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Bidirectional association between migraine and rheumatoid arthritis: two longitudinal follow-up studies with a national sample cohort

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ABSTRACT

Objective To investigate the bidirectional association between migraine and rheumatoid arthritis (RA).

Design Two longitudinal follow-up studies.

Setting Data collected from a national cohort between 2002 and 2013 by the Korean National Health Insurance Service-Health Screening Cohort.

Participants In cohort 1, matching resulted in the inclusion of 31 589 migraine patients and 126 356 control I participants. In cohort 2, matching resulted in the inclusion of 9287 RA patients and 37 148 control II participants.

Primary and secondary outcome measures The HRs for RA in patients with migraine (cohort 1) and migraine in patients with RA (cohort 2) were analysed using stratified Cox proportional hazard models after adjusting for autoimmune disease, Charlson Comorbidity Index scores without rheumatoid diseases, obesity (body mass index), smoking and history of alcohol intake. Subgroup analyses stratified by age, sex, income and region of residence were also performed.

Results The incidence of RA in the migraine group (2.0% (640/31 589)) was higher than that in the control I group (1.4% (1709/126 356), p<0.001). The adjusted HR for RA in the migraine without aura group was 1.48 (95% CIs=1.34 to 1.63, p<0.001).

The incidence of migraine in the RA group (6.4% (590/9287)) was higher than that in the control II group (4.6% (1721/37 148), p<0.001). The adjusted HR for migraine without aura in the RA group was 1.35 (95% CI=1.23 to 1.49, p<0.001).

Conclusion Migraine increases the risk of RA, and RA is also associated with an increased risk of migraine.

Strengths and limitations of this study

- ► The strength of this study is that it is an evaluation of the bidirectional association between migraine and rheumatoid arthritis using a large Korean sample population with a long follow-up period.
- ► Owing to the large number of participants, we could match enough control participants in a 1:4 ratios, maintaining the statistical power in the subgroup analyses.
- ► One limitation is that confounding variables related to socioeconomic factors, such as occupation, physical inactivity, diet and nutrition, were not available, as this study evaluated the associations using medical claim codes.

INTRODUCTION

Migraine is a primary headache characterised by neurological symptoms and recurrent episodic attacks with various triggers.[1] The complete pathophysiological mechanism is still unknown, but several causes of migraine have been suggested. A variety of factors, including those involving the central nervous system, the immune system, inflammation, genetics and vascular ischemia, can contribute to the development of migraine attacks.[2] The main mechanisms that have been suggested to underlie the development of a migraine are hypothalamic activation, alterations in thalamocortical circuits, altered brain connectivity, brainstem activation, cortical spreading depression and the release of calcitonin gene-related peptide (CGRP).[3 4] The clinical features of a migraine attack are divided into the premonitory phase, the aura phase, the headache phase and the postdrome phase based on hormonal and nervous system changes.[3]

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease involving synovitis in multiple joints. There are several causative factors involved in the pathophysiology of RA, including genetic, environmental and immunological factors.[5–7] The inflammatory responses in RA are not limited to synovitis and can become systemic. RA has been reported to be associated with multiple systemic diseases, including cardiovascular disease, lung disease and neuropsychiatric disease.[8]

Recently, RA has been found to be associated with migraine. Only a few studies have reported an association between migraine and RA. Wang *et al*[9] published a longitudinal study showing that patients with migraines had a high risk of developing RA, but the results were unidirectional. One study reported that patients with severe headaches or migraines were much more likely to develop RA than their counterparts, but the interpretation of those results was limited because of the use of a cross-sectional study design.[10] In a questionnaire study assessing the prevalence of migraines in patients with rheumatic disease, there was little difference between the group with rheumatic diseases and the control group.[11] It has been suggested that the shared pathophysiological mechanisms involving inflammatory processes and autoimmune responses explain the association between migraine and RA.[9 11]

Based on the common pathophysiologic mechanisms of inflammation, vascular endothelial cells and the immune system between migraine and RA, we hypothesised that there might be a bidirectional association between migraine and RA.[12–15] Two longitudinal follow-up studies were designed to test this hypothesis. In each study, the control group was matched with the study group according to age, sex, income and region of residence. To exclude potential confounding effects, the Charlson Comorbidity Index (CCI), body mass index (BMI), smoking, alcohol consumption and autoimmune disease histories were used for adjustment.

MATERIALS AND METHODS

Study population and data collection

This national cohort study used data from the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) covering the period from 1 January 2002 through 31 December 2013. Written informed consent was not required because the data were sorted and analysed using random numbers for research purposes. A detailed description of these data can be found in online supplemental file 1.[16]

Patients and public involvement

No patients or public were involved in this study.

Participant selection

The Korean NHIS-HEALS study included 514 866 individuals with 497 931 549 medical claim codes. Two cohorts were constructed.

Cohort 1: risk for incident RA in persons with migraine

We enrolled those with migraine, as defined by the International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) code G43. Migraine was classified as migraine with aura and migraine without aura (ICD-10: G431), as in our previous studies.[17 18] Migraine was identified if participants were diagnosed with these conditions at least two times.[19] The case definition included two separate visits associated with a diagnosis of migraine, with the first visit selected as the index date. The migraine group was matched 1:4 with the control I group, which was composed of individuals who were not diagnosed with migraine from 2002 to 2013. Matching was based on age group, sex, income group and region of residence. To avoid selection bias, the control I participants were arranged using random numbers and then selected from top to bottom. Assuming that the matched control I participants were involved at the same time as each matched migraine participant, we set the index date for both the migraine participant and the matched control participants as the date of the diagnosis of migraine. Control participants who died before the index date were replaced by other control participants. Participants with histories of RA prior to the index date were excluded from both the migraine and control groups. After matching the participants in cohort 1, we analysed the occurrence of RA in patients with migraine with aura and their controls and in patients with migraine without aura and their controls.

Cohort 2: risk for incident migraine in persons with RA

RA was defined as in previous studies that reported the prevalence and incidence of RA in Korea.[20 21] RA was selected based on the relevant ICD-10 codes (M05 or M06) and a prescription for a biologic agent or any disease-modifying antirheumatic drug (DMARD). RA was identified if participants were diagnosed with these conditions at least two times.[19] The case definition included two separate visits associated with a diagnosis of RA and medical treatment for RA, with the first visit selected as the index date. The RA group was matched 1:4 with the control II group, which was composed of individuals who were not diagnosed with RA from 2002 to 2013. Matching was based on age group, sex, income group and region of residence. To avoid selection bias, the control II participants were arranged using random numbers and then selected from top to bottom. Assuming that the matched control II participants were involved at the same time as each matched RA participant, we set the index date for both the RA patients and their matched controls as the date of the RA diagnosis. Control participants who died before the index date were replaced by other control participants. Participants with a history of migraine prior to the index date were excluded from both the RA and control groups. After matching in cohort 2, we analysed the occurrence of migraine with/without aura in patients with RA.

Variables

The age groups were classified using 5-year intervals: 40–44, 45–49, 50–54… and >80 years. A total of nine age groups were designated. The income groups were divided into five classes (class 1 (lowest income)–class 5 (highest income)). The region of residence was divided into 16 areas according to the administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu,

Incheon, Gwangju, Daejeon and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam and Jeju) areas.[19] Tobacco smoking was categorised according to the current smoking state (nonsmoker, ex-smoker and current smoker). Alcohol consumption was categorised according to the frequency (<1 time a week and ≥1 time a week). Obesity was measured using BMI (kg/m^2) and categorised as <18.5 (underweight), ≥18.5–<23 (normal), ≥23–<25 (overweight), ≥25–<30 (obese I) and ≥30 (obese II) according to the Regional Office for the Western Pacific 2000.[16 22]

Autoimmune disease was defined as psoriasis (B02), systemic lupus erythematosus (M32), systemic sclerosis (M34), Sjogren syndrome (M350), dermatopolymyositis (M33), and polyarteritis nodosa and related conditions (M30). The CCI was calculated for 16 comorbidities, excluding rheumatic diseases, and analysed as a continuous variable (0 (no comorbidity) through 28 (multiple comorbidities)).[23]

Statistical analyses

In cohorts 1 and 2, χ^2 tests were used to compare demographic and general characteristics between groups within each study.

In cohort 1, a stratified Cox proportional hazards model was used to estimate the HR for RA (dependent variable) in patients with migraine (independent variable). In cohort 2, another stratified Cox proportional hazards model was applied to estimate the HR for migraine (dependent variable) in patients with RA (independent variable). Age, sex, income and region of residence were used to stratify the participants, and the 95% CIs were calculated. In the adjusted model, we adjusted for CCI scores (continuous variable), BMI group, smoking, alcohol consumption and autoimmune disease history (categorical variable). The Kaplan-Meier method and the log-rank test were used for the survival analysis.

For the subgroup analyses, we divided the participants by age and sex (<60 years and >60 years; men and women). Other subgroup analyses were performed by income (low (groups 1–3) and high (groups 4 and 5)) and region of residence (urban and rural). The cut-off value for age was determined by the median value. Additionally, we analysed HRs according to the presence of an aura.

Our data were analysed using two-tailed tests (p value<0.05). The results were statistically analysed using SPSS V.22.0 (IBM) and SAS V.9.4 (SAS Institute).

RESULTS

Cohort 1

The results of the 1:4 matching yielded 31 589 migraine patients and 126 356 control I participants (table 1 and figure 1). The mean follow-up time from the index date to the last date (31 December 2013) or date of death was approximately the same in both the migraine (76.3 months, SD=36.9) and control I groups (76.0 months, SD=37.1). The interval from the index date to the diagnosis of RA was 41.8 months (SD=31.5) in the migraine group and 37.1 months (SD=31.3) in the control I group.

The incidence of RA was higher in the migraine group (2.0% (640/31 589)) than in the control I group (1.4% (1709/126 356), p<0.001, table 1). The general characteristics (age, sex, income and region of residence) of the participants were the same after matching (p=1.000). The adjusted HR for RA in the migraine without aura group was 1.48 (95% CI=1.34 to 1.63, p<0.001, table 2; figure 2). The adjusted HR for RA in the migraine with aura group was 1.23 (95% CI=0.91 to 1.67, p=0.183).

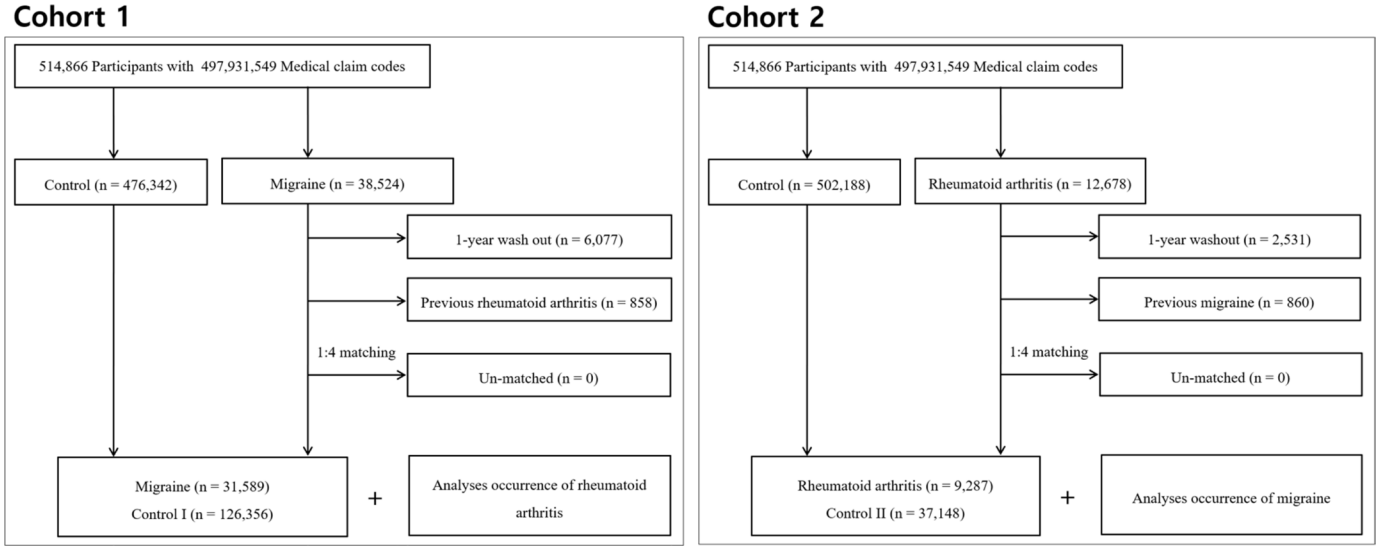

Figure 1 Schematic illustration of the participant selection process that was used in this study. Cohort 1: Of 514 866 participants, 31 589 migraine patients were matched with 126 356 control I participants for age group, sex, income group and region of residence. Cohort 2: Of 514 866 participants, 9287 rheumatoid arthritis patients were matched with 37 148 control II participants for age group, sex, income group and region of residence.

Table 1 General characteristics of the participants

Characteristics	Cohort 1			Cohort 2		
	Migraine (n, %)	Control I (n, %)	P value	Rheumatoid arthritis (n, %)	Control II (n, %)	P value
Number (n)	31 589	126 356		9287	37 148	
Age (years)			1.000			1.000
40–44	1528 (4.8)	6112 (4.8)		374 (4.0)	1496 (4.0)	
45–49	4776 (15.1)	19 104 (15.1)		1253 (13.5)	5012 (13.5)	
50–54	5730 (18.1)	22 920 (18.1)		2095 (22.6)	8380 (22.6)	
55–59	4666 (14.8)	18 664 (14.8)		1718 (18.5)	6872 (18.5)	
60–64	4423 (14.0)	17 692 (14.0)		1419 (15.3)	5676 (15.3)	
65–69	4446 (14.1)	17 784 (14.1)		1204 (13.0)	4816 (13.0)	
70–74	3417 (10.8)	13 668 (10.8)		761 (8.2)	3044 (8.2)	
75–79	1806 (5.7)	7224 (5.7)		351 (3.8)	1404 (3.8)	
>80	797 (2.5)	3188 (2.5)		112 (1.2)	448 (1.2)	
Sex			1.000			1.000
Male	10 169 (32.2)	40 676 (32.2)		2625 (28.3)	10 500 (28.3)	
Female	21 420 (67.8)	85 680 (67.8)		6662 (71.7)	26 648 (71.7)	
Income			1.000			1.000
1 (lowest)	5692 (18.0)	22 768 (18.0)		1569 (16.9)	6276 (16.9)	
2	4698 (14.9)	18 792 (14.9)		1267 (13.6)	5068 (13.6)	
3	5235 (16.6)	20 940 (16.6)		1548 (16.7)	6192 (16.7)	
4	6574 (20.8)	26 296 (20.8)		1969 (21.2)	7876 (21.2)	
5 (highest)	9390 (29.7)	37 560 (29.7)		2934 (31.6)	11 736 (31.6)	
Region of residence			1.000			1.000
Urban	12 225 (38.7)	48 900 (38.7)		3738 (40.3)	14 952 (40.3)	
Rural	19 364 (61.3)	77 456 (61.3)		5549 (59.8)	22 196 (59.8)	
CCI (score)*			<0.001†			0.226
0	31 054 (98.3)	123 330 (97.6)		9116 (98.2)	36 383 (97.9)	
1	56 (0.2)	466 (0.4)		17 (0.2)	113 (0.3)	
2	55 (0.2)	482 (0.4)		29 (0.3)	120 (0.3)	
≥3	424 (1.3)	2078 (1.6)		125 (1.4)	532 (1.4)	
BMI			0.025†			0.119
<18.5 (underweight)	771 (2.4)	3158 (2.5)		169 (1.8)	814 (2.2)	
≥18.5–<23 (normal)	11 438 (36.2)	45 410 (35.9)		3334 (35.9)	13 079 (35.2)	
≥23–<25 (overweight)	8450 (26.8)	33 879 (26.8)		2476 (26.7)	10 134 (27.3)	
≥25–<30 (obese I)	9983 (31.6)	39 667 (31.4)		2985 (32.1)	11 878 (32.0)	
≥30 (obese II)	947 (3.0)	4242 (3.4)		323 (3.5)	1243 (3.4)	
Smoking			<0.001†			0.330
Non-smoker or ex-smoker	28 146 (89.1)	110 973 (87.8)		8283 (89.2)	33 000 (88.8)	
Current smoker	3443 (10.9)	15 383 (12.2)		1004 (10.8)	4148 (11.2)	
Drinking alcohol			<0.001†			<0.001†
<1 time a week	26 747 (84.7)	104 041 (82.3)		7890 (85.0)	30 983 (83.4)	
≥1 time a week	4842 (15.3)	22 315 (17.7)		1397 (15.0)	6165 (16.6)	
Autoimmune disease	8119 (25.7)	25 433 (20.1)	<0.001†	2798 (30.1)	7769 (20.9)	<0.001†
Migraine	31 589 (100.0)	0 (0.0)	<0.001†	590 (6.4)	1721 (4.6)	<0.001†

Continued

Table 1 Continued

Characteristics	Cohort 1			Cohort 2		
	Migraine (n, %)	Control I (n, %)	P value	Rheumatoid arthritis (n, %)	Control II (n, %)	P value
With aura	2287 (7.2)	0 (0.0)	<0.001†	40 (0.4)	114 (0.3)	0.063
Without aura	29 302 (92.8)	0 (0.0)	<0.001†	550 (5.9)	1607 (4.3)	<0.001†
Rheumatoid arthritis	640 (2.0)	1709 (1.4)	<0.001†	9287 (100.0)	0 (0.0)	<0.001†

*CCI was calculated without rheumatic diseases.
†χ^2 test, significance at p<0.05.
BMI, body mass index; CCI, Charlson Comorbidity Index.

In all subgroup analyses, higher adjusted HRs for RA were observed in the migraine group (each p<0.05, table 3). The adjusted HR was 1.46 (95% CI=1.33 to 1.60) in all participants, 2.40 (95% CI=1.72 to 3.36) in <60-year-old men, 1.45 (95% CI=1.28 to 1.64) in <60-year-old women, 1.76 (95% CI=1.30 to 2.39) in ≥60-year-old men and 1.25 (95% CI=1.06 to 1.49) in ≥60-year-old women. The adjusted HR was 1.35 (95% CI=1.19 to 1.53) in the low-income group and 1.58 (95% CI=1.39 to 1.80) in the high-income group. Both urban and rural categories in the migraine group had higher adjusted HRs for RA.

Cohort 2

The results of the 1:4 matching yielded 9287 RA patients and 37 148 control II participants (table 1 and figure 1). The mean follow-up time from the index date to the last date (31 December 2013) or date of death was approximately the same in both the RA (78.4 months, SD=37.3) and control II groups (78.3 months, SD=37.4). The interval from the index date to the diagnosis of migraine was 41.4 months (SD=31.1) in the RA group and 40.4 months (SD=31.6) in the control II group.

The incidence of migraine was higher in the RA group (6.4% (590/9287)) than in the control II group (4.6% (1721/37 148), p<0.001, table 1). The general characteristics (age, sex, income and region of residence) of the participants were the same after matching (p=1.000). The adjusted HR for migraine without aura in the RA group was 1.35 (95% CI=1.23 to 1.49, p<0.001, table 2 and figure 2). The adjusted HR for migraine with aura in the RA group was 1.36 (95% CI=0.95 to 1.96, p=0.094).

In subgroup analyses, higher adjusted HRs for migraine were observed in the RA group, except in ≥60-year-old

Table 2 Crude and adjusted HRs (95% CI) in cohorts 1 and 2

Characteristics	HR			
	Crude*	P value	Adjusted*†	P value
Cohort 1				
HRs for rheumatoid arthritis in migraine with aura				
Migraine	1.32 (0.97 to 1.78)	0.078	1.23 (0.91 to 1.67)	0.183
Control I	1.00		1.00	
HRs for rheumatoid arthritis in migraine without aura				
Migraine	1.52 (1.38 to 1.67)	<0.001‡	1.48 (1.34 to 1.63)	<0.001‡
Control I	1.00		1.00	
Cohort 2				
HR for migraine with aura				
RA	1.40 (0.98 to 2.01)	0.065	1.36 (0.95 to 1.96)	0.094
Control II	1.00		1.00	
HR for migraine without aura				
RA	1.38 (1.26 to 1.53)	<0.001‡	1.35 (1.23 to 1.49)	<0.001‡
Control II	1.00		1.00	

*Stratified model for age, sex, income and region of residence.
†Adjusted model for autoimmune disease, Charlson Comorbidity Index (except rheumatoid diseases), obesity (body mass index), smoking and alcohol intake histories.
‡Cox-proportional hazard regression model, significance at p<0.05.
RA, rheumatoid arthritis.

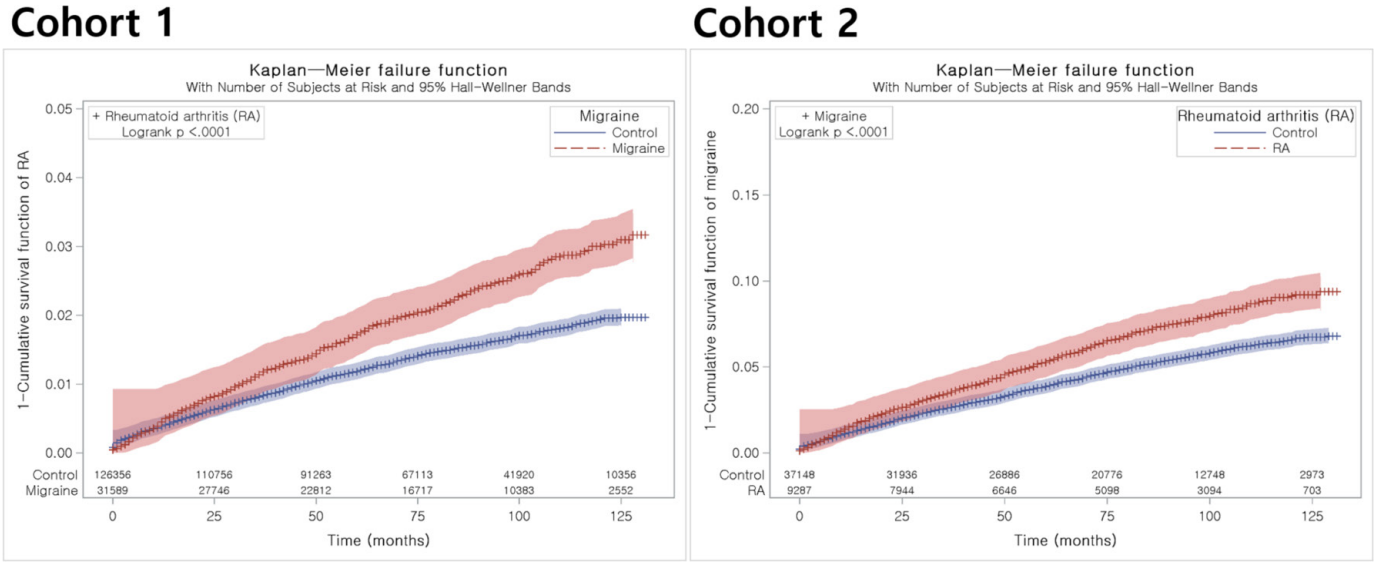

Figure 2 Kaplan-Meier survival analysis. Cohort 1: The group with migraine had a higher cumulative proportion of patients with RA than did the control I group. Cohort 2: The group with RA had a higher cumulative proportion of patients with migraine than did the control II group. RA, rheumatoid arthritis.

men (each p<0.05, table 4). The adjusted HR was 1.35 (95% CI=1.23 to 1.49) in all participants, 1.87 (95% CI=1.32 to 2.66) in <60-year-old men, 1.40 (95% CI=1.23 to 1.59) in <60-year-old women and 1.24 (95% CI=1.05 to 1.46) in ≥60-year-old women. The adjusted HRs were 1.38 (95% CI=1.21 to 1.57) in the low-income group and 1.33 (95% CI=1.16 to 1.53) in the high-income group. Both urban and rural categories in the RA group had higher adjusted HRs for migraine.

DISCUSSION

This study showed a bidirectional association between migraine and RA in an adult population. The HR for RA was 1.46 in the migraine patients compared with control participants. In the subgroup analyses according to age, sex, income and region of residence, the risk of RA was consistently higher in migraine patients than in the controls. Migraineurs and control I participants were of the same age composition because an age-adjusted model was used in the analysis. The risk of migraine was 1.35 times higher in RA patients than in non-RA control participants. In the age, sex, income and region of residence subgroup analyses, RA patients had a consistently higher risk of migraine except among men aged >60 years. In addition, Kaplan-Meier survival analysis showed that the cumulative proportion of patients with RA increased over time in the group with migraines, and the cumulative proportion of patients with migraine also increased over time in the group with RA.

In our study, the prevalence of migraine was approximately 7.5% (38 524/514 866). Approximately 7.6% of migraine patients had an aura, which was lower than that reported in other studies.[24] Most subgroup analyses showed a correlation between migraine and RA in this study. However, RA was not associated with an increased risk of migraine in men aged >60 years. This result may be related to the age-specific and sex-specific prevalence of migraine. The prevalence of migraine is higher in women than in men,[1 25 26] and the most common age group affected by migraine is 25–55 years, after which the prevalence decreases.[1] Considering that our study only analysed participants aged >40 years, and the prevalence of migraine in Korea peaks at the ages of 19–29 years for men and 40–49 years for women,[27] it is not surprising that an increased risk of migraine was not found in male RA patients aged >60 years. Rather, the possibility that the late-onset migraine mimics were misclassified as migraine with or without aura cannot be ruled out.[28]

Only a few previous studies have reported an association between migraine and RA. In a previous UK study assessing the prevalence of migraine in patients with rheumatic disorders, migraine was diagnosed in 12% of patients with RA. However, the prevalence of migraine was evaluated with a questionnaire, and there was little difference in the prevalence of migraine between the RA and control groups.[11] Kalaydjian *et al*[10] reported that patients with RA were significantly more likely to be diagnosed with severe headaches or migraine (OR=1.95, 95% CI 1.68 to 2.25). However, this study was limited by the use of a cross-sectional design. In a Danish study, the incidence of patients with RA was significantly higher in the migraine group than in the group without migraine (OR=2.09, 95% CI 1.41 to 3.10).[29] Wang *et al*, in a longitudinal study, showed a unidirectional association and reported that patients with migraines had a relatively high risk of developing RA. The mean age values of the sample population were 48.3 years (SD=15.5) in the migraine group and 48.5 years (SD=15.8) in the non-migraine group.[9] In cohort 1, the mean ages were 59.4 (SD=10.2) years in the migraine group and 59.3 (SD=10.2) years in the control I group. In

Table 3 Crude and adjusted HRs (95% CI) of migraine (independent variable) for rheumatoid arthritis (dependent variable) according to age, sex, income and region of residence (cohort 1)

	HRs for rheumatoid arthritis			
Characteristics	Crude*	P value	Adjusted*†	P value
Total participants (n=1 57 945)				
Migraine	1.50 (1.37 to 1.64)	<0.001‡	1.46 (1.33 to 1.60)	<0.001‡
Control I	1.00		1.00	
Age <60 years, men (n=25 925)				
Migraine	2.48 (1.78 to 3.45)	<0.001‡	2.40 (1.72 to 3.36)	<0.001‡
Control I	1.00		1.00	
Age <60 years, women (n=57 575)				
Migraine	1.49 (1.32 to 1.69)	<0.001‡	1.45 (1.28 to 1.64)	<0.001‡
Control I	1.00		1.00	
Age ≥60 years, men (n=24 920)				
Migraine	1.81 (1.33 to 2.44)	<0.001‡	1.76 (1.30 to 2.39)	<0.001‡
Control I	1.00		1.00	
Age ≥60 years, women (n=49 525)				
Migraine	1.28 (1.08 to 1.52)	0.004‡	1.25 (1.06 to 1.49)	0.009‡
Control I	1.00		1.00	
Low income (n=78 125)				
Migraine	1.39 (1.22 to 1.58)	<0.001‡	1.35 (1.19 to 1.53)	<0.001‡
Control I	1.00		1.00	
High income (n=79 820)				
Migraine	1.63 (1.43 to 1.85)	<0.001‡	1.58 (1.39 to 1.80)	<0.001‡
Control I	1.00		1.00	
Urban (n=61 125)				
Migraine	1.53 (1.31 to 1.78)	<0.001‡	1.47 (1.27 to 1.72)	<0.001‡
Control I	1.00		1.00	
Rural (n=96 820)				
Migraine	1.49 (1.33 to 1.67)	<0.001‡	1.45 (1.29 to 1.62)	<0.001‡
Control I	1.00		1.00	

*Stratified model for age, sex, income and region of residence.
†Adjusted model for autoimmune disease, Charlson Comorbidity Index (except rheumatoid diseases), obesity (body mas index), smoking and alcohol intake histories.
‡Cox-proportional hazard regression model, significance at p<0.05.

cohort 2, the mean ages were 58.3 (SD=9.1) years in the RA group and 58.2 (SD=9.2) years in the control II group.

This national cohort study is the first to show a bidirectional association between migraine and RA. Owing to the availability of a large cohort, we were able to include a randomly selected control group that was matched for age, sex, income and region of residence. As these health claim data from the Korean NHIS are affected by access to medical care, which in turn is affected by socioeconomic status, it is important to match participants based on socioeconomic factors such as income and region of residence. We adjusted for CCI scores, which are based on age and comorbidities, by surveying the medical records; the CCI is used to predict 1-year mortality in internal medicine patients.[30] In addition to the CCI scores, BMI, smoking, alcohol consumption and autoimmune disease history, which are factors that could affect the relationship between migraine and RA, were used for adjustment. Unlike in a previous study,[9] migraines were subcategorised according to the presence or absence of an aura in our study.

Migraine and RA were diagnosed by physicians two or more times in our study. Migraine was classified according to the presence or absence of an aura based on the ICD-10 codes (G43, G431). Unlike in previous studies that used questionnaires, in which the prevalence of migraine could have been affected by recall bias,[27] our study used relatively accurate inclusion criteria. To increase the accuracy of the diagnosis of RA, prescriptions for a biologic agent or any DMARD were used as a criterion. Because

Table 4 Crude and adjusted HRs (95% CI) of rheumatoid arthritis (independent variable) for migraine (dependent variable) according to age, sex, income and region of residence (cohort 2)

	HRs for migraine			
Characteristics	Crude*	P value	Adjusted*†	P value
Total participants (n=46 435)				
RA	1.39 (1.26 to 1.52)	<0.001‡	1.35 (1.23 to 1.49)	<0.001‡
Control II	1.00		1.00	
Age <60 years old, men (n=7015)				
RA	1.98 (1.39 to 2.80)	<0.001‡	1.87 (1.32 to 2.66)	0.001‡
Control II	1.00		1.00	
Age <60 years old, women (n=20 185)				
RA	1.44 (1.27 to 1.64)	<0.001‡	1.40 (1.23 to 1.59)	<0.001‡
Control II	1.00		1.00	
Age ≥60 years, men (n=6110)				
RA	1.19 (0.84 to 1.70)	0.328	1.16 (0.81 to 1.65)	0.418
Control II	1.00		1.00	
Age ≥60 years, women (n=13 125)				
RA	1.26 (1.07 to 1.48)	0.006‡	1.24 (1.05 to 1.46)	0.012‡
Control II	1.00		1.00	
Low income (n=21 920)				
RA	1.41 (1.24 to 1.61)	<0.001‡	1.38 (1.21 to 1.57)	<0.001‡
Control II	1.00		1.00	
High income (n=24 515)				
RA	1.36 (1.19 to 1.56)	<0.001‡	1.33 (1.16 to 1.53)	<0.001‡
Control II	1.00		1.00	
Urban (n=18 690)				
RA	1.36 (1.17 to 1.58)	<0.001‡	1.32 (1.13 to 1.54)	<0.001‡
Control II	1.00		1.00	
Rural (n=27 745)				
RA	1.41 (1.25 to 1.58)	<0.001‡	1.38 (1.22 to 1.55)	<0.001‡
Control II	1.00		1.00	

*Stratified model for age, sex, income and region of residence.
†Adjusted model for autoimmune disease, Charlson Comorbidity Index (except rheumatoid diseases), obesity (body mass index), smoking and alcohol intake histories.
‡Cox-proportional hazard regression model, significance at p<0.05.
RA, rheumatoid arthritis.

prevalence varies by ethnicity and residential area, there may be differences in prevalence among studies.

The possible shared pathophysiological mechanisms between migraine and RA are still unclear. With the development of migraine pathophysiology, migraine is not just vascular headache, but is recognised as complex and various neurological dysfunctions.[3] The pathophysiological theory of migraine moved from vascular theory based on mechanistic models to neuroinflammation theory, specific molecules (such as CGRP and pituitary adenylate cyclase-activating peptide) and proinflammatory substances.[12] Hormonal and neurological changes trigger migraine symptoms by inducing vasodilation, the release of vascular factors, including growth factors, cytokines, nitric oxide, norepinephrine and CGRPs and interactions with endothelial cells. Vascular endothelial cells may contribute to migraine.[13]

RA is a systemic inflammatory disease. In RA patients, this inflammatory response is not confined to the synovial space and extends to systemic reactions, including endothelial dysfunction.[14] Metabolic abnormalities and changes in intracellular levels of certain metabolites are linked with the inflammatory phenotype of immune cells associated with autoimmune diseases such as RA.[14] Several immune pathways highly associated with endothelial progenitor cell (EPC) dysfunction, such as type I Interferon (IFN), Tumour necrosis factor (TNFα), Vascular endothelial growth factor (VEGF)/VEGF

receptor and neutrophil-activating cytokines, are known to affect systemic conditions such as RA. The role of EPCs as mediators of crosstalk between vascular repair and immunity and the regulation of EPC levels and functions by inflammatory cytokines in systemic diseases are important.[15] We hypothesised that the common pathophysiologic mechanism of inflammation, vascular endothelial cells and the immune system between migraine and RA could contribute to the bidirectional association between migraine and RA.

Comorbidities in patients with migraine and RA include depression, obesity and sleep disturbances. In particular, depression is a comorbidity that is common between migraine and RA.[19 31] Cortical spreading depression in patients with migraine affects cortical neuron sensitivity and releases substances that stimulate meningeal vessels, causing the dilatation and inflammation of blood vessels known as sterile neurogenic inflammation. Impaired serotonin metabolism in migraineurs plays a major role in the pathophysiology of depression.[32–34] Many studies have also found an association between RA and depression.[35 36] Peripheral inflammation associated with RA is usually associated with neural inflammation in the brain in patients with depression.[37 38] Biological factors, including inflammatory pathways, appear to be important in the pathophysiology of the bidirectional association between depression and RA.[39 40] Serotonin has been shown to be associated with the pathogenesis of RA.[41]

Obesity and sleep disturbance are also comorbidities between migraine and RA. Adipose tissue is considered a neuroendocrine organ that participates in multiple pathophysiological immune and inflammatory processes, including those underlying the development of migraine.[42] A recent systemic review and meta-analysis showed that the risk of migraine is elevated in obese persons.[43] According to a study in Israel, obesity is significantly independently associated with RA. The mechanisms by which obesity may lead to RA are still being studied, but several potential mechanisms include chronic inflammation, vitamin D deficiency in patients with autoimmune diseases and sex hormones.[44]

The relationship between migraines and sleep is reciprocal. Sleep disturbances are important risk factors for migraine, and migraine interferes with the quality of sleep.

A study found an elevated risk of severe sleep disturbances in patients with migraine (OR 5.4, 95% CI=2 to 15.5).[45] Sleep disturbances are common in patients with RA. Patients with RA suffer from a variety of symptoms, including joint pain, that lead to a poor quality of life, and that pain is closely related to sleep disturbances.[46]

Some limitations of this study should be considered. In all participants, the adjusted HR for RA was 1.46 (95% CI=1.33 to 1.60, p<0.001), whereas the adjusted HR for RA in the migraine with aura group was not significant. Moreover, in a previous study, the multivariable-adjusted HR for RA in the migraine group was 1.91 (95% CI=1.58 to 2.31),[9] which was lower than the HR in our study. Glucocorticoids are used in patients with severe migraine, and they may have affected the prevalence of RA. Glucocorticoids are a DMARD that can lead to rapid symptom improvement and disease-modifying effects in patients with RA.[5] Glucocorticoids have been widely prescribed to patients with severe refractory, recurrent, and status migraine and to patients with RA.[47] The detailed history of medications used for migraine could not be considered in our study.

Structural issues, such as temporomandibular joint (TMJ) destruction and atlantoaxial instability, can trigger migraine attacks in RA patients. RA is a systemic inflammatory disease that affects the articular surfaces of the joints, including the TMJ. TMJ disorder typically includes bilateral pain, tenderness and swelling around the deep preauricular area.[48] RA patients also have upper cervical spine instability, which can include neck pain and occipital headache. RA alters the stability of the cervical spine through a combination of periarticular bone loss and juxta-articular bone erosions and osteoporosis due to inflammation of the synovial membrane.[49 50] The diagnosis of RA is subject to relatively strict diagnostic criteria, and the algorithm for identifying RA in the National Health Insurance Claims database has been validated in previous studies; however, the diagnosis of migraine tends to rely on symptoms. It is possible that the risk of migraine in RA was overestimated because some migraine mimics were misclassified as migraines.

We have included information on lifestyle factors that could influence the relationship between migraine and RA. However, other socioeconomic factors, such as occupation, physical inactivity, diet and nutrition, were not considered in this study. There were no missing data from diagnosed patients, but it should be taken into consideration that this study may not have included asymptomatic or untreated patients. There was also limited information on disease severity for migraine and RA. Considering the prevalence of migraine in Korea and the fact that new-onset migraine in the elderly population is rare, our study is limited by not including patients <40 years of age.

CONCLUSION

Two longitudinal follow-up studies using a Korean national cohort showed a bidirectional association between migraine and RA, in which migraine increases the risk of RA, and RA is also associated with an increased risk of migraine.

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