# Gout as a risk factor for acute myocardial infarction: evidence from competing risk model analysis

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## ABSTRACT

Chronic inflammation, a hallmark of gout, is implicated in the pathogenesis of atherosclerosis. Thus, in theory, gout can be expected to increase the risk of acute myocardial infarction (AMI). Yet, results from several epidemiological studies have been inconclusive. A retrospective cohort study was conducted using the National Health Insurance Research Database of Taiwan dated from 2000 to 2013. The study cohort comprised 3581 patients with gout (the gout cohort) and 14,324 patients without gout (the non-gout cohort). The primary outcome was the incidence of AMI. To estimate the effect of gout on the risk of AMI, the Lunn-McNeil competing risk model was fitted to estimate cause-specific hazard ratios (HRs) and their 95% confidence intervals (CIs). The cumulative incidence of AMI was significantly higher in the gout cohort than in the non-gout cohort, resulting in an adjusted HR of 1.36 (95% CI 1.04 to 2.76). Further, HRs of gout with incident AMI were higher in patients without hypertension, diabetes mellitus, or hyperlipidemia (ranging from 1.63 to 2.09) than in those with each of these comorbidities (ranging from 0.95 to 1.13). The results of this study suggest that patients with gout have an increased risk of AMI. The AMI risk associated with gout was conditional on patients' cardiovascular risk profile. Future work is needed to confirm these findings.

## Significance of this study

### What is already known about this subject?

- Epidemiological studies have indicated that the incidence and prevalence of gout are increasing worldwide. In patients with gout, the inflammatory response associated with gout plays an important role in the initiation and progression of atherosclerosis, and the promotion of a prothrombotic environment that leads to acute coronary events such as angina or acute myocardial infarction (AMI).
- The association between gout and risk of AMI has been examined in relatively few epidemiological studies, and the results have been inconclusive.

### What are the new findings?

- This population-based longitudinal study based on a competing risk model analysis demonstrated that patients with gout had an increased risk of AMI as compared with those without gout.
- Moreover, the elevated risk of AMI associated with gout was conditional on patients' cardiovascular risk profile.

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

- The results from the present study suggest that a gout attack should be a signal to assess the cardiovascular risk profile, when a patient seeks medical attention.

## INTRODUCTION

Acute myocardial infarction (AMI) is the most common acute manifestation of coronary artery disease (CAD), which is the most common cardiovascular disease.[1] AMI is associated with undesirably high rates of morbidity and mortality; approximately 15% of AMI cases are fatal.[2] Therefore, an exploration of AMI risk factors for primary prevention should be a major public health priority.

Gout is the most prevalent form of inflammatory arthritis in high-income countries.[3 4] Epidemiological studies have indicated that the incidence and prevalence rates of gout are increasing worldwide.[5 6] In patients with gout, the gout-related inflammatory response plays an important role in the initiation and progression of atherosclerosis, and the promotion of a prothrombotic environment that leads to acute coronary events such as angina or AMI.[7] Thus, in theory, gout can be expected to increase the risk of AMI. Yet, this important hypothesis has been examined in a number of epidemiological studies, and the results have been inconclusive.[8–13] Growing concern has

mounted regarding whether people with gout have an elevated risk of AMI. For a conclusive study, one would need to have a large cohort of high-risk individuals who had been followed up for long enough to accrue a sufficient number of outcome events. Therefore, in the current study, we aimed to determine the magnitude of the association between gout and AMI in a large population-based cohort study.

## MATERIALS AND METHODS

### Study design and data source

The present study was a retrospective cohort study using a population-based claims data from the National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Insurance (NHI) program was instituted in 1995 and is a single-payer, universal, compulsory healthcare system for nearly all 23.7 million residents in Taiwan. The NHIRD contains comprehensive healthcare data including insurant sex and date of birth, inpatient and outpatient care facilities, disease diagnostic codes in the format of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), procedures, surgeries, drug prescriptions, dates of clinical visits or hospitalization, and expenditures. The NHIRD has previously been used for high-quality epidemiological research,[14 15] and information on diagnoses, drug prescriptions, and hospitalizations has been shown to be of good validity.[16–18] The data of this study were obtained from the Longitudinal Health Insurance Database (LHID) 2000. The details of LHID 2000 have been described previously.[19] Briefly, LHID 2000 is a cohort dataset of original medical claims data that includes one million beneficiaries randomly sampled from the registry of NHIRD dated between January 1, 2000, and December 31, 2013. There was no significant difference in the distributions of age, sex, and healthcare costs between the individuals in LHID 2000 and all enrollees in NHIRD.[20]

### Study subjects

Patients who had a primary diagnosis of gout (ICD-9-CM code 274) during the study period from January 1, 2000, to December 31, 2008, were identified for the gout cohort and were compared with a comparison cohort composed of patients who had never been diagnosed with gout during the study period (hereafter, non-gout cohort). We designated the index year as the year of primary diagnosis of gout for the subjects with gout and the matched year of physician visits for subjects without gout (the non-gout cohort). Each patient with gout was matched to four patients without gout using age, sex, the index year, and propensity scores as matching variables. Propensity score matching is a statistical matching technique that can reduce potential confounding effects caused by unbalanced covariates in observational studies.[21] The propensity scores were calculated by logistic regression to estimate the probability of the disease status given the baseline variables, including age, sex, the index year, and the following comorbidities: hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM codes 272.0, 272.1, 272.2, and 272.4), cerebrovascular disease (ICD-9-CM codes 430–438), chronic kidney disease (ICD-9-CM codes 582, 583, 585, and 586), chronic obstructive pulmonary disease (ICD-9-CM codes 490–496), alcoholic liver disease (ICD-9-CM codes 571.0, 571.1, 571.2, and 571.3), and malignant neoplasms (ICD-9-CM codes 140–239). To identify patients with gout with sufficient accuracy, all gout cases had at least three records of outpatient diagnosis. Because we use a claims database, the inability to define gout based on clinical classification criteria[22] in the present study was primarily because of the lack of clinical detail and laboratory parameters. However, the utility and validity of gout diagnoses in claims databases have been assessed and have been shown to be reasonably robust.[23] Patients were excluded if they were less than 20 years of age (n=303), had unknown sex (n=25), were ever diagnosed with MI before the index year (n=1077), or had a frequency of outpatient visits less than three during the period between January 1, 2000, and December 31, 2008 (n=7571). After excluding those patients, 3581 patients with gout formed the gout cohort and 14,324 patients without gout formed the non-gout cohort in the present study (figure 1).

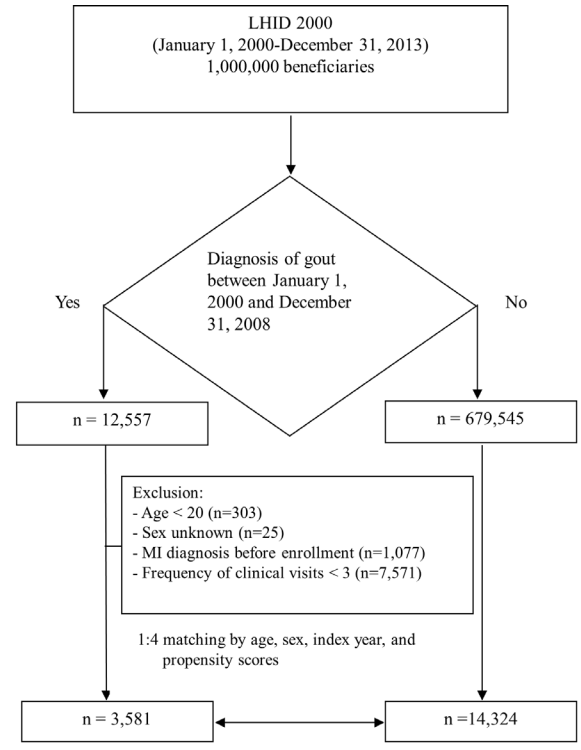


**Figure 1** Study flowchart. AMI, acute myocardial infarction; LHID, longitudinal health insurance database; MI, myocardial infarction.

### Ascertainment of AMI

The primary clinical outcome was the incidence of AMI. We determined patients with AMI as having primary diagnosis of the ICD-9-CM code of 410. All patients were followed up from the index year until a first primary AMI diagnosis, death (as indicated by withdrawal from the NHI), or the end of the observation period (December 31, 2013), whichever occurred first.

### Covariate assessment and adjustment

Covariates included sex, age, the index year, and aforementioned comorbidities, as indicated by propensity scores. Inpatient and outpatient files were used to ascertain whether patients under study had comorbidities. In this study, hypertension, diabetes mellitus, and hyperlipidemia were used as substitute variables of obesity, chronic obstructive pulmonary disease as a surrogate measure of smoking status, and alcoholic liver disease as an indicator of alcohol consumption. Comorbidities were defined in a patient if he or she was diagnosed for any of the aforementioned diseases on at least two outpatient claims or one inpatient claim during the study period. The propensity score including the aforementioned covariates was treated as a potential confounder and was included in regression models for adjustment.

### Data analysis

$\chi^2$ and t-tests were used to examine the differences in the distributions of the categorical and continuous variables, respectively, between cohorts. The Kaplan-Meier method was used for survival analysis to estimate the cumulative incidence of AMI in the study cohorts, and the log-rank test was performed to compare the risk of AMI between the gout and non-gout cohorts. In the present study, deaths occurring among study subjects during the study period, as indicated by withdrawals from the NHI program, were treated as competing events. However, causes of death, particularly AMI-associated deaths, were not available in the claims dataset of the NHIRD. To estimate the effect of gout on the risk of AMI, the Lunn-McNeil competing risk model was fitted to estimate HRs and their 95% CIs. The Lunn-McNeil model estimates the cause-specific HRs but allows for the modelling of non-informative censoring mechanisms as competing events.[24] Of note, the cause-specific hazards model is an appropriate of approach to establish a potentially causal relationship between an exposure of interest and an outcome.[25] The proportional hazards assumption made by the model was checked by Schoenfeld residuals.[26] The results showed that the proportional hazards assumption was violated ($p<0.001$). Therefore, an interaction term between a function of time and predictors was fitted in the regression models. To test the robustness of our findings, we conducted further stratified analyses according to the following stratified factors: sex, hypertension, diabetes mellitus, and hyperlipidemia. Then, we assessed the interactions using likelihood ratio test among the factors of gout and sex, hypertension, diabetes mellitus, and hyperlipidemia by including the main terms of aforementioned factors and the product terms of gout and the remaining factors, respectively, in the Lunn-McNeil model. In addition to the primary analysis, We also performed sensitivity analysis on the basis of excluding subjects who died during the study period. A two-tailed p value of $<0.05$ was considered statistically significant. All analyses were performed using SAS V.9.4.

## RESULTS

The demographics and clinical characteristics of the study cohorts are summarized in table 1. The study subjects were predominantly male in both gout and non-gout cohorts (80.7%), and the mean age was 49.9 and 50.0 years, respectively, for the gout cohort and the non-gout cohort. There were no significant differences in the distributions of age and sex between the gout cohort and the non-gout cohort due to the matching scheme. However, the gout cohort had significantly higher proportions of comorbidities than the non-gout cohort, including hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, alcoholic liver disease, and malignant neoplasms. After propensity score matching with comorbidities, there were no significant differences in comorbidities between the cohorts. In addition, the gout cohort had a significantly higher frequency of outpatient visits than the non-gout cohort.

During the follow-up of 41,100 person-years (PYs) in the gout cohort, there were 80 newly diagnosed patients with AMI. The corresponding incidence rate was 19.46 per 10,000 PYs. Comparatively, there were 182 patients with

**Table 1** Distributions of baseline demographics in the gout and non-gout cohorts before and after propensity score matching

| | Age-matched and sex-matched cohorts | | | Propensity score-matched cohorts | | |
|---|---|---|---|---|---|---|
| Variable | Gout cohort (n=3581) | Non-gout cohort (n=14 324) | P value | Gout cohort (n=3581) | Non-gout cohort (n=10 743) | P value |
| Age, years (mean±SD) | 49.9±15.3 | 50±16.9 | 0.849 | 49.9±15.3 | 49.6±15.6 | 0.264 |
| Sex, n (%) | | | 1.000 | | | 0.903 |
| Female | 692 (19.3) | 2768 (19.3) | | 692 (19.3) | 2086 (19.4) | |
| Male | 2889 (80.7) | 11,556 (80.7) | | 2889 (80.7) | 8657 (80.6) | |
| Comorbidity, n (%) | | | | | | |
| Hypertension | 1980 (55.3) | 3628 (25.3) | <0.001 | 1980 (55.3) | 6006 (55.9) | 0.522 |
| Diabetes mellitus | 1039 (29.0) | 1782 (12.4) | <0.001 | 1039 (29.0) | 3168 (29.5) | 0.589 |
| Hyperlipidemia | 1289 (36.0) | 2009 (14.0) | <0.001 | 1289 (36.0) | 3847 (35.8) | 0.841 |
| Cerebrovascular disease | 393 (11.0) | 867 (6.1) | <0.001 | 393 (11.0) | 1168 (10.9) | 0.865 |
| COPD | 979 (27.3) | 2422 (16.9) | <0.001 | 979 (27.3) | 2903 (27.0) | 0.712 |
| Chronic kidney disease | 504 (14.1) | 508 (3.5) | <0.001 | 504 (14.1) | 1496 (13.9) | 0.824 |
| Alcoholic liver disease | 69 (1.9) | 176 (1.2) | 0.0013 | 69 (1.9) | 175 (1.6) | 0.233 |
| Malignant neoplasms | 1363 (38.1) | 4184 (29.2) | <0.001 | 1363 (38.1) | 4078 (38.0) | 0.913 |
| No. of annual outpatient visits (mean±SD) | 23.2±15.6 | 12.0±12.4 | <0.001 | 23.2±15.6 | 18.4±15.1 | <0.001 |

The propensity scores were calculated by logistic regression to estimate the probability of the disease status given the baseline variables, including age, sex, the index year, and the following comorbidities: hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, COPD, chronic kidney disease, alcoholic liver disease, and malignant neoplasms.
COPD, chronic obstructive pulmonary disease.

**Table 2** Global and sex-specific associations between gout and risk of AMI

| | Gout cohort | | | Non-gout cohort | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AMI cases (n) | PYs | Incidence rate (per 10,000) | AMI cases (n) | PYs | Incidence rate (per 10,000) | Crude HR (95% CI) | Adjusted HR (95% CI) | P value for interaction |
| Total | 80 | 41,100 | 19.46 | 182 | 124,020 | 14.68 | 1.33 (1.02 to 2.73) | 1.36 (1.04 to 2.76) | |
| Sex | | | | | | | | | 0.020 |
| Female | 7 | 7920 | 8.84 | 38 | 23,932 | 15.88 | 0.56 (0.25 to 1.26) | 0.55 (0.25 to 1.24) | |
| Male | 73 | 33,179 | 22.00 | 144 | 100,088 | 14.39 | 1.53 (1.16 to 2.03) | 1.57 (1.18 to 2.08) | |

HRs were adjusted for age, sex, the index year, comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, alcoholic liver disease, and malignant neoplasms, as well as frequency of annual outpatient visits for the global association and were adjusted for age, the index year, aforementioned comorbidities, and frequency of annual outpatient visits for sex-specific associations between gout and risk of AMI.
P value for interaction refers to the interactive effect of sex and gout on the risk of AMI.
AMI, acute myocardial infarction; PYs, person-years.

AMI in the non-gout cohort during the follow-up period of 124,020 PYs. The corresponding incidence rate was 14.68 per PY. Accordingly, the gout cohort had a significantly increased risk of AMI as compared with the non-gout cohort (adjusted HR 1.36, 95% CI 1.04 to 2.76) (table 2). The Kaplan-Meier curves for the cumulative risk of AMI among the two cohorts are shown in figures 2 and 3. The crude cumulative incidence of AMI was significantly higher in the gout cohort than in the non-gout cohort. The log-rank test revealed a significant difference in the cumulative incidence of AMI between the two cohorts over the entire Kaplan-Meier curve (p=0.033) (figure 2). After propensity score matching, the adjusted cumulative incidence of AMI was still significantly higher in the gout cohort than in the non-gout cohort (p=0.024) (figure 3). Subsequently, we assessed the association between gout and risk of AMI stratified by sex. The results showed that men with gout had a 1.57-fold greater risk for developing AMI using patients without gout as reference after adjusting for potential confounders (adjusted HR 1.57, 95% CI 1.18 to 2.08), while no significant association was detected in women (adjusted HR 0.55, 95% CI 0.25 to 1.24). The joint effect of sex and gout on the risk of AMI was statistically significant (p=0.020) (table 2). We further performed sensitivity analyses on the basis of excluding subjects who died during the study period. As shown in table 3, the overall results were not altered substantially. Gout was associated with a significantly increased risk of AMI (adjusted HR 1.45, 95% CI 1.08 to 2.95). Similarly, the excess risk of AMI associated with gout was more pronounced in men than in women; the adjusted HRs for men and women were 1.66 (95% CI 1.22 to 2.28) and 0.57 (95% CI 0.22 to 1.48), respectively.

In the subgroup analyses, HRs of gout with incident MI were higher in patients without hypertension, diabetes mellitus, or hyperlipidemia (ranging from 1.63 (95% CI 1.18 to 2.25) to 2.09 (95% CI 1.30 to 3.35)) than those in patients with these comorbidities (ranging from 0.95 (95% CI 0.60 to 1.52) to 1.13 (95% CI 0.82 to 1.56)). There was a significant interaction of gout with hypertension (p=0.036), diabetes mellitus (p=0.047), and hyperlipidemia (p=0.049), respectively, in the risk of AMI (table 4).

A differential pattern of association between gout and risk of AMI was demonstrated according to the annual frequency of outpatient visits for gout. Relative to patients without gout, a higher HR was noted among patients having the highest annual frequency of outpatient visits (>12) for gout (adjusted HR 1.54, 95% CI 1.09 to 2.14). A trend with a significant increase in HRs with increasing annual

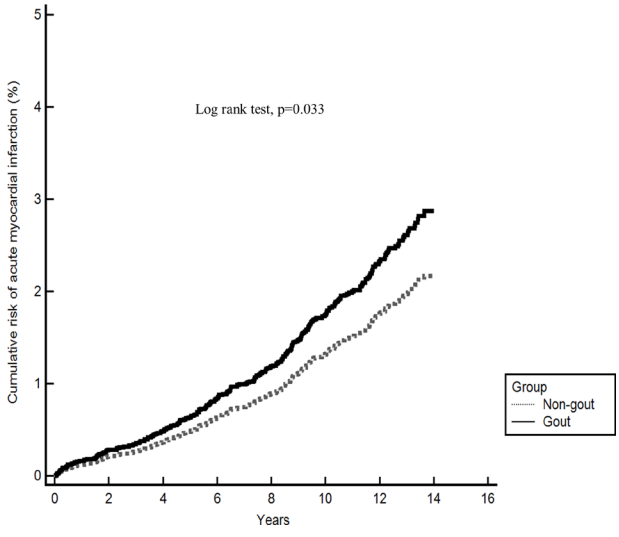


**Figure 2** Kaplan-Meier analysis of the crude cumulative incidence of acute myocardial infarction in the the gout cohort and non-gout cohort.

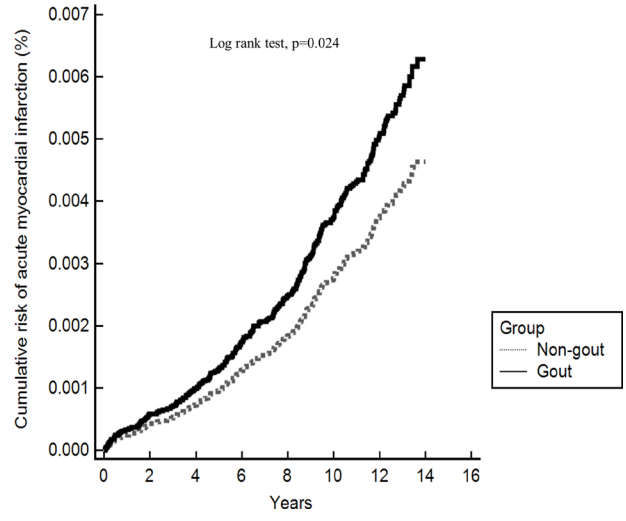


**Figure 3** Kaplan-Meier analysis of the propensity score-matched cumulative incidence of acute myocardial infarction in the the gout cohort and non-gout cohort.

**Table 3** Sensitivity analyses of global and sex-specific associations between gout and risk of AMI based on excluding subjects who died during the study period

| | Gout cohort (n=3247) | | | Non-gout cohort (n=9953) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AMI cases (n) | PYs | Incidence rate (per 10,000) | AMI cases (n) | PYs | Incidence rate (per 10,000) | Crude HR (95% CI) | Adjusted HR (95% CI) | P value for interaction |
| Total | 64 | 38,177 | 16.76 | 138 | 117,118 | 11.78 | 1.42 (1.06 to 1.91) | 1.45 (1.08 to 2.95) | |
| Sex | | | | | | | | | 0.042 |
| Female | 5 | 7298 | 6.85 | 27 | 22,639 | 11.93 | 0.58 (0.22 to 1.50) | 0.57 (0.22 to 1.48) | |
| Male | 59 | 30,879 | 17.81 | 111 | 94,479 | 11.75 | 1.63 (1.19 to 2.23) | 1.66 (1.22 to 2.28) | |

HRs were adjusted for age, sex, the index year, comorbidities, including hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, alcoholic liver disease, and malignant neoplasms, as well as frequency of annual outpatient visits for the global association, and were adjusted for age, the index year, aforementioned comorbidities, and frequency of annual outpatient visits for sex-specific associations between gout and risk of AMI.
P value for interaction refers to the interactive effect of sex and gout on the risk of AMI.
AMI, acute myocardial infarction; PYs, person-years.

frequency of outpatient visits for gout was noted (p=0.004) (table 5).

## DISCUSSION

This population-based longitudinal study using a nationwide claims dataset made available by Taiwan's NHIRD demonstrated that patients with gout had an increased risk of AMI as compared with those without gout in an ethnic Chinese population. Therefore, the results from the present study suggest that a gout attack should be an incentive to assess the cardiovascular risk profile, when a patient seeks medical attention.

It has been noted that the inflammatory activity associated with gout can itself be proatherogenic and promote a prothrombotic environment that leads to acute coronary events.[27 28] Thus, in theory, gout can be expected to increase the risk of AMI. Yet, this important hypothesis has been examined in several epidemiological studies, and the results mostly, but not invariably, support the role of gout as a risk factor for CAD, including MI.[8–13 27 29 30] The Framingham study,[9] the Multiple Risk Factor Intervention Trial,[10] the British Columbia Linked Health Database,[13] and the Health Professional Follow-up Study[29] reported that patients with gout have an increased risk of MI. However, Gelber *et al* prospectively collected data from two longitudinal cohorts and observed that prior gout was not associated with an increased risk of MI.[8] In addition, a case–control study conducted in an aggregate Dutch primary care population revealed that gout was not an independent risk indicator of CAD.[27] Our estimates of elevated risks of AMI in patients with gout in an ethnic Chinese population are consistent with previous findings of gout as a risk factor for AMI.[11–13 29 30] Although similar NHIRD datasets were used in the study by Kuo *et al*[12] and our study, the novelty of the present study is application of competing risk models to analyze the association between gout and AMI, a disease with undesirably high rates of mortality. Furthermore, the present study demonstrated that the HR of AMI appeared to increase with increasing annual frequency of outpatient visits for gout. This suggests that the severity of gout, as indicated by frequency of outpatient visits, is a significant risk factor of AMI. Indeed, a meta-analysis suggests that patients with gout have an increased risk of AMI.[31] An increased risk of incident AMI in patients with gout raises a question regarding the role of chronic inflammation and interleukin-1β pathways (via NLRP3 inflammasome activation) in the pathogenesis of AMI.[32] Inflammation associated with gout may play an important role in the initiation and progression of atherosclerosis, as well as in plaque disruption and thrombotic complications.[33] The role of inflammation among patients with gout in the pathogenesis of AMI needs to be examined in future studies.

**Table 4** Association between gout and risk of AMI stratified by status of hypertension, diabetes mellitus, and hyperlipidemia

| | Gout cohort | | | Non-gout cohort | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | AMI cases (n) | PYs | Incidence rate (per 10,000) | AMI cases (n) | PYs | Incidence rate (per 10,000) | Crude HR (95% CI) | Adjusted HR (95% CI) | P value for interaction |
| Hypertension | | | | | | | | | 0.036 |
| No | 29 | 18,108 | 16.02 | 42 | 53,799 | 7.81 | 2.06 (1.28 to 3.31) | 2.09 (1.30 to 3.35) | |
| Yes | 51 | 22,991 | 22.18 | 140 | 70,221 | 19.94 | 1.11 (0.81 to 1.53) | 1.13 (0.82 to 1.56) | |
| Diabetes mellitus | | | | | | | | | 0.047 |
| No | 57 | 29,017 | 19.64 | 106 | 87,423 | 12.12 | 1.62 (1.17 to 2.23) | 1.63 (1.18 to 2.25) | |
| Yes | 23 | 12,082 | 19.04 | 76 | 36,596 | 20.77 | 0.92 (0.58 to 1.47) | 0.95 (0.60 to 1.52) | |
| Hyperlipidemia | | | | | | | | | 0.049 |
| No | 56 | 25,866 | 21.65 | 107 | 78,757 | 13.59 | 1.60 (1.16 to 2.21) | 1.64 (1.19 to 2.27) | |
| Yes | 24 | 15,234 | 15.75 | 75 | 45,262 | 16.57 | 0.95 (0.60 to 1.50) | 0.95 (0.60 to 1.50) | |

HRs were adjusted for age, sex, the index year, comorbidities including hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, alcoholic liver disease, and malignant neoplasms, as well as frequency of annual outpatient visits.
P for interaction refers to the interactive effects of hypertension and gout, diabetes mellitus and gout, and hyperlipidemia and gout, respectively, on the risk of AMI.
AMI, acute myocardial infarction; PYs, person-years.

**Table 5** Relationship of the risk of AMI associated with frequency of annual outpatient visits for gout

| Annual frequency of outpatient visits for gout | AMI cases (n) | PYs | Incidence rate (per 10,000) | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| Non-gout cohort | 182 | 124,020 | 14.68 | 1.00 (ref.) | 1.00 (ref.) |
| ≤12 | 59 | 31,646 | 18.64 | 1.28 (0.95 to 1.71) | 1.40 (0.85 to 1.88) |
| >12 | 21 | 9454 | 22.21 | 1.50 (1.06 to 2.86) | 1.54 (1.09 to 2.14) |
| P value for trend | | | | <0.001 | 0.004 |

HRs were adjusted for age, sex, the index year, and comorbidities including hypertension, diabetes mellitus, hyperlipidemia, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, alcoholic liver disease, and malignant neoplasms.
AMI, acute myocardial infarction; PYs, person-years.

In the present study, we found that the association between gout and risk of AMI was more evident in men than in women. The British Columbia Linked Health Database revealed that the magnitude of excess risk of AMI associated with gout is higher in women than in men.[11] In comparison, the epidemiological Framingham study found that the association of AMI with gout was observed only in men.[9] Indeed, sex-related differences in the association between gout and AMI remain poorly understood. As gout predominantly affects men, and only a handful of studies have included women, and there remains controversy about the strength of sex-related associations.[9 11 13] The reasons for differences in the findings is likely related to differences in country setting, age structure of the population examined, and confounders adjusted in the analyses.

We noted that the association of gout with incident AMI was more robust in patients without each CAD risk factor (hypertension, diabetes, or hyperlipidemia) (adjusted HR 1.63–2.09) than in patients with the presence of each CAD risk factor, respectively (adjusted HR 0.95–1.13). This indicates that in patients with known CAD/MI risk factors, gout contributes much less to the risk of AMI. The reasons for this phenomenon are unclear, which need to be explored in future studies.

The strengths of this study are that it was based on a large and representative population cohort extracted from the NHI system which covers 99% of the population in Taiwan. This allowed us to perform our analysis in a real-life setting in an unselected patient population. In addition, bias from selection, non-response, or poor recall was minimized because of the use of routine database records.

The results of the present study need to be interpreted within the context of some limitations. Studies that are based on insurance claims data are often flawed because the information on confounders contained in insurance data is often limited.[34] We did not have information on some potential covariates from the claims dataset, such as serum uric acid concentrations, and these could therefore not be included in the modelling process. Several potential confounders that are associated with AMI also cannot be obtained from the claims dataset, such as life-related variables including cigarette smoking, alcohol consumption, and obesity. In the present study, we used comorbidities of chronic obstructive pulmonary disease as surrogate measures of smoking, alcoholic liver disease as an indicator of alcohol consumption, and hypertension, diabetes, and hyperlipidemia as proxy variables of obesity. These surrogate covariates were included in the regression models for adjustment. However, unmeasured or residual confounding could introduce bias in our estimates. In addition, medications such as hypertensive medications would affect AMI. In turn, medications are potential confounders in the present study. However, our study tried to reduce the confounding effect of medications by adjusting for comorbidities associated with medication treatments. Moreover, the study may have bias because only International Classification of Disease codes were used to define gout. This may have led to overdiagnosis, although the study defined incident disease by at least three records of outpatient diagnosis within 1 year.

## CONCLUSIONS

In conclusion, the present study provides population-based evidence supporting the hypothesis that patients with gout have an increased risk of AMI. The AMI risk associated with gout was conditional on patients' cardiovascular risk profile. Further prospective studies are necessary to confirm our study results.

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