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Original Article

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Atopic Disorders and Their Risks of Migraine: A Nationwide Population-Based Cohort Study

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ABSTRACT

Purpose: Migraine is a relatively common neurologic disorder. A possible link between atopic disorders and migraine has been suggested. This study investigated atopic disorders and their risks of migraine in the Korean population.
Methods: From the Korean National Health Insurance Service database, patients aged ≥ 20 years who underwent health screening between January and December of 2009 were enrolled. To evaluate the risk of migraine, Cox proportional hazards regression analyses were performed.
Results: In multivariable analysis, the atopic dermatitis group (adjusted hazard ratio [aHR], 1.28; 95% confidence interval [CI], 1.23–1.33), asthma group (aHR, 1.32; 95% CI, 1.30–1.34) and allergic rhinitis group (aHR, 1.45; 95% CI, 1.44–1.46) had significantly increased risks of migraine compared to their respective control groups ($P < 0.001$). The patients with 1 (aHR, 1.43; 95% CI, 1.42–1.44), 2 (aHR, 1.50; 95% CI, 1.47–1.53), and 3 (aHR, 1.64; 95% CI, 1.43–1.88) atopic disorders had significantly increased risks of migraine compared to the control group ($P < 0.001$).
Conclusions: Our results demonstrate that patients with atopic disorders may have increased risk of migraine and that the larger the number of concomitant atopic disorders, the higher the risk of migraine.

Keywords: Epidemiology; atopic dermatitis; allergic rhinitis; asthma; migraine

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic inflammatory skin disorder that has complex pathogenesis including barrier dysfunction and immune dysregulation driven by interactions between genetic and environmental factors.[1] Recently, it has been suggested that AD is associated with various systemic diseases including atopic comorbidities.[2,3] The spectrum of atopic disorders includes AD, allergic rhinitis (AR), asthma, and eosinophilic esophagitis related to type 2-dominant immune response.[4]

Migraine is a common neurologic disorder that affects approximately 1 billion people worldwide.[5] It is characterized by severe episodic unilateral headache and can be

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Disclosure

There are no financial or other issues that might lead to conflict of interest.

accompanied by nausea, vomiting, photophobia, and phonophobia.[6] Although the pathogenesis of migraine is not clearly elucidated, it could be associated with the activation and sensitization of the trigeminovascular system, vasoactive peptides, and neurogenic inflammation.[5]

The possible link between atopic disorders and migraine has been suggested but controversial.[7,8] The similarities between the 2 disorders are that both have [common triggering factors such as food, exercise,] as well as [environmental factors, and common inflammatory environments.][7] Several case series studies on the relationship between the 2 diseases have been reported. Moreover, studies have reported improvement of migraine after immunotherapy in patients with atopic disorders.[8-10] Most of the previous studies were case series, and there was a limitation in that they were held in a hospital-based setting with a limited number of study participants.[11-13] Recently, large-scale and population-based studies have been published; however, most of them were limited to children or targeted only asthma or AR.[14-16]

In this study, we investigated the relationship between atopic disorders and risk of migraine in the Korean population using the National Health Insurance System (NHIS) claims database.

MATERIALS AND METHODS

Data source

The Korean NHIS database is managed by the Korean government and covers approximately 97% of the Korean population. Medical aid program covers the remaining 3% of the population with low income, which has been integrated into the NHIS database. The Korean population is encouraged to undergo a regular health check-up every 2 years, and their medical care needs are monitored throughout the life cycle. The health screening database of the Korean NHIS was used in this study. The NHIS data are based on the International Classification of Disease, Tenth Revision, Clinical Modification (ICD-10-CM) codes.

Study population

From the NHIS database, patients aged ≥ 20 years who underwent health screening from January and December of 2009 were included. In addition, patients diagnosed with migraine prior to enrollment were excluded. Finally, 3,607,599 subjects included in this study were at ≥ 20 years of age had visited a clinic or a hospital at least 3 times during the study period, and had ICD-10 diagnostic code for either AD (L20), AR (J301–304), or asthma (J45–46) (**Figure A**).[17] Subjects with AD (n = 13,900), asthma (n = 93,329) or AR (n = 463,510) and controls with none of the 3 atopic disorders (n = 3,092,798), controls without AD (n = 3,593,699), controls without asthma (n = 3,514,270), and controls without AR (n = 3,144,089) were analyzed (**Figure B**). The subjects were followed up from 2009 to 2019 to identify newly diagnosed migraine (G43).

Data and baseline comorbidities

Information on height (m), weight (kg), waist circumference (cm), systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, low-density lipoprotein, high-density lipoprotein, body mass index (BMI) (kg/m^2), smoking status (non-smoker, ex-smoker, or current smoker), alcohol consumption (non-drinker, mild drinker [< 30 g/day], or heavy drinker [≥ 30 g/day]), physical activity (yes/no), and socioeconomic status (dichotomized as ≤ 20% vs. > 20% of the median) were obtained from the NHIS health check-up data. Comorbid diseases including hypertension, dyslipidemia, diabetes mellitus were

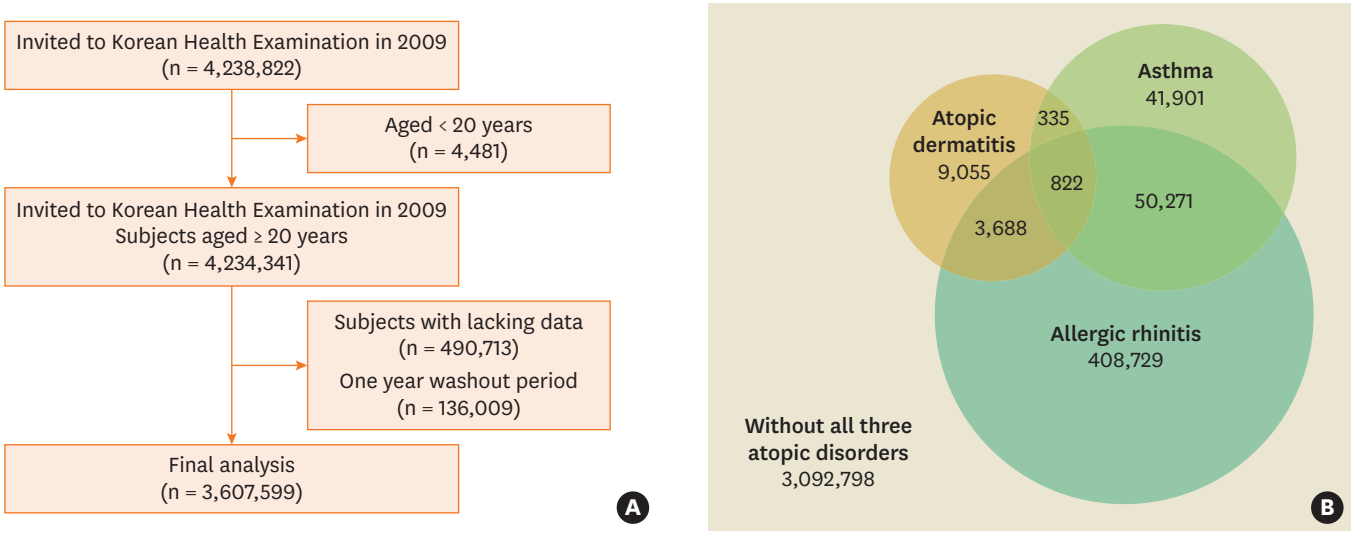

Figure. (A) Flowchart of enrolled subjects. (B) Distribution of the study population enrolled in the study.

defined based on both ICD-10 codes and prescribed medications, and myocardial infarction (MI), ischemic stroke, anxiety disorder, bipolar disorder and depression were defined based on ICD-10 codes during the study period.

Statistical analyses and ethics statement

The baseline demographic characteristics of the study population are described as numbers and percentages or as means ± standard deviations (SDs). Differences in clinical characteristics according to the presence of concurrent atopic disorders were analyzed using Student's *t*-test or χ^2 test. To evaluate the risk for migraine, Cox proportional hazards regression analyses were performed. Multivariable hazard ratio (HR) and 95% confidence interval (CI) were calculated to assess the risk of migraine after adjusting for confounding factors. Model 1 was not adjusted. Model 2 was adjusted for age and sex. Model 3 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, and dyslipidemia. Model 4 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, MI and ischemic stroke. Model 5 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, anxiety disorder, bipolar disorder and depression. Model 6 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, MI, ischemic stroke anxiety disorder, bipolar disorder and depression. Subgroup analyses were performed according to age and sex. Statistical analyses were performed using SAS software ver. 9.4 (SAS Institute, Cary, NC, USA). Two-sided $P < 0.05$ was considered to indicate statistical significance. This study was approved by the Ethics Committee of Seoul St. Mary's Hospital, The Catholic University of Korea (IRB No. KC21ZISI0784) and conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Baseline characteristics of the study population

Subjects with AD (n = 13,900), asthma (n = 93,329), or AR (n = 463,510), and controls with none of the 3 atopic disorders (n = 3,092,798), controls without AD (n = 3,593,699), controls

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without asthma (n = 3,514,270), and controls without AR (n = 3,144,089) were included and the baseline clinical characteristics are summarized in **Table 1**.

Table 1. Characteristics of the study population

Characteristics	Atopic dermatitis		Asthma		Allergic rhinitis		One or more atopic disorders	
	No (n = 3,593,699)	Yes (n = 13,900)	No (n = 3,514,270)	Yes (n = 93,329)	No (n = 3,144,089)	Yes (n = 463,510)	No (n = 3,092,798)	Yes (n = 514,801)
Age group (yr)								
20–29	469,110 (13.05)	2,136 (15.37)	467,702 (13.31)	3,544 (3.8)	428,854 (13.64)	42,392 (9.15)	426,005 (13.77)	45,241 (8.79)
30–39	721,950 (20.09)	2,246 (16.16)	715,569 (20.36)	8,627 (9.24)	641,454 (20.4)	82,742 (17.85)	637,098 (20.60)	87,098 (16.92)
40–49	950,159 (26.44)	2,662 (19.15)	936,587 (26.65)	16,234 (17.39)	834,193 (26.53)	118,628 (25.59)	826,472 (26.72)	126,349 (24.54)
50–59	741,520 (20.63)	2,746 (19.76)	723,942 (20.60)	20,324 (21.78)	642,813 (20.45)	101,453 (21.89)	632,269 (20.44)	111,997 (21.76)
60–60	463,126 (12.89)	2,427 (17.46)	441,809 (12.57)	23,744 (25.44)	389,684 (12.39)	75,869 (16.37)	376,572 (12.18)	88,981 (17.28)
≥ 70	247,834 (6.90)	1,683 (12.11)	228,661 (6.51)	20,856 (22.35)	207,091 (6.59)	42,426 (9.15)	194,382 (6.28)	55,135 (10.71)
Sex								
Male	2,080,158 (57.88)	7,246 (52.13)	2,044,787 (58.19)	42,617 (45.66)	1,868,233 (59.42)	219,171 (47.29)	1,843,330 (59.60)	244,074 (47.41)
Female	1,513,541 (42.12)	6,654 (47.87)	1,469,483 (41.81)	50,712 (54.34)	1,275,856 (40.58)	244,339 (52.71)	1,249,468 (40.40)	270,727 (52.59)
Smoking								
Non	2,059,360 (57.30)	8,542 (61.45)	2,005,490 (57.07)	62,412 (66.87)	1,762,109 (56.05)	305,793 (65.97)	1,729,053 (55.91)	338,849 (65.82)
Ex	535,803 (14.91)	2,201 (15.83)	523,606 (14.90)	14,398 (15.43)	465,456 (14.80)	72,548 (15.65)	457,678 (14.80)	80,326 (15.60)
Current	998,536 (27.79)	3,157 (22.71)	985,174 (28.03)	16,519 (17.70)	916,524 (29.15)	85,169 (18.37)	906,067 (29.30)	95,626 (18.58)
Drinker								
Non	1,780,130 (49.53)	7,920 (56.98)	1,726,048 (49.12)	62,002 (66.43)	1,521,279 (48.39)	266,771 (57.55)	1,487,913 (48.11)	300,137 (58.30)
Mild	1,512,417 (42.09)	5,132 (36.92)	1,491,070 (42.43)	26,479 (28.37)	1,347,608 (42.86)	169,941 (36.66)	1,332,736 (43.09)	184,813 (35.90)
Heavy	301,152 (8.38)	848 (6.10)	297,152 (8.46)	4,848 (5.19)	275,202 (8.75)	26,798 (5.78)	272,149 (8.80)	29,851 (5.80)
Exercise	653,557 (18.19)	2,597 (18.68)	638,804 (18.18)	17,350 (18.59)	566,712 (18.02)	89,442 (19.30)	557,562 (18.03)	98,592 (19.15)
BMI (kg/m^2)								
< 18.5	134,279 (3.74)	548 (3.94)	131,395 (3.74)	3,432 (3.68)	118,292 (3.76)	16,535 (3.57)	116,183 (3.76)	18,644 (3.62)
< 23	1,403,983 (39.07)	5,455 (39.24)	1,377,866 (39.21)	31,572 (33.83)	1,232,384 (39.20)	177,054 (38.20)	1,214,618 (39.27)	194,820 (37.84)
< 25	884,770 (24.62)	3,330 (23.96)	865,206 (24.62)	22,894 (24.53)	771,881 (24.55)	116,219 (25.07)	759,651 (24.56)	128,449 (24.95)
< 30	1,043,730 (29.04)	4,077 (29.33)	1,017,067 (28.94)	30,740 (32.94)	910,762 (28.97)	137,045 (29.57)	894,176 (28.91)	153,631 (29.84)
≥ 30	126,937 (3.53)	490 (3.53)	122,736 (3.49)	4,691 (5.03)	110,770 (3.52)	16,657 (3.59)	108,170 (3.50)	19,257 (3.74)
Diabetes	232,473 (6.47)	1,086 (7.81)	224,790 (6.40)	8,769 (9.40)	202,353 (6.44)	31,206 (6.73)	197,256 (6.38)	36,303 (7.05)
Hypertension	561,854 (15.63)	2,325 (16.73)	544,239 (15.49)	19,940 (21.37)	491,570 (15.63)	72,609 (15.67)	480,211 (15.53)	83,968 (16.31)
Dyslipidemia	456,536 (12.70)	2,060 (14.82)	443,463 (12.62)	15,133 (16.21)	395,164 (12.57)	63,432 (13.69)	386,906 (12.51)	71,690 (13.93)
MI	14,519 (0.40)	109 (0.78)	13,604 (0.39)	1,024 (1.10)	12,085 (0.38)	2,543 (0.55)	11,515 (0.37)	3,113 (0.60)
Stroke	50,924 (1.42)	372 (2.68)	47,921 (1.36)	3,375 (3.62)	42,315 (1.35)	8,981 (1.94)	40,379 (1.31)	10,917 (2.12)
Anxiety	196,179 (5.46)	1,359 (9.78)	184,286 (5.24)	13,252 (14.20)	151,824 (4.83)	45,714 (9.86)	145,376 (4.70)	52,162 (10.13)
Bipolar disorder	5,533 (0.15)	36 (0.26)	5,310 (0.15)	259 (0.28)	4,673 (0.15)	896 (0.19)	4,520 (0.15)	1,049 (0.20)
Depression	94,862 (2.64)	702 (5.05)	89,292 (2.54)	6,272 (6.72)	74,797 (2.38)	20,767 (4.48)	71,707 (2.32)	23,857 (4.63)
Age (yr)	46.50 ± 14.02	48.88 ± 15.96	46.23 ± 13.91	56.87 ± 14.33	46.15 ± 13.98	48.94 ± 14.11	45.96 ± 13.88	49.78 ± 14.43
BMI (kg/m^2)	23.70 ± 3.48	23.67 ± 3.28	23.69 ± 3.48	24.12 ± 3.43	23.69 ± 3.51	23.76 ± 3.22	23.68 ± 3.51	23.79 ± 3.25
WC (cm)	80.30 ± 9.48	80.43 ± 9.53	80.25 ± 9.46	82.21 ± 9.90	80.30 ± 9.46	80.25 ± 9.55	80.27 ± 9.45	80.46 ± 9.62
SBP (mmHg)	122.43 ± 15.00	122.55 ± 15.22	122.37 ± 14.98	124.83 ± 15.78	122.50 ± 15.00	121.96 ± 14.98	122.46 ± 14.98	122.30 ± 15.12
DBP (mmHg)	76.34 ± 10.05	76.10 ± 9.98	76.32 ± 10.05	76.91 ± 10.10	76.41 ± 10.07	75.83 ± 9.95	76.40 ± 10.07	75.96 ± 9.97
FPG (mg/dL)	97.26 ± 24.08	97.41 ± 24.55	97.19 ± 24.05	99.83 ± 25.17	97.27 ± 24.25	97.24 ± 22.95	97.22 ± 24.22	97.54 ± 23.27
TC (mg/dL)	194.90 ± 41.37	195.53 ± 43.20	194.83 ± 41.30	197.62 ± 43.96	194.84 ± 41.30	195.29 ± 41.83	194.80 ± 41.26	195.47 ± 42.01
HDL (mg/dL)	56.37 ± 32.68	57.50 ± 35.44	56.37 ± 32.53	56.78 ± 38.28	56.36 ± 32.00	56.48 ± 37.00	56.35 ± 31.91	56.52 ± 36.99
LDL (mg/dL)	121.03 ± 217.52	123.54 ± 262.05	121.10 ± 219.77	118.79 ± 115.77	121.32 ± 224.42	119.18 ± 165.14	121.33 ± 225.22	119.28 ± 165.54
TG* (mg/dL)	112.73 (112.67–112.8)	112.40 (111.33–113.47)	112.65 (112.58–112.72)	116.06 (115.65–116.46)	113.02 (112.94–113.09)	110.83 (110.65–111.01)	112.96 (112.89–113.03)	111.39 (111.22–111.56)

Values are presented as number (%) or mean ± standard deviation.
BMI, body mass index; MI, myocardial infarction; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides
*Data were log-transformed before analysis.

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Risk of migraine in patients with atopic disorders

Table 2 shows the incidence rates of migraine and the risk of migraine in the presence of atopic disorders. The incidence rates of migraine per 1,000 person-years were 23.06 and 16.49 in the AD group vs control group without AD, 27.12 and 16.25 in the asthma group vs control group without asthma, and 25.23 and 15.29 in the AR group vs control group without AR.

In multivariable Cox proportional hazards regression analyses after adjusting for age, sex, smoking, drinking, physical activity, hypertension, diabetes, and dyslipidemia (model 3), the AD group (HR, 1.32; 95% CI, 1.27–1.38), asthma group (HR, 1.39; 95% CI, 1.37–1.41) and AR group (HR, 1.50; 95% CI, 1.48–1.51) showed a significantly increased risk of migraine compared to their respective control groups ($P < 0.001$). In model 4 which was additionally adjusted for MI and ischemic stroke, the results were similar to those of model 3. After additionally adjusting for mental disorders in model 6, the risk of migraine was slightly lower than in models 3 and 4, but significantly higher than in the AD group (HR, 1.28; 95% CI, 1.23–1.33), asthma group (HR, 1.32; 95% CI, 1.30–1.34) and AR group (HR, 1.45; 95% CI, 1.44–1.46) compared to their respective control group ($P < 0.001$).

Risk of migraine according to concurrent atopic disorders

Tables 3 and **4** show the risk of migraine in the presence of concurrent atopic disorders. In multivariable Cox proportional hazards regression analyses (model 4), the aHRs of migraine in the presence of 1, 2, and 3 atopic disorders were 1.48 (95% CI, 1.46–1.49), 1.58 (95% CI, 1.56–1.61), and 1.79 (95% CI, 1.56–2.06), respectively ($P < 0.001$) (**Table 3**). In model 6, the aHRs were 1.43 (95% CI, 1.42–1.44), 1.50 (95% CI, 1.47–1.53), and 1.64 (95% CI, 1.43–1.88), respectively ($P < 0.001$). Among them, the risk of migraine was the highest in patients with both AD and asthma (model 6: aHR, 1.79; 95% CI, 1.45–2.22) ($P < 0.001$) (**Table 4**).

Risk of migraine in subgroups by age and sex

As a result of analyzing the age subgroups according to atopic disorders, the risk of migraine was the highest in patients in their 30s and 40s in those with asthma, AR, and 1 or more atopic disorders (**Supplementary Table S1**). In the AD group, the risk was the highest in those in their 30s, but there was no statistical significance. Subgroup analysis by sex revealed a significantly higher risk of migraine in men for all 3 atopic disorders (**Supplementary Table S2**).

Follow-up duration until the diagnosis of migraine in patients with atopic disorders

As a result of analyzing the migraine onset time difference in patients with atopic disorders, mean duration (mean ± SD) was 8.14 ± 2.54 in patients with 1 or more atopic disorders, and the asthma group showed the shortest onset duration (7.83 ± 2.78) (**Supplementary Table S3**). The mean onset duration were 8.18 ± 2.51, 7.88 ± 2.75, and 7.72 ± 2.78, respectively compared to controls in the presence of 1, 2, and 3 atopic disorders.

DISCUSSION

In this nationwide population-based cohort study, we found significantly increased risk of migraine among adult patients with AD, asthma, or AR compared to their respective control group. The risk of migraine was significantly increased in patients with a larger number of concurrent atopic disorders. Notably, patients with concurrent AD and asthma showed the highest risk compared to controls without any atopic disorder. In this study, various

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Table 2. Risks and incidence rates of migraine in patients with atopic disorders

Characteristics	Number	Migraine	Person-years	IR	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Atopic dermatitis										
No	3,593,699	505,738	30,673,370	16.49	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	13,900	2,625	113,815	23.06	1.40 (1.35–1.46)	1.32 (1.28–1.38)	1.32 (1.27–1.38)	1.32 (1.27–1.37)	1.28 (1.23–1.33)	1.28 (1.23–1.33)
Asthma										
No	3,514,270	488,551	30,056,578	16.25	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	93,329	19,812	730,607	27.12	1.67 (1.65–1.693)	1.39 (1.37–1.41)	1.39 (1.37–1.41)	1.38 (1.36–1.40)	1.32 (1.30–1.34)	1.32 (1.30–1.34)
Allergic rhinitis										
No	3,144,089	412,756	26,998,339	15.29	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	463,510	95,607	3,788,846	25.23	1.65 (1.64–1.66)	1.50 (1.49–1.51)	1.50 (1.48–1.51)	1.49 (1.48–1.50)	1.45 (1.44–1.46)	1.45 (1.44–1.46)
One or more atopic disorders										
No	3,092,798	402,939	26,594,549	15.15	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Yes	514,801	105,424	4,192,636	25.15	1.66 (1.65–1.67)	1.49 (1.48–1.50)	1.49 (1.48–1.50)	1.49 (1.48–1.50)	1.44 (1.43–1.45)	1.44 (1.43–1.45)

Model 1 was not adjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, and dyslipidemia.
Model 4 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction and stroke.
Model 5 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, anxiety disorder, bipolar disorder and depression.
Model 6 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, stroke, anxiety disorder, bipolar disorder and depression.
IR, incidence rate (per 1,000 person-years).

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Table 3. Risks and incidence rates of migraine according to concurrent atopic disorders

No. of atopic disorders*	Number	Migraine	Person-years	IR	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
0	3,092,798	402,939	26,594,549	15.15	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
1	459,685	93,007	3,758,349	24.75	1.63 (1.62–1.65)	1.48 (1.47–1.49)	1.48 (1.47–1.49)	1.48 (1.46–1.49)	1.43 (1.42–1.44)	1.43 (1.42–1.44)
2	54,294	12,214	427,942	28.54	1.89 (1.85–1.92)	1.59 (1.57–1.62)	1.59 (1.56–1.62)	1.58 (1.56–1.61)	1.50 (1.48–1.53)	1.50 (1.47–1.53)
3	822	203	6,345	31.99	2.12 (1.84–2.43)	1.81 (1.58–2.08)	1.80 (1.57–2.07)	1.79 (1.56–2.06)	1.65 (1.44–1.89)	1.64 (1.43–1.88)

Model 1 was not adjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, and dyslipidemia.
Model 4 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction and stroke.
Model 5 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, anxiety disorder, bipolar disorder and depression.
Model 6 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, stroke, anxiety disorder, bipolar disorder and depression.
IR, incidence rate (per 1,000 person-years).
*Number of atopic disorders per person.

Table 4. Risks and incidence rates of migraine according to combinations of atopic disorders

Atopic dermatitis	Asthma	Allergic rhinitis	Number	Migraine	Person-years	IR	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
No	No	No	3,092,798	402,939	26,594,549	15.15	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Yes	408,729	83,273	3,357,057	24.81	1.64 (1.63–1.65)	1.50 (1.49–1.51)	1.49 (1.48–1.51)	1.49 (1.48–1.50)	1.45 (1.44–1.46)	1.45 (1.44–1.46)
	Yes	No	41,901	8,228	325,747	25.26	1.67 (1.63–1.71)	1.36 (1.33–1.39)	1.36 (1.33–1.39)	1.35 (1.32–1.38)	1.30 (1.27–1.33)	1.30 (1.27–1.33)
		Yes	50,271	11,298	396,017	28.53	1.88 (1.85–1.92)	1.58 (1.55–1.61)	1.58 (1.55–1.61)	1.57 (1.55–1.60)	1.49 (1.47–1.52)	1.49 (1.46–1.52)
Yes	No	No	9,055	1,506	75,545	19.94	1.32 (1.25–1.39)	1.26 (1.19–1.32)	1.25 (1.19–1.32)	1.25 (1.19–1.32)	1.23 (1.17–1.29)	1.23 (1.17–1.29)
		Yes	3,688	833	29,427	28.31	1.87 (1.75–2.00)	1.70 (1.59–1.82)	1.69 (1.58–1.81)	1.69 (1.58–1.81)	1.61 (1.50–1.72)	1.60 (1.50–1.72)
	Yes	No	335	83	2,498	33.23	2.20 (1.77–2.73)	1.91 (1.54–2.36)	1.90 (1.53–2.36)	1.89 (1.53–2.35)	1.80 (1.45–2.23)	1.79 (1.45–2.22)
		Yes	822	203	6,345	31.99	2.12 (1.84–2.43)	1.81 (1.58–2.07)	1.80 (1.57–2.07)	1.79 (1.56–2.06)	1.65 (1.44–1.89)	1.64 (1.43–1.88)

Model 1 was not adjusted.
Model 2 was adjusted for age and sex.
Model 3 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, and dyslipidemia.
Model 4 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction and stroke.
Model 5 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, anxiety disorder, bipolar disorder and depression.
Model 6 was adjusted for age, sex, smoking status, alcohol consumption, physical activity, hypertension, diabetes mellitus, dyslipidemia, myocardial infarction, stroke, anxiety disorder, bipolar disorder and depression.
IR, incidence rate (per 1,000 person-years).

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lifestyle habits and comorbidities that could potentially be related to migraine development were adjusted as variable, and we observed that lifestyle habits (smoking status, alcohol consumption, physical activity) and mental disorder (anxiety disorder, bipolar disorder and depression) had a more significant effect on the risk of migraine.

Although there is ongoing debate about a possible link between atopic disorders and migraine, several studies have demonstrated an association between the 2.[7,18,19] Arguments about correlation between the 2 disorders began with a report that food allergy could trigger migraine.[20] Previous reports have shown that allergens are associated with migraine, and that symptoms of migraine improve after immunotherapy, food avoidance, or anti-allergic therapies in patients with both migraine and allergy.[8,9,20-22] There are also reports suggesting that patients with migraine have more personal or family history of atopic disorders, and that the incidence of migraine is increased in allergic patients.[12,13,23-25] However, most of the previous studies have limitations in that they are case reports, questionnaire studies, or single-institution studies, and that they included a limited number of study participants.[11,12,26] Recently, population-based studies have been performed to overcome these limitations whereas most of them have still targeted children and adolescents or have examined the correlation between migraine and atopic disorders other than AD.[15,27] Previous studies have evaluated the risk of migraine in children with atopic disorders, and the increased risk of migraines has been explained by several stimuli in the brain development process caused by allergic diseases.[27] However, in this study, we analyzed the risk of migraine in patients older than 20 years to determine the effect of atopic disorders on the risk of migraine in adults. This study is meaningful in that it is a large-scale, population-based study that analyzed the correlation between migraine and atopic disorders including AD in the adult population, which has not previously been conducted.

In a recent questionnaire study of an adult population, mild (adjusted relative risk ratio [aRRR], 1.50; 95% CI, 1.38–1.64) and severe migraine (aRRR, 1.80; 95% CI, 1.50–2.17) were associated with AD.[18] Previous epidemiological studies in children suggested that atopic disorders at a pediatric age can affect brain development and increase the risk of migraine.[15,27] A population-based study in Taiwan found higher association of migraine and AR (adjusted odds ratio [aOR], 2.17; 95% CI, 2.09–2.26), asthma (aOR, 1.76; 95% CI, 1.66–1.87), and AD (aOR, 1.74; 95% CI, 1.58–1.93) compared to controls in children aged 7 to 18 years.[27] According to a previous study, boys showed greater risk of migraine than girls.[27] Moreover, the risk of migraine increased with the number of concurrent atopic disorders, in consistent with our results.[27]

Although the exact mechanisms explaining the link between atopic disorders and migraine have not yet been elucidated, there is some evidence that the 2 diseases share a pathogenic process. First, the inflammatory environments in atopic disorders and migraine have similarities. Studies have suggested alteration in brain excitability, sensitization of the trigeminovascular system, dilatation of intracranial arteries, and sterile neuroinflammation as the main pathogenesis of migraine.[28,29] There is some evidence that calcitonin gene-related peptide (CGRP) which plays a critical role in the pathophysiology of migraine, induces Langerhans cell cytokine polarization favoring T helper 2 cell recruitment, up-regulation of interleukin 4, and mast cell degranulation, and CGRP is increased in AD lesions.[30-33] In addition, inflammatory mediators such as histamine, leukotrienes, and prostaglandins are elevated in migraine attack, which are also important immune modulators in atopic disorders.[15,27]

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Previous studies have shown that allergen triggered allergic responses release inflammatory mediators or elevate neuropeptide mediated by mast cells, inducing airway hypersensitivity in patients with asthma.[6] In migraine, mast cells in the dura matter may secrete pro-inflammatory and vasodilatory molecules, which could activate the trigeminal pain pathway underlying migraine pathogenesis.[7,14] Furthermore, parasympathetic hyperactivity is considered to be involved in both asthma and migraine.[6,24] Cholinergic stimulation could [trigger bronchospasm in asthma, and could activate trigeminal pain pathway] as well as [induce degranulation of meningeal mast cell in migraine.][6]

Nasal congestion, discharge and sneezing in AR require sensitive trigeminal transmission which is associated with migraine, and the inflammatory response that occurs in AR are suggested to be involved in migraine aggravation and development through activation of immune responses.[11]

Secondly, atopic disorders and migraine have several common risk factors and comorbidities, which can serve as a link between the 2 disorders. Atopic disorders are associated with mental health-related diseases such as depression, anxiety, attention deficit and hyperactivity disorder, and sleep disorder, which are suggested to have a bidirectional association with migraine.[34-42] Although the mechanism of these associations needs to be clarified, it can be explained by imbalance of the dopaminergic system and serotonin neurotransmitters, ovarian hormone fluctuation, altered autonomic regulation, and somatization.[42,43] A recent large genome-wide study has shown that migraine has a genetic correlation with psychiatric disorders, which suggests a common genetic basis or shared pathways between the 2.[42] Furthermore, interaction might be explained as a stressor that significantly increases the risk of each other, and stress as a trigger can induce migraine attacks, escalating in frequency and shortening the intervals of migraine.[44]

In subgroup analyses by age, no significant correlation was observed in patients with AD, whereas patients with asthma or AR showed the highest risk of migraine in those in their 30s and 40s. In subgroup analyses by sex, the risk of migraine was higher in both sexes with atopic disorders. However, the increased risk of migraine was higher in men than in women. Although this population-based study analyzed temporal associations between 2 disorders, whether sex and age affect the risk of migraine in patients with atopic disorders and the exact mechanisms need further research.

There are several limitations to this study. First, diagnosis of atopic disorders and migraine was made on the basis of NHIS claim data, without direct review of medical records. Secondly, some patients included in this study may have had migraine before enrollment at this study. In addition, since only patients who visited the hospital and were diagnosed were included in the study, patients who did not visit the hospital were not included, imparting possibility of selection bias. Thirdly, NHIS database records lack detailed information about family history, severity of diseases, presence of aura, and type of migraine.

Despite these limitations, the strengths of our study are its large sample size and nationally representative study population. The NHIS data used in this study are managed by the Korean government to provide public health information, indicating data stability. Furthermore, different from other studies, we controlled for confounding factors of BMI, smoking status, alcohol consumption status, physical activity level and various comorbidities which could affect the development of migraine.

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Taken together, our results demonstrated that patients with atopic disorders may have an increased risk of migraine, and that the larger the number of concomitant atopic disorders, the higher the risk of migraine.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Risk of migraine in atopic subgroups stratified according to age group

Click here to view

Supplementary Table S2

Risk of migraine in atopic subgroups stratified according to sex

Click here to view

Supplementary Table S3

Follow-up duration until the migraine onset in each patient with atopic disorders

Click here to view

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