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ORIGINAL ARTICLE

Gout as a risk factor for osteoporosis: epidemiologic evidence from a population-based longitudinal study involving 108,060 individuals

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Abstract

Summary Is gout a risk factor for future osteoporosis? This large population-based study comprising two matched groups of individuals with and without gout demonstrates that patients with gout have a 20% increase in the risk of developing osteoporosis in future through an 8-year follow-up.

Introduction To examine if gout is associated with an increased risk of osteoporosis.

Methods We conducted a nationwide population-based retrospective matched-cohort study. Two matched cohorts ($n = 36{,}458$ with gout and 71,602 without gout) assembled and recruited from the Longitudinal Health Insurance Dataset containing 1 million subjects. Exclusion criteria were missing data, age < 20 years, short follow-up period, and pre-existing osteoporosis. Both cohorts were followed up until incident osteoporosis, death, or the end of the study. Person-year data and incidence rates were evaluated. A multivariable Cox model was used to derive an adjusted hazard ratio (aHR) after controlling for socioeconomic proxy, geographical difference, glucocorticoid and allopurinol exposure, various prespecified medical conditions, and comorbidities.

Results Men comprised 72.8% of the cohorts. With a follow-up of 183,729 and 359,900 person-years for the gout and non-gout cohorts, 517 and 811 incidents of osteoporosis occurred, respectively, after excluding osteoporosis incidents in the first 3 years of follow-up. The cumulative incidence of osteoporosis was statistically higher in the gout cohort than in the non-gout cohort, at 3.3 versus 2.1% ($P = 0.0036$, log-rank). Our Cox model showed a 1.2-fold increase in the incidence of osteoporosis in the gout cohort, with an aHR of 1.2 (95% confidence interval, 1.06–1.35).

Conclusions This first population-based epidemiologic study supports the hypothesis that compared with individuals without gout; those with gout have a modest increase in the risk of developing osteoporosis in future.

Keywords Gout · Longitudinal study · NHIRD · Osteoporosis

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Introduction

Gout is a common disease with a prevalence of 0.5 to 0.6% in the general population [1, 2]. It is regarded as a lifestyle-related disease and is associated with obesity, dietary factors, alcohol consumption, metabolic syndrome, hypertension, and chronic kidney disease [2]. For example, people who drink ≥ 50 g of alcohol per day harbor an increased risk of gout, demonstrating a multivariate relative risk of 2.53 [95% confidence interval (CI), 1.73–3.70] [3].

In recent years, it has been demonstrated that gout is a risk factor for or has a positive association with various medical illnesses. For example, gout is associated with atrial fibrillation, necessitating the prescription of anticoagulants or antiarrhythmics for patients [hazard ratio (HR), 1.21; 95% CI, 1.11–1.33] [4]. We previously demonstrated in a massive (entire

cohort comprised 3,694,377 individuals) nationwide population-based study that among nondiabetic subjects aged ≥ 50 years, those with gout were 1.1 times more likely to die from cardiovascular disease compared with those without gout [5]. However, little is known regarding the association of gout with subsequent osteoporosis development.

Osteoporosis is characterized by a low bone mass and leads to a fragile skeletal condition associated with an increased risk of the highly feared osteoporotic fracture. These fragility fractures are always low-trauma fractures that occur by falling from a standing height or less and are not related to major trauma such as that caused by a motor vehicle accident. Gout and osteoporosis are two discrete lifestyle-related diseases and are becoming major public health concerns [6, 7]. These two diseases have not yet been investigated adequately with regard to the etiologic role of gout as a risk factor for osteoporosis. The past few years have seen only four other studies, three on Caucasians and one on East Asians, designed to determine the association between gout and osteoporotic fractures at various sites [8–11]. Although these four papers contain high-quality data, the results are conflicting. Using the example of hip fracture as a study outcome, two of these four studies revealed a neutral risk [8, 10], whereas the other two [9, 11] demonstrated modestly increased risk in patients with gout compared with that in those without gout. To the best of our knowledge, there has been no research testing the hypothesis that gout is associated with osteoporosis.

The rationale for conducting a study like ours is that gout is the most common type of inflammatory arthritis in adults, resulting from either renal underexcretion or uric acid overproduction. Monosodium urate crystal deposits in the joints, soft tissues, or organs activate the NLRP3 inflammasome, resulting in the rapid production of interleukin (IL)-1 and increase in the IL-6 and tumor necrosis factor-alpha (TNF-alpha) levels. These cytokines have been proven to enhance bone resorption. We, therefore, hypothesized that gout is associated with an increased risk of osteoporosis based on the pathogenesis proven above.

Methods

Source of data

We designed a population-based retrospective cohort study using data from the Longitudinal Health Insurance Dataset (LHID). LHID consists of all the original claims data for the reimbursement of one million insured subjects randomly sampled from the Taiwan National Health Insurance Research Database (NHIRD) and structured for research purposes (http://nhird.nhri.org.tw/en/index.html). The dataset primarily consists of 10 registration files, namely, registries for contracted beds, specialty services, and medical facilities, a supplementary registry for contracted medical facilities, and registries for board-certified specialists, medical personnel, catastrophic illness patients, medical services, drug prescriptions, and beneficiaries. These data files were deidentified by scrambling the identification codes of both patients and medical facilities. We have previously utilized LHID and NHIRD to conduct several clinical, epidemiologic studies aiming to answer clinical queries [5, 12–16]. Physician-diagnosed disease is reflected in the medical claim by the *International Classification of Diseases, 9th edition, with clinical modification* (ICD-9-CM) codes, either as a single code or in combination. For example, osteoporotic fracture is defined by a combination of two codes: any site of pathological fracture due to osteoporosis (ICD-9-CM codes: 733.0x + 733.1x).

Ethics statement

This research was initiated after obtaining approval from the Kuang Tien General Hospital Institutional Review Board with the certificate number KTGH IRB-10449. This study also strictly adhered to confidentiality guidelines that are in accordance with the regulations set forth by the Taiwan Personal Information Protection Act. The research was conducted in accordance with the Declaration of Helsinki, as revised in 1989. The IRB has waived the need to obtain a written informed consent from the patients.

Assembly of studied cohorts

Gout cohort

There were 75,985 subjects who had at least one medical claim of gout in the dataset. We restricted the study population to subjects aged ≥ 20 years with physician-diagnosed gout ($n = 36{,}020$) after excluding those aged < 20 ($n = 2262$), those who had less than three medical visits for gout ($n = 27{,}852$), those with pre-existing osteoporosis disease ($n = 2122$), and those who had a follow-up period of less than 2 years in the dataset ($n = 7729$) (Fig. 1).

Physician-diagnosed gout in this country adheres to the American College of Rheumatology classification criteria, adopting the gold standard for diagnosis, which denotes the presence of monosodium urate monohydrate (MSU) crystals in the synovial fluid or tophus. Clinically, the diagnosis of gout always considers factors such as male sex, previous patient-reported arthritis attack, onset within 1 day, joint redness, first metatarsophalangeal joint involvement, hypertension or one or more cardiovascular diseases, imaging findings such as a double-contour sign on ultrasound or urate on dual-energy computed tomography, radiographic gout-related erosion, and serum uric acid concentration exceeding 5.88 mg/dL [17, 18].

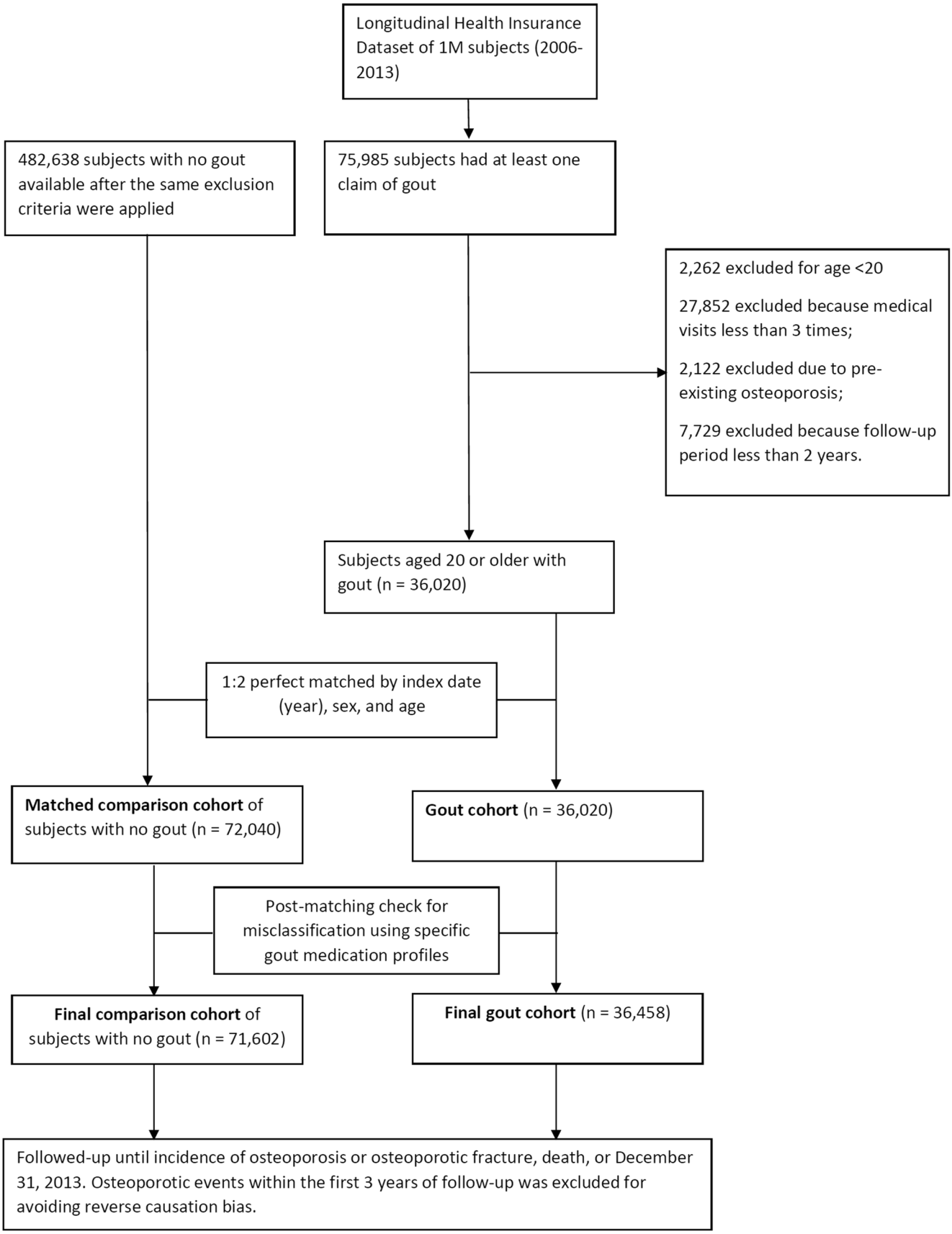

Fig. 1 Consort diagram showing detailed steps for assembling the two study cohorts

Comparison cohort

A total of 482,638 subjects without gout were available after applying similar exclusion criteria as those for the gout cohort. To avoid allocation bias, this non-gout cohort had been verified to maintain gout-free in the dataset throughout the entire follow-up period. A random matching algorithm was applied to select two participants with no gout to form the comparison cohort perfect matched by the index date, sex, and age of each patient with gout. The finally assembled cohort of patients with gout contained 36,020 subjects, whereas the comparison cohort contained 72,040 subjects.

Post-matching check for misclassification

We used the drug profile such as benzbromarone and febuxostat prescription of the selected participants to check if any gout cases were misclassified as non-gout comparators. A total of 438 misclassified participants were detected and subsequently moved cross-over to the gout cohort. Finally, the gout cohort had 36,458 individuals, and the non-gout comparison cohort had 71,602 participants.

Outcome measures

The primary outcome measure in this study was physician-diagnosed osteoporosis, defined as at least three different medical claims issued in the outpatient setting or at least one claim issued in the inpatient setting. The secondary outcome measures were the incidence of thoracolumbar vertebral compression fracture and hip fracture. To avoid the reverse causation phenomenon (protopathic bias), subjects with osteoporotic outcomes during the first 3 years of follow-up were excluded from the overall risk calculation.

In Taiwan, a clinical diagnosis of osteoporosis can be made in subjects who sustain a low-impact fracture, or by the measurement of spine and hip bone mineral density (BMD) with results showing a value for BMD 2.5 or more standard deviation (SD) below the young adult female reference mean (T-score less than or equal to − 2.5 SD) [19]. The Caucasian female normative database is adopted as a reference for T-scores which should apply to Taiwanese postmenopausal women and may also be applied to Taiwanese men. When the spine and hip cannot be measured, the Taiwanese Guidelines for the Prevention and Treatment of Osteoporosis published by the Taiwanese Osteoporosis Association also suggests a value of BMD be measured at the one third (33%) radius site to assist in making the diagnosis of osteoporosis. Also, any vertebral body deformation of more than 20% can be diagnosed as osteoporosis according to the Taiwanese Guidelines.

Confounding variables

Table 1 shows that the two cohorts were balanced with respect to the index date, age, and sex after matching. We used categorized insurance premium as a proxy for socioeconomic status of the participating subjects. Residential area in the southern part of the country indicates more sunshine exposure. All the relevant medical comorbidities, including morbid obesity [20], smoking-related diagnosis [21], alcohol use disorder [22], hypertension [23, 24], dyslipidemia [25, 26], diabetes mellitus [25], kidney disease [27], and rheumatoid arthritis (RA) [28, 29], were significantly more common in the gout cohort (Table 1). RA was considered because a recent South Korean population-based study disclosed that a large percentage (90.8%) of postmenopausal women with RA enrolled in the study had osteoporosis [28]. Compared with the general population without RA, Taiwanese patients with RA have a higher incidence of hip fractures at a relatively younger age, with 3260 events versus 72 events per 100,000 person-years [29]. Chronic obstructive pulmonary disease was recently included in the smoking-related diagnoses panel [30]. A meta-analysis of over 80 studies in adults found that use of ≥ 5 mg/day of prednisolone (or equivalent) was associated with significant reductions in bone mineral density and an increase in fracture risk within 3 to 6 months of steroid initiation; this increased fracture risk was independent of patient age, gender, and the underlying disease [31]. Thus, we categorized glucocorticoid exposure of an enrollee using a cutoff value of 135 mg hydrocortisone equivalent. Glucocorticoid exposure at baseline was calculated as the sum of the dosages of any oral corticosteroid prescription 1 year after the index date for each cohort, converted to hydrocortisone equivalents (4 mg of hydrocortisone = 1 mg of prednisolone = 5 mg of cortisone acetate = 0.8 mg methylprednisolone = 0.8 mg of triamcinolone = 0.4 mg of paramethasone = 0.15 mg of betamethasone = 0.15 mg of dexamethasone) [32]. Vitamin D prescription was also assessed in both study cohorts. In the calculation of the adjusted hazard ratio (aHR) from a planned Cox proportional hazard model, these comorbidities were required to be included in the model as confounding variables. For urate-lowering treatment, we examined allopurinol exposure and long-term allopurinol exposure which was defined as a prescription of allopurinol at least 100 mg daily for at least 30 days in a year, as well as benzbromarone and febuxostat exposure [11].

Follow-up of patients

All participants in both cohorts were followed up until the occurrence of osteoporosis or osteoporotic fracture, death, or December 31, 2013, whichever occurred first. Osteoporotic events within the first 3 years of follow-up were excluded from risk estimation (Fig. 1).

Table 1 Demographics and comorbidities at baseline between the gout cohort and the age-, sex-, and index date-matched comparison cohort without gout. Gout attack frequency and exposure to gout medication were post-baseline measures

Characteristic	Gout cohort		Comparison cohort		*P* value
N	36,458		71,602		
Variables	No.	%	No.	%	
Age, mean years (SD)	52.65 (15.96)		52.10 (16.12)		Matched
Age group, years					Matched
20–29	2850	7.8	5697	8.0	
30–39	5432	14.9	10,828	15.1	
40–49	7418	20.3	14,734	20.6	
50–59	8817	24.2	17,427	24.3	
60–69	5654	15.5	11,017	15.4	
70–79	4460	12.2	8539	11.9	
80–89	1659	4.6	3048	4.3	
≥ 90	168	0.5	312	0.4	
Gender					Matched
Male	26,548	72.8	52,112	72.8	
Female	9910	27.2	19,490	27.2	
Residential area					< 0.0001
Northern	17,149	47.0	34,265	47.9	
Central	8293	22.7	16,712	23.3	
Southern	9277	25.4	17,991	25.1	
East	1118	3.1	1530	2.1	
Outer islands	621	1.7	1104	1.5	
Insurance premium (New Taiwan dollar)					< 0.0001
< 15,000	12,832	35.2	26,086	36.4	
15,000–21,999	11,838	32.5	22,175	31.0	
≥ 22,000	11,788	32.3	23,341	32.6	
Comorbidities					
Morbid obesity	564	1.5	392	0.5	< 0.0001
Smoking-related diagnosis	2498	6.9	3961	5.5	< 0.0001
Alcohol use disorder	717	2.0	693	1.0	< 0.0001
Hypertension	15,560	42.7	18,227	25.5	< 0.0001
Dyslipidemia	7433	20.4	5572	7.8	< 0.0001
Diabetes mellitus	6325	17.3	8602	12.0	< 0.0001
Kidney disease	2211	6.1	1999	2.8	< 0.0001
Rheumatoid arthritis	877	2.4	563	0.8	< 0.0001
Glucocorticoid exposure†					0.06
No steroid use	36,403	99.9	71,530	99.9	
< 135 mg hydrocortisone equivalent	5	0.01	9	0.01	
≥ 135 mg hydrocortisone equivalent	50	0.1	63	0.1	
Vitamin D prescription	1	0.002	3	0.004	0.7
Urate-lowering treatment					
Allopurinol exposure (yes/no)	1372	3.8	279	0.4	< 0.0001
Long-term allopurinol exposure (> 30 days/year)					< 0.0001
100 mg daily	67	0.2	15	0.02	
200 mg daily	70	0.2	9	0.01	
≥ 300 mg daily	108	0.3	26	0.04	
Febuxostat exposure (yes/no)	7	0.02	0	0	0.0002
Benzbromarone exposure (yes/no)	1363	3.7	0	0	< 0.0001

Table 1 (continued)

Characteristic	Gout cohort		Comparison cohort		*P* value
N	36,458		71,602		
Variables	No.	%	No.	%	
Gout attack frequency					< 0.0001
1 episode/year	7387	20.5	0	0	
2 episodes/year	11,019	30.6	0	0	
3 episodes/year	5480	15.2	0	0	
4 episodes/year	3451	9.6	0	0	
≥ 5 episodes/year	7807	21.7	0	0	

Statistical analysis

Descriptive analysis was required to produce Fig. 1 and Table 1. Chi-square test was performed for the categorical data in Table 1. Person-time for each stratum in a cohort is the sum total of times that each of the subjects in that stratum was followed up. The incidence rate ratio (IRR) was presented along with its corresponding 95% confidence interval (CI) for each stratum, which coincides with the 5% convention of statistical significance in hypothesis testing. The adjusted hazard ratio (aHR) and its 95% CI were calculated from a Cox model controlling for age, sex, and all the abovementioned medical comorbidities. Sensitivity analysis was performed to examine the effect of the differential time lag from follow-up on the changes in risk represented as aHR of the osteoporotic outcome. The cumulative osteoporosis incidence (proportion) for each cohort was derived using the Kaplan–Meier method after excluding the outcomes within the first 3 years of follow-up and compared using the log-rank test. In the examination of the predictors of osteoporosis development in the gout cohort, factors such as glucocorticoid exposure (no steroid use, < 135 or ≥ 135 mg hydrocortisone equivalent), urate-lowering treatment (no treatment, allopurinol exposure, long-term allopurinol exposure, and benzbromarone exposure), and gout attack frequency (1 or 2–3 or ≥ 4 episodes per year) were included in the multivariable Cox model. The authors wrote the manuscript according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations to improve the quality of this observational study. The output, code, and data analysis for this paper were generated using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Men comprised 72.8% of the entire cohort (Table 1). The mean age of the participants was approximately 52 years. Nearly 57% of the study subjects were aged ≥ 50 years. Compared with those without gout, patients with gout had a significantly higher rate of morbid obesity (1.5 vs. 0.5%), smoking-related diagnosis (6.9 vs. 5.5%), alcohol use disorder (2 vs. 1%), hypertension (42.7 vs. 25.5%), dyslipidemia (20.4 vs. 7.8%), diabetes mellitus (17.3 vs. 12%), kidney disease (6.1 vs. 2.8%), and RA (2.4 vs. 0.8%). Less than 1% of the study subjects had glucocorticoid exposure in both study cohorts and had no statistical difference ($P = 0.06$) (Table 1).

With a follow-up of 183,729 and 359,900 person-years for the gout and non-gout cohorts, 517 and 811 study subjects received consistent diagnoses of osteoporosis given by a physician, respectively. The incidence rates of osteoporosis per 100,000 patients per year were 2.81 in the gout cohort and 2.25 in the comparison cohort, with an incidence rate ratio equal to 1.25 (95% CI, 1.12–1.39) (Table 2). The crude HR was also statistically significant, showing a 25% increase in the risk with an HR of 1.25 (95% CI, 1.12–1.39). This modest increase of the risk sustained even after the multivariate Cox model adjusting for the abovementioned confounding factors with an aHR of 1.2 (95% CI, 1.06–1.35; $P = 0.0036$) (Table 1).

For the secondary outcome measures, gout cohort harbored a modest but statistically non-significant increase of the risk for thoracolumbar vertebral compression fractures, having the IRR, crude HR, and adjusted HR as 1.09 (95% CI, 0.77–1.54), 1.09 (95% CI, 0.77–1.54), and 1.03 (95% CI, 0.70–1.51), respectively. For the outcome of hip fracture, the multivariate adjusted HR was 1.56 (95% CI, 0.28–8.65) for the gout cohort versus the comparison cohort (Table 2).

Our study also reveals an interesting finding that men and women have different levels of osteoporosis risk, with a significant increase in the risk for male patients with gout (aHR = 1.33, 95% CI, 1.10–1.61; $P = 0.0028$). The numerically increased risk for female patients, however, did not reach statistical significance (aHR = 1.11, 95% CI, 0.95–1.30; $P = 0.18$) (Table 2).

Sensitivity analysis was performed to examine the effect of the differential time lag of follow-up on the stratified risk of osteoporosis. From the fourth follow-up year and beyond, the

Table 2 Incidence of osteoporosis, thoracolumbar vertebral compression fracture, and hip fracture beyond the first 3 follow-up years and the crude and adjusted hazard ratios (HRs) derived from the Cox model for the gout cohort compared with that from the comparison non-gout cohort stratified by patient characteristics

	Gout cohort ($N = 31,844$)			Comparison cohort ($N = 62,444$)			Incidence rate ratio	Crude HR	Adjusted HR	*P* value
Variables	Event	PYs	Rate	Event	PYs	Rate	(95% CI)	(95% CI)	(95% CI)	
Osteoporosis	517	183,729.0	2.81	811	359,899.5	2.25	**1.25 (1.12–1.39)**	**1.25 (1.12–1.39)**	**1.20 (1.06–1.35)**	**0.0036**
Thoracolumbar vertebral compression fracture	50	183,729.0	0.27	90	359,899.5	0.25	1.09 (0.77–1.54)	1.09 (0.77–1.54)	1.03 (0.70–1.51)	0.89
Hip fracture	3	183,729.0	0.02	3	359,899.5	0.01	1.96 (0.40–9.71)	1.95 (0.39–9.68)	1.56 (0.28–8.65)	0.61
Gender										
Male	222	135,651.8	1.64	310	265,573.9	1.17	**1.40 (1.18–1.67)**	**1.40 (1.18–1.66)**	**1.33 (1.10–1.61)**	**0.0028**
Female	295	48,078.2	6.14	501	94,325.6	5.31	**1.16 (1.00–1.33)**	**1.16 (1.00–1.34)**	1.11 (0.95–1.30)	0.18
Age										
20–39	29	42,909.0	0.68	21	85,980.8	0.24	**2.77 (1.58–4.85)**	**2.77 (1.58–4.86)**	**1.90 (1.01–3.58)**	**0.0466**
40–59	137	83,065.3	1.65	209	164,339.9	1.27	**1.30 (1.05–1.61)**	**1.30 (1.04–1.61)**	1.11 (0.88–1.42)	0.38
60–79	299	49,754.9	6.01	513	94,770.7	5.41	1.11 (0.96–1.28)	1.10 (0.96–1.27)	1.16 (1.00–1.35)	0.06
≥ 80	52	8000.8	6.50	68	14,808.1	4.59	1.42 (0.99–2.03)	1.43 (0.99–2.05)	**1.66 (1.12–2.48)**	**0.0124**
Residential area										
Northern	193	86,404.2	2.23	320	172,262.2	1.86	**1.20 (1.01–1.44)**	**1.20 (1.00–1.43)**	1.11 (0.91–1.35)	0.29
Central	140	41,829.2	3.35	218	83,985.2	2.60	**1.29 (1.04–1.59)**	**1.29 (1.04–1.59)**	**1.28 (1.02–1.62)**	**0.0368**
Southern	146	46,421.9	3.15	229	89,318.4	2.56	1.23 (1.00–1.51)	1.23 (1.00–1.51)	1.19 (0.95–1.49)	0.13
East	27	5464.6	4.94	26	7836.1	3.32	1.49 (0.87–2.55)	1.53 (0.89–2.62)	1.56 (0.87–2.82)	0.14
Outer islands	11	3610.1	3.05	18	6497.6	2.77	1.10 (0.52–2.33)	1.11 (0.53–2.35)	1.11 (0.47–2.63)	0.81
Insurance premium										
< 15,000 NTD	256	63,363.0	4.04	397	129,383.6	3.07	**1.32 (1.13–1.54)**	**1.32 (1.13–1.54)**	**1.25 (1.05–1.48)**	**0.0109**
15,000–21,999 NTD	181	60,842.6	2.97	287	114,424.6	2.51	1.19 (0.98–1.43)	1.19 (0.99–1.43)	1.12 (0.91–1.38)	0.28
≥ 22,000 NTD	80	59,524.4	1.34	127	116,091.3	1.09	1.23 (0.93–1.63)	1.22 (0.92–1.61)	1.19 (0.88–1.62)	0.25
Morbid obesity										
No	510	181,144.7	2.82	804	358,200.8	2.24	**1.25 (1.12–1.40)**	**1.25 (1.12–1.40)**	**1.20 (1.07–1.36)**	**0.0029**
Yes	7	2585.3	2.71	7	1698.7	4.12	0.66 (0.23–1.87)	0.62 (0.22–1.77)	0.59 (0.17–2.02)	0.40
Smoking-related diagnosis										
No	468	172,494.0	2.71	746	341,906.7	2.18	**1.24 (1.11–1.40)**	**1.24 (1.11–1.39)**	**1.18 (1.04–1.34)**	**0.0103**
Yes	49	11,236.0	4.36	65	17,992.8	3.61	1.21 (0.83–1.75)	1.21 (0.84–1.75)	1.33 (0.88–1.98)	0.17
Alcohol use disorder										
No	506	180,450.9	2.80	807	356,689.8	2.26	**1.24 (1.11–1.39)**	**1.24 (1.11–1.38)**	**1.20 (1.06–1.35)**	**0.0040**
Yes	11	3279.1	3.35	4	3209.7	1.25	2.69 (0.86–8.45)	2.71 (0.86–8.52)	1.64 (0.44–6.12)	0.46
Hypertension										
No	220	108,031.9	2.04	470	274,462.8	1.71	**1.19 (1.01–1.40)**	**1.19 (1.01–1.39)**	**1.27 (1.07–1.51)**	**0.0072**

Table 2 (continued)

Variables	Gout cohort ($N = 31,844$)			Comparison cohort ($N = 62,444$)			Incidence rate ratio	Crude HR	Adjusted HR	*P* value
	Event	PYs	Rate	Event	PYs	Rate	(95% CI)	(95% CI)	(95% CI)	
Yes	297	75,698.1	3.92	341	85,436.7	3.99	0.98 (0.84–1.15)	0.97 (0.83–1.13)	1.09 (0.92–1.29)	0.31
Dyslipidemia										
No	377	148,689.2	2.54	719	335,505.5	2.14	**1.18 (1.04–1.34)**	**1.18 (1.04–1.34)**	**1.18 (1.03–1.35)**	**0.0183**
Yes	140	35,040.8	4.00	92	24,394.0	3.77	1.06 (0.81–1.38)	1.02 (0.79–1.33)	1.18 (0.90–1.54)	0.25
Diabetes mellitus										
No	408	154,016.7	2.65	664	319,386.8	2.08	**1.27 (1.13–1.44)**	**1.27 (1.12–1.44)**	**1.22 (1.06–1.39)**	**0.0048**
Yes	109	29,713.3	3.67	147	40,512.7	3.63	1.01 (0.79–1.30)	1.01 (0.79–1.30)	1.08 (0.83–1.41)	0.59
Kidney disease										
No	486	173,689.4	2.80	784	350,788.2	2.23	**1.25 (1.12–1.40)**	**1.25 (1.12–1.40)**	**1.19 (1.05–1.35)**	**0.0063**
Yes	31	10,040.6	3.09	27	9111.3	2.96	1.04 (0.62–1.75)	1.04 (0.62–1.75)	1.32 (0.76–2.29)	0.33
Rheumatoid arthritis										
No	509	179,753.4	2.83	797	357,447.0	2.23	**1.27 (1.14–1.42)**	**1.27 (1.13–1.42)**	**1.22 (1.08–1.38)**	**0.0014**
Yes	8	3976.6	2.01	14	2452.5	5.71	**0.35 (0.15–0.84)**	**0.36 (0.15–0.85)**	**0.36 (0.14–0.93)**	**0.0347**
Glucocorticoid exposure										
No steroid use	515	183,628.6	2.80	811	359,721.0	2.25	**1.24 (1.11–1.39)**	**1.24 (1.11–1.39)**	**1.19 (1.06–1.35)**	**0.0042**
< 135 mg hydrocortisone equivalent	0	4.0	0.00	0	27.5	0	6.88 (–)	NA	NA	–
≥ 135 mg hydrocortisone equivalent	2	97.4	20.53	0	151.0	0	NA	NA	NA	–
Urate-lowering treatment										
Allopurinol exposure	29	7449.7	3.89	2	1387.8	1.44	2.70 (0.64–11.32)	2.60 (0.62–10.89)	1.56 (0.34–7.27)	0.57

Bold type numerals denote achieving statistically significant

Adjustments were made in Cox models for gender, age, residential area, insurance premium, comorbidities including obesity, smoking-related diagnosis, alcohol use disorder, hypertension, dyslipidemia, diabetes, kidney disease, and rheumatoid arthritis, oral corticosteroid exposure, and allopurinol exposure

The southern part of the country indicates more sunshine exposure

Thoracolumbar vertebral compression fracture = ICD-9-CM code 733.13

Hip fracture = ICD-9-CM code 733.14

Event number of osteoporosis, *PYs* person-years, *Rate* incidence per 1000 PYs, *HR* hazard ratio, *CI* confidence interval, *NA* not applicable, *NTD* New Taiwan dollar

Table 3 Sensitivity analysis by differential lag time during follow-up showing the respective incidences of osteoporosis and adjusted hazard ratio

	Gout cohort			Comparison cohort			Adjusted HR (95% CI)	*P* value
Follow-up, years	Event	PYs	Rate	Event	PYs	Rate		
4th	195	16,621.7	11.73	342	32,971.2	10.37	**1.23 (1.02–1.48)**	**0.03**
5th	149	24,690.2	6.03	222	47,234.0	4.70	1.19 (0.95–1.49)	0.14
6th	91	32,568.8	2.79	149	63,902.3	2.33	1.17 (0.88–1.57)	0.28
7th	56	41,792.9	1.34	74	81,931.3	0.90	1.40 (0.95–2.05)	0.09
> 7	26	68,056.4	0.38	24	133,860.7	0.18	**2.54 (1.41–4.56)**	**0.0019**

The Cox proportional hazard models were performed to adjust for gender, age, residential area, insurance premium, obesity, smoking-related diagnosis, alcohol use disorder, comorbidities including hypertension, hyperlipidemia, diabetes mellitus, kidney disease, and rheumatoid arthritis, and exposure to oral corticosteroid and allopurinol

Event number of osteoporosis, *PYs* person-years, *Rate* incidence per 1000 PYs. Bold type numerals denote achieving statistically significant

risk of osteoporosis was sustained in the same direction of increase in the fourth and beyond the seventh years of follow-up, having reached statistical significance (Table 3). The risk more than doubled to reach 2.54 (95% CI, 1.41–4.56; $P = 0.0019$) in the eighth year of follow-up. We constructed a multivariate Cox model to derive the cumulative incidence function excluding the first 3 years of follow-up events. Figure 2 depicts the cumulative incidence of osteoporosis, which is 3.3 and 2.1%, respectively, for the gout and non-gout cohorts ($P = 0.0036$, log-rank) after excluding the first 3 years of follow-up.

Table 4 demonstrates the results of our multivariate Cox model to analyze the differential risk among different categorizations, such as pre-set age groups, within a patient characteristic in the gout cohort, with crude and aHRs of osteoporosis stratified by different patient characteristics. Women harbored up to a threefold increased risk of osteoporosis (aHR, 2.99; 95% CI, 2.49–3.59) as compared with men. There was a progressive elevation of osteoporosis risk with age: when compared with the risk in the 20–39-year age group, aHR was 1.79 (95% CI, 1.17–2.72) in the 40–59-year age group, 6.75 (95% CI, 4.43–10.30) in the 60–79-year age group, and 7.05 (95% CI, 3.59–13.94) in the ≥ 80-year age group. Gout patients with alcohol use disorders had an increased risk of osteoporosis in our study (aHR = 2.24, 95% CI, 1.22–4.10), as shown in Table 4. Patients who dwelled in the central region (aHR = 1.52, 95% CI, 1.22–1.89), southern region (aHR = 1.39, 95% CI, 1.12–1.73), and the eastern region (aHR = 2.04, 95% CI, 1.35–3.07) had an increased risk of osteoporosis when compared with people in the northern part of the country. Patients with dyslipidemia harbored an increased risk of osteoporosis when compared with those without dyslipidemia (aHR = 1.26, 95% CI, 1.03–1.54). Finally, gout patients who took glucocorticoid steroid at the dose ≥ 135 mg hydrocortisone equivalent had a statistically significant increase of the osteoporosis risk with an aHR of 2.77 (95% CI, 1.36–5.61) in our study.

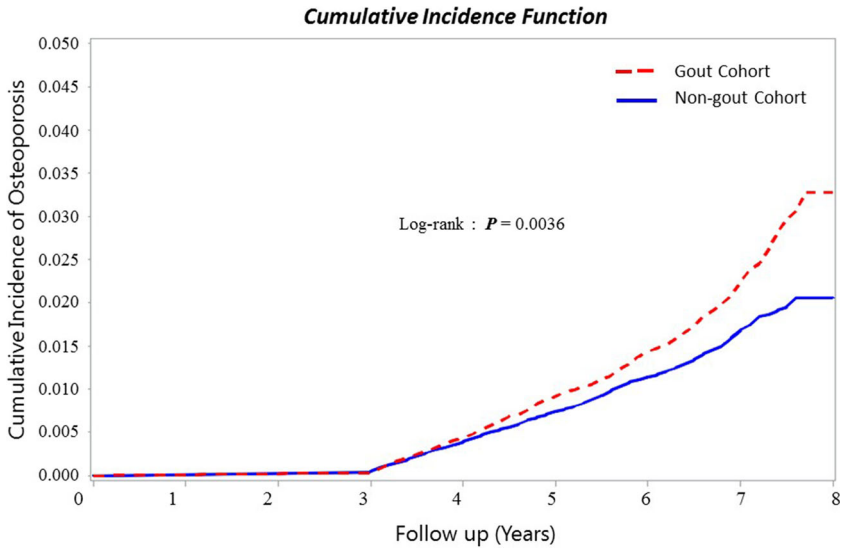

Fig. 2 Cumulative incidence of osteoporosis, which is 3.3 and 2.1%, respectively, in the gout and non-gout cohorts ($P = 0.0036$, compared with log-rank) after excluding the first 3 years of follow-up

Table 4 Cox model-derived crude and multivariate adjusted hazard ratios (HRs) of osteoporosis development stratified by patient characteristics in the gout cohort

	Gout cohort ($N = 31,844$)		
Variables	Osteoporosis outcome ($n = 517$)	Crude hazard ratio (95% confidence interval)	Adjusted hazard ratio (95% confidence interval)
Gender			
Male (ref)	222	1	1
Female	295	**3.84**** **(3.22–4.57)**	**2.99**** **(2.49–3.59)**
Age, years			
20–39 (ref)	29	1	1
40–59	137	**2.45**** **(1.64–3.66)**	**1.79** **(1.17–2.72)**
60–79	299	**9.08**** **(6.20–13.29)**	**6.75**** **(4.43–10.30)**
≥ 80	52	**10.39**** **(6.60–16.37)**	**7.05**** **(3.59–13.94)**
Residential area			
Northern (ref)	193	1	1
Central	140	**1.50*** (1.21–1.87)**	**1.52*** (1.22–1.89)**
Southern	146	**1.42** (1.14–1.76)**	**1.39** (1.12–1.73)**
East	27	**2.27**** **(1.52–3.40)**	**2.04*** (1.35–3.07)**
Outer islands	11	1.32 (0.72–2.42)	1.43 (0.78–2.64)
Insurance premium			
< 15,000 NTD (ref)	256	1	1
15,000–21,999 NTD	181	**0.73** (0.60–0.88)**	0.88 (0.72–1.07)
≥ 22,000 NTD	80	**0.33**** **(0.26–0.42)**	0.81 (0.61–1.09)
Morbid obesity			
No (ref)	510	1	1
Yes	7	1.00 (0.48–2.12)	1.24 (0.59–2.62)
Smoking-related diagnosis			
No (ref)	468	1	1
Yes	49	**1.69*** (1.25–2.26)**	1.21 (0.89–1.64)
Alcohol use disorder			
No (ref)	506	1	1
Yes	11	1.24 (0.68–2.26)	**2.24** (1.22–4.10)**
Hypertension			
No (ref)	220	1	1
Yes	297	**1.98**** **(1.66–2.35)**	0.85 (0.70–1.03)
Dyslipidemia			
No (ref)	377	1	1
Yes	140	**1.64**** **(1.35–1.99)**	**1.26* (1.03–1.54)**
Diabetes mellitus			
No (ref)	408	1	1
Yes	109	**1.44*** (1.17–1.78)**	0.82 (0.66–1.02)
Kidney disease			
No (ref)	486	1	1
Yes	31	1.16 (0.81–1.67)	0.74 (0.51–1.07)
Rheumatoid arthritis			
No (ref)	509	1	1
Yes	8	0.75 (0.38–1.51)	0.50 (0.25–1.01)
Glucocorticoid exposure			
No steroid use	515	1	1
< 135 mg hydrocortisone equivalent	0	NA	NA
	2	**3.27*** (1.63–6.56)**	**2.77** (1.36–5.61)**

Table 4 (continued)

	Gout cohort ($N = 31,844$)		
≥ 135 mg hydrocortisone equivalent			
Urate-lowering treatment			
No urate-lowering treatment	432	1	1
Allopurinol exposure	29	1.41 (0.97–2.06)	0.69 (0.37–1.29)
Long-term allopurinol exposure	3	0.83 (0.27–2.57)	0.15 (0.01–1.98)
Benzbromarone exposure	30	**1.55* (1.07–2.24)**	0.87 (0.52–1.47)
Gout attack frequency			
1 episode/year	121	1	1
2–3 episodes/year	218	0.96 (0.77–1.20)	0.93 (0.75–1.17)
≥ 4 episodes/year	157	1.02 (0.80–1.29)	0.94 (0.73–1.19)

The Cox proportional hazard models were performed to adjust for gender, age, residential area, insurance premium, obesity, smoking-related diagnosis, alcoholism-related diagnosis, comorbidities including hypertension, hyperlipidemia, diabetes mellitus, kidney disease, and rheumatoid arthritis and oral corticosteroid exposure, urate-lowering medication, and gout attack frequency

Bold type numerals denote achieving statistically significant. *NTD* New Taiwan dollar, *Ref* reference

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$

Discussion

We discovered that there is a modest increase in the risk of developing osteoporosis in future in patients with gout compared with their non-gout counterparts after excluding events in the first 3 years of follow-up from our multivariate Cox model. The cumulative incidence of osteoporosis in the gout cohort is 3.3% from the fourth to the eighth years of follow-up in contrast with 2.1% in the non-gout cohort. To the best of our knowledge, this is the first population-based cohort study to demonstrate the positive association between gout and subsequent osteoporosis development. Our study further shows that the risk in terms of aHR may double, reaching a 2.5-fold increase after 7 years of follow-up. These findings support our hypothesis based on preclinical study results and should stimulate more prospective studies to confirm our results. If the risk of osteoporosis in patients with gout is proven to be consistent, these patients should receive a personalized risk assessment and screening for osteoporosis.

A systematic literature search for human studies examining the association between gout and subsequent osteoporosis in Medical Literature Analysis and Retrieval System Online yielded only four relevant papers with conflicting results [8–11]. These four cohort studies were conducted to examine the risk of *osteoporotic fracture* in patients with gout, although it was unknown in the first place if there was a real association existing between gout and osteoporosis. All the studies were population-based cohort studies published between 2015 and 2017 with outcome measures limited to osteoporotic fracture and not osteoporosis. One utilized data from the Nurse's Health Study (NHS), which prospectively collected data from female participants only, and can be considered a prospective cohort study [9]. NHS, which examined the outcomes of non-vertebral fractures with incidents of wrist and hip fractures, found that the adjusted relative risk for hip fracture was 1.38 (95% CI, 1.14–1.68) in female participants with gout. Although Kim et al.'s study [10] using a US commercial health plan dataset discovered a neutral risk for hip fractures with an aHR of 0.83 (95% CI, 0.65–1.07), Dennison et al.'s study [11] using the Danish registry dataset revealed a statistically significant increased risk of hip fracture with an aHR of 1.28 (95% CI, 1.17–1.39). More well-designed population-based studies are required in the near future to give us a clear picture of the association between gout and osteoporotic fracture, particularly the hip fracture. In terms of the risk of overall osteoporotic fractures in patients with gout, both retrospective cohort studies from Denmark and Taiwan revealed a similarly modest increase in the risk with aHR was 1.25 (95% CI, 1.08–1.44) in the Danish study and 1.17 (95% CI, 1.14–1.21) in the Taiwanese study [8, 11].

However, there is no study examining the association between gout and osteoporosis in the literature to compare with ours. We postulate that statistical significance cannot be demonstrated in any study with a follow-up duration of < 8 years.

The strengths of our study are, first, the male to female ratio of the gout cohort. Men accounted for 73% of the patients, a ratio similar to that of many prominent studies in the literature. Second, our study has a sufficient follow-up duration. Third,

the protopathic bias (causation reversal) was eliminated by excluding the initial outcomes in the first 3 years of follow-up when calculating the risk. Fourth, we performed a perfect random matching of the non-gout cohort balanced with respect to index date, sex, and age, and a post-matching check to eliminate the misclassification bias. Fifth, the demographic characteristics of our gout cohort demonstrate that gout is associated with a higher frequency of other cardiometabolic medical comorbidities such as morbid obesity, alcohol use disorder, hypertension, dyslipidemia, diabetes mellitus, and kidney disease. Lastly, the entire cohort comprised 108,060 study subjects, making the risk estimates more precise.

We think the data has spoken for the positive association between gout and subsequent osteoporosis. Prior to this study, clinicians would not have linked gout with osteoporosis and thus may have skipped discussing future osteoporosis risk during personalized counseling if other classical risk factors such as low BMD were absent. Until proven otherwise, our study results support the implementation of osteoporosis education for patients with gout.

There exist certain potential limitations in our study. In this claim-based research, serum uric acid concentration, serum 25-hydroxyvitamin D, serum parathyroid hormone, and pro-inflammatory cytokines such as IL-1, IL-6, and TNF-alpha and serial BMD data were not available for analysis. Dietary factors, physical activity data, and the interactions of thousands of medications may contribute to the modification of the risk estimate. However, recall bias is not present as it would be in a questionnaire or telephone interview research. Moreover, the algorithm we used to place comparators into the non-gout cohort was able to exclude any individual with late-onset gout, and there was no dropout from any cohort in this study.

Further research can examine the difference in the rate of developing osteoporosis between gout with appropriate care and those with inappropriate care.

Conclusion

The results of our population-based longitudinal study involving 108,060 individuals provide epidemiologic evidence that gout may be a risk factor for future osteoporosis. The effects of osteoporosis only surfaced after the first 3 years of follow-up. The cumulative incidence of osteoporosis is statistically higher in patients with gout when compared with that in those without gout, 3.3 versus 2.1%.

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Compliance with ethical standards

This research was initiated after obtaining approval from the Kuang Tien General Hospital Institutional Review Board with the certificate number KTGH IRB-10449. This study also strictly adhered to confidentiality guidelines that are in accordance with the regulations set forth by the Taiwan Personal Information Protection Act. The research was conducted in accordance with the Declaration of Helsinki, as revised in 1989. The IRB has waived the need to obtain a written informed consent from the patients.

Conflicts of interest None.

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