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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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Manuscripts

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7 2 **migraine: A longitudinal follow-up study using a national**
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3 **24 Abstract**
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5 **25 Objective:** Growing evidence has supported the association between migraine and stroke, but
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8 **26** the causative association remains unclear at present. According to stroke type, we aimed to
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10 **27** investigate the risk of stroke in patients with migraine using a national sample cohort from
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12 **28** Korea.

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14 **29 Design:** A longitudinal follow-up study

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17 **30** Setting: Data from 2002 to 2013 national cohort collected by Korean Health Insurance
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19 **31** Review and Assessment were used.

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21 **32 Participants:** We extracted the data from patients with migraine (n = 41,585) and 1:4-
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24 **33** matched controls (n = 166,340) and analyzed the occurrence of ischemic and hemorrhagic
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26 **34** strokes. The migraine group included participants diagnosed with migraine (ICD-10: G43) \geq
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28 **35** 2 times. Hemorrhagic stroke (I60-I62) and ischemic stroke (I63) were determined using
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30 **36** admission histories. The crude and adjusted hazard ratios (HRs) were calculated using Cox
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32 **37** proportional hazard models, and the 95% confidence intervals (CIs) were determined.
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35 **38** Subgroup analyses based on age and sex were also performed.

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37 **39 Results:** The rates of ischemic stroke were higher in the migraine group (2.3% [964/41, 585])
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40 **40** than in the control group (2.0% [3,294/163,046], $P < 0.001$). The adjusted HR of ischemic
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42 **41** stroke was 1.18 (95% CI = 1.10-1.26) in the migraine group ($P < 0.001$). The strongest
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44 **42** association between migraine and ischemic stroke was found in young women. The
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46 **43** contribution of migraine to the occurrence of ischemic stroke was also observed in middle
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48 **44** aged women, old women, and young men (each $P < 0.05$). The risk of hemorrhagic stroke did
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50 **45** not reach statistical significance.

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52 **46 Conclusion:** Migraine is associated with an increased risk of ischemic stroke but not
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55 **47** hemorrhagic stroke.
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3 48 Keywords: migraine, stroke, cohort study, Korea
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8 50 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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10 51 * Migraine is associated with the increased risk of developing ischemic stroke.
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12 52 * The strongest association between migraine and ischemic stroke was found in young
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14 53 women (20-39 years old).
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16 54 * A higher risk of hemorrhagic stroke in patients with migraine did not reach statistical
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18 55 significance, but it awaits further confirmation.
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72 **Introduction**

73 Migraine is a common neurovascular disorder characterized by recurrent disabling episodes
74 of headache, most often unilateral headache. The headache is partly accompanied with visual
75 or sensory symptoms, namely, aura.¹ The annual prevalence of migraine is approximately
76 8%–15% worldwide,^{2,3} and in Korea, the estimated incidence is 6.1%.⁴ Migraine appears to
77 present at a relatively young age (< 45 years); it is more prevalent in women than men, with a
78 prevalence of > 25% in the 35–39-year-old female population worldwide.¹ The use of
79 migraine as an independent risk factor for cardiovascular events has been debated for many
80 years, but it is an established risk factor for ischemic stroke.⁵

81 Stroke is a cerebrovascular condition involving limitation of blood flow to the brain due
82 to blockage or rupture in the cerebrovascular system.⁶ Stroke is responsible for approximately
83 700,000 deaths annually in the Western world.⁷ In Korea, the estimated stroke incidence is
84 approximately 795,000 in people aged ≥ 30 years.⁸ More than 80% of stroke cases are
85 ischemic, and the rest are hemorrhagic; ischemic and hemorrhagic strokes differ with regard
86 to risk factors, genetic predisposition, and mortality rates.^{9,10}

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

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

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3 96 migraine and ischemic stroke (adjusted hazard ratio [HR]: 1.24, confidence interval [CI]:
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5 97 1.12–1.38).³ Similarly, an increased risk of ischemic stroke has been consistently found in
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7 98 migraineurs, especially in those with migraine with aura.^{3 14-17} Furthermore, growing
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9 99 evidence has supported the association between migraine and hemorrhagic stroke,^{18 19} but the
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12 100 causative association remains unclear at present. Given that stroke is a leading cause of
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14 101 mortality, validation of the association between migraine and stroke may facilitate treatment
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17 102 and prognosis in such cases.

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19 103 Herein, by using a national Korean population-based sample cohort, we examined the
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21 104 association between migraine and stroke. We extracted data for patients with migraine and a
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23 105 1:4-matched control group and analyzed the occurrence of ischemic stroke and hemorrhagic
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26 106 stroke in this cohort. Subgroup analyses according to age and sex were also performed.
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30 108 **Materials and Methods**

31 109 **Study Population and Data Collection**

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35 110 The ethics committee of Hallym University (2014-I148) approved the use of these data. The
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37 111 Institutional Review Board exempted the requirement for written informed consent.

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39 112 This national cohort study used data from the Korean National Health Insurance
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41 113 Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly
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43 114 from the entire population database to prevent non-sampling errors. Approximately 2% of the
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45 115 samples (one million) were selected from the entire Korean population (50 million). The
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47 116 selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and
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49 117 income level [41 categories]) using randomized stratified systematic sampling methods via
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51 118 proportional allocation to represent the entire population. A previous study verified the
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54 119 appropriateness of the sample after data selection.²⁰ The National Health Insurance Sharing

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3 120 Service provides a detailed description of the methods used to perform these procedures.²¹
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5 121 This cohort database included (i) personal information, (ii) health insurance claim codes
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7 122 (procedures and prescriptions), (iii) diagnostic codes using the International Classification of
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9 123 Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using
10
11 124 the Korean Standard Classification of disease), (v) socio-economic data (residence and
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13 125 income), and (vi) medical examination data for each participant from 2002 to 2013.

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16 126 All Korean citizens are recognized by a 13-digit resident registration number from birth
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18 127 to death. Therefore, exact population statistics have been determined using this database. All
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20 128 Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit
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22 129 resident registration number to register individual patients in the medical insurance system.
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24 130 Therefore, the risk of overlapping medical records is minimal, even if a patient moves from
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26 131 one place to another. All medical treatments in Korea are tracked without exception using the
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28 132 Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice
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30 133 of death must be provided to an administrative entity before a funeral can be held. Medical
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32 134 doctors record the date and cause of death on a death certificate.
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40 136 **Participant Selection**

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42 137 Out of 1,125,691 cases with 114,369,638 medical claim codes, participants who were
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44 138 diagnosed with migraine (ICD-10: G43) were included. Among them, participants who were
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46 139 treated ≥ 2 times ($n = 45,587$) were selected. The participants were followed up for 12 years.

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49 140 The history of admission for hemorrhagic stroke (I60: Subarachnoid hemorrhage, I61:
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51 141 Intracerebral hemorrhage, and I62: Other nontraumatic intracranial hemorrhage) and
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53 142 ischemic stroke (I63: Cerebral infarction) was identified using ICD-10 codes. We selected the
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3 143 participants who were treated ≥ 1 times. These methods were used in other studies evaluating
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5 144 the incidence of stroke in Korea.^{8 22}
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8 145 The migraine participants were matched 1:4 with participants (control group) who were
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10 146 never diagnosed with a migraine from 2002 through 2013 in this cohort. The control groups
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12 147 were selected from the mother population (n = 1,080,104). The matches were processed for
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14 148 age, group, sex, income group, region of residence, and past medical histories (hypertension,
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16 149 diabetes, and dyslipidemia). To prevent selection bias when selecting the matched
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18 150 participants, we sorted the control group participants using a random number order, and they
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20 151 were then selected from top to bottom. It was assumed that the matched control participants
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22 152 were involved at the same time as each matched migraine participant (index date). Therefore,
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24 153 control group members who died before the index date were excluded. In both the migraine
25
26 154 and control groups, participants with histories of hemorrhagic or ischemic stroke before the
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28 155 index date were excluded. In the migraine group, 438 participants were excluded. The
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30 156 migraine participants for whom we could not identify sufficient numbers of matching
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32 157 participants were excluded (n = 185). We excluded participants under 20 years old (n =
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34 158 3,379). Finally, 1:4 matching resulted in the inclusion of 41,585 migraine participants and
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36 159 166,340 control participants (Fig.1).
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45 161 **Variables**

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47 162 The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34..., and 85+ years
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49 163 old. A total of 14 age groups were designated. The income groups were initially divided into
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51 164 41 classes (one health aid class, 20 self-employment health insurance classes, and 20
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53 165 employment health insurance classes). These groups were re-categorized into 11 classes
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55 166 (class 1 [lowest income]–class 11 [highest income]). Region of residence was divided into 16
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3 167 areas according to administrative district. These regions were regrouped into urban (Seoul,
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5 168 Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon,
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7 169 Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk,
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10 170 Gyeongsangnam, and Jeju) areas.

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12 171 The past medical histories of the participants were evaluated using ICD-10 codes. For
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14 172 the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E14), and dyslipidemia
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16 173 (E78) were assessed if the participants were treated ≥ 2 times.
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20 21 175 **Statistical Analyses**

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23 176 Chi-square tests were used to compare the general characteristics between the migraine and
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25 177 control groups. For analysis of the HRs of migraine on hemorrhagic stroke and ischemic
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27 178 stroke, Cox proportional hazard models were used, and 95% CIs were calculated. In these
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29 179 analyses, crude (simple) and adjusted (age, sex, income, region of residence, hypertension,
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31 180 diabetes, and dyslipidemia) models were used. For the subgroup analysis, we divided the
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33 181 participants by age and sex (20–39 years old, 40–59 years old, 60+ years old; men and
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35 182 women). Two-tailed analyses were conducted, and P values less than 0.05 were considered
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37 183 significant. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY,
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39 184 USA).
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49 186 **Results**

50 187 The mean follow-up was 80.9 (standard deviation [SD] = 41.6) months in migraine patients
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52 188 and 80.9 (SD = 41.6) months in controls. The rates of hemorrhagic stroke were not higher in
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54 189 the migraine group (0.7% [295/41,585]) than the control group (0.7% [1,113/166,340], P =
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56 190 0.370, Table 1). The rates of ischemic stroke were higher in the migraine group (2.3%

191 [964/41,585]) than the control group (2.0% [3,294/163,046]. $P < 0.001$). The general
 192 characteristics (age, sex, income, region of residence, hypertension, diabetes, and
 193 dyslipidemia histories) of participants were the same due to the matching protocol ($P =$
 194 1.000).

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196 **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)	

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198 *Chi-square test. Significance at $P < 0.05$

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200 The crude and adjusted HRs of hemorrhagic stroke were 1.06 (95% CI = 0.93–1.21, $P =$
 201 0.369) and 1.06 (95% CI = 0.93–1.21, $P = 0.371$), respectively, in the migraine group (Table
 202 2). The crude and adjusted HRs of ischemic stroke were 1.17 (95% CI = 1.09–1.26) and 1.18
 203 (95% CI = 1.10–1.26), respectively, in the migraine group (each $P < 0.001$).

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207 **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	

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

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

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3 212 In the subgroup analyses, all crude and adjusted HRs of hemorrhagic stroke did not reach
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5 213 statistical significance (Table 3). For patients with ischemic stroke, young men, young
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7 214 women, middle aged men, old men, and old women showed statistical significance (each $P <$
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9 215 0.05). The significant adjusted HRs were 2.15 (95% CI = 1.15–4.02) in < 40 -year-old men;
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11 216 2.54 (95% CI = 1.55–4.15) in < 40 -year-old women; 1.36 (95% CI = 1.36–1.64) in 40–59-
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13 217 year-old women; and 1.17 (95% CI = 1.06–1.29) in ≥ 60 -year-old women.
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236 **Table 3 Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and**
 237 **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)	

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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

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

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

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240 **Discussion**

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

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

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3 264 There is a growing body of evidence regarding the increased risk of ischemic stroke in
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5 265 migraine without aura. Notably, a significant association was found in cases of ischemic
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7 266 stroke resulting from cervical artery dissection.²⁸ In addition, genetic overlaps among
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10 267 migraine without aura, large artery stroke, and cardio-embolic stroke have been identified.²⁹
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12 268 However, strong evidence has been not reported. A recent large population-based study
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14 269 demonstrated an insignificant risk of ischemic stroke in patients with migraine without aura
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17 270 but an increased risk in patients with migraine with aura.³ The study suggested that the
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19 271 difference may be due to lipid profile, susceptibility to thrombosis, and genetic
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21 272 predisposition.³ A meta-analysis found that there was no significant association between
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23 273 migraine without aura and ischemic stroke.¹⁷ In the present study, we did not differentiate
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26 274 between migraine subtypes, such as migraine with and without aura, when analyzing the risk
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28 275 of stroke. Given this, the risk of ischemic stroke in migraine was relatively low despite
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30 276 statistical significance compared to that of other studies investigating specific conditions.

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33 277 Notably, in this study, migraine was not linked to an increased risk of hemorrhagic stroke.
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35 278 In contrast to the present study, a recent meta-analysis, based on 4 case-control and 4 cohort
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37 279 studies, concluded that migraine may increase the risk of hemorrhagic stroke.¹⁹ However, a
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39 280 recent large population-based case-control study did not show an association with
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42 281 hemorrhagic stroke type, including intracerebral hemorrhage and subarachnoid hemorrhage.
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44 282 ³⁰ Migraine was an independent risk factor for aneurismal rupture (OR = 2.4; CI 95% 1.1–
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46 283 5.1) in a case-control study,³¹ and even if headache is a premonitory symptom of aneurismal
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48 284 rupture, recall biases might have affected the study results. Above all, a relatively small
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50 285 number of hemorrhagic stroke cases might have resulted in decreased statistical power.

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53 286 Consistent with the results of previous studies, the strongest association between migraine
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55 287 and ischemic stroke was found in young women. The contribution of migraine to the

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3 288 occurrence of ischemic stroke was shown to decrease as age increases. Considering that the
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5 289 predisposing factors of stroke increase the incidence of ischemic stroke with age,³² migraine
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7 290 itself rather than other risk factors could be implicated in the increased risk of ischemic
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9 291 stroke. Notably, we identified a significant association of migraine with ischemic stroke in
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11 292 middle aged and old women in this study. In contrast, a recent large population-based cohort
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13 293 study in Taiwan, with a relatively short follow-up duration of 3.6 years, did not show a
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15 294 significant association in the subset groups of women and those aged < 45 years.³ This
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17 295 discrepancy might be due to differences in the study design, follow-up duration, and ethnic
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19 296 composition of the study population. In addition, we demonstrated a significant association of
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21 297 ischemic stroke in young men with migraine. Recently, a trend of this association was also
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23 298 reported,³ but it requires further confirmation due to the lack of evidence at present.

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26 299 The present study has several strengths. The results of this study are consistent with those
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28 300 of our previous studies utilizing the HIRA-NSC.³³⁻³⁵ We examined a very large,
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30 301 representative, and nationwide population. Because the NHIS data cover all citizens of Korea
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32 302 without exception, no participants were lost during follow-up. The control group was
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34 303 randomly selected and matched based on age, sex, income, region of residence, and medical
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36 304 history to decrease any confounding effects. An adjusted hazard model was used to further
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38 305 minimize the impact of confounders. Considering that migraine attacks could be frequently
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40 306 repeated, we opted to include patients with migraine who underwent treatment at least twice
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42 307 based on the ICD-10 code to enhance the validity of the study [G43]. In a previous study, the
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44 308 prevalence of migraine in Korea was reported as being approximately 6.1%.⁴ This value
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46 309 appeared to be slightly higher than that in the present study, which was 3.7%
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48 310 (41,585/1,125,691) based on strict inclusion criteria of migraine. In addition, the patients with
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50 311 migraine were followed up for 12 years in the present study. Long study periods enable
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3 312 recruitment of a large study population and enable researchers to observe and analyze the
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5 313 delayed effects of migraine on stroke.
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8 314 However, the present study has certain limitations that should be addressed in future
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10 315 studies. First, the heterogeneity of migraine was not considered in the present study.
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12 316 Considering that the association could be modulated according to migraine subtype,³⁶ the
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14 317 present study could not draw a causative association. A firm correlation between the
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16 318 frequency of migraine attacks and the risk of stroke was found,³⁷ but it could not be assessed
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18 319 using this database. Similarly, the duration and severity of migraine were inconsistent among
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20 320 the study population. Patients with migraine who had mild complaints could not undergo
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22 321 consultation at the clinic; therefore, the impact of migraine on stroke may be underestimated
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24 322 in this study. Third, although this study attempted to include a representative large population
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26 323 and subsequently matched and adjusted for possible confounders, the risk factors for stroke in
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28 324 patients with migraine, such as cigarette smoking, obesity, and migraine-specific drugs, were
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30 325 not available in the insurance database.^{11 37}
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38 **Conclusion**

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40 328 Based on a large population-based cohort study in Korea, migraine increased the risk of
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42 329 ischemic stroke but not of hemorrhagic stroke. The subgroup of patients at the highest risk of
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44 330 ischemic stroke was young women.
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51
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3 336 **DATA SHARING STATEMENT**
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5 337 No additional data are available.
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9

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16 342 Korea.
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21 344 **COMPETING INTERESTS STATEMENT**
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23 345 There are no competing interests for any author.
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28 347 **AUTHOR CONTRIBUTIONS**
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30 348 As first authors, SYL wrote the manuscript. DJO and JSL analyzed and interpreted the data.
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32 349 IGK performed the data processing. HGC conceptualized, wrote and reviewed the
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34 350 manuscript.
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22 459 **Figure legend**

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24 460 **Fig. 1** A schematic illustration of the participant selection process that was used in the present
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26 461 study. Out of a total of 1,125,691 participants, 41,585 migraine participants were matched
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28 462 with 166,340 control participants for age, group, sex, income group, region of residence, and
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30 463 past medical histories.
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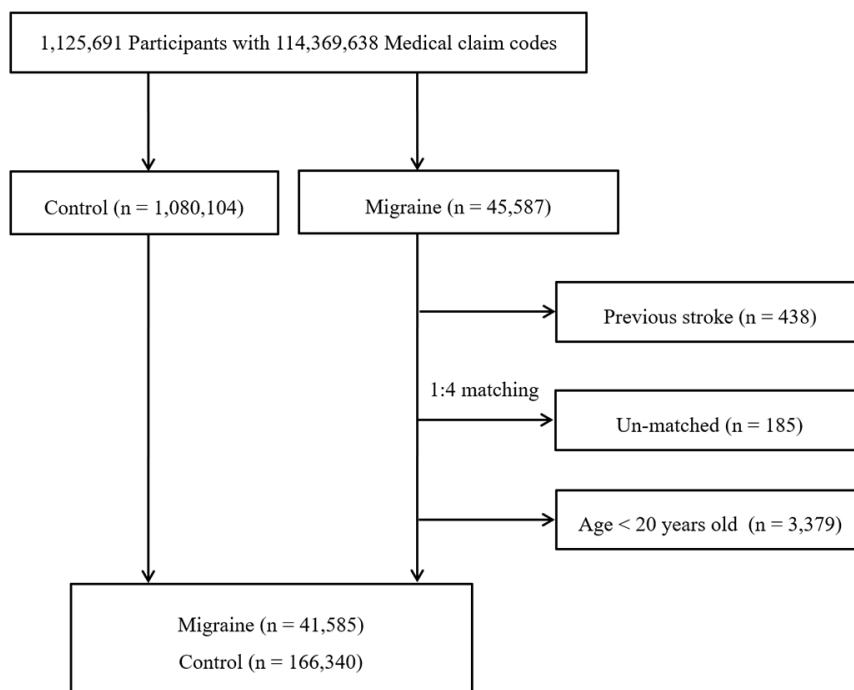


Fig.1

101x101mm (300 x 300 DPI)

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

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

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

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			Page
		Reporting Item	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

1 2 3 4 5 6	Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4-5
7 8 9 10 11	Objectives	#3	State specific objectives, including any prespecified hypotheses	5
12 13 14	Study design	#4	Present key elements of study design early in the paper	5
15 16 17 18 19 20 21 22	Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
23 24 25 26 27	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6-7
28 29 30 31 32		#6b	For matched studies, give matching criteria and number of exposed and unexposed	6-7
33 34 35 36 37 38 39 40	Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
41 42 43 44 45 46 47 48 49 50 51 52	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
53 54 55	Bias	#9	Describe any efforts to address potential sources of bias	5-8
56 57 58 59 60	Study size	#10	Explain how the study size was arrived at	7

1	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7	
2		Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
3			#12b	Describe any methods used to examine subgroups and interactions	8
4			#12c	Explain how missing data were addressed	NA
5			#12d	If applicable, explain how loss to follow-up was addressed	NA
6			#12e	Describe any sensitivity analyses	NA
7			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.
8	#13b	Give reasons for non-participation at each stage		NA	
9	#13c	Consider use of a flow diagram		7	
10	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	
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1		#14b	Indicate number of participants with missing data for each	8-13
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6		#14c	Summarise follow-up time (eg, average and total amount)	8
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17	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	8-13
18			adjusted estimates and their precision (eg, 95% confidence	
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27		#16b	Report category boundaries when continuous variables were	NA
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38	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups	13-14
39			and interactions, and sensitivity analyses	
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43	Key results	#18	Summarise key results with reference to study objectives	16
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46	Limitations	#19	Discuss limitations of the study, taking into account sources	
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1	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19
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8	Generalisability	#21	Discuss the generalisability (external validity) of the study	16-18
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14	Funding	#22	Give the source of funding and the role of the funders for the	20
15			present study and, if applicable, for the original study on	
16			which the present article is based	
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BMJ Open

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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Secondary Subject Heading:	Epidemiology, Neurology, Ear, nose and throat/otolaryngology
Keywords:	EPIDEMIOLOGY, Migraine < NEUROLOGY, Stroke < NEUROLOGY

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3 **24 Abstract**
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5 **25 Objective:** Accumulating evidence has supported the association between migraine and
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8 **26** stroke, but the causative association remains unclear. We aimed to investigate the risks of
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11 **27** different types of stroke in patients with migraine.

12 **28 Design:** A longitudinal follow-up study

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14 **29 Setting:** Data collected from a national cohort between 2002 and 2013 by the Korean Health
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17 **30** Insurance Review and Assessment

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19 **31 Participants:** We extracted the data from patients with migraine (n = 41,585) and 1:4
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22 **32** matched controls (n = 166,340) and analyzed the occurrence of ischemic and hemorrhagic
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24 **33** strokes. The migraine group included participants treated for migraine (ICD-10: G43) \geq 2
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26 **34** times. Hemorrhagic stroke (I60-I62) and ischemic stroke (I63) were determined based on the
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28 **35** admission histories. The crude and adjusted hazard ratios (HRs) were calculated using Cox
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30 **36** proportional hazard models, and the 95% confidence intervals (CIs) were determined.
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33 **37** Subgroup analyses stratified by age and sex were also performed.

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35 **38 Results:** Higher rates of ischemic stroke were observed in the migraine group (2.3%
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38 [964/41,585]) than in the control group (2.0% [3,294/166,340], $P < 0.001$). The adjusted HR
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40 **40** for ischemic stroke was 1.18 (95% CI = 1.10-1.26) in the migraine group ($P < 0.001$).
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42 **41** Compared with control subjects, participants who reported migraine with aura and migraine
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44 **42** without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15 (95% CI =
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46 **43** 1.06-1.24), respectively, for ischemic stroke, but no increased risk of hemorrhagic stroke. In
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48 **44** our subgroup analysis, a strong association between migraine and ischemic stroke was
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50 **45** observed in young patients, specifically young women. The contribution of migraine to the
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53 **46** occurrence of ischemic stroke was also observed in middle-aged women and old women
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3 47 (each $P < 0.05$). The risk of hemorrhagic stroke did not reach statistical significance in any
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5 48 age group.

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8 49 **Conclusion:** Migraine is associated with an increased risk of ischemic stroke, but not
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10 50 hemorrhagic stroke.

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12 51 Keywords: migraine, stroke, cohort study, Korea
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16 17 53 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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19 54 1. The strengths of the present study particularly result from the large cohort based on a
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21 55 complete, national patient sample and the long follow-up period.

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24 56 2. We designed a cohort study to evaluate the risks of different types of stroke in migraineurs.

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26 57 3. Migraine should be considered in assessments of the risk of ischemic stroke, particularly in
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28 58 young women.

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30 59 4. Confounders linking migraine to stroke, such as cigarette smoking, obesity, and
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32 60 prescription information, were not available in the present cohort study based on claim data.

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36 37 62 **Introduction**

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40 63 Migraine is a common neurovascular disorder characterized by recurrent disabling episodes
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42 64 of headache, most often unilateral headache. The headache is often accompanied by visual or
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44 65 sensory symptoms, namely, aura.¹ The annual prevalence of migraine is approximately 8–
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46 66 15% worldwide,^{2,3} and in Korea, the estimated incidence is 6.1%.⁴ Migraine appears to
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48 67 present at a relatively young age (< 45 years); it is more prevalent in women than men, with a
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50 68 prevalence $> 25\%$ in the 35–39-year-old female population worldwide.¹ The inclusion of
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52 69 migraine as an independent risk factor for cardiovascular events has been debated for many
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54 70 years, but it is an established risk factor for ischemic stroke.⁵

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3 71 Stroke is a cerebrovascular condition characterized by limited blood flow to the brain due
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5 72 to a blockage or rupture in the cerebrovascular system.⁶ Stroke is responsible for
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7 73 approximately 700,000 deaths annually in the Western world.⁷ In Korea, the estimated stroke
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9 74 incidence is approximately 795,000 in people aged ≥ 30 years.⁸ More than 80% of stroke
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11 75 cases are ischemic stroke, and the remaining cases are hemorrhagic stroke; ischemic and
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13 76 hemorrhagic strokes differ with regard to risk factors, genetic predisposition, and mortality
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15 77 rates.^{9 10}

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19 78 To date, several underlying physiological mechanisms have been suggested to explain the
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21 79 association between migraine and stroke. The risk factors for stroke in migraineurs have been
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23 80 widely evaluated, and common comorbidities, including hypertension, obesity, dyslipidemia,
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25 81 and smoking, were validated.¹¹ In addition, specific genetic etiologies associated with
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27 82 vasculopathy can manifest in both patients suffering from migraine and stroke.¹² A recent
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29 83 investigation employing a mutant mouse model of migraine also indicated that shared genetic
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31 84 risk factors rendered the brain more vulnerable to ischemic stroke.¹³

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35 85 Moreover, migraine itself carries an increased risk of ischemic stroke. Migraine is
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37 86 associated with an increased risk of perioperative ischemic stroke in a large cohort of surgical
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39 87 patients, suggesting that migraine should be included in the perioperative risk assessment.¹⁴
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41 88 Recently, a population-based case-control study in Taiwan reported an association between
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43 89 migraine and ischemic stroke (adjusted hazard ratio [HR]: 1.24, confidence interval [CI]:
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45 90 1.12–1.38).³ Similarly, an increased risk of ischemic stroke has been consistently observed in
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47 91 migraineurs, especially in those diagnosed with migraine with aura.^{3 15-18} Furthermore,
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49 92 accumulating evidence has supported the association between migraine and hemorrhagic
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51 93 stroke,^{19 20} but the causative association currently remains unclear.

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3 94 Given the differences in the natures of hemorrhagic stroke and ischemic stroke in
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5 95 patients, including risk factors and genetic predispositions,^{9 10} we hypothesized that the
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8 96 contributions of migraine to an increased risk of stroke differ according to the stroke type.
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10 97 Thus, stroke types should be analyzed separately. Additionally, stroke is a leading cause of
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12 98 mortality; therefore, validation of the association between migraine and stroke may facilitate
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14 99 treatment and prognosis in these cases. Here, using a national Korean population-based
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17 100 sample cohort, we examined the associations between migraine and different types of stroke.
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21 102 **Materials and Methods**

22 103 **Study population and data collection**

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26 104 The ethics committee of Hallym University (2014-I148) approved the use of these data. The
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28 105 Institutional Review Board exempted the requirement for written informed consent.

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30 106 This national cohort study used data from the Korean National Health Insurance
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33 107 Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly
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35 108 from the entire population database to prevent nonsampling errors. Approximately 2% of the
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37 109 samples (one million) were selected from the entire Korean population (50 million). The
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39 110 selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and
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41 111 income level [41 categories]) using randomized, stratified, systematic sampling methods via
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43 112 proportional allocation to represent the entire population. A previous study verified the
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45 113 appropriateness of the sample after data selection.²¹ The National Health Insurance Sharing
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47 114 Service provides a detailed description of the methods used to perform these procedures.²²
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49 115 This cohort database included (i) personal information, (ii) health insurance claim codes
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52 116 (procedures and prescriptions), (iii) diagnostic codes based on the International Classification
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55 117 of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using
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3 118 the Korean Standard Classification of disease), (v) socioeconomic data (residence and
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5 119 income), and (vi) medical examination data for each participant from 2002 to 2013.

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7 120 All Korean citizens are recognized by a 13-digit resident registration number from birth
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9 121 to death. Therefore, exact population statistics have been determined using this database. All
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11 122 Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit
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13 123 resident registration number to register individual patients in the medical insurance system.
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15 124 Therefore, the risk of overlapping medical records is minimal, even if a patient moves from
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17 125 one place to another. All medical treatments in Korea are tracked without exception using the
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19 126 Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice
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21 127 of death must be provided to an administrative entity before a funeral can be held. Medical
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23 128 doctors record the date and cause of death on a death certificate.
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30 130 **Patients and public involvement**

31 131 No patients or public were involved in the present study.

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36 133 **Participant Selection**

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38 134 Of the 1,125,691 patients with 114,369,638 medical claim codes, participants diagnosed with
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40 135 migraine (ICD-10: G43) were included. Among these participants, those who were treated \geq
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42 136 2 times ($n = 45,587$) were selected. The participants were followed for 12 years.

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45 137 The history of admission for hemorrhagic stroke (I60: Subarachnoid hemorrhage, I61:
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47 138 Intracerebral hemorrhage, and I62: Other nontraumatic intracranial hemorrhage) and
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49 139 ischemic stroke (I63: Cerebral infarction) was identified using ICD-10 codes. We selected the
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51 140 participants who were treated ≥ 1 time. These methods were used in other studies evaluating
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53 141 the incidence of stroke in Korea.^{8 23}
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3 142 The participants with migraine were matched 1:4 with participants (control group) who
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5 143 had never been diagnosed with a migraine from 2002 through 2013 in this cohort. The control
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7 144 group was selected from the total population (n = 1,080,104). The matches were processed
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10 145 for age, group, sex, income group, region of residence, and past medical histories (age, sex,
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12 146 income, region of residence, hypertension, diabetes, and dyslipidemia histories). We sorted
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14 147 the participants in the control group using a random number order and then selected them
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17 148 from top to bottom to prevent selection bias when selecting the matched control participants.
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19 149 We assumed that the matched control participants were enrolled at the same time as each
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21 150 matched participant with migraine (index date). Therefore, control group members who died
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23 151 before the index date were excluded. In both the migraine and control groups, participants
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25 152 with histories of hemorrhagic or ischemic stroke before the index date were excluded. In the
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27 153 migraine group, 438 participants were excluded. The participants with migraine for whom we
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29 154 were unable to identify sufficient numbers of matching participants were excluded (n = 185).
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31 155 We excluded participants aged less than 20 years (n = 3,379). Finally, 1:4 matching resulted
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33 156 in the inclusion of 41,585 participants with migraine (migraine with aura = 3,458, migraine
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35 157 without aura = 38,127) and 166,340 control participants (Fig. 1).
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159 **Variables**

160 The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34..., and 85+ years
161 old. Fourteen age groups were designated. The income groups were initially divided into 41
162 classes (one health aid class, 20 self-employment health insurance classes, and 20
163 employment health insurance classes). These groups were recategorized into 11 classes (class
164 1 [lowest income]–class 11 [highest income]). The region of residence was divided into 16
165 areas according to administrative district. These regions were regrouped into urban (Seoul,

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3 166 Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon,
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5 167 Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk,
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7 168 Gyeongsangnam, and Jeju) areas. The past medical histories of the participants were
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10 169 evaluated using ICD-10 codes. For an accurate diagnosis, hypertension (I10 and I15),
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12 170 diabetes (E10-E14), and dyslipidemia (E78) were recorded if the participants were treated ≥ 2
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14 171 times. Moreover, we further included variables including congestive heart failure, myocardial
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16 172 infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression
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18 173 histories that might affect the association between migraine and stroke using the Charlson
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20 174 Comorbidity Index and subsequently performed the analysis with the added variables.
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26 176 **Statistical Analyses**

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28 177 Chi-square tests were used to compare the general characteristics between the migraine and
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30 178 control groups. For the analysis of the HRs of migraine for hemorrhagic stroke and ischemic
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32 179 stroke, Cox proportional hazard models were used, and 95% CIs were calculated. In these
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34 180 analyses, crude (simple) and adjusted (age, sex, income, region of residence, hypertension,
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36 181 diabetes, dyslipidemia, congestive heart failure, myocardial infarction, peripheral vascular
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38 182 disease, pulmonary disease, liver disease, and depression histories) models were used. For the
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40 183 subgroup analysis, we stratified the participants by age and sex (20–39 years old, 40–59 years
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42 184 old, 60+ years old; men and women). Two-tailed analyses were conducted, and P values less
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44 185 than 0.05 were considered significant. The results were statistically analyzed using SPSS v.
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46 186 21.0 software (IBM, Armonk, NY, USA).
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3 **188 Results**
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5 189 The mean follow-up period was 80.9 (standard deviation [SD] = 41.6) months for patients
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7 190 with migraine and 80.9 (SD = 41.6) months for controls. The rates of hemorrhagic stroke
8
9 191 were similar in the migraine group (0.7% [295/41,585]) and the control group (0.7%
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11 [1,113/166,340], P = 0.370, Table 1). Higher rates of ischemic stroke were observed in the
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13 192 migraine group (2.3% [964/41,585]) than in the control group (2.0% [3,294/166,340], P <
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15 193 0.001). The general characteristics (age, sex, income, region of residence, hypertension,
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17 194 diabetes, and dyslipidemia histories) of participants were the same due to the matching
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19 195 protocol (P = 1.000).
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26 **198 Table 1** General characteristics of the participants
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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*

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

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202 The crude and adjusted HRs for hemorrhagic stroke were 1.06 (95% CI = 0.93–1.21, $P =$
 203 0.369) and 1.10 (95% CI = 0.96–1.25, $P = 0.172$), respectively, in the migraine group (Table
 204 2). The crude and adjusted HRs for ischemic stroke were 1.17 (95% CI = 1.09–1.26) and 1.18
 205 (95% CI = 1.08–1.25), respectively, in the migraine group (each $P < 0.001$).

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209 **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	

210
211 * Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

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

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3 214 In the subgroup analyses, none of the crude and adjusted HRs for hemorrhagic stroke
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5 215 reached statistical significance (Table 3). Among the patients with ischemic stroke, young
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7 216 women, middle-aged women, and old women showed statistically significant differences
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9 217 (each $P < 0.05$). The significant adjusted HRs were 2.31 (95% CI = 1.39–3.82) in young
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11 218 women (20-39 years old); 1.32 (95% CI = 1.08–1.61) in middle-aged women (40-59 years
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13 219 old); and 1.18 (95% CI = 1.06–1.30) in ≥ 60 -year-old women. Moreover, descriptive
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15 220 statistical analyses of the migraine prevalence and ischemic stroke occurrence within
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17 221 subgroups revealed statistically significant differences in young men, young women, middle-
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19 222 aged women, old men, and old women. On the other hand, the risk of hemorrhagic stroke in
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21 223 patients with migraine was not significantly different from the control group (Supplement
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24 224 table 1).
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234 **Table 3** Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic
 235 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

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

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3 238 † Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction,
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5 239 peripheral vascular disease, pulmonary disease, liver disease, and depression histories.
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3 240 Compared with the control group, participants who reported migraine with aura and
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5 241 migraine without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15
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7 242 (95% CI = 1.06-1.24) for ischemic stroke, respectively, but no increased risk of hemorrhagic
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9 243 stroke (Table 4).
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264 **Table 4** Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic
 265 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	

266
 267 * Cox proportional hazard regression model; differences were considered significant at $P < 0.05$.

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

270 **Discussion**

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

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

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3 294 factors may precipitate the susceptibility to CSD, which may explain the association between
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5 295 migraine and stroke.²⁸

7 296 A growing body of evidence regarding the increased risk of ischemic stroke in patients
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10 297 with migraine without aura. Consistent with the findings from patients reporting migraine
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12 298 with aura, participants who reported migraine without aura had an increased adjusted HR of
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14 299 1.15 (95% CI = 1.06-1.24) for ischemic stroke compared with the control group. Notably, a
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16 300 significant association was observed in cases of ischemic stroke resulting from cervical artery
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18 301 dissection.²⁹ In addition, genetic overlaps among subjects with migraine without aura, large
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20 302 artery stroke, and cardio-embolic stroke have been identified.³⁰ However, strong evidence has
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22 303 been not reported. A recent large population-based study reported an statistically insignificant
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24 304 risk of ischemic stroke in patients with migraine without aura but an increased risk in patients
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26 305 with migraine with aura.³ The study suggested that the difference may be due to changes in
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28 306 the lipid profile, the susceptibility to thrombosis, and genetic predisposition.³ A meta-analysis
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30 307 did not identify a significant association between migraine without aura and ischemic
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32 308 stroke.¹⁸ In the present study, we did not differentiate between migraine subtypes, such as
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34 309 migraine with and without aura, when analyzing the risk of stroke. Therefore, the risk of
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36 310 ischemic stroke in participants with migraine was relatively low but statistically significant
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38 311 compared to other studies investigating specific conditions.

40 312 Notably, in the present study, migraine was not associated with an increased risk of
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42 313 hemorrhagic stroke. In contrast to the findings from the present study, a recent meta-analysis
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44 314 based on 4 case-control and 4 cohort studies concluded that migraine may increase the risk of
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46 315 hemorrhagic stroke.²⁰ However, a recent large population-based case-control study did not
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48 316 show an association with different types of hemorrhagic stroke, including intracerebral
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50 317 hemorrhage and subarachnoid hemorrhage.³¹ Migraine was an independent risk factor for

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2
3 318 aneurismal rupture (odds ratio [OR] = 2.4; 95% CI 1.1–5.1) in a case-control study,³² and
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5 319 even if headache is a premonitory symptom of aneurismal rupture, recall biases might have
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8 320 affected the results of the study. Overall, the relatively small number of hemorrhagic stroke
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10 321 cases might have resulted in decreased statistical power.

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12 322 In our subgroup analysis, a strong correlation between migraine and ischemic stroke was
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14 323 observed in young patients, specifically young women (20-39 years old). Based on a
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16 324 consensus statement from the European Headache Federation (EHF),³³ the use of a combined
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18 325 hormonal contraceptive may further increase the risk of ischemic stroke in patients with
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20 326 migraine, specifically migraine with aura, supporting our results. Because the predisposing
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22 327 factors for stroke increase the incidence of ischemic stroke with age,³⁴ migraine itself rather
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24 328 than other risk factors might be implicated in the increased risk of ischemic stroke. In
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26 329 contrast, a recent large, population-based cohort study in Taiwan with a relatively short
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28 330 follow-up duration of 3.6 years did not show a significant association in the subgroups of
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30 331 women and patients aged < 45 years.³ This discrepancy might be due to differences in the
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32 332 study design, follow-up duration, and ethnic composition of the study population. Recently, a
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34 333 similar trend for this association was also reported,³ but it requires further confirmation due
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36 334 to the lack of evidence at present.

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38 335 The present study has several strengths. The results of this study are consistent with the
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40 336 findings of our previous studies utilizing the HIRA-NSC.³⁵⁻³⁷ We examined a very large,
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42 337 representative, and nationwide population. Because the NHIS data cover all citizens of Korea
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44 338 without exception, no participants were lost during follow-up. The control group was
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46 339 randomly selected and matched based on age, sex, income, region of residence, and medical
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48 340 history to decrease any confounding effects. An adjusted hazard model was used to further
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50 341 minimize the impacts of confounders. Because migraine attacks might be frequently repeated,

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3 342 we opted to include patients with migraine who underwent treatment at least twice based on
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5 343 the ICD-10 code to increase the validity of the study [G43]. In a previous study, the
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7 344 prevalence of migraine in Korea was reported to be approximately 6.1%.⁴ This value
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9 345 appeared to be slightly higher than the value reported in the present study, which was 3.7%
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11 346 (41,585/1,125,691), based on strict inclusion criteria for migraine. In addition, the patients
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13 347 with migraine were followed for 12 years in the present study. Long study periods enable the
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15 348 recruitment of a large study population and allow researchers to observe and analyze the
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17 349 delayed effects of migraine on stroke.
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21 350 However, the present study has certain limitations that should be addressed in future
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23 351 studies. First, we were unable to extract information on stroke subtypes and location from the
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25 352 data used in the present study. The impact of migraine on each type of pathophysiology might
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27 353 vary when considering different functional outcomes, survival, and recurrence according to
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29 354 stroke subtype.^{38 39} However, in the present study, the distribution of stroke subtypes was not
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31 355 available. The classification of stroke type can lead to a significantly decreased incidence of
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33 356 each disease. As an insufficient number of cases cause inappropriate comparisons due to
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35 357 lower statistical power, the inclusion of the distribution of stroke subtypes would hamper our
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37 358 ability to draw a clear conclusion from the available data. In particular, the absolute incidence
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39 359 of hemorrhagic stroke is very low in general practice; therefore, most of studies did not
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41 360 provide information about subtypes, such as the presence of an aneurysm, although the
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43 361 association is positive in public health studies.³¹ Second, a firm correlation between the
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45 362 frequency of migraine attacks and the risk of stroke has been reported,⁴⁰ but we were unable
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47 363 to confirm this correlation using the claim data analyzed in the present study. Similarly, the
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49 364 duration and severity of migraine were inconsistent among the study population. Patients
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51 365 with migraine who had mild complaints may not have received a consultation at the clinic;
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3 366 therefore, the impact of migraine on stroke may be underestimated in this study. Third,
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5 367 although this study attempted to include a large, representative patient population and
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7 368 subsequently matched and adjusted for possible confounders, the risk factors for stroke in
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9 369 patients with migraine, such as cigarette smoking, obesity, and migraine-specific drugs, were
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11 370 not available in the insurance database.^{11 40} Finally, in the present study, the incidence of
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13 371 migraine was 3.7% (41,585 of 1,125,691 participants) after employing a strict matching
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15 372 protocol. Before matching, the incidence of migraine in Korea was 4.1% (45,587 of
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17 373 1,125,691 participants). This value is consistent with previous cohort study in Korea,
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19 374 indicating that the overall prevalence rate of migraine was 6.1%,⁸ despite the use of different
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21 375 study designs. Given the global prevalence of migraine of approximately 8–15%,^{9 10} the
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23 376 incidence of migraine in Korea is relatively low because of limited claim data. Only patients
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25 377 with migraine who visited the hospital are recorded. In other words, data are not available for
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27 378 patients with weak migraine symptoms or patients who do not visit a hospital, leading to a
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29 379 lower incidence. Based on a population-based epidemiological study of migraine in Korea,
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31 380 only 24.4% of patients ever consulted a doctor for headache and only 3.3% of patients were
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33 381 prescribed a drug by a doctor.¹¹

382

383 **Conclusions**

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

387

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3 389 We thank the participants and examiners of Korean Health Insurance Review and Assessment
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5 390 for participating in this cohort study and providing the data, respectively.
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10 392 **DATA SHARING STATEMENT**
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12 393 No additional data are available.
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16
17 395 **FUNDING STATEMENT**
18

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20
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23 398 Korea.
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28 400 **COMPETING INTERESTS STATEMENT**
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30 401 None of the authors have competing interests to declare.
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35 403 **AUTHORS' CONTRIBUTIONS**
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37 404 As the first author, SYL wrote the manuscript. DJO and JSL analyzed and interpreted the
38
39 405 data. IGK processed the data. HGC conceptualized, wrote, and reviewed the manuscript.
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44 407 **References**
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27
28 516 **Figure Legend**

29
30 517 **Fig. 1** A schematic illustrating the participant selection process used in the present study. Of
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32 518 a total of 1,125,691 participants, 41,585 participants with migraine were matched with
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34 519 166,340 control participants for age, group, sex, income level, region of residence, and past
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36 520 medical histories.
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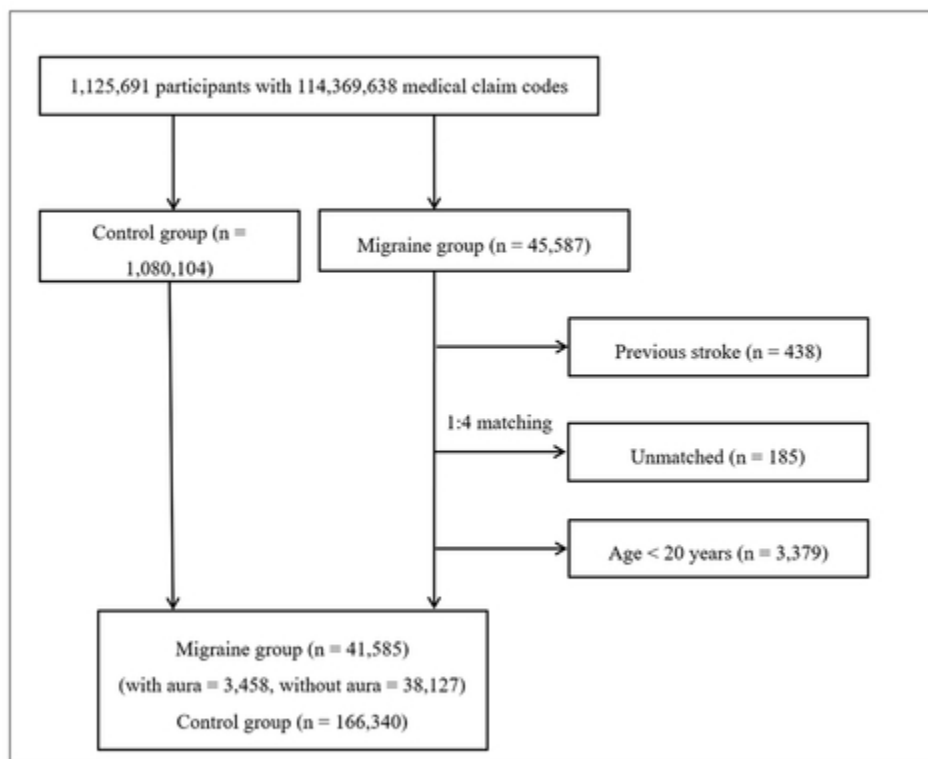


Figure 1

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	Non-Migraine	P-value	Migraine	Non-Migraine	P-value
	(n = 2,948)	(n = 11,792)		(n = 7,979)	(n = 31,916)	
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, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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

1	Background /	#2	Explain the scientific background and rationale for the	4-5
2				
3	rationale		investigation being reported	
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6	Objectives	#3	State specific objectives, including any prespecified	5
7				
8			hypotheses	
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12	Study design	#4	Present key elements of study design early in the paper	5
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15	Setting	#5	Describe the setting, locations, and relevant dates, including	5-6
16				
17			periods of recruitment, exposure, follow-up, and data	
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22	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of	6-7
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24			selection of participants. Describe methods of follow-up.	
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28		#6b	For matched studies, give matching criteria and number of	6-7
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30			exposed and unexposed	
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33	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	7-8
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35			confounders, and effect modifiers. Give diagnostic criteria, if	
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37			applicable	
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40				
41	Data sources /	#8	For each variable of interest give sources of data and details	5-8
42				
43	measurement		of methods of assessment (measurement). Describe	
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45			comparability of assessment methods if there is more than	
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47			one group. Give information separately for for exposed and	
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49			unexposed groups if applicable.	
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53	Bias	#9	Describe any efforts to address potential sources of bias	5-8
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56	Study size	#10	Explain how the study size was arrived at	7
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1	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7	
2		Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
3			#12b	Describe any methods used to examine subgroups and interactions	8
4			#12c	Explain how missing data were addressed	NA
5			#12d	If applicable, explain how loss to follow-up was addressed	NA
6			#12e	Describe any sensitivity analyses	NA
7		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
8	#13b		Give reasons for non-participation at each stage	NA	
9	#13c		Consider use of a flow diagram	7	
10	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	
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1		#14b	Indicate number of participants with missing data for each	8-13
2			variable of interest	
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6		#14c	Summarise follow-up time (eg, average and total amount)	8
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10	Outcome data	#15	Report numbers of outcome events or summary measures	NA
11			over time. Give information separately for exposed and	
12			unexposed groups if applicable.	
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17	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	8-13
18			adjusted estimates and their precision (eg, 95% confidence	
19			interval). Make clear which confounders were adjusted for	
20			and why they were included	
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27		#16b	Report category boundaries when continuous variables were	NA
28			categorized	
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33		#16c	If relevant, consider translating estimates of relative risk into	NA
34			absolute risk for a meaningful time period	
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38	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups	13-14
39			and interactions, and sensitivity analyses	
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43	Key results	#18	Summarise key results with reference to study objectives	16
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46	Limitations	#19	Discuss limitations of the study, taking into account sources	
47			of potential bias or imprecision. Discuss both direction and	
48			magnitude of any potential bias.	
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1	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19
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9	Generalisability	#21	Discuss the generalisability (external validity) of the study	16-18
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14	Funding	#22	Give the source of funding and the role of the funders for the	20
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17			present study and, if applicable, for the original study on	
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19			which the present article is based	
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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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4 1 **Risk of ischemic stroke in patients with migraine: A**
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7 2 **longitudinal follow-up study using a national sample**
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10 3 **cohort in Korea**
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3 **24 Abstract**
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5 **25 Objective:** Accumulating evidence has supported the association between migraine and
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8 **26** stroke, but the causative association remains unclear. We aimed to investigate the risks of
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11 **27** different types of stroke in patients with migraine.

12 **28 Design:** A longitudinal follow-up study

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14 **29 Setting:** Data collected from a national cohort between 2002 and 2013 by the Korean Health
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17 **30** Insurance Review and Assessment

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19 **31 Participants:** We extracted the data from patients with migraine (n = 41,585) and 1:4
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21
22 **32** matched controls (n = 166,340) and analyzed the occurrence of ischemic and hemorrhagic
23
24 **33** strokes. The migraine group included participants treated for migraine (ICD-10: G43) \geq 2
25
26 **34** times. Hemorrhagic stroke (I60-I62) and ischemic stroke (I63) were determined based on the
27
28 **35** admission histories. The crude and adjusted hazard ratios (HRs) were calculated using Cox
29
30 **36** proportional hazard models, and the 95% confidence intervals (CIs) were determined.
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33 **37** Subgroup analyses stratified by age and sex were also performed.

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35 **38 Results:** Higher rates of ischemic stroke were observed in the migraine group (2.3%
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37
38 [964/41,585]) than in the control group (2.0% [3,294/166,340], $P < 0.001$). The adjusted HR
39
40 **40** for ischemic stroke was 1.18 (95% CI = 1.10-1.26) in the migraine group ($P < 0.001$).
41
42 **41** Compared with control subjects, participants who reported migraine with aura and migraine
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44 **42** without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15 (95% CI =
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46 **43** 1.06-1.24), respectively, for ischemic stroke, but no increased risk of hemorrhagic stroke. In
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48 **44** our subgroup analysis, a strong association between migraine and ischemic stroke was
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51 **45** observed in young patients, specifically young women. The contribution of migraine to the
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54 **46** occurrence of ischemic stroke was also observed in middle-aged women and old women
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3 47 (each $P < 0.05$). The risk of hemorrhagic stroke did not reach statistical significance in any
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5 48 age group.

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8 49 **Conclusion:** Migraine is associated with an increased risk of ischemic stroke, but not
9
10 50 hemorrhagic stroke.

11
12 51 Keywords: migraine, stroke, cohort study, Korea

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16 17 53 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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19 54 1. The strengths of the present study particularly result from the large cohort based on a
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21 55 complete, national patient sample and the long follow-up period.

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23
24 56 2. We designed a cohort study to evaluate the risks of different types of stroke in migraineurs.

25
26 57 3. Migraine should be considered in assessments of the risk of ischemic stroke, particularly in
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28 58 young women.

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30 59 4. Confounders linking migraine to stroke, such as cigarette smoking, obesity, and
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32 60 prescription information, were not available in the present cohort study based on claim data.

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36 37 62 **Introduction**

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40 63 Migraine is a common neurovascular disorder characterized by recurrent disabling episodes
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42 64 of headache, most often unilateral headache. The headache is often accompanied by visual or
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44 65 sensory symptoms, namely, aura.¹ The annual prevalence of migraine is approximately 8–
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46 66 15% worldwide,^{2,3} and in Korea, the estimated incidence is 6.1%.⁴ Migraine appears to
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48 67 present at a relatively young age (< 45 years); it is more prevalent in women than men, with a
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50 68 prevalence $> 25\%$ in the 35–39-year-old female population worldwide.¹ The inclusion of
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52 69 migraine as an independent risk factor for cardiovascular events has been debated for many
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54 70 years, but it is an established risk factor for ischemic stroke.⁵

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3 71 Stroke is a cerebrovascular condition characterized by limited blood flow to the brain due
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5 72 to a blockage or rupture in the cerebrovascular system.⁶ Stroke is responsible for
6
7 73 approximately 700,000 deaths annually in the Western world.⁷ In Korea, the estimated stroke
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9 74 incidence is approximately 795,000 in people aged ≥ 30 years.⁸ More than 80% of stroke
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11 75 cases are ischemic stroke, and the remaining cases are hemorrhagic stroke; ischemic and
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13 76 hemorrhagic strokes differ with regard to risk factors, genetic predisposition, and mortality
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15 77 rates.^{9 10}

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19 78 To date, several underlying physiological mechanisms have been suggested to explain the
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21 79 association between migraine and stroke. The risk factors for stroke in migraineurs have been
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23 80 widely evaluated, and common comorbidities, including hypertension, obesity, dyslipidemia,
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25 81 and smoking, were validated.¹¹ In addition, specific genetic etiologies associated with
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27 82 vasculopathy can manifest in both patients suffering from migraine and stroke.¹² A recent
28
29 83 investigation employing a mutant mouse model of migraine also indicated that shared genetic
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31 84 risk factors rendered the brain more vulnerable to ischemic stroke.¹³

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35 85 Moreover, migraine itself carries an increased risk of ischemic stroke. Migraine is
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37 86 associated with an increased risk of perioperative ischemic stroke in a large cohort of surgical
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39 87 patients, suggesting that migraine should be included in the perioperative risk assessment.¹⁴
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41 88 Recently, a population-based case-control study in Taiwan reported an association between
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43 89 migraine and ischemic stroke (adjusted hazard ratio [HR]: 1.24, confidence interval [CI]:
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45 90 1.12–1.38).³ Similarly, an increased risk of ischemic stroke has been consistently observed in
46
47 91 migraineurs, especially in those diagnosed with migraine with aura.^{3 15-18} Furthermore,
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49 92 accumulating evidence has supported the association between migraine and hemorrhagic
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51 93 stroke,^{19 20} but the causative association currently remains unclear.

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3 94 Given the differences in the natures of hemorrhagic stroke and ischemic stroke in
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5 95 patients, including risk factors and genetic predispositions,^{9 10} we hypothesized that the
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8 96 contributions of migraine to an increased risk of stroke differ according to the stroke type.
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10 97 Thus, stroke types should be analyzed separately. Additionally, stroke is a leading cause of
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12 98 mortality; therefore, validation of the association between migraine and stroke may facilitate
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14 99 treatment and prognosis in these cases. Here, using a national Korean population-based
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16
17 100 sample cohort, we examined the associations between migraine and different types of stroke.
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21 102 **Materials and Methods**

22 103 **Study population and data collection**

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26 104 The ethics committee of Hallym University (2014-I148) approved the use of these data. The
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28 105 Institutional Review Board exempted the requirement for written informed consent.

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30 106 This national cohort study used data from the Korean National Health Insurance
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33 107 Service-National Sample Cohort (NHIS-NSC). The Korean NHIS selects samples directly
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35 108 from the entire population database to prevent nonsampling errors. Approximately 2% of the
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37 109 samples (one million) were selected from the entire Korean population (50 million). The
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39 110 selected data were classified into 1,476 levels (age [18 categories], sex [2 categories], and
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41 111 income level [41 categories]) using randomized, stratified, systematic sampling methods via
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43 112 proportional allocation to represent the entire population. A previous study verified the
44
45 113 appropriateness of the sample after data selection.²¹ The National Health Insurance Sharing
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47 114 Service provides a detailed description of the methods used to perform these procedures.²²
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49 115 This cohort database included (i) personal information, (ii) health insurance claim codes
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52 116 (procedures and prescriptions), (iii) diagnostic codes based on the International Classification
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55 117 of Disease-10 (ICD-10), (iv) death records from the Korean National Statistical Office (using
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3 118 the Korean Standard Classification of disease), (v) socioeconomic data (residence and
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5 119 income), and (vi) medical examination data for each participant from 2002 to 2013.

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8 120 All Korean citizens are recognized by a 13-digit resident registration number from birth
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10 121 to death. Therefore, exact population statistics have been determined using this database. All
11
12 122 Koreans are required to enroll in the NHIS. All Korean hospitals and clinics use the 13-digit
13
14 123 resident registration number to register individual patients in the medical insurance system.
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16 124 Therefore, the risk of overlapping medical records is minimal, even if a patient moves from
17
18 125 one place to another. All medical treatments in Korea are tracked without exception using the
19
20 126 Health Insurance Review & Assessment (HIRA) system. In Korea, the law states that a notice
21
22 127 of death must be provided to an administrative entity before a funeral can be held. Medical
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24 128 doctors record the date and cause of death on a death certificate.
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30 130 **Patients and public involvement**

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33 131 No patients or public were involved in the present study.
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37 133 **Participant Selection**

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40 134 Of the 1,125,691 patients with 114,369,638 medical claim codes, participants diagnosed with
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42 135 migraine (ICD-10: G43) were included. Among these participants, those who were treated \geq
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44 136 2 times ($n = 45,587$) were selected. The participants were followed for 12 years.

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47 137 The history of admission for hemorrhagic stroke (I60: Subarachnoid hemorrhage, I61:
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49 138 Intracerebral hemorrhage, and I62: Other nontraumatic intracranial hemorrhage) and
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51 139 ischemic stroke (I63: Cerebral infarction) was identified using ICD-10 codes. We selected the
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53 140 participants who were treated ≥ 1 time. These methods were used in other studies evaluating
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56 141 the incidence of stroke in Korea.^{8 23}
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3 142 The participants with migraine were matched 1:4 with participants (control group) who
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5 143 had never been diagnosed with a migraine from 2002 through 2013 in this cohort. The control
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7 144 group was selected from the total population (n = 1,080,104). The matches were processed
8
9 145 for age, group, sex, income group, region of residence, and past medical histories (age, sex,
10
11 146 income, region of residence, hypertension, diabetes, and dyslipidemia histories). We sorted
12
13 147 the participants in the control group using a random number order and then selected them
14
15 148 from top to bottom to prevent selection bias when selecting the matched control participants.
16
17 149 We assumed that the matched control participants were enrolled at the same time as each
18
19 150 matched participant with migraine (index date). Therefore, control group members who died
20
21 151 before the index date were excluded. In both the migraine and control groups, participants
22
23 152 with histories of hemorrhagic or ischemic stroke before the index date were excluded. In the
24
25 153 migraine group, 438 participants were excluded. The participants with migraine for whom we
26
27 154 were unable to identify sufficient numbers of matching participants were excluded (n = 185).
28
29 155 We excluded participants aged less than 20 years (n = 3,379). Finally, 1:4 matching resulted
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31 156 in the inclusion of 41,585 participants with migraine (migraine with aura = 3,458, migraine
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33 157 without aura = 38,127) and 166,340 control participants (Fig. 1).
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159 **Variables**

160 The age groups were classified using 5-year intervals: 20-24, 25-29, 30-34..., and 85+ years
161 old. Fourteen age groups were designated. The income groups were initially divided into 41
162 classes (one health aid class, 20 self-employment health insurance classes, and 20
163 employment health insurance classes). These groups were recategorized into 11 classes (class
164 1 [lowest income]–class 11 [highest income]). The region of residence was divided into 16
165 areas according to administrative district. These regions were regrouped into urban (Seoul,

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3 166 Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon,
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5 167 Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk,
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7 168 Gyeongsangnam, and Jeju) areas. The past medical histories of the participants were
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10 169 evaluated using ICD-10 codes. For an accurate diagnosis, hypertension (I10 and I15),
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12 170 diabetes (E10-E14), and dyslipidemia (E78) were recorded if the participants were treated ≥ 2
13
14 171 times. Using the Charlson Comorbidity Index, we selected some of confounders that might
15
16 172 affect the association between migraine and stroke as confounders based on literature review.
17
18 173 We performed the analysis with added variables, including congestive heart failure,²⁴
19
20 174 myocardial infarction,²⁵ peripheral vascular disease,²⁶ pulmonary disease,²⁷ liver disease,²⁸
21
22 175 and depression histories.^{29 30} Thus, the new model was adjusted for age, sex, income, region
23
24 176 of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial
25
26 177 infarction, peripheral vascular disease, pulmonary disease, liver disease, and depression
27
28 178 histories.

179

180 **Statistical Analyses**

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

189 than 0.05 were considered significant. The results were statistically analyzed using SPSS v.
190 21.0 software (IBM, Armonk, NY, USA).

191

192 **Results**

193 The mean follow-up period was 80.9 (standard deviation [SD] = 41.6) months for patients
194 with migraine and 80.9 (SD = 41.6) months for controls. The rates of hemorrhagic stroke
195 were similar in the migraine group (0.7% [295/41,585]) and the control group (0.7%
196 [1,113/166,340], $P = 0.370$, Table 1). Higher rates of ischemic stroke were observed in the
197 migraine group (2.3% [964/41,585]) than in the control group (2.0% [3,294/166,340], $P <$
198 0.001). The general characteristics (age, sex, income, region of residence, hypertension,
199 diabetes, and dyslipidemia histories) of participants were the same due to the matching
200 protocol ($P = 1.000$).

201

202 **Table 1** General characteristics of the participants

Characteristics	Total participants		P-value
	Migraine (n, %)	Control (n, %)	
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 $P < 0.001$).

213 **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	

214

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

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

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3 218 In the subgroup analyses, none of the crude and adjusted HRs for hemorrhagic stroke
4
5 219 reached statistical significance (Table 3). Among the patients with ischemic stroke, young
6
7 220 women, middle-aged women, and old women showed statistically significant differences
8
9 221 (each $P < 0.05$). The significant adjusted HRs were 2.31 (95% CI = 1.39–3.82) in young
10
11 222 women (20-39 years old); 1.32 (95% CI = 1.08–1.61) in middle-aged women (40-59 years
12
13 223 old); and 1.18 (95% CI = 1.06–1.30) in ≥ 60 -year-old women. Moreover, descriptive
14
15 224 statistical analyses of the migraine prevalence and ischemic stroke occurrence within
16
17 225 subgroups revealed statistically significant differences in young men, young women, middle-
18
19 226 aged women, old men, and old women. On the other hand, the risk of hemorrhagic stroke in
20
21 227 patients with migraine was not significantly different from the control group (Supplement
22
23 228 table 1).
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238 **Table 3** Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic
 239 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)	

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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

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

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3 242 † Model adjusted for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, congestive heart failure, myocardial infarction,
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5 243 peripheral vascular disease, pulmonary disease, liver disease, and depression histories.
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3 244 Compared with the control group, participants who reported migraine with aura and
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5 245 migraine without aura had increased adjusted HRs of 1.44 (95% CI = 1.09-1.89) and 1.15
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7 246 (95% CI = 1.06-1.24) for ischemic stroke, respectively, but no increased risk of hemorrhagic
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10 247 stroke (Table 4).

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268 **Table 4** Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of migraine for hemorrhagic stroke and ischemic
 269 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	

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

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

274 **Discussion**

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

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

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3 298 factors may precipitate the susceptibility to CSD, which may explain the association between
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5 299 migraine and stroke.³⁵
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8 300 A growing body of evidence regarding the increased risk of ischemic stroke in patients
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10 301 with migraine without aura. Consistent with the findings from patients reporting migraine
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12 302 with aura, participants who reported migraine without aura had an increased adjusted HR of
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14 303 1.15 (95% CI = 1.06-1.24) for ischemic stroke compared with the control group. Notably, a
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16 304 significant association was observed in cases of ischemic stroke resulting from cervical artery
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18 305 dissection.³⁶ In addition, genetic overlaps among subjects with migraine without aura, large
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20 306 artery stroke, and cardio-embolic stroke have been identified.³⁷ However, strong evidence has
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22 307 been not reported. A recent large population-based study reported an statistically insignificant
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24 308 risk of ischemic stroke in patients with migraine without aura but an increased risk in patients
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26 309 with migraine with aura.³ The study suggested that the difference may be due to changes in
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28 310 the lipid profile, the susceptibility to thrombosis, and genetic predisposition.³ A meta-analysis
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30 311 did not identify a significant association between migraine without aura and ischemic
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32 312 stroke.¹⁸ In the present study, we did not differentiate between migraine subtypes, such as
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34 313 migraine with and without aura, when analyzing the risk of stroke. Therefore, the risk of
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36 314 ischemic stroke in participants with migraine was relatively low but statistically significant
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38 315 compared to other studies investigating specific conditions.
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41 316 Notably, in the present study, migraine was not associated with an increased risk of
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43 317 hemorrhagic stroke. In contrast to the findings from the present study, a recent meta-analysis
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45 318 based on 4 case-control and 4 cohort studies concluded that migraine may increase the risk of
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47 319 hemorrhagic stroke.²⁰ However, a recent large population-based case-control study did not
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49 320 show an association with different types of hemorrhagic stroke, including intracerebral
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51 321 hemorrhage and subarachnoid hemorrhage.³⁸ Migraine was an independent risk factor for
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3 322 aneurismal rupture (odds ratio [OR] = 2.4; 95% CI 1.1–5.1) in a case-control study,³⁹ and
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5 323 even if headache is a premonitory symptom of aneurismal rupture, recall biases might have
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7 324 affected the results of the study. Overall, the relatively small number of hemorrhagic stroke
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9 325 cases might have resulted in decreased statistical power.

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12 326 In our subgroup analysis, a strong correlation between migraine and ischemic stroke was
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14 327 observed in young patients, specifically young women (20-39 years old). Based on a
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16 328 consensus statement from the European Headache Federation (EHF),⁴⁰ the use of a combined
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18 329 hormonal contraceptive may further increase the risk of ischemic stroke in patients with
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20 330 migraine, specifically migraine with aura, supporting our results. Because the predisposing
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22 331 factors for stroke increase the incidence of ischemic stroke with age,⁴¹ migraine itself rather
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24 332 than other risk factors might be implicated in the increased risk of ischemic stroke. In
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26 333 contrast, a recent large, population-based cohort study in Taiwan with a relatively short
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28 334 follow-up duration of 3.6 years did not show a significant association in the subgroups of
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30 335 women and patients aged < 45 years.³ This discrepancy might be due to differences in the
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32 336 study design, follow-up duration, and ethnic composition of the study population. Recently, a
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34 337 similar trend for this association was also reported,³ but it requires further confirmation due
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36 338 to the lack of evidence at present.

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39 339 The present study has several strengths. The results of this study are consistent with the
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41 340 findings of our previous studies utilizing the HIRA-NSC.⁴²⁻⁴⁴ We examined a very large,
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43 341 representative, and nationwide population. Because the NHIS data cover all citizens of Korea
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45 342 without exception, no participants were lost during follow-up. The control group was
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47 343 randomly selected and matched based on age, sex, income, region of residence, and medical
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49 344 history to decrease any confounding effects. An adjusted hazard model was used to further
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51 345 minimize the impacts of confounders. Because migraine attacks might be frequently repeated,

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3 346 we opted to include patients with migraine who underwent treatment at least twice based on
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5 347 the ICD-10 code to increase the validity of the study [G43]. In a previous study, the
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7 348 prevalence of migraine in Korea was reported to be approximately 6.1%.⁴ This value
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9 349 appeared to be slightly higher than the value reported in the present study, which was 3.7%
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12 350 (41,585/1,125,691), based on strict inclusion criteria for migraine. In addition, the patients
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14 351 with migraine were followed for 12 years in the present study. Long study periods enable the
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16 352 recruitment of a large study population and allow researchers to observe and analyze the
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18 353 delayed effects of migraine on stroke.
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21 354 However, the present study has certain limitations that should be addressed in future
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23 355 studies. First, we were unable to extract information on stroke subtypes and location from the
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25 356 data used in the present study. The impact of migraine on each type of pathophysiology might
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27 357 vary when considering different functional outcomes, survival, and recurrence according to
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29 358 stroke subtype.^{38 45} However, in the present study, the distribution of stroke subtypes was not
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31 359 available. The classification of stroke type can lead to a significantly decreased incidence of
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33 360 each disease. As an insufficient number of cases cause inappropriate comparisons due to
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35 361 lower statistical power, the inclusion of the distribution of stroke subtypes would hamper our
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37 362 ability to draw a clear conclusion from the available data. In particular, the absolute incidence
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39 363 of hemorrhagic stroke is very low in general practice; therefore, most of studies did not
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41 364 provide information about subtypes, such as the presence of an aneurysm, although the
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43 365 association is positive in public health studies.³⁸ Second, a firm correlation between the
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45 366 frequency of migraine attacks and the risk of stroke has been reported,⁴⁶ but we were unable
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47 367 to confirm this correlation using the claim data analyzed in the present study. Similarly, the
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49 368 duration and severity of migraine were inconsistent among the study population. Patients
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51 369 with migraine who had mild complaints may not have received a consultation at the clinic;
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3 370 therefore, the impact of migraine on stroke may be underestimated in this study. Third,
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5 371 although this study attempted to include a large, representative patient population and
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7 372 subsequently matched and adjusted for possible confounders, the risk factors for stroke in
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9 373 patients with migraine, such as cigarette smoking, obesity, and migraine-specific drugs, were
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11 374 not available in the insurance database.^{11 46} Finally, in the present study, the incidence of
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13 375 migraine was 3.7% (41,585 of 1,125,691 participants) after employing a strict matching
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15 376 protocol. Before matching, the incidence of migraine in Korea was 4.1% (45,587 of
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17 377 1,125,691 participants). This value is consistent with previous cohort study in Korea,
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19 378 indicating that the overall prevalence rate of migraine was 6.1%,⁴ despite the use of different
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21 379 study designs. Given the global prevalence of migraine of approximately 8–15%,^{2,3} the
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23 380 incidence of migraine in Korea is relatively low because of limited claim data. Only patients
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25 381 with migraine who visited the hospital are recorded. In other words, data are not available for
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27 382 patients with weak migraine symptoms or patients who do not visit a hospital, leading to a
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29 383 lower incidence. Based on a population-based epidemiological study of migraine in Korea,
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31 384 only 24.4% of patients ever consulted a doctor for headache and only 3.3% of patients were
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33 385 prescribed a drug by a doctor.⁴⁷
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42 387 **Conclusions**

43
44 388 Based on a large population-based cohort study in Korea, migraine increased the risk of
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46 389 ischemic stroke, but not hemorrhagic stroke. The subgroup of patients at the highest risk of
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48 390 developing ischemic stroke was young women.
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12 397 No additional data are available.
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23 402 Korea.
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28 404 **COMPETING INTERESTS STATEMENT**
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30 405 None of the authors have competing interests to declare.
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35 407 **AUTHORS' CONTRIBUTIONS**
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37 408 As the first author, SYL wrote the manuscript. DJO and JSL analyzed and interpreted the
38
39 409 data. IGK processed the data. HGC conceptualized, wrote, and reviewed the manuscript.
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44 411 **References**
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537 Figure Legend

17 538 **Fig. 1** A schematic illustrating the participant selection process used in the present study. Of
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19 539 a total of 1,125,691 participants, 41,585 participants with migraine were matched with
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21 540 166,340 control participants for age, group, sex, income level, region of residence, and past
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24 541 medical histories.
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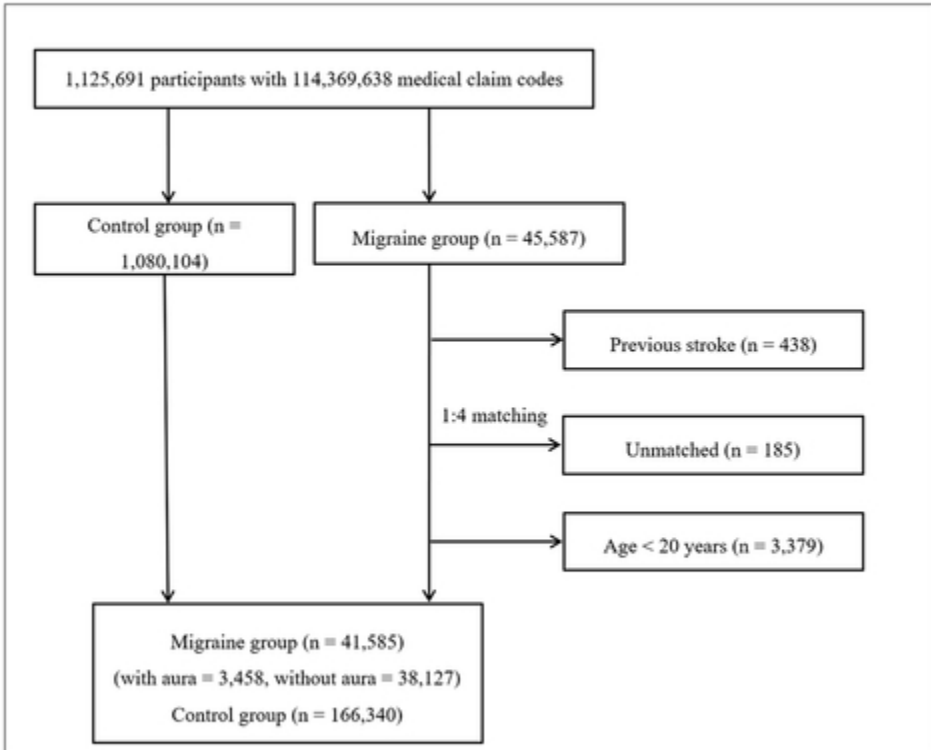


Figure 1

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)	

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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	Non-Migraine	P-value	Migraine	Non-Migraine	P-value
	(n = 2,948)	(n = 11,792)		(n = 7,979)	(n = 31,916)	
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, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

			Page
		Reporting Item	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

1	Background /	#2	Explain the scientific background and rationale for the	4-5
2				
3	rationale		investigation being reported	
4				
5				
6	Objectives	#3	State specific objectives, including any prespecified	5
7				
8			hypotheses	
9				
10				
11	Study design	#4	Present key elements of study design early in the paper	5
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14				
15	Setting	#5	Describe the setting, locations, and relevant dates, including	5-6
16				
17			periods of recruitment, exposure, follow-up, and data	
18				
19			collection	
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22	Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of	6-7
23				
24			selection of participants. Describe methods of follow-up.	
25				
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27				
28		#6b	For matched studies, give matching criteria and number of	6-7
29				
30			exposed and unexposed	
31				
32				
33	Variables	#7	Clearly define all outcomes, exposures, predictors, potential	7-8
34				
35			confounders, and effect modifiers. Give diagnostic criteria, if	
36				
37			applicable	
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41	Data sources /	#8	For each variable of interest give sources of data and details	5-8
42				
43	measurement		of methods of assessment (measurement). Describe	
44				
45			comparability of assessment methods if there is more than	
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47			one group. Give information separately for for exposed and	
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49			unexposed groups if applicable.	
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53	Bias	#9	Describe any efforts to address potential sources of bias	5-8
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56	Study size	#10	Explain how the study size was arrived at	7
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1	Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7	
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8	Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8	
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14		#12b	Describe any methods used to examine subgroups and interactions	8	
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19		#12c	Explain how missing data were addressed	NA	
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23		#12d	If applicable, explain how loss to follow-up was addressed	NA	
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26		#12e	Describe any sensitivity analyses	NA	
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29	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	
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41		#13b	Give reasons for non-participation at each stage	NA	
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44		#13c	Consider use of a flow diagram	7	
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47	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	
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1		#14b	Indicate number of participants with missing data for each	8-13
2				
3			variable of interest	
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6		#14c	Summarise follow-up time (eg, average and total amount)	8
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10	Outcome data	#15	Report numbers of outcome events or summary measures	NA
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12			over time. Give information separately for exposed and	
13				
14			unexposed groups if applicable.	
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17	Main results	#16a	Give unadjusted estimates and, if applicable, confounder-	8-13
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19			adjusted estimates and their precision (eg, 95% confidence	
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21			interval). Make clear which confounders were adjusted for	
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23			and why they were included	
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27		#16b	Report category boundaries when continuous variables were	NA
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29			categorized	
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33		#16c	If relevant, consider translating estimates of relative risk into	NA
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35			absolute risk for a meaningful time period	
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38	Other analyses	#17	Report other analyses done—e.g., analyses of subgroups	13-14
39				
40			and interactions, and sensitivity analyses	
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43	Key results	#18	Summarise key results with reference to study objectives	16
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46	Limitations	#19	Discuss limitations of the study, taking into account sources	
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48			of potential bias or imprecision. Discuss both direction and	
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50			magnitude of any potential bias.	
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1	Interpretation	#20	Give a cautious overall interpretation considering objectives,	19
2			limitations, multiplicity of analyses, results from similar	
3			studies, and other relevant evidence.	
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8	Generalisability	#21	Discuss the generalisability (external validity) of the study	16-18
9			results	
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14	Funding	#22	Give the source of funding and the role of the funders for the	20
15			present study and, if applicable, for the original study on	
16			which the present article is based	
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