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Increased Risk of Cardio-Cerebrovascular Diseases in Migraine Patients: A Nationwide Population-Based, Longitudinal Follow-Up Study in South Korea

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Background and Purpose Migraine is reportedly associated with several cardio-cerebrovascular diseases (CCDs), but some of these diseases have not received sufficient attention. We thus attempted to determine the associations of migraine with peripheral arterial disease (PAD), ischemic heart disease (IHD), atrial fibrillation/flutter (AF), ischemic stroke (IS), and hemorrhagic stroke (HS).

Methods The study population was recruited by applying International Classification of Diseases, Tenth Revision (ICD-10) codes to the database of the Korean National Health Insurance Service from 2002 to 2018. Cumulative incidence curves were plotted to compare the incidence rates of CCDs between the migraine (ICD-10 code G43; *n*=130,050) and nonmigraine (*n*=130,050) groups determined using 1:1 propensity-score matching. Cox proportional-hazards regression models were used to obtain adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for CCDs in patients with any migraine, migraine with aura (*n*=99,751), and migraine without aura (*n*=19,562) compared with nonmigraine controls.

Results For all CCDs, the cumulative incidence rates were higher in the migraine group than the nonmigraine group ($p<0.001$ in log-rank test). Any migraine, irrespective of the presence of aura, was associated with PAD (aHR 2.29, 95% CI 2.06–2.53), IHD (aHR 2.17, 95% CI 2.12–2.23), AF (aHR 1.84, 95% CI 1.70–1.99), IS (aHR 2.91, 95% CI 2.67–3.16), and HS (aHR 2.46, 95% CI 2.23–2.71). aHR was higher in female than in male migraineurs for all of the CCDs.

Conclusions Associations of migraine with CCDs have been demonstrated, which are stronger in females than in males.

Keywords migraine; cardiovascular diseases; cerebrovascular diseases; stroke.

INTRODUCTION

Migraine is a common primary headache syndrome characterized by recurrent episodes of moderate-to-severe headache and specific accompanying symptoms including nausea/vomiting, photophobia, and phonophobia.[1] A third of affected patients have auras, which are transient neurological symptoms.[2] Migraine has been reported to be associated with several cardio-cerebrovascular diseases (CCDs).[3-5] The associations have been stronger in females than in males, in younger than in elderly migraineurs, and in migraine with aura (MA) than in migraine without aura (MO).[5-7]

However, the CCD risk associated with migraine is smaller than that associated with conventional vascular risk factors.[3] In addition, there is a large gap between the ages at onset of migraine and CCD. Migraine episodes generally begin after puberty, and about 90% of the patients experience their first migraine attack when they are younger than 50 years.[6]

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Migraine often decreases in frequency or resolves completely in later life, especially in postmenopausal females,[4,6,8] whereas CCDs mostly develop later in life.[6] These characteristics make it difficult to determine the relationship between migraine and CCD. Confirming the association thus requires long-term longitudinal follow-up from a migraine diagnosis until CCD occurrence,[4] and the study population needs to be large enough to achieve statistical significance. These aspects could at least partially explain differences in the results for the associations between migraine and several CCDs obtained to date.[9,10]

Accordingly, using the long-term data of a nationwide population-based cohort in South Korea, the present study longitudinally investigated the associations of migraine with various CCDs, including peripheral arterial disease (PAD), ischemic heart disease (IHD), atrial fibrillation/flutter (AF), ischemic stroke (IS), and hemorrhagic stroke (HS).

METHODS

Data source

We used the big data extracted from the claims database of the Korean National Health Insurance Service (NHIS), which covers approximately 98% of the total Korean population as a mandatory health insurance system.[11] For insurance reimbursement, all hospitals and clinics in South Korea need to submit to the NHIS all data on medical treatment courses, including diagnoses, prescriptions, and medical procedures, which are coded using the International Classification of Diseases, Tenth Revision (ICD-10) and Korean Drug and Anatomical Therapeutic Chemical Codes.[11] All of the medical services are assessed for their appropriateness by the Health Insurance Review and Assessment system.[11] The NHIS database can be used for academic research. The National Health Insurance Sharing Service (NHISS) provides a customized data set sampled based on the NHIS database after anonymization and de-identification at the request of investigators (https://nhiss.nhis.or.kr). The present national cohort study was performed using the customized data service. This study was exempted from the need to be reviewed and the need to obtain informed consents from the study cohort by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (SCHBC 2018-09-021).

Study population

Fig. 1 shows a flowchart of patient and control-group recruitment. The included patients were sampled from approximately 47 million Korean people. The migraine group consisted of subjects aged between 20 and 49 years who were diagnosed with migraine (defined as ICD-10 diagnostic code G43) between January 1, 2003 and December 31, 2004. To ensure the accuracy of diagnoses, the study only included patients who had at least two outpatient clinic visits or one hospitalization with the principal diagnosis of migraine during this period. The index visit was defined as the first visit or hospitalization during which a principal diagnosis of migraine was made. The exclusion criteria for the migraine group were

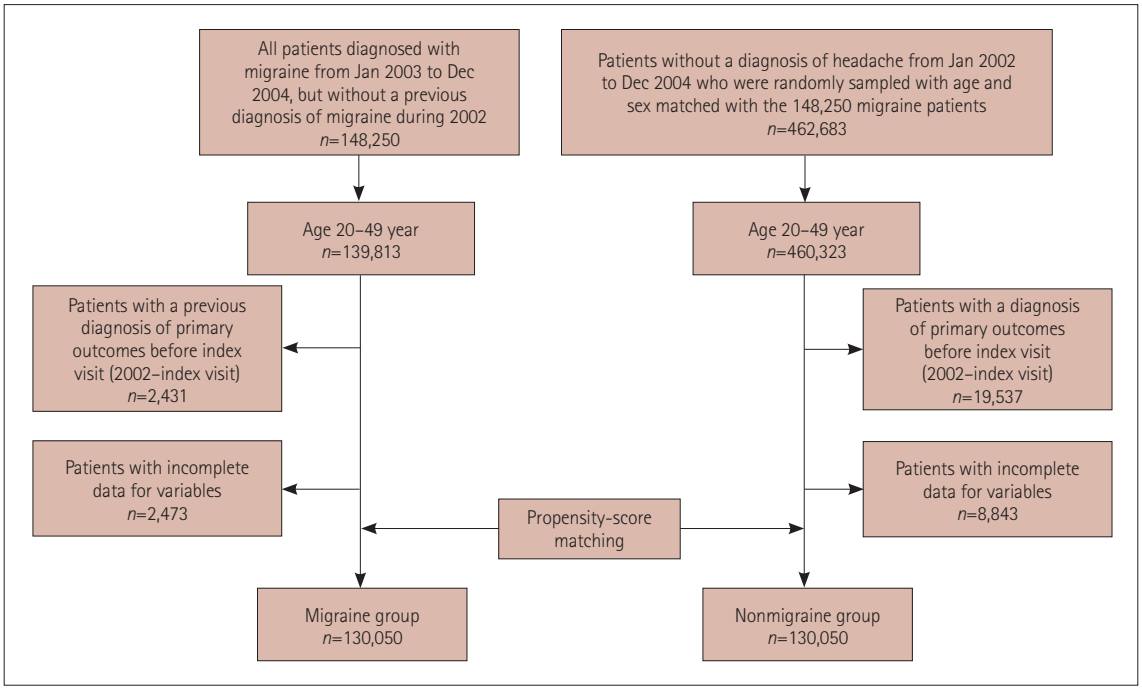

Fig. 1. Flowchart of study patient selection.

1) a diagnosis of migraine during 2002 (to increase the probability of including only new incident cases during 2003 and 2004), 2) a previous diagnosis of CCDs (PAD, IHD, AF, IS, HS, or sequalae of cerebrovascular disease [code I69]) before the index visit, or 3) incomplete data for variables. The nonmigraine group was sampled from the subjects aged between 20 and 49 years who were not diagnosed with any headache (codes G43, G44, and R51) between January 1, 2002 and December 31, 2004, and did not have a previous diagnosis of CCDs before the index visit or incomplete data for variables.

Propensity-score matching (PSM) was used to determine each final group, with 130,050 subjects included in each of the migraine and nonmigraine groups. The migraine group was classified into three subgroups according to the subcategories of G43: MA (G43.1, *n*=99,751), MO (G43.0, *n*=19,562), and other migraine (migraine codes other than G43.1 and G43.0, *n*=10,737). The detailed patient composition is presented in Table 1.

Variables and outcomes

The following clinical information was obtained for all included patients (ICD-10 diagnostic codes are within parentheses):[12,13] hypertension (I10–I13, I15), diabetes mellitus (E10–E14), hyperlipidemia (E78), valvular heart disease (I01, I05–I09, I34–I39, Q22, Q23), chronic kidney disease (N18, N19), chronic obstructive lung disease (J42–J45 [except for J43.0]), chronic liver disease (K73–K75, B18), and alcohol-related diseases (K70, F10, G31.2, E24.4, G62.1, T51.9, K85.2, K86.0, G72.1). Data were also collected on age, sex, income level (≤40th, 41–70th, ≥71st percentiles), and urbanization level (stratified into three levels).

The NHISS provided the analyzable data from the index visit until the end of 2018. These data were used to follow up all included patients from their index visit until the occurrence of CCDs, death, or last clinic visit (or hospitalization), whichever came first. The primary outcome was the occurrence of PAD, IHD, AF, IS, or HS. These outcomes were defined as follows:[12,13]

1) PAD was defined as code I70 or I73, and was confirmed if computed tomography (CT) or catheter lower extremity angiography was performed within 1 month before PAD was diagnosed.

2) IHD was defined as codes I20–I25 and was confirmed if electrocardiography (EKG), CT, or catheter coronary angiography, treadmill test, or echocardiography was performed within 1 month before IHD was diagnosed.

3) AF was defined as code I48, and was confirmed if EKG or 24-hr Holter monitoring was performed within 1 month before AF was diagnosed.

4) IS and HS were defined as codes I63 and I60–I62, respectively, and were confirmed if brain CT or magnetic resonance imaging was performed within 1 month before the diagnosis.

Statistical analyses

Group comparisons were performed using the chi-square test or independent two-samples t-test for each categorical and continuous variable. Cumulative incidence curves were plotted using the Kaplan-Meier method, and log-rank tests were performed to compare the incidence rates for the primary outcomes between the migraine and nonmigraine groups. A Cox proportional-hazards regression model was adopted to calculate hazard ratios (HRs) of migraine (any migraine, MA, or MO vs. nonmigraine) for the primary outcomes.

The validity for the proportional-hazards assumption was tested using a log-log plot,[14] and three Cox models were considered: 1) Model 1, univariate; 2) Model 2, adjusted for age and sex; and 3) Model 3, adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, valvular heart disease, chronic kidney disease, chronic liver disease, alcohol-related disease, chronic obstructive lung disease, income level, and urbanization level. Crude HRs and adjusted HRs (aHRs) with 95% confidence intervals (CIs) were obtained.

PSM was performed to reduce selection bias resulting from differences between the migraine and nonmigraine groups and also to balance the distribution of confounders. PSM was implemented using the PSMATCH procedure in the SAS program. The matching variables were age, sex, hypertension, diabetes, hyperlipidemia, valvular heart disease, chronic kidney disease, chronic obstructive pulmonary disease, chronic liver disease, alcohol-related disease, income level, and urbanization level. The ratio of the nonmigraine group to the migraine group was set to 1:1 using the greedy method with a 0.05 caliper width.

Table 1. Composition of the included patients

	Any migraine				Nonmigraine	Total
	Total	MA	MO	Other migraine		
Females	92,812	70,005	14,368	8,439	92,019	184,831
Males	37,238	29,746	5,194	2,298	38,031	75,269
Total	130,050	99,751	19,562	10,737	130,050	260,100

MA, migraine with aura; MO, migraine without aura.

In a data analysis room provided by the NHISS, statistical analyses were performed using SAS Enterprise Guide (version 7.1; SAS, Cary, NC, USA) and R software (version 3.3.0; The R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-tailed, and p values <0.05 were considered statistically significant.

RESULTS

Table 2 compares the basic characteristics between the migraine and nonmigraine groups. There were no significant intergroup differences in the prevalence rates of chronic kidney disease and chronic obstructive pulmonary disease. After applying PSM there were still significant intergroup differences in age, sex, and the prevalence rates of hypertension, diabetes mellitus, hyperlipidemia, valvular heart disease, chronic liver disease, alcohol-related disease, and urbanization and income levels.

The median follow-up period was 14.8 years (interquartile range, 13.7 to 15.9 years) for the migraine group and 15.7 years (interquartile range, 14.8 to 16.5 years) for the nonmigraine group. For all of the primary outcomes, the cumulative incidence rates were significantly higher in the migraine group than the nonmigraine group (p<0.001 in log-rank test) (Fig. 2).

For each outcome, the log-log curves for the groups were approximately parallel, indicating that each model satisfied the proportional-hazards assumption for a Cox model (Supplementary Fig. 1 in the online-only Data Supplement). Table 3 lists the results of crude and adjusted Cox proportional-hazards regression models of migraine (vs. nonmigraine) for the primary outcomes. Any migraine, MA, and MO were significantly associated with all of the primary outcomes in both the crude and adjusted models. There was no definite difference in aHR between MA and MO (<0.5) in IHD, AF, IS, and HS. Meanwhile, the aHR was higher in the MO group than the MA group for PAD (2.75 vs. 2.17).

The crude and adjusted Cox proportional-hazards models were applied to each sex group separately (Table 4). The significant association of any migraine and its subgroups with PAD, IHD, AF, IS, and HS persisted for both sexes in the adjusted analyses. The aHRs for all of the primary outcomes were higher in females than in males.

Table 2. Comparison of basic characteristics between the migraine and nonmigraine groups

Variable	Migraine (n=130,050)	Nonmigraine (n=130,050)	p
Age (yr)	36.7±8.0	36.8±7.9	0.013
Sex, female	92,812 (71.4)	92,019 (70.8)	<0.001
Hypertension	6,175 (4.7)	6,746 (5.2)	<0.001
Diabetes mellitus	3,508 (2.7)	4,181 (3.2)	<0.001
Hyperlipidemia	4,733 (3.6)	4,291 (3.3)	<0.001
Valvular heart disease	60 (0.0)	109 (0.1)	0.001
Chronic kidney disease	148 (0.1)	121 (0.1)	0.113
Chronic obstructive pulmonary disease	6,558 (5.0)	6,397 (4.9)	0.149
Chronic liver disease	4,578 (3.5)	4,850 (3.7)	0.005
Alcohol-related disease	1,582 (1.2)	1,459 (1.1)	0.026
Income level, percentile			0.004
≤40th	41,184 (31.7)	40,361 (31.0)	
41–70th	42,065 (32.3)	41,925 (32.2)	
≥71st	46,801 (36.0)	47,764 (36.7)	
Urbanization level			0.004
1 (urban)	60,653 (46.6)	62,988 (48.4)	
2	56,092 (43.1)	54,035 (41.5)	
3 (rural)	13,305 (10.2)	13,027 (10.0)	

Data are mean±SD or n (%) values.

DISCUSSION

Higher CCD risk associated with migraine

This nationwide population-based study found that migraine—regardless of the presence of aura—was associated with incident CCDs, including PAD, IHD, AF, IS, and HS. There have been only a few previous reports on the association of migraine with PAD. A population-based study found no meaningful association of PAD with migraine (aHR 1.12, 95% CI 0.96–1.30),[5] whereas another recent study found that it was significantly associated with migraine (aHR 1.65, 95% CI 1.48–1.84),[15] which is consistent with our findings (aHR 2.29, 95% CI 2.06–2.53).

Most previous cohort studies have found a significant association of migraine with IHD,[16,17] which is in agreement with our results. The aHRs for the IHD risk in those studies ranged from 0.98 to 2.50,[17] which is consistent with our aHR of 2.17. A few longitudinal cohort studies have found AF to be significantly associated with migraine.[5,18] The aHR for incident AF ranged from 1.25 to 1.30, which is lower than that of 1.84 in our cohort.

Numerous studies have explored the relationships between migraine and cerebrovascular diseases. IS mostly has been associated with migraine,[19-21] with aHR ranging from 1.12 to 2.49,[20] which is lower than our aHR of 2.91. Some studies failed to find an association of HS with migraine, while other studies (including meta-analyses of multiple studies) have demonstrated significant associations.[5,20-23] Among these studies, the highest aHR of migraine for HS was 2.13,[22] which is also lower than our value of 2.46.

Together our results showed that the risks of all incident CCDs in our patients with migraine were higher than in previous studies.

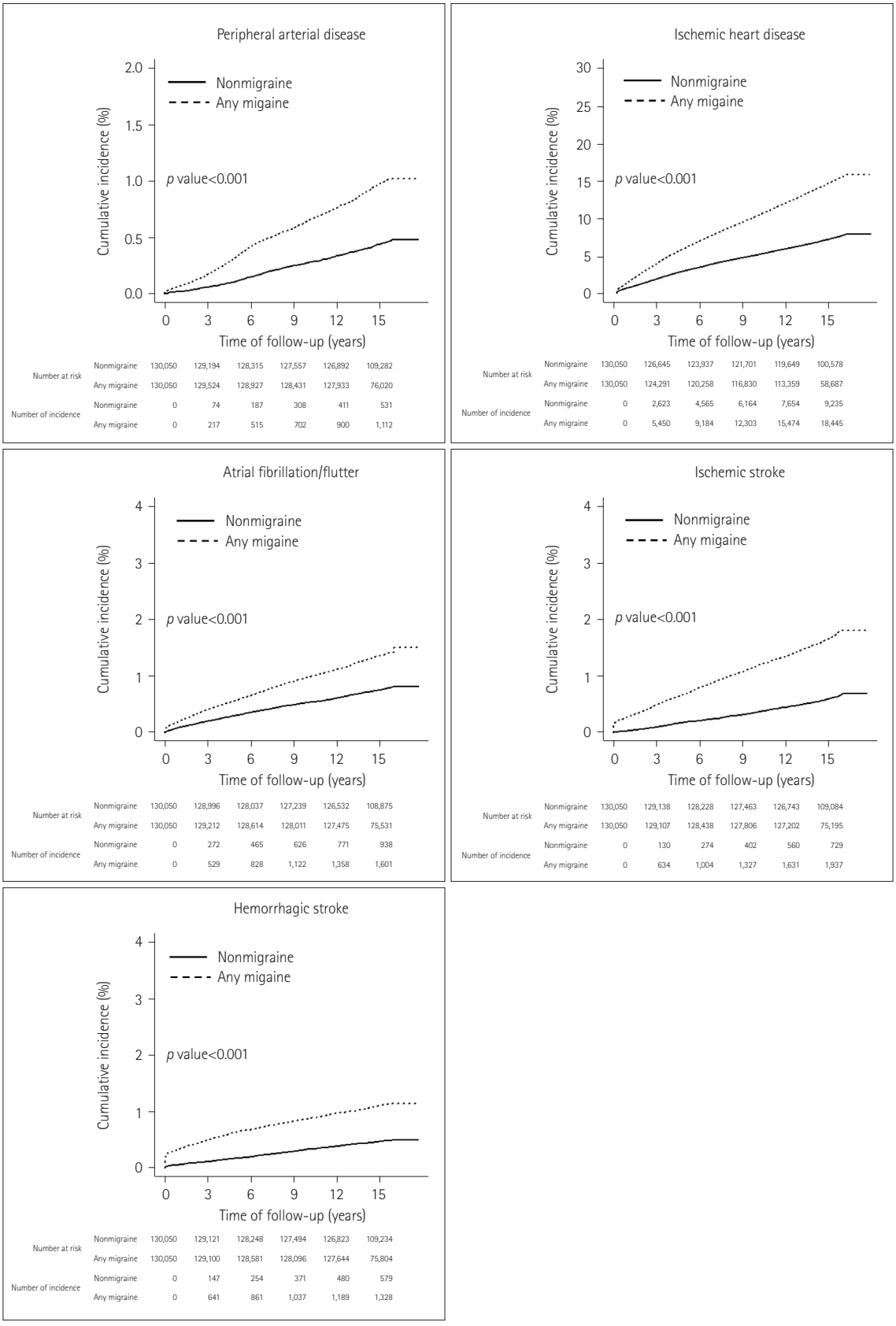

Fig. 2. Comparison of cumulative incidence rates for cardio-cerebrovascular events between the migraine and nonmigraine groups. *P* values were calculated in log-rank tests.

Table 3. Cox proportional-hazards models for cardio-cerebrovascular diseases

	Events, *n* (%)	Person-years	Crude rate*	Univariate (Model 1)		Multivariate (Model 2)		Multivariate (Model 3)	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
PAD	1,686 (0.65)								
Nonmigraine	559 (0.43)	1,801,606	0.31	1 (reference)		1 (reference)		1 (reference)	
Any migraine	1127 (0.87)	1,575,447	0.72	2.22 (2.00–2.45)	<0.001	2.26 (2.04–2.50)	<0.001	2.29 (2.06–2.53)	<0.001
MA	828 (0.83)	1,214,011	0.68	2.12 (1.90–2.36)	<0.001	2.15 (1.93–2.40)	<0.001	2.17 (1.95–2.42)	<0.001
MO	196 (1.00)	237,770	0.82	2.55 (2.17–3.01)	<0.001	2.68 (2.28–3.16)	<0.001	2.75 (2.33–3.23)	<0.001
IHD	28,358 (10.90)								
Nonmigraine	9,638 (7.41)	1,864,085	5.17	1 (reference)		1 (reference)		1 (reference)	
Any migraine	18,720 (14.39)	1,691,639	11.07	2.11 (2.06–2.17)	<0.001	2.15 (2.10–2.20)	<0.001	2.17 (2.12–2.23)	<0.001
MA	14,041 (14.08)	1,301,729	10.79	2.06 (2.01–2.12)	<0.001	2.08 (2.03–2.14)	<0.001	2.10 (2.05–2.16)	<0.001
MO	2,794 (14.28)	255,206	10.95	2.09 (2.00–2.18)	<0.001	2.20 (2.10–2.29)	<0.001	2.24 (2.15–2.34)	<0.001
AF	2,597 (1.00)								
Nonmigraine	977 (0.75)	1,803,717	0.54	1 (reference)		1 (reference)		1 (reference)	
Any migraine	1,620 (1.25)	1,577,368	1.03	1.80 (1.66–1.95)	<0.001	1.82 (1.68–1.97)	<0.001	1.84 (1.70–1.99)	<0.001
MA	1,179 (1.18)	1,215,347	0.97	1.70 (1.56–1.85)	<0.001	1.71 (1.57–1.86)	<0.001	1.73 (1.59–1.88)	<0.001
MO	248 (1.27)	237,883	1.04	1.82 (1.59–2.10)	<0.001	1.89 (1.65–2.18)	<0.001	1.92 (1.67–2.21)	<0.001
IS	2,764 (1.06)								
Nonmigraine	784 (0.60)	1,803,510	0.43	1 (reference)		1 (reference)		1 (reference)	
Any migraine	1,980 (1.52)	1,579,857	1.25	2.8 (2.58–3.04)	<0.001	2.87 (2.64–3.12)	<0.001	2.91 (2.67–3.16)	<0.001
MA	1,482 (1.49)	1,217,616	1.22	2.73 (2.50–2.97)	<0.001	2.77 (2.54–3.02)	<0.001	2.80 (2.57–3.06)	<0.001
MO	284 (1.45)	238,229	1.13	2.52 (2.19–2.90)	<0.001	2.69 (2.35–3.10)	<0.001	2.76 (2.40–3.17)	<0.001
HS	1,931 (0.74)								
Nonmigraine	595 (0.46)	1,801,129	0.33	1 (reference)		1 (reference)		1 (reference)	
Any migraine	1,336 (1.03)	1,573,577	0.85	2.40 (2.18–2.64)	<0.001	2.43 (2.21–2.68)	<0.001	2.46 (2.23–2.71)	<0.001
MA	968 (0.97)	1,212,787	0.80	2.26 (2.04–2.51)	<0.001	2.28 (2.06–2.52)	<0.001	2.30 (2.08–2.55)	<0.001
MO	202 (1.03)	237,324	0.85	2.40 (2.05–2.82)	<0.001	2.50 (2.13–2.93)	<0.001	2.56 (2.18–3.01)	<0.001

Model 2: Model 1 adjusted for age and sex; Model 3: Model 1 adjusted for age, sex, hypertension, diabetes mellitus, hyperlipidemia, valvular heart disease, chronic kidney disease, chronic liver disease, alcohol-related disease, chronic obstructive lung disease, income level, and urbanization level.
*Crude rate: per 10,000 person-years.
AF, atrial fibrillation/flutter; CI, confidence interval; HR, hazard ratio; HS, hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; MA, migraine with aura; MO, migraine without aura; PAD, peripheral arterial disease.

The reason for higher aHRs for CCDs

The higher aHRs for incident CCDs in our study may be attributable to differences in characteristics between our participants and those in previous studies. Our study population consisted of migraine patients who visited clinics or hospitals, and so were more likely to have experienced more-severe or frequent migraine attacks of longer duration than those who take over-the-counter drugs without a clinic visit. In particular, 76.7% of all migraine patients in our study were given the code of MA, indicating a higher prevalence of aura compared with the general migraine population. Although the severity and duration of migraine have not been proven to be associated with CCDs, there is evidence that an increased frequency of migraine attack is correlated with a higher risk of cerebrovascular diseases, especially in patients with MA.[6,24] Moreover, cardiovascular diseases are also more likely to be associated with MA than with MO.[7,17,19] These characteristics of a clinic-based study population could explain the higher aHRs for CCDs in our data compared with the results of other studies.

In addition, the duration of the follow-up period might have affected our results. A previous study of the Women's Ischemia Syndrome Evaluation found no significant association between migraine and cardiovascular events at a median follow-up of 4.4 years.[25] In contrast, another study found a significantly increased risk of cardiovascular diseases at a median follow-up of 6.5 years.[10] Such time dependency of cardiovascular outcomes was again noted in recent meta-analyses, which showed higher risks of myocardial infarction and all-cause mortality among studies with longer follow-ups.[17,26] Therefore, the long duration of the follow-up in the present study may have increased the difference in the risk between patients with and without migraine. The cumulative incidence curves in Fig. 2 show that the group differences in the cumulative incidence rates of CCDs increased over time. This means that

Table 4. Cox proportional-hazards models for cardio-cerebrovascular diseases, stratified by sex

	Events, *n* (%)	Person-years	Crude rate*	Univariate (Model 1)		Multivariate (Model 2)		Multivariate (Model 3)	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
PAD									
Females	1,214 (0.66)								
Nonmigraine	382 (0.42)	1,304,620	0.29	1 (reference)		1 (reference)		1 (reference)	
Any migraine	832 (0.90)	1,146,067	0.73	2.37 (2.10–2.68)	<0.001	2.41 (2.13–2.72)	<0.001	2.41 (2.13–2.72)	<0.001
MA	590 (0.84)	869,445	0.68	2.22 (1.95–2.53)	<0.001	2.25 (1.97–2.56)	<0.001	2.25 (1.97–2.56)	<0.001
MO	152 (1.06)	177,525	0.86	2.80 (2.32–3.37)	<0.001	2.95 (2.45–3.56)	<0.001	2.96 (2.46–3.58)	<0.001
Males	472 (0.63)								
Nonmigraine	177 (0.47)	496,986	0.36	1 (reference)		1 (reference)		1 (reference)	
Any migraine	295 (0.79)	429,741	0.69	1.87 (1.55–2.26)	<0.001	1.92 (1.60–2.32)	<0.001	1.99 (1.65–2.4)	<0.001
MA	238 (0.80)	344,566	0.69	1.89 (1.55–2.30)	<0.001	1.94 (1.59–2.35)	<0.001	1.99 (1.64–2.42)	<0.001
MO	44 (0.85)	60,246	0.73	1.99 (1.43–2.77)	<0.001	2.07 (1.49–2.88)	<0.001	2.18 (1.57–3.04)	<0.001
IHD									
Females	18,022 (9.75)								
Nonmigraine	5,687 (6.18)	1,341,213	4.24	1 (reference)		1 (reference)		1 (reference)	
Any migraine	12,335 (13.29)	1,221,910	10.09	2.35 (2.28–2.43)	<0.001	2.37 (2.30–2.45)	<0.001	2.38 (2.30–2.45)	<0.001
MA	9,011 (12.87)	925,651	9.73	2.27 (2.19–2.35)	<0.001	2.29 (2.21–2.36)	<0.001	2.29 (2.21–2.37)	<0.001
MO	1,906 (13.27)	189,262	10.07	2.34 (2.22–2.47)	<0.001	2.44 (2.32–2.57)	<0.001	2.46 (2.33–2.59)	<0.001
Males	10,336 (13.73)								
Nonmigraine	3,951 (10.39)	522,871	7.56	1 (reference)		1 (reference)		1 (reference)	
Any migraine	6,385 (17.15)	469,728	13.59	1.78(1.71–1.86)	<0.001	1.82 (1.75–1.90)	<0.001	1.87 (1.79–1.94)	<0.001
MA	5,030 (16.91)	376,077	13.37	1.76 (1.68–1.83)	<0.001	1.79 (1.72–1.87)	<0.001	1.83 (1.76–1.91)	<0.001
MO	888 (17.10)	65,944	13.47	1.77 (1.64–1.90)	<0.001	1.83 (1.70–1.96)	<0.001	1.90 (1.77–2.04)	<0.001
AF									
Females	1,639 (0.89)								
Nonmigraine	566 (0.62)	1,305,125	0.43	1 (reference)		1 (reference)		1 (reference)	
Any migraine	1,073 (1.16)	1,146,067	0.94	2.03 (1.83–2.25)	<0.001	2.04 (1.85–2.26)	<0.001	2.05 (1.85–2.27)	<0.001
MA	750 (1.07)	869,648	0.86	1.88 (1.68–2.09)	<0.001	1.89 (1.69–2.10)	<0.001	1.89 (1.69–2.11)	<0.001
MO	172 (1.20)	177,394	0.97	2.10 (1.77–2.49)	<0.001	2.15 (1.81–2.55)	<0.001	2.16 (1.82–2.57)	<0.001
Males	958 (1.27)								
Nonmigraine	411 (1.08)	498,593	0.82	1 (reference)		1 (reference)		1 (reference)	
Any migraine	547 (1.47)	431,300	1.27	1.48 (1.30–1.68)	<0.001	1.51 (1.33–1.71)	<0.001	1.54 (1.35–1.75)	<0.001
MA	429 (1.44)	345,698	1.24	1.45 (1.26–1.66)	<0.001	1.48 (1.29–1.69)	<0.001	1.50 (1.31–1.72)	<0.001
MO	76 (1.46)	60,489	1.26	1.46 (1.14–1.87)	0.002	1.51 (1.18–1.93)	0.001	1.56 (1.22–1.99)	<0.001
IS									
Females	1,726 (0.93)								
Nonmigraine	423 (0.456)	1,305,012	0.32	1 (reference)		1 (reference)		1 (reference)	
Any migraine	1,303 (1.40)	1,147,780	1.14	3.38 (3.03–3.78)	<0.001	3.42 (3.07–3.82)	<0.001	3.41 (3.05–3.81)	<0.001
MA	951 (1.36)	871,302	1.09	3.26 (2.91–3.66)	<0.001	3.29 (2.93–3.69)	<0.001	3.27 (2.92–3.67)	<0.001
MO	176 (1.22)	177,563	0.99	2.95 (2.47–3.51)	<0.001	3.11 (2.61–3.71)	<0.001	3.10 (2.60–3.70)	<0.001
Males	1,038 (1.38)								
Nonmigraine	361 (0.95)	498,499	0.72	1 (reference)		1 (reference)		1 (reference)	
Any migraine	677 (1.82)	432,076	1.57	2.12 (1.87–2.41)	<0.001	2.20 (1.94–2.50)	<0.001	2.28 (2.01–2.60)	<0.001
MA	531 (1.79)	346,313	1.53	2.08 (1.82–2.38)	<0.001	2.15 (1.88–2.46)	<0.001	2.22 (1.94–2.55)	<0.001
MO	93 (1.79)	60,666	1.53	2.08 (1.65–2.61)	<0.001	2.19 (1.75–2.76)	<0.001	2.33 (1.85–2.93)	<0.001
HS									
Females	1,253 (0.68)								

Table 4. Cox proportional-hazards models for cardio-cerebrovascular diseases, stratified by sex (continued)

	Events, *n* (%)	Person-years	Crude rate*	Univariate (Model 1)		Multivariate (Model 2)		Multivariate (Model 3)	
				HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Nonmigraine	349 (0.38)	1,303,953	0.27	1 (reference)		1 (reference)		1 (reference)	
Any migraine	904 (0.97)	1,143,994	0.79	2.75 (2.43–3.11)	<0.001	2.77 (2.44–3.13)	<0.001	2.77 (2.45–3.14)	<0.001
MA	642 (0.92)	868,452	0.74	2.58 (2.26–2.94)	<0.001	2.59 (2.28–2.95)	<0.001	2.60 (2.28–2.96)	<0.001
MO	149 (1.04)	177,083	0.84	2.92 (2.41–3.54)	<0.001	3.02 (2.49–3.65)	<0.001	3.06 (2.52–3.70)	<0.001
Males	678 (0.90)								
Nonmigraine	246 (0.65)	497,177	0.49	1 (reference)		1 (reference)		1 (reference)	
Any migraine	432 (1.16)	429,583	1.01	1.91 (1.63–2.24)	<0.001	1.94 (1.66–2.28)	<0.001	1.99 (1.70–2.32)	<0.001
MA	326 (1.10)	344,335	0.95	1.80 (1.53–2.13)	<0.001	1.83 (1.55–2.16)	<0.001	1.86 (1.58–2.20)	<0.001
MO	53 (1.02)	60,241	0.88	1.67 (1.24–2.25)	<0.001	1.72 (1.28–2.31)	<0.001	1.79 (1.33–2.42)	<0.001

*Crude rate: per 10,000 person-years.
AF, atrial fibrillation/flutter; CI, confidence interval; HR, hazard ratio; HS, hemorrhagic stroke; IHD, ischemic heart disease; IS, ischemic stroke; MA, migraine with aura; MO, migraine without aura; PAD, peripheral arterial disease.

while migraine may be a minor medical problem in early life, it can be a marker for the risk of CCD in later life.

Putative mechanisms underlying the migraine–CCD association

The association between MA and cerebrovascular diseases is well understood in terms of disorders in the same organ. The underlying mechanisms include symptom similarity between aura and stroke, vasospasm/cortical spreading depression (oligemia), patent foramen ovale (microemboli or vasoactive substances reaching the brain via a right-to-left shunt), secondary MA (e.g., CADASIL or moyamoya disease), and a shared genetic or biological risk (e.g., endothelial dysfunction, arterial dissection, hypercoagulability, poor cholesterol profile, or elevated Framingham risk score).[6,8,27,28] However, the relationships between migraine and vascular diseases in organs other than the brain are less well explained. While the mechanism remains uncertain, previously commented shared risks between migraine and vascular diseases can explain such an association.[28] Moreover, the frequent use of non-steroidal anti-inflammatory drugs or prolonged immobility during migraine has been proposed as a mechanism.[5,29,30]

Different risks of CCDs between sexes and migraine types

Another important finding of our study was that the CCD risks associated with migraine were all higher in females than in males. Higher risks in females have also been found in previous investigations of the associations of migraine with IHD,[17] IS,[19] and HS.[23] This could be partially explained by migraine attacks being more frequent, longer, and more severe in females than in males. Hormone differences between the sexes, especially fluctuations in estrogen, seem to be principally involved in the higher prevalence and severity of migraine in females.[29,31] Estrogen withdrawal triggers migraine episodes, and episodes of migraine are more frequent around the time of menstruation.[29]

Moreover, there is some evidence that menopausal vasomotor symptoms (VMS) are associated with migraine history and cardiovascular events. Specifically, a study analyzing the SWAN (Study of Women's Health Across the Nation) data found that a history of migraine diagnosis predicted an increased frequency of VMS, including hot flashes (p=0.0036) and night sweats (p=0.0138).[32] Using the same data, another study found that females with frequent baseline VMS (≥6 days/2 weeks relative to no VMS) had a higher risk of subsequent cerebrovascular events (aHR 1.51, 95% CI 1.05–2.17).[33] In addition, a recent analysis of data from The Women's Health Initiative CaD study revealed that the number of menopausal symptoms (≥2 menopausal symptoms vs. none) is associated with a higher occurrence of cardiovascular disease (aHR 1.35, 95% CI 1.18–1.54).[34] The menopausal VMS has been reported to be associated with vascular risk factors such as hypertension,[35] diabetes,[36] and dyslipidemia,[37] and also with arterial stiffness,[38,39] endothelial dysfunction,[39] and proinflammatory cytokines such as interleukin-8 and tumor necrosis factor alpha.[40] Moreover, migraine was reported to be associated with an increased risk of hypertension in menopausal females based on data from a large French cohort (aHR 1.29, 95% CI 1.24–1.35).[41] Thus, the stronger association between migraine and CCDs in females could be linked to cyclic and lifetime changes of female hormones and their interaction with vascular conditions in susceptible individuals.

Aura and risk of CCDs

The risks of IHD,[17] stroke,[19-21,26] and AF[18] have been reported to be higher in MA than in MO. In particular, a recent meta-analysis of migraine cohort studies demonstrated a signifi-

cantly increased risk of IS in MA but not in MO.[20] However, the difference in the risks was not definite between MA and MO in our study; instead, the risk of PAD was higher in MO than in MA (aHR 2.75 vs. 2.17). The reason for these results differing between studies is unclear, but it could be due to a shortcoming in our data—no verification of the accuracy of migraine categorization; that is, some of our cases given the diagnostic code of MO during the patient recruitment period might have been actually MA. In the real-world clinical setting of South Korea, any diagnostic code in the migraine category is sufficient to warrant the prescription of migraine medications to be reimbursed by national insurance.

Strengths, comparison with a Korean NHIS study, and limitations

The main strength of our study was its longitudinal investigation of a very large nationwide migraine population during a long-term follow-up period. A previous study of the association between migraine and stroke (similar to our study) based on the South Korea NHIS national sample cohort (41,585 migraine patients) between 2002 and 2013 found an increased risk of IS (aHR 1.18, 95% CI 1.10−1.26) but not of HS in patients with migraine.[21] This differs from our results of a higher aHR for IS (aHR 2.91, 95% CI 2.67−3.16) and a significant association with HS (aHR 2.46, 95% CI 2.23−2.71). These discrepancies might be due to the differences as discussed above in the follow-up period, the sample size, and the criteria used to recruit the migraine group. The mean follow-up period was shorter in that previous study than in our study (6.7 years vs. 13.3 years for the migraine group and 14.5 years for the nonmigraine group), which could have decreased the aHR. In addition, the previous study analyzed nonnationwide NHIS sample cohort data (about one million samples, representing 2% of the entire South Korean population), and included elderly migraineurs aged ≥50 years (comprising 45.5% of the total migraine patients in the study), which is potentially another factor decreasing the aHR. In contrast, we tried to include only new incident cases of migraineurs aged 20 and 49 years. This approach would facilitate tracing the occurrence of CCDs along time after the incidence of migraine. In addition, the inclusion of younger migraineurs would increase the migraine-associated risk of CCDs, because there is evidence that the risk of stroke is higher in younger migraineurs.[21,23,42,43]

Our study had some limitations, mainly arising from its analysis of claims data. Migraine and CCDs were diagnosed based on ICD codes from the NHIS database, which raises concern about their diagnostic accuracy. Errors in diagnostic codes may be inherent in such claims data since they are formed by medical providers to obtain insurance reimbursement rather than being inherently designed for research purposes.[11] This is supported by on average 70% of diagnostic codes corresponding to the actual diagnoses on medical charts. To increase the accuracy of the diagnoses, we included only migraine patients with at least two outpatient clinic visits or one hospitalization, and ascertained from the data the execution of examinations required to diagnose CCDs. Nonetheless, erroneous categorizations of migraine types might have been present. On the other hand, our efforts to increase the accuracy of migraine diagnoses in a clinic-based population could have precluded our study population from being representative of typical migraine patients. This approach seems to have resulted in the proportion of MA patients in this study being larger than that in the general migraine population.

In addition, we were not able to obtain detailed information about the migraine presentation (e.g., its frequency, severity, or duration), additional vascular risk factors (e.g., smoking or obesity), or drugs potentially affecting the incidence of CCDs (e.g., migraine-specific drugs or oral contraceptives).[6,8,42]

Lastly, patients with migraine are likely to visit clinics more frequently than those without migraine. This means that patients with migraine may have more chances of being diagnosed with CCDs than those without migraine, and so the CCD risks associated with migraine might have been overestimated (informed-presence bias).

In conclusion, the present nationwide population-based longitudinal cohort study found significant associations of migraine with PAD, IHD, AF, IS, and HS, which were stronger in females than in males.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.3.323.

Availability of Data and Material

The datasets generated or analyzed during the current study may be accessed via NHISS (http://nhiss. nhis.or.kr). However, the researchers have to submit a study proposal for acquiring approval from each institutional review board, which is also reviewed by the NHIS review committee. In addition, the raw data cannot be retrieved from the NHISS server, and only can be analyzed in 'Data analysis room' provided by NHISS.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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