

Association between keratoconus and the risk of adolescent- or adult-onset atopic dermatitis

To the Editor,

Keratoconus (KCN), which is a bilateral, asymmetric, and progressive ectatic condition, is the main cause of keratoplasty in the developed world. The KCN affected cornea has a conical shape, resulting in significant visual impairment and visual morbidity.¹ The corneal protrusion and thinning typically presents in adolescence and progresses until the third or fourth decade of life, when it usually stabilizes.² Despite a high prevalence, the etiology and pathophysiology of KCN remain unclear.

Both KCN and atopic dermatitis (AD) are multifactorial conditions with multiple etiologies including biochemical, physical, biomechanical, genetic, and environmental triggers.²⁻⁴ Both the cornea stroma and human skin are composed of large amounts of collagen components and have a high water content. To the best of

our knowledge, few cohort studies have investigated whether KCN is a risk factor for subsequent development of AD. Therefore, we designed a nationwide, population-based cohort, retrospective, matched cohort study to investigate the risk of AD following KCN in Taiwan.

This study included 3869 new-onset KCN patients recruited between 2004 and 2011 from the Taiwan National Health Insurance Research Database. KCN patients aged ≥ 12 years were identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), code 371.6. The age-, sex-, and comorbidity (asthma and allergic rhinitis)-matched control group included 23 214 non-KCN patients selected from the Taiwan Longitudinal Health Insurance Database, 2000. We collected and tracked information for each patient from the index date until December 2013. The baseline

TABLE 1 Risk of atopic dermatitis (AD) in the keratoconus and control groups

Characteristics	Keratoconus				Controls				IRR (95% CI)	P-value
	N	AD	PY	Rate ^a	N	AD	PY	Rate ^a		
All	3869	231	21 127	109.34	23 214	973	127 738	76.17	1.44 (1.24-1.66)	<.0001
Age (y)										
12-19	830	44	4648	94.66	5043	187	28 207	66.30	1.43 (1.03-1.98)	.0335
20-29	1703	128	9444	135.54	10 175	465	57 071	81.48	1.66 (1.37-2.02)	<.0001
30-39	834	37	4344	85.17	4983	212	26 102	81.22	1.05 (0.74-1.49)	.7897
≥ 40	502	22	2691	81.75	3013	109	16 358	66.63	1.23 (0.78-1.94)	.3813
Sex										
Male	2150	86	12 024	71.52	12 899	373	71 931	51.86	1.38 (1.09-1.74)	.0072
Female	1719	145	9103	159.29	10 315	600	55 807	107.51	1.48 (1.24-1.78)	<.0001
Comorbidity										
Asthma	154	14	841	166.47	926	42	4895	85.80	1.94 (1.06-3.55)	.0316
AR	14	1	91	109.89	84	2	448	44.64	2.46 (0.22-27.17)	.4616
Location										
North	2453	138	13 467	102.47	12 612	490	69 279	70.73	1.45 (1.20-1.75)	.0001
Central	569	32	3142	101.85	4143	161	22 875	70.38	1.45 (0.99-2.11)	.0562
South	787	58	4177	138.86	6033	310	33 226	93.30	1.49 (1.12-1.97)	.0055
East	60	3	341	87.98	426	12	2358	50.89	1.73 (0.49-6.13)	.3959

Note: Poisson regression analysis was performed to calculate the incidence rate ratio.

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; IRR, incidence rate ratio; PY: person-years.

^aRate: per 10 000 person-years.

demographics and comorbidities of KCN patients and non-KCN controls were shown in Table S1.

Incidence and risk of adolescent- or adult-onset AD (ICD-9-CM, code 691 with age ≥ 12 years) were compared between the two groups in Table 1. During the follow-up period, there was a higher incidence rate of AD in KCN patients (109.34/10 000 person-years [PY]) than in the age-matched controls (76.17/10 000 PY) leading to a significant difference in the incidence rate ratio (IRR) of AD (1.44, 95% confidence interval [CI] = 1.24-1.66, $P < .0001$) between the groups. KCN patients aged 20-29 years exhibited the highest incidence of AD (133.54/10 000 PY), followed by those aged 12-19 years (94.66/10 000 PY), resulting in significantly higher IRR values for KCN patients than for controls within the same age ranges: 1.66 (95% CI = 1.37-2.02; $P < .0001$) for aged 20-29 years and 1.43 (95% CI = 1.03-1.98; $P = .0355$) for aged 12-19 years. The significant differences in the incidence rate of AD were found between the women with KCN (IRR = 1.48; 95% CI = 1.24-1.78; $P < .0001$), men with KCN (IRR = 1.38, 95% CI = 1.09-1.74, $P = .0072$), and patient

residents in the northern (IRR = 1.45, 95% CI = 1.20-1.75, $P = .0001$) or southern region (IRR = 1.49, 95% CI = 1.12-1.97, $P = .0055$), and their respective controls.

Kaplan-Meier analyses revealed higher cumulative incidence rates of AD in the KCN group than in the control group; log-rank test findings were also significant ($P < .0001$; Figure S1).

Table 2 provides the crude and adjusted hazard ratios [HRs] for AD during the follow-up period. After adjusting for age, sex, and the selected comorbidities, KCN remained an independent risk factor for AD (adjusted HR, 1.44; 95% CI = 1.25-1.67; $P < .05$). In both groups, patients aged between 12-19 years (adjusted HR, 1.25; 95% CI = 1.01-1.55; $P < .05$) and between 20-29 years (adjusted HR, 1.50; 95% CI = 1.24-1.81; $P < .05$), women (adjusted HR, 2.18; 95% CI = 1.93-2.45; $P < .05$), and residents in the southern region (adjusted HR, 1.85; 95% CI = 1.10-3.09; $P < .05$) were at a higher risk for the development of AD. All selected comorbidities were not independent risk factors for AD.

A significantly decreased hydration of stratum corneum is the common alteration of skin and corneal characteristics observed in KCN patients.⁵ Stratum corneum hydration was also significantly lower in skin lesions than in uninvolved skin in AD patients.⁶ Concurrent alterations in the water hydration of the skin and cornea may reflect an association between KCN and AD. In addition, thinning and ectasia of the cornea are the main features of KCN, which are attributed to the decrease in the collagen content of the cornea due to degradation of the extracellular matrix.⁷ Overexpression of the matrix metalloproteinase (MMP) family of proteins that includes collagenases and gelatinases might play a role in this change.⁷ Enhanced expression of proteolytic enzymes, such as gelatinases, MMP-2, and MMP-9, which work as extracellular matrix-degrading enzymes is probably related to the remodeling of skin tissue in AD.⁸ These similar changes in the extracellular matrices related to an overexpression proteolytic enzymes may imply an association between AD and KCN.

Furthermore, despite being regarded as a non-inflammatory condition, some inflammatory molecules including interleukins (ILs) and tumor necrosis factor (TNF) have been found in the tears of KCN patients.^{7,9} Several studies have shown that ILs and TNF regulate the expression of MMPs, implicating chronic inflammatory events in the pathogenesis of KCN.^{7,9} It is worth noting that members of the IL-1 family of cytokines that mediate innate immune responses play an important pathophysiological role in skin inflammation in AD.^{3,10} These inflammatory molecules may be a link between AD and KCN. Finally, mechanical damage to the cornea or oxidative stress in the cornea due to eye discomfort or rubbing is found in an AD animal model¹¹ and is regarded as a leading cause in the development of KCN.¹² Therefore, atopic syndromes resulting in itching and eye rubbing may be key factors in triggering an early manifestation of KCN.¹²

In conclusion, this study showed that the risk of adolescent- or adult-onset AD was significantly higher in KCN patients. KCN remained an independent risk factor after adjusting for other confounders in the cohort, particularly in patients aged 12-29 years and female sex. These results suggest that clinicians should inform KCN patients about the risk of adolescent- or adult-onset AD.

TABLE 2 Crude and adjusted hazard ratios of Cox proportional hazard regressions and 95% confidence interval for atopic dermatitis in the study cohort during the follow-up period

Cohort	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Keratoconus		
Yes	1.44* (1.25-1.66)	1.48* (1.28-1.70)
No	1.00	1.00
Age (y)		
12-19	1.02 (0.83-1.27)	1.27* (1.02-1.57)
20-29	1.30* (1.07-1.57)	1.53* (1.26-1.85)
30-39	1.19 (0.96-1.47)	1.23 (1.00-1.52)
≥ 40	1.00	1.00
Sex		
Female	2.10* (1.87-2.36)	2.18* (1.96-2.45)
Male	1.00	1.00
Comorbidity		
Asthma		
Yes	1.22 (0.93-1.59)	1.26 (0.96-1.65)
No	1.00	1.00
Allergic rhinitis		
Yes	0.69 (0.22-2.13)	0.68 (0.22-2.13)
No	1.00	1.00
Location		
North	1.36 (0.82-2.27)	1.38 (0.83-2.30)
Central	1.33 (0.79-2.25)	1.39 (0.82-2.36)
South	1.77* (1.06-2.96)	1.85* (1.10-3.09)
East	1.00	1.00

Note: Adjusted hazard ratio for developing atopic dermatitis was calculated using the Cox proportional hazard regression analysis. Abbreviations: CI, confidence interval.

* $P < .05$

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CONFLICT OF INTEREST

Dr Chang has nothing to disclose. Dr Weng has nothing to disclose. Dr Wang has nothing to disclose. Dr Tseng has nothing to disclose. Dr Wang has nothing to disclose. Dr Jan has nothing to disclose. Dr Ko has nothing to disclose. Dr Tsai has nothing to disclose. Dr Chen has nothing to disclose. Dr Liou has nothing to disclose. Dr Jan has nothing to disclose.

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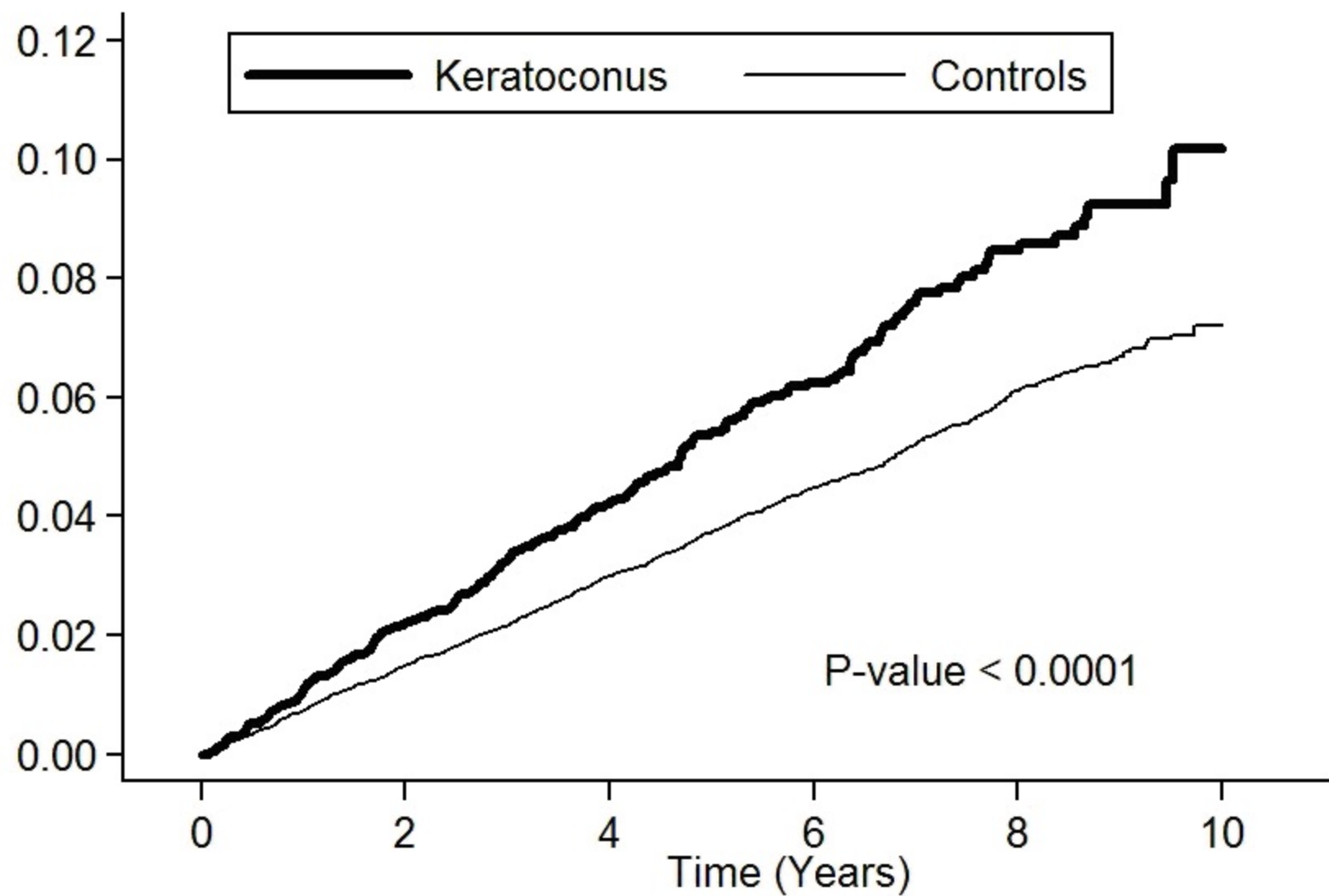
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.



Number at risk

Keratoconus 3869

3776

2571

1548

756

0

Controls 23214

22813

15550

9378

4542

0

Online supporting information for the Letter to the editor entitled:

Association between Keratoconus and the Risk of Adolescent- or Adult-Onset Atopic Dermatitis

In Depth Introduction of Keratoconus and Atopic Dermatitis

Keratoconus (KCN) may be multifactorial in origin based on the environmental, physical, biochemical, and genetic evaluation of its cellular etiology and pathophysiology.¹ Several reports showed that KCN affects all ethnicities and both sexes.¹⁻³ The disease may also be associated with eye rubbing related to allergic eye disease and systemic disorders such as Turner syndrome and Down syndrome and connective tissue disorders including Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum.^{1, 2, 4}

Atopic dermatitis (AD), a common, chronic, inflammatory skin disease, is characterized by recurrent eczematous lesions with intense itching. Clinical manifestations of AD include pruritus, pain, sleep disturbance, and mental health disorders, which negatively impact quality of life.⁵⁻⁷ Originally regarded as a childhood disorder, AD is also highly prevalent in adults and is now recognized as a lifelong condition with defects of the epidermal barrier.⁶ There has been a worldwide increase in the lifetime prevalence of AD as it is one of the most common chronic diseases in developed countries.^{8, 9} Major pathophysiological mechanisms of AD include abnormalities of epidermal structure and function and cutaneous inflammation.⁶ Some important stratum corneum abnormalities are also associated with AD, including decreased hydration, increased water loss,¹⁰⁻¹² and, elevated activity of proteases.^{13, 14} Ocular complications due to eye rubbing stimulated by itching or discomfort in AD patients have become clinically important worldwide.

Supplemental Methods

Database

Data used in this study were taken from the National Health Insurance Research Database (NHIRD), provided by the National Health Research Institute (NHRI) in Taiwan. For each enrollee, the NHIRD records coded

information on patient demographics such as birth date, sex, and residential area, as well as the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnoses and prescription details, procedures, and expenditure claims, regardless of whether the patient was under ambulatory care or during hospitalization. The Institutional Review Board of Chi Mei Medical Center granted this study exemption from ethics review on the basis that the patient identification was double de-identified and encrypted, and informed consent was waived.

Patient selection and relative variables

Two groups were enrolled in this retrospective cohort study: a new-onset KCN group and a matched non-KCN control group. Patient information from both groups was collected from January 1, 2004, to December 31, 2011, and both groups were traced until the end of 2013. In total, there were 3,869 KCN patients ≥ 12 years with the ICD-9-CM code 371.6 diagnosis. Patients with unknown gender or missing data were excluded, as were individuals diagnosed with AD (ICD-9-CM code 691) before KCN.

For each KCN patient, six non-KCN controls were randomly chosen from the longitudinal Health Insurance Database 2000, which is a subset of the NHIRD containing overall claim data for 1,000,000 beneficiaries from the 2000 registry and constructed from the NHIRD by the NHRI using a systematic sampling method. Controls ($n = 23,214$) were matched with KCN patients by age (± 30 days), sex, and index date, which was defined as the first day of diagnosis for KCN patients. We excluded controls if they were diagnosed with KCN or AD before the index date. To determine the incidence of adolescent- or adult-onset AD, each participant in both groups was tracked from the index date until the end of 2013 or death, whichever was earlier. Each participant's demographic data were recorded. Additionally, data regarding their comorbidities including asthma (ICD-9-CM code 477), and allergic conjunctivitis (ICD-9-CM code 493) were collected because these are decisive risks for AD. Comorbidities were included only if the condition occurred in an inpatient setting or if they appeared in three or more ambulatory care claims within 1 year before the index date.

Statistical analysis

All statistical analyses were performed using SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA). The Pearson's chi-square test was performed to analyze baseline demographics and comorbidities between the KCN and control groups. The incidence of AD was measured as the sum of KCN patients detected during the follow-up divided by the total person-years (PY) for each group by age, sex, and selected comorbidities. The incidence rate ratio (IRR), which compared the risk of AD between the KCN and non-KCN control groups, was calculated using Poisson regression analysis. Cox proportional hazards regression analysis was performed to calculate the difference in the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of the risk of developing AD. Kaplan–Meier method was utilized to plot the cumulative incidence rate curves and log-rank test was used to analyze the difference. Statistical significance was defined as $p < 0.05$.

Supplemental Results

Supplemental Table 1S

From the beginning of 2004 to the end of 2011, after excluding ineligible subjects, 3,869 KCN patients and 23,214 controls were recruited. Table 1S shows baseline demographics and comorbidities of KCN patients and non-KCN controls. The average age of the KCN patients and controls was 28.96 (SD, 12.58) and 28.94 (SD, 12.62) years, respectively. Of the 3,869 KCN patients, 2,150 (55.57%) were men and 1,719 (44.43%) were women, with 830 (21.45%) aged 12–19 years, 1,703 (44.02%) 20–29 years, 834 (21.56%) 30–39 years, and 502 (12.97%) ≥ 40 years. Regarding comorbidities of the 3,869 KCN patients, 154 (3.98%) have asthma, and 14 (0.36%) have allergic rhinitis. With regard to geographic distribution, the most common region of residence of the patients diagnosed as having KCN was the northern region (2453; 63.40%), followed by the southern (787; 20.34%), central (569; 14.71%), and eastern regions (60; 1.55%).

Table 1S. Demographic characteristics and comorbidities between the keratoconus and control groups

	Keratoconus (N = 3869)	Controls (N = 23214)	<i>p</i> -value
Age (years; mean $\pm$ SD)	28.96 $\pm$ 12.58	28.94 $\pm$ 12.62	0.9408
	Number (%)	Number (%)	
Age group (years)			0.9850
12–19	830 (21.45)	5043 (21.72)	
20–29	1703 (44.02)	10175 (43.83)	
30–39	834 (21.56)	4983 (21.47)	
≥ 40	502 (12.97)	3013 (12.98)	
Sex			0.9960
Male	2150 (55.57)	12899 (55.57)	
Female	1719 (44.43)	10315 (44.43)	
Baseline comorbidity			
Asthma	154 (3.98)	926 (3.99)	0.9798
Allergic rhinitis	14 (0.36)	84 (0.36)	1.0000
Location			<0.0001
North	2453 (63.40)	12612 (54.33)	
Central	569 (14.71)	4143 (17.85)	
South	787 (20.34)	6033 (25.99)	
East	60 (1.55)	426 (1.84)	

Note: Demographic characteristics and comorbidities between the keratoconus and control groups were compared using Pearson chi-square tests.

Supplemental Figure 1S

Figure Legend

Figure 1S. Cumulative incidence of atopic dermatitis in patients with keratoconus and controls during the follow-up period.

In Depth Discussion

After a thorough review of relevant research, we found that our study is the largest-scale population-based study to explore the relationship between KCN and subsequent adolescence- or adult-onset AD. We analyzed 3,869 KCN patients and 23,214 age- and sex-matched controls and found that the incidence rate of AD in KCN patients was 1.44 times higher than that in controls and that the relative risk of AD in KCN patients was increased by 1.44 times in the full cohort after adjusting for age, sex, asthma, and allergic rhinitis.

An association between AD and KCN has been postulated for many years, but there is conflicting evidence on whether AD is more common in KCN patients than in the general population. Several case–control studies have reported inconsistent findings on whether AD is a contributing factor in the diagnosis of KCN. Sashia et al. conducted a case–control study of 2679 KCN patients and their age- and sex-adjusted controls and showed that KCN patients had an odds ratio of 7.79 for developing AD (95% confidence interval, 6.21–10.21).¹⁵ However, in another case–control study that enrolled 229 KCN patients and 2290 controls by Hyun et al., there was no significant difference in the proportion of AD patients (7.0% in KCN group versus 6.5% in control group [P = 0.76]).¹⁶ Although some cohort studies have shown conflicting results regarding the risk of KCN after AD,^{16, 17} our unpublished data were collected from an investigation of patients with atopic keratoconjunctivitis and AD, asthma, or allergic rhinitis, and showed that these atopic characteristics are associated with high incidence rates of KCN at follow-up (data not shown). On the other hand, few cohort studies have ever evaluated the relationship in the opposite direction, namely, the risk of developing AD following KCN. Our study is the largest nationwide, population-based cohort study to investigate the risk of AD in KCN patients in Taiwan, to date.

The incidence rate of AD was significantly higher in KCN patients aged 12–19 years and 20–29 years (Table 1). Moreover, KCN patients aged 12–19

years and 20–29 years maintained a significant risk for development of AD after accounting for sex and comorbidities (Table 2). Because no previous study has shown the influence of age on the development of AD in KCN patients, we attempted to understand these findings based on the onset and time of manifestation in AD and KCN. Although AD has conventionally been regarded as largely a pediatric disease, more recent studies have found that approximately one in four adults developed AD during adolescence or adulthood and suggested a considerable heterogeneity in the signs and clinical manifestations of adolescent- or adult-onset AD.^{18, 19} Corneal thinning and protrusion usually become apparent during the second decade of the life, i.e., during puberty, in KCN patients.^{4, 20} These manifestations typically progress until the fourth decade of life, when they usually stabilize.⁴

We found that the incidence rate of AD was higher in women with KCN (Table 1) and the female sex was a significant risk factor in developing AD after accounting for age and comorbidities in both groups (Table 2). No studies have evaluated the influence of gender in the association between AD and KCN. Several studies report that KCN affects both sexes, although they are inconsistent and unclear on whether significant differences between the sexes exist.^{2, 21, 22} AD with a female preponderance, particularly in adolescence and adulthood, has been widely observed.^{7, 23–25} A possible explanation is that Th2 inflammation is exacerbated by estradiol and other female sex hormones in girls and women with AD from puberty onwards.^{26, 27} In addition, dehydroepiandrosterone (DHEA), a steroid hormone with a male preponderance and a key immunomodulatory hormone, appears to have an inhibitory effect on Th2 inflammation and is protective against the development of AD.^{28, 29} We attempted to explain the higher incidence rate of AD in women with KCN as related to the more common incidence of AD in adolescent and adult women.

The incidence rate of AD was significantly higher in the KCN patients living in the southern region (Table 1), and residents in the southern region maintained a significant risk for the development of AD after accounting for other confounders (Table 2). AD was well known to vary by environmental factors such as temperature, humidity, or other climatic factors. Taiwan is an east Asian country with a half tropical climate in the southern region and a half

subtropical climate in the northern region because the Tropic of Cancer crosses central Taiwan. The weather of the southern region is hot and sunny with little rainfall in the whole year as compared with the northern region. We attempted to explain the linkage between residents in the southern region and AD on the basis of the high temperature and UV exposure in southern Taiwan, which are significant risk factors of AD.

There are several strengths in our study. First, our study was a nationwide, population-based cohort study enrolling a large sample of KCN patients, leading to superior statistical power and precision in risk appraisal. Second, patients with visual disturbances visit ophthalmologists and those with skin problems visit dermatologists rather than general physicians in Taiwan, resulting in decreased chances of misdiagnosis and reduced selection bias in referral centers. Finally, the study was a cohort study with longitudinal data of up to 10 years and potential confounding bias was limited by controlling for asthma, and allergic rhinitis.

There are several limitations in this study. Because medical histories of each participant in our study can only be tracked back to 1996, we cannot confirm whether the patients and controls had a history of KCN or AD before January 1996. Meanwhile, adults usually do not know about their medical history from early childhood. Most AD cases start in early childhood, and in many cases, AD disappears again and may come back later. Whether the cases and controls had AD or not during their infancy or early childhood could not be confirmed on the basis of the incomplete registered insurance claims data, which could only be tracked back to 1996, causing a bias in our study. Furthermore, patients with skin problems may visit different physicians, including family practitioners, internists, pediatricians, and dermatologists, who may use different medical terms to denote AD and various criteria to diagnose AD, which can result in recall or reporting bias. Additionally, several important systemic disorders, including Turner syndrome and Down syndrome, and connective diseases, such as Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and osteogenesis imperfecta, could not be assessed as confounding factors due to their rare incidences. Finally, incorrect classification is a possibility because the diagnosis of KCN, AD, and other comorbidities relied on ICD-9-codes.

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