ORIGINAL ARTICLE

Purine-Rich Foods, Dairy and Protein Intake, and the Risk of Gout in Men

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ABSTRACT

BACKGROUND

Various purine-rich foods and high protein intake have long been thought to be risk factors for gout. Similarly, the possibility that the consumption of dairy products has a role in protecting against gout has been raised by metabolic studies. We prospectively investigated the association of these dietary factors with new cases of gout.

METHODS

Over a 12-year period, we prospectively examined the relationship between purported dietary risk factors and new cases of gout among 47,150 men who had no history of gout at base line. We used a supplementary questionnaire to ascertain whether participants met the American College of Rheumatology survey criteria for gout. Diet was assessed every four years by means of a food-frequency questionnaire.

RESULTS

During the 12 years of the study, we documented 730 confirmed new cases of gout. The multivariate relative risk of gout among men in the highest quintile of meat intake, as compared with those in the lowest quintile, was 1.41 (95 percent confidence interval, 1.07 to 1.86; P for trend=0.02), and the corresponding relative risk associated with seafood intake was 1.51 (95 percent confidence interval, 1.17 to 1.95; P for trend=0.02). In contrast, the incidence of gout decreased with increasing intake of dairy products; the multivariate relative risk among men in the highest quintile, as compared with those in the lowest quintile, was 0.56 (95 percent confidence interval, 0.42 to 0.74; P for trend <0.001). The level of consumption of purine-rich vegetables and the total protein intake were not associated with an increased risk of gout.

CONCLUSIONS

Higher levels of meat and seafood consumption are associated with an increased risk of gout, whereas a higher level of consumption of dairy products is associated with a decreased risk. Moderate intake of purine-rich vegetables or protein is not associated with an increased risk of gout.

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Gout is the most common form of inflammatory arthritis in men, affecting as many as 3.4 million men in the United States.[1,2] Patients with gout are typically advised to avoid habitual intake of purine-rich foods such as meats, seafood, purine-rich vegetables, and animal protein (as a proxy for purines),[3,4] but the associations have not been confirmed by prospective studies. Although protein-rich diets tend to contain large quantities of purines, the uricosuric effect associated with such diets may, in fact, even reduce the serum uric acid level, which would reduce the risk of gout.[4-6]

Several studies have suggested that there may be an inverse association between the level of consumption of dairy products and the serum uric acid level[7,8]; the evidence of such an association includes a significant increase in the uric acid level that was induced by a dairy-free diet in a four-week randomized clinical trial.[9] However, no studies, to our knowledge, have investigated the link between dairy-product consumption and the incidence of gout. To examine these issues, we prospectively evaluated the relationship between the reported intake of purine-rich foods, dairy foods, and protein and the incidence of gout in a cohort of 47,150 men who had no history of gout at base line.

METHODS

STUDY POPULATION

The Health Professionals Follow-up Study is an ongoing longitudinal study involving 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were 40 to 75 years of age in 1986. The participants returned a mailed questionnaire in 1986 concerning diet, medical history, and medications. Of the 49,932 men who provided complete dietary information, 2782 (5.6 percent) reported a history of gout on the base-line questionnaire. These men were excluded from our analysis, leaving 47,150 participants.

ASSESSMENT OF DIET

To assess dietary intake, we used a semiquantitative food-frequency questionnaire that inquired about the average consumption of more than 130 foods and beverages during the previous year.[10,11] The dietary information was updated in 1990 and 1994. Nutrient intake 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.[11] Food and nutrient intakes assessed by means of this dietary questionnaire have been validated against two one-week diet records in this cohort.[10,12]

ASSESSMENT OF COVARIATES

At base line and every two years thereafter, the participants provided information on their weight, the regular use of medications, and medical conditions. The rate of follow-up for this cohort exceeded 90 percent during the study period.

ASCERTAINMENT OF NEW CASES OF GOUT

On each biennial questionnaire, the men indicated whether they had received a diagnosis of gout from a physician. In 2001, the 1332 men with self-reported new cases of gout between 1986 and 1998 were sent a supplementary questionnaire to confirm the report and to ascertain whether the case met the American College of Rheumatology survey criteria for gout.[13] The primary end point of this study was a newly diagnosed case of gout that met 6 or more of the 11 criteria for gout (more than one attack of acute arthritis, maximal inflammation developing within one day, attack of oligoarthritis, redness observed over joints, painful or swollen first metatarsophalangeal joint, unilateral attack in first metatarsophalangeal joint, unilateral attack in tarsal joint, tophus, hyperuricemia, asymmetric swelling within a joint, and complete termination of an attack).[13]

The response rate for the supplementary gout questionnaire was 80 percent (1064 of 1332 men), and 69 percent of the cases in men with self-reported gout who returned the questionnaire (730 of 1064) met the definition for the primary end point. To confirm the validity of the criteria for gout used in the survey in our cohort, two board-certified rheumatologists reviewed the medical records of a sample of 76 of the men who had reported having gout and had consented to the release of their medical records. Of these 76 men, 26 (34 percent) did not have relevant and complete records. Among the remaining 50 men, the rate of concordance between the diagnosis of gout according to the criteria of the American College of Rheumatology and the diagnosis of gout according to our review of the medical records was 94 percent (47 of 50). We further evaluated the robustness of our results by using other definitions of gout, ranging from a participant's report that a physician had diagnosed gout (most lenient) to the presence of a tophus or the detection of crystals on arthrocentesis (strictest).

STATISTICAL ANALYSIS

We computed the person-time of follow-up for each man as the interval between the date on which the 1986 questionnaire was returned and the date of a diagnosis of gout, death from any cause, or the end of the study period, whichever came first. For the men who did not return the supplementary gout questionnaire, follow-up data were censored at the time of their first report of gout.

In order to represent the long-term dietary patterns of individual men, our primary analysis used cumulative average dietary intakes based on the information from the 1986, 1990, and 1994 dietary questionnaires.[14,15] We used Cox proportional-hazards modeling to estimate the multivariate relative risk of a new case of gout (SAS software, SAS Institute). Responses regarding the individual food items were converted to average daily servings. The average daily intakes of individual items were combined in order to compute the totals for food groups: total meat (a main or mixed dish of beef, pork, or lamb; processed meat, including sausage, salami, and bologna; bacon; hot dogs; hamburgers; poultry, including chicken and turkey; chicken liver; and beef liver); seafood (tuna; dark fish; other fish; and shrimp, lobster, or scallops); purine-rich vegetables (peas, beans, lentils, spinach, mushrooms, oatmeal, and cauliflower); and dairy products (low-fat dairy products, including skim or low-fat milk, sherbet, low-fat yogurt, and cottage or ricotta cheese; high-fat dairy products, including whole milk, cream, butter, sour cream, ice cream, cream cheese, and other cheeses; and all dairy products, including all of the above).

The average daily intake of each food group was categorized into quintiles. Protein intake (animal protein, dairy protein, nondairy animal protein, vegetable protein, and total protein) was also categorized into quintiles according to the percentage of total energy obtained from each type of protein (the nutrient density[16]). In multivariate models of nutrient density,[16] we simultaneously included energy intake, the percentages of energy derived from fat and specific types of protein, and other potentially confounding variables. Other variables considered in multivariate models included age (as a continuous variable), alcohol use (in seven categories), body-mass index (the weight in kilograms divided by the square of the height in meters, in six categories), the use or nonuse of diuretics, history of hypertension (yes or no), history of chronic renal failure (yes or no), and fluid intake (in quintiles). To assess the trends, we used the median values of intake in each category, so as to minimize the influence of outliers. We assessed possible effect modification by food groups and by alcohol use (or nonuse) or the body-mass index (<25 vs. ≥25). We tested the significance of the interaction using the likelihood-ratio test. For all relative risks, we calculated 95 percent confidence intervals. All P values are two-sided.

RESULTS

During the 12-year follow-up, we documented 730 confirmed new cases of gout that met the criteria of the American College of Rheumatology. Eighty-eight percent of the men with gout reported podagra, 35 percent midfoot involvement, 72 percent hyperuricemia, and 11 percent a tophus. Only 11 percent had undergone arthrocentesis, and of these, 65 percent reported having urate crystals in their joint fluid. The incidence of gout increased with age and peaked between 55 and 69 years (Table 1).

BASE-LINE CHARACTERISTICS

The base-line characteristics of the cohort according to dietary factors are shown in Table 2. The average daily intake of alcohol tended to decrease with increasing intake of protein or dairy products. A history of hypertension was slightly more com-

Table 1. Incidence of Gout among Men, According to Five-Year Age Groups.*

Age Group	Person-Yr of Follow-up	No. of Cases	Incidence per 1000 Person-Yr
<45 Yr	50,204	49	1.0
45–49 Yr	74,547	110	1.5
50–54 Yr	76,576	114	1.5
55–59 Yr	72,928	130	1.8
60–64 Yr	72,078	130	1.8
65–69 Yr	63,503	111	1.7
≥70 Yr	68,097	86	1.3

* Data are for cases that met the criteria for the primary end point (6 or more of the following 11 criteria for gout established by the American College of Rheumatology: more than one attack of acute arthritis, maximal inflammation developing within one day, attack of oligoarthritis, redness observed over joints, painful or swollen first metatarsophalangeal joint, unilateral attack in first metatarsophalangeal joint, unilateral attack in tarsal joint, tophus, hyperuricemia, asymmetric swelling within a joint, and complete termination of an attack).[13]

Table 2. Base-Line Characteristics of the Men According to Quintiles of Intake of Purine-Rich Food Groups, Dairy Products, and Protein.

Variable	Mean Daily Intake	Mean Age	Mean Animal-Protein Intake	Mean Alcohol Consumption	Mean Body-Mass Index*	Use of Diuretics	History of Hypertension
	servings/day	*yr*	*% of energy*	*g/day*		*percent*	
Total meat							
Quintile 1	0.5	55	12.0	9	24	8	21
Quintile 3	1.2	55	13.9	11	25	9	21
Quintile 5	2.5	54	14.8	13	25	8	20
Seafood							
Quintile 1	0.04	54	12.2	10	25	8	20
Quintile 3	0.2	54	13.2	12	25	9	21
Quintile 5	0.8	55	15.6	11	25	10	23
Purine-rich vegetables							
Quintile 1	0.2	55	13.7	10	25	9	22
Quintile 3	0.6	55	13.7	11	25	9	20
Quintile 5	1.5	55	13.5	11	25	9	22
Dairy products							
Quintile 1	0.5	54	13.3	12	25	9	22
Quintile 3	1.6	54	13.5	11	25	9	21
Quintile 5	4.2	55	14.3	10	25	8	19
Low-fat dairy products							
Quintile 1	0.04	54	12.9	13	25	9	20
Quintile 3	0.69	54	13.6	11	25	9	22
Quintile 5	2.74	55	14.8	9	25	9	21
Total protein							
Quintile 1	14.2	54	9.3	17	24	9	20
Quintile 3	18.4	54	13.3	11	25	8	20
Quintile 5	23.6	56	18.7	7	25	12	24
Animal protein							
Quintile 1	8.9	55	8.9	15	24	8	19
Quintile 3	13.4	54	13.4	11	25	8	20
Quintile 5	18.9	55	18.9	7	25	10	23
All participants	—	54	13.6	11	25	9	21

* The body-mass index is the weight in kilograms divided by the square of the height in meters.

mon among the men in the highest quintile of protein intake than among the men in the other quintiles (Table 2).

PURINE-RICH FOODS

Increased meat intake was associated with an increased risk of gout. The multivariate relative risk among the men in the highest quintile of total meat intake, as compared with those in the lowest quintile, was 1.41 (95 percent confidence interval, 1.07 to 1.86; P for trend=0.02) (Table 3). Among individual meat items, only the intake of beef, pork, or lamb as a main dish was associated with an increased risk of gout (P for trend=0.01) (Table 4).

Increased seafood intake was associated with an increased risk of gout. The multivariate relative risk among men in the highest quintile of seafood intake, as compared with those in the lowest quintile, was 1.51 (95 percent confidence interval, 1.17 to 1.95; P for trend=0.02) (Table 3). Increased intake of all individual seafood items was associated with an increased risk of gout (P for trend <0.05 for all items) (Table 4).

The level of consumption of purine-rich vegetables was not associated with the risk of gout (Table 3). Similarly, intake of individual purine-rich vegetable items was not associated with the risk of gout.

CONSUMPTION OF DAIRY PRODUCTS

The incidence of gout decreased with increasing intake of dairy products (Table 3). The multivariate relative risk of gout among men in the highest quintile of dairy intake, as compared with those in the

Table 3. Relative Risk of a New Case of Gout According to Intake of Purine-Rich Food Groups and Dairy Products.*

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Relative Risk per Additional Daily Serving
Total meat intake (servings/day)	<0.81	0.81–1.12	1.13–1.46	1.47–1.92	>1.92	
No. of cases/no. of person-yr	116/93,473	138/95,857	163/95,963	152/96,487	161/96,153	
Age-adjusted RR (95% CI)	1.0	1.20 (0.94–1.54)	1.48 (1.16–1.87)	1.51 (1.17–1.94)	1.77 (1.35–2.31)	1.37 (1.18–1.58)
Multivariate RR (95% CI)	1.0	1.07 (0.84–1.37)	1.28 (1.00–1.63)	1.26 (0.97–1.63)	1.41 (1.07–1.86)	1.21 (1.04–1.41)
Seafood intake (servings/day)	<0.15	0.15–0.28	0.29–0.36	0.37–0.56	>0.56	
No. of cases/no. of person-yr	71/64,193	171/120,274	163/97,175	154/94,868	171/101,423	
Age-adjusted RR (95% CI)	1.0	1.41 (1.10–1.81)	1.54 (1.21–1.98)	1.43 (1.11–1.85)	1.53 (1.20–1.96)	1.07 (1.02–1.12)†
Multivariate RR (95% CI)	1.0	1.35 (1.05–1.74)	1.45 (1.13–1.87)	1.38 (1.06–1.79)	1.51 (1.17–1.95)	1.07 (1.01–1.12)†
Purine-rich–vegetable intake (servings/day)	<0.35	0.35–0.50	0.51–0.71	0.72–1.05	>1.05	
No. of cases/no. of person-yr	137/92,144	147/92,919	150/93,165	163/102,976	133/96,729	
Age-adjusted RR (95% CI)	1.0	1.05 (0.83–1.32)	1.15 (0.91–1.45)	1.11 (0.87–1.40)	0.97 (0.75–1.24)	0.95 (0.78–1.16)
Multivariate RR (95% CI)	1.0	0.99 (0.79–1.25)	1.10 (0.87–1.40)	1.06 (0.84–1.36)	0.96 (0.74–1.24)	0.97 (0.79–1.19)
Total intake of dairy products (servings/day)	<0.88	0.88–1.35	1.36–1.91	1.92–2.88	>2.88	
No. of cases/no. of person-yr	201/94,123	165/93,040	132/98,103	130/97,729	102/94,937	
Age-adjusted RR (95% CI)	1.0	0.85 (0.69–1.04)	0.66 (0.53–0.83)	0.62 (0.49–0.78)	0.52 (0.40–0.67)	0.79 (0.73–0.86)
Multivariate RR (95% CI)	1.0	0.83 (0.68–1.03)	0.66 (0.53–0.83)	0.64 (0.51–0.82)	0.56 (0.42–0.74)	0.82 (0.75–0.90)
Intake of low-fat dairy products (servings/day)	<0.20	0.20–0.56	0.57–0.99	1.00–1.67	>1.67	
No. of cases/no. of person-yr	173/92,742	181/90,972	146/93,197	129/104,040	101/96,982	
Age-adjusted RR (95% CI)	1.0	1.06 (0.86–1.31)	0.83 (0.67–1.04)	0.67 (0.54–0.84)	0.56 (0.43–0.72)	0.76 (0.69–0.83)
Multivariate RR (95% CI)‡	1.0	1.01 (0.82–1.25)	0.80 (0.64–1.00)	0.67 (0.53–0.85)	0.58 (0.45–0.76)	0.79 (0.71–0.87)
Intake of high-fat dairy products (servings/day)	<0.34	0.34–0.63	0.64–0.99	1.00–1.64	>1.64	
No. of cases/no. of person-yr	142/94,708	161/93,886	144/94,448	141/99,037	142/95,853	
Age-adjusted RR (95% CI)	1.0	1.18 (0.94–1.47)	1.07 (0.85–1.35)	1.03 (0.81–1.30)	1.10 (0.86–1.41)	1.01 (0.91–1.11)
Multivariate RR (95% CI)‡	1.0	1.09 (0.87–1.37)	0.98 (0.77–1.25)	0.92 (0.72–1.18)	1.00 (0.77–1.29)	0.99 (0.89–1.10)

* RR denotes relative risk, and CI confidence interval. The age-adjusted models were adjusted for the total energy intake as well as age; the multivariate models were adjusted for age, total energy intake, body-mass index, use of diuretics, presence or absence of a history of hypertension, presence or absence of a history of renal failure, and intake of alcohol, fluid, total meats, seafood, purine-rich vegetables, and dairy products.
† In order to reflect the distribution of seafood intake, the data represent the relative risk per additional weekly serving.
‡ The multivariate model included the intake of low-fat dairy products and high-fat dairy products instead of that of total dairy products.

lowest quintile, was 0.56 (95 percent confidence interval, 0.42 to 0.74; P for trend <0.001). The inverse association was limited to the consumption of low-fat dairy products (Table 3); the multivariate relative risk among men who drank two or more (8-oz [240-ml]) glasses of skim milk per day, as compared with men who drank less than one glass per month, was 0.54 (95 percent confidence interval, 0.40 to 0.73; P for trend <0.001) (Table 4). A similar inverse association was observed between the level of consumption of low-fat yogurt and the risk of gout (P for trend=0.07). There were no other individual dairy products the consumption of which was significantly associated with the risk of gout.

PROTEIN INTAKE

Total protein intake and animal-protein intake were not associated with the risk of gout (Table 5). However, the multivariate relative risk of gout among the men in the highest quintile of vegetable-protein intake, as compared with those in the lowest quintile, was 0.73 (95 percent confidence interval, 0.56 to 0.96), and the corresponding relative risk associated with dairy-protein intake was 0.52 (95 percent confidence interval, 0.40 to 0.68) (Table 5). When we repeated these analyses using energy-adjusted protein values[16] instead of the percentage of total energy accounted for by a given type of protein, the results did not materially change.

RISK ACCORDING TO FOOD INTAKE AND BODY-MASS INDEX OR ALCOHOL USE OR NONUSE

The associations between most dietary factors and the risk of gout did not vary according to body-mass index or whether or not the man drank alco-

Table 4. Relative Risk of a New Case of Gout According to Level of Consumption of Individual Foods.*

Variable	Subgroup Defined According to Frequency of Intake					P Value for Trend
Beef, pork, or lamb as a main dish (4–6 oz [112–168 g]) — no. of servings	<1/mo	1–3/mo	1/wk	≥2/wk		
No. of cases/no. of person-yr	35/35,019	139/99,787	218/147,990	326/187,608		
Age-adjusted RR (95% CI)	1.0	1.39 (0.96–2.02)	1.55 (1.08–2.22)	1.92 (1.35–2.75)		<0.001
Multivariate RR (95% CI)	1.0	1.22 (0.84–1.77)	1.29 (0.89–1.85)	1.50 (1.04–2.17)		0.01
Canned tuna fish (3–4 oz [84–112 g]) — no. of servings	<1/mo	1–3/mo	≥1/wk			
No. of cases/no. of person-yr	113/86,341	321/214,182	283/169,266			
Age-adjusted RR (95% CI)	1.0	1.14 (0.92–1.41)	1.29 (1.03–1.60)			0.02
Multivariate RR (95% CI)	1.0	1.13 (0.91–1.40)	1.28 (1.03–1.60)			0.02
Dark-meat fish (3–5 oz [84–140 g]) — no. of servings	<1/mo	1–3/mo	≥1/wk			
No. of cases/no. of person-yr	259/192,004	320/197,436	136/78,492			
Age-adjusted RR (95% CI)	1.0	1.19 (1.01–1.40)	1.28 (1.03–1.57)			0.01
Multivariate RR (95% CI)	1.0	1.17 (0.99–1.39)	1.32 (1.06–1.64)			0.009
Other fish (3–5 oz) — no. of servings	<1/mo	1–3/mo	≥1/wk			
No. of cases/no. of person-yr	70/69,329	344/215,679	298/181,252			
Age-adjusted RR (95% CI)	1.0	1.57 (1.21–2.04)	1.61 (1.24–2.09)			0.003
Multivariate RR (95% CI)	1.0	1.52 (1.17–1.97)	1.55 (1.18–2.02)			0.009
Shrimp, lobster, or scallops as a main dish — no. of servings	<1/mo	1–3/mo	≥1/wk			
No. of cases/no. of person-yr	235/190,431	411/240,804	72/38,150			
Age-adjusted RR (95% CI)	1.0	1.39 (1.18–1.64)	1.57 (1.20–2.05)			<0.001
Multivariate RR (95% CI)	1.0	1.23 (1.04–1.45)	1.30 (0.99–1.70)			0.01
Skim milk or low-fat milk (8-oz [240-ml] glass) — no. of servings	<1/mo	1/mo–1/wk	2–4/wk	5/wk–1/day	≥2/day	
No. of cases/no. of person-yr	175/85,186	137/72,680	187/115,693	151/129,581	64/61,569	
Age-adjusted RR (95% CI)	1.0	0.91 (0.72–1.14)	0.78 (0.63–0.96)	0.57 (0.46–0.71)	0.52 (0.39–0.69)	<0.001
Multivariate RR (95% CI)	1.0	0.84 (0.67–1.05)	0.74 (0.60–0.92)	0.57 (0.46–0.71)	0.54 (0.40–0.73)	<0.001
Low-fat yogurt (1 cup [0.24 liter]) — no. of servings	<1/mo	1–3/mo	1/wk	≥2/wk		
No. of cases/no. of person-yr	449/262,922	150/105,560	55/39,543	47/45,594		
Age-adjusted RR (95% CI)	1.0	0.83 (0.69–1.00)	0.85 (0.64–1.12)	0.63 (0.47–0.85)		0.002
Multivariate RR (95% CI)	1.0	0.87 (0.72–1.05)	0.91 (0.68–1.21)	0.76 (0.56–1.03)		0.07
Whole milk (8-oz glass) — no. of servings	<1/mo	1–3/mo	1/wk	≥2/wk		
No. of cases/no. of person-yr	506/327,820	92/47,699	22/20,725	80/55,401		
Age-adjusted RR (95% CI)	1.0	1.25 (1.00–1.57)	0.71 (0.47–1.10)	0.97 (0.76–1.23)		0.68
Multivariate RR (95% CI)	1.0	1.23 (0.98–1.55)	0.74 (0.48–1.13)	1.06 (0.83–1.35)		0.76

* RR denotes relative risk, and CI confidence interval. The age-adjusted relative risks were adjusted for total energy intake as well as age; multivariate relative risks were adjusted for age, total energy intake, body-mass index, use of diuretics, presence or absence of a history of hypertension, presence or absence of a history of renal failure, and intake of alcohol, fluid, and purine-rich vegetables. In addition, the multivariate relative risk, associated with beef, pork, or lamb as a main dish was adjusted for seafood and dairy-product intake; the multivariate relative risks associated with individual seafood items were adjusted for total meat and dairy-product intake; and the multivariate relative risks associated with dairy products were adjusted for total meat and seafood intake.

hol; the exception was seafood intake, the association of which with the risk of gout was significantly stronger among men with a body-mass index of less than 25 than among those with a body-mass index of 25 or higher (P for trend=0.009 and 0.31, respectively; P for interaction=0.04) (Fig. 1).

OTHER DEFINITIONS OF DIETARY EXPOSURE

When we repeated our analyses using the base-line dietary intake and the dietary intakes as updated every four years without cumulative averaging, the results were similar. When we used other definitions of gout, the magnitude of the associations with particular food groups tended to increase as the specificity of the case definition increased, but null associations remained null. For example, as we substituted progressively more specific definitions, moving from self-reported gout (which applied to 1332 men), to gout as defined by the criteria of the American College of Rheumatology (730 men), to

Table 5. Relative Risk of a New Case of Gout According to Protein Consumption.*

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Value for Trend
Total protein intake (% of energy)	<15.9	15.9–17.5	17.6–18.9	19.0–20.7	>20.7	
No. of cases/no. of person-yr	145/95,422	132/96,652	163/96,523	133/95,865	157/93,472	
Age-adjusted RR (95% CI)	1.0	0.89 (0.70–1.12)	1.08 (0.86–1.35)	0.86 (0.68–1.09)	1.01 (0.80–1.27)	0.97
Multivariate RR (95% CI)	1.0	0.92 (0.72–1.16)	1.14 (0.90–1.43)	0.92 (0.72–1.17)	1.07 (0.84–1.36)	0.61
Animal-protein intake (% of energy)	<10.7	10.7–12.3	12.4–13.8	13.9–15.7	>15.7	
No. of cases/no. of person-yr	137/95,949	127/96,843	148/96,529	167/95,517	151/93,095	
Age-adjusted RR (95% CI)	1.0	0.92 (0.72–1.17)	1.05 (0.83–1.33)	1.18 (0.94–1.48)	1.06 (0.84–1.34)	0.23
Multivariate RR (95% CI)	1.0	0.88 (0.69–1.12)	0.99 (0.78–1.26)	1.10 (0.87–1.39)	0.96 (0.74–1.23)	0.75
Vegetable-protein intake (% of energy)	<4.2	4.2–4.7	4.8–5.2	5.3–5.9	>5.9	
No. of cases/no. of person-yr	179/92,881	141/95,241	143/96,227	158/96,739	109/96,845	
Age-adjusted RR (95% CI)	1.0	0.76 (0.61–0.95)	0.76 (0.61–0.94)	0.82 (0.66–1.02)	0.56 (0.44–0.71)	<0.001
Multivariate RR (95% CI)	1.0	0.85 (0.68–1.07)	0.88 (0.70–1.11)	0.99 (0.79–1.26)	0.73 (0.56–0.96)	0.11
Dairy-protein intake (% of energy)	<1.3	1.3–1.9	2.0–2.7	2.8–3.9	>3.9	
No. of cases/no. of person-yr	190/94,836	172/95,950	150/95,953	121/96,228	97/94,966	
Age-adjusted RR (95% CI)	1.0	0.90 (0.74–1.11)	0.78 (0.63–0.96)	0.62 (0.50–0.78)	0.52 (0.41–0.66)	<0.001
Multivariate RR (95% CI)	1.0	0.91 (0.74–1.12)	0.80 (0.64–0.99)	0.64 (0.51–0.81)	0.52 (0.40–0.68)	<0.001
Nondairy-animal-protein intake (% of energy)	<8.1	8.1–9.6	9.7–11.1	11.2–13.6	>13.6	
No. of cases/no. of person-yr	107/95,849	123/96,717	160/96,425	168/95,717	172/93,226	
Age-adjusted RR (95% CI)	1.0	1.12 (0.87–1.46)	1.46 (1.14–1.87)	1.52 (1.19–1.94)	1.57 (1.22–2.00)	<0.001
Multivariate RR (95% CI)	1.0	1.00 (0.77–1.30)	1.25 (0.97–1.60)	1.24 (0.96–1.59)	1.18 (0.90–1.53)	0.10

* RR denotes relative risk, and CI confidence interval. The age-adjusted models were adjusted for total energy intake as well as age; the multivariate relative risks associated with total protein intake were adjusted for age, total energy intake, body-mass index, use of diuretics, presence or absence of a history of hypertension, presence or absence of a history of renal failure, and intake of alcohol, fluid, and total fat; the multivariate relative risks associated with animal-protein intake and vegetable-protein intake were adjusted for the above variables and mutually for animal protein and vegetable protein; and the multivariate relative risks associated with dairy-protein and nondairy-animal-protein intake were adjusted for the above variables and mutually for dairy protein, nondairy animal protein, and vegetable protein.

tophaceous or crystal-proven gout (118 men), the multivariate relative risk among men in the highest quintile of seafood intake, as compared with those in the lowest quintile, increased from 1.33 (95 percent confidence interval, 1.11 to 1.60) to 1.51 (95 percent confidence interval, 1.17 to 1.95) to 3.24 (95 percent confidence interval, 1.49 to 7.07). The corresponding relative risks associated with the quintile of intake of low-fat dairy products were 0.61 (95 percent confidence interval, 0.50 to 0.73), 0.58 (95 percent confidence interval, 0.45 to 0.76), and 0.38 (95 percent confidence interval, 0.18 to 0.78), respectively, and the corresponding relative risks associated with drinking two or more glasses of skim milk per day, as compared with drinking less than one glass per month, were 0.59 (95 percent confidence interval, 0.47 to 0.73), 0.54 (95 percent confidence interval, 0.40 to 0.73), and 0.21 (95 percent confidence interval, 0.07 to 0.62), respectively.

DISCUSSION

In this large prospective cohort study involving men, we found an increased risk of gout with higher meat consumption or seafood consumption but not with higher consumption of animal or vegetable protein or purine-rich vegetables. Furthermore, we found a strong inverse association between the consumption of dairy products, especially low-fat dairy products, and the incidence of gout. These associations were independent of both the other dietary factors we studied and other purported risk factors for gout, such as high body-mass index, older age, hypertension, alcohol use, use of diuretics, and chronic renal failure.

The suspicion that there is a link between purine-rich diets and gout has been based on metabolic experiments in animals and humans that examined the effect of the artificial short-term loading of purified purine on the serum uric acid level (not on gouty arthritis).[17-20] Although these studies provide a theoretical basis for the effect of a purine-rich diet on hyperuricemia and, conceivably, on the eventual development of gout, several important hurdles remain before these data can be applied to clinical practice or public health efforts.

First, little is known about the precise identity and quantity of individual purines in most foods,

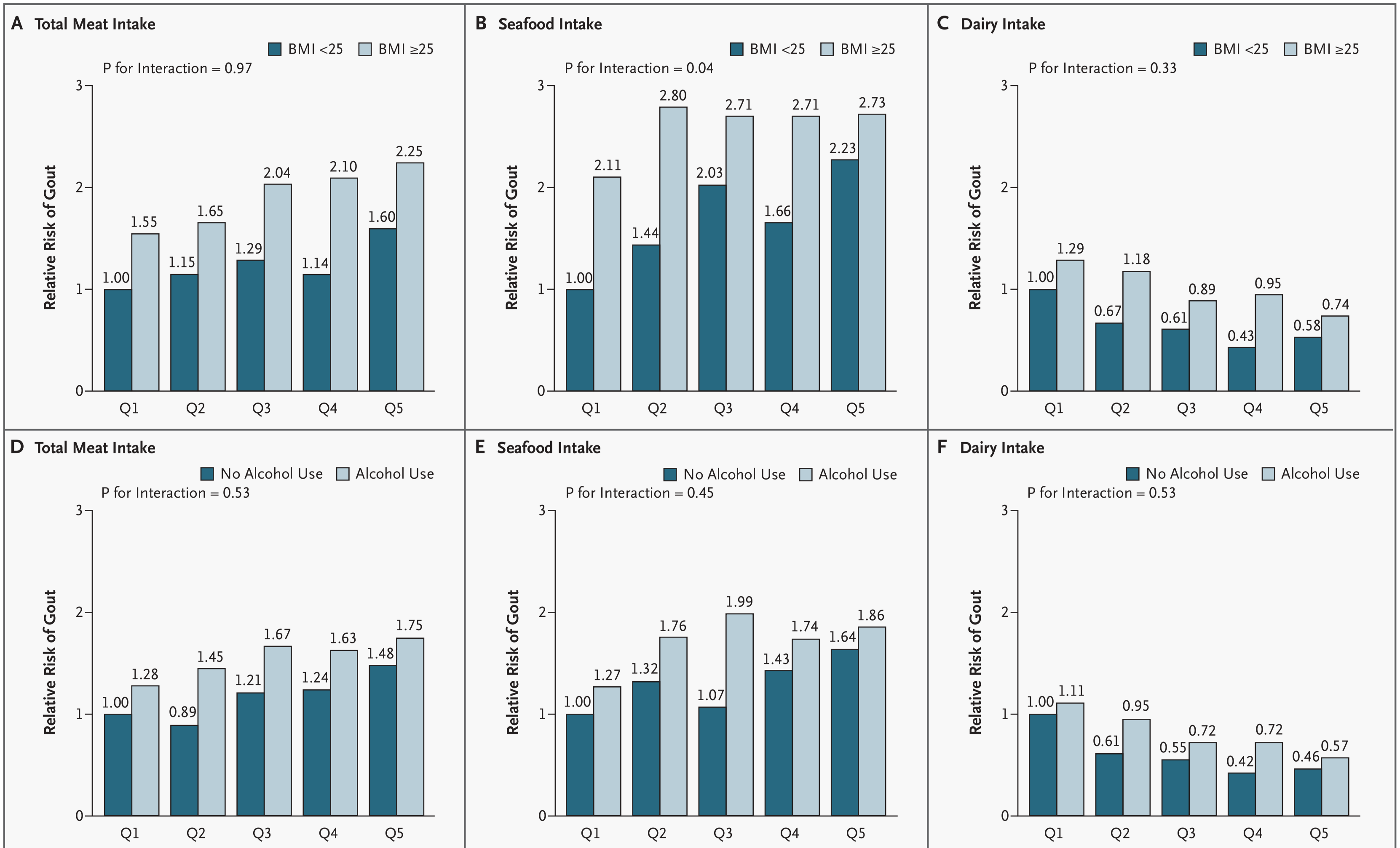

Figure 1. Multivariate Relative Risk of a New Case of Gout According to Quintile of Intake of Various Food Groups and Body-Mass Index (Panels A, B, and C) or Alcohol Use or Nonuse (Panels D, E, and F).

The reference group for the comparisons in Panels A, B, and C was the men in the lowest quintile for intake of the given food group who had a body-mass index (BMI) of less than 25. The reference group for the comparisons in Panels D, E, and F was the men in the lowest quintile for intake of the given food group who did not drink alcohol. The relative risks were adjusted for age, total energy intake, body-mass index, use or nonuse of diuretics, presence or absence of a history of hypertension, presence or absence of a history of renal failure, and intake of alcohol, fluid, total meats, seafood, purine-rich vegetables, and dairy foods. Q denotes quintile; Q1 represents the lowest quintile, and Q5 the highest quintile.

especially when they are cooked or processed.[5] In addition, the bioavailability of various purines contained in different foods varies substantially. For example, dietary experiments have shown that the bioavailability is greater for RNA than for an equivalent amount of DNA,[20] greater for ribonucleotides than for nucleic acid,[21] and greater for adenine than for guanine.[17] Finally, the outcome examined in these metabolic studies was hyperuricemia, rather than gout,[17-21] and a substantial proportion of patients with hyperuricemia will not have gouty arthritis.[22,23] Thus, it has been difficult to predict whether a certain "purine-rich" food or food group that is commonly consumed actually affects the risk of gout and, if it does, to what extent.

Our study overcame these hurdles by examining common foods or food groups and new cases of gout, and it provides clinically relevant information: each additional daily serving of meat was associated with a 21 percent increase in the risk of gout, and each additional weekly serving of seafood was associated with a 7 percent increase in risk. This effect may be greater in patients who already have gout: because renal urate clearance is relatively impaired in most patients with gout, the absorption of dietary purines causes a steeper increase in the blood uric acid level than do equivalent quantities in persons with normouricemia.[24,25]

We found that the risk of gout associated with seafood intake was significantly higher among men who were not overweight than among men who were overweight. These results suggest that there may be a substantial difference between these subgroups in purine-to-uric-acid metabolism, uric acid excretion specifically related to seafood intake, or both. It remains to be elucidated how these findings are related to hyperuricemia associated with overweight that may occur through both increased production and decreased renal excretion of uric acid[3,4,26]; it is also unclear why the interaction appears to be limited to seafood intake. Confirmation of these findings by future studies might result in more refined and comprehensive dietary recommendations for the prevention of gout, given the emerging role of fish intake in the prevention of coronary heart disease.[27]

We did not find a significant association between gout and the consumption of purine-rich vegetables, either as a group or individually. The variation in the risk of gout associated with different purine-rich foods may be explained by the variation in the amounts and types of purine content and their bioavailability for purine-to-uric-acid metabolism.[5,17-21] It has been suggested that moderation in dietary purine consumption is indicated for patients who habitually eat large amounts of purine-containing foods, of either animal or vegetable origin[3,4]; however, our results suggest that this type of dietary restriction may be applicable to purines of animal origin but not to purine-rich vegetables.

We found a strong inverse relation between consumption of dairy products, especially low-fat dairy products, and the incidence of gout. The ingestion of milk proteins (casein and lactalbumin) has been shown to reduce serum uric acid levels in healthy subjects because of the uricosuric effect of these proteins.[8] Conversely, a significant increase in the uric acid level was induced by a dairy-free diet in a four-week randomized clinical trial.[9] Since dairy products are low in purine content, dairy protein may exert its urate-lowering effect without providing the concomitant purine load contained in other protein sources such as meat and seafood. Although other nutrients in dairy products may be responsible for the inverse association, there is currently no relevant biologic or metabolic evidence available.

A higher total intake of animal or vegetable protein was not associated with an increased risk of gout. Actually, our results regarding vegetable-protein intake suggest that protein from vegetable sources may have a protective effect, although its magnitude appeared to be smaller than that provided by dairy protein. High-protein diets are associated with increased urinary uric acid excretion and may reduce the blood uric acid level.[5,6,28-30] In a recent open-label study involving 13 patients, a dietary intervention was used that included an increased proportional intake of protein; the study showed a significant reduction in the rate of recurrent attacks of gout.[31] These data support our findings that the consumption of protein does not increase the risk of gout but, rather, may actually decrease the risk and that the protein content of foods may not be a good surrogate for their purine content.

Several strengths and potential limitations of our study deserve comment. Our study was substantially larger than previous studies concerning gout,[1,5,23,32-35] and dietary data were prospectively collected and validated.[10,12] Potentially biased recall of diet was avoided, because the intake data were collected before gout was diagnosed. Our findings are most directly generalizable to men 40 years of age or older (the population with the highest prevalence of gout[23]) who have no history of gout. As in other epidemiologic studies of gout,[1,23,32-34] our primary case definition of gout did not require the observation of urate crystals in joint fluid. Although the presence of a tophus or urate crystals in joint fluid would be diagnostic of gout,[13] the sensitivity of these findings is too low, especially in a population-based study, because arthrocentesis is performed infrequently.

In our study, fulfillment of 6 of the 11 American College of Rheumatology survey criteria for gout[13] showed a high degree of concordance with reviews of the medical records, and the incidence of gout fulfilling these criteria in our cohort agreed closely with the estimated incidence among male physicians in the Johns Hopkins Precursor Study[1] (1.5 and 1.7 per 1000 person-years, respectively). Furthermore, when we evaluated the effect of various definitions of gout, our findings appeared to be robust, and the magnitude of the associations tended to increase with increasing specificity of the case definition.

Our study was observational; thus, we cannot rule out the possibility that unmeasured factors might contribute to the observed associations. Overall, however, our findings provide prospective evidence that meat consumption and seafood consumption are associated with an increased risk of gout, whereas consumption of dairy products, especially low-fat dairy products, is associated with a substantially reduced risk of gout. In contrast, moderate intake of purine-rich vegetables or protein is not associated with an increased risk of gout.

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