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# Migraines and keloids: a 15-year Taiwan claim database analysis

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## ABSTRACT

**Background** Fibroproliferative lesions with intractable pruritus, pain and hyperesthesia that cause uncontrolled scar growth are known as keloids. Migraines are common upsetting headache disorders characterised by frequent recurrence and attacks aggravated by physical activity. Both keloids and migraines can cause physical exhaustion and discomfort in patients; they have similar pathophysiological pathways, that is, the transforming growth factor- $\beta$ 1 gene and neurogenic inflammation.

**Objective** To investigate subsequent development of migraines in patients with keloids.

## Methods

Data were retrieved from the Taiwan National Health Insurance Research Database. The keloids group included patients aged 20 years and older with a recent diagnosis of keloids (n=9864). The non-keloids group included patients without keloids matched for gender and age at 1–4 ratio (n=39456). Migraine risk between groups was measured by Cox proportional hazards regression models. Incidence rates and hazard ratios were calculated.

**Results** During the study period, 103 keloids patients and 323 non-keloids patients developed migraines. The keloids patients had a 2.29-fold greater risk of developing migraines compared with the non-keloids group after adjustment for covariates (1.81 vs 0.55 per 1000 person-years, respectively). In the keloids group, female or patients younger than 50 years were prone to developing migraines.

**Conclusion** The higher tendency to develop migraines in the keloids group in comparison with the non-keloids group suggests that keloids could be a predisposing risk factor for migraine development in adults. Keloids patients who complain of headaches should be examined for migraines.

## INTRODUCTION

Keloids are a fibroproliferative disorder in which excess collagen production causes uncontrolled scar growth beyond the original wound borders.<sup>1</sup> A keloid appears as a firm tumour with a shiny surface, occasionally with telangiectasia or hyperpigmentation, and is usually accompanied by hyperesthesia, intractable pruritus and pain. Keloids tend to develop in skin areas with high tension such as the sternum, chest, shoulder and back. The occurrence rate is reportedly higher in black and Asian populations compared with other ethnic populations. Keloids have a high recurrence rate, and growth usually continues even after therapeutic interventions.<sup>2</sup>

A migraine is a highly prevalent distressing primary headache disorder which usually occurs in younger subjects and is more common in females than in males at a ratio of 3:1.<sup>3</sup> Migraines are characterised by frequent attacks of unilateral, pulsating headaches aggravated by physical activity. The two main subtypes are migraines with aura and migraines without aura. In the migraine with aura subtype, the aura precedes the headache. By far, the most common aura phenomenon is visual disturbance, followed by somatosensory symptoms.<sup>4</sup> The many factors associated with migraine attacks include hormone imbalance, stress and auditory hypersensitivity. However, the exact pathomechanism of migraines remains unknown.

Transforming growth factor (TGF)- $\beta$ 1 is a major cytokine involved in tissue repair.<sup>5</sup> Studies indicate that this profibrotic growth factor has important roles in both keloids and migraines pathophysiology. Another similarity between keloids and migraines is that both occur primarily in younger populations. Besides, neurogenic inflammation pathways involving the release of histamine, calcitonin gene-related peptide (CGRP) and substance P (SP), also play a crucial role in diseases pathogenesis. Thus, we hypothesised that keloids and migraines are linked through common pathways, particularly those related to the TGF- $\beta$ 1 gene. However, there are, so far, no population-based data accessible for exploring correlations between keloids and migraines, this research analysed claims data contained in the National Health Insurance Research Database (NHIRD) in Taiwan.

## MATERIAL AND METHODS

### Data source

The claims data source used in this cohort study was the Taiwan NHIRD, a secondary encrypted database administered by the Taiwan National Health Insurance system launched in March 1995. The NHIRD contains detailed medical information for approximately 99% of the 23.75 million beneficiaries in Taiwan, including records of pharmacy or medical services and enrollment data. Diseases are coded in International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format. The NHIRD has been used in numerous health-related research papers published in top-tier scientific journals.<sup>6,7</sup> The database is publicly available for research purposes, and the confidentiality of patient data is protected by the Taiwan Personal Electronic Data Protection Law. All NHIRD data used for research purposes are deidentified, and

any personal information is anonymised before release of data. Therefore, informed consent was not needed.

### Study design

Medical claims data for years 1996–2010 were used to identify the two cohorts analysed in this study: a keloids cohort (9864 patients) and a non-keloids cohort. To maximise accuracy of the data, the analysis was limited to patients with medical claims data showing at least two diagnoses of keloids (ICD-9-CM code 701.4) received during outpatient visits or at least one diagnosis of keloids received during an inpatient visit.<sup>6</sup> Additionally, the cohorts were limited to patients who had an ICD-9 code for keloids assigned by a dermatologist. The index date for the keloids cohort was defined as the date of the first keloids diagnosis. Individuals who had been diagnosed with migraine (ICD-9-CM code 346) before the index date (n=383) and those aged less than 20 years were excluded. In the period of follow-up, the occurrence of migraine was defined as at least two diagnoses of migraine in outpatient visits or at least one diagnosis of migraine in an inpatient visit. Only records in which an ICD-9-CM code for migraine had been assigned by a neurologist were used.<sup>8,9</sup> After eliminating patients in the study cohort, another 39456 controls without keloids were identified and fourfold matched for index year (year of keloids diagnosis), gender and age. All included patients were followed up until 31 December 2010, or until the migraine occurrence.

### Measures and definition

Together with demographic risk factors (age and gender), relevant concurrent comorbidities before the index date were identified by ICD-9-CM codes contained in the claims records. Relevant comorbidities were defined as hypertension (ICD-9-CM codes 401–405), hyperlipidaemia (ICD-9-CM code 272), stroke (ICD-9-CM codes 430–438), diabetes mellitus (ICD-9-CM code 250), coronary artery disease (ICD-9-CM codes 410–414), fibromyalgia (ICD-9-CM code 729.0 and 729.1), insomnia (ICD-9-CM code 307.4 and 780.5), depression (ICD-9-CM code 296.2, 296.3, 300.4 and 311), anxiety (ICD-9-CM code 300.00, 300.01, 300.02), obesity (ICD-9-CM code 278), asthma (ICD-9-CM code 493) and alcohol attributed disease (ICD-9-CM codes 291.0–9, 303, 305.0, 357.5, 425.5, 535.3, 571.0–3980.0 and V11.3). A comorbidity was considered concurrent if an ICD-9-CM code for the comorbidity had been assigned in at least two separate outpatient claims during the study period.

### Statistical analysis

The distributions of categorical demographic and clinical characteristics between the keloids and non-keloids control cohorts were compared by  $\chi^2$  test; mean age and follow-up time (y) were compared by Student's t-test and Wilcoxon rank-sum test as appropriate. In both cohorts, survival time was calculated until an ambulatory visit for migraine, hospitalisation or the end of the study period (31 December 2010), whichever came first. Migraine incidence rates per 1000 person-years were calculated and compared by Poisson regression analysis. The difference in cumulative incidence of migraine between the keloids and non-keloids cohorts was estimated by Kaplan-Meier analysis and two-tailed log-rank test. Multivariate models were adjusted for gender, age and relevant comorbidities (hypertension, hyperlipidaemia, stroke, diabetes mellitus, coronary artery disease, asthma, fibromyalgia, insomnia, depression, anxiety, alcohol attributed disease and obesity). We used univariable

and multivariable Cox proportional hazard regression models to examine HRs and 95% CIs for migraine in keloids patients when the proportional hazards assumption was satisfied. All data were analysed using SAS, V.9.4 (SAS Institute); a  $p < 0.05$  in a two-tailed test was considered statistically significant.

## RESULTS

### Patients and demographics

Of the 9864 keloids patients enrolled in this study during the follow-up period, migraine was observed in 103 of the 9864 (1.04%) keloids patients and in 323 of the 39456 (0.82%) non-keloids patients. **Table 1** compares the demographic characteristics and comorbidities between the keloids and non-keloids cohorts. Age and gender were similar in the two cohorts: in both cohorts, approximately 85% patients were younger than 50 years old, and approximately 62% patients were female. Compared with the non-keloids cohort, the keloids cohort had significantly higher percentages of patients with comorbidities. During observation time, the incidence of migraine was significantly ( $p < 0.05$ ) higher in the keloids cohort compared with the non-keloids cohort.

### Migraine incidence and risk

**Table 2** stratifies the migraine incidence rates and HRs by age, gender and concurrent comorbidity. During the follow-up period, migraine was observed in 1.04% (103) of the keloids patients and in 0.82% (323) of the non-keloids patients. The overall migraine risk was 2.29 times greater in the keloids cohort compared with the non-keloids cohort (1.81 vs 0.55 per 1000 person-years, respectively) after adjustment for age, gender and relevant comorbidities. In both the keloids and non-keloids cohorts, gender-specific analyses revealed a higher incidence of migraine in women compared with men (2.37 vs 0.88 per 1000 person-years, respectively, in the keloids cohort; 0.69 vs 0.30 per 1000 person-years, respectively, in the non-keloids cohort). Compared with the non-keloids cohort, however, the keloids cohort had a significantly higher migraine risk in both men (adjusted HR 2.02, 95% CI 1.73 to 4.28) and women (adjusted HR 2.37, 95% CI 1.92 to 3.29). Age-specific risk comparisons further demonstrated that, inpatients under 50 years old, migraine risk was significantly higher in the keloids cohort compared with the non-keloids cohort. Regardless of concurrent comorbidity, migraine risk was higher in the keloids cohort than in the non-keloids cohort.

**Figure 1** compares the Kaplan-Meier curves for the cumulative incidence of migraine between the keloids and non-keloids groups at the 15-year follow-up. The baseline risk of migraine development was significantly ( $p < 0.001$ ) higher in the keloids group (2.39%) compared with the non-keloids group (0.82%). The Kaplan-Meier curves also illustrated that the cumulative incidence of migraine was significantly higher in the keloids group compared with the non-keloids group.

### Risks factors for migraine in keloids group

**Table 3** shows the Cox regression analysis results, which revealed that risk factors for migraine in the keloids group were stroke (adjusted HR 4.75; 95% CI 2.72 to 8.33), fibromyalgia (adjusted HR 3.09; 95% CI 1.85 to 5.17), insomnia (adjusted HR 2.32; 95% CI 1.41 to 3.84), anxiety (adjusted HR 2.04; 95% CI 1.32 to 3.16), asthma (adjusted HR 1.71; 95% CI 1.10 to 2.65) and female gender (adjusted HR 2.35; 95% CI 1.42 to 3.90).

## DISCUSSION

After adjusting for these covariates, the results of this study suggest that the keloids group were more likely to develop

**Table 1** Baseline characteristics between patients with and without keloids

Variables	Keloids		P value
	Yes (n=9864)	No (n=39456)	
Migraine patients, n (%)	103 (1.04)	323 (0.82)	<0.05
Period of migraine development, years, (median, IQR)	3.1 (1.1–5.3)	8.2 (5.0–10.7)	<0.001
Mean age at migraine diagnosis, years	36.9 (13.3)	44.1 (15.7)	<0.001
Age group, n (%)			
18–49	8392 (85.08)	33 568 (85.08)	
≥50	1472 (14.92)	5888 (14.92)	1.000
Gender, n (%)			
Men	3735 (37.86)	14 940 (37.86)	
Women	6129 (62.14)	24 516 (62.14)	1.000
Comorbidity, n (%)			
Hypertension	1761 (17.85)	4630 (11.73)	<0.001
Diabetes mellitus	1238 (12.55)	3120 (7.91)	<0.001
Hyperlipidemia	2062 (20.90)	4993 (12.65)	<0.001
Stroke	283 (2.87)	641 (1.62)	<0.001
Coronary artery disease	262 (2.66)	469 (1.19)	<0.001
Asthma	1362 (13.81)	4544 (11.52)	<0.001
Fibromyalgia	4593 (46.56)	13 031 (33.03)	<0.001
Insomnia	4070 (41.26)	10 116 (25.64)	<0.001
Depression	1189 (12.05)	2620 (6.64)	<0.001
Anxiety	2366 (23.99)	5648 (14.31)	<0.001
Obesity	244 (2.47)	652 (1.65)	<0.001
Alcohol attributed disease	240 (2.43)	660 (1.67)	<0.001

migraine compared with the non-keloids group. However, the keloids group had a higher prevalence of comorbidities. Additional stratification analysis revealed that patients younger than 50 years had a significantly higher migraine risk compared with their older counterparts, which demonstrated that early onset of keloids increased the risk of migraine. In both genders, migraine risk was significantly higher in the keloids group compared with the non-keloids group. In the keloids group, migraine risk was higher in women than in men. These results are consistent with several reports that the prevalence of migraine is generally higher in women than in men and widely varies by age.<sup>3</sup> Migraine risk in both genders reportedly increases with age from adolescence to approximately 40–45 years and then declines

thereafter.<sup>3</sup> Regardless of comorbidity, the overall data showed a significantly higher migraine risk in the keloids group compared with the non-keloids group. In the keloids group, comorbidities specifically associated with increased migraine risk were stroke, fibromyalgia, insomnia, anxiety and asthma. To the best of our knowledge, this study is the first population-based analysis of the association between keloids and migraine.

The exact underlying mechanism of this association is unknown. However, independent lines of evidence in multiple studies indicate that keloids and migraines have a common pathophysiology. First, cumulative evidence indicates that TGF- $\beta$ 1 has a pivotal role in both keloids and migraines.<sup>5</sup> In keloids patients, TGF- $\beta$ 1 stimulates keloid fibroblast proliferation and collagen

**Table 2** Migraine risk and analyses by demographic characteristics and comorbidities among patients with or without keloids

Variables	Keloids cohort		Non-keloids cohort		Compared with non- keloids cohort	
	Migraine	Rate*	Migraine	Rate*	Crude HR (95% CI)	Adjusted HR† (95% CI)
Overall	103	1.81	323	0.55	3.57 (2.82 to 4.52)‡	2.29 (1.80 to 2.92)‡
Gender						
Men	19	0.88	68	0.30	3.16 (1.85 to 5.40)‡	2.02 (1.17 to 3.51)§
Women	84	2.37	255	0.69	3.69 (2.84 to 4.79)‡	2.37 (1.81 to 3.10)‡
Stratify by age						
18–49	84	1.71	213	0.42	4.35 (3.34 to 5.67)‡	2.65 (2.02 to 3.47)‡
≥50	19	2.43	110	1.25	2.13 (1.29 to 3.49)§	1.46 (0.88–2.39)¶
Comorbidity**						
No	10	0.48	41	0.12	4.21 (2.09 to 8.44)‡	3.49 (1.74 to 7.02)‡
Yes	93	2.55	282	1.06	2.57 (2.01 to 3.30)‡	2.16 (1.68 to 2.78)‡

\*Rate, per 1000 person-years.

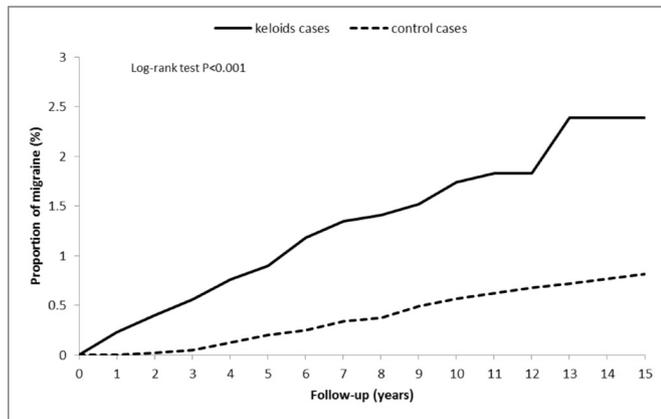
†Calculated by multivariate Cox proportional hazard regression model.

‡p<0.001.

§p<0.05.

¶P: non-significant.

\*\*Patients with any examined comorbidities were classified as the comorbidity group.



**Figure 1** Cumulative incidence of migraine among keloids cohort and non-keloids controls (log-rank test,  $p < 0.001$ ).

synthesis and induces production of molecules (eg, VEGF and PDGF) that promote collagen deposition and tissue angiogenesis. In Chen *et al*,<sup>10</sup> microarray assays revealed TGF- $\beta$ 1 gene upregulation in keloids patients. Another study by Ishizaki *et al*<sup>11</sup> reported higher plasma TGF- $\beta$ 1 levels in patients with migraines compared with patients without migraines. In another study, Bø *et al*<sup>12</sup> reported that TGF- $\beta$ 1 levels in cerebrospinal fluid cytokines were higher in patients with migraines compared with a control group of patients without migraines. Saygi *et al*<sup>13</sup> further reported a significantly higher frequency of TGF- $\beta$ 1 polymorphisms in migraine patients compared with healthy controls. In Eiser,<sup>14</sup> TGF- $\beta$ 1 activation appeared to mediate morbidities associated with keloids in African-Americans. A cross-sectional study by Adotama *et al*<sup>15</sup> showed that keloids patients had a significantly higher prevalence of hypertension and obesity compared with controls without keloids. Hypertension is positively associated with keloid severity, which implies that hypertension may be an indicator of keloid deterioration. Moreover, ear keloids are significantly associated with obesity.<sup>16</sup> In the present study, the high prevalence of morbidities in the keloids cohort suggests that morbidities may contribute to the underlying pathogenesis of keloids.

Second, interaction between mast cell hyperplasia and myofibroblast differentiation has been documented in fibrotic disease<sup>17</sup>; additionally, meningeal and brain mast cells linked with dural neurons modulate meningeal nociceptor activity and migraine genesis.<sup>18</sup> According to recent studies, activated mast cells can stimulate keloid formation by using proinflammatory cytokines (including tumour necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-6 and platelet activating factor to produce TGF- $\beta$ 1 (aprofibrotic factor) and histamine (a vasoactive amine). Accordingly, Chen *et al*<sup>10</sup> and Messadi *et al*<sup>19</sup> demonstrated the upregulation

of genes of proinflammatory cytokines (eg, IL-1 $\alpha$ , IL-1 $\beta$ , IL-6 and TNF- $\alpha$ ) in keloid fibroblasts. A migraine attack increases platelet activating factor, which is responsible for dermal scarring,<sup>17</sup> and eventually causes continuous platelet activation and hyperfunction in the cerebral circulation. Mast cells have essential contributing roles in the occurrence of keloids and migraine.

Third, neurogenic inflammation resulting in vasodilation and increased vascular permeability can also cause migraine attacks. These phenomena are modulated by a series of neuropeptides released, including CGRP and SP. Studies show that expressions of SP and CGRP are significantly increased in keloid tissue and that SP expression is elevated in keloid tissue and plasma.<sup>20</sup> Cohen *et al*<sup>21</sup> indicated that keloids have abnormally high histamine content and that the histamine contents parallel the collagen formation rate. Histamine causes the release of CGRP and SP from free nerve endings in the skin. Interactions between mast cells and CGRP sensitise trigeminal afferents and trigeminal ganglia. Heatley *et al*<sup>22</sup> reported that subjects with migraines exhibit increased plasma histamine levels, both ictally and interictally. Through its sustained effects on neurogenic inflammation pathways, histamine plays a crucial role in migraine pathogenesis.

Finally, the immune mediated mechanisms in vascular endothelia are involved in the pathophysiology underlying migraine. Toll-like receptors (TLRs), the key regulators of innate immune function, participate in the inflammatory responses activation in the brain. Bagabir *et al*<sup>23</sup> reported that keloid scar tissue has increased epidermal expression of TLR-6 and TLR-7 and increased dermal expression of TLR-8. Persistent TLR4 activation through release of proinflammatory cytokines, for example, IL-6, IL-8 and monocyte chemoattractant protein-1, has been implicated as a cause of fibrotic skin. Chen *et al*<sup>24</sup> reported that TLRs participate in fibrosis of scar tissue through the TLRs-TGF- $\beta$ -Smad signalling pathway, and Jang *et al*<sup>25</sup> reported that TLR expression in human skin fibroblasts is modulated by histamine. Rafiei *et al*<sup>26</sup> reported that TLR-4 polymorphism is a genetic risk factor for migraine; Su *et al*<sup>27</sup> further showed that inhibiting TLR-4 can alleviate hyperalgesia induced by dural inflammation during migraine. Thus, the immune response initiated by TLR activation increases proinflammatory cytokine production and immune cell recruitment, which then promote both scar formation and migraine development.

Interestingly, the calcium channel blocker verapamil has been used as both a keloid scar modulator and a migraine prophylactic.<sup>28</sup> During the healing process, calcium acts as a vital intracellular messenger and effector of fibroblasts; verapamil is capable of reducing inflammation, extracellular matrix production and cell growth by interfering with synthesis of arachidonic acid, enhancement of collagenase secretion and reduction of the cytosolic concentration of the calcium-calmodulin complex in keloids.<sup>29</sup> Yin *et al*<sup>30</sup> reported the risk of migraine increased with the serum calcium levels by 1 mg/dL; the authors also demonstrated that migraine and increased calcium levels shared a similar genetic basis. In migraine, verapamil is thought to alleviate cerebral vasoconstriction not only by reducing Ca<sup>2+</sup> cellular influx, but also by blocking hyperalgesia through nitric oxide inhibition. Therefore, the overlapping treatment modality indicates that Ca<sup>2+</sup> may have a common etiological role in migraines and keloids.

A remarkable strength of this research is the use of a dataset for a large population sample from various geographical regions. The use of this dataset provided sufficient statistical power for analysing the association between keloids and subsequent migraine. Second, the population analysed in this Taiwan study was predominantly Asian, which is known to have a

**Table 3** Significant predictors of migraine after keloids

Variables	Adjusted HR* (95% CI)
Stroke	4.75 (2.72 to 8.33)†
Fibromyalgia	3.09 (1.85 to 5.17)†
Insomnia	2.32 (1.41 to 3.84)†
Female gender	2.35 (1.42 to 3.90)†
Anxiety	2.04 (1.32 to 3.16)†
Asthma	1.71 (1.10 to 2.65)‡

\* Calculated by stepwise Cox proportional hazards regression method.

†  $p < 0.001$ .

‡  $p < 0.05$ .

high prevalence of keloids. Analysing this population provided important genomic insights into the roles of ancestry in keloids and migraine. Finally, the NHIRD dataset contains original claim records for insurance purposes rather than for academic study, which would attenuate bias in patient selection. For these reasons, this dataset has already been applied in numerous published researches in recent academic journals.

However, this study has potential limitations. First, some patients with keloids may be reluctant to seek professional medical help for their skin conditions due to extreme embarrassment. Despite the low cost of medical treatment in Taiwan, they may still prefer to consult local pharmacists or practitioners of complementary medicine. Hence, this study may have underestimated the actual incidence of keloids. Additionally, all insurance claims were reviewed and audited by medical reimbursement specialists, which further supported the validity and accuracy of the migraine diagnoses. Furthermore, the validity of the database has been established in several similar studies with large samples and long-follow periods;<sup>6-9</sup> the finding regarding the association between keloids and migraines was reliable. Second, the database did not contain information about the anatomic location, number, or severity of keloids and possible insults leading to keloid formation. Additionally, the database did not contain complete clinical information of laboratory examination results, migraine frequency and severity. Therefore, the potential roles of various risk factors in the association between keloids and migraines could not be investigated. Further mechanistic studies are warranted to clarify the roles of these risk factors. Moreover, detailed research is suggested to explore the changes in TGF- $\beta$ 1 or neurogenic inflammation and immune function. Finally, the results of this study of data for a predominantly Asian population in Taiwan may not be generalisability to other ethnic populations.

## CONCLUSIONS

This study found that keloids patients have a higher than normal migraine risk, regardless of concurrent comorbidities. This hypothesis is supported by evidence that keloids release numerous inflammatory mediators and neurogenic biomarkers that activate the trigeminovascular system, which then contributes to development of migraine attacks. Age younger than 50

years and female gender are risk factors for migraines. Moreover, keloids patients with concurrent stroke, fibromyalgia, insomnia, anxiety or asthma have a higher than normal migraine risk. Thus, adult patients being treated for keloids should also be examined for migraine symptoms. Further studies are also needed to clarify the mechanisms of migraines and associated risk factors in patients with keloids to determine the ideal clinical interventions for preventing and treating migraines.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** This study was conducted according to the principles of the Declaration of Helsinki and was approved to fulfil the condition for exemption by the ethical review board of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT (II) 20160016).

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**Data availability statement** All data relevant to the study are included in the article or uploaded as online supplemental information. All relevant data are within the manuscript.

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### What is already known on the subject

- ▶ Keloids are fibroproliferative lesions with intractable pruritus, pain and hyperesthesia that cause uncontrolled scar growth.
- ▶ Migraines are common upsetting headache disorders characterised by frequent recurrence and attacks aggravated by physical activity.

### Main messages

- ▶ This is the first population-based analysis of the association between keloids and migraines.
- ▶ The keloids patients had a 2.29-fold greater risk of developing migraines compared with the non-keloids group. In the keloids group, female or patients younger than 50 years were prone to developing migraines.
- ▶ Keloids could be a predisposing risk factor for migraine development in adults. Therefore, keloids patients who have headaches should be examined for migraines.

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