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# The Independent Impact of Gout on the Risk of Acute Myocardial Infarction Among Elderly Women: A Population-Based Study

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## Abstract

**OBJECTIVE—**Men with gout have been found to have an increased risk of acute myocardial infarction (AMI), but no corresponding data are available among women. We evaluated the potential independent association between gout and the risk of AMI among elderly women, aged ≥65 years.

**METHODS—**We conducted a population-based cohort study using the British Columbia Linked Health Database and compared incidence rates of AMI between 9,642 gout patients and 48,210 controls, with no history of ischemic heart disease. Cox proportional hazards models stratified by gender were used to estimate the relative risk (RR) for AMI, adjusting for age, co-morbidities, and prescription medication use.

**RESULTS—**Over 7-year median follow-up, we identified 3,268 incident AMI cases, 996 among women. Compared to women without gout, the multivariate RRs among women with gout were 1.39 (95% CI, 1.20–1.61) for all AMI and 1.41 (95% CI, 1.19–1.67) for non-fatal AMI. These RRs were significantly larger than those among men (multivariate RRs for all AMI and non-fatal AMI, 1.11 and 1.11; P-values for interaction, 0.003 and 0.005, respectively).

**CONCLUSION—**These population-based data suggest that women with gout have an increased risk for AMI and the magnitude of excess risk is higher than in men.

### Keywords

Gout; Epidemiology; Cardiovascular Disease

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**CONFLICT OF INTEREST DISCLOSURES**

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## INTRODUCTION

Gout is a common and painful inflammatory arthritis affecting up to 9% and 6% of elderly men and women, respectively.[1] Studies have reported that men with gout have an increased risk of coronary heart disease (CHD) independent of other cardiovascular risk factors.[2, 3] A recent meta-analysis showed a larger effect of hyperuricemia on CHD risk in women than men.[4] While this suggests that the impact of gout may be stronger among women than men, no relevant data are available. Thus, we investigated the association between gout and risk of acute myocardial infarction (AMI) among elderly women (≥65 years) in British Columbia (BC), Canada. We focused on elderly individuals because complete BC PhamaCare prescription coverage is limited to this group, and gout occurs predominantly after menopause among women.

## METHODS

### Study Population

The BC Linked Health Database (BCLHD) is a health data resource covering the entire province (2005 population, 4.3 million) and contains integrated longitudinal data on health care visits, hospitalizations, and drug prescriptions.[5] From the BCLHD, we created the BC Musculoskeletal Cohort of approximately 3.5 million individuals with any musculoskeletal diagnosis between 1991 and 2004.[6] The current cohort study consists of 9,642 individuals with gout (3,890 females) and 48,210 controls (19,450 females) matched (1:5 ratio) by age, sex, date of gout diagnosis (index date), and length of medical record. Prevalent cases of gout or ischemic heart disease recorded in the first three years were excluded.

### Exposure Assessment

We ascertained gout using International Classification of Diseases 9$^{th}$ Revision (ICD-9) codes (274.x). Validation studies of these codes have reported positive predictive values (PPV) ranging from 61% in a US managed care setting [7] to 100% in US Veterans Affairs rheumatology clinic setting.[8] In our cohort, gout incidence rates (per 1000 person-years) in age categories 65–84 and ≥85 years were 5.7 and 6.5 among men, and 2.5 and 2.9 among women,[6] respectively, corresponding with estimates in the General Practice Research Database.[9]

### AMI Assessment

From hospitalization data, we identified incident AMI outcomes using ICD-9 codes (410.x). Validity of these codes are well-established with PPV up to 95%.[10] Incidence rates of AMI per 1000 person-years in this cohort were 6.7 and 10.7 for women and men respectively, consistent with Canadian estimates.[11]

### Statistical Analysis

Individuals were followed from baseline (index date for gout cases; matched date for controls) to AMI, deregistration from medical service plan, death, or end of study (March 31, 2004), whichever came first. We used Cox proportional hazards models, stratified by gender, to estimate the relative risk (RR) of AMI in multivariate analyses (PROC PHREG, SAS Institute Inc, Cary, NC), adjusting for age, co-morbid conditions (hypertension, diabetes, chronic obstructive pulmonary disease, and hyperlipidemia), Charlson comorbidity score,[12] and monthly prescription medication use (non-steroidal anti-inflammatory drugs, aspirin, glucocorticoids, statins, anticoagulants, hormone replacement therapy, and diuretics) as time-dependent covariates. We tested the significance of the interaction by gender with a likelihood ratio test. All p-values were two-sided.

## RESULTS

Over 7-year median follow-up, we identified 3,268 incident AMI cases, 996 among women. Baseline characteristics of women and men according to history of gout are shown in Table 1.

In unadjusted analyses, gout was associated with higher risk of AMI (RR, 1.67; 95% CI, 1.45–1.93) among women (Table 2). After adjusting for age, co-morbidities, and prescription drug use, the multivariate RR was 1.39 (95% CI, 1.20–1.61). This RR among women was significantly larger than that among men (multivariate RR, 1.11; 95% CI, 0.99–1.23; p-value for interaction, 0.003). A significant gender difference with similar RRs was observed for non-fatal, but not fatal, AMI events.

## DISCUSSION

In this population-based study of elderly Canadians, we found a 39% increased risk for AMI among women with gout. This association was independent of age, co-morbidities, and use of prescription drugs, and was significantly stronger than that among men. These findings fill the gap in knowledge about the relation between gout and AMI among women.

Gender differences in serum uric acid levels [13, 14] and perhaps uric acid metabolism [14] may explain the stronger risk of AMI associated with gout among women compared to men. Serum urate levels in men are about 1 mg/dl higher than in women during adulthood, although levels in women increase around natural menopause.[13, 14] Thus, the relative physiologic impact of having gout or a certain level of hyperuricemia may be stronger among women than men. Furthermore, reports have shown higher mean uric acid levels among female gout patients.[13, 14] It is conceivable that a higher level of uric acid among women with gout could lead to a higher impact on the risk of AMI compared to men. Similar to previous studies,[13, 14] we found higher frequencies of diuretic use and hypertension among women with gout. However, frequencies of these factors were also higher among women without gout and the differential gender impact on AMI risk persisted even after adjusting for these covariates.

Our findings expand on previous studies showing an independent impact of gout on AMI risk in men, including the Multiple Risk Factor Intervention Trial [2, 15] and Health Professionals Follow-up Study [3]. Although the Framingham Heart Study attempted to evaluate the impact of gout in both genders, only one incident AMI case among women precluded meaningful analyses.[16] A Taiwanese study showed that frequency of gouty attacks was associated with electrocardiographic evidence of AMI in females, but its cross-sectional design barred establishment of temporal relations.[17]

There are several potential mechanisms for the associations observed. The contribution of hyperuricemia to cardiovascular disease (CVD) risk has been postulated based on patho-physiological mechanisms including vascular smooth muscle cell proliferation and inflammation and platelet adhesiveness and aggregation.[18] Correspondingly, a recent meta-analysis found an independent impact of hyperuricemia on CHD risk.[4] Inflammation associated with gout may also play a role in potential mechanisms including promotion of atherogenesis and thrombogenesis, similar to other inflammatory arthritides associated with CVD.[15, 19–20]

Study strengths and limitations deserve comment. We used a population-based cohort of Canadian women and men, thus, findings are likely to be applicable to the general population. Because we used diagnostic codes to define gout, some misclassification of diagnosis is inevitable. However, any non-differential misclassification would have likely

biased estimates towards the null and it remains conceivable that the associations are stronger with more specific case definitions for gout. Nevertheless, the gender ratios of incidence rates for both gout and AMI in this cohort were similar to published estimates [9] [11], indicating that the possibility of differential ascertainment between genders is unlikely. Thus, if the association between gout and AMI exists as shown in prospective studies among men [2–3, 15], then our comparison employing the same definition of gout in both genders leads to a conclusion that the association is stronger among women. Nevertheless, confirmation of our findings using more specific case definitions of gout would be valuable. Our administrative data precluded adjustment for life-style factors for AMI such as smoking. However, because smoking is not an independent risk factor for gout exposure, findings will likely persist even with adjustment, as was the case in previous studies.[2–3, 15]

In conclusion, this population-based study suggests that women with gout have an increased risk for AMI, and the magnitude of excess risk is higher than men. These findings provide support for the aggressive management of cardiovascular risk factors for gout patients of both genders.

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**Table 1**

Baseline Characteristics According to History of Gout Diagnosis*

| Characteristics | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | No Gout (n=19,450) | Gout (n=3,890) | P† | No Gout (n=28,760) | Gout (n=5,752) | P† |
| Age, mean ± SD years | 75.0 ± 6.8 | 75.0 ± 6.8 | 0.99 | 73.3 ± 6.4 | 73.9 ± 6.4 | 0.991 |
| Co-morbid medical conditions | | | | | | |
| Hypertension | 9,220 (47.4 ) | 2,552 (65.6 ) | 0.001 | 10,944 (38.1) | 3,206 (55.7) | 0.001 |
| COPD | 3,811 (19.6) | 1,007 (25.6) | 0.001 | 5,898 (20.5) | 1,387 (24.1) | 0.001 |
| Diabetes | 2,197 (11.3) | 719 (18.5) | 0.001 | 4,035 (14.0) | 884 (15.4) | 0.008 |
| Hyperlipidemia | 2,140 (11.0) | 571 (14.7) | 0.001 | 2,652 (9.2) | 741 (12.9) | 0.001 |
| Charlson comorbidity score, mean ± SD | 1.1 ± 1.7 | 1.4 ± 1.8 | 0.001 | 1.3 ± 1.8 | 1.4 ± 1.8 | 0.31 |
| Prescription medication use | | | | | | |
| NSAID | 10,055 (51.7) | 3,168 (81.4) | 0.001 | 12,835 (44.6) | 4,604 (80.0) | 0.001 |
| Diuretic | 3,910 (20.1) | 1,312 (33.7) | 0.001 | 3,494 (12.2) | 1,239 (21.5) | 0.001 |
| Statin | 1,830 (9.4) | 508 (13.1) | 0.001 | 1,914 (6.7) | 512 (8.9) | 0.001 |
| Aspirin | 1,418 (7.3) | 326 (8.4) | 0.018 | 1,619 (5.6) | 351 (6.1) | 0.158 |
| Glucocorticoid | 1,364 (7.0) | 368 (9.5) | 0.001 | 1,637 (5.7) | 422 (7.3) | 0.001 |
| Anticoagulant | 628 (3.2) | 227 (5.8) | 0.001 | 1,225 (4.3) | 368 (6.4) | 0.001 |
| Hormone replacement therapy | 952 (4.9) | 153 (3.9) | 0.010 | -- | -- | -- |

*Values are the number (percentage) unless otherwise indicated;

†P-value by chi-square or t-test.; COPD = chronic obstructive pulmonary disease, NSAID = non-steroidal anti-inflammatory drug.

**Table 2**

Relative Risk (RR) for AMI, Non-Fatal, and Fatal AMI According to History of Gout, Stratified by Gender

| | Females | | | | Males | | | | P value for Interaction by Gender |
|---|---|---|---|---|---|---|---|---|---|
| | No. of AMI | Incidence (/1000 PY) | Crude RR (95% CI) | Multivariate RR* (95% CI) | No. of AMI | Incidence (/1000 PY) | Crude RR (95% CI) | Multivariate RR* (95% CI) | |
| **All AMI** | | | | | | | | | |
| No Gout | 752 | 6.03 | 1.0 (referent) | 1.0 (referent) | 1,837 | 10.34 | 1.0 (referent) | 1.0 (referent) | 0.003 |
| Gout | 244 | 10.04 | 1.67 (1.45, 1.93) | 1.39 (1.20, 1.61) | 435 | 12.23 | 1.19 (1.07, 1.32) | 1.11 (0.99, 1.23) | |
| **Non-Fatal AMI** | | | | | | | | | |
| No Gout | 552 | 4.42 | 1.0 (referent) | 1.0 (referent) | 1,420 | 7.99 | 1.0 (referent) | 1.0 (referent) | 0.005 |
| Gout | 183 | 7.53 | 1.71 (1.44, 2.02) | 1.41 (1.19, 1.67) | 335 | 9.42 | 1.18 (1.05, 1.33) | 1.11 (0.98, 1.25) | |
| **Fatal AMI** | | | | | | | | | |
| No Gout | 200 | 1.60 | 1.0 (referent) | 1.0 (referent) | 417 | 2.35 | 1.0 (referent) | 1.0 (referent) | 0.30 |
| Gout | 61 | 2.51 | 1.57 (1.18, 2.09) | 1.33 (0.99, 1.78) | 100 | 2.81 | 1.19 (0.96, 1.49) | 1.10 (0.88, 1.38) | |

RR = relative risk; 95% CI = 95% confidence interval; PY = person-years

*Multivariate models were adjusted for age (continuous), baseline history of co-morbid medical condition [hypertension, diabetes, hyperlipidemia, and chronic obstructive pulmonary disease] (yes, no), baseline Charlson comorbidity score (continuous), and monthly prescription medication use [NSAID, diuretic, statin, anticoagulant, aspirin, hormone replacement therapy, and glucocorticoid] (yes, no) as time-varying covariates.

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