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Gout and the risk of epilepsy

A population-based cohort study

Hung-Lin Chen, PhD[a,b], Yi-Chao Hsu, PhD[c], Chang-Hsu Chen, MD[d], Pei-Jen Wang, BS[a], Cheng-Li Lin, MSc[e], Sheng-Han Cheng, MD[f,*], Kuang-Hsi Chang, PhD[a,g,h,*]

Abstract

Gout is a chronic disease related to uric acid metabolism. It involves crystals of uric acid accumulating in the joints, causing joint pain and releasing cytokines that trigger inflammation. Inflammation is a key component in the pathogenesis of epilepsy. Thus, we conducted a cohort study to investigate if epilepsy is associated with gout and determine the risk of epilepsy in patients with gout.

The gout cohort was obtained from the Registry of Catastrophic Illnesses Patient Database (RCIPD). We identified 104,238 patients who were aged 20 years or more and newly diagnosed with gout between 2000 and 2011 and 3 outpatient visits or history of gout-specific hospitalization between 2000 and 2011. Patients without gout were frequency matched with the gout cohort at a 2:1 ratio according to age, sex, comorbidities, and year of gout diagnosis.

The gout cohort showed a 1.27-fold higher overall crude hazard ratio (HR) for epilepsy compared with the control cohort. After we adjusted the analyses by age, sex, and comorbidities the gout patients displayed an increased risk of epilepsy compared with the control group (adjusted HR = 1.25, 95% confidence interval = 1.15–1.36).

This study revealed a significantly higher risk of epilepsy in patients with gout. It provides further evidence for the debate around the effect of gout on brain health.

Abbreviations: aHR = adjusted HR, CAD = coronary artery disease, cHR = crude HR, CIs = confidence intervals, CNS = central nervous system, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2000 = Longitudinal Health Insurance Database 2000, MSU = monosodium urate, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, NSAIDs = nonsteroidal anti-inflammatory drugs, PY = person-years, RCIPD = Registry of Catastrophic Illnesses Patient Database.

Keywords: epilepsy, gout, inflammation, Registry of Catastrophic Illnesses Patient Database

1. Introduction

Gout is a chronic inflammatory disease related to uric acid metabolism.[1] Sustained hyperuricemia leads to intra- and/or peri-articular monosodium urate (MSU) crystal accumulation.[2] While free MSU crystals are phagocytosed by immune cells including resident macrophages and other mononuclear cells, it triggers inflammation via the NALP-3 inflammasome, which stimulates secretion of the cytokine IL-1β into the blood.[3–5]

Gout constitutes an increasing burden of disease worldwide. The prevalence of gout in the United States and the United Kingdom is 3.9% and 2.49%, respectively. In Taiwan, the

Editor: Antonio Palazón-Bru.

Data availability statement: Data are available from the NHIRD published by Taiwan National Health Insurance Bureau. Due to the "Personal Information Protection Act," data cannot be made publicly available (http://nhird.nhri.org.tw/en/index.html).

This study was supported by Tung's Taichung MetroHarbor Hospital research grant (TTMHH-107R0016 and TTMHH-109R0010), Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW108-TDU-B-212–133004), China Medical University Hospital, Academia Sinica Stroke Biosignature Project (BM10701010021), MOST Clinical Trial Consortium for Stroke (MOST 108–2321-B-039–003-), Tseng-Lien Lin Foundation, Taichung, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan.

The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the present study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

[a] Department of Medical Research, Tungs' Taichung MetroHarbor Hospital, Taichung, [b] Department of Nursing, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli Miao, [c] Institute of Biomedical Sciences, Mackay Medical College, New Taipei, [d] Division of Nephrology, Tungs' Taichung MetroHarbor Hospital, [e] Management Office for Health Data, China Medical University Hospital, Taichung, [f] Division of Allergy, Immunology and Rheumatology, Tung's Taichung MetroHarbor Hospital, [g] Graduate Institute of Biomedical Sciences, China Medical University, Taichung, [h] General Education Center, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli, Taiwan.

[*] Correspondence: Kuang-Hsi Chang, Department of Medical Research (e-mail: kuanghsichang@gmail.com); Sheng-Han Cheng, Division of Allergy, Immunology and Rheumatology, Tung's Taichung MetroHarbor Hospital, Taichung, Taiwan (e-mail: t12349@ms.sltung.com.tw).

How to cite this article: Chen HL, Hsu YC, Chen CH, Wang PJ, Lin CL, Cheng SH, Chang KH. Gout and the risk of epilepsy: A population-based cohort study. Medicine 2020;99:26(e20823).

Received: 9 December 2019 / Received in final form: 8 April 2020 / Accepted: 18 May 2020

http://dx.doi.org/10.1097/MD.0000000000020823

prevalence of gout is 6.25%, which is a significantly higher prevalence compared with that in many other countries.[6] Although there are several options for treating gout, treatment outcomes are not as good as could be expected.

Recent studies have revealed that gout may be associated with neurologic disorders, such as autoimmune and neurodegenerative dementia and Alzheimer's disease.[7–9] These neurologic diseases are associated with inflammation, which is a condition that can be induced in patients with gout. In addition, there is accumulating evidence to suggest that inflammation also plays a critical role in the pathology of epilepsy.[10,11] Epilepsy is one of the most common brain disorders and can evoke severe physical and psychological complications in patients who suffer with it. Currently, epilepsy affects more than 50 million people worldwide. Dysregulation of inflammation is related to the development of epilepsy. Although the role played by inflammation in the pathology of epilepsy is not clear, it is possible that impaired inflammatory processes cause abnormal neural connectivity and hyper-excitability of neuronal networks, leading to epilepsy.

The risk of stroke, diabetes, ischemic heart disease, and hypertension has been shown to increase with both gout and epilepsy.[12–15] However, there is currently no direct evidence to support any association between gout and epilepsy. Therefore, we conducted this cohort study to determine the risk of epilepsy in patients with gout.

2. Methods

2.1. Data sources

Data were acquired from the National Health Insurance Research Database (NHIRD), which holds data relating to inpatient care, ambulatory care, medication, and expenses from 1996 to 2011. Since the compulsory single-payer National Health Insurance (NHI) program of Taiwan began in 1995, more than 99% of the 23.75 million residents of Taiwan have enrolled in this program. To ensure the NHI reimbursement data are legal for public research, all personal identification data are removed to maintain privacy and confirm all data are de-identified prior to being released. Following privacy protocols, for all files that needed to be linked this linking was achieved via encrypted identification numbers. This retrospective cohort study utilized a subset of the NHIRD, including files from the Registry of Catastrophic Illnesses Patient Database (RCIPD) and the Longitudinal Health Insurance Database 2000 (LHID2000). Diseases in the NHIRD data were defined using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This cohort study was approved by the Ethical Review Board of China Medical University (CMUREC-101–012).

2.2. Sampled patients

The gout cohort from the RCIPD included patients who were aged more than 20 years and newly diagnosed with gout (ICD-9-CM Code 274) and 3 outpatient visits or history of gout-specific hospitalization between 2000 and 2011. The RCIPD aims to track patients who have major or catastrophic illnesses, including cancer, end-stage renal disease, mental illness, congenital illness, and several autoimmune diseases, including gout. When patients are registered on the RCIPD, the Bureau of NHI routinely reviews the original medical charts to validate the diagnosis of a catastrophic illness. The index date represented the date of a diagnosis of gout. Patients were excluded if they had been diagnosed of epilepsy (ICD-9-CM Code 345) before the index date or had an incomplete medical history or follow-up within 6 months. The control cohort included patients without a history of gout who were randomly selected from the LHID2000. We first selected the controls whose age, sex, and comorbidities matched the corresponding gout patient. Among the controls from the first step, we randomly selected 2 controls who were still enrolled in the NHI program in the same year as the corresponding year of gout diagnosis of the gout patient. Then, we assigned that year as the index year of the controls. Furthermore, the index year plus a randomly assigned month and date will be the index date of the controls. The frequency of matching between the control and gout cohorts was a 2:1 ratio, based on age (in 5-year bands), sex, comorbidities, and the year of gout diagnosis, using the same exclusion criteria (see Fig. 1).

2.3. Outcomes

All patients were tracked from the index date until a diagnosis of epilepsy (ICD-9-CM 345) or censoring due to death or the end date of the database (December 31, 2011).

2.4. Comorbidities

Baseline comorbidities included in the analysis were as follows: diabetes (ICD-9-CM Code 250), hypertension (ICD-9-CM Codes 401–405), head injury (ICD-9-CM Codes 850–854, 959.01), coronary artery disease (CAD) (ICD-9-CM Codes 410–414), stroke (ICD-9-CM Codes 430–438), and autoimmune disease (ICD-9-CM Codes 710.0, 710.1, 710.2, 710.3, 710.4, and 696.0). The follow-up times for the case and control groups were 7.42 (SD = 3.21) years and 7.24 (SD = 3.26) years, respectively.

2.5. Statistical analysis

The distribution of categorical characteristics between the gout and the control cohorts were described and compared using Pearson's chi-squared test for categorical variables and a two-sample *t* test for continuous variables. The cumulative incidence of epilepsy between the gout and control cohorts was assessed using the Kaplan–Meier method, and the differences between the groups were assessed using a log-rank test. The incidence densities (per 1000 person-years) of epilepsy were estimated according to various risk factors. Univariate and multivariate Cox-proportional hazard regression models were adopted to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of developing epilepsy. In addition, the Cox model was used to assess the risk of epilepsy development in the gout cohort compared with the control cohort. All data analyses were performed using SAS for Windows (Version 9.4; SAS Institute, Inc, Cary, NC). A two-tailed *P* value of .05 was considered statistically significant.

3. Results

3.1. Demographic characteristics and comorbidities in the gout and control cohorts

The demographic characteristics and comorbidities of the gout and control cohorts are shown in Table 1. The gout cohort contained 51,893 patients and the control cohort contained 103,057 patients. There were no statistical differences in the distributions of age and sex between the gout and control cohorts (the mean age was ~52 years). In the gout cohort, 53.9% of patients were older than 50 years old, and 72.4% were men. No

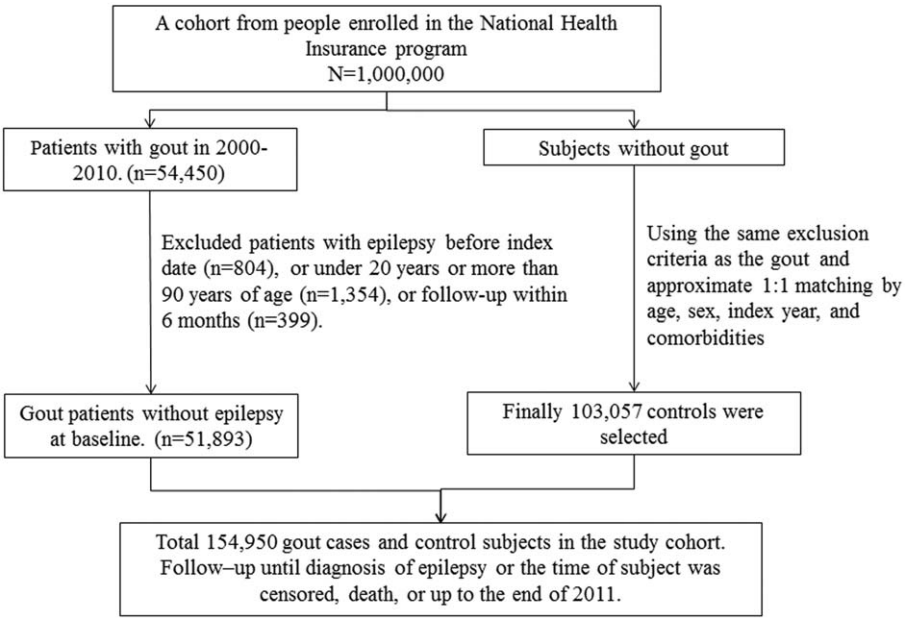

Figure 1. Flow diagram for study participants.

significantly different prevalence of diabetes, hypertension, stroke, CAD, head injury, or autoimmune disease was observed between the gout and control cohorts.

3.2. Cox model analysis of risk factors related to epilepsy development

The overall incidence of epilepsy was 1.27-fold higher in the gout cohort compared with the control cohort (2.39 vs 1.87 per 1000 person-years, 95% CI = 1.17–1.38) (Table 2). Even after being adjusted for age, sex, and comorbidities, patients with gout were still associated with an increased risk of epilepsy compared with those without gout (adjusted HR [aHR] = 1.25, 95% CI = 1.15–1.36). Multivariable analysis also showed that the incidence of epilepsy increased with age. After adjustment for potential risk factors, the risk of epilepsy incidence was 1.28-fold higher in patients aged 35 to 49 years (95% CI = 1.07–1.53), 1.54-fold higher in those aged 50 to 64 years (95% CI = 1.29–1.85), and 2.57-fold higher in those aged 65 years or more (95% CI = 2.14–3.09), compared with patients aged 34 years or less. Sex also affected the risk of developing epilepsy (aHR of male to female = 1.29, 95% CI = 1.17–1.41). All comorbidities investigated increased the incidence of epilepsy in patients with the exception of autoimmune disease. A higher risk of epilepsy was apparent for patients with the comorbidities of diabetes (aHR = 1.18, 95% CI = 1.05–1.33), hypertension (aHR = 1.61, 95% CI = 1.45–1.79), stroke (aHR = 2.86, 95% CI = 2.51–3.26), CAD (aHR = 1.20, 95% CI = 1.09–1.32), and head injury (aHR = 2.11, 95% CI = 1.83–2.43).

Table 1

Demographic characteristics and comorbidities in cohorts with and without gout.

Variable	Gout cohort (n = 51,893)		Control group (n = 103,057)		*P*
Age (years)					
≤34	8570	16.5%	16,977	16.5%	.992
35–49	15,395	29.7%	30,622	29.7%	
50–64	14,923	28.8%	29,672	28.8%	
65+	13,005	25.1%	25,786	25.0%	
Mean ± SD*	52.29 ± 16.17		51.98 ± 16.43		<.001
Follow years					
Mean ± SD*	7.47 ± 3.16		7.32 ± 3.19		<.001
Male	37,553	72.4%	74,521	72.3%	.822
Comorbidity					
Diabetes	5785	11.1%	11,358	11.0%	.458
Hypertension	23,490	45.3%	46,569	45.2%	.773
Stroke	2042	3.9%	3885	3.8%	.113
CAD	10,459	20.2%	20,622	20.0%	.506
Head injury	2563	4.9%	4921	4.8%	.159
Autoimmune disease	45	0.1%	65	0.1%	.122

CAD = coronary artery disease.
Chi-square test.
* *t* test.

Table 2

The incidence and risk factors for epilepsy.

Variables	No. of event	PY	IR	cHR (95% CI)	aHR (95% CI)
Gout					
No	1411	754,238	1.87	1.00	1.00
Yes	926	387,780	2.39	1.27 (1.17–1.38)	1.25 (1.15–1.36)
Age, year					
≤34	186	194,173	0.96	1.00	1.00
35–49	483	364,715	1.32	1.37 (1.16–1.63)	1.28 (1.07–1.53)
50–64	667	331,580	2.01	2.10 (1.78–2.47)	1.54 (1.29–1.85)
65+	1001	251,550	3.98	4.22 (3.61–4.93)	2.57 (2.14–3.09)
Sex					
Female	669	312,322	2.14	1.00	1.00
Male	1668	829,696	2.01	1.07 (0.98–1.17)	1.29 (1.17–1.41)
Diabetes					
No	1980	1,032,474	1.92	1.00	1.00
Yes	357	109,545	3.26	1.73 (1.54–1.93)	1.18 (1.05–1.33)
Hypertension					
No	805	651,858	1.23	1.00	1.00
Yes	1532	490,161	3.13	2.55 (2.34–2.78)	1.61 (1.45–1.79)
Stroke					
No	2049	1,109,800	1.85	1.00	1.00
Yes	288	32,218	8.94	5.03 (4.45–5.69)	2.86 (2.51–3.26)
CAD					
No	1572	927,574	1.69	1.00	1.00
Yes	765	214,444	3.57	2.12 (1.95–2.32)	1.20 (1.09–1.32)
Head injury					
No	2125	1,094,214	1.94	1.00	1.00
Yes	212	47,804	4.43	2.32 (2.02–2.68)	2.11 (1.83–2.43)
Autoimmune disease					
No	2334	1,141,374	2.04	1.00	1.00
Yes	3	644	4.66	2.33 (0.75–7.24)	2.51 (0.81–7.78)

aHR = adjusted hazard ratio, cHR = crude hazard ratio, IR = incidence rate, per 1000 person-years, No. of event: number of patients with epilepsy, PY = person-years, multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, stroke, CAD, head injury, and autoimmune disease.

3.3. Incidence and HRs of epilepsy stratified by age, sex, and comorbidity: comparison between gout and control cohorts

When samples were stratified by age, the relative risk of epilepsy was significantly higher in the gout cohort compared with the control cohort in all stratified ages (≤34 years: aHR = 1.63, 95% CI = 1.22–2.18; 35–49 years: aHR = 1.22, 95% CI = 1.02–1.47; 50–64 years: aHR = 1.27, 95% CI = 1.09–1.48; ≥65 years: aHR = 1.18, 95% CI = 1.04–1.34). After stratification by sex, the gout cohort still displayed a significantly higher relative risk of developing epilepsy compared with the control cohort, regardless of sex (female: aHR = 1.34, 95% CI = 1.15–1.56; male: aHR = 1.22, 95% CI = 1.10–1.34). The final sample stratification was by comorbidity. The risk of epilepsy was increased in the gout cohort compared with the control cohort with or without a comorbidity (no comorbidity: aHR = 1.29, 95% CI = 1.09–1.52; comorbidity: aHR = 1.24, 95% CI = 1.13–1.36) (Table 3).

Table 3

Incidence of epilepsy by age, sex, and comorbidity and Cox model measured hazards ratio for patients with gout compared those without gout.

	Control group			Gout cohort				
Variables	No. of event	PY	IR	No. of event	PY	IR	cHR (95% CI)	aHR (95% CI)
Age, years								
≤34	100	128,105	0.78	86	66,068	1.30	1.67 (1.25–2.22)	1.63 (1.22–2.18)
35–49	296	241,724	1.22	187	122,991	1.52	1.24 (1.03–1.49)	1.22 (1.02–1.47)
50–64	402	219,499	1.83	265	112,081	2.36	1.29 (1.10–1.50)	1.27 (1.09–1.48)
65+	613	164,910	3.72	388	86,640	4.48	1.20 (1.06–1.36)	1.18 (1.04–1.34)
Sex								
Female	394	206,868	1.90	275	105,454	2.61	1.37 (1.17–1.60)	1.34 (1.15–1.56)
Male	1017	547,370	1.86	651	282,326	2.31	1.24 (1.12–1.37)	1.22 (1.10–1.34)
Comorbidity								
No	357	371,927	0.96	237	190,303	1.25	1.29 (1.10–1.52)	1.29 (1.09–1.52)
Yes	1054	382,311	2.76	689	197,477	3.49	1.26 (1.15–1.39)	1.24 (1.13–1.36)

aHR = adjusted hazard ratio, cHR = crude hazard ratio, IR = incidence rate, per 1,000 person-years, No. of event: number of patients with epilepsy, PY = person-years, multivariable analysis including age, sex, and comorbidities of diabetes, hypertension, stroke, CAD, head injury, and autoimmune disease.

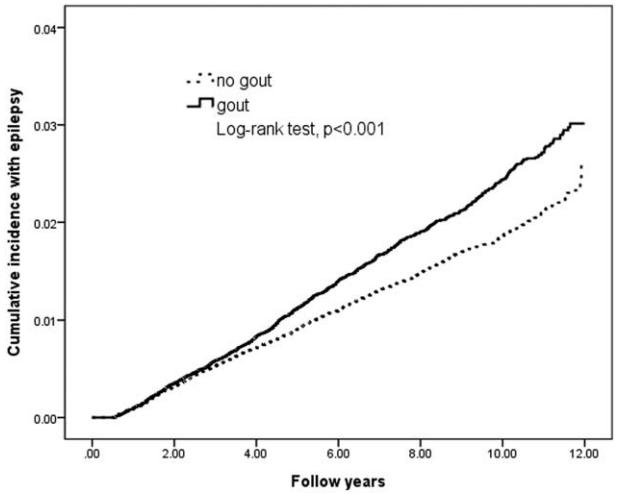

Figure 2. A comparison of cumulative incidence of epilepsy for patients with (solid line) or without (dashed line) gout.

3.4. Cumulative incidence of epilepsy in the gout and control cohorts

The mean follow-up periods of the gout and control cohorts were 7.42 years and 7.24 years, respectively. The cumulative incidence curves of epilepsy were estimated using a Kaplan–Meier analysis, and the results showed a significantly higher rate in the gout cohort compared with that in the control cohort (log-rank test $P < .001$; Fig. 2).

4. Discussion

Our analysis clearly indicated that a high level of coincidence between epilepsy and gout exists. There was a statistically significant increased risk of epilepsy in patients with gout compared with patients without gout. The epileptogenesis is still vague.[16,17] There is some evidence to indicate that stroke, brain tumors, and traumatic brain injury may lead to the development of epilepsy.[18–20] Chronic inflammation is considered to play a critical role in epileptogenesis and increase the risk of epilepsy. Gout is a common arthritic disease that causes chronic inflammation by inducing cytokines. Cytokines may cross the blood–brain barrier to activate innate immunity and the transition to adaptive immunity in the central nervous system (CNS).[21] Evidence exists which suggests an association between inflammation of the CNS and epilepsy.[22,23]

One of the major symptoms of gout is pain, which could be another important connection between epilepsy and gout. The perception of pain involves activity in the cerebral cortex and extensive cortical networks. Several studies have indicated that abnormal circuitry between the thalamus and the cerebral cortex could make some contribution to the mechanism that results in seizures. Unusual electrical activity in the cortical area which comes from the perception of pain may induce seizures in patients with gout.

However, although inflammation and pain could be reasons for the increased risk of epilepsy in patients with gout, a limitation of this study is that the NHIRD cannot provide sufficiently convincing data to reach a firm conclusion. It will be necessary to conduct more clinical and experimental studies, such as molecular biological studies or the use of animal models.

The connection between gout and epilepsy has rarely been studied. This was the first nationwide study to evaluate a possible relationship between having gout and being at increased risk of developing epilepsy. Significantly, this study analyzed a national database which included all patients with gout in Taiwan and included data related to inpatient care, ambulatory care, dental care, prescription drugs, and costs. Since there is only one compulsory social insurance program in Taiwan, the NHI program covers almost 100% of Taiwan's residents. This study enrolled 51,893 patients with gout, which was similar to the number in another national study in which the total number of gout patients in Taiwan was 56,595, between 1995 and 2010.[6] The long follow-up period (1996–2011) in this study provided an accurate assessment of possible epilepsy occurrence.

However, there are several potential limitations to this study. For example, it lacked original clinical data, such as blood tests and electroencephalograms of patients to confirm gout and epilepsy diagnoses, since the NHIRD does not store these clinical data. To overcome this limitation, the gout and epilepsy diagnoses in this study were determined by ICD-9-CM Codes, which are determined by highly trained clinicians; ICD-9-CM Codes for disease diagnoses in the NHIRD have been frequently and consistently used in other studies.[6,24] Another major limitation of the NHIRD is the lack of lifestyle information, such as smoking frequency and level of alcohol consumption. Nevertheless, the confounding effects of smoking and alcohol can be ignored since gout is a sex-specific disease.

Compared with 2 nationwide studied in the United States, the prevalence of hypertension, CAD and diabetes in gout patients were significantly lower in present study.[25,26] The mean age of gout patients was 52 and 71 years in our study and Keenan's study, respectively. The male ratios were 72% and 99%, respectively.[25] The differences in age and sex distribution resulted in the lower prevalence of comorbidities in our study. The obesity prevalences were 16.7 (BMI $\geq$ 27) and 32.8 (BMI $\geq$ 30) in the Taiwan population and non-gout population in the United States, respectively.[26,27] The large differences in obesity prevalence between 2 populations led to the lower prevalence of comorbidities in our study. However, a previous Taiwan study reported that 45.57% of 7690 gout patients had hypertension from 2002 to 2011, which was consistent with our results.[28] Our study had exclusion criteria that were similar to those of the 2 nationwide studies in the United States; however, we additionally excluded patients who were diagnosed with epilepsy (ICD-9-CM Code 345) before the index date. This exclusion criterion might have decreased the prevalence of comorbidities in participants of our study. In spite of the potential over-diagnosis in the gout cohort, strict fines from the Taiwan Bureau of National Health Insurance may have minimized the impact of misclassification, and this bias result may have under-estimated the risk of epilepsy in gout patients. In addition, the prevalence of hypertension, diabetes, and CAD in gout patients varies among different regions and this may be due to ethnicity or lifestyle, such as food and exercise habits.

Furthermore, in Taiwan, a significantly lower proportion of women smokes and drinks alcohol compared with men. Other risk factors associated with epilepsy, such as diet, environment, and family history, were not available in the NHIRD either, so we cannot estimate the effects of these factors on the risk of developing epilepsy in patients with gout.

The role of gout in brain diseases has recently been debated.[29] One study indicated that people who have gout have a 24%

lower risk of Alzheimer's after stratification by age, sex, lifestyle, and weight.[8] However, another study found that people with gout may have a 17% to 20% higher risk of dementia.[9] Our study revealed that people who had gout showed a 25% increased risk of epilepsy. Thus, we have provided further clear evidence to show the adverse effects of gout in relation to brain diseases. Gout causes inflammation leading to the release of cytokines, which may be a possible risk factor for epilepsy. Our previous study showed that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of epilepsy in patients with rheumatoid arthritis.[24] NSAIDs are also used as gout medications. Thus, when gout patients seek treatment for pain relief during the early stages of the disease, this may also help lower their risk of epilepsy. Due to the limitations of the NHI database, further clinical studies are required to delineate the biological mechanisms by which gout results in an increased risk of epilepsy.

Author contributions

Conceptualization: KH Chang
Formal analysis: KH Chang, CL Lin
Investigation: all authors
Methodology: KH Chang, CL Lin
Project administration: HL Chen, KH Chang.
Supervision: KH Chang
Visualization: all authors
Writing – original draft preparation: KH Chang, HL Chen
Writing – review & editing: KH Chang, HL Chen

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