



Allergic Conjunctivitis and the Associated Risk of Migraine Among Children: A Nationwide Population-based Cohort Study

I-Chung Wang MD, Jeng-Dau Tsai MD, Te-Chun Shen MD, Cheng-Li Lin MS, Tsai-Chung Li PhD & Chang-Ching Wei MD

To cite this article: I-Chung Wang MD, Jeng-Dau Tsai MD, Te-Chun Shen MD, Cheng-Li Lin MS, Tsai-Chung Li PhD & Chang-Ching Wei MD (2016): Allergic Conjunctivitis and the Associated Risk of Migraine Among Children: A Nationwide Population-based Cohort Study, Ocular Immunology and Inflammation, DOI: [10.1080/09273948.2016.1178303](https://doi.org/10.1080/09273948.2016.1178303)

To link to this article: <http://dx.doi.org/10.1080/09273948.2016.1178303>



Published online: 06 Jul 2016.



Submit your article to this journal [↗](#)



Article views: 11



View related articles [↗](#)



View Crossmark data [↗](#)

ORIGINAL ARTICLE

Allergic Conjunctivitis and the Associated Risk of Migraine Among Children: A Nationwide Population-based Cohort Study

I-Chung Wang, MD¹, Jeng-Dau Tsai, MD^{2,3}, Te-Chun Shen, MD^{4,5}, Cheng-Li Lin, MS^{6,7}, Tsai-Chung Li, PhD⁷, and Chang-Ching Wei, MD^{1,5}

¹Children's Hospital of China Medical University Hospital, Taichung, Taiwan, ²Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan, ³Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan, ⁴Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, ⁵School of Medicine, China Medical University, Taichung, Taiwan, ⁶Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, and ⁷Institute of Biostatistics, China Medical University, Taichung, Taiwan

ABSTRACT

Purpose: To investigate the risk of migraine in children with allergic conjunctivitis (AC).

Methods: In this population-based cohort study, 309 138 children with AC and 309 138 non-AC controls were included between 2000 and 2007. By 2008 end, the incidences of migraine in both cohorts, and the AC-to-non-AC cohort hazard ratios (HRs) were measured.

Results: The incidence of migraine during the study period was 1.92-fold higher in the AC cohort than in the non-AC cohort. The risk was greater for boys with AC and children aged <6 years. The mean time-interval between physician-diagnosed AC to physician-diagnosed migraine was 3.67 years (SD = 2.19). The risk of migraine development in the AC cohort increased with follow-up time and was highest during 4–5 years after AC diagnosis. The children with AC more likely had migraine without than with aura.

Conclusions: Children with AC had a higher incidence and subsequent risk of migraine.

Keywords: Allergic conjunctivitis, children, cohort study, migraine

Allergic conjunctivitis (AC) is a group of common diseases that affects the ocular surface and is usually associated with type 1 hypersensitivity reactions. Previous population studies estimate a prevalence of childhood AC of 15–40%.¹ Most atopic children with AC also have other allergic diseases, such as allergic rhinitis and asthma. The ocular symptoms of AC may also affect the clinical burden of comorbid allergic diseases.^{2,3}

Migraine is a common, multifactorial, recurrent neurovascular headache in children. It is characterized by severe headache, nausea, vomiting, photophobia, and lacrimation. Visual aura is the most common aura, which precedes migraine headache.⁴ Migraine headache greatly affects children's quality of life in many aspects, in terms of missing school, learning

disabilities, decreased home and family interactions, and decreased socialization with peers.^{5,6} Moreover, migraine headache may persist into adulthood.⁷

The ocular autonomic symptoms of migraine, such as lacrimation, conjunctival injection, eyelid edema, and soreness, are similar to the symptoms of AC.¹ Although the possible link between migraine and allergic diseases has been extensively studied for more than a century, most of the studies were hospital-based, with limited numbers of cases, and mainly focused on adulthood migraine and failed to demonstrate a causal relationship between migraine and allergy.⁸ In addition, studies that addressed childhood AC and subsequent migraine risks were limited.⁸ Recently, immunologic evidence supports the association between allergy and migraine.

Received 21 September 2015; revised 14 January 2016; accepted 11 April 2016; published online 6 July 2016

Correspondence: Chang-Ching Wei Children's Hospital of China Medical University Hospital, School of Medicine, China Medical University, No 2, Yu-Der Road, Taichung 40402, Taiwan. E-mail: weilonger@gmail.com

Investigators found elevated allergy-related pro-inflammatory mediators, such as histamine, prostaglandin F_{2a}, and cysteinyl leukotrienes during episodes of migraine headache.^{9–13} Despite historical interest, no large-population human epidemiologic study has investigated the association between AC and the subsequent risk of migraine in children. Identification of the trigger factors of migraine will improve the understanding of the mechanisms by which migraine evolves and is useful in the development of effective treatments of migraine and prevention of migraine-associated disabilities and healthcare burdens. Therefore, we conducted a nationwide population-based cohort study to investigate the development of migraine in children diagnosed with AC. We hypothesized that children with AC would increase the future risk of migraine.

MATERIALS AND METHODS

Data Sources

In this population-based cohort study, data were obtained from reimbursement claims in the universal National Health Insurance Research Database (NHIRD). These claims data are available from Taiwan's National Health Insurance, which is a government-run, single-payer, modest cost-sharing program that covers almost all citizens and contracts with all hospitals in Taiwan.^{14,15} We used a dataset consisting of a randomly selected sample of half of all insured children in Taiwan.^{16–20} Because of personal electronic data privacy regulations, the insureds' records are encrypted before being released to researchers; thus, informed consent was not required in this study. Although the identification information was scrambled, this study also received approval from the institutional review board of China Medical University Hospital (CMUH104-REC2-115). The *International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)* was used for diagnosis.

Study Design and Subjects

We identified patients aged <18 years with newly diagnosed AC between 2000 and 2007 as the AC cohort. To improve diagnostic reliability and avoid overestimation of incidence, AC was defined as the presence of at least three records with ICD-9-CM codes 372.05, 372.10, and 372.14 in any diagnosis field of inpatient claims or ambulatory claims. The date of AC diagnosis was considered the baseline. In this study, we used the method of 1:1 matching to screen the control subjects in order to control the potential confounders. Hence, we randomly selected one non-AC child for each AC child by using frequency matching by sex, age (in 1-year intervals), urbanization of residential area, and baseline year.

Migraine was defined as at least two records with ICD-9-CM code 364 in any diagnosis field of inpatient or ambulatory claims. In Taiwan, the diagnostic criteria of migraine is established and based on the diagnostic criteria of *The International Classification of Headache Disorders*, 2nd edition (ICDH-II). Therefore, the diagnoses of migraine should be correct and reliable.²¹ Subjects with a history of migraine before baseline or those lacking information on age, sex, or urbanization of residence area were excluded. The comorbidities of AC and migraine were identified and defined according to the ICD-9-CM code, including allergic rhinitis (477); asthma (493); chronic sinusitis (473); obstructive sleep apnea (327.23); anxiety (300); depression (311); obesity (278); and hypertension (401–405).²² From the claim data and ICD-9-CM code, we have identified unspecified headache (784.0); migraine (346.0–346.9); tension headache (307.81 and 339.1); and cluster headache (339.0) from both AC and non-AC groups. All of the subjects were followed up until migraine diagnosis, death, loss to follow-up, withdrawal from the insurance system, or the end of 2008. A flowchart of study participant selection is listed in Figure 1.

Statistical Analysis

In this cohort study, we used person-years as the denominator for estimating the incidence rate considered for individual follow-up duration in the study. The date of diagnosis of AC was used as the index date to initiate follow-up person-years measurement. The follow-up person-years were measured for each child from the index date to the date the children were diagnosed with migraine, or were censored because of loss to follow-up, death, or withdrawal from the insurance system, or at the end of 2008. Follow-up person-years were used to estimate the incidence density rates (IR) and hazard ratios (HRs) of migraine for the AC cohort, which were compared with those of the non-AC cohort, based on age, sex, and urbanization. HR was determined by using the Cox proportional hazard regression model. The Cox model was also used to estimate the HR of migraine associated with the annual mean medical visits for AC. Furthermore, we analyzed if the association varied with the length of the follow-up period after AC diagnosis. A Kaplan–Meier plot showed the probability of migraine-free survival, and a log-rank test was used to test the difference between the AC and non-AC cohorts. We performed all data analyses by using SAS statistical software, version 9.2, for Windows (SAS Institute Inc., Cary, NC). Kaplan–Meier survival curves were plotted by using R software, version 2.14.1 (R Development Core Team, Vienna, Austria). A 2-sided *p* value of <0.05 was considered statistically significant.

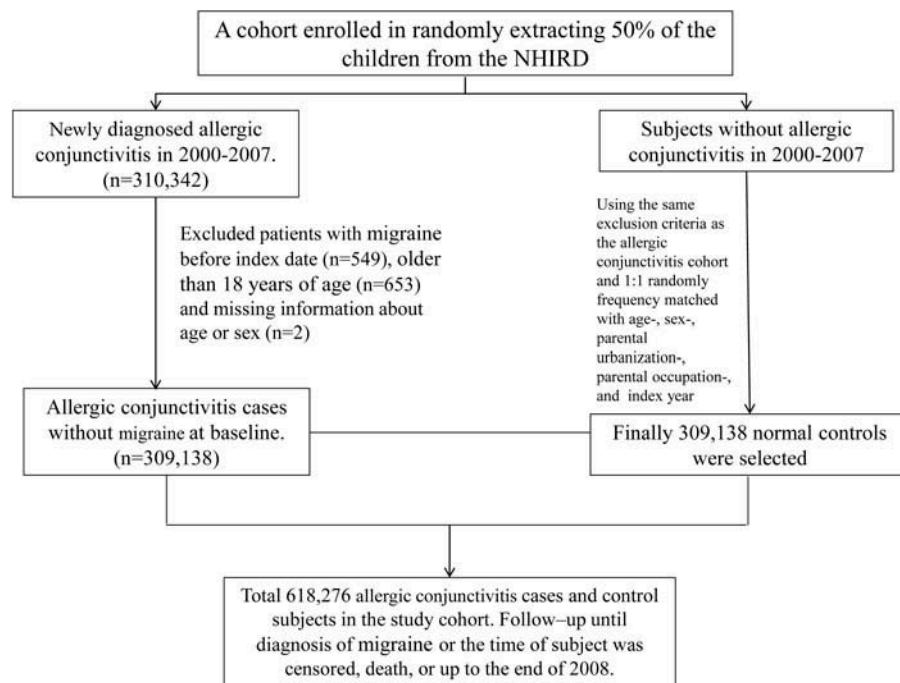


FIGURE 1. Flowchart of study participant selection. NHIRD, National Health Insurance Research Database.

RESULTS

In this study, 309 138 subjects in the AC cohort and 309 138 in the non-AC cohort were enrolled (Table 1). Most (81.1%) of the subjects were aged <12 years. The AC cohort had more boys (53%) and were residents of highly urbanized areas (67.6%). The incidence rates of most of the following comorbidities were significantly higher in the AC group than in the non-AC group, except for obstructive sleep apnea: allergic rhinitis (28.2% vs. 1.35%, $p<0.001$); asthma (14.8% vs. 8.42%, $p<0.001$); chronic rhinosinusitis (3.70% vs. 1.86%, $p<0.001$); anxiety (0.18% vs. 0.12%, $p<0.001$); depression (0.05% vs. 0.03%, $p<0.001$); obesity (0.15% vs. 0.10%, $p<0.001$); and hypertension (0.06% vs. 0.03%, $p<0.001$), respectively (Table 1). AC children have a higher occurrence rate of unspecified headache (12.5% vs. 8.89%, $p<0.001$), migraine (0.59% vs. 0.28%, $p<0.001$), and tension headache (0.32% vs. 0.18%, $p<0.001$) compared with non-AC children (Table 1). Figure 2 illustrates the migraine-free survival rate of the AC cohort in comparison with that of the non-AC cohort. The mean (SD) follow-up period was 5.88 (2.12) years in the AC cohort and 5.82 (2.15) years in the non-AC cohort. The migraine-free survival rate was significantly lower in the AC cohort than in the non-AC cohort (Figure 1; log-rank test, $p<0.001$). The mean time-interval between physician-diagnosed AC to physician-diagnosed migraine was 4.32 (SD = 2.59), 3.83 (SD = 2.12), 2.06 (SD = 1.41) years for AC diagnosed age 11 years, respectively. The incidence of migraine was 1.92-fold higher in the AC cohort than in the non-AC cohort (10.8 vs. 5.23 per 10 000 person-years; Table 2). An age-specific

analysis showed that the incidence of migraine significantly increased with age in both cohorts. The adjusted HR for migraine decreased from 2.29 (95% confidence interval, CI: 1.94–2.70) for subjects aged <6 years to 1.77 (95% CI: 1.60–1.96) for those aged 6–11 years and to 1.98 (95% CI: 1.63–2.40) for those aged ≥12 years in the AC cohort in comparison with the non-AC cohort. A sex-specific analysis showed that the prevalence of migraine was approximately twofold higher in girls in both cohorts. By contrast, the adjusted HR (2.04; 95% CI: 1.80–2.31) for migraine was higher for the boys in the AC cohort than for the boys in the non-AC cohort. Urbanization level-specific analyses showed that the adjusted HR of migraine increased in the AC cohort but not in the non-AC cohort, regardless of living in areas of least urbanization. The age-specific analysis in Table 3 shows that the incidence rates of migraine in girls were 7.42, 14.3, and 32.5 per 10 000 person-years in the <6, 6–11, and ≥12-year age groups, respectively, and those in boys were 6.30, 10.1, and 15.9 per 10 000 person-years in the <6, 6–11, and ≥12-year age groups, respectively. The HR of migraine in the girls was 5.29 (95% CI: 4.39–6.37) in the ≥12-year age group when compared with the <6-year age group in girls and 2.99 (95% CI: 2.32–3.85) in boys. Table 4 shows the association between the frequency of medical visits per year for AC and the incidence of migraine. Compared with the non-AC cohort, the risk of migraine in the AC cohort increased from 1.17 (95% CI: 1.07–1.28) for those with ≤2 visits to 14.6 (95% CI: 13.1–16.3) for those with >4 visits (trend test, $p<0.0001$). This pattern of increased risks was similar for both sexes (Table 4). Table 5

TABLE 1. Demographics and comorbidities of headache between children with and without allergic conjunctivitis (AC).

	Non-AC (<i>n</i> = 309 138)		AC (<i>n</i> = 309 138)		<i>p</i> value ^a
	<i>n</i>	(%)	<i>n</i>	(%)	
Age, years, mean (SD) ^b	7.16	3.62	7.15	3.60	0.62
Stratified age					0.99
<6	125 221	40.5	125 221	40.5	
6–11	150 225	48.6	150 225	40.6	
≥12	33 692	10.9	33 692	10.9	
Sex					0.99
Girl	145 223	47.0	145 223	47.0	
Boy	163 915	53.0	163 915	53.0	
Urbanization ^c					0.99
1 (highest)	114 231	37.0	114 231	37.0	
2	94 458	30.6	94 458	30.6	
3	52 428	17.0	52 428	17.0	
4 (lowest)	48 021	15.5	48 021	15.5	
Comorbidity					
Allergic rhinitis	41 630	13.5	87 101	28.2	<0.001
Asthma	26 036	8.42	45 615	14.8	<0.001
Anxiety	386	0.12	568	0.18	<0.001
Depression	91	0.03	149	0.05	<0.001
Obesity	307	0.10	458	0.15	<0.001
Hypertension	82	0.03	188	0.06	<0.001
Chronic sinusitis	5752	1.86	11 449	3.70	<0.001
Obstructive sleep apnea	3	0.00	1	0.00	0.32
Headache					
Unspecified headache	27 477	8.89	38 618	12.5	<0.001
Migraine	878	0.28	1815	0.59	<0.001
Tension headache	557	0.18	978	0.32	<0.001
Cluster headache	0	0.00	0	0.00	

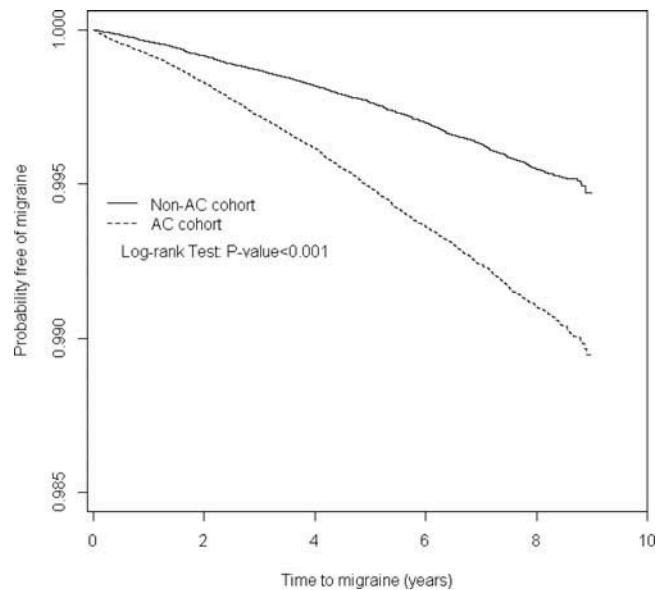
^a χ^2 -test.^b*t*-test.^cThe urbanization level was categorized by the population density of the residential area into four levels, with level 1 as the most urbanized and level 4 as the least urbanized.

FIGURE 2. The Kaplan–Meier analysis of probability free of migraine for allergic conjunctivitis (AC) cohort compared with non-AC cohort.

TABLE 2. Incidence rate and relative risk of migraine in children with allergic conjunctivitis (AC) compared with children without AC, stratified by demographics in Cox proportional hazard regression.

	Non-AC			AC			Adjusted HR ^a	95% CI
	Migraine case	Person-years	IR	Migraine case	Person-years	IR		
All	941	1 799 284	5.23	1961	1 818 708	10.8	1.92	1.77, 2.08 ^b
Stratified age								
<6	203	761 073	2.67	522	772 086	6.76	2.29	1.94, 2.70 ^b
6–11	582	913 444	6.37	1114	920 577	12.1	1.77	1.60, 1.96 ^b
≥12	156	124 767	12.5	325	126 045	25.8	1.98	1.63, 2.40 ^b
Sex								
Girl	564	827 013	6.82	1112	834 593	13.3	1.83	1.65, 2.03 ^b
Boy	377	972 270	3.88	849	984 114	8.63	2.04	1.80, 2.31 ^b
Urbanization								
1 (highest)	328	667 432	4.91	726	676 859	10.7	2.03	1.78, 2.32 ^b
2	305	552 611	5.52	586	558 216	10.5	1.74	1.51, 2.00 ^b
3	161	307 493	5.24	327	310 092	10.6	1.85	1.52, 2.24 ^b
4 (lowest)	147	271 747	5.41	322	273 541	11.8	2.12	1.74, 2.58 ^b
Allergic rhinitis								
No	790	1 581 729	4.99	1306	1 338 842	9.75	1.92	1.76, 2.10 ^b
Yes	151	217 555	6.94	655	479 865	13.7	1.92	1.61, 2.29 ^b
Asthma								
No	857	1 661 684	5.16	1628	1 562 427	10.4	1.92	1.76, 2.08 ^b
Yes	84	137 600	6.10	333	256 280	13.0	1.93	1.52, 2.46 ^b

AC, allergic conjunctivitis; IR, incidence rate, per 10 000 person-years; HR, hazard ratio.

^aAdjusted HR (hazard ratio), adjusted for age, sex, and comorbidity of chronic rhinosinusitis, anxiety, depression, obesity, hypertension, allergic rhinitis, asthma, chronic sinusitis, and obstructive sleep apnea.

^b $p < 0.001$.

TABLE 3. Incidence rate and relative risk of migraine in children with allergic conjunctivitis (AC) stratified by age in both genders in Cox proportional hazard regression.

	Migraine case	Person-years	IR	Adjusted HR ^a	95% CI
Girls					
<6	236	318 070	7.42	1.00	Reference
6–11	632	441 441	14.3	1.94	1.67, 2.25 ^b
≥12	244	75 083	32.5	5.29	4.39, 6.37 ^b
<i>p</i> for trend					<0.001
Boys					
<6	286	454 016	6.30	1.00	Reference
6–11	482	479 136	10.1	1.58	1.36, 1.83 ^b
≥12	81	50 962	15.9	2.99	2.32, 3.85 ^b
<i>p</i> for trend					<0.001

IR, incidence rate, per 10 000 person-years; HR, hazard ratio.

^aAdjusted HR, adjusted for age, sex, and comorbidity of chronic rhinosinusitis, anxiety, depression, obesity, hypertension, allergic rhinitis, asthma, chronic sinusitis, and obstructive sleep apnea.

^b $p < 0.001$.

describes the risk of migraine stratified according to median follow-up duration. The risk of migraine gradually increased since the first year of AC diagnosis (HR = 1.86; 95% CI: 1.49–2.32) and increased to the highest level when followed for 4–5 years (HR = 2.14; 95% CI: 1.84–2.49), following which the risk decreased with time. In the AC cohort, 209 children (10.7%) had migraine with aura and 284 children (14.5%) had migraine without aura. In the non-AC cohort, 96 children (10.2%) had migraine with aura and 170 children (18.1%) had migraine without aura ($p = 0.08$; Table 6).

DISCUSSION

This is the first population-based cohort study that provides evidence of the incidence and relative risk of migraine in children with AC. For a century, numerous studies reported the association between migraine and allergic diseases.^{23–28} However, studies that address childhood AC and the subsequent risk of migraine are rare.²³ In addition, most of the studies were hospital-based, with limited numbers of cases, and mainly focused on associated adulthood migraine but failed

TABLE 4. Risk of migraine by allergic conjunctivitis-related medical visits per year in Cox proportional hazard regression.

Average frequency for medical visit, per years	Migraine case	Person-years	IR	Adjusted HR ^a	95% CI
All					
None	941	1 799 284	5.23	1.00	Reference
≤2	1029	1 591 644	6.47	1.17	1.07, 1.28 ^c
3–4	356	1 58 201	22.5	4.00	3.53, 4.53 ^c
>4	576	68 863	83.6	14.6	13.1, 16.3 ^c
<i>p</i> for trend					<0.001
Girls					
None	564	827 013	6.82	1.00	Reference
≤2	581	725 392	8.01	1.12	1.00, 1.26 ^b
3–4	192	75 722	25.4	3.42	2.90, 4.04 ^c
>4	339	33 479	101.3	13.6	11.9, 15.7 ^c
<i>p</i> for trend					<0.001
Boys					
None	377	972 270	3.88	1.00	Reference
≤2	448	866 252	5.17	1.25	1.09, 1.43 ^c
3–4	164	82 478	19.9	4.87	4.04, 5.87 ^c
>4	237	35 384	67.0	16.1	13.6, 19.1 ^c
<i>p</i> for trend					<0.001

IR, incidence rate, per 10 000 person-years; HR, hazard ratio.

^aAdjusted HR, adjusted for age, sex, and comorbidity of chronic rhinosinusitis, anxiety, depression, obesity, hypertension, allergic rhinitis, asthma, chronic sinusitis, and obstructive sleep apnea.

^b*p*<0.01.

^c*p*<0.001.

TABLE 5. Incidence rate and relative risk of migraine in children with allergic conjunctivitis (AC) compared with children without AC stratified by follow-up years in Cox proportional hazard regression.

Follow time	Non-AC			AC			Adjusted HR ^a	95% CI
	Migraine case	Person-years	IR	Migraine case	Person-years	IR		
≤1 years	120	308 178	3.89	247	3 087 413	8.00	1.86	1.49, 2.32 ^b
2–3 years	272	581 409	4.68	587	585 343	10.0	2.01	1.73, 2.32 ^b
4–5 years	248	72 613	34.2	558	73 366	76.1	2.14	1.84, 2.49 ^b
≥6 years	301	432 726	6.96	569	442 156	12.9	1.76	1.53, 2.03 ^b

IR, incidence rate, per 10 000 person-years; HR, hazard ratio.

^aAdjusted HR, adjusted for age, sex, and comorbidity of chronic rhinosinusitis, anxiety, depression, obesity, hypertension, allergic rhinitis, asthma, chronic sinusitis, and obstructive sleep apnea.

^b*p*<0.001.

TABLE 6. Frequency of childhood migraine subtype in allergic conjunctivitis (AC) cohort and non-AC cohort.

Migraine subtype (ICD-9CM codes)	Non-AC (<i>n</i> = 941)		AC (<i>n</i> = 1961)		<i>p</i> value ^a
	<i>n</i>	(%)	<i>n</i>	(%)	
Migraine with aura (346.0)	96	10.2	209	10.7	0.08
Migraine without aura (346.1)	170	18.1	284	14.5	
Variants of migraine (346.2)	100	10.6	190	9.7	
Other forms of migraine (346.8)	32	3.4	58	3.0	
Migraine, unspecified (346.9)	543	57.7	1220	62.2	

^a χ^2 -test.

to demonstrate a causal relationship between the disorders. In 1949, Zussman reported the association between allergy of the eye and migraine headache in one case.²³ From the 1920s to the 1960s, some anecdotal reports described patients who developed migraine after allergic reactions to specific allergens, with the migraine improving after avoiding specific trigger foods or administering immunotherapy.^{24,25} Since 1990, evidence regarding the high prevalence of migraine among patients with allergic diseases, such as allergic conjunctivitis, allergic rhinitis, atopic dermatitis, and asthma has accumulated as a result of case-control studies. Although some previous studies have

shown that AC is associated with migraine, most of these studies did not specifically discuss the association between AC and migraine; nor did they confirm whether the migraine occurred after AC was diagnosed.^{26–28} The present study showed an increased subsequent risk of migraine in children with AC regardless of age, sex, and urbanization of residual area. An earlier onset of AC was associated with an increased risk of migraine. The risk of migraine was greatest after 4–5 years of AC diagnosis. In addition, children with AC who had frequent AC-related medical visits had relatively higher risks of migraine attack. Thus, physicians need to be aware of migraine symptoms when children are diagnosed with AC.

Although migraine is less common in children than in adults, it can begin in childhood and increase in prevalence with age, from 3% in young children to 15% in adolescents. Our study showed that the incidence rate of childhood migraine was 5.23 of 10 000 person-years in the non-AC cohort and 10.8 of 10 000 person-years in the AC cohort. Furthermore, the results suggest that the incidence of migraine increased with age, peaking in adolescence with a fourfold increase from that in preschool children, in both cohorts. However, the risk of migraine was greatest in children <6 years in the AC cohort compared with the non-AC cohort. The incidence rate of migraine increased with age in both sexes, with similar sex distribution in children aged <12 years and prominent female preponderance thereafter, which is consistent with the results of a previous study. Female individuals have a higher incidence of migraine after puberty, which is associated with pulsatile release of gonadotropin-releasing hormone from the hypothalamus, and the resetting of hypothalamic hormones is considered to play an important role in the main neural pathway of migraine by altering the trigeminovascular system.^{29,30}

Our results revealed the adjusted HR for migraine decreased with AC diagnosed age in the AC cohort in comparison with the non-AC cohort. The mean time-interval between physician-diagnosed AC to physician-diagnosed migraine increased with AC diagnosed age. It indicates that younger children with AC had higher subsequent risks of migraine, and they need a longer time to make the diagnosis of migraine. This phenomenon may be explained by the fact that young children may not express themselves well, and it takes more observation time for physicians to diagnose migraine. This may be related to the important developmental change in the neural network of the brain, as the nervous system may respond differently to external stimuli and/or disease during brain maturation.³⁰ Our study also showed that the risk of migraine increases significantly as the frequency for medical visits increased, suggesting that the children with AC who require greater medical help are at higher risk of migraine attack. This serves as a reminder for physicians to pay more attention to children with AC and the associated migraine symptoms. In addition, atopic disorders are significantly more commonly reported

in adulthood migraine with aura (21.6%) than in that without aura.²⁶ Our results revealed a small elevated prevalence of migraine with aura in children with AC, but the difference was not statistically significant.

The pathogenesis of migraine is generally considered as the alteration of brain excitability, intracranial arterial dilatation, sensitization of the trigeminovascular system, and neurogenic inflammation.^{29,31–33} Several inflammatory mediators, including histamine, prostaglandins, and leukotrienes, were elevated during migraine attacks,^{9–13} and these mediators are also involved in the pathogenesis of AC.^{21,34,35} The level of leukotriene E₄, a stable final metabolite of leukotrienes, is elevated in patients with migraine¹⁰ and is similar to findings in patients with allergic diseases.³⁶ Prostaglandins, which are arachidonic acid metabolites synthesized by stimulated mast cells via the cyclooxygenase pathway, are important mediators of pain and inflammation, and involved in the pathogenesis of migraine. A previous study showed that the concentration of prostaglandins F_{2a} in children with migraine was significantly higher during headache than during non-headache periods.¹³ Histamine is released by special mast cells located around the brain nerve endings and increases the release of NO, causing vasodilation by H₁ and H₂ receptors, and increasing vascular permeability that leads to local neurogenic inflammation.³⁷ These mediators play a critical role in neurogenic switching, which is involved in a crossover mechanism between two different forms of inflammation, namely immunologic and neurologic inflammations.³⁸ These proinflammatory mediators were also related to the ocular inflammation of AC.^{21,34,35} The trigeminovascular pathway includes the first-order nociceptors in the trigeminal ganglion innervating the meninges; the second-order trigeminothalamic tract neurons receiving sensory inputs from the meninges, periorbital skin, and neck muscles; the third-order thalamocortical neurons processing pain signals from the trigeminal nerve, such as the meninges; and finally, the cortical neurons located in the first somatosensory cortex.³⁹ Because the periorbital area is part of the trigeminovascular pathway, AC may trigger peripheral trigeminovascular neurons, decrease their threshold of response to stimuli, and increase their magnitude of response.⁴ As a consequence, these neurons start to respond to the dura stimuli to which they initially showed minimal or no response. Based on the aforementioned theory, we hypothesize that AC is a trigger in the development of migraine and shows the possible link between AC and migraine.

This study has several limitations. The diagnoses of AC and migraine were based on the ICD-9-CM codes, which were strictly determined by related specialists and physicians according to the standard clinical diagnosis criteria. Therefore, the diagnoses should be correct and reliable. Although our results revealed migraine was the most common type of specified headache, most children with headache were coded as 'unspecified headache'. This implies that migraine

may be underdiagnosed, particularly in young children and those with mild or infrequent symptoms. Children with mild symptoms, which may not be recognized by caregivers may be only treated with over-the-counter medications. Doctors' specializations may also interfere with the diagnosis. Neurologists may be more aware of migraine headache than other specialists and physicians.

In conclusion, our results show that the incidence rate and risk of migraine increased in all age groups, especially in children <6 years and in girls after puberty. In addition, children with AC who need greater medical help are at higher risk of migraine, especially boys. Finally, children with earlier onset of AC are also at higher risk of migraine attacks in their later life. All these findings suggest that AC may be a trigger in the development of migraine and should remind the physician to pay more attention to children with AC and associated migraine symptoms.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

I-Chung Wang and Jeng-Dau Tsai made equal contribution to this study. I-Chung Wang, Jeng-Dau Tsai, Chang-Ching Wei, and Te-Chun Shen conceptualized and designed the study, drafted the manuscript, and approved the final manuscript as submitted. Cheng-Li Lin, Tsai-Chung Li conducted the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. Chang-Ching Wei coordinated and supervised the data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

FUNDING

The study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092), NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

REFERENCES

- Katellaris CH. Ocular allergy in the Asia Pacific region. *Asia Pac Allergy*. 2011;1:108–114.
- Bousquet J, van Cauwenberge P, Khaltaev N, et al. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108:S147–S334.
- Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol*. 2011;11:471–476.
- Burstein R, Noseda R, Borsook D. Migraine: Multiple Processes, Complex Pathophysiology. *J Neurosci*. 2015;35:6619–6629.
- Powers SW, Patton SR, Hommel KA, et al. Quality of life in childhood migraines: Clinical impact and comparison to other chronic illnesses. *Pediatrics*. 2003;112:E1–E5.
- Arruda MA, Bigal ME. Migraine and migraine subtypes in preadolescent children Association with school performance. *Neurology*. 2012;79:1881–1888.
- Bille B. A 40-year follow-up of school children with migraine. *Cephalalgia*. 1997;17:488–491.
- Ozge A, Oksuz N, Ayta S, et al. Atopic disorders are more common in childhood migraine and correlated headache phenotype. *Pediatr Int*. 2014;56:868–872.
- Gazerani P, Pourpak Z, Ahmadiani A, et al. A correlation between migraine, histamine and immunoglobulin E. *Scand J Immunol*. 2003;57:286–290.
- Bockowski L, Sobaniec W, Zelazowska-Rutkowska B. Proinflammatory plasma cytokines in children with migraine. *Pediatr Neurol*. 2009;41:17–21.
- LaMancusa R, Pulcinelli FM, Ferroni P, et al. Blood leukotrienes in headache: correlation with platelet activity. *Headache*. 1991;31:409–414.
- Ince H, Aydin OF, Alacam H, et al. Urinary leukotriene E4 and prostaglandin F2a concentrations in children with migraine: a randomized study. *Acta Neurol Scand*. 2014;130:188–192.
- Wilson AM, Orr LC, Sims EJ, et al. Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. *Clin Exp Allergy*. 2001;31:61–68.
- Davis K, Huang AT. Learning from Taiwan: Experience with universal health insurance. *Ann Intern Med*. 2008;148:313–314.
- Wei CC, Tsai JD, Lin CL, et al. Increased risk of idiopathic nephrotic syndrome in children with atopic dermatitis. *Pediatr Nephrol*. 2014;29:2157–2163.
- Wei CC, Chang CH, Lin CL, et al. Neonatal jaundice and increased risk of attention-deficit hyperactivity disorder: a population-based cohort study. *J Child Psychol Psychiatry*. 2015;56:460–467.
- Wei CC, Lin CL, Shen TC, et al. Increased incidence of juvenile-onset systemic lupus erythematosus among children with asthma. *Pediatr Allergy Immunol*. 2014;25:374–379.
- Wei CC, Lin CL, Shen TC, et al. Risk of idiopathic nephrotic syndrome among children with asthma: a nationwide, population-based cohort study. *Pediatr Res*. 2015;78:212–217.
- Wei CC, Lin CL, Shen TC, et al. Occurrence of common allergic diseases in children with idiopathic nephrotic syndrome. *J Epidemiol*. 2015;25:370–377.
- Wei CC, Lin CL, Shen TC, et al. Risk of idiopathic nephrotic syndrome among children with asthma: a nationwide, population-based cohort study. *Pediatr Res*. 2015;78:212–217.
- Olesen J, Steiner TJ. The International Classification of Headache Disorders, 2nd edn. (ICDH-II). *J Neurol Neurosurg Psychiatry*. 2004;75:808–811.
- Giannini G, Cevoli S, Sambati L, et al. Migraine: risk factor and comorbidity. *Neurol Sci*. 2012;33Suppl 1:S37–S41.
- Zussman BM. Allergy of the eye associated with migraine headache; case report. *Ann Allergy*. 1949;7:524–527.
- Warren T, Vaughan MD. Allergic migraine. *JAMA*. 1927;88:1383–1386.
- Shapiro RS, Eisenberg BC. Allergic Headache. *Ann Allergy*. 1965;23:123–126.
- Wang IC, Tsai JD, Lin CL, et al. Allergic rhinitis and associated risk of migraine among children: a nationwide population-based cohort study. *Int Forum Allergy Rhinol*. 2015.

27. Ku M, Silverman B, Prifti N, et al. Prevalence of migraine headaches in patients with allergic rhinitis. *Ann Allergy Asthma Immunol.* 2006;97:226–230.
28. Ozturk A, Degirmenci Y, Tokmak B, et al. Frequency of migraine in patients with allergic rhinitis. *Pak J Med Sci.* 2013;29:528–531.
29. Pietrobon D, Moskowitz MA. Pathophysiology of Migraine. *Annu Rev Physiol.* 2013;75:365–391.
30. Borsook D, Erpelding N, Lebel A, et al. Sex and the migraine brain. *Neurobiol Dis.* 2014;68:200–214.
31. Capuano A, De Corato A, Lisi L, et al. Proinflammatory-activated trigeminal satellite cells promote neuronal sensitization: relevance for migraine pathology. *Mol Pain.* 2009;5:43.
32. Longoni M, Ferrarese C. Inflammation and excitotoxicity: role in migraine pathogenesis. *Neurol Sci.* 2006;27Suppl 2:S107–S110.
33. Cutrer FM, Smith JH. Human studies in the pathophysiology of migraine: genetics and functional neuroimaging. *Headache.* 2013;53:401–412.
34. Irani AM. Ocular mast cells and mediators. *Immunol Allergy Clin North Am.* 2008;28:25–42.
35. McGill JJ, Holgate ST, Church MK, et al. Allergic eye disease mechanisms. *Br J Ophthalmol.* 1998;82:1203–1214.
36. Mai XM, Bottcher MF, Bruhammar M, et al. Urinary inflammatory mediators and inhalation of hypertonic saline in children. *Allergy.* 2005;60:60–64.
37. Krabbe AA, Olesen J. Headache provocation by continuous intravenous infusion of histamine. Clinical results and receptor mechanisms. *Pain.* 1980;8:253–259.
38. Meggs WJ. Neurogenic switching: a hypothesis for a mechanism for shifting the site of inflammation in allergy and chemical sensitivity. *Environ Health Perspect.* 1995;103:54–56.
39. Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of the pain and strain of migraine. *J Comp Neurol.* 2005;493:9–14.