CLINICAL RESEARCH STUDY

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Alcohol Quantity and Type on Risk of Recurrent Gout Attacks: An Internet-based Case-crossover Study

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ABSTRACT

OBJECTIVES: Although beer and liquor have been associated with risk of incident gout, wine has not. Yet anecdotally, wine is thought to trigger gout attacks. Further, how much alcohol intake is needed to increase the risk of gout attack is not known. We examined the quantity and type of alcohol consumed on risk of recurrent gout attacks.

METHODS: We conducted a prospective Internet-based case-crossover study in the US among participants with gout and who had at least one attack during the 1 year of follow-up. We evaluated the association of alcohol intake over the prior 24 hours as well as the type of alcoholic beverage with risk of recurrent gout attack, adjusting for potential time-varying confounders.

RESULTS: This study included 724 participants with gout (78% men, mean age 54 years). There was a significant dose-response relationship between amount of alcohol consumption and risk of recurrent gout attacks ($P < .001$ for trend). The risk of recurrent gout attack was 1.36 (95% confidence interval [CI], 1.00-1.88) and 1.51 (95% CI, 1.09-2.09) times higher for >1-2 and >2-4 alcoholic beverages, respectively, compared with no alcohol consumption in the prior 24 hours. Consuming wine, beer, or liquor was each associated with an increased risk of gout attack.

CONCLUSIONS: Episodic alcohol consumption, regardless of type of alcoholic beverage, was associated with an increased risk of recurrent gout attacks, including potentially with moderate amounts. Individuals with gout should limit alcohol intake of all types to reduce the risk of recurrent gout attacks.

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KEYWORDS: Alcohol; Case-crossover; Gout attacks; Internet; Triggers

Gout, a crystal-induced arthritis associated with hyperuricemia,[1] is currently the most common inflammatory arthritis, affecting 8.3 million US adults.[2] Recurrent attacks constitute the main clinical burden of gout. Despite available urate-lowering therapies, the risk of recurrent gout attacks remains high, with the risk of having at least one attack in a year being 69%.[3] Strategies to prevent not only disease onset but also recurrent attacks are needed, given the rising incidence and prevalence of gout.[2,4-6]

Alcohol has been recognized anecdotally as a potential risk factor for recurrent gout attacks. However, most studies to date have focused on alcohol consumption in relation to the risk of initial occurrence of gout.[7-9] In a large prospective cohort study, total alcohol consumption was strongly associated with an increased risk of incident gout.[8] Additionally, the risk of incident gout varied by type of beverage

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consumed, with an increased risk observed for beer and liquor but not wine.[8] However, patients often report wine as a trigger for recurrent gout attacks, and historic depictions of gout often included wine, although this may have been related in part to lead contamination in the Roman era. Previously, we have reported that overall alcohol consumption increased the risk of recurrent gout attacks; however, due to insufficient cases at the time, we were unable to evaluate whether moderate intakes of alcohol and whether specific types of alcoholic beverage were associated with an increased risk of recurrent gout attack.[10] Further, gout treatment guidelines vary regarding recommendations about quantity and type of alcohol intake.[11-13] Clarification of the risk for recurrent gout attacks imparted by specific types of alcoholic beverages would have practical clinical implications for management of patients with established gout.

CLINICAL SIGNIFICANCE

- Episodic intake of any type of alcohol, whether it is beer, wine, or liquor, can increase risk of gout attacks.
- Increasing amounts of alcohol intake of any type, even at moderate levels, can increase risk of gout attacks.
- Clinicians and patients with gout should therefore consider limiting the consumption of all types of alcohol, not just beer.

To address this knowledge gap, we analyzed 724 gout subjects that were recruited prospectively from across the US in an Internet-based study. We used a case-crossover study design to quantify the risk of gout attack in relation to amount of alcohol consumption, particularly moderate intakes, and evaluated whether the effect on recurrent gout attacks varied by consumption of specific type of alcoholic beverage.

METHODS

Study Design

The Boston University online gout study is an Internet-based case-crossover study conducted over the period of 2003-2012 to examine a set of putative risk factors for recurrent gout attacks. The details of the study have been described previously.[10,14,15] In brief, we constructed a Web site (https://dcc2.bumc.bu.edu/GOUT) on an independent secure server within the Boston University Medical Center domain. Recruitment occurred primarily by means of an advertisement on Google linked to the search term "gout." Individuals were directed to the study Web site when they clicked on this link. The study design and timing of exposure assessments are illustrated in **Figure 1**. With this study design, each subject serves as his or her own control. This self-matching eliminates confounding by factors that are constant within an individual but differ among study subjects (eg, sex, race, socioeconomic status).

Study Sample

The study Web site provided information about the study, and for interested potential participants, administered a screening questionnaire that collected sociodemographic information, gout-related data (eg, features, duration, medications used, number of gout attacks in the prior 12 months), comorbidities, and other medication use. Eligible subjects were those who reported a gout attack within the previous year, were age 18 years or older, were residents of the US, provided informed consent, and agreed to release medical records. We reviewed the medical records and checklist completed by their physician of the components of the American College of Rheumatology (ACR) Preliminary Classification Criteria for Gout.[16] Two rheumatologists (DJH, TN) reviewed all medical records and checklists to determine whether subjects met a diagnosis of gout according to the ACR criteria, using similar methods of confirmation as used in the Health Professional Follow-Up Study.[8] This study was approved by the institutional review board of Boston University Medical Center.

Ascertainment of Gout Attacks

For each gout attack that occurred during the 1-year follow-up period, we collected the onset date of the attack, anatomical location of the attack, clinical symptoms and signs (maximal pain within 24 hours, redness, swelling), medications used to treat the attack (eg, colchicine, nonsteroidal anti-inflammatory drugs [NSAIDs], systemic or intra-articular glucocorticoids), and whether a health care professional was seen for attack management. This method of identifying gout attacks is in keeping with approaches used in gout trials,[17-19] and the provisional definition of flare in patients with established gout that includes only patient-reported elements.[20] We additionally restricted our gout attack definitions to those that were treated with at least one gout-related medication typically used to treat attacks (listed above), those with first metatarsophalangeal involvement, those with maximal pain within 24 hours, those with redness, and those with a combination of these features (ie, those with at least 2, 3, or all 4 features).

Ascertainment of Risk Factors

Subjects were queried about the frequency and quantity of a set of putative risk factors (eg, dietary factors, medication use, physical activity, geography) during the 24 hours before that gout attack (hazard period).[15,21] The same questions also were asked over a 24-hour period when they were attack-free (control period) at study entry (for those subjects who entered the study during an intercritical period), and at 3, 6, 9, and 12 (for those subjects who entered the study at the time of a gout attack) months of follow-up (**Figure 1**).

Standardized questions about alcohol intake included the number of servings of wine, beer (including light

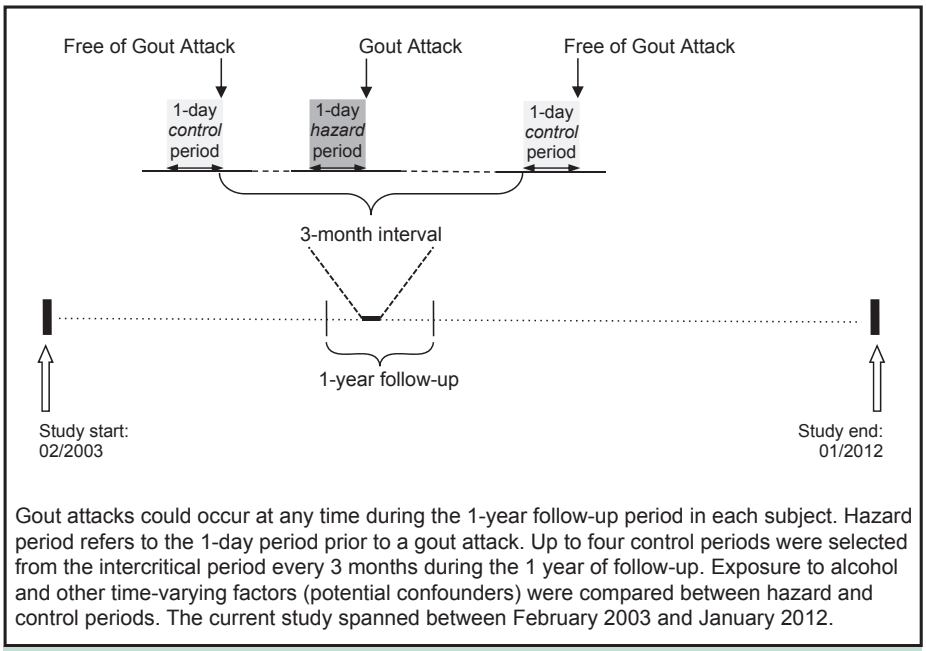

Figure 1 Case-crossover study design and timing of exposure measurements in relation to gout attacks.

beer, ciders, and malt beverages), or liquor (either straight or in a mixed drink) consumed during the prior 24-hour period for control and hazard periods. Explanation and pictorial depiction of standard serving sizes (ie, a 12-ounce bottle or can of beer; a 5-ounce glass of wine; and 1-1.5 ounces of liquor)[22] were provided with color images. Information on potential confounders, such as diuretic use, food and beverage intake from which purine consumption could be calculated,[15] and gout-related medication also were collected during the control and hazard periods.

Statistical Analysis

The total amount of alcohol intake (grams/day) was estimated based on number of servings reported in a 24-hour period as ([0.57 * # of cocktails (liquor)/day] + [0.44 * # of bottles/cans of beer/day] + [0.40 * # of glasses of wine/day]) * 28.35.[23] This latter term represents 28.35 grams of alcohol per fluid ounce. One typical drink is approximately 15 grams of alcohol.[24] We divided total amount of alcohol consumption in the hazard and control periods into 7 categories: no alcohol consumption, >0-1 drink, >1-2, >2-4, >4-6, >6-8, and more than 8 drinks. Moderate alcohol intake is considered to be no more than 2 drinks per day for men and no more than 1 drink per day for women.[22] We grouped the daily consumption of each specific alcoholic beverage into the following categories based on their distribution: for wine, no wine consumption, >0-1, >1-2, and >2 servings; for beer and for liquor, no consumption, >0-2, >2-4, >4-6, and >6 servings.

We examined the relation of total alcohol intake over 24 hours to the risk of recurrent gout attacks using conditional logistic regression, which takes into account the matching of each subject's own hazard and control periods.[25] In multivariable regression models, we adjusted for diuretic use, purine intake, gout-related medication use (allopurinol, colchicine, NSAIDs, other urate-lowering therapies), and water intake. To better depict the dose-response relation between alcohol consumption and risk of gout attacks, we used quadratic spline regression to smooth the dose-risk curve.[26] We then evaluated the association of alcohol intake with risk of gout attacks according to subgroups defined by sex, age (<55 vs ≥55 years), and body mass index (BMI; <30 vs ≥30). We also evaluated the joint effects of purine intake (<850 mg [median value for 24-hour intake]

Table 1 Baseline Characteristics of Participants in the Internet-based Case-crossover Study of Gout, 2003-2012

Participant Characteristic	n = 724
Age, y: mean (SD), range	54.5 (12.5), 21-88
BMI, kg/m^2: mean (SD), range	32.1 (6.9), 14.7-69.9
Male: n (%)	568 (78.5)
Disease duration: mean years (SD), range	8.0 (9.3), 1-55
White: n (%)	642 (88.7)
Completed college: %	58.1
Household income ≥$50,000: %	58.6
Mean number of alcoholic beverages per 24-hour period (calculated from 3380 24-hour hazard and control periods)	1.2

BMI = body mass index.

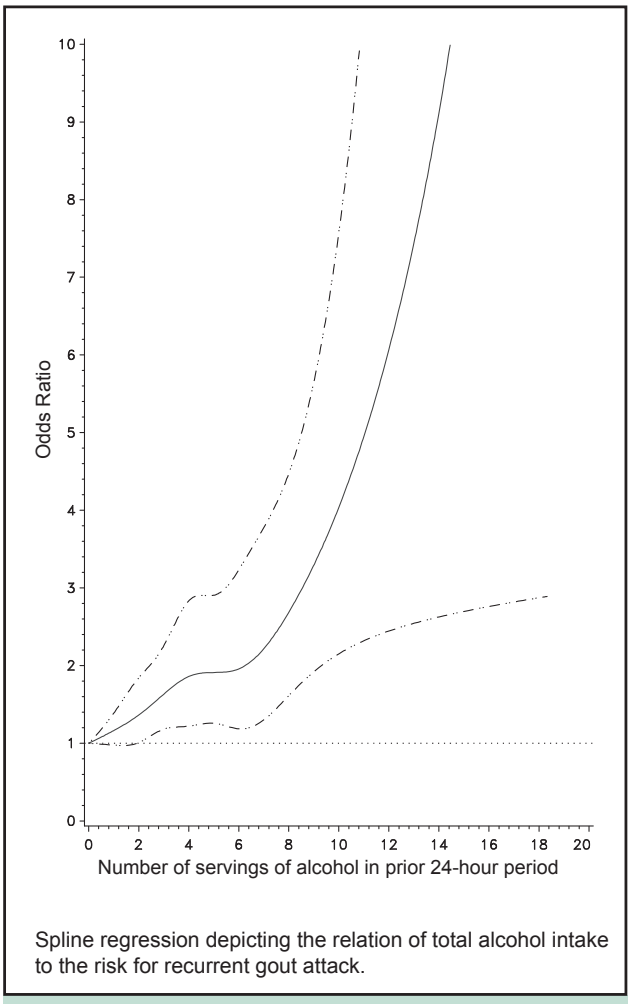

Figure 2 Effect of alcohol consumption on risk of recurrent gout attack.

vs ≥850 mg), diuretic use, allopurinol use, colchicine use, and NSAID use with alcohol intake in the prior 24 hours. Finally, we assessed the independent effect of each specific type of alcoholic beverage with conditional logistic regression adjusting for potential confounders listed above as well as consumption of the other types of alcoholic beverages.

RESULTS

There were 724 participants (mean age 54 years) who completed both hazard and control period questionnaires over a consecutive 12-month period between February 2003 and January 2012. As shown in Table 1, the majority of participants was male (78%), obese (mean BMI 32 kg/m^2), and white (89%). Participants were recruited from 49 states and the District of Columbia. Of these participants, 614 (85%) met the ACR Preliminary Classification Criteria for Gout. Approximately 48% were on urate-lowering therapy (allopurinol: 44%; other: 4%); 25% used colchicine for prophylaxis or gout attacks, while 38% used NSAIDs for prophylaxis and gout attacks.

During the 1-year follow-up period, there were 1434 gout attacks, primarily occurring in the lower extremity (92%), particularly in the first metatarsophalangeal joint, and had features of maximal pain within 24 hours, or redness (89%). Eighty-nine percent of these gout attacks were treated with colchicine, NSAIDs, systemic or intra-articular glucocorticoids, or a combination thereof.

Approximately 44% of subjects reported any alcohol intake during hazard, control, or both periods. The mean number of standard servings of alcohol was 1.0 during a control period and 1.4 during a hazard period. The risk of recurrent gout attacks increased as the amount of alcohol consumption increased (Figure 2). While having up to one drink in a 24-hour period did not increase the risk of attack significantly (odds ratio [OR] 1.13; 95% confidence interval [CI], 0.80-1.58), consuming >1-2 drinks in a 24-hour period was associated with 36% higher risk of recurrent attack (OR 1.36; 95% CI, 1.00-1.88), compared with those with no alcohol intake in that period, indicating that a moderate amount of alcohol intake within a 24-hour period may increase the risk of recurrent gout attacks (Table 2).

When we limited our analyses to only those subjects who fulfilled the ACR Preliminary Classification Criteria for

Table 2 Total Alcohol Intake Over the Prior 24-hour Period and the Risk of Recurrent Gout Attacks

Number of Servings of Alcohol Over the Prior 24-hour Period	Number of Hazard Periods (n = 1434)	Number of Control Periods (n = 946)	Crude OR	Adjusted OR* (95% CI)
0	856	1222	1.0	1.0 (referent)
>0-1	93	145	1.12	1.13 (0.80-1.58)
>1-2	121	185	1.26	1.36 (1.00-1.88)
>2-4	178	223	1.60	1.51 (1.09-2.09)
>4-6	94	105	2.13	1.87 (1.19-2.93)
>6-8	48	40	2.65	2.33 (1.28-4.24)
>8	44	26	3.90	3.13 (1.63-6.02)
P for linear trend				<.001

CI = confidence interval; OR = odds ratio.

*Adjusted for purine intake, allopurinol or other urate-lowering therapy, nonsteroidal anti-inflammatory drug, colchicine, diuretic use, and water intake in prior 24-hour period.

Gout (n = 614), the results did not change substantially, with the multivariable adjusted ORs (95% CI) being 1.09 (0.76-1.55), 1.36 (0.96-1.93), 1.50 (1.07-2.18), 2.05 (1.26-3.35), 2.50 (1.33-4.71), and 3.40 (1.63-7.09) for >0-1, >1-2, >2-4, >4-6, >6-8, and >8 servings, respectively, compared with no alcohol intake in the prior 24 hours. When we used more stringent definitions of gout attack, the results also were similar. For example, requiring at least 2 of the following features: first metatarsophalangeal involvement, maximal pain within 24 hours, redness, use of a typical gout attack treatment (n = 687), the corresponding multivariable adjusted ORs were 1.10 (0.78-1.56), 1.38 (0.99-1.92), 1.43 (1.03-1.99), 2.05 (1.30 -3.24), 2.42 (1.32-4.42), and 3.42 (1.76-6.67), respectively.

Participants were required to complete their control period questionnaires once every 3 months. It was possible that control periods may have over-represented certain days of the week; for example, when Internet access may have been more accessible, such as in the office. We therefore performed additional analyses according to weekday versus weekend reporting. The effect estimates of alcohol consumption for weekdays were similar to those for the weekend; the adjusted ORs of recurrent gout attacks for >1-2 drinks in the prior 24 hours were 1.48 for weekdays and 1.30 for weekends.

Moderate alcohol consumption (ie, up to 2 drinks/day for men and up to 1 drink/day for women) was associated with a 41% increased risk of recurrent gout attacks for men (adjusted OR 1.41; 95% CI, 1.00-2.01), but not for women (adjusted OR 1.06; 95% CI, 0.49-2.30) compared with those who did not drink any alcohol in the prior 24-hour period, although there were too few women to precisely estimate this effect ($P = .4$ for interaction by sex).

The combined effects of alcohol intake with concurrent intake of purines and use of gout-related medications are shown in **Table 3**. Increasing numbers of servings of alcohol in combination with either high purine consumption or diuretic use were associated with higher risk of recurrent gout attacks. In contrast, use of allopurinol mitigated the effects of alcohol intake, as did colchicine, although to a lesser extent. NSAID use did not modify the effect of alcohol intake.

As shown in **Table 4**, each type of alcoholic beverage intake was associated with an increased risk of recurrent gout attacks. Consuming >1-2 servings of wine over the prior 24 hours significantly increased the risk of recurrent gout attack (adjusted OR 2.38; 95% CI, 1.57-3.62). For beer, having up to 2 servings and >2-4 servings were associated with a nonsignificant 29% and statistically significant 75% higher risk for recurrent gout attack, respectively, compared with no such intake. There also was an increased risk of recurrent gout attacks with increasing amounts of liquor consumption, with those consuming >2-4 servings of such beverages having 1.67 times higher risk of an attack compared with no such intake in the prior 24-hour period.

Similar findings were observed when analyses were limited to those participants who reported only drinking one type of alcoholic beverage during the course of the study. Compared with no intake of each specific type of alcoholic beverage during the prior 24 hours, the adjusted ORs for a recurrent gout attack were 3.96 (95% CI 1.84-8.52), 3.63

Table 3 Combined Effects of Alcohol Intake and Other Time-varying Risk Factors (Purine Intake, Diuretic Use, Allopurinol Use, Colchicine Use, NSAID use) on Risk of Gout Attack

Exposure to Risk Factor in Prior 24 Hours	Number of Alcohol Servings in Prior 24 Hours	Adjusted OR† (95% CI)
Purine intake		
<850 mg*	0	1.0 (ref)
<850 mg	>0-1	0.88 (0.54-1.45)
<850 mg	>1-2	1.50 (1.01-2.23)
<850 mg	>2	1.83 (1.24-2.68)
≥850 mg	0	2.35 (1.88-2.93)
≥850 mg	>0-1	3.16 (2.00-4.99)
≥850 mg	>1-2	2.65 (1.66-4.24)
≥850 mg	>2	4.17 (2.95-5.89)
Diuretic use		
No	0	1.0 (ref)
No	>0-1	1.26 (0.85-1.86)
No	>1-2	1.38 (0.96-1.97)
No	>2	1.61 (1.17-2.20)
Yes	0	2.40 (0.59-3.62)
Yes	>0-1	2.12 (1.02-4.42)
Yes	>1-2	3.44 (1.70-6.93)
Yes	>2	5.82 (2.94-11.53)
Allopurinol use		
No	0	1.0 (ref)
No	>0-1	1.04 (0.70-1.55)
No	>1-2	1.58 (1.08-2.31)
No	>2	1.74 (1.26-2.41)
Yes	0	0.45 (0.33-0.62)
Yes	>0-1	0.61 (0.32-1.17)
Yes	>1-2	0.43 (0.24-0.79)
Yes	>2	0.70 (0.42-1.17)
Colchicine use		
No	0	1.0 (ref)
No	>0-1	1.17 (0.81-1.68)
No	>1-2	1.37 (0.97-1.93)
No	>2	1.70 (1.24-2.32)
Yes	0	0.82 (0.55-1.20)
Yes	>0-1	0.59 (0.24-1.47)
Yes	>1-2	1.03 (0.45-2.40)
Yes	>2	1.18 (0.63-2.19)
NSAID use		
No	0	1.0 (ref)
No	>0-1	1.06 (0.72-1.56)
No	>1-2	1.44 (1.00-2.06)
No	>2	1.72 (1.25-2.37)
Yes	0	1.36 (1.03-1.80)
Yes	>0-1	1.62 (0.84-3.16)
Yes	>1-2	1.45 (0.80-2.62)
Yes	>2	2.03 (1.29-3.19)

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.

*Median value of purine intake in prior 24 hours.

†Mutually adjusted for each other as well as other urate-lowering therapies and water intake.

Table 4 Specific Alcoholic Beverage Intake Over the Prior 24-hour Period and Risk of Recurrent Gout Attacks

Number of Servings of Specific Alcoholic Beverages Over the Prior 24-hour Period	Number of Hazard Periods (n = 1434)	Number of Control Periods (n = 1946)	Adjusted OR*	Adjusted OR† (95% CI)
Wine				
0	1194	1664	1.0	1.0
>0-1	102	133	1.26	1.25 (0.87-1.80)
>1-2	89	80	2.34	2.38 (1.57-3.62)
>2	49	69	1.35	1.41 (0.86-2.32)
P for linear trend			<.001	<.001
Beer				
0	1124	1601	1.0	1.0
>0-2	92	129	1.28	1.29 (0.91-1.83)
>2-4	99	114	1.73	1.75 (1.19-2.59)
>4-6	52	49	2.56	2.60 (1.40-4.81)
>6	67	53	2.40	2.32 (1.25-4.31)
P for linear trend			<.001	.001
Hard liquor				
0	1199	1673	1.0	1.0
>0-2	68	113	0.97	0.92 (0.62-1.37)
>2-4	60	57	1.66	1.67 (1.00-2.78)
>4-6	75	86	1.63	1.56 (0.95-2.57)
>6	31	17	2.97	2.79 (1.26-6.16)
P for linear trend			.002	.005

*Adjusted for purine intake, allopurinol or other urate-lowering therapy, nonsteroidal anti-inflammatory drug, colchicine, and diuretic use, in prior 24-hour period.

†Additionally mutually adjusted for other types of alcohol intake.

(95% CI, 1.92-6.87), and 4.44 (95% CI, 1.17-16.91) for consumption of up to 2 servings of wine, beer, and liquor, respectively.

DISCUSSION

Anecdotally, while alcohol has been thought to trigger gout attacks, the results from our study confirm that alcohol intake, potentially even moderate amounts, increases the risk of recurrent gout attacks in a short time following consumption. Further, all types of alcoholic beverages, whether it was wine, beer, or liquor, were associated, to varying degrees, with an increased risk for recurrent gout attacks. These effects were stronger in the presence of high purine intake and diuretic use, while mitigated to varying degrees by allopurinol and colchicine use; NSAIDs did not modify the effects of alcohol intake on risk of recurrent gout attacks.

Ethanol ingestion can increase serum urate through both decreased urate excretion and increased urate production. Reduced renal urate excretion can occur because of lactic acidemia associated with acute excessive alcohol intake, as well as the acidemia associated with fasting that is often concomitant with such intake.[27,28] Metabolism of ethanol also accelerates adenosine triphosphate degradation into uric acid precursors.[28-30] While alcohol definitively has been associated with hyperuricemia,[31-33] and variably associated with incident gout,[7-9] the findings of our study support the importance of alcohol, regardless of type, as a trigger in established gout.

Why might wine not increase the risk for *incident* gout in an observational cohort, yet appear to increase the risk of recurrent gout attacks? One might expect the effects of ethanol to be similar regardless of the type of alcoholic beverage. Indeed, all types of alcohol can lead to increased urate levels due to a variety of mechanisms, including ethanol content, thereby increasing the risk of gout attacks. However, one may expect a greater effect of beer on hyperuricemia than other types of alcohol because it not only contains ethanol, but also has high levels of guanosine, a purine that is highly absorbable.[27,34] On the other hand, individuals who drink wine often have a healthier lifestyle than those who drink beer or spirits. For instance, wine drinkers tend to buy healthier foods and follow healthier diets than beer drinkers.[35-38] Thus, the lack of association between wine and incident gout from an observational study may be related to residual confounding from other healthy lifestyle factors. By using a case-crossover study design to assess the triggering effects of alcohol consumption, we minimize such "healthy lifestyle factors" that vary greatly among individuals but are relatively consistent within an individual.

Additionally, risk factors for triggering recurrent gout attacks among individuals with established gout may not be the same as those for incident gout among individuals who are free of gout. Individuals with established gout may have altered renal handling compared with those who do not have gout (ie, at risk for incident gout), and therefore risk factors may affect the 2 groups differently. Further, the short-term

effects of a risk factor may differ from its long-term effects. An example of such a paradoxical phenomenon is the well-known increased flare risk during urate-lowering therapy initiation, whereas over the long term, such therapy reduces the risk of flares.

Several characteristics of this study are worth noting. The case-crossover study is an ideal design to assess the acute effect of triggers. Because each participant serves as his/her own control, this study design eliminates the effects of time-invariant confounding factors among individuals.[39] Recruitment of a large number of participants from all over the US through the Internet highlights a novel aspect of this study. Finally, the online design enabled participants to enter data in real time, thereby minimizing the potential for recall bias.

Our study has some limitations as well. First, although we collected information on major potential time-varying confounders and adjusted for them in the analyses, residual confounding bias may remain. Second, because it is widely assumed that alcohol may trigger gout attacks, recall bias and differential reporting is a possibility. We attempted to minimize these biases by collecting information on a broad range of potential exposures, capturing data in real-time, and ensuring that the study participants were not primed regarding study hypotheses. Third, as with many epidemiologic studies, dietary intake was not independently verified. Fourth, allowing some flexibility for participants to choose which day of the week, albeit within a fixed time window, to complete a control period questionnaire can potentially introduce bias. Nevertheless, when we performed additional analyses stratified according to weekday versus weekend reporting, results did not vary materially. Finally, like other epidemiologic studies of gout[8] and what is common in clinical practice, most of our participants did not have a crystal-proven diagnosis of gout. However, the majority in our study met ACR Preliminary Classification Criteria for gout or had a physician diagnosis of gout, and the clinical characteristics of participants in our study are similar to what would be expected of gout patients.

In summary, the present study supports the role of episodic alcohol intake in triggering gout attacks, even for moderate amounts and regardless of type of alcohol. Thus, in addition to the general medical management of their gout, individuals with established gout should consider limiting all types of alcohol intake as another preventive strategy to reduce their risk for recurrent gout attacks.

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