Alcohol intake and risk of incident gout in men: a prospective study

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Summary

Background The association between alcohol consumption and risk of gout has been suspected since ancient times, but has not been prospectively confirmed. Additionally, potential differences in risk of gout posed by different alcoholic beverages have not been assessed.

Methods Over 12 years (1986–98) we used biennial questionnaires to investigate the relation between alcohol consumption and risk of incident gout in 47 150 male participants with no history of gout at baseline. We used a supplementary questionnaire to ascertain whether reported cases of gout met the American College of Rheumatology survey gout criteria.

Findings We documented 730 confirmed incident cases of gout. Compared with men who did not drink alcohol, the multivariate relative risk (RR) of gout was 1·32 (95% CI 0·99–1·75) for alcohol consumption 10·0–14·9 g/day, 1·49 (1·14–1·94) for 15·0–29·9 g/day, 1·96 (1·48–2·60) for 30·0–49·9 g/day, and 2·53 (1·73–3·70) for ≥50 g/day (p for trend <0·0001). Beer consumption showed the strongest independent association with the risk of gout (multivariate RR per 12-oz serving per day 1·49; 95% CI 1·32–1·70). Consumption of spirits was also significantly associated with gout (multivariate RR per drink or shot per day 1·15; 95% CI 1·04–1·28); however, wine consumption was not (multivariate RR per 4-oz serving per day 1·04; 95% CI 0·88–1·22).

Interpretation Alcohol intake is strongly associated with an increased risk of gout. This risk varies substantially according to type of alcoholic beverage: beer confers a larger risk than spirits, whereas moderate wine drinking does not increase the risk.

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Introduction

Gout is the most common inflammatory arthritis in men.[1] The association between heavy alcohol consumption and increased risk of gout has long been suspected; however, the association has not been prospectively confirmed. Metabolic studies have shown that hyperuricaemia (not gout per se) can be induced by alcohol loading.[2–5] Furthermore, hyperuricaemia has been proposed as a marker for ethanol ingestion.[5,6] These findings provided the basis that alcohol might eventually cause gout through hyperuricaemia. Findings of several case-control studies[7,8] and a cohort study[9] showed a significant association between alcohol consumption and gout, but these studies retrospectively ascertained alcohol consumption and did not adjust for potential confounders except for age. Prospective analyses have failed to confirm the association but have been limited by small sample size and lack of relevant variables.[1,10–12]

Risk of gout could conceivably vary depending on type of alcoholic beverage (ie, beer, wine, and spirits), as does the risk of other diseases,[13,14] but no data are available. Findings of a case-control study suggested that the high purine content in beer might play an important part in the risk of gout augmenting the hyperuricaemic effect of alcohol itself.[8] If different alcoholic beverages have different effects on risk of gout, this fact would have practical implications for gout prevention and management.

To examine these issues, we prospectively assessed the relation between total alcohol consumption and type of alcoholic beverage and risk of incident gout in a cohort of 47 150 men with no history of gout.

Methods
Study population

The Health Professionals Follow-up Study is an ongoing longitudinal study of 51 529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were predominantly white (91%) and aged 40–75 years in 1986. The participants returned a mailed questionnaire in 1986 about diet, medical history, and medications. Of the 49 932 men who provided complete information on diet and age, 2782 (5·6%) reported a history of gout on the baseline questionnaire. These men were excluded from our analysis. The Partners Health Care System institutional review board approved this study; return of a completed questionnaire was accepted by the institutional review board as implied informed consent.

Procedures

We assessed average daily alcohol consumption with a semiquantitative food-frequency questionnaire, which included separate questions about beer, wine, and spirits. We used standard portions; a 12 oz (355 mL) bottle or can of beer, a 4 oz (118 mL) glass of wine, and a shot of spirits (44 mL). For each beverage, participants reported their usual average consumption in the preceding year, with nine response categories. We determined alcohol intake by multiplying the consumption of each beverage by its ethanol content (12·8 g for beer, 11·0 g for wine, and 14·0 g for

	Alcohol intake (g/day)							
	0	0·1–4·9	5·0–9·9	10·0–14·9	15·0–29·9	30·0–49·9	≥50	Overall
Number	11 196	11 429	6897	6002	6183	4056	1387	47 150
Age (years)	55	54	54	55	54	55	55	54 (10)
Body-mass index (kg/m2)	25	25	25	25	25	25	25	25 (5)
Diuretic use*	9%	8%	8%	9%	9%	11%	12%	9%
History of hypertension*	22%	19%	20%	19%	21%	25%	27%	21%
History of renal failure*	0·2%	0·1%	0·1%	0·1%	0·1%	0·1%	0·1%	0·1%
Dietary intake (servings per day)								
Total meat intake	1·3	1·3	1·3	1·4	1·4	1·5	1·6	1·4 (0·7)
Seafood intake	0·3	0·4	0·4	0·4	0·4	0·3	0·3	0·3 (0·3)
Purine-rich vegetables intake	0·7	0·7	0·7	0·7	0·7	0·7	0·7	0·7 (0·5)
Dairy foods intake	2·0	2·0	1·9	1·9	1·9	1·8	1·9	1·9 (1·4)

Values are means except *percentages. Numbers in parentheses are SD.

Table 1: **Baseline characteristics according to categories of alcohol intake (1986)**

spirits)[15] and summing the values. Alcohol intake was updated in 1990 and 1994, and a similar question about light beer (containing 11·3 g of ethanol) was added in 1994.

We assessed the validity of self-reported alcohol consumption by comparing estimates from the food-frequency questionnaire with two 7-day dietary records among 127 participants.[16] The Spearman correlation coefficients between alcohol use assessed on the basis of the first and second questionnaires and dietary records were 0·83 and 0·86, respectively.

Nutrient intake was also assessed by use of the food frequency questionnaire, and was computed from the reported frequency of consumption of each specified unit of food or beverage and from published data on the nutrient content of the specified portions.[17] The reproducibility and validity of this dietary questionnaire in this cohort have been previously reported.[18]

At baseline, and every 2 years thereafter, the participants provided information on weight, regular use of medications (including diuretics), and medical conditions (including hypertension and chronic renal failure). We calculated body-mass index by dividing the weight in kg by the square of the height in metres. The follow-up rate for this cohort was >90% during the study period.

In every biennial questionnaire, participants indicated whether they had received a physician diagnosis of gout. In 2001, we mailed participants with self-reported incident gout between 1986 and 1998 (n=1332) a supplementary questionnaire to confirm the report and to ascertain whether the American College of Rheumatology survey gout criteria were met.[19] The primary end point in this study was an incident case of gout that met six or more of the 11 gout criteria.[19] The response rate for the supplementary gout questionnaire was 80%, and 69% of the self-reported gout cases who returned the questionnaire met the primary end point definition (n=730). To confirm the validity of the survey gout criteria in our cohort, we reviewed the relevant medical records from a sample of 50 of the men who had reported gout. The concordance rate of confirming the report of gout between the gout survey criteria and the medical record review was 94%. We further assessed the robustness of our results by use of other gout outcome

definitions including self-reported physician-diagnosed gout (most sensitive) and cases that reported a tophus or crystal-proven gout (most specific; n=118).

Statistical analysis

We calculated person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of diagnosis of gout, death from any cause, or the end of the study period, whichever came first. Men who died or had reported having gout on previous questionnaires were excluded from subsequent follow-up.

To represent long-term alcohol intake patterns of individual participants, we used cumulative average intakes based on the information from 1986, 1990, and 1994 dietary questionnaires.[20,21] Thus, the incidence of gout from 1986 through 1990 was related to the alcohol intake reported in the 1986 questionnaire, and incidence from 1990 through 1994 was related to the average intake reported on the 1986 and 1990 questionnaires. We repeated our analyses with baseline alcohol intake (1986) or updated alcohol intake every 4 years without cumulative averaging.

We used Cox proportional hazards modelling to estimate the relative risk (RR) for incident gout in all multivariate analyses (by use of PROC PHREG, SAS Institute, Cary, NC, USA). We categorised daily ethanol intake into seven categories: none, 0·1–4·9 g, 5·0–9·9 g, 10·0–14·9 g, 15·0–29·9 g, 30·0–49·9 g, and 50·0 g or more.[22] We categorised frequency of intake of individual alcoholic beverages into five categories: less than one per month, one per month to one per week, two to four per week, five per week to one per day, and two or more per day. Multivariate models were adjusted for age (continuous), total energy intake (continuous), body-mass index (five categories), use of diuretics (yes or no), history of hypertension (yes or no), history of chronic renal failure (yes or no), daily average intake of meats, seafood, purine-rich vegetables, and dairy foods, and fluid (quintiles). Trends in gout risk across total alcohol intake and alcoholic beverages were assessed in Cox proportional hazards models by use of the median values of intake for each category to minimise the effects of outliers. The RRs for the continuous measures for the individual

	Alcohol intake (g/day)							
	0	0·1–4·9	5·0–9·9	10·0–14·9	15·0–29·9	30·0–49·9	≥50	p for trend
Number of participants	105	164	109	90	126	97	39	··
Person-years	94 691	131 093	75 844	58 643	69 090	37 331	11 241	··
Age-adjusted relative risk	1·0 (referent)	1·13 (0·89–1·45)	1·30 (0·99–1·70)	1·37 (1·03–1·81)	1·63 (1·26–2·11)	2·30 (1·75–3·04)	3·02 (2·09–4·36)	<0·0001
Multivariate relative risk*	1·0 (referent)	1·09 (0·85–1·40)	1·25 (0·95–1·64)	1·32 (0·99–1·75)	1·49 (1·14–1·94)	1·96 (1·48–2·60)	2·53 (1·73–3·70)	<0·0001

Values in parentheses are 95% CI. *Adjusted for age, total energy intake, body-mass index, diuretic use, history of hypertension, history of renal failure, intake of total meats, seafood, purine-rich vegetables, dairy foods, and fluid.

Table 2: **Relative risk for incident gout according to daily alcohol intake**
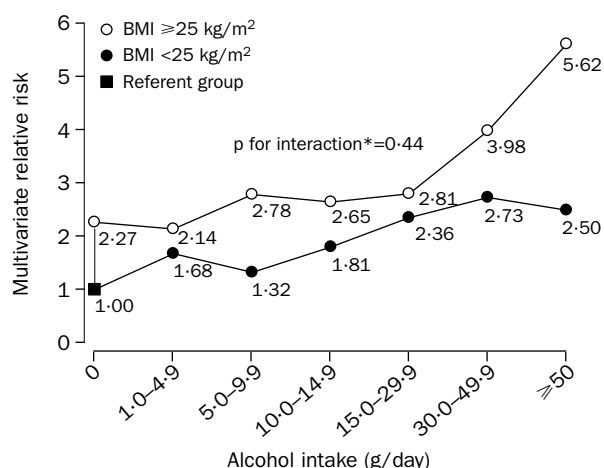
Multivariate relative risk of incident gout according to body-mass index (BMI) and alcohol intake

Relative risks (RRs) adjusted for age, total energy intake, diuretic use, history of hypertension, history of renal failure, and intake of total meats, seafood, purine-rich vegetables, dairy foods, and fluid. Referent group for all comparisons was men with BMI <25 kg/m^2 who did not drink alcohol. All p values for comparisons with the referent group were <0·05, except for the category of BMI <25 kg/m^2 and alcohol intake 5·0–9·9 g/day (p=0·36). *Interaction between BMI (<25 kg/m^2 vs ≥25 kg/m^2) and alcohol intake.

alcoholic beverages indicate the increase in risk associated with an average increment of one serving per day of the standard portion size. We did analyses stratified by alcohol use and by body-mass index (<25 kg/m^2 vs ≥25 kg/m^2) to assess possible effect modification. We tested the significance of the interaction with a likelihood ratio test by comparing a model with the main effects of each food group and the stratifying variable and the interaction terms with a reduced model with only the main effects. For all RRs, we calculated 95% CIs. All p values are two-sided.

Role of the funding source
The funding sources had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

Results
During 12 years of follow-up, there were 730 newly diagnosed cases meeting American College of Rheumatology criteria for gout. The characteristics of the cohort according to alcohol consumption at baseline are shown in table 1. History of hypertension and diuretic use were slightly more common at higher levels of daily alcohol consumption. With increasing alcohol consumption, total meat intake increased slightly. Age, body-mass index, and other variables were similar across the categories of daily alcohol consumption (table 1).

Increasing alcohol intake was associated with increasing risk of gout (table 2). Compared with men who did not drink alcohol, the age-adjusted RRs of gout increased from 1·30 (95% CI 0·99–1·70) for alcohol consumption 5·0–9·9 g/day to 3·02 (2·09–4·36) for ≥50 g/day (p for trend <0·0001). After adjusting for other risk factors for gout, the RRs of gout were attenuated but remained significant (p for trend <0·0001; table 2). The multivariate RR per 10 g increase in daily alcohol intake was 1·17 (95% CI 1·11–1·22).

The figure summarises the multivariate RRs of gout according to body-mass index (<25 kg/m^2 vs ≥25 kg/m^2) and alcohol intake. There was no significant interaction between the two variables (p=0·44).

Among individual alcoholic beverages, the magnitude of the association for the risk of gout was the largest for beer, followed by spirits. Wine was not associated with risk of incident gout (table 3). Compared with men who did not drink beer, the multivariate RR for men who drank 2–4 servings of beer per week was 1·27 (95% CI 1·00–1·62) and the RR increased with increasing beer consumption (p for trend <0·0001). The multivariate RR for men who drank two or more servings of beer per day was 2·51 (95% CI 1·77–3·55). Correspondingly, the multivariate RR for an increase in intake of one serving of beer per day was 1·49 (95% CI 1·32–1·70; table 3).

Compared with men who did not drink spirits, men who drank spirits as infrequently as one serving per month to one per week had a significantly increased risk of gout (multivariate RR 1·27; 95% CI 1·03–1·56). Men who drank two or more servings of spirits per day had a RR of 1·60 (95% CI 1·19–2·16; p for trend=0·009). The multivariate RR for an increase of one serving of spirits per day was 1·15 (95% CI 1·04–1·28; table 3).

The RR for men who drank two or more glasses of wine per day compared with those who drank less than one glass per month was 1·05 (95% CI 0·64–1·72) and there was no significant trend with increasing levels of wine consumption (p for trend=0·66; table 3). The null association persisted regardless of type of wine (ie, white or red, data not shown; p values for trend >0·4).

When we repeated our analyses using baseline alcohol and dietary intakes or updated alcohol and dietary intakes without cumulative averaging, the results were similar (table 4). When we used other gout outcome definitions,

	Frequency of Intake					Relative risk per serving per day
	<1/month	1/month–1/week	2–4/week	5/week–1/day	>2/day	
Beer						
Number of participants	255	219	135	76	45	..
Person-years	196 496	155 658	78 367	33 619	13 794	..
Age-adjusted relative risk	1·0 (referent)	1·10 (0·91–1·32)	1·37 (1·11–1·70)	1·83 (1·41–2·37)	2·64 (1·92–3·64)	1·51 (1·35–1·69)
Multivariate relative risk*	1·0 (referent)	1·01 (0·82–1·24)	1·27 (1·00–1·62)	1·75 (1·32–2·32)	2·51 (1·77–3·55)	1·49 (1·32–1·70)
Spirits						
Number of participants	267	202	118	79	64	..
Person-years	220 206	125 158	66 901	42 472	23 195	..
Age-adjusted relative risk	1·0 (referent)	1·34 (1·11–1·61)	1·44 (1·16–1·79)	1·51 (1·17–1·95)	2·22 (1·68–2·93)	1·33 (1·20–1·47)
Multivariate relative risk*	1·0 (referent)	1·27 (1·03–1·56)	1·25 (0·98–1·59)	1·22 (0·93–1·60)	1·60 (1·19–2·16)	1·15 (1·04–1·28)
Wine						
Number of participants	256	259	137	60	18	..
Person-years	171 934	176 883	82 345	38 210	8 561	..
Age-adjusted relative risk	1·0 (referent)	0·99 (0·83–1·18)	1·12 (0·91–1·38)	1·06 (0·80–1·40)	1·38 (0·85–2·23)	1·13 (0·96–1·32)
Multivariate relative risk*	1·0 (referent)	0·84 (0·69–1·01)	0·90 (0·71–1·15)	0·82 (0·61–1·11)	1·05 (0·64–1·72)	1·04 (0·88–1·22)

Values in parentheses are 95% CI.*Adjusted for the other two alcoholic beverages and for age, total energy intake, body-mass index, diuretic use, history of hypertension, history of renal failure, intake of total meats, seafood, purine-rich vegetables, dairy foods, and fluid.

Table 3: Relative risk for incident gout according to individual alcoholic beverage intake

	Alcohol Intake (g/day)							p for trend
	0	0·1–4·9	5·0–9·9	10·0–14·9	15·0–29·9	30·0–49·9	>50	
Self-reported gout	1·0 (referent)	1·01 (0·86–1·17)	1·03 (0·87–1·23)	1·12 (0·93–1·34)	1·19 (1·00–1·41)	1·56 (1·30–1·87)	1·93 (1·50–2·49)	<0·0001
Gout with ≥5 ACR criteria	1·0 (referent)	1·13 (0·90–1·42)	1·28 (0·99–1·64)	1·35 (1·04–1·76)	1·50 (1·18–1·92)	2·00 (1·54–2·61)	2·36 (1·64–3·41)	<0·0001
Gout with ≥6 ACR criteria	1·0 (referent)	1·09 (0·85–1·40)	1·25 (0·95–1·64)	1·32 (0·99–1·75)	1·49 (1·14–1·94)	1·96 (1·48–2·60)	2·53 (1·73–3·70)	<0·0001
Gout with ≥6 ACR criteria†	1·0 (referent)	1·09 (0·86–1·38)	1·20 (0·92–1·57)	1·37 (1·05–1·79)	1·41 (1·09–1·83)	1·88 (1·44–2·46)	2·51 (1·75–3·62)	<0·0001
Gout with ≥6 ACR criteria‡	1·0 (referent)	1·18 (0·94–1·49)	1·29 (1·00–1·67)	1·44 (1·11–1·87)	1·61 (1·25–2·06)	2·15 (1·66–2·78)	2·21 (1·54–3·17)	<0·0001
Gout with ≥7 ACR criteria	1·0 (referent)	1·03 (0·77–1·37)	1·14 (0·83–1·57)	1·28 (0·92–1·78)	1·40 (1·03–1·90)	2·22 (1·61–3·04)	2·31 (1·47–3·64)	<0·0001
Tophus or crystal-proven gout	1·0 (referent)	1·22 (0·62–2·42)	1·62 (0·79–3·33)	2·42 (1·20–4·90)	2·09 (1·03–4·25)	3·41 (1·64–7·10)	4·10 (1·50–11·18)	<0·0001

Values in parentheses are 95% CI.*Adjusted for age, total energy intake, body-mass index, diuretic use, history of hypertension, history of renal failure, and intake of total meats, seafood, purine-rich vegetables, dairy foods, and fluid. ACR criteria=American College of Rheumatology survey criteria for gout; six or more of the 11 criteria were required to meet our primary endpoint. †With updated alcohol intake without cumulative averaging as exposure. ‡With baseline alcohol intake (1986) as exposure. Tophus or crystal-proven gout: reported presence of tophus or urate crystal in joint-fluid without evidence of infection.

Table 4: **Alcohol intake and multivariate relative risk of incident gout according to various definitions of gout***

our overall results remained robust and the magnitude of associations tended to get larger with increasing specificity of the case definition (table 4).

Discussion

We prospectively assessed the long-suspected link between alcohol intake and incidence of gout in a large cohort of men. We validated the self-reported cases of gout by use of the American College of Rheumatology criteria[19] and we found a strong association between alcohol consumption and incident gout. The risk of gout was significantly raised with alcohol intake as low as 10·0–14·9 g/day and the magnitude of the association rose with increasing intake. The risk of gout was 2·5 times higher among men who consumed 50 g or more of alcohol per day compared with those who abstained from alcohol. These associations were independent of dietary and other purported risk factors of gout such as body-mass index, age, hypertension, use of diuretics, and chronic renal failure. The magnitude of these independent associations increased further when we restricted our analyses to those with a tophus or crystal-proven gout.

Several cohort studies have previously assessed the association between alcohol intake and gout, but have been limited by small sample size and lack of comprehensive adjustment of relevant variables.[1,9–12] The findings of the Normative Aging Study[10] suggested a marginal association between alcohol intake and gout (84 cases) but the association was not significant. Subsequently, another analysis of the same cohort[11] also failed to confirm an independent association between alcohol intake and gout itself, although there was a significant independent association between alcohol use and uric acid level. In the Framingham Study,[9] investigators retrospectively assessed alcohol intake after the onset of gout and showed a significantly increased alcohol intake among gout patients in an age-adjusted analysis but without further adjustment for other risk factors. In the Johns Hopkins Precursor Study[1,12] and the Meharry Cohort study[12] no association was found between alcohol intake measured at study baseline (in the third decade of life) and incident gout (60 cases) but the effect of alcohol consumption later in life could not be assessed because of a shortage of data. The present study included a large number of incident gout cases (n=730) verified by the American College of Rheumatology criteria and comprehensively adjusted for relevant variables including dietary factors, which were absent in previous cohort studies.[1,9–12]

A number of mechanisms have been implicated in the pathogenesis of alcohol-induced hyperuricaemia, including both decreased urate excretion[5,7,23,24] and increased production.[3,4] The former is via conversion of alcohol to lactic acid, which reduces renal uric acid excretion by competitively inhibiting uric acid secretion by the proximal tubule.[2,8,25,26] The confounding effect of fasting often associated with heavy drinking has been implicated as the cause of decreased urinary excretion via induction of acetoacetic and beta-hydroxybutyric acidaemia.[8,27] Additionally, ethanol administration has been shown to increase uric acid production by increasing adenosine triphosphate degradation to adenosine monophosphate, a uric acid precursor.[3] This process was later shown to involve acetate conversion to acetyl CoA in the metabolism of ethanol.[4] Factors not related to uric acid implicated in the pathogenesis of alcohol-associated gout include the frequent coexistence in heavy drinkers of other provocative factors, such as concurrent trauma and hypothermia of the lower extremities.[23,26] These factors may explain why alcoholic gouty patients tend to have lower concentrations of urate in serum than non-alcoholics during acute attacks of gout.[23]

We found differences in the risk of gout for the three alcoholic beverages. Two or more beers per day increased the risk of gout 2·5-fold compared with no beer intake, whereas the same frequency of spirits intake increased the risk by 1·6 times compared with no spirits intake. Correspondingly, beer increased the risk of gout per serving per day more than twice as much as did spirits (49% and 15%, respectively), even though alcohol content per serving was less for beer than spirits (12·8 g *vs* 14·0 g, respectively). Further, wine consumption of two 4-oz glasses or more per day was not associated with an increased risk of gout. These findings suggest that certain non-alcoholic components that vary across these alcoholic beverages play an important role in the incidence of gout. One candidate for this non-alcoholic component is the variation in purine contents among the individual alcoholic beverages.[28] Beer is the only alcoholic beverage acknowledged to have a large purine content, which is predominantly guanosine.[28] Guanosine is more readily absorbed than other nucleosides, nucleotides, or bases.[8,28] Thus, the effect of ingested purine in beer on uric acid in blood might be sufficient to augment the hyperuricaemic effect of alcohol itself producing a greater risk of gout than spirits or wine.[8,28] Whether there might be other non-alcoholic risk factors in beer, or protective factors in wine, remains unknown. Although we cannot rule out the possibility that wine drinking could still have an effect if

substantially more than 2 glasses per day were consumed, our data suggest that moderate wine drinking does not increase the risk of gout.

Several strengths and potential limitations of our study deserve comment. Our study was substantially larger than previous studies,[1,7–12] providing adequate power to detect clinically important associations. As in other epidemiological studies of gout,[1,9–12] our primary definition of gout did not require observation of urate crystal in joint-fluid examination. Although presence of tophus or urate crystal in joint fluid would be diagnostic of gout,[19] the sensitivity of these findings is too low, especially in a population study such as ours, because arthrocentesis is done infrequently. Thus, its application would probably miss most cases of gout. In our study, fulfilment of six of the 11 American College of Rheumatology survey criteria[19] showed a high-degree of concordance with medical record review, and the rate of gout fulfilling the criteria in our cohort closely agreed with that estimated among male physicians in the Johns Hopkins Precursor Study[1] (1·5 *vs* 1·7 per 1000 person-years, respectively). Furthermore, when we assessed the effect of various gout definitions, our findings were robust and the magnitude of associations tended to increase with increasing specificity of the case definition. Potential biased recall of diet was avoided in this study because the intake data were collected before the diagnosis of gout.

The restriction to health professionals in our cohort is both a strength and a limitation. The cohort of well-educated men reduces potential for confounding associated with socioeconomic status and we were able to obtain high quality data with little loss to follow-up. Although the absolute rates of gout and distribution of alcohol intake might not be representative of a random sample of US men, the biological effects of alcohol on gout should be similar. Our findings are most directly generalisable to men aged 40 years and older (the most gout-prevalent population[10]) with no history of gout. Given the potential effect of female hormones on the risk of gout in women[29] and an increased role of high purine intake on uric acid levels among patients with existing gout,[30] prospective studies of these populations are necessary. Further, the effect of individual alcoholic beverages on uric acid metabolism should be studied.

In conclusion, our prospective data indicate that alcohol intake is strongly associated with an increased risk of gout. This increased risk varies substantially according to type of alcoholic beverage: beer confers a larger risk than spirits, whereas moderate wine drinking does not increase the risk.

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