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Original article

Alcohol-related diseases and alcohol dependence syndrome is associated with increased gout risk: A nationwide population-based cohort study

suppl. Informations

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ABSTRACT

Objective: Alcohol intake is strongly associated with hyperuricemia, which may cause gout. This study evaluated the risk of gout in patients with alcohol-related diseases and alcohol dependence syndrome.
Methods: We used the Taiwan National Health Insurance Research Database (NHIRD) to conduct a nationwide population-based cohort study to assess the risk of gout and gout incidence in patients with alcohol-related diseases and alcohol dependence syndrome (as defined by the International Classification of Diseases, Ninth Revision). In the NHIRD records from 1998 to 2008, we identified 11,675 cases of alcohol-related diseases. The control group comprised 23,350 cases without alcohol-related diseases propensity score–matched (1 case: 2 controls) for age, age group, and sex.
Results: The results revealed that alcohol-related diseases were significantly associated with gout risk (adjusted hazard ratio 1.88; $P < 0.0001$). Of the alcohol-related disease cases, 34.1% of the patients had alcohol dependence syndrome (males 34.8%; females 32.4%), and alcohol dependence was independently associated with gout occurrence (relative risk [RR] 2.01; $P < 0.0001$). Severe alcohol-dependent patients (who were also the heavy benzodiazepines users), were associated with an increased risk of gout (RR 1.71 to 4.21, $P \leq 0.0182$).
Conclusion: Physicians should be aware of the association between alcohol dependence syndrome and gout occurrence, and alcohol use assessment and measures to prevent alcohol dependence should be implemented in the integrative care for patients with gout.

1. Introduction

Gout is the most common form of inflammatory arthritis, for which hyperuricemia, and consequently the intra-articular deposition of monosodium urate crystals, is a prerequisite [1]. The prevalence of gout in the US was 3.9% [2], 1.4–2.5% in the UK [3,4], 0.9% in France [5], 1.4% in Germany [3], 3.2% (European ancestry) to 6.1% (Māori ancestry) in New Zealand [6], and 4.62% (general populations) to 10.42% (aborigenes) in Taiwan [7,8]. Despite the availability of urate-lowering therapies in Taiwan, the prevalence of gout remains high compared with that in other countries.

Alcohol has been recognized as a potential risk factor for gout occurrence and is considered a trigger for acute gouty arthritis and recurrent gout attacks [9,10]. In addition, heavy alcohol consumption was associated with an increased risk of gout [9]. A prospective Internet-based case-crossover study reported that episodic alcohol consumption was associated with an increased risk of recurrent gout attacks [10]. A large prospective cohort study revealed that alcohol intake was strongly associated with increased gout incidence [9]. Moreover, metabolic studies have shown that alcohol consumption increases serum lactate levels, thus blocking renal excretion of urates [11,12]. These findings established that

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alcohol causes buildup of uric acid crystals in joints, eventually leading to gout.

Names of many conditions found in the International Classification of Diseases, Ninth Revision (ICD-9) reveal alcohol as the cause; example include alcoholic psychoses, alcoholic polyneuropathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic fatty liver, acute alcoholic hepatitis, alcoholic cirrhosis of liver, alcoholic liver damage, alcohol dependence syndrome, and alcohol abuse. If various alcohol-related diseases differentially affect the risk of gout, it would have practical implications for gout prevention and management. The complex association between alcohol-related diseases and gout requires further investigation. Therefore, we conducted a nationwide population-based retrospective cohort study to evaluate how alcohol-related diseases affect the risk of gout; the study utilized the large data set of the National Health Insurance (NHI) program in Taiwan. In addition to investigating the association between alcohol-related diseases and gout, we investigated the presence of alcohol dependence in the records of patients with alcohol-related diseases receiving detoxification or withdrawal treatments, including the use of diazepam, chlordiazepoxide, oxazepam, and lorazepam.

2. Method

2.1. Data source

The NHI is a single-payer program in Taiwan established in 1995, covering over 98% of the population. Currently, the National Health Research Institutes in Miaoli, Taiwan, manage the National Health Insurance Research Database (NHIRD; www.nhri.org.tw/nhird/). The NHIRD is one of the largest nationwide population-based databases in the world and provides linked data, including patient demographic, registration data, diagnoses, prescriptions during hospital stays, outpatient claims data from hospitals and general practices, and the dispensing claims from hospitals, general practitioners, and community pharmacies, for epidemiological research [13]. The NHIRD has been used in numerous studies that have been published in peer-reviewed journals [13]. This study used the NHIRD Longitudinal Health Insurance Database (LHID) 2010, a nationally representative group of 1,000,000 beneficiaries who enrolled in the NHI in 2010, randomly sampled from the 2010 Registry for Beneficiaries of the NHIRD. LHID 2010 contains all original claims data from January 1, 2010, to December 31, 2010, of these beneficiaries (http://nhird.nhri.org.tw). Medical records from 1996 to 2010 of all selected individuals were analyzed in this study.

2.2. Study population

This study estimated the risk of gout following a diagnosis of alcohol-related diseases and alcohol dependence. The participants were followed from 1998 to 2010 (13 years) to assess the development of gout. In this retrospective cohort study, patients with and without first occurrence of alcohol-related diseases and gout were identified from the LHID 2010. In the linked data, all patient diagnoses were identified using the ICD-9 Clinical Modification (ICD-9-CM) codes. We analyzed the data to verify their eligibility as per the inclusion criteria.

The selection process of the study population is illustrated in Appendix A, Figure S1 (See the supplementary material associated with this article online). To avoid overestimating the incidence of gout, we excluded patients with a diagnosis of alcohol-related disease before January 1, 1998, and after January 1, 2009; if the development of gout correlates with the duration of the alcohol-related disease, including patients diagnosed with alcohol-related diseases before 1998 would result in overestimation of the risk of gout. We identified patients aged 20 and over who were alive as of December 31, 2010, as our study cohort. We excluded patients over 100 years of age, those not using gout medication (e.g., colchicine, xanthine oxidase inhibitor [allopurinol], and uricosuric agents [probenecid, sulfinpyrazone, and benzbromarone]), and those with 2 or fewer outpatient claims. In addition, we excluded patients who developed gout before the diagnosis of an alcohol-related disease. Furthermore, patients diagnosed with gout before December 31, 1998, were excluded to avoid overestimating the risk of gout in patients with alcohol-related diseases.

From the outpatient records from January 1, 1998, we identified 11,675 cases of alcohol-related diseases, diagnosed by a physician after 1998, including alcoholic psychoses (ICD-9-CM 291.x), alcohol dependence syndrome (303.x), alcohol abuse (305.0), alcoholic polyneuropathy (357.5), alcoholic cardiomyopathy (425.5), alcoholic gastritis (535.3), alcoholic fatty liver (571.0), acute alcoholic hepatitis (571.1), alcoholic cirrhosis of liver (571.2), alcoholic liver damage (571.3), and alcohol deterrents causing adverse effects in therapeutic use (E947.3) (Table 1). These subjects formed the alcohol-related diseases group. The control group comprised 23,350 subjects (1:2) who were propensity score–matched for age, age group, and sex (Appendix A, Figure S1). Appendix A, Table S1 presents the alcohol dependence patients receiving detoxification or withdrawal treatments, including the use of diazepam (Anatomical Therapeutic Chemical [ATC] code N05BA01), chlordiazepoxide (N05BA02), oxazepam (N05BA04), and lorazepam (N05BA06). The date of the first diagnosis for any alcohol-related disease was used as the index date for the alcohol-related diseases group, and January 1, 1998, was used as the index date for the control group. Subjects with gout were followed from the index date to the date of first diagnosis of gout. Subjects without gout were followed from the index date to December 31, 2010.

2.3. Outcomes and potential confounders

The outcome of interest in our study was a documentation of gout (ICD-9-CM code 274.x) by a physician or a rheumatologist in the outpatient claims. To enhance the accuracy of identifying the outcome of interest, we confirmed the diagnosis of gout by identifying in the diagnosis records at least one outpatient visit with a prescription of one or more gout medications (colchicine, xanthine oxidase inhibitor [allopurinol], and uricosuric agents [probenecid, sulfinpyrazone, benzbromarone]; Appendix A, Table S2).

We identified the potential confounders for gout in the study population: aboriginal living areas (yes/no), urbanization level (yes/no), socioeconomic status, and the Charlson comorbidity index (CCI) score. The CCI scores for the enhanced ICD-9-CM coding algorithm includes any condition that required 3 or more outpatient visits, as follows: myocardial infarction (1 point), congestive heart failure (1 point), peripheral vascular disease (1 point), dementia (1 point), chronic pulmonary disease (1 point), rheumatologic disease (1 point), peptic ulcer disease (1 point), diabetes mellitus (1 point uncomplicated), diabetes mellitus (2 points if end-organ damage), hemiplegia or paraplegia (2 points), renal disease (1 point), any malignancy (2 points), metastatic solid tumor (6 points), and AIDS (6 points) [14]. The CCI scores were categorized into four levels (0, 1–2, 3–4, and ≥ 5). Cases of mild liver disease (1 point) and liver disease (3 points if moderate to severe) were not included because alcohol-related diseases are related to liver diseases. The study project was reviewed and approved by the Institutional Review Committee of Kaohsiung Medical University Hospital (KMUHIRB-EXEMPT(I)-20150050), Taiwan.

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Table 1
Study population stratified by the various alcohol-related diseases.

	ICD-9-CM codes	All cases, *n* = 11675	Males, *n* = 8182	Females, *n* = 3493	Males vs females	
					P-value	OR (95% CI)
Alcoholic psychoses, *n* (%)	291.x	1164 (10.0)	935 (11.4)	229 (6.6)	1.01×10^{-16}	1.87 (1.61–2.17)
Alcohol dependence syndrome, *n* (%)	303.x	3976 (34.1)	2843 (34.8)	1133 (32.4)	1.60×10^{-2}	1.15 (1.06–1.25)
Alcohol abuse, *n* (%)	305.0	2179 (18.7)	1515 (18.5)	664 (19.0)	5.34×10^{-1}	1.02 (0.92–1.13)
Alcoholic polyneuropathy, *n* (%)	357.5	99 (0.9)	83 (1.0)	16 (0.5)	1.94×10^{-3}	2.20 (1.29–3.77)
Alcoholic cardiomyopathy, *n* (%)	425.5	5 (0.0)	4 (0.1)	1 (0.0)	1.0000	1.75 (0.20–15.78)
Alcoholic gastritis, *n* (%)	535.3	913 (7.8)	496 (6.1)	417 (11.9)	1.38×10^{-25}	0.51 (0.44–0.58)
Alcoholic fatty liver, *n* (%)	571.0	3026 (25.9)	1948 (23.8)	1078 (30.9)	3.42×10^{-15}	0.67 (0.61–0.73)
Acute alcoholic hepatitis, *n* (%)	571.1	1020 (8.7)	854 (10.4)	166 (4.8)	1.18×10^{-25}	2.31 (1.94–2.74)
Alcoholic cirrhosis of liver, *n* (%)	571.2	877 (7.5)	781 (9.6)	96 (2.8)	9.55×10^{-44}	3.65 (2.94–4.53)
Alcoholic liver damage, unspecified, *n* (%)	571.3	2175 (18.6)	1863 (22.8)	312 (8.9)	5.90×10^{-77}	2.97 (2.62–3.37)
Alcohol deterrents causing adverse effects in therapeutic use, *n* (%)	E947.3	10 (0.1)	8 (0.1)	2 (0.1)	7.33×10^{-1}	1.66 (0.35–7.80)

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification. *P*-value, Fisher's Exact test. Odds ratios (OR) with 95% confidence intervals (CI) and *P*-values were determined after adjusted age using a logistic regression analysis.

2.4. Statistical analysis

We performed a propensity analysis through logistic regression to obtain a 4-digit match of the propensity score for each patient with the covariates, including age, age group, and sex. The odds ratio (OR) was calculated between males and females in patients with alcohol-related diseases alone after adjustment for age. Continuous and categorical variables (i.e., the demographic characteristics of the study population) were analyzed using the *t*-test and the chi-square test, respectively, and compared between the alcohol-related diseases and control groups. The incident rate ratio (IRR) was calculated using a generalized linear model (PROC GENMOD) to perform a Poisson regression analysis (a log-linear model). Sensitivity analysis: alcohol-related diseases were defined as ≥ 3 outpatient claims (per variable) and gout patients were defined as ≥ 3 gout medications in outpatient; alcohol-related diseases were defined as ≥ 3 outpatient claims (any variable) and gout patients were defined as ≥ 3 gout medications in outpatient. The hazard ratios (HRs) and 95% confidence intervals (CI) for gout were calculated using the Cox proportional-hazards model. The Kaplan–Meier method was used to estimate survival curves for each group, and the log-rank test was used to test the homogeneity between survival curves. The relative risk (RR) of gout events with and without alcohol-related diseases was calculated using a Cox proportional-hazards model. Survival times were calculated from the date of alcohol-related diseases occurrence to either the onset date of the gout event or to the end of the study (December 31, 2010). Potential risk factors, including age group, sex, aboriginal region, urbanization level, socioeconomic status (monthly income level), and CCI scores, were incorporated into the model. Daily exposure benzodiazepines of diazepam, chlordiazepoxide, oxazepam, and lorazepam dose: the accumulate benzodiazepines dose divided by the total follow-up days (by the first diagnosed alcohol dependence date until the index date of gout or to study end). We classified the average benzodiazepines dose by using 2 approaches: stratifying the benzodiazepines exposure into yes or no and categorizing the per day milligram (mg) according to a quartile method. The benzodiazepines dose–response were measured, and the relationship between the diverse benzodiazepines exposure levels and the risk of gout was further analyzed using multiple Cox proportional-hazards model. All statistical analyses were performed using the SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA). The significance level was set at $P < 0.05$.

3. Results

3.1. Characteristics of the study population

Table 1 presents the alcohol-related diseases according to ICD-9-CM codes, stratified by sex. Of the alcohol-related diseases cases, 34.1% had alcohol dependence syndrome (males 34.8%; females 32.4%). In addition, the incidence of alcohol liver diseases differed significantly between males and females ($P < 0.0001$). Table 2 presents the demographic characteristics of the study population. We identified 11,675 alcohol-related diseases cases and included 23,350 matched controls in the analysis; the average age was 48.2 ± 13.2 years for the alcohol-related disease group and 48.0 ± 13.4 years for the controls group. The differences between the alcohol-related disease and control groups were non-significant when stratified by age, age group, and sex ($P > 0.05$). The differences between the alcohol-related diseases and control groups in terms of potential risk factors (including aboriginal region, urbanization level, socioeconomic status, and CCI scores) were significant ($P < 0.0001$). Patients in the alcohol-related disease group with comorbidities had a higher frequency of diabetes mellitus and mild liver disease compared with the controls (15.0% vs. 8.6%, and 49.6% vs. 15.2%, respectively; $P < 0.0001$).

In total, 912 (7.81%) cases of gout were identified. In univariate and multivariate analyses, we found that alcohol-related diseases were significantly associated with gout (IRR 2.40 and HR 1.88, $P < 0.0001$; Table 3). In sensitivity analysis 1, the HR was calculated from the alcohol-related disease cases that included 3 or more outpatient claims (per variable) and 3 or more gout medication prescriptions. The risk of gout increased slightly in the alcohol-related disease group after controlling for covariates (HR 2.02; 95% CI 1.76–2.32). Similarly, the risk estimates slightly increased in sensitivity analysis 2 (HR 2.07; 95% CI 1.81–2.36), suggesting a positive relationship between alcohol-related diseases and gout. The Kaplan–Meier curves for gout occurrence in individuals with and without alcohol-related diseases differed significantly (log-rank test $P < 0.0001$; Appendix A, Figure S2). Among patients with alcohol-related diseases, the cumulative incidence of gout was

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Table 2
Characteristics of subjects with alcohol-related diseases and the 1:2 propensity score–matched controls.

	Alcohol-related diseases	Controls	*P*-value
n	11,675	23,350	
Gout patients, n (%)			
1–2 gout medications	249 (2.1)	371 (1.6)	
≥ 3 gout medications	663 (5.7)	1077 (4.6)	<0.0001
Combined patients	912 (7.8)	1448 (6.2)	<0.0001
Age mean (SD), years	48.2 (13.2)	48.0 (13.4)	0.3506
Age group, n (%)			
20–30	913 (7.8)	2027 (8.7)	
31–40	2399 (20.6)	4693 (20.1)	
41–50	3442 (29.5)	6832 (29.3)	
51–60	2887 (24.7)	5518 (23.6)	
61–70	1273 (10.9)	2711 (11.6)	
>70	761 (6.5)	1569 (6.7)	0.8145
Sex, n (%)			
Males	8182 (70.1)	16,513 (70.7)	
Females	3493 (29.9)	6837 (29.3)	0.2170
Aboriginal region			
No	11,359 (97.3)	23,175 (99.3)	
Yes	316 (2.7)	175 (0.7)	<0.0001
Urbanization level, n (%)			
No	6021 (51.6)	10,587 (45.3)	
Yes	5654 (48.4)	12,763 (54.7)	<0.0001
Socioeconomic status (NTD), n (%)			
<17280	5535 (47.4)	11,025 (47.2)	
17281–22880	3959 (33.9)	6606 (28.3)	
22881–28800	509 (4.4)	1250 (5.4)	
28801–36300	625 (5.4)	1558 (6.7)	
36301–45800	522 (4.5)	1364 (5.8)	
>45800	525 (4.5)	1547 (6.6)	<0.0001
Comorbidities			
Myocardial infarction	54 (0.5)	92 (0.4)	0.3790
Congestive heart failure	374 (3.2)	425 (1.8)	<0.0001
Peripheral vascular disease	315 (2.7)	454 (1.9)	<0.0001
Cerebrovascular disease	900 (7.7)	1046 (4.5)	<0.0001
Rheumatologic disease	305 (2.6)	380 (1.6)	<0.0001
Renal disease	265 (2.3)	350 (1.5)	<0.0001
Diabetes mellitus	1746 (15.0)	2014 (8.6)	<0.0001
Mild liver disease	5792 (49.6)	3546 (15.2)	<0.0001
Moderate severe liver disease	167 (1.4)	35 (0.1)	<0.0001
Any Tumor	659 (5.6)	764 (3.3)	<0.0001
Charlson comorbidity index (CCI), Mean (SD)	1.2 (1.6)	0.7 (1.2)	<0.0001
CCI, n (%)			
0	4991 (42.8)	14,645 (62.7)	
1–2	4943 (42.3)	6859 (29.4)	
3–4	1212 (10.4)	1372 (5.9)	
≥ 5	529 (4.5)	474 (2.0)	<0.0001

SD: standard deviation; NTD: Taiwan New Dollar. Comorbidities was defined as ≥ 3 outpatient claims. Data of continuous and categorical variables were analyzed by *t*-test and chi-square test to make comparisons between alcohol-related diseases and controls. The mild liver disease and moderate or severe liver disease were not included in the CCI scores due to alcohol-related diseases related to liver diseases.

6.37% after 5 years (2.48% among the controls). We also showed that the risk of gout for males without alcohol-related diseases (HR 2.83; $P<0.0001$), for females with alcohol-related diseases (HR 1.42; $P=0.0014$), and for males with alcohol-related diseases (HR 3.00; $P<0.0001$) was significantly higher than for females without alcohol-related diseases (Table 4). The results reveal that alcohol-related diseases are common risk factors for gout between both the sexes.

Appendix A, Table S3 reveals that, excluding subjects with a diagnosis of gout before that of an alcohol-related disease, alcohol-related diseases (including alcohol dependence syndrome, acute alcoholic hepatitis and alcoholic liver damage) were significantly associated with gout occurrence compared with controls. However, in patients with alcohol-related diseases (per variables ≥ 3 outpatient claims), the association between four diseases – alcoholic psychoses, alcohol dependence syndrome, alcoholic cardiomyopathy, and alcoholic liver damage – and the risk of gout remained significant (RR 1.37, 1.57, 12.13, and 1.33, respectively; Appendix A, Table S4). Although no significant associations were observed between pooled alcoholic liver disease and gout (RR 1.07, $P=0.3733$), with no controlling CCI scores, alcoholic liver disease can be related to gout occurrence (RR 1.30, $P=0.0006$; Appendix A, Table S4). In this statistical model, Charlson comorbidity index could affect the risk of gout.

To further evaluate the effect of alcohol dependence syndrome and alcoholic liver disease on gout risk, the study subjects were classified into five groups: matched controls with non-liver disease, non-alcohol dependence and non-alcoholic liver disease, alcohol dependence and non-alcoholic liver disease, non-alcohol dependence and alcoholic liver disease, and alcohol dependence and alcoholic liver disease. The risk of gout events for the five groups was 4.98%, 6.94%, 12.29%, 9.29%, and 12.99%, respectively (Table 5).

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Table 3
Alcohol-related diseases is associated with gout.

	Gout/total subjects, incidence %	Person-years at risk	Incidence rate per 1000 person-years (95% CI)	IRR (95% CI)	Adjusted HR (95% CI)	*P*-value
Males cohort set						
Controls	1258/16513, 7.62	206054.86	6.11 (6.08–6.13)	1.00	1.00	
Alcohol-related diseases	759/8182, 9.28	52748.06	14.39 (14.27–14.51)	2.36 (2.26–2.58)	1.81 (1.64–1.99)	< 0.0001
Female cohort set						
Controls	190/6837, 2.78	87766.34	2.16 (2.15–2.18)	1.00	1.00	
Alcohol-related diseases	153/3493, 4.38	24329.08	6.29 (6.21–6.37)	2.91 (2.35–3.59)	2.48 (1.97–3.13)	< 0.0001
Total cohort set						
Controls	1448/23350, 6.20	293821.20	4.93 (4.91–4.95)	1.00	1.00	
Alcohol-related diseases	912/11675, 7.81	77077.13	11.83 (11.75–11.92)	2.40 (2.21–2.61)	1.88 (1.72–2.06)	< 0.0001
Sensitivity analysis 1[a]						
Controls	1077/22979, 4.69	291019.52	3.70 (3.69–3.71)	1.00	1.00	
Alcohol-related diseases	283/3426, 10.58	22231.38	12.73 (12.56–12.90)	3.44 (3.02–3.92)	2.02 (1.76–2.32)	< 0.0001
Sensitivity analysis 2[b]						
Controls	1077/22979, 4.69	291019.52	3.70 (3.69–3.71)	1.00	1.00	
Alcohol-related diseases	313/3787, 8.27	24680.19	12.68 (12.53–12.84)	3.43 (3.02–3.89)	2.07 (1.81–2.36)	< 0.0001

Incident rate ratio (IRR) was calculated using PROC GENMOD as to perform a Poisson regression analysis (a log-linear model). Hazard ratios (HRs) with 95% confidence intervals (CI) and their *P*-values were calculated and adjusted for age group, aboriginal region, urbanization level, socioeconomic status, CCI score and, for the combined group, sex, using a Cox proportional-hazards regression model.

[a] Sensitivity analysis 1: alcohol-related diseases were defined as ≥ 3 outpatient claims (per variable) and gout patients were defined as ≥ 3 gout medications in outpatient.

[b] Sensitivity analysis 2: alcohol-related diseases were defined as ≥ 3 outpatient claims (any variable) and gout patients were defined as ≥ 3 gout medications in outpatient.

Table 4
Joint effects of alcohol-related diseases and sex in gout.

Alcohol-related diseases	Sex	Gout events	Total	RR (95% CI)	*P*-value	Adjusted RR (95% CI)	*P*-value
No	Females	190 (2.78)	6837	1.00		1.00	
No	Males	1258 (7.62)	16,513	2.74 (2.20–3.41)	< 0.0001	2.83 (2.43–3.30)	< 0.0001
Yes	Females	153 (4.38)	3498	1.58 (1.19–2.10)	0.0017	1.42 (1.14–1.76)	0.0014
Yes	Males	759 (9.28)	8182	3.34 (2.68–4.16)	< 0.0001	3.00 (2.56–3.53)	< 0.0001

Relative risk (RR) with 95% confidence intervals (CI) and their *P*-values were calculated using a Cox proportional-hazards regression model. Adjusted RR was calculated and adjusted for age group, aboriginal region, urbanization level, socioeconomic status and CCI score using a Cox proportional-hazards regression model.

Compared with the matched controls with non-liver disease, after controlling for CCI scores and covariates, the relative risk (95% CI) of gout events for the other four groups was 1.24 (1.12–1.38), 2.01 (1.63–2.47), 1.23 (1.04–1.45) and 1.59 (1.11–2.30), respectively (Table 5). Compared with the non-alcohol dependence and non-alcoholic liver disease, the relative risk of gout events for the other three groups was 1.62 ($P < 0.0001$), 0.99 ($P = 0.9239$), and 1.29 ($P = 0.1824$), respectively. The results suggest that alcohol dependence and not alcoholic liver disease is an independent risk factor for gout occurrence.

Benzodiazepines are used in pharmacotherapy for detoxification or alcohol withdrawal treatment in patients with alcohol dependence syndrome. Table 6 illustrates the relationship between alcohol-dependent patients and gout risk, stratified by the use and non-use of various benzodiazepines. The alcohol-dependent patients used diazepam, oxazepam, or lorazepam and were significantly associated with the risk of gout (RR 1.75, 1.88, and 1.47, respectively; $P \leq 0.0040$). Apart from alcohol-dependent patients benzodiazepines use analyzed by scores and dosage were associated with an increased risk of gout (per score RR 1.42, $P < 0.0001$ and pre dosage (1 mg/day) RR 1.10, 1.04, 1.02, 1.05 in diazepam, chlordiazepoxide, oxazepam, and lorazepam, respectively, $P \leq 0.0402$; Table 6). The aforementioned results suggest a positive relationship between long-term alcohol dependence and gout risk, thus it showed that alcohol dependence was the major risk factor of gout.

4. Discussion

We prospectively assessed the association between chronic diseases and conditions causally linked with alcohol consumption and gout incidence in a large cohort. We validated the presence of alcohol-related diseases, alcohol dependence, and gout cases by using ICD-9-CM diagnosis code, benzodiazepines use, and use of gout medication (e.g., colchicine, xanthine oxidase inhibitor, and uricosuric agents). We identified a strong association between alcohol-related diseases/alcohol-dependent patients and gout incidence (adjusted HR 1.88 and adjusted RR 2.01). Furthermore, our results showed that alcohol-related diseases are common risk factors for gout in both the sexes; our results also revealed that alcoholic psychoses, alcoholic cardiomyopathy and alcoholic liver damage are associated with the risk of gout.

Hyperuricemia, caused by the overproduction of urate and more commonly by the renal urate underexcretion, can cause gout [15]. In one cohort study, patients with urate levels of > 540 umol/L had a 22% cumulative incidence of developing gouty arthritis during a 5-year period [16]. Notably, uric acid is considered a "danger signal." In gout, crystals of monosodium urate (MSU), a crystallized form of uric acid, nucleate in the joints, kidneys, and other tissues, where they trigger inflammation [17]. Genome-wide association studies have identified common polymorphisms in several genes involved in the renal urate-transport system (or the uric acid transportasome) that are associated with gout, including SLC2A9, ABCG2, SLC17A3, and SLC22A12 [18,19]. Underexcretion is the most common cause of gout incidence and possibly of 80%–90% of hyperuricemia [20]. Therefore, the mechanisms responsible for urate transport in the kidneys and the primary therapeutic sites of actions for gout medications at the proximal renal tubule have considerable clinical value [21]; SLC2A9, similar to SLC22A12, is a uric acid transporter that can be inhibited using a uricosuric agent (benzbromarone) to prevent the reuptake of uric acid and thus increase its renal excretion [22,23].

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Table 5
Alcohol dependence is independently associated with gout.

	Gout events, *n* (%)	Total participants, *n*	Adjusted RR (95% CI)	*P*-value	Adjusted RR (95% CI)	*P*-value
1–2 gout medications						
Matched controls with non-liver disease[a]	272 (1.43)	19,072	1.00			
Non-alcohol dependence and non-alcoholic liver disease[b]	178 (2.14)	8321	1.44 (1.19–1.75)	0.0002	1.00	
Alcohol dependence and non-alcoholic liver disease	27 (3.61)	748	2.32 (1.56–3.45)	<0.0001	1.61 (1.07–2.41)	0.0216
Non-alcohol dependence and alcoholic liver disease	37 (2.13)	1735	1.20 (0.84–1.70)	0.3159	0.83 (0.58–1.19)	0.3107
Alcohol dependence and alcoholic liver disease	7 (3.37)	208	1.84 (0.87–3.93)	0.1134	1.28 (0.60–2.73)	0.5237
≥ 3 gout medications						
Matched controls with non-liver disease[a]	713 (3.65)	19,513	1.00			
Non-alcohol dependence and non-alcoholic liver disease[b]	429 (5.50)	8572	1.19 (1.05–1.34)	0.0059	1.00	
Alcohol dependence and non-alcoholic liver disease	74 (9.31)	795	1.98 (1.55–2.52)	<0.0001	1.67 (1.30–2.13)	<0.0001
Non-alcohol dependence and alcoholic liver disease	137 (7.47)	1835	1.24 (1.03–1.50)	0.0256	1.04 (0.86–1.27)	0.6658
Alcohol dependence and alcoholic liver disease	23 (10.27)	224	1.58 (1.04–2.40)	0.0335	1.33 (0.87–2.02)	0.1874
Combined group						
Matched controls with non-liver disease[a]	985 (4.98)	19,785	1.00			
Non-alcohol dependence and non-alcoholic liver disease[b]	607 (6.94)	8750	1.24 (1.12–1.38)	<0.0001	1.00	
Alcohol dependence and non-alcoholic liver disease	101 (12.29)	822	2.01 (1.63–2.47)	<0.0001	1.62 (1.31–2.00)	<0.0001
Non-alcohol dependence and alcoholic liver disease	174 (9.29)	1872	1.23 (1.04–1.45)	0.0140	0.99 (0.84–1.18)	0.9239
Alcohol dependence and alcoholic liver disease	30 (12.99)	231	1.59 (1.11–2.30)	0.0127	1.29 (0.89–1.86)	0.1824

Alcohol dependence and alcoholic liver disease were defined as ≥ 3 outpatient claims. RR with 95% confidence intervals (CI) and their *P*-values were calculated and adjusted for age group, sex, aboriginal region, urbanization level, socioeconomic status and CCI score using a Cox proportional-hazards regression model. The mild liver disease and moderate or severe liver disease were not included in the CCI scores.

[a] The 3565 patients of mild liver disease and moderate or severe liver disease were not included in the matched controls with non-liver disease group

[b] Non-alcohol dependence and non-alcoholic liver disease: other alcohol-related diseases, excluding alcohol dependence and alcoholic liver disease patients

A number of mechanisms have been implicated in the pathogenesis of alcohol-induced hyperuricemia, which can both alter or retard the excretion of uric acid [9,11,12,24]. In one cohort study, increased alcohol intake was associated with an increased risk of gout: a 1.17-fold increase per 10 g in daily alcohol intake [9]. In an Internet-based case-crossover study, the risk of recurrent gout attack, regardless of alcoholic beverage type, was 1.36 and 1.51 times higher for > 1–2 and > 2–4 alcoholic beverages, respectively, compared with no alcohol consumption in the previous 24 hours [10]. Bhole et al. using data from the Framingham Heart Study described the associations of different alcoholic beverages with gout [25]. They concluded that both beer and liquor (spirits) intake were associated with gout (relative risk [RR] 7.10, 95% CI 1.70–29.62 and 2.66, 95% CI 1.24–5.72 in women; RR 2.00, 95% CI 1.26–3.19 and 1.82, 95% CI 1.26–2.63 in men) [25]. Consistently, the findings of our study support the importance of alcohol intake, regardless of gender, as a risk factor of gout. All types of alcohol can lead to increase urate levels due a variety of mechanisms, including ethanol content, thereby increasing the risk of gout attacks [10]. Beers are major components of hyperuricemia and gout, because it not only contains ethanol, but also contain high purine intake has high levels of guanosine, a purine that is highly absorbable [9,10]. Alcohol-induced turnover of adenosine triphosphate (ATP) during the conversion of acetate to acetyl-CoA is a part of ethanol metabolism [11]. Acute alcohol consumption produces lactate. Because lactate is an antiuricosuric agent, it reduces renal urate excretion by competitively inhibiting the secretion of uric acid by the proximal tubule and exacerbation of hyperuricemia [9,12]. This study contributes to clarifying how alcohol-related diseases and alcohol dependence affect the risk of gout. Gout is a complex disease caused by multiple genetic and environmental factors. Our previous study revealed that alcohol use and ABCG2 Q141K are independently and jointly associated with the risk of gout [26]. ABCG2 is a well-studied hyperuricemic gene that encodes a secretory urate transporter in the kidney [27].

Our study has several strengths and potential limitations. Our study used a large-size data set from the NHI program in Taiwan, providing adequate statistical power to detect clinically important associations. Although the poor validation of medical record ICD-9 diagnoses of gout in the veterans affairs database has been testified [28], we validated the association between alcohol dependence and gout by assessing benzodiazepines use and use of gout medication (colchicine, xanthine oxidase inhibitor, and uricosuric agents). Furthermore, the findings of assessing how various alcohol-related diseases affected gout definitions were robust, and the magnitude of the associations increased with more specificity of the case definition (from 11.83 to 12.68/12.73 per 1000 person-years; Table 3).

The NHIRD is primarily a health insurance database and contains limited information on alcohol use. Therefore, we do not have the details of the alcohol type (e.g., wine, beer, or liquor) and the amount consumed, which can provide information on the amount of purines being metabolized into uric acid and the lactate production inhibiting the uric acid secretion. Nevertheless, the names of the conditions found in ICD-9-CM reveal chronic diseases and conditions causally linked with alcohol consumption. We avoided potential temporality bias by using prospectively recorded data for

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Table 6
Association between benzodiazepines use and gout in alcohol dependence patients.

	Gout events, *n* (%)	Alcohol dependence patients, *n*	Adjusted RR (95% CI)	*P*-value
Diazepam (N05BA01)				
Non-use	75, 4.95	1514	1.00	
Use	228, 9.42	2421	1.75 (1.34–2.29)	<0.0001
Daily exposure diazepam dose				
Non	75, 4.95	1514	1.00	
≤0.02	19, 2.86	665	0.60 (0.36–1.00)	0.0511
0.02–0.05	33, 6.12	539	1.33 (0.88–2.01)	0.1748
0.05–0.17	49, 8.03	610	1.59 (1.11–2.3)	0.0123
>0.17	127, 20.92	607	3.44 (2.54–4.66)	<0.0001
Increase 1 mg/day	303, 7.70	3935	1.10 (1.08–1.13)	<0.0001
Chlordiazepoxide (N05BA02)				
Non-use	271, 7.31	3705	1.00	
Use	32, 13.91	230	1.45 (1.00–2.09)	0.0513
Daily exposure chlordiazepoxide dose				
Non	271, 7.31	3705	1.00	
≤0.05	3, 5.00	60	0.67 (0.21–2.09)	0.4893
0.05–0.14	3, 5.45	55	0.60 (0.19–1.86)	0.3737
0.14–0.44	10, 17.24	58	1.70 (0.90–3.20)	0.1013
>0.44	16, 28.07	57	2.45 (1.46–4.10)	0.0007
Increase 1 mg/day	303, 7.70	3935	1.04 (1.00–1.08)	0.0402
Oxazepam (N05BA04)				
Non-use	275, 7.31	3762	1.00	
Use	28, 16.18	173	1.88 (1.26–2.79)	0.0018
Daily exposure oxazepam dose				
Non	275, 7.31	3762	1.00	
≤0.14	2, 4.55	44	0.59 (0.15–2.37)	0.4540
0.14–0.40	6, 14.29	42	1.80 (0.8–4.04)	0.1566
0.40–2.55	5, 11.63	43	1.21 (0.50–2.93)	0.6800
>2.55	15, 34.09	44	3.72 (2.19–6.30)	<0.0001
Increase 1 mg/day	303, 7.70	3935	1.02 (1.00–1.04)	0.0150
Lorazepam (N05BA06)				
Non-use	79, 5.33	1481	1.00	
Use	224, 9.13	2454	1.47 (1.13–1.91)	0.0040
Daily exposure chlordiazepoxide dose				
Non	79, 5.33	1481	1.00	
≤0.01	21, 3.32	632	0.65 (0.40–1.06)	0.0824
0.01–0.05	37, 5.85	633	1.03 (0.69–1.52)	0.8912
0.05–0.25	51, 8.99	567	1.44 (1.01–2.05)	0.0455
>0.25	115, 18.49	622	2.63 (1.95–3.55)	<0.0001
Increase 1 mg/day	303, 7.70	3935	1.05 (1.03–1.07)	<0.0001
Benzodiazepines scores				
0	31, 3.73	832	1.00	
1	81, 6.61	1226	1.71 (1.13–2.59)	0.0114
2	145, 9.10	1594	2.20 (1.48–3.27)	<0.0001
3	43, 16.04	268	3.13 (1.94–5.05)	<0.0001
4	3, 20.00	15	4.21 (1.28–13.85)	0.0182
Increase score of benzodiazepines use	303, 7.70	3935	1.42 (1.24–1.62)	<0.0001

Diazepam, chlordiazepoxide, oxazepam or lorazepam component apply 1 point to each; no use received a score of 0. The benzodiazepines scores were obtained from summing up the presence of each medication use in alcohol dependence patients. Relative risk (RR) with 95% confidence intervals (CI) and their *P*-values were calculated and adjusted for age group, sex, aboriginal regions, urbanization level, socioeconomic status and CCI score using a Cox proportional-hazards regression model. Trend analysis: RR was determined under an additive model with a 1-degree-of-freedom test using a Cox proportional-hazards regression model. Daily exposure benzodiazepines of diazepam, chlordiazepoxide, oxazepam, and lorazepam dose: the accumulate benzodiazepines dose divided by the total follow-up days (by the first diagnosed alcohol dependence date until the index date of gout or to study end). The benzodiazepines dose–response (daily exposure dose) was analyzed after adjusted covariates using a Cox proportional-hazards regression model.

patients diagnosed with gout after a diagnosis of alcohol-related diseases; therefore, recall bias of alcohol use and other errors association with self-reporting were minimized. Our findings revealed that different alcohol-related diseases have different effects on the risk of gout (Appendix A, Table S4). In particular, alcohol dependence syndrome affects the risk of gout. No significant association was observed in this data set between pooled alcoholic liver disease and gout risk, suggesting that in this statistical model, comorbidities could affect gout risk. Although alcoholic liver damage still remained significantly in gout risk, in patients with alcohol dependence syndrome affect the risk of gout than in patients with alcoholic liver disease. Alcoholic psychoses may be involved in the pathogenesis of hallucinations in alcohol dependence [29]. We observed significant association between alcoholic psychoses and gout incidence (adjusted RR 1.37, $P=0.0345$). Our results also showed that a significant association was observed between a combination of alcoholic psychoses and alcohol dependence and the incidence of gout (adjusted RR 1.49, $P<0.0001$).

Alcohol abuse is the repeated (recurring) harmful use of ethanol despite its negative consequences; persons with alcohol dependence have impaired self-control, severe alcohol problems, and affective symptoms and are less likely to maintain controlled drinking than those without these symptoms [30]. Although alcohol dependence is the most severe form of alcohol abuse, we observed

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no significant association between alcohol abuse and gout incidence (6.54%). Although the biological effects of alcohol on gout may be similar, we hypothesize that the long-term effects of alcohol consumption affect the risk of gout. Moreover, this data set indicates a significant relationship between alcohol-dependent patients (benzodiazepines scores and dosage in the 4th quartile) and gout risk (adjusted RR 1.71–4.21 and adjusted RR 2.45–3.72; Table 6). Monoamine oxidases (MAOs) are involved in several psychiatric conditions, including chronic stress, major depressive disorder, and alcohol dependence [31]. Our previous study revealed that the monoamine oxidase A (MAOA, Xp11.3) enzyme activity was associated with gout risk [32]. The consistent results suggest that alcohol dependence is a crucial determinant of the risk of gout.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data (Figures S1-S2, Tables S1-S4) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jbspin.2016.02.024.

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