39,895)					
Migraine		0.462	0.464	0.002*	0.002*
Yes	0.92 (0.75-1.14)	0.92 (0.75-1.14)	1.17 (1.06-1.29)	1.17 (1.06-1.29)	
No	1.00	1.00	1.00	1.00	

* Cox-proportional hazard regression model, Significance at $P < 0.05$

† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories

Discussion

Migraine appeared to increase the risk of ischemic stroke but not of hemorrhagic stroke. The risk of ischemic stroke was 1.18-fold greater in the patients with migraine than in the matched control subjects, even after adjustment for confounding factors. In the subgroup analyses by age and sex, the relationship with ischemic stroke was observed primarily in young women, middle aged women, old women, and young men, all of whom showed a significant correlation. In contrast, the risk of hemorrhagic stroke was not higher in patients with migraine than in the matched control patients.

Migraine, especially migraine with aura, is an established risk factor for ischemic stroke. Migraine with aura especially increased the risk of ischemic stroke based on the results of large population-based cohort studies and meta-analyses.[3 14-17] Cortical spreading depression (CSD) is a self-propagating wave of depolarization across the cerebral cortex at a slow velocity, 3 to 5 mm/min.[23] CSD has been implicated in migraine with aura, which plays a critical role in the pathophysiology of ischemic stroke. In an experimental study, CSD induced tone alterations in resistance vessels, causing hypoperfusion in tissue at risk for progressive damage, namely, cortical spreading ischemia.[24] In addition, the inflammatory cascade of the neurovascular system, characterized by endothelial dysfunction and coagulation abnormalities, may contribute to the development of ischemic stroke. In the aura phase, the endothelium activates coagulation and thrombosis, which are mediated by inflammatory cytokines and endothelial biomarkers.[25 26] Moreover, specific genetic etiologies, such as Factor V Leiden G 619 1A, prothrombin G20210A, and familial hemiplegic migraine type 1, were reported in migraine with aura. These shared genetic factors may precipitate the susceptibility to CSD, which may explain the association between migraine and stroke.[27]

There is a growing body of evidence regarding the increased risk of ischemic stroke in migraine without aura. Notably, a significant association was found in cases of ischemic stroke resulting from cervical artery dissection.[28] In addition, genetic overlaps among migraine without aura, large artery stroke, and cardio-embolic stroke have been identified.[29] However, strong evidence has been not reported. A recent large population-based study demonstrated an insignificant risk of ischemic stroke in patients with migraine without aura but an increased risk in patients with migraine with aura.[3] The study suggested that the difference may be due to lipid profile, susceptibility to thrombosis, and genetic predisposition.[3] A meta-analysis found that there was no significant association between migraine without aura and ischemic stroke.[17] In the present study, we did not differentiate between migraine subtypes, such as migraine with and without aura, when analyzing the risk of stroke. Given this, the risk of ischemic stroke in migraine was relatively low despite statistical significance compared to that of other studies investigating specific conditions.

Notably, in this study, migraine was not linked to an increased risk of hemorrhagic stroke. In contrast to the present study, a recent meta-analysis, based on 4 case-control and 4 cohort studies, concluded that migraine may increase the risk of hemorrhagic stroke.[19] However, a recent large population-based case-control study did not show an association with hemorrhagic stroke type, including intracerebral hemorrhage and subarachnoid hemorrhage.[30] Migraine was an independent risk factor for aneurismal rupture (OR = 2.4; CI 95% 1.1–5.1) in a case-control study,[31] and even if headache is a premonitory symptom of aneurismal rupture, recall biases might have affected the study results. Above all, a relatively small number of hemorrhagic stroke cases might have resulted in decreased statistical power.

Consistent with the results of previous studies, the strongest association between migraine and ischemic stroke was found in young women. The contribution of migraine to the

occurrence of ischemic stroke was shown to decrease as age increases. Considering that the predisposing factors of stroke increase the incidence of ischemic stroke with age,[32] migraine itself rather than other risk factors could be implicated in the increased risk of ischemic stroke. Notably, we identified a significant association of migraine with ischemic stroke in middle aged and old women in this study. In contrast, a recent large population-based cohort study in Taiwan, with a relatively short follow-up duration of 3.6 years, did not show a significant association in the subset groups of women and those aged < 45 years.[3] This discrepancy might be due to differences in the study design, follow-up duration, and ethnic composition of the study population. In addition, we demonstrated a significant association of ischemic stroke in young men with migraine. Recently, a trend of this association was also reported,[3] but it requires further confirmation due to the lack of evidence at present.

The present study has several strengths. The results of this study are consistent with those of our previous studies utilizing the HIRA-NSC.[33-35] We examined a very large, representative, and nationwide population. Because the NHIS data cover all citizens of Korea without exception, no participants were lost during follow-up. The control group was randomly selected and matched based on age, sex, income, region of residence, and medical history to decrease any confounding effects. An adjusted hazard model was used to further minimize the impact of confounders. Considering that migraine attacks could be frequently repeated, we opted to include patients with migraine who underwent treatment at least twice based on the ICD-10 code to enhance the validity of the study [G43]. In a previous study, the prevalence of migraine in Korea was reported as being approximately 6.1%.[4] This value appeared to be slightly higher than that in the present study, which was 3.7% (41,585/1,125,691) based on strict inclusion criteria of migraine. In addition, the patients with migraine were followed up for 12 years in the present study. Long study periods enable

recruitment of a large study population and enable researchers to observe and analyze the delayed effects of migraine on stroke.

However, the present study has certain limitations that should be addressed in future studies. First, the heterogeneity of migraine was not considered in the present study. Considering that the association could be modulated according to migraine subtype,[36] the present study could not draw a causative association. A firm correlation between the frequency of migraine attacks and the risk of stroke was found,[37] but it could not be assessed using this database. Similarly, the duration and severity of migraine were inconsistent among the study population. Patients with migraine who had mild complaints could not undergo consultation at the clinic; therefore, the impact of migraine on stroke may be underestimated in this study. Third, although this study attempted to include a representative large population and subsequently matched and adjusted for possible confounders, the risk factors for stroke in patients with migraine, such as cigarette smoking, obesity, and migraine-specific drugs, were not available in the insurance database.[11 37]

Conclusion

Based on a large population-based cohort study in Korea, migraine increased the risk of ischemic stroke but not of hemorrhagic stroke. The subgroup of patients at the highest risk of ischemic stroke was young women.

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DATA SHARING STATEMENT

No additional data are available.

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COMPETING INTERESTS STATEMENT

There are no competing interests for any author.

AUTHOR CONTRIBUTIONS

As first authors, SYL wrote the manuscript. DJO and JSL analyzed and interpreted the data. IGK performed the data processing. HGC conceptualized, wrote and reviewed the manuscript.

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Figure legend

Fig. 1 A schematic illustration of the participant selection process that was used in the present study. Out of a total of 1,125,691 participants, 41,585 migraine participants were matched with 166,340 control participants for age, group, sex, income group, region of residence, and past medical histories.

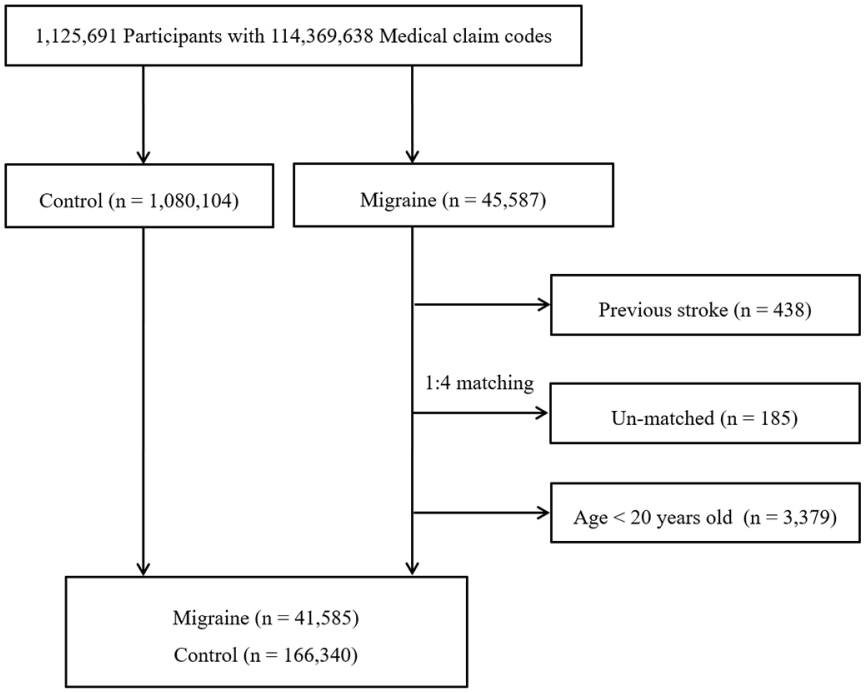

Fig.1

101x101mm (300 x 300 DPI)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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. Give information separately for for exposed and unexposed groups if applicable.	5-8
Bias	#9	Describe any efforts to address potential sources of bias	5-8
Study size	#10	Explain how the study size was arrived at	7

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
	#12b	Describe any methods used to examine subgroups and interactions	8
	#12c	Explain how missing data were addressed	NA
	#12d	If applicable, explain how loss to follow-up was addressed	NA
	#12e	Describe any sensitivity analyses	NA
Participants	#13a	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. Give information separately for exposed and unexposed groups if applicable.	NA
	#13b	Give reasons for non-participation at each stage	NA
	#13c	Consider use of a flow diagram	7
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8-13

	#14b	Indicate number of participants with missing data for each variable of interest	8-13
	#14c	Summarise follow-up time (eg, average and total amount)	8
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	NA
Main results	#16a	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	8-13
	#16b	Report category boundaries when continuous variables were categorized	NA
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13-14
Key results	#18	Summarise key results with reference to study objectives	16
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.	

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16-18
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	20

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Increased risk of ischemic stroke in patients with migraine: A longitudinal follow-up study using a national sample cohort in Korea

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Abstract

Objective: Accumulating evidence has supported the association between migraine and stroke, but the causative association remains unclear. We aimed to investigate the risks of different types of stroke in patients with migraine.

Design: A longitudinal follow-up study

Setting: Data collected from a national cohort between 2002 and 2013 by the Korean Health Insurance Review and Assessment

Participants: We extracted the data from patients with migraine (n = 41,585) and 1:4 matched controls (n = 166,340) and analyzed the occurrence of ischemic and hemorrhagic strokes. The migraine group included participants treated for migraine (ICD-10: G43) ≥ 2 times. Hemorrhagic stroke (I60-I62) and ischemic stroke (I63) were determined based on the admission histories. The crude and adjusted hazard ratios (HRs) were calculated using Cox proportional hazard models, and the 95% confidence intervals (CIs) were determined. Subgroup analyses stratified by age and sex were also performed.

Results: Higher rates of ischemic stroke were observed in the migraine group (2.3% [964/41,585]) than in the control group (2.0% [3,294/166,340], P < 0.001). The adjusted HR for ischemic stroke was 1.18 (95% CI = 1.10-1.26) in the migraine group (P < 0.001). Compared with control subjects, participants who reported migraine with aura and migraine without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15 (95% CI = 1.06-1.24), respectively, for ischemic stroke, but no increased risk of hemorrhagic stroke. In our subgroup analysis, a strong association between migraine and ischemic stroke was observed in young patients, specifically young women. The contribution of migraine to the occurrence of ischemic stroke was also observed in middle-aged women and old women

(each P < 0.05). The risk of hemorrhagic stroke did not reach statistical significance in any age group.

Conclusion: Migraine is associated with an increased risk of ischemic stroke, but not hemorrhagic stroke.

Keywords: migraine, stroke, cohort study, Korea

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. The strengths of the present study particularly result from the large cohort based on a complete, national patient sample and the long follow-up period.
2. We designed a cohort study to evaluate the risks of different types of stroke in migraineurs.
3. Migraine should be considered in assessments of the risk of ischemic stroke, particularly in young women.
4. Confounders linking migraine to stroke, such as cigarette smoking, obesity, and prescription information, were not available in the present cohort study based on claim data.

Introduction

Migraine is a common neurovascular disorder characterized by recurrent disabling episodes of headache, most often unilateral headache. The headache is often accompanied by visual or sensory symptoms, namely, aura.[1] The annual prevalence of migraine is approximately 8–15% worldwide,[2 3] and in Korea, the estimated incidence is 6.1%.[4] Migraine appears to present at a relatively young age (< 45 years); it is more prevalent in women than men, with a prevalence > 25% in the 35–39-year-old female population worldwide.[1] The inclusion of migraine as an independent risk factor for cardiovascular events has been debated for many years, but it is an established risk factor for ischemic stroke.[5]

Stroke is a cerebrovascular condition characterized by limited blood flow to the brain due to a blockage or rupture in the cerebrovascular system.[6] Stroke is responsible for approximately 700,000 deaths annually in the Western world.[7] In Korea, the estimated stroke incidence is approximately 795,000 in people aged ≥ 30 years.[8] More than 80% of stroke cases are ischemic stroke, and the remaining cases are hemorrhagic stroke; ischemic and hemorrhagic strokes differ with regard to risk factors, genetic predisposition, and mortality rates.[9 10]

To date, several underlying physiological mechanisms have been suggested to explain the association between migraine and stroke. The risk factors for stroke in migraineurs have been widely evaluated, and common comorbidities, including hypertension, obesity, dyslipidemia, and smoking, were validated.[11] In addition, specific genetic etiologies associated with vasculopathy can manifest in both patients suffering from migraine and stroke.[12] A recent investigation employing a mutant mouse model of migraine also indicated that shared genetic risk factors rendered the brain more vulnerable to ischemic stroke.[13]

Moreover, migraine itself carries an increased risk of ischemic stroke. Migraine is associated with an increased risk of perioperative ischemic stroke in a large cohort of surgical patients, suggesting that migraine should be included in the perioperative risk assessment.[14] Recently, a population-based case-control study in Taiwan reported an association between migraine and ischemic stroke (adjusted hazard ratio [HR]: 1.24, confidence interval [CI]: 1.12–1.38).[3] Similarly, an increased risk of ischemic stroke has been consistently observed in migraineurs, especially in those diagnosed with migraine with aura.[3 15-18] Furthermore, accumulating evidence has supported the association between migraine and hemorrhagic stroke,[19 20] but the causative association currently remains unclear.

Given the differences in the natures of hemorrhagic stroke and ischemic stroke in patients, including risk factors and genetic predispositions,[9 10] we hypothesized that the contributions of migraine to an increased risk of stroke differ according to the stroke type. Thus, stroke types should be analyzed separately. Additionally, stroke is a leading cause of mortality; therefore, validation of the association between migraine and stroke may facilitate treatment and prognosis in these cases. Here, using a national Korean population-based sample cohort, we examined the associations between migraine and different types of stroke.

Materials and Methods

Study population and data collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The Institutional Review Board exempted the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly from the entire population database to prevent nonsampling errors. Approximately 2% of the samples (one million) were selected from the entire Korean population (50 million). The selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized, stratified, systematic sampling methods via proportional allocation to represent the entire population. A previous study verified the appropriateness of the sample after data selection.[21] The National Health Insurance Sharing Service provides a detailed description of the methods used to perform these procedures.[22] This cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes based on the International Classification of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using

the Korean Standard Classification of disease), (v) socioeconomic data (residence and income), and (vi) medical examination data for each participant from 2002 to 2013.

All Korean citizens are recognized by a 13-digit resident registration number from birth to death. Therefore, exact population statistics have been determined using this database. All Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit resident registration number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. All medical treatments in Korea are tracked without exception using the Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice of death must be provided to an administrative entity before a funeral can be held. Medical doctors record the date and cause of death on a death certificate.

Patients and public involvement

No patients or public were involved in the present study.

Participant Selection

Of the 1,125,691 patients with 114,369,638 medical claim codes, participants diagnosed with migraine (ICD-10: G43) were included. Among these participants, those who were treated ≥ 2 times (n = 45,587) were selected. The participants were followed for 12 years.

The history of admission for hemorrhagic stroke (I60: Subarachnoid hemorrhage, I61: Intracerebral hemorrhage, and I62: Other nontraumatic intracranial hemorrhage) and ischemic stroke (I63: Cerebral infarction) was identified using ICD-10 codes. We selected the participants who were treated ≥ 1 time. These methods were used in other studies evaluating the incidence of stoke in Korea.[8 23]

The participants with migraine were matched 1:4 with participants (control group) who had never been diagnosed with a migraine from 2002 through 2013 in this cohort. The control group was selected from the total population (n = 1,080,104). The matches were processed for age, group, sex, income group, region of residence, and past medical histories (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories). We sorted the participants in the control group using a random number order and then selected them from top to bottom to prevent selection bias when selecting the matched control participants. We assumed that the matched control participants were enrolled at the same time as each matched participant with migraine (index date). Therefore, control group members who died before the index date were excluded. In both the migraine and control groups, participants with histories of hemorrhagic or ischemic stroke before the index date were excluded. In the migraine group, 438 participants were excluded. The participants with migraine for whom we were unable to identify sufficient numbers of matching participants were excluded (n = 185). We excluded participants aged less than 20 years (n = 3,379). Finally, 1:4 matching resulted in the inclusion of 41,585 participants with migraine (migraine with aura = 3,458, migraine without aura = 38,127) and 166,340 control participants (Fig. 1).

Variables

The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34…, and 85+ years old. Fourteen age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 11 classes (class 1 [lowest income]–class 11 [highest income]). The region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul,

Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas. The past medical histories of the participants were evaluated using ICD-10 codes. For an accurate diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were recorded if the participants were treated ≥ 2 times. Moreover, we further included variables including congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories that might affect the association between migraine and stroke using the Charlson Comorbidity Index and subsequently performed the analysis with the added variables.

Statistical Analyses

Chi-square tests were used to compare the general characteristics between the migraine and control groups. For the analysis of the HRs of migraine for hemorrhagic stroke and ischemic stroke, Cox proportional hazard models were used, and 95% CIs were calculated. In these analyses, crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories) models were used. For the subgroup analysis, we stratified the participants by age and sex (20–39 years old, 40–59 years old, 60+ years old; men and women). Two-tailed analyses were conducted, and P values less than 0.05 were considered significant. The results were statistically analyzed using SPSS v. 21.0 software (IBM, Armonk, NY, USA).

Results

The mean follow-up period was 80.9 (standard deviation [SD] = 41.6) months for patients with migraine and 80.9 (SD = 41.6) months for controls. The rates of hemorrhagic stroke were similar in the migraine group (0.7% [295/41,585]) and the control group (0.7% [1,113/166,340], P = 0.370, Table 1). Higher rates of ischemic stroke were observed in the migraine group (2.3% [964/41,585]) than in the control group (2.0% [3,294/166,340], P < 0.001). The general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories) of participants were the same due to the matching protocol (P = 1.000).

Table 1 General characteristics of the participants

Characteristics	Total participants		
	Migraine (n, %)	Control (n, %)	P-value
Age (years)			1.000
20-24	1,994 (4.8)	7,976 (4.8)	
25-29	2,649 (6.4)	10,596 (6.4)	
30-34	3,640 (8.8)	14,560 (8.8)	
35-39	4,309 (10.4)	17,236 (10.4)	
40-44	4,859 (11.7)	19,436 (11.7)	
45-49	5,187 (12.5)	20,748 (12.5)	
50-54	4,512 (10.9)	18,048 (10.9)	
55-59	3,508 (8.4)	14,032 (8.4)	
60-64	3,209 (7.7)	12,836 (7.7)	
65-69	3,049 (7.3)	12,196 (7.3)	

70-74	2,328 (5.6)	9,312 (5.6)	
75-79	1,423 (3.4)	5,692 (3.4)	
80-84	651 (1.6)	2,604 (1.6)	
85+	267 (0.6)	1,068 (0.6)	
Sex			1.000
Male	10,476 (25.2)	41,904 (25.2)	
Female	31,109 (74.8)	124,436 (74.8)	
Income			1.000
1 (lowest)	837 (2.0)	3,348 (2.0)	
2	3,170 (7.6)	12,680 (7.6)	
3	3,004 (7.2)	12,016 (7.2)	
4	3,131 (7.5)	12,524 (7.5)	
5	3,345 (8.0)	13,380 (8.0)	
6	3,615 (8.7)	14,460 (8.7)	
7	3,908 (9.4)	15,632 (9.4)	
8	4,411 (10.6)	17,644 (10.6)	
9	4,908 (11.8)	19,632 (11.8)	
10	5,456 (13.1)	21,824 (13.1)	
11 (highest)	5,800 (13.9)	23,200 (13.9)	
Region of residence			1.000
Urban	17,959 (43.2)	71,836 (43.2)	
Rural	23,626 (56.8)	94,504 (56.8)	
Hypertension	16,209 (39.0)	64,836 (39.0)	1.000
Diabetes	7,261 (17.5)	29,044 (17.5)	1.000

Dyslipidemia	12,837 (30.9)	51,348 (30.9)	1.000
Congestive heart failure	2,030 (4.9)	6,761 (4.1)	< 0.001*
Myocardial infarction	913 (2.2)	3,330 (2.0)	0.013*
Peripheral vascular disease	7,942 (19.1)	20,217 (12.2)	< 0.001*
Pulmonary disease	29,540 (71.0)	94,811 (57.0)	< 0.001*
Liver disease	5,087 (12.2)	15,317 (9.2)	< 0.001*
Depression	7,808 (18.8)	15,269 (9.2)	< 0.001*
Hemorrhagic stroke	295 (0.7)	1,113 (0.7)	0.370
Ischemic stroke	964 (2.3)	3,294 (2.0)	< 0.001*

*Chi-square test. Differences were considered significant at $P < 0.05$.

The crude and adjusted HRs for hemorrhagic stroke were 1.06 (95% CI = 0.93–1.21, P = 0.369) and 1.10 (95% CI = 0.96–1.25, P = 0.172), respectively, in the migraine group (Table 2). The crude and adjusted HRs for ischemic stroke were 1.17 (95% CI = 1.09–1.26) and 1.18 (95% CI = 1.08–1.25), respectively, in the migraine group (each $P < 0.001$).

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine		0.369		0.172		< 0.001*		< 0.001*
Yes	1.06 (0.93-1.21)		1.10 (0.96-1.25)		1.17 (1.09-1.26)		1.17 (1.08-1.25)	
No	1.00		1.00		1.00		1.00	

* Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

† Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

In the subgroup analyses, none of the crude and adjusted HRs for hemorrhagic stroke reached statistical significance (Table 3). Among the patients with ischemic stroke, young women, middle-aged women, and old women showed statistically significant differences (each $P < 0.05$). The significant adjusted HRs were 2.31 (95% CI = 1.39–3.82) in young women (20-39 years old); 1.32 (95% CI = 1.08–1.61) in middle-aged women (40-59 years old); and 1.18 (95% CI = 1.06–1.30) in ≥ 60-year-old women. Moreover, descriptive statistical analyses of the migraine prevalence and ischemic stroke occurrence within subgroups revealed statistically significant differences in young men, young women, middle-aged women, old men, and old women. On the other hand, the risk of hemorrhagic stroke in patients with migraine was not significantly different from the control group (Supplement table 1).

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Young men (20-39 years old, n = 15,550)								
Migraine		0.158		0.330		0.017*		0.107
Yes	1.56 (0.84-2.89)		1.37 (0.73-2.59)		2.15 (1.15-4.02)		1.72 (0.89-3.32)	
No	1.00		1.00		1.00		1.00	
Young women (20-39 years old, n = 47,410)								
Migraine		0.726		0.879		< 0.001*		0.001*
Yes	1.10 (0.64-1.92)		1.05 (0.59-1.84)		2.54 (1.55-4.15)		2.31 (1.39-3.82)	
No	1.00		1.00		1.00		1.00	
Middle-aged men (40-59 years old, n = 22,090)								
Migraine		0.721		0.668		0.565		0.418
Yes	1.07 (0.73-1.56)		1.09 (0.74-1.61)		0.93 (0.71-1.21)		0.89 (0.68-1.17)	

No	1.00	1.00	1.00	1.00
Middle-aged women (40-59 years old, n = 68.240)				
Migraine	0.582	0.388	0.002*	0.006*
Yes	1.07 (0.84-1.38)	1.12 (0.87-1.44)	1.35 (1.12-1.64)	1.32 (1.08-1.61)
No	1.00	1.00	1.00	1.00
Old men (≥ 60 years old, n = 14,740)				
Migraine	0.115	0.068	0.275	0.353
Yes	1.29 (0.94-1.78)	1.36 (0.98-1.88)	1.09 (0.93-1.27)	1.08 (0.92-1.26)
No	1.00	1.00	1.00	1.00
Old women (≥ 60 years old, n = 39,895)				
Migraine	0.462	0.757	0.002*	0.002*
Yes	0.92 (0.75-1.14)	0.97 (0.78-1.20)	1.17 (1.06-1.29)	1.18 (1.06-1.30)
No	1.00	1.00	1.00	1.00

* Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

† Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

Compared with the control group, participants who reported migraine with aura and migraine without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15 (95% CI = 1.06-1.24) for ischemic stroke, respectively, but no increased risk of hemorrhagic stroke (Table 4).

Table 4 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine with Aura (n = 17,290)								
Migraine		0.531		0.506		0.006*		0.009*
Yes	1.17 (0.72-1.90)		1.19 (0.72-1.96)		1.45 (1.11-1.88)		1.44 (1.09-1.89)	
No	1.00		1.00		1.00		1.00	
Migraine without Aura (n = 190,635)								
Migraine		0.446		0.213		< 0.001*		< 0.001*
Yes	1.05 (0.92-1.20)		1.09 (0.95-1.25)		1.16 (1.07-1.24)		1.15 (1.06-1.24)	
No	1.00		1.00		1.00		1.00	

* Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

† Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

Discussion

Migraine appeared to increase the risk of ischemic stroke, but not hemorrhagic stroke. The risk of ischemic stroke was 1.18-fold greater in the patients with migraine than in the matched control subjects, even after adjustment for confounding factors. In the subgroup analyses stratified by age and sex, significant correlations with ischemic stroke were primarily observed in young women, middle-aged women, and old women. In contrast, the risk of hemorrhagic stroke was similar in patients with migraine and the matched control patients.

Migraine, particularly migraine with aura, is an established risk factor for ischemic stroke. In this study, compared with the control group, participants who reported migraine with aura had an increased adjusted HR of 1.44 (95% CI = 1.09-1.89) for ischemic stroke. Migraine with aura particularly increases the risk of ischemic stroke, based on the results of large population-based cohort studies and meta-analyses.[3 15-18] Cortical spreading depression (CSD) is a self-propagating wave of depolarization across the cerebral cortex at a slow velocity of 3 to 5 mm/min.[24] CSD has been implicated in migraine with aura, which plays a critical role in the pathophysiology of ischemic stroke. In an experimental study, CSD altered the tone of resistance vessels, causing hypoperfusion in tissues at risk for progressive damage, namely, cortical spreading ischemia.[25] In addition, the inflammatory cascade of the neurovascular system, which is characterized by endothelial dysfunction and coagulation abnormalities, may contribute to the development of ischemic stroke. In the aura phase, the endothelium activates coagulation and thrombosis, which are mediated by inflammatory cytokines and endothelial biomarkers.[26 27] Moreover, specific genetic etiologies, such as Factor V Leiden G 619 1A, prothrombin G20210A, and familial hemiplegic migraine type 1, have been reported in patients diagnosed with migraine with aura. These shared genetic

factors may precipitate the susceptibility to CSD, which may explain the association between migraine and stroke.[28]

A growing body of evidence regarding the increased risk of ischemic stroke in patients with migraine without aura. Consistent with the findings from patients reporting migraine with aura, participants who reported migraine without aura had an increased adjusted HR of 1.15 (95% CI = 1.06-1.24) for ischemic stroke compared with the control group. Notably, a significant association was observed in cases of ischemic stroke resulting from cervical artery dissection.[29] In addition, genetic overlaps among subjects with migraine without aura, large artery stroke, and cardio-embolic stroke have been identified.[30] However, strong evidence has been not reported. A recent large population-based study reported an statistically insignificant risk of ischemic stroke in patients with migraine without aura but an increased risk in patients with migraine with aura.[3] The study suggested that the difference may be due to changes in the lipid profile, the susceptibility to thrombosis, and genetic predisposition.[3] A meta-analysis did not identify a significant association between migraine without aura and ischemic stroke.[18] In the present study, we did not differentiate between migraine subtypes, such as migraine with and without aura, when analyzing the risk of stroke. Therefore, the risk of ischemic stroke in participants with migraine was relatively low but statistically significant compared to other studies investigating specific conditions.

Notably, in the present study, migraine was not associated with an increased risk of hemorrhagic stroke. In contrast to the findings from the present study, a recent meta-analysis based on 4 case-control and 4 cohort studies concluded that migraine may increase the risk of hemorrhagic stroke.[20] However, a recent large population-based case-control study did not show an association with different types of hemorrhagic stroke, including intracerebral hemorrhage and subarachnoid hemorrhage. [31] Migraine was an independent risk factor for

aneurismal rupture (odds ratio [OR] = 2.4; 95% CI 1.1–5.1) in a case-control study,[32] and even if headache is a premonitory symptom of aneurismal rupture, recall biases might have affected the results of the study. Overall, the relatively small number of hemorrhagic stroke cases might have resulted in decreased statistical power.

In our subgroup analysis, a strong correlation between migraine and ischemic stroke was observed in young patients, specifically young women (20-39 years old). Based on a consensus statement from the European Headache Federation (EHF),[33] the use of a combined hormonal contraceptive may further increase the risk of ischemic stroke in patients with migraine, specifically migraine with aura, supporting our results. Because the predisposing factors for stroke increase the incidence of ischemic stroke with age,[34] migraine itself rather than other risk factors might be implicated in the increased risk of ischemic stroke. In contrast, a recent large, population-based cohort study in Taiwan with a relatively short follow-up duration of 3.6 years did not show a significant association in the subgroups of women and patients aged < 45 years.[3] This discrepancy might be due to differences in the study design, follow-up duration, and ethnic composition of the study population. Recently, a similar trend for this association was also reported,[3] but it requires further confirmation due to the lack of evidence at present.

The present study has several strengths. The results of this study are consistent with the findings of our previous studies utilizing the HIRA-NSC.[35-37] We examined a very large, representative, and nationwide population. Because the NHIS data cover all citizens of Korea without exception, no participants were lost during follow-up. The control group was randomly selected and matched based on age, sex, income, region of residence, and medical history to decrease any confounding effects. An adjusted hazard model was used to further minimize the impacts of confounders. Because migraine attacks might be frequently repeated,

we opted to include patients with migraine who underwent treatment at least twice based on the ICD-10 code to increase the validity of the study [G43]. In a previous study, the prevalence of migraine in Korea was reported to be approximately 6.1%.[4] This value appeared to be slightly higher than the value reported in the present study, which was 3.7% (41,585/1,125,691), based on strict inclusion criteria for migraine. In addition, the patients with migraine were followed for 12 years in the present study. Long study periods enable the recruitment of a large study population and allow researchers to observe and analyze the delayed effects of migraine on stroke.

However, the present study has certain limitations that should be addressed in future studies. First, we were unable to extract information on stroke subtypes and location from the data used in the present study. The impact of migraine on each type of pathophysiology might vary when considering different functional outcomes, survival, and recurrence according to stroke subtype.[38 39] However, in the present study, the distribution of stroke subtypes was not available. The classification of stroke type can lead to a significantly decreased incidence of each disease. As an insufficient number of cases cause inappropriate comparisons due to lower statistical power, the inclusion of the distribution of stroke subtypes would hamper our ability to draw a clear conclusion from the available data. In particular, the absolute incidence of hemorrhagic stroke is very low in general practice; therefore, most of studies did not provide information about subtypes, such as the presence of an aneurysm, although the association is positive in public health studies.[31] Second, a firm correlation between the frequency of migraine attacks and the risk of stroke has been reported,[40] but we were unable to confirm this correlation using the claim data analyzed in the present study. Similarly, the duration and severity of migraine were inconsistent among the study population. Patients with migraine who had mild complaints may not have received a consultation at the clinic;

therefore, the impact of migraine on stroke may be underestimated in this study. Third, although this study attempted to include a large, representative patient population and subsequently matched and adjusted for possible confounders, the risk factors for stroke in patients with migraine, such as cigarette smoking, obesity, and migraine-specific drugs, were not available in the insurance database.[11 40] Finally, in the present study, the incidence of migraine was 3.7% (41,585 of 1,125,691 participants) after employing a strict matching protocol. Before matching, the incidence of migraine in Korea was 4.1% (45,587 of 1,125,691 participants). This value is consistent with previous cohort study in Korea, indicating that the overall prevalence rate of migraine was 6.1%,[8] despite the use of different study designs. Given the global prevalence of migraine of approximately 8–15%,[9 10] the incidence of migraine in Korea is relatively low because of limited claim data. Only patients with migraine who visited the hospital are recorded. In other words, data are not available for patients with weak migraine symptoms or patients who do not visit a hospital, leading to a lower incidence. Based on a population-based epidemiological study of migraine in Korea, only 24.4% of patients ever consulted a doctor for headache and only 3.3% of patients were prescribed a drug by a doctor.[11]

Conclusions

Based on a large population-based cohort study in Korea, migraine increased the risk of ischemic stroke, but not hemorrhagic stroke. The subgroup of patients at the highest risk of developing ischemic stroke was young women.

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DATA SHARING STATEMENT

No additional data are available.

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COMPETING INTERESTS STATEMENT

None of the authors have competing interests to declare.

AUTHORS' CONTRIBUTIONS

As the first author, SYL wrote the manuscript. DJO and JSL analyzed and interpreted the data. IGK processed the data. HGC conceptualized, wrote, and reviewed the manuscript.

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Figure Legend

Fig. 1 A schematic illustrating the participant selection process used in the present study. Of a total of 1,125,691 participants, 41,585 participants with migraine were matched with 166,340 control participants for age, group, sex, income level, region of residence, and past medical histories.

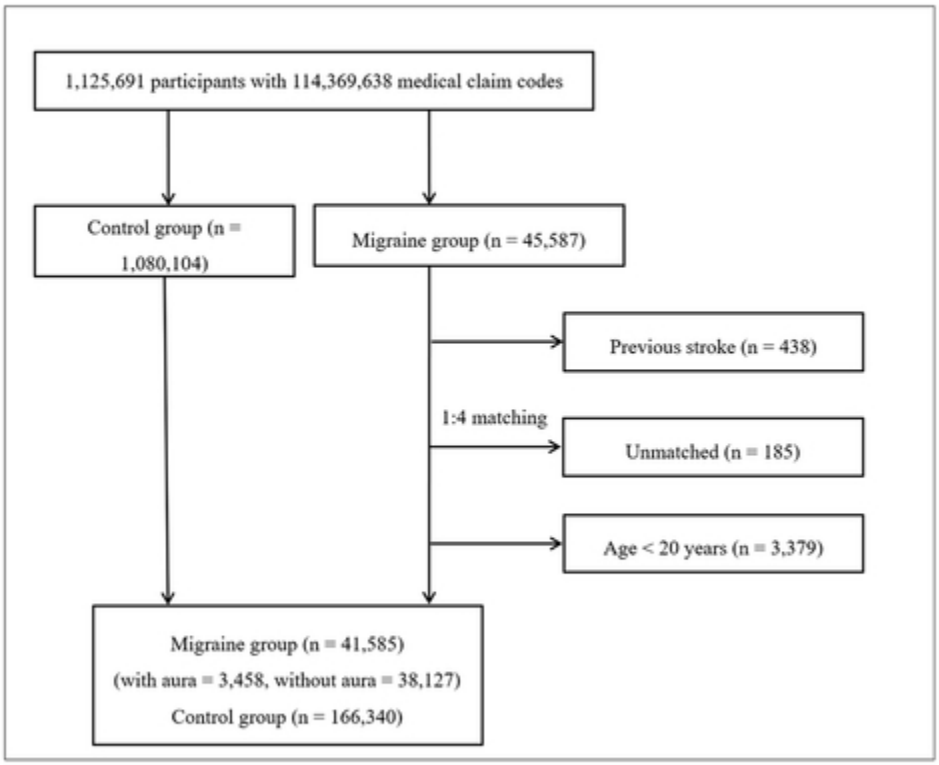

Figure 1

42x42mm (300 x 300 DPI)

S1. Subgroup analysis of migraine prevalence and stroke occurrence

Characteristics	**Young men (20-39 years old, n = 15,550)**			**Young women (20-39 years old, n = 47,410)**		
	Migraine (n = 3,110, %)	Non-Migraine (n = 12,440)	P-value	Migraine (n = 9,482)	Non-Migraine (n = 37,928)	P-value
Ischemic stroke			0.015*			< 0.001*
Yes	15 (0.48)	28 (0.22)		26 (0.27)	41 (0.11)	
No	3,095 (99.52)	12,412 (99.78)		9,456 (99.73)	37,887 (99.89)	
Hemorrhagic stroke			0.157			0.727
Yes	14 (0.45)	36 (0.28)		16 (0.17)	58 (0.15)	
No	3,096 (99.55)	12,404 (99.72)		9,466 (99.73)	37,870 (99.85)	
Characteristics	**Middle-aged men (40-59 years old, n = 22,090)**			**Middle-aged women (40-59 years old, n = 68,240)**		
	Migraine (n = 4,418)	Non-Migraine (n = 17,672)	P-value	Migraine (n = 9,482)	Non-Migraine (n = 37,928)	P-value
Ischemic stroke			0.560			0.002*
Yes	68 (1.54)	294 (1.66)		138 (1.46)	409 (1.08)	
No	4,350 (98.46)	17,378 (98.34)		13,648 (98.54)	54,952 (98.92)	

Hemorrhagic stroke			0.157			0.727
Yes	34 (0.77)	127 (0.72)		78 (0.82)	291 (0.77)	
No	4,384 (99.23)	17,545 (99.28)		13,570 (99.18)	54,301 (99.23)	
Characteristics	**Old men (≥ 60 years old, n = 14,740)**			**Old women (≥ 60 years old, n = 39,895)**		
	Migraine (n = 2,948)	Non-Migraine (n = 11,792)	P-value	Migraine (n = 7,979)	Non-Migraine (n = 31,916)	P-value
Ischemic stroke			0.015*			0.002*
Yes	205 (7.0)	756 (6.4)		512 (6.4)	1,766 (5.5)	
No	2,743 (93.0)	11,036 (93.6)		7,467 (93.6)	30,150 (94.5)	
Hemorrhagic stroke			0.157			0.465
Yes	50 (1.7)	155 (1.3)		103 (1.3)	446 (1.4)	
No	2,898 (98.3)	11,637 (98.7)		7,876 (98.7)	31,470 (98.6)	

* Chi-square test; differences were considered significant at $P < 0.05$.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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. Give information separately for for exposed and unexposed groups if applicable.	5-8
Bias	#9	Describe any efforts to address potential sources of bias	5-8
Study size	#10	Explain how the study size was arrived at	7

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
	#12b	Describe any methods used to examine subgroups and interactions	8
	#12c	Explain how missing data were addressed	NA
	#12d	If applicable, explain how loss to follow-up was addressed	NA
	#12e	Describe any sensitivity analyses	NA
Participants	#13a	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. Give information separately for exposed and unexposed groups if applicable.	NA
	#13b	Give reasons for non-participation at each stage	NA
	#13c	Consider use of a flow diagram	7
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8-13

	#14b	Indicate number of participants with missing data for each variable of interest	8-13
	#14c	Summarise follow-up time (eg, average and total amount)	8
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	NA
Main results	#16a	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	8-13
	#16b	Report category boundaries when continuous variables were categorized	NA
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13-14
Key results	#18	Summarise key results with reference to study objectives	16
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.	

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16-18
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	20

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Risk of ischemic stroke in patients with migraine: A longitudinal follow-up study using a national sample cohort in Korea

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Risk of ischemic stroke in patients with migraine: A longitudinal follow-up study using a national sample cohort in Korea

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Abstract

Objective: Accumulating evidence has supported the association between migraine and stroke, but the causative association remains unclear. We aimed to investigate the risks of different types of stroke in patients with migraine.

Design: A longitudinal follow-up study

Setting: Data collected from a national cohort between 2002 and 2013 by the Korean Health Insurance Review and Assessment

Participants: We extracted the data from patients with migraine (n = 41,585) and 1:4 matched controls (n = 166,340) and analyzed the occurrence of ischemic and hemorrhagic strokes. The migraine group included participants treated for migraine (ICD-10: G43) ≥ 2 times. Hemorrhagic stroke (I60-I62) and ischemic stroke (I63) were determined based on the admission histories. The crude and adjusted hazard ratios (HRs) were calculated using Cox proportional hazard models, and the 95% confidence intervals (CIs) were determined. Subgroup analyses stratified by age and sex were also performed.

Results: Higher rates of ischemic stroke were observed in the migraine group (2.3% [964/41,585]) than in the control group (2.0% [3,294/166,340], P < 0.001). The adjusted HR for ischemic stroke was 1.18 (95% CI = 1.10-1.26) in the migraine group (P < 0.001). Compared with control subjects, participants who reported migraine with aura and migraine without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15 (95% CI = 1.06-1.24), respectively, for ischemic stroke, but no increased risk of hemorrhagic stroke. In our subgroup analysis, a strong association between migraine and ischemic stroke was observed in young patients, specifically young women. The contribution of migraine to the occurrence of ischemic stroke was also observed in middle-aged women and old women

(each P < 0.05). The risk of hemorrhagic stroke did not reach statistical significance in any age group.

Conclusion: Migraine is associated with an increased risk of ischemic stroke, but not hemorrhagic stroke.

Keywords: migraine, stroke, cohort study, Korea

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. The strengths of the present study particularly result from the large cohort based on a complete, national patient sample and the long follow-up period.
2. We designed a cohort study to evaluate the risks of different types of stroke in migraineurs.
3. Migraine should be considered in assessments of the risk of ischemic stroke, particularly in young women.
4. Confounders linking migraine to stroke, such as cigarette smoking, obesity, and prescription information, were not available in the present cohort study based on claim data.

Introduction

Migraine is a common neurovascular disorder characterized by recurrent disabling episodes of headache, most often unilateral headache. The headache is often accompanied by visual or sensory symptoms, namely, aura.[1] The annual prevalence of migraine is approximately 8–15% worldwide,[2 3] and in Korea, the estimated incidence is 6.1%.[4] Migraine appears to present at a relatively young age (< 45 years); it is more prevalent in women than men, with a prevalence > 25% in the 35–39-year-old female population worldwide.[1] The inclusion of migraine as an independent risk factor for cardiovascular events has been debated for many years, but it is an established risk factor for ischemic stroke.[5]

Stroke is a cerebrovascular condition characterized by limited blood flow to the brain due to a blockage or rupture in the cerebrovascular system.[6] Stroke is responsible for approximately 700,000 deaths annually in the Western world.[7] In Korea, the estimated stroke incidence is approximately 795,000 in people aged ≥ 30 years.[8] More than 80% of stroke cases are ischemic stroke, and the remaining cases are hemorrhagic stroke; ischemic and hemorrhagic strokes differ with regard to risk factors, genetic predisposition, and mortality rates.[9 10]

To date, several underlying physiological mechanisms have been suggested to explain the association between migraine and stroke. The risk factors for stroke in migraineurs have been widely evaluated, and common comorbidities, including hypertension, obesity, dyslipidemia, and smoking, were validated.[11] In addition, specific genetic etiologies associated with vasculopathy can manifest in both patients suffering from migraine and stroke.[12] A recent investigation employing a mutant mouse model of migraine also indicated that shared genetic risk factors rendered the brain more vulnerable to ischemic stroke.[13]

Moreover, migraine itself carries an increased risk of ischemic stroke. Migraine is associated with an increased risk of perioperative ischemic stroke in a large cohort of surgical patients, suggesting that migraine should be included in the perioperative risk assessment.[14] Recently, a population-based case-control study in Taiwan reported an association between migraine and ischemic stroke (adjusted hazard ratio [HR]: 1.24, confidence interval [CI]: 1.12–1.38).[3] Similarly, an increased risk of ischemic stroke has been consistently observed in migraineurs, especially in those diagnosed with migraine with aura.[3 15-18] Furthermore, accumulating evidence has supported the association between migraine and hemorrhagic stroke,[19 20] but the causative association currently remains unclear.

Given the differences in the natures of hemorrhagic stroke and ischemic stroke in patients, including risk factors and genetic predispositions,[9 10] we hypothesized that the contributions of migraine to an increased risk of stroke differ according to the stroke type. Thus, stroke types should be analyzed separately. Additionally, stroke is a leading cause of mortality; therefore, validation of the association between migraine and stroke may facilitate treatment and prognosis in these cases. Here, using a national Korean population-based sample cohort, we examined the associations between migraine and different types of stroke.

Materials and Methods

Study population and data collection

The ethics committee of Hallym University (2014-I148) approved the use of these data. The Institutional Review Board exempted the requirement for written informed consent.

This national cohort study used data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly from the entire population database to prevent nonsampling errors. Approximately 2% of the samples (one million) were selected from the entire Korean population (50 million). The selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and income level [41 categories]) using randomized, stratified, systematic sampling methods via proportional allocation to represent the entire population. A previous study verified the appropriateness of the sample after data selection.[21] The National Health Insurance Sharing Service provides a detailed description of the methods used to perform these procedures.[22] This cohort database included (i) personal information, (ii) health insurance claim codes (procedures and prescriptions), (iii) diagnostic codes based on the International Classification of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using

the Korean Standard Classification of disease), (v) socioeconomic data (residence and income), and (vi) medical examination data for each participant from 2002 to 2013.

All Korean citizens are recognized by a 13-digit resident registration number from birth to death. Therefore, exact population statistics have been determined using this database. All Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit resident registration number to register individual patients in the medical insurance system. Therefore, the risk of overlapping medical records is minimal, even if a patient moves from one place to another. All medical treatments in Korea are tracked without exception using the Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice of death must be provided to an administrative entity before a funeral can be held. Medical doctors record the date and cause of death on a death certificate.

Patients and public involvement

No patients or public were involved in the present study.

Participant Selection

Of the 1,125,691 patients with 114,369,638 medical claim codes, participants diagnosed with migraine (ICD-10: G43) were included. Among these participants, those who were treated ≥ 2 times (n = 45,587) were selected. The participants were followed for 12 years.

The history of admission for hemorrhagic stroke (I60: Subarachnoid hemorrhage, I61: Intracerebral hemorrhage, and I62: Other nontraumatic intracranial hemorrhage) and ischemic stroke (I63: Cerebral infarction) was identified using ICD-10 codes. We selected the participants who were treated ≥ 1 time. These methods were used in other studies evaluating the incidence of stoke in Korea.[8 23]

The participants with migraine were matched 1:4 with participants (control group) who had never been diagnosed with a migraine from 2002 through 2013 in this cohort. The control group was selected from the total population (n = 1,080,104). The matches were processed for age, group, sex, income group, region of residence, and past medical histories (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories). We sorted the participants in the control group using a random number order and then selected them from top to bottom to prevent selection bias when selecting the matched control participants. We assumed that the matched control participants were enrolled at the same time as each matched participant with migraine (index date). Therefore, control group members who died before the index date were excluded. In both the migraine and control groups, participants with histories of hemorrhagic or ischemic stroke before the index date were excluded. In the migraine group, 438 participants were excluded. The participants with migraine for whom we were unable to identify sufficient numbers of matching participants were excluded (n = 185). We excluded participants aged less than 20 years (n = 3,379). Finally, 1:4 matching resulted in the inclusion of 41,585 participants with migraine (migraine with aura = 3,458, migraine without aura = 38,127) and 166,340 control participants (Fig. 1).

Variables

The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34…, and 85+ years old. Fourteen age groups were designated. The income groups were initially divided into 41 classes (one health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 11 classes (class 1 [lowest income]–class 11 [highest income]). The region of residence was divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul,

Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas. The past medical histories of the participants were evaluated using ICD-10 codes. For an accurate diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia (E78) were recorded if the participants were treated ≥ 2 times. Using the Charlson Comorbidity Index, we selected some of confounders that might affect the association between migraine and stroke as confounders based on literature review. We performed the analysis with added variables, including congestive heart failure,[24] myocardial infarction,[25] peripheral vascular disease,[26] pulmonary disease,[27] liver disease,[28] and depression histories.[29 30] Thus, the new model was adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

Statistical Analyses

Chi-square tests were used to compare the general characteristics between the migraine and control groups. For the analysis of the HRs of migraine for hemorrhagic stroke and ischemic stroke, Cox proportional hazard models were used, and 95% CIs were calculated. In these analyses, crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories) models were used. For the subgroup analysis, we stratified the participants by age and sex (20–39 years old, 40–59 years old, 60+ years old; men and women). Two-tailed analyses were conducted, and P values less

than 0.05 were considered significant. The results were statistically analyzed using SPSS v. 21.0 software (IBM, Armonk, NY, USA).

Results

The mean follow-up period was 80.9 (standard deviation [SD] = 41.6) months for patients with migraine and 80.9 (SD = 41.6) months for controls. The rates of hemorrhagic stroke were similar in the migraine group (0.7% [295/41,585]) and the control group (0.7% [1,113/166,340], P = 0.370, Table 1). Higher rates of ischemic stroke were observed in the migraine group (2.3% [964/41,585]) than in the control group (2.0% [3,294/166,340], P < 0.001). The general characteristics (age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia histories) of participants were the same due to the matching protocol (P = 1.000).

Table 1 General characteristics of the participants

Characteristics	Total participants		
	Migraine (n, %)	Control (n, %)	P-value
Age (years)			1.000
20-24	1,994 (4.8)	7,976 (4.8)	
25-29	2,649 (6.4)	10,596 (6.4)	
30-34	3,640 (8.8)	14,560 (8.8)	
35-39	4,309 (10.4)	17,236 (10.4)	
40-44	4,859 (11.7)	19,436 (11.7)	
45-49	5,187 (12.5)	20,748 (12.5)	
50-54	4,512 (10.9)	18,048 (10.9)	

55-59	3,508 (8.4)	14,032 (8.4)	
60-64	3,209 (7.7)	12,836 (7.7)	
65-69	3,049 (7.3)	12,196 (7.3)	
70-74	2,328 (5.6)	9,312 (5.6)	
75-79	1,423 (3.4)	5,692 (3.4)	
80-84	651 (1.6)	2,604 (1.6)	
85+	267 (0.6)	1,068 (0.6)	
Sex			1.000
Male	10,476 (25.2)	41,904 (25.2)	
Female	31,109 (74.8)	124,436 (74.8)	
Income			1.000
1 (lowest)	837 (2.0)	3,348 (2.0)	
2	3,170 (7.6)	12,680 (7.6)	
3	3,004 (7.2)	12,016 (7.2)	
4	3,131 (7.5)	12,524 (7.5)	
5	3,345 (8.0)	13,380 (8.0)	
6	3,615 (8.7)	14,460 (8.7)	
7	3,908 (9.4)	15,632 (9.4)	
8	4,411 (10.6)	17,644 (10.6)	
9	4,908 (11.8)	19,632 (11.8)	
10	5,456 (13.1)	21,824 (13.1)	
11 (highest)	5,800 (13.9)	23,200 (13.9)	
Region of residence			1.000
Urban	17,959 (43.2)	71,836 (43.2)	

Rural	23,626 (56.8)	94,504 (56.8)	
Hypertension	16,209 (39.0)	64,836 (39.0)	1.000
Diabetes	7,261 (17.5)	29,044 (17.5)	1.000
Dyslipidemia	12,837 (30.9)	51,348 (30.9)	1.000
Congestive heart failure	2,030 (4.9)	6,761 (4.1)	< 0.001*
Myocardial infarction	913 (2.2)	3,330 (2.0)	0.013*
Peripheral vascular disease	7,942 (19.1)	20,217 (12.2)	< 0.001*
Pulmonary disease	29,540 (71.0)	94,811 (57.0)	< 0.001*
Liver disease	5,087 (12.2)	15,317 (9.2)	< 0.001*
Depression	7,808 (18.8)	15,269 (9.2)	< 0.001*
Hemorrhagic stroke	295 (0.7)	1,113 (0.7)	0.370
Ischemic stroke	964 (2.3)	3,294 (2.0)	< 0.001*

*Chi-square test. Differences were considered significant at $P < 0.05$.

The crude and adjusted HRs for hemorrhagic stroke were 1.06 (95% CI = 0.93–1.21, P = 0.369) and 1.10 (95% CI = 0.96–1.25, P = 0.172), respectively, in the migraine group (Table 2). The crude and adjusted HRs for ischemic stroke were 1.17 (95% CI = 1.09–1.26) and 1.18 (95% CI = 1.08–1.25), respectively, in the migraine group (each $P < 0.001$).

Table 2 Crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine		0.369		0.172		< 0.001*		< 0.001*
Yes	1.06 (0.93-1.21)		1.10 (0.96-1.25)		1.17 (1.09-1.26)		1.17 (1.08-1.25)	
No	1.00		1.00		1.00		1.00	

* Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

† Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

In the subgroup analyses, none of the crude and adjusted HRs for hemorrhagic stroke reached statistical significance (Table 3). Among the patients with ischemic stroke, young women, middle-aged women, and old women showed statistically significant differences (each $P < 0.05$). The significant adjusted HRs were 2.31 (95% CI = 1.39–3.82) in young women (20-39 years old); 1.32 (95% CI = 1.08–1.61) in middle-aged women (40-59 years old); and 1.18 (95% CI = 1.06–1.30) in ≥ 60-year-old women. Moreover, descriptive statistical analyses of the migraine prevalence and ischemic stroke occurrence within subgroups revealed statistically significant differences in young men, young women, middle-aged women, old men, and old women. On the other hand, the risk of hemorrhagic stroke in patients with migraine was not significantly different from the control group (Supplement table 1).

Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Young men (20-39 years old, n = 15,550)								
Migraine		0.158		0.330		0.017*		0.107
Yes	1.56 (0.84-2.89)		1.37 (0.73-2.59)		2.15 (1.15-4.02)		1.72 (0.89-3.32)	
No	1.00		1.00		1.00		1.00	
Young women (20-39 years old, n = 47,410)								
Migraine		0.726		0.879		< 0.001*		0.001*
Yes	1.10 (0.64-1.92)		1.05 (0.59-1.84)		2.54 (1.55-4.15)		2.31 (1.39-3.82)	
No	1.00		1.00		1.00		1.00	
Middle-aged men (40-59 years old, n = 22,090)								
Migraine		0.721		0.668		0.565		0.418
Yes	1.07 (0.73-1.56)		1.09 (0.74-1.61)		0.93 (0.71-1.21)		0.89 (0.68-1.17)	

No	1.00	1.00	1.00	1.00	
Middle-aged women (40-59 years old, n = 68.240)					
Migraine		0.582	0.388	0.002*	0.006*
Yes	1.07 (0.84-1.38)	1.12 (0.87-1.44)	1.35 (1.12-1.64)	1.32 (1.08-1.61)	
No	1.00	1.00	1.00	1.00	
Old men (≥ 60 years old, n = 14,740)					
Migraine		0.115	0.068	0.275	0.353
Yes	1.29 (0.94-1.78)	1.36 (0.98-1.88)	1.09 (0.93-1.27)	1.08 (0.92-1.26)	
No	1.00	1.00	1.00	1.00	
Old women (≥ 60 years old, n = 39,895)					
Migraine		0.462	0.757	0.002*	0.002*
Yes	0.92 (0.75-1.14)	0.97 (0.78-1.20)	1.17 (1.06-1.29)	1.18 (1.06-1.30)	
No	1.00	1.00	1.00	1.00	

* Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

† Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

Compared with the control group, participants who reported migraine with aura and migraine without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15 (95% CI = 1.06-1.24) for ischemic stroke, respectively, but no increased risk of hemorrhagic stroke (Table 4).

Table 4 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic stroke

Characteristics	Hemorrhagic stroke				Ischemic stroke			
	Crude	P-value	Adjusted†	P-value	Crude	P-value	Adjusted†	P-value
Migraine with Aura (n = 17,290)								
Migraine		0.531		0.506		0.006*		0.009*
Yes	1.17 (0.72-1.90)		1.19 (0.72-1.96)		1.45 (1.11-1.88)		1.44 (1.09-1.89)	
No	1.00		1.00		1.00		1.00	
Migraine without Aura (n = 190,635)								
Migraine		0.446		0.213		< 0.001*		< 0.001*
Yes	1.05 (0.92-1.20)		1.09 (0.95-1.25)		1.16 (1.07-1.24)		1.15 (1.06-1.24)	
No	1.00		1.00		1.00		1.00	

* Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

† Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression histories.

Discussion

Migraine appeared to increase the risk of ischemic stroke, but not hemorrhagic stroke. The risk of ischemic stroke was 1.18-fold greater in the patients with migraine than in the matched control subjects, even after adjustment for confounding factors. In the subgroup analyses stratified by age and sex, significant correlations with ischemic stroke were primarily observed in young women, middle-aged women, and old women. In contrast, the risk of hemorrhagic stroke was similar in patients with migraine and the matched control patients.

Migraine, particularly migraine with aura, is an established risk factor for ischemic stroke. In this study, compared with the control group, participants who reported migraine with aura had an increased adjusted HR of 1.44 (95% CI = 1.09-1.89) for ischemic stroke. Migraine with aura particularly increases the risk of ischemic stroke, based on the results of large population-based cohort studies and meta-analyses.[3 15-18] Cortical spreading depression (CSD) is a self-propagating wave of depolarization across the cerebral cortex at a slow velocity of 3 to 5 mm/min.[31] CSD has been implicated in migraine with aura, which plays a critical role in the pathophysiology of ischemic stroke. In an experimental study, CSD altered the tone of resistance vessels, causing hypoperfusion in tissues at risk for progressive damage, namely, cortical spreading ischemia.[32] In addition, the inflammatory cascade of the neurovascular system, which is characterized by endothelial dysfunction and coagulation abnormalities, may contribute to the development of ischemic stroke. In the aura phase, the endothelium activates coagulation and thrombosis, which are mediated by inflammatory cytokines and endothelial biomarkers.[33 34] Moreover, specific genetic etiologies, such as Factor V Leiden G 619 1A, prothrombin G20210A, and familial hemiplegic migraine type 1, have been reported in patients diagnosed with migraine with aura. These shared genetic

factors may precipitate the susceptibility to CSD, which may explain the association between migraine and stroke.[35]

A growing body of evidence regarding the increased risk of ischemic stroke in patients with migraine without aura. Consistent with the findings from patients reporting migraine with aura, participants who reported migraine without aura had an increased adjusted HR of 1.15 (95% CI = 1.06-1.24) for ischemic stroke compared with the control group. Notably, a significant association was observed in cases of ischemic stroke resulting from cervical artery dissection.[36] In addition, genetic overlaps among subjects with migraine without aura, large artery stroke, and cardio-embolic stroke have been identified.[37] However, strong evidence has been not reported. A recent large population-based study reported an statistically insignificant risk of ischemic stroke in patients with migraine without aura but an increased risk in patients with migraine with aura.[3] The study suggested that the difference may be due to changes in the lipid profile, the susceptibility to thrombosis, and genetic predisposition.[3] A meta-analysis did not identify a significant association between migraine without aura and ischemic stroke.[18] In the present study, we did not differentiate between migraine subtypes, such as migraine with and without aura, when analyzing the risk of stroke. Therefore, the risk of ischemic stroke in participants with migraine was relatively low but statistically significant compared to other studies investigating specific conditions.

Notably, in the present study, migraine was not associated with an increased risk of hemorrhagic stroke. In contrast to the findings from the present study, a recent meta-analysis based on 4 case-control and 4 cohort studies concluded that migraine may increase the risk of hemorrhagic stroke.[20] However, a recent large population-based case-control study did not show an association with different types of hemorrhagic stroke, including intracerebral hemorrhage and subarachnoid hemorrhage. [38] Migraine was an independent risk factor for

aneurismal rupture (odds ratio [OR] = 2.4; 95% CI 1.1–5.1) in a case-control study,[39] and even if headache is a premonitory symptom of aneurismal rupture, recall biases might have affected the results of the study. Overall, the relatively small number of hemorrhagic stroke cases might have resulted in decreased statistical power.

In our subgroup analysis, a strong correlation between migraine and ischemic stroke was observed in young patients, specifically young women (20-39 years old). Based on a consensus statement from the European Headache Federation (EHF),[40] the use of a combined hormonal contraceptive may further increase the risk of ischemic stroke in patients with migraine, specifically migraine with aura, supporting our results. Because the predisposing factors for stroke increase the incidence of ischemic stroke with age,[41] migraine itself rather than other risk factors might be implicated in the increased risk of ischemic stroke. In contrast, a recent large, population-based cohort study in Taiwan with a relatively short follow-up duration of 3.6 years did not show a significant association in the subgroups of women and patients aged < 45 years.[3] This discrepancy might be due to differences in the study design, follow-up duration, and ethnic composition of the study population. Recently, a similar trend for this association was also reported,[3] but it requires further confirmation due to the lack of evidence at present.

The present study has several strengths. The results of this study are consistent with the findings of our previous studies utilizing the HIRA-NSC.[42-44] We examined a very large, representative, and nationwide population. Because the NHIS data cover all citizens of Korea without exception, no participants were lost during follow-up. The control group was randomly selected and matched based on age, sex, income, region of residence, and medical history to decrease any confounding effects. An adjusted hazard model was used to further minimize the impacts of confounders. Because migraine attacks might be frequently repeated,

we opted to include patients with migraine who underwent treatment at least twice based on the ICD-10 code to increase the validity of the study [G43]. In a previous study, the prevalence of migraine in Korea was reported to be approximately 6.1%.[4] This value appeared to be slightly higher than the value reported in the present study, which was 3.7% (41,585/1,125,691), based on strict inclusion criteria for migraine. In addition, the patients with migraine were followed for 12 years in the present study. Long study periods enable the recruitment of a large study population and allow researchers to observe and analyze the delayed effects of migraine on stroke.

However, the present study has certain limitations that should be addressed in future studies. First, we were unable to extract information on stroke subtypes and location from the data used in the present study. The impact of migraine on each type of pathophysiology might vary when considering different functional outcomes, survival, and recurrence according to stroke subtype.[38 45] However, in the present study, the distribution of stroke subtypes was not available. The classification of stroke type can lead to a significantly decreased incidence of each disease. As an insufficient number of cases cause inappropriate comparisons due to lower statistical power, the inclusion of the distribution of stroke subtypes would hamper our ability to draw a clear conclusion from the available data. In particular, the absolute incidence of hemorrhagic stroke is very low in general practice; therefore, most of studies did not provide information about subtypes, such as the presence of an aneurysm, although the association is positive in public health studies.[38] Second, a firm correlation between the frequency of migraine attacks and the risk of stroke has been reported,[46] but we were unable to confirm this correlation using the claim data analyzed in the present study. Similarly, the duration and severity of migraine were inconsistent among the study population. Patients with migraine who had mild complaints may not have received a consultation at the clinic;

therefore, the impact of migraine on stroke may be underestimated in this study. Third, although this study attempted to include a large, representative patient population and subsequently matched and adjusted for possible confounders, the risk factors for stroke in patients with migraine, such as cigarette smoking, obesity, and migraine-specific drugs, were not available in the insurance database.[11 46] Finally, in the present study, the incidence of migraine was 3.7% (41,585 of 1,125,691 participants) after employing a strict matching protocol. Before matching, the incidence of migraine in Korea was 4.1% (45,587 of 1,125,691 participants). This value is consistent with previous cohort study in Korea, indicating that the overall prevalence rate of migraine was 6.1%,[4] despite the use of different study designs. Given the global prevalence of migraine of approximately 8–15%,[2 3] the incidence of migraine in Korea is relatively low because of limited claim data. Only patients with migraine who visited the hospital are recorded. In other words, data are not available for patients with weak migraine symptoms or patients who do not visit a hospital, leading to a lower incidence. Based on a population-based epidemiological study of migraine in Korea, only 24.4% of patients ever consulted a doctor for headache and only 3.3% of patients were prescribed a drug by a doctor.[47]

Conclusions

Based on a large population-based cohort study in Korea, migraine increased the risk of ischemic stroke, but not hemorrhagic stroke. The subgroup of patients at the highest risk of developing ischemic stroke was young women.

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DATA SHARING STATEMENT

No additional data are available.

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COMPETING INTERESTS STATEMENT

None of the authors have competing interests to declare.

AUTHORS' CONTRIBUTIONS

As the first author, SYL wrote the manuscript. DJO and JSL analyzed and interpreted the data. IGK processed the data. HGC conceptualized, wrote, and reviewed the manuscript.

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Figure Legend

Fig. 1 A schematic illustrating the participant selection process used in the present study. Of a total of 1,125,691 participants, 41,585 participants with migraine were matched with 166,340 control participants for age, group, sex, income level, region of residence, and past medical histories.

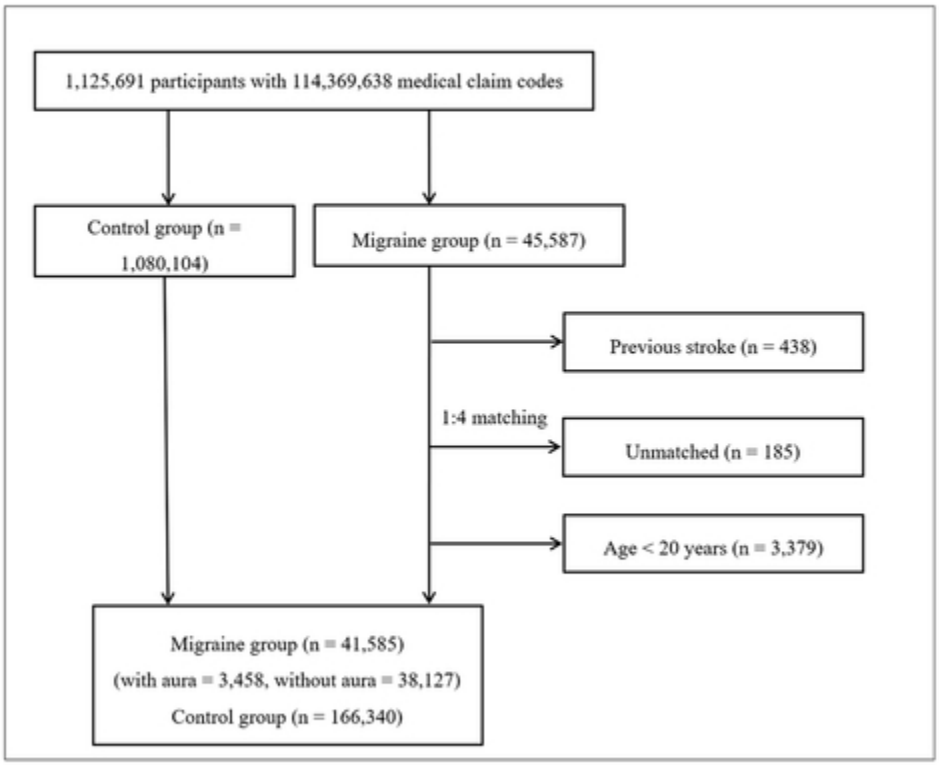

Figure 1

42x42mm (300 x 300 DPI)

S1. Subgroup analysis of migraine prevalence and stroke occurrence

Characteristics	**Young men (20-39 years old, n = 15,550)**			**Young women (20-39 years old, n = 47,410)**		
	Migraine (n = 3,110, %)	Non-Migraine (n = 12,440)	P-value	Migraine (n = 9,482)	Non-Migraine (n = 37,928)	P-value
Ischemic stroke			0.015*			< 0.001*
Yes	15 (0.48)	28 (0.22)		26 (0.27)	41 (0.11)	
No	3,095 (99.52)	12,412 (99.78)		9,456 (99.73)	37,887 (99.89)	
Hemorrhagic stroke			0.157			0.727
Yes	14 (0.45)	36 (0.28)		16 (0.17)	58 (0.15)	
No	3,096 (99.55)	12,404 (99.72)		9,466 (99.73)	37,870 (99.85)	
Characteristics	**Middle-aged men (40-59 years old, n = 22,090)**			**Middle-aged women (40-59 years old, n = 68,240)**		
	Migraine (n = 4,418)	Non-Migraine (n = 17,672)	P-value	Migraine (n = 9,482)	Non-Migraine (n = 37,928)	P-value
Ischemic stroke			0.560			0.002*
Yes	68 (1.54)	294 (1.66)		138 (1.46)	409 (1.08)	
No	4,350 (98.46)	17,378 (98.34)		13,648 (98.54)	54,952 (98.92)	

Hemorrhagic stroke			0.157			0.727
Yes	34 (0.77)	127 (0.72)		78 (0.82)	291 (0.77)	
No	4,384 (99.23)	17,545 (99.28)		13,570 (99.18)	54,301 (99.23)	
Characteristics	**Old men (≥ 60 years old, n = 14,740)**			**Old women (≥ 60 years old, n = 39,895)**		
	Migraine (n = 2,948)	Non-Migraine (n = 11,792)	P-value	Migraine (n = 7,979)	Non-Migraine (n = 31,916)	P-value
Ischemic stroke			0.015*			0.002*
Yes	205 (7.0)	756 (6.4)		512 (6.4)	1,766 (5.5)	
No	2,743 (93.0)	11,036 (93.6)		7,467 (93.6)	30,150 (94.5)	
Hemorrhagic stroke			0.157			0.465
Yes	50 (1.7)	155 (1.3)		103 (1.3)	446 (1.4)	
No	2,898 (98.3)	11,637 (98.7)		7,876 (98.7)	31,470 (98.6)	

* Chi-square test; differences were considered significant at $P < 0.05$.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2

Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
	#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
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. Give information separately for for exposed and unexposed groups if applicable.	5-8
Bias	#9	Describe any efforts to address potential sources of bias	5-8
Study size	#10	Explain how the study size was arrived at	7

Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
	#12b	Describe any methods used to examine subgroups and interactions	8
	#12c	Explain how missing data were addressed	NA
	#12d	If applicable, explain how loss to follow-up was addressed	NA
	#12e	Describe any sensitivity analyses	NA
Participants	#13a	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. Give information separately for exposed and unexposed groups if applicable.	NA
	#13b	Give reasons for non-participation at each stage	NA
	#13c	Consider use of a flow diagram	7
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8-13

	#14b	Indicate number of participants with missing data for each variable of interest	8-13
	#14c	Summarise follow-up time (eg, average and total amount)	8
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	NA
Main results	#16a	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	8-13
	#16b	Report category boundaries when continuous variables were categorized	NA
	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	13-14
Key results	#18	Summarise key results with reference to study objectives	16
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.	

Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19
Generalisability	#21	Discuss the generalisability (external validity) of the study results	16-18
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	20