Association of gout with CAD and effect of antigout therapy on CVD risk among gout patients

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ABSTRACT

Hyperuricemia has been identified as an independent risk factor for coronary artery disease (CAD), with a dose–response association. In this study, we explored the causal association between gout and antigout medication and the risk of incidental CAD. We sampled data from the National Health Insurance Research Database and recruited 37,091 patients as the gout cohort, and 37,091 controls. Our primary endpoint was the diagnosis of CAD during follow-up. The overall study population was followed up until CAD diagnosis, withdrawal from the National Health Insurance program, or the end of the study. Cox proportional hazards regression models were used to examine the effect of gout on the risk of CAD, represented by the HR with the 95% CI. Patients with gout were at greater risk of CAD, compared with those without gout: HR=1.49 after adjusting for potential confounders. Non-steroidal anti-inflammatory drugs and prednisolone use was associated with a reduced risk of CAD; HR=0.63 and 0.50, respectively. Patients with gout, treated with antigout medication, exhibited a reduced risk of CAD compared with non-gout patients. Among patients with gout, those on antigout therapy had 32% lower risk compared with those not on antigout therapy: adjusted HR=0.68, 95% CI 0.63 to 0.73. Gout increases the risk of CAD, and the use of antigout medication reduces CAD risk. These results indicate that gout or hyperuricemia is a modifiable risk factor for CAD.

BACKGROUND

The association between high levels of serum uric acid (UA) and cardiovascular disease (CVD) has long been recognized, although this has been refuted in a number of studies. Serum UA is a final enzymatic product of purine metabolism. Many studies have demonstrated that UA is a biologically active compound that can increase inflammatory mediators of vascular damage. However, UA has potentially protective effects as a strong antioxidant, approaching the potency of vitamin C. Hyperuricemia is generally defined as serum UA concentration exceeding the limit of solubility (around 6.8 mg/dL). There are no universally accepted criteria to define hyperuricemia and serum UA levels ranging...

Significance of this study

What is already known about this subject?

- The association between high levels of serum uric acid (UA) and cardiovascular disease (CVD) has long been recognized.
- UA is a biologically active compound that can increase inflammatory mediators of vascular damage.
- UA has potentially protective effects as a strong antioxidant, approaching the potency of vitamin C.
- Previous studies have frequently failed to distinguish whether serum UA is merely a marker for risk or a causative agent in CVD, or whether treatment targeting serum UA levels affects outcomes.

What are the new findings?

- The adjusted HR (aHR) on CVD risk was 1.49 (95% CI 1.43 to 1.56) in the gout cohort, compared with the non-gout cohort, after adjusting for age, sex, comorbidities, and medication (non-steroidal anti-inflammatory drugs and prednisolone).
- Compared with controls, patients with gout who were not treated with antigout medication had a significantly increased risk of coronary artery disease (CAD) (aHR=1.62, 95% CI 1.55 to 1.69), followed by patients who had a history of treatment with antigout medication (aHR=1.10, 95% CI 1.02 to 1.18).
- Patients with gout receiving treatment exhibited a significantly lower risk of CAD (aHR=0.68, 95% CI 0.63 to 0.73) compared with patients with gout who were not treated with antigout medication.

How might these results change the focus of research or clinical practice?

- This study supports the hypothesis that there is an increased risk of CAD among patients with gout, particularly among patients who are not treated with antigout medication, and the reduced risk in patients with gout with antigout medication treatment. Our findings indicate that gout or hyperuricemia is a modifiable risk factor for CAD.
from 5.6 to 7.7 mg/dL in men and from 4.9 to 7.0 mg/dL in women have been used.1 Hyperuricemia and gout are closely related conditions affecting the quality of life and work productivity and are prevalent worldwide. Krishnan et al reported that hyperuricemia and untreated gout were poor prognostic markers among patients with a recent acute myocardial infarction.15 Two recent studies in 2016 also reported that higher serum UA levels were independently associated with a dose–response increased risk of coronary artery disease (CAD).16,17 CVD is one of the most common non-communicable diseases, predicted to be the major cause of morbidity and mortality in developing nations.18 The majority of CVD deaths are due to CAD. Therefore, prevention of CVD and, specifically, CAD, is clearly a major public health issue. Growing concern has mounted regarding the premature morbidity and mortality associated with CAD and there has been a recent focus on modifying risk factors and reversing the global epidemic.

Both asymptomatic hyperuricemia and gout have been identified as independent risk factors for the development and progression of CVD, CVD mortality, and all-cause mortality.6,19,20 However, studies have frequently failed to distinguish whether serum UA is merely a marker for risk or a causative agent in CVD, or whether treatment targeting serum UA levels affects outcomes. In this retrospective cohort study, we postulated that hyperuricemia was a modifiable risk factor with a dose–response association with CAD and used a nationwide data set to determine whether gout was a predictor of CAD. We also explored the association between antigout medication treatment and CAD. We hypothesized, first, that patients with gout may have a higher risk of CAD than the general population, after adjustment for other possible demographic and metabolic confounders; and second, that antigout medication may lower CAD risk.

**METHODS**

**Data source**

In this retrospective cohort study, we used the data obtained through the Longitudinal Health Insurance Database 2000 (LHID 2000), from the National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program was implemented in Taiwan in 1995, and provides universal coverage for most Taiwanese residents.21 The NHIRD contains data of outpatient visits, hospital admissions, prescriptions, and vital status of 99% of the 23.74 million population of Taiwan. The details of LHID 2000 have been described previously.22,23 Every disease diagnosis made in Taiwan is evaluated by the National Bureau of Health Insurance. Any misdiagnosis is penalized with 100-fold of the healthcare expenses reimbursed by NHI for a claimed disease diagnosis.

**Sampled subjects**

Patients with newly diagnosed gout (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM code 274) were identified between January 1, 2000 and December 31, 2011; the index date was set as the day of gout diagnosis. Patients with a history of CAD (ICD-9-CM codes 410–414) before the index date were excluded. The CAD or coronary heart disease (ICD-9-CM codes 410–414) was coded when there were symptoms (chest pain as angina, or shortness of breath or heart attack) and coronary ischemic change (noted in ECG or single-photon emission CT or cardiac catheterization). The cohort without gout (ICD-9-CM code 274) was identified during the same period from the LHID 2000 using exclusion criteria comparable to the gout cohort. Each patient with gout was matched to 1 non-gout control using propensity scores. The propensity

| Table 1  Characteristics between subjects with and without gout |
|-----------------|-----------------|-----------------|-----------------|
| **Variables**   | **Gout** (n=37,091) | **Non-gout** (n=37,091) | **Standard difference** |
| Age, y (n, %)   |                  |                  |                  |
| 20–49           | 20,472 (55.2)    | 19,829 (53.5)    | 0.035            |
| 50–64           | 10,237 (27.6)    | 10,580 (28.5)    | 0.021            |
| ≥65             | 6382 (17.2)      | 6682 (18.0)      | 0.021            |
| Age, y (mean, SD) | 48.9 (15.2)     | 49.2 (15.6)      | 0.022            |
| Gender (n, %)   |                  |                  |                  |
| Female          | 8935 (24.1)      | 9211 (24.8)      | 0.017            |
| Male            | 28,156 (75.9)    | 27,880 (75.2)    | 0.017            |
| Comorbidity (n, %) |              |                  |                  |
| HT              | 13,131 (35.4)    | 13,417 (36.2)    | 0.016            |
| Diabetes        | 3248 (8.76)      | 3338 (9.00)      | 0.009            |
| HL              | 11,445 (30.9)    | 11,638 (31.4)    | 0.011            |
| Stroke          | 865 (2.33)       | 907 (2.45)       | 0.007            |
| Asthma          | 1993 (5.37)      | 2045 (5.51)      | 0.006            |
| COPD            | 3011 (8.12)      | 3134 (8.45)      | 0.012            |
| CKD             | 329 (0.89)       | 325 (0.88)       | 0.001            |
| Medications (n, %) |              |                  |                  |
| NSAID           | 13,021 (35.1)    | 11,743 (31.7)    | 0.07             |
| Prednisolone    | 3972 (10.7)      | 3951 (10.7)      | 0.002            |

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HL, hyperlipidemia; HT, hypertension; NSAID, non-steroidal anti-inflammatory drug.
scores were calculated by logistic regression to estimate the probability of the disease status given the baseline variables, including age, sex, year of index date, non-steroidal anti-inflammatory drugs (NSAID) and prednisolone medication, and the following comorbidities: hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), stroke (ICD-9-CM codes 430–438), asthma (ICD-9-CM code 493), chronic obstructive pulmonary disease (COPD) (ICD-9-CM code 496) and chronic kidney disease (CKD) (ICD-9-CM codes 580–589). The selection of these covariates was based on the common risk factors in CAD and gout. 24–26 Asthma and COPD were highly correlated with smoking consumption. 27,28 Thus, we performed the multivariate analysis with age, sex and comorbidities adjustment. Both cohorts were followed up until a diagnosis of CAD was made, subjects were censored for withdrawal from the NHI program, or the date of December 31, 2011 was reached, whichever occurred first.

Statistical analysis
We compared the distribution of age, sex, comorbidities, and use of medication between the gout and non-gout cohorts using standardized differences. A value of standardized mean difference of 0.1 or less indicated a negligible difference in the mean between the gout and non-gout cohorts. The Kaplan-Meier method was used to estimate the cumulative incidence of CAD between gout and non-gout cohorts, with significance based on the log-rank test. The incidence density of CAD was estimated among different risk factors and it was stratified according to sex, age, comorbidity, and medications. Univariable and multivariable Cox proportional hazards models were performed to estimate the HR and 95% CIs of developing CAD associated with gout. Variables in the multivariable model included age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, asthma, COPD, CKD and medication (NSAIDs and prednisolone). For further data analysis, we assessed the effects of antigout drugs (including allopurinol and benzbromarone) on the risk for CAD and compared this with the non-gout cohort. The Statistical Analysis System (SAS) V9.4 software (SAS Institute) was used for data analysis. A two-tailed p value <0.05 was considered statistically significant.

RESULTS
We included 37,091 patients in the gout cohort and 37,091 patients in the non-gout cohort; distribution of age, sex, comorbidities, and use of medication between the 2 cohorts were comparable (table 1). Mean age was 48.9 years in the gout cohort and 49.2 years in the non-gout cohort. The majority of subjects were aged 20–49 years (55.2% gout cohort vs 53.5% non-gout cohort), and were male (75.9% vs 75.2%). The most prevalent comorbidity was hypertension (35.4% vs 36.2%) in both cohorts, followed by hyperlipidemia (30.9% vs 31.4%), diabetes (8.76% vs 9.00%), and COPD (8.12% vs 8.45%). Both cohorts had a medication history of NSAIDs (35.1% vs 31.7%) and prednisolone (10.7% vs 10.7%). The mean follow-up period was 6.91±3.35 years and 6.89±3.33 years in the gout cohort and in the non-gout cohort, respectively.

The cumulative incidence curves of CAD showed that the gout cohort had a significantly higher risk of developing CAD than the non-gout cohort (p<0.001, log-rank test) (figure 1).

Potential confounders for association of gout with risk were age, sex, comorbidities (hypertension, diabetes, hyperlipidemia, stroke, asthma, COPD, CKD), and medication (NSAIDs and prednisolone) (table 2). Compared with patients aged ≤49 years old, the risk of CAD was 2.09-fold higher among patients aged 50–64 years (95% CI 1.98 to 2.21), and 2.52-fold higher among patients aged ≥65 years (95% CI 2.36 to 2.68). The adjusted HR (aHR) of CAD was 1.19-fold higher among women than among men (95% CI 1.13 to 1.25). Hypertension (aHR=2.13, 95% CI 2.02 to 2.24), diabetes (aHR=1.14, 95% CI 1.07 to 1.22), hyperlipidemia (aHR=1.41, 95% CI 1.35 to 1.48), COPD (aHR=1.19, 95% CI 1.11 to 1.28), and CKD (aHR=1.39, 95% CI 1.17 to 1.63) were also associated with CAD. In the multivariable model, the risk of CAD was lower among patients treated with NSAIDs (aHR=0.63, 95% CI 0.60 to 0.67) and prednisolone (aHR=0.50, 95% CI 0.46 to 0.54).

Risk of CAD was greater in patients with gout compared with those without gout in all subgroups defined according to their demographic and clinical risk factors for CAD (figure 2, table 3). The CAD incidence was higher in women than in men, increased with age, and increased with comorbidity.

We analyzed the incidence and HR of CAD with or without antigout drug treatment (table 4). Compared with controls, patients with gout who were not treated with antigout medication had a significantly increased risk of CAD (aHR=1.62, 95% CI 1.55 to 1.69), followed by patients who had a history of treatment with antigout medication (aHR=1.10, 95% CI 1.02 to 1.18).

Patients with gout receiving treatment exhibited a significantly lower risk of CAD (table 5; aHR=0.68, 95% CI 0.63

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**Figure 1** Cumulative incidence of coronary artery disease between subjects with and without gout.

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Table 2  The risk factors for coronary artery disease

| Variable | Event | PY  | Rate | cHR (95% CI) | aHR (95% CI) |
|----------|-------|-----|------|-------------|-------------|
| Age, y   |       |     |      |             |             |
| 20–49    | 2456  | 300,623 | 8.17 | 1.00        | 1.00        |
| 50–64    | 3246  | 137,220 | 23.7 | 2.86 (2.71 to 3.01) | 2.09 (1.98 to 2.21) |
| ≥65      | 2501  | 73,994  | 33.8 | 4.01 (3.80 to 4.24) | 2.52 (2.36 to 2.68) |
| Gender   |       |     |      |             |             |
| Female   | 2470  | 120,695 | 20.5 | 1.39 (1.32 to 1.45) | 1.19 (1.13 to 1.25) |
| Male     | 5733  | 391,143 | 14.7 | 1.00        | 1.00        |
| HT       |       |     |      |             |             |
| No       | 3182  | 349,847 | 9.10 | 1.00        | 1.00        |
| Yes      | 5021  | 161,991 | 31.0 | 3.34 (3.19 to 3.49) | 2.13 (2.02 to 2.24) |
| Diabetes |       |     |      |             |             |
| No       | 7047  | 474,513 | 14.9 | 1.00        | 1.00        |
| Yes      | 1156  | 37,325  | 31.0 | 2.02 (1.90 to 2.15) | 1.14 (1.07 to 1.22) |
| HL       |       |     |      |             |             |
| No       | 4430  | 359,507 | 12.3 | 1.00        | 1.00        |
| Yes      | 3773  | 152,330 | 24.8 | 2.00 (1.91 to 2.09) | 1.41 (1.35 to 1.48) |
| Stroke   |       |     |      |             |             |
| No       | 7963  | 502,696 | 15.8 | 1.00        | 1.00        |
| Yes      | 240   | 9142   | 26.3 | 1.59 (1.40 to 1.81) | 0.72 (0.64 to 0.82) |
| Asthma   |       |     |      |             |             |
| No       | 7596  | 488,154 | 15.6 | 1.00        | 1.00        |
| Yes      | 607   | 23,684  | 25.6 | 1.60 (1.48 to 1.74) | 1.05 (0.96 to 1.15) |
| COPD     |       |     |      |             |             |
| No       | 7130  | 476,086 | 15.0 | 1.00        | 1.00        |
| Yes      | 1073  | 35,752  | 30.0 | 1.95 (1.83 to 2.08) | 1.19 (1.11 to 1.28) |
| CKD      |       |     |      |             |             |
| No       | 8066  | 508,497 | 15.9 | 1.00        | 1.00        |
| Yes      | 137   | 3340   | 41.0 | 2.48 (2.10 to 2.94) | 1.39 (1.17 to 1.65) |
| NSAID    |       |     |      |             |             |
| No       | 6197  | 303,067 | 20.5 | 1.00        | 1.00        |
| Yes      | 2006  | 208,771 | 9.61 | 0.49 (0.47 to 0.51) | 0.63 (0.60 to 0.67) |
| Prednisolone |   |     |      |             |             |
| No       | 7559  | 447,788 | 16.9 | 1.00        | 1.00        |
| Yes      | 644   | 64,049  | 10.1 | 0.61 (0.56 to 0.66) | 0.50 (0.46 to 0.54) |

Event: n of coronary artery disease (CAD). Rate: incidence rate per 1000 person-years.
aHR, adjusted HR (multivariable analysis including age, gender, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, asthma, COPD, CKD, and medications of NSAID and prednisolone); cHR, crude HR; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HL, hyperlipidemia; HT, hypertension; NSAID, non-steroidal anti-inflammatory drug; PY, person-years.

Discussion

We found conflicting results regarding the patients with gout who did not have higher prevalence of comorbidities except CKD in table 1. This was most likely because the subjects without gout were significantly older than the patients with gout. The mean age was 49.2 years (SD=15.6) and 48.9 years (SD=15.4) in the non-gout cohort and gout cohort, respectively (p=0.022).

In this study, patients with gout had a 1.49-fold (p<0.001, table 2) higher risk of CAD than controls (representing the general population) across the 10-year study period. Moreover, compared with controls, patients with gout who were not treated with antigout medication had a higher risk of CAD, but use of antigout medication was associated with a reduced risk of CAD. These findings support our initial hypotheses and the results were statistically significant after adjustment for age, sex, and potential confounding variables, such as comorbidities. The present study demonstrates for the first time the causal relationship between gout (treated and untreated) and CAD by using a nationwide cohort data set and a follow-up study design. Analyses stratified by sex, age, and comorbidities showed that, among patients with gout, the following parameters were associated with an increased risk of CAD: female sex, the elder, lack of comorbidities, and lack of treatment with NSAIDs or prednisolone.

In this nationwide retrospective study, we evaluated the risk of CAD between the gout and control groups. Based on age, sex, medication records, and comorbidities, each patient with gout was matched to 1 control subject. However, evidence indicated that menopause increased the...
Figure 2  Adjusted HRs of coronary artery disease stratified by sex, age, and comorbidity between patients with gout compared with non-gout cohort.

Table 3  HRs of coronary artery disease between subjects with and without gout

| Variables   | Gout                     | Non-gout                  |                  |                  |
|-------------|--------------------------|---------------------------|-----------------|-----------------|
|             | Event (n) | PY     | Rate   | Event (n) | PY     | Rate   | cHR (95% CI) | aHR (95% CI) |
| Gender      |           |        |        |           |        |        |              |              |
| Female      | 1425      | 58,947 | 24.2   | 1045      | 61,748 | 16.9   | 1.43 (1.32 to 1.55) | 1.38 (1.28 to 1.50) |
| Male        | 3465      | 197,499| 17.5   | 2268      | 193,644| 11.7   | 1.50 (1.42 to 1.58) | 1.55 (1.47 to 1.63) |
| Age, year   |           |        |        |           |        |        |              |              |
| 20–49       | 1538      | 153,712| 10.0   | 918       | 146,911| 6.25   | 1.60 (1.48 to 1.74) | 1.67 (1.54 to 1.81) |
| 50–64       | 1898      | 66,831 | 28.4   | 1348      | 70,390 | 19.2   | 1.48 (1.38 to 1.59) | 1.46 (1.36 to 1.56) |
| ≥65         | 1454      | 35,903 | 40.5   | 1047      | 38,091 | 27.5   | 1.47 (1.36 to 1.59) | 1.42 (1.31 to 1.53) |
| Comorbidity |           |        |        |           |        |        |              |              |
| No          | 1099      | 127,648| 8.61   | 509       | 122,201| 4.17   | 2.07 (1.86 to 2.29) | 2.19 (1.97 to 2.44) |
| Yes         | 3791      | 128,797| 29.4   | 2804      | 133,191| 21.1   | 1.40 (1.33 to 1.47) | 1.35 (1.28 to 1.41) |

Event: n of coronary artery disease (CAD). Rate: incidence rate per 1000 person-years. Comorbidity: subjects with any comorbidity of hypertension, diabetes, hyperlipidemia, stroke, asthma, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) were classified into the comorbidity group.
aHR, adjusted HR (multivariable analysis including age, gender, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, asthma, COPD, CKD, and medications of NSAID and prednisolone); cHR, crude HR; NSAID, non-steroidal anti-inflammatory drug; PY, person-years.

Table 4  Association of gout with risk of CAD subgroups defined by antigout therapy status

| Variable | n    | Event (n) | PY     | Rate | cHR (95% CI) | aHR (95% CI) |
|----------|------|-----------|--------|------|--------------|--------------|
| Non-gout | 37,091| 3313      | 255,392| 13   | 1            | 1            |
| Gout     |      |           |        |      |              |              |
| Without drug | 28,563| 4014      | 195,616| 20.5 | 1.58 (1.51 to 1.66) | 1.62 (1.55 to 1.69) |
| With drug | 8528 | 876       | 60,929 | 14.4 | 1.11 (1.03 to 1.20) | 1.10 (1.02 to 1.18) |

Event: n of CAD. Rate: incidence rate per 1000 person-years. Model: univariable and multivariable Cox proportional hazards models in all participants estimate the risk of developing CAD in 2 gout groups (without drug and with drug) compared with that in non-gout.
aHR, adjusted HR (multivariable analysis including age, gender, and comorbidities of hypertension, diabetes, hyperlipidemia, stroke, asthma, COPD, and medications of NSAID and prednisolone); CAD, coronary artery disease; cHR, crude HR; NSAID, non-steroidal anti-inflammatory drug; PY, person-years.
of women, who are more likely to have a higher prevalence of hypertension and high-density lipoprotein-cholesterol levels than men; furthermore, menopause is also associated with a higher risk of CAD.34 35

Hyperuricemia is known to be correlated with a greater risk for coronary artery calcification in young adults, which is a surrogate measure of coronary atherosclerosis.7 Two studies recently demonstrated that higher serum UA levels were independently associated with a dose-response increased risk of CAD incidence.16 17 In the Atherosclerosis Risk in Communities Study, the OR for developing CAD was 2.59 for subjects who had a serum acid level >9.0 mg/dL.48 Krishnan et al reported that hyperuricemia and untreated gout were poor prognostic markers among patients with a recent acute myocardial infarction.15 The following mechanisms underlying the causal association between soluble UA and CVD have been postulated. First, UA may stimulate vascular smooth cell proliferation, reduce nitric oxide production and result in endothelial dysfunction associated with CVD.37 The endothelin-1, exerting a competent vasoconstrictive effect by binding to the receptors ETA and ETB in human vascular cells, has been postulated as a potential mechanism of an association between hyperuricemia and CVD.3 38 The URAT-1, a specific renal urate-anion exchange transporter as a key factor for the regulation of blood urate levels and primarily responsible for renal reabsorption of UA in the proximal convoluted tubule, is expressed in the vascular endothelial cells, as well as in the vascular smooth muscle cells.39 The presence of URAT-1 in endothelial cells may explain the intracellular effects of urate in endothelial cells and that microvascular changes caused by hyperuricemia found in earlier rat studies, independent of hypertension or the presence of urate crystals.40 Second, inflammation is considered a key factor during the development of CAD via atherothrombosis.41 The UA has been demonstrated to be independently associated with levels of C-reactive protein (CRP), interleukin 6 (IL-6) and IL-18, and tumor necrosis factor-alpha (TNF-α).42 Studies in rats revealed that an artificial increase in serum UA levels results in hypertension that can be ameliorated with allopurinol.43 44 These data suggest that serum UA levels may play a role in oxidative stress and may explain why UA is associated with carotid intimal-medial thickness.45 46 Third, ischemic and dying cells release UA, which is likely to activate the immune system through dendritic cells and CD8+ T cells. Additionally, the induction of heat shock protein-70, one of the local inflammation-related proteins, can be blocked by allopurinol.47 Overall, these data suggest that UA may also play a role in the inflammatory process occurring during ischemia. Our preliminary finding that the use of antigout medication, including allopurinol and benzbro-maronine, in patients with gout is associated with a low risk of CAD (aHR=0.68, p<0.001, table 4) may support the possible role of purinergic modulators in treating CAD.

A further finding in this study is that NSAIDs, commonly used in the treatment of acute gout, decreased the risk of CAD (aHR=0.63, p<0.001, table 2). The immune inflammatory reaction is involved in the pathogenesis of gout, with increased CRP levels, blood neutrophil counts, and levels of cytokines, including IL-1, IL-2, IL-6, and TNF-α.48 Conversely, the inflammatory reaction and associated markers are also potential etiological factors for CAD.40 NSAIDs with anti-inflammatory effects may have a role in supporting our findings.

Our study has some limitations. First, variables such as cigarette smoking, body mass index and other lifestyle factors, which may be associated with the development of CAD, were not included in our study because of the lack of data. Second, the serum UA levels are also not available in the NHIRD. Third, the population was enriched with CAD associated with gout. Finally, because all definitions of variables were based on the diagnoses made by physicians, misidentification may bias the study results. Therefore, the results should be interpreted with caution.

**CONCLUSION**

In conclusion, our study provides the first nationwide population-based evidence supporting the hypothesis that there is an increased risk of CAD among patients with gout, particularly among patients who are not treated with antigout medication, and the reduced risk in patients with gout with antigout medication treatment, after controlling for demographic characteristics, comorbidities, and anti-inflammatory agent use. Our findings indicate that gout or hyperuricemia is a modifiable risk factor for CAD. Further prospective clinical trials are necessary to confirm this hypothesis.

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Competing interests None declared.

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