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Fructose-Rich Beverages and the Risk of Gout in Women

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Abstract

Context—Fructose-rich beverages such as sugar-sweetened soda and orange juice can increase serum uric acid levels and thus, the risk of gout, but prospective data on the relation is limited.

Objective—To examine the relation between intake of fructose-rich beverages and fructose and the risk of incident gout among women.

Design—Prospective cohort study over 22 years (1984-2006)

Setting—The Nurses' Health Study

Participants—78,906 women with no history of gout at baseline who provided information on intake of beverages and fructose through validated food-frequency questionnaires.

Main outcome measures—Incident cases of gout that met the American College of Rheumatology survey criteria for gout.

Results—During 22 years of follow-up, we documented 778 confirmed incident cases of gout. Increasing intake of sugar-sweetened soda was independently associated with increasing risk of gout. Compared with consumption of <1 serving/month, the multivariate relative risk of gout was 1.74 (95% confidence interval [CI], 1.19 to 2.25) for 1 serving/day and 2.39 (1.34 to 4.26) for ≥ 2 serving/day (P for trend<0.001). The corresponding RRs for orange juice were 1.41 (95% CI, 1.03 to 1.93) and 2.42 (95% CI, 1.27 to 4.63) (P for trend=0.02). The absolute risk differences corresponding to these RRs were 36 and 68 cases per 100,000 person-years for sugar-sweetened soda and 14 and 47 per 100,000 cases person-years for orange juice. Diet soft drinks were not associated with the risk of gout (P for trend=0.27). Compared with the lowest quintile of fructose

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intake, the multivariate relative risk of gout in the top quintile was 1.62 (95% CI, 1.20 to 2.19) (P for trend=0.004) (risk difference of cases 28 per 100,000 person-years).

Conclusion—These prospective data suggest that consumption of fructose-rich beverages increases the risk of incident gout among women, although their contribution to the risk of gout in the population is likely modest given the low incidence rate among women.

Keywords

Gout; soda; juice; fructose; prospective; cohort; women

INTRODUCTION

Gout is a common and excruciatingly painful inflammatory arthritis. Emerging evidence suggests that gout is strongly associated with the metabolic syndrome and may lead to myocardial infarction,[1, 2], diabetes, and premature death.[2] Gout has historically been considered a male disease,[3, 4] but growing evidence suggests a substantial disease burden of gout among elderly women (up to 5% of women > 70 years old) whose representation in the general population has grown with increasing longevity.[5, 6]

The increasing disease burden of gout over last few decades in the US (e.g. annual incidence of 16/100,000 in 1977 vs 42/100,000 in 1996[6]) coincided with a substantial increase in soft drink and fructose consumption.[7] Although sugar-sweetened beverages contain low levels of purine (i.e. the precursor of uric acid), they contain large amounts of fructose, which is the only carbohydrate known to increase uric acid levels.[8-10] In humans, acute oral or intravenous administration of fructose results in a rapid increase in serum uric acid via accentuated degradation of purine nucleotides and increased purine synthesis.[11, 12] Furthermore, this urate-raising effect was found to be exaggerated in individuals with hyperuricemia[9] or a history of gout.[8] A recent prospective study of men found that sugar-sweetened sodas, fruit juices, and fructose were associated with a substantially increased risk of gout among men.[13] To date, no other cohort study has investigated this relation. Furthermore, because animal experiments [14] and two National Health and Nutrition Examination Survey (NHANES) studies have suggested that the magnitude of urate-raising effect of sugar-sweetened soft drinks may be weaker among women than among men,[15] extrapolation of data on this potentially important risk factor for gout from men to women should be done with caution.

To address these issues, we prospectively evaluated the relation between intake of fructose-rich beverages and fructose and the incidence of gout in a cohort of 78,906 women with no history of gout.

METHODS

Study Population

The Nurses' Health Study (NHS) was established in 1976 when 121,700 female registered nurses who were predominantly white (95%) and were 30 and 55 years of age living in 11 states completed a mailed questionnaire providing detailed information about their medical history, lifestyles, and other risk factors. The information is updated every 2 years to identify newly diagnosed diseases and the follow-up rate exceeds 90%. In 1980, a food frequency questionnaire was added and in 1984, participants were asked about intake of sodas in detail. For our analysis, we excluded women with a previous diagnosis of gout before 1984 or participants who did not complete more than 10 items on the 1984 dietary questionnaire, leaving 78,906 eligible women who were followed from 1984 to 2006. 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.

Assessment of Beverages, Fructose, and Other Dietary Intake

To assess dietary intake including soft drink intake, we used a validated food-frequency questionnaire that inquired about the average use of foods and beverages during the previous year.[4, 16-19] The dietary questionnaires were completed in 1980, 1984, 1986, 1990, 1994, 1998, and 2002. Starting from 1984, participants were asked how often on average during the previous year they had consumed sugar-sweetened soda ("Coke, Pepsi, or other cola with sugar," "caffeine-free Coke, Pepsi, or other cola with sugar," and "other carbonated beverages with sugar") and diet sodas ("low-calorie cola with caffeine," "low-calorie caffeine-free cola," and "other low-calorie beverages"). Different types of fruits and fruit juices (including orange juice, apple juice, grape fruit juice, tomato juice and other fruit juices) were also assessed. We summed the intake of single items to create a total of sugar-sweetened soda, diet soda, and fruit juice consumption. The participants could choose from 9 frequency responses (never, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 5 per day, and 6 or more per day). Nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion sizes.[17] Values for nutrients were derived from the US Department of Agriculture sources[20] and supplemented with information from manufacturers. Half of the disaccharide sucrose is fructose, which is split from sucrose in the small intestine.[21] Therefore, total fructose intake is equal to the intake of free fructose plus half the intake of sucrose.[21] Food intake assessed by this dietary questionnaire has been validated previously against two 1-week diet records in this cohort.[16, 22] Specifically, the correlation coefficients between questionnaire and multiple dietary records were 0.84 for cola-type soft drinks (sugar-sweetened and diet combined), 0.36 for other carbonated soft drinks, 0.84 for orange juice, and 0.56 for fruit punch in this cohort and were 0.84 for sugar-sweetened sweetened cola, 0.55 for other sugar-sweetened sodas, 0.73 for diet cola, 0.74 for other diet sodas, 0.78 for orange juice, 0.77 for apple juice, 0.75 for grapefruit juice, and 0.89 for other fruit juices in the Health Professionals Follow-up Study.[22, 23]

Assessment of Non-dietary Factors

At baseline, and every two years thereafter, the participants provided information on weight, regular use of medications (including diuretics), and medical conditions (including hypertension).[19] These data have been found to be reliable in validation studies and many studies have demonstrated the ability to predict risk of relevant future diseases. Body-mass index was calculated by dividing the updated weight in kilograms by the square of the baseline height in meters.

Ascertainment of Incident Cases of Gout

We ascertained incident cases of gout using the American College of Rheumatology survey gout criteria, as previously described.[4, 18, 19] Briefly, in 1982, 1984, 1986, 1988, 2002 and thereafter, biennial questionnaires asked whether participants had received a physician diagnosis of gout and, if so, the date of first occurrence. Starting in 2001, we mailed a supplementary questionnaire to those participants with self-reported incident gout diagnosed in 1980 onward, to confirm the report and to ascertain the American College of Rheumatology survey gout criteria.[4, 18, 19, 24] The primary end point in this study was an incident case of gout that met 6 or more of the 11 gout criteria (i.e., more than one attack of acute arthritis; maximum inflammation developed within one day; oligoarthritis attack; redness observed over joints; painful or swollen first metatarsophalangeal joint; unilateral first metatarsophalangeal joint attack; unilateral tarsal joint attack; tophus; hyperuricemia; asymmetric swelling within a joint; complete termination of an attack).[4, 18, 19, 24] The

overall response rate for the supplementary gout questionnaire was 81%, similar to that observed in the Health Professionals Follow-up Study.[4] Two board-certified rheumatologists reviewed the medical records from a consecutive sample of 56 women from this cohort in 2001. The concordance between the diagnosis of gout following the American College of Rheumatology survey criteria[24] and our review of the relevant medical records was 91% (51/56), similar to that found in men in the Health Professionals Follow-up Study.[4]

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the 1984 questionnaire (i.e. the first questionnaire with detailed intake information on soft drinks and fruit juices) to the date of diagnosis of gout, death from any cause, or the end of the study period (June 2006), whichever came first. Women who died or had reported having gout on previous questionnaires were excluded from subsequent follow-up.

To represent long-term average intakes of fructose and fructose-rich beverages by individual participants, we used cumulative average intakes based on the dietary information from baseline to the latest point of follow-up as a time-varying variable.[4, 18, 19, 25, 26] For example, the incidence of gout from 1984 through 1986 was related to the intake reported on the 1984 questionnaire, and incidence from 1986 through 1990 was related to the average of intakes reported on the 1984 and 1986 questionnaires, and incidence from 1990 through 1994 was related to the average of intakes reported on the 1984, 1986, and 1990 questionnaires. Secondary analyses using only information from the baseline questionnaire (1984) yielded similar results.

We used Cox proportional hazards modeling (PROC PHREG) to estimate the relative risk (RR) for incident gout in all multivariate analyses (Version 9.1, SAS Institute Inc, Cary, NC). For these analyses, soda and juice consumption was categorized into 6 groups: <1 per month, 1 per month to 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day and 2 or more per day. Free fructose and total fructose intake were categorized into quintiles for percentage of energy (nutrient density[27]). Multivariate models for soda and juice consumption were adjusted for the following variables in a time-varying manner: age (continuous), total energy intake (continuous), alcohol (none, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, 15.0 to 29.9, 30.0 to 49.9, and ≥ 50.0 g/day), body-mass index (<21, 21-22.9, 23-24.9, 25-29.9, 30-34.9, and ≥35 kg/m^2), menopause status (yes or no), use of hormonal replacement (yes or no), use of diuretics (thiazide or furosemide) (yes or no), history of hypertension (yes or no), coffee intake (0, <1, 1 to 3 and ≥4 cups per day), and daily mean intake of meats, seafood, dairy foods, and total vitamin C (quintiles).[4, 18, 19] Similarly, we evaluated the association with fruit intake (individual fruits and total fruit) while adjusting for the same covariates and simultaneously for intake of soda and juices. In multivariate nutrient-density models for fructose intake,[27] we simultaneously included energy intake, the percentages of energy derived from protein and carbohydrate (or non-fructose carbohydrate), intake of vitamin C and alcohol, and other non-dietary variables. The coefficients from these models can be interpreted as the estimated effect of substituting a specific percentage of energy from fructose for the same percentage of energy from non-fructose carbohydrates (or fat).[25, 27] For example, to estimate the effect of substituting fructose for the equivalent energy from fat, the model included percent of energy from non-fructose carbohydrate and total protein. Trends in gout risk across categories of soda, juice or fructose intake were assessed in Cox proportional hazards models by using the median values of intake for each category to minimize the influence of outliers. We conducted analyses stratified by body mass index (< 30 kg/m^2 vs ≥ 30 kg/m^2), by alcohol use (yes or no), and low-fat dairy intake (≤ 0.57 servings/day [median value] vs > 0.57 servings/day) 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 intake and the stratifying variable and the interaction

terms with a reduced model with only the main effects. For all RRs, we calculated 95% confidence intervals (CIs). All P values are two-sided.

RESULTS

Baseline Characteristics

During 22 years of follow-up, we documented 778 newly diagnosed cases meeting American College of Rheumatology criteria for gout (638 [82%] with podagra, 576 [74%] hyperuricemia, 342 [44%] tarsal joint involvement, and 109 [14%] tophus). The characteristics of the cohort according to consumption levels of sugar-sweetened soda and free fructose at baseline are shown in Table 1. With increasing sugar-sweetened soda consumption, intake of fructose, sucrose, meat, high-fat dairy foods, and coffee tended to increase, but mean age and intake of low-fat dairy and fruit tended to decrease (Table 1). Alcohol intake was lower in the middle categories of sugar-sweetened soda consumption. With increasing free fructose consumption, body mass index and intake of alcohol, coffee, meat, and high-fat dairy foods tended to decrease, but intake of fruit and vitamin C tended to increase (Table 1).

Sugar-sweetened Soda Intake and Incident Gout

Increasing intake of sugar-sweetened soda was associated with increasing risk of gout (P for trend <0.001) (Table 2). Compared with consumption of less than one serving per month, the multivariate relative risk (RR) of gout was 1.74 (95% CI, 1.19 to 2.25) for 1 serving /day and 2.39 (1.34 to 4.26) for ≥2 servings/day (P for trend<0.001). The corresponding absolute risk differences were 36 and 68 cases per 100,000 person years. In contrast, diet soda intake was not associated with the risk of gout (P for trend=0.27).

Fruit Juice Intake and Incident Gout

Orange juice intake was associated with the risk of gout (Table 3). Of note, orange juice was by far the highest contributor of free fructose intake (17%) among juices in this cohort followed by apple juice 2.9% and other juices 2.6% at the mid-point of the follow-up. Compared with women who consumed less than a glass (6 oz) of orange juice per month, the multivariate RR for gout was 1.41 (95% CI, 1.03 to 1.93) for 1 serving /day and 2.42 (95% CI, 1.27 to 4.63) for ≥ 2 servings/day (P for trend=0.02) (Table 3). The corresponding absolute risk differences were 14 and 47 cases per 100,000 person years. There was no significant trend between intake of other juices and the risk of gout (multivariate P =0.11). No other individual fructose-rich food item (e.g. apples or oranges) was significantly associated with the risk of gout. Similarly, total fruit intake was not associated with the risk of gout (P for trend = 0.8).

Fructose Intake and Incident Gout

Increasing fructose intake was associated with increasing risk of gout (Table 4). Compared with women in the lowest quintile of free fructose, the multivariate relative risk (RR) of gout in the top quintile was 1.43 (95% CI, 1.09 to 1.88) (P for trend=0.02) when substituting fructose for the equivalent energy from fat. The corresponding RR increased after we adjusted for total carbohydrate intake to reflect the substitution effect of fructose for other types of carbohydrates (multivariate RR= 1.62; 95% CI, 1.20 to 2.19) (P for trend=0.004). The corresponding absolute risk difference was 28 cases per 100,000 person years. Similar trends were observed with intake of total fructose (i.e. free fructose plus half the intake of sucrose), although the magnitudes of associations tended to be smaller (Table 4). When we examined fructose intake as a continuous variable, the multivariate RR for a 5% increment in energy from free fructose, as compared with equivalent energy intake from other types of

carbohydrates, was 1.86 (95% CI,1.44 to 2.40) and the corresponding RR for total fructose was 1.47 (95% CI,1.20 to 1.80).

Risk According to Body Mass Index, Alcohol Use, and Dairy Intake

We also conducted stratified analyses to evaluate whether the association between sweetened soda and fructose consumption and the risk of gout varied according to body mass index, alcohol use, and dairy intake. Relative risks from these stratified analyses consistently suggested associations similar to those from main analyses, and there was no significant interaction with these variables (all P values for interaction ≥ 0.14) (Table 5).

DISCUSSION

In this large prospective study of women, we found that the risk of incident gout increased with increasing intake of sugar sweetened soda. In contrast, diet soda intake was not associated with the risk of incident gout. Women who consumed one serving of sugar-sweetened soda had a 74% higher risk of incident gout and women who consumed two servings or more had 2.4 times increased risk. Similarly, women who consumed two servings or more of orange juice showed a 2.4 times increased risk of incident gout. Furthermore, the risk of gout was significantly increased with increasing intake of fructose, the main suspected ingredient behind the increased risk. These associations were independent of risk factors for gout such as body mass index, age, hypertension, menopause, diuretic use, alcohol, and intake of dairy, meat, seafood, coffee, and vitamin C. These findings confirm the associations observed in the recent prospective study of men[13] and provide the first prospective evidence among women that fructose and fructose-rich beverages are important risk factors to be considered in the primary prevention of gout.

While the relative risks of gout associated with fructose-rich beverages among women were substantial, the corresponding absolute risk differences were modest given the low incidence rate of gout among women. For example, the magnitudes of relative risks associated with sugar-sweetened sodas or orange juice were comparable to those associated with alcoholic beverages (RR for ≥ 2 servings per day, 1.60 for liquor vs 2.5 for beer) among men.[18] However, the corresponding absolute risk differences were less than one case per 1,000 person years. While the relative risk data suggest a substantial biologic link, the risk difference data suggest that their contribution to the risk of gout in the population is likely modest given the low incidence rate among women. Because the urate-raising effect of fructose is greatest in patients with gout and hyperuricemia,[8-10, 28] our findings may be even more relevant in those patients.

Previous animal experiments[14, 29, 30] and NHANES studies[15, 31] suggest that the magnitude of urate-raising effect of fructose or sugar-sweetened sodas may be weaker among females than among males. For example, an analysis based on NHANES III found that the increase in serum uric acid level associated with sugar-sweetened soda intake was significantly larger among men than women, although the association among women was still statistically significant.[15] This potential gender difference has been thought be due to sex hormones because studies in rats have shown that female sex hormones protect against the development of hyperinsulinemia associated with high fructose intake.[14, 29, 30] Because hyperinsulinemia decreases renal excretion of urate and correlates with higher serum uric acid levels,[32] the protective effect of estrogen may lead to an attenuated impact of fructose on serum uric acid levels. Nevertheless, as gout among women occurs predominantly after menopause, when the female hormonal influence substantially declines, the gender difference of the fructose effect on the risk of gout may be less apparent than that on serum uric acid levels observed in the general population that included premenopausal women.

Fructose induces uric acid production by increasing ATP degradation to AMP, a uric acid precursor (Figure 1).[12, 28, 33] Fructose phosphorylation in the liver uses ATP, and the accompanying phosphate depletion limits regeneration of ATP from ADP, which in turn serves as substrate for the catabolic pathway to uric acid formation.[34] Thus, within minutes after fructose infusion, plasma (and later urinary) uric acid concentrations are increased.[28] In conjunction with purine nucleotide depletion, rates of purine synthesis *de novo* are accelerated, thus potentiating uric acid production.[11] In contrast, glucose and other simple sugars do not have the same effect.[35] Furthermore, fructose could indirectly increase serum uric acid level and the risk of gout by increasing insulin resistance and circulating insulin levels.[36] Experimental studies in animal models and from short-term feeding trials among humans suggest that higher fructose intake contributes to insulin resistance, impaired glucose tolerance, and hyperinsulinemia.[23, 37, 38] In contrast, glucose intake had no similar adverse effects.[38]

Our findings have practical implications for the prevention of gout in women. As conventional dietary recommendations for gout have focused on restriction of purine intake, lowpurine diets are often high in carbohydrates including fructose-rich foods.[39] Our data provide prospective evidence that fructose poses an increased risk for gout among women, thus supporting the importance of reducing fructose intake. Interestingly, this recommendation is consistent with Osler's diets prescription as a means to prevent gout over 100 years ago, as reflected in his 1893 text[40] - “The sugar should be reduced to a minimum.”[35] Furthermore, because fructose intake is associated with increased serum insulin levels, insulin resistance, and increased adiposity,[23, 37, 38] the overall negative health impact from fructose is expected to be larger in women with a history of gout, 70% of whom suffer from the metabolic syndrome.[32]

Several strengths and potential limitations of our study deserve comment. Our study had a large number of cases of confirmed female incident gout and dietary data including beverage and fructose intake information were prospectively collected and validated. While there were a relatively large number of cases in the highest fructose quintile groups, the numbers in the top intake categories of fructose-rich beverage items were small. Nevertheless, it was reassuring that the next top categories also showed significant positive associations with a dose-response relationship. Potential biased recall of diet was avoided in this study because the intake data were collected before the diagnosis of gout. Because dietary consumption was self-reported by questionnaire, some misclassification of exposure is inevitable. However, self-reported dietary consumption has been extensively validated in sub-samples of this cohort,[16, 22] and any remaining misclassification would have likely biased the results toward the null. The use of repeated dietary assessments in the analyses not only accounts for changes in dietary consumption over time but also decreases measurement error. The validity of gout ascertainment in this cohort and our companion male cohort[4, 18, 19] has been documented by the high-degree of concordance with medical record review.

The restriction to registered nurses in our cohort is both a strength and a limitation. The cohort of well-educated women minimizes potential for confounding associated with socioeconomic status, and we were able to obtain high quality data with minimal loss to follow-up. Although the absolute rates of gout and related measures as well as distribution of fructose intake may not be representative of a random sample of US women, the biological effects of fructose intake on gout (as reflected in relative risks) should be similar. Our findings are most directly generalizable to middle-age and elderly white women with no history of gout. Since the prevalence of risk factors for gout and its incidence tend to be higher in the general population and among African Americans, the magnitude of the absolute risk increase associated with these beverages might be greater than the increase we observed.

In conclusion, our findings provide prospective evidence that consumption of sugar-sweetened sodas, orange juice, and fructose is associated with an increased risk of incident gout among women, although their contribution to the risk of gout in the population is likely modest given the low incidence rate among women. In contrast, diet soda intake is not associated with the risk of gout. Physicians should be aware of the impact of these beverages on the risk of gout, a common and excruciatingly painful arthritis.

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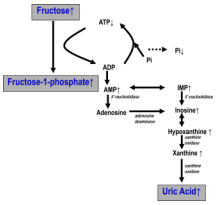

Figure 1. Mechanism of Fructose-Induced Hyperuricemia

Fructose induces uric acid production by increasing ATP degradation to AMP, a uric acid precursor. The phosphorylation of fructose to fructose-l-phosphate causes ATP to be degraded to ADP. Fructose-l- phosphate traps inorganic phosphate, and ADP is converted back to ATP by using inorganic phosphate. The net result is reduced levels of intracellular ATP and inorganic phosphate (Pi) combined with a buildup of AMP, which also leads to increased IMP concentration. Elevated AMP and IMP levels activate the catabolic pathways leading to increased synthesis of uric acid, accounting for hyperuricemia. (See text for details).

Table 1

Baseline Characteristics According to Sugar-Sweetened Soda and Fructose Consumption (1984)*

Variable	Sugar-Sweetened Soda Intake (servings/day)						Free Fructose Intake (% of energy, range)				
	<1/mo	1/mo-1/wk	2-4/wk	5-6/wk	1/day	≥2/day	Quintile 1 (<3.7)	Quintile 2 (3.71-4.6)	Quintile 3 (4.61-5.45)	Quintile 4 (5.46-6.6)	Quintile 5 (>6.6)
Participants (n)	41974	17880	11766	2737	3039	1510	21712	15229	13424	12778	15763
Age (yr)	51 (7)	51 (7)	49 (7)	48 (7)	48 (7)	47 (7)	50 (7)	50 (7)	51 (7)	51 (7)	51 (7)
Body mass index (kg/m^2)	25.1 (4.6)	24.6 (4.5)	24.8 (4.7)	24.7 (4.9)	24.7 (5.1)	25.3 (5.9)	25.1 (4.8)	25.0 (4.6)	24.9 (4.5)	24.8 (4.5)	24.8 (4.7)
Diuretic use, N (%)	5813 (14)	1916(11)	1105 (9)	270 (10)	307 (10)	45 (10)	2398 (11)	1759 (12)	1632 (12)	1664 (13)	2113 (13)
History of hypertension, N (%)	9796 (23)	3565 (20)	2219 (19)	538 (20)	595 (20)	304 (20)	4342 (20)	3149 (21)	2857 (21)	2869 (22)	3800 (24)
Menopause, N (%)	21420 (52)	8532 (49)	4672 (40)	1014 (38)	1138 (38)	466 (31)	9292 (44)	6981 (47)	6462 (49)	6459 (52)	8048 (52)
Postmenopausal hormone use, N (%**)	5155 (24)	2027(24)	1026(22)	270 (27)	257 (23)	118 (25)	2171 (23)	1694 (24)	1616 (25)	1569 (24)	1803 (22)
Alcohol intake (g/d)	7.3 (11.7)	6.5 (10.5)	6.1 (10.1)	6.4 (10.5)	6.3 (10.9)	6.7 (12.9)	10.1 (14.9)	7.0 (10.6)	6.1 (9.3)	5.3 (8.4)	4.2 (7.6)
Total meat intake (servings/day)	1.4 (0.7)	1.5 (0.7)	1.6 (0.7)	1.7 (0.7)	1.7 (0.8)	1.7 (0.8)	1.7 (0.8)	1.5 (0.7)	1.5 (0.7)	1.4 (0.7)	1.2 (0.7)
Seafood intake (servings/day)	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.2 (0.2)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)
Low-fat dairy foods intake (servings/day)	1.0 (1.0)	0.9 (0.9)	0.8 (0.9)	0.7 (0.9)	0.7 (0.8)	0.5 (0.8)	0.8 (0.9)	1.0 (1.0)	1.0 (1.0)	1.0 (1.0)	0.9 (0.9)
High-fat dairy foods intake (servings/day)	1.3 (1.4)	1.5(1.4)	1.7(1.5)	1.8(1.6)	1.8(1.5)	1.8(1.7)	1.6(1.6)	1.5(1.4)	1.4(1.3)	1.4(1.3)	1.2(1.2)
Coffee intake (servings/day)	1.8 (1.8)	1.8(1.8)	1.8(1.7)	1.6(1.7)	1.6(1.7)	1.3(1.7)	2.1(1.9)	1.9(1.8)	1.7(1.7)	1.6(1.6)	1.4(1.6)
Total fruit intake (servings/day)	1.5 (1.1)	1.4 (1.0)	1.3 (0.9)	1.2 (0.9)	1.1 (0.9)	0.9 (0.9)	0.8 (0.5)	1.2 (0.7)	1.5 (0.8)	1.8 (1.0)	2.1 (1.4)
Total vitamin C intake (mg/day)	376(423)	316(348)	281(308)	266(295)	251(285)	222(270)	260(353)	305(345)	341(371)	376(396)	438(427)
Free fructose (% of energy)	4.7 (2.1)	4.8(1.9)	5.4(1.8)	6.4(1.8)	7.2(2.0)	11.2(3.4)	2.8(0.7)	4.2(0.3)	5.0(0.2)	6.0(0.3)	8.5(2.1)
Sucrose (% of energy)	8.3 (3.2)	9.3(3.2)	10.2(3.0)	11.1(3.2)	11.4(3.4)	12.9(4.1)	7.6(3.6)	8.7(2.9)	9.2(2.8)	9.8(2.8)	11.1(3.2)

Total meat included main or mixed dish of beef/pork/lamb, processed meat, (sausage/salami/bologna), bacon, hot dogs, hamburgers, poultry (chicken or turkey), chicken liver, and beef liver

Seafood included tuna, dark fish, other fish, and shrimp/lobster/scallops.

Low-fat dairy foods included skim/low-fat milk, sherbet, yogurt, and cottage/ricotta cheese.

High-fat dairy foods included whole milk, cream, butter, sour cream, ice cream, cream cheese, and other cheese.

Total fruit included oranges; apples or pears; bananas; strawberries; grapes or raisins; cantaloupe; watermelon; blueberries; grapefruit; prunes; and peaches, apricots or plums.

Total vitamin C included dietary vitamin C and supplemental vitamin C.

% of Energy = percentage of energy from the corresponding nutrient

* Data presented are means (standard deviations) unless otherwise indicated. Data, except age, were directly standardized to the age distribution of the entire cohort.

** Percentage among postmenopausal women only.

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Table 2

Relative Risk of Incident Gout According to Soda Consumption

Variable	Frequency of Intake (servings, 12oz)						P Value for Trend
Sugar Sweetened Sodas	*<1/mo*	*1/mo-1/wk*	*2-4/wk*	*5-6/wk*	*1/day*	*≥2/day*	
No. of cases	383	187	129	35	31	13	–
Person-years	789469	387106	282172	66390	47634	17379	–
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.12 (0.94, 1.33)	1.07 (0.88, 1.31)	1.42 (1.00, 2.02)	2.09 (1.44, 3.02)	3.05 (1.74, 5.35)	<0.001
Multivariate RR (95% CI)*	1.0 (referent)	1.09 (0.91, 1.30)	0.98 (0.79, 1.20)	1.25 (0.88, 1.79)	1.74 (1.19, 2.55)	2.39 (1.34, 4.26)	<0.001
Diet Sodas	*<1/mo*	*1/mo-1/wk*	*2-4/wk*	*5-6/wk*	*1/day*	*≥2/day*	
No. of cases	166	113	183	125	124	67	–
Person-years	477343	236365	349267	190142	212000	125035	–
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.12 (0.88, 1.42)	1.01 (0.81, 1.25)	1.19 (0.94, 1.51)	1.18 (0.93, 1.50)	1.22 (0.91, 1.63)	0.09
Multivariate RR(95% CI)*	1.0 (referent)	1.15 (0.90, 1.47)	1.05 (0.84, 1.30)	1.24 (0.97, 1.58)	1.18 (0.93, 1.51)	1.18 (0.87, 1.58)	0.27
Sugar Sweetened Cola	*<1/mo*	*1/mo-1/wk*	*2-4/wk*	*5-6/wk*	*≥1/day*	*≥2/day*	
No. of cases	467	173	79	28	20	11	–
Person-years	939926	359293	195219	45889	34622	15202	–
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.11 (0.93, 1.32)	0.85 (0.67, 1.09)	1.48 (1.01, 2.18)	1.67 (1.06, 2.63)	2.68 (1.47, 4.92)	0.001
Multivariate RR*	1.0 (referent)	1.00 (0.83, 1.21)	0.71 (0.55, 0.91)	1.16 (0.78, 1.73)	1.29 (0.81, 2.05)	1.97 (1.05, 3.67)	0.14
Other Sodas	*<1/mo*	*1/mo-1/wk*	*2-4/wk*	*≥5-6/wk*			
No. of cases	518	197	49	14			–
Person-years	1072271	412787	85493	19600			–
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.12 (0.95, 1.32)	1.21 (0.90, 1.63)	1.76 (1.03, 2.99)			0.01
Multivariate RR(95% CI)*	1.0 (referent)	1.11 (0.93, 1.34)	1.19 (0.87, 1.63)	1.55 (0.89, 2.69)			0.07

RR = relative risk; CI = confidence interval; BMI = body mass index.

Sugar-sweetened sodas included “Coke, Pepsi, or other cola with sugar,” “caffeine-free Coke, Pepsi, or other cola with sugar,” and “other carbonated beverages with sugar”.

Diet sodas included “low-calorie cola with caffeine,” “low-calorie caffeine-free cola,” and “other low-calorie beverages”.

Sugar-sweetened Cola included “Coke, Pepsi, or other cola with sugar” and “caffeine-free Coke, Pepsi, or other cola with sugar”.

Other sodas refer to “other carbonated beverages with sugar”.

Age-BMI-alcohol adjusted models were also adjusted for total energy.

* Adjusted for age, total energy intake, body mass index, menopause status, use of hormonal replacement, diuretic use, history of hypertension, and alcohol, total meats, seafood, dairy products, total vitamin C, coffee, and the beverages presented in this table.

Table 3

Relative Risk of Incident Gout According to Intake of Orange Juice and Other Fruit Juices

Variable	Frequency of Intake						P Value for Trend
Orange Juice (small glass, 6oz)	*<1/mo*	*1/mo-1/wk*	*2-4/wk*	*5-6/wk*	*1/day*	*≥2/day*	
No. of cases	71	145	277	171	103	11	–
Person-years	213647	346219	506760	268532	236894	18099	–
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.33 (1.00, 1.77)	1.39 (1.07, 1.81)	1.59 (1.20, 2.10)	1.48 (1.09, 2.01)	2.52 (1.33, 4.77)	0.008
Multivariate RR (95% CI)**	1.0 (referent)	1.27 (0.95, 1.69)	1.30 (0.99, 1.70)	1.50 (1.12, 2.00)	1.41 (1.03, 1.93)	2.42 (1.27, 4.63)	0.02
Other Fruit Juices (small glass, 6oz)	*<1/mo*	*1/mo-1/wk*	*2-4/wk*	*5-6/wk*	*1/day*	*≥2/day*	
No. of cases	35	119	360	153	100	11	–
Person-years	120428	294862	678629	280509	183424	32299	–
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.30 (0.89, 1.89)	1.49 (1.05, 2.11)	1.47 (1.01, 2.13)	1.60 (1.09, 2.37)	1.08 (0.54, 2.13)	0.21
Multivariate RR(95% CI)**	1.0 (referent)	1.28 (0.88, 1.88)	1.50 (1.05, 2.14)	1.54 (1.06, 2.26)	1.67 (1.12, 2.49)	1.14 (0.57, 2.27)	0.11

RR = relative risk; CI = confidence interval; BMI = body mass index.

Age-BMI-alcohol adjusted models were also adjusted for total energy.

*Fruit juice includes orange juice, apple juice, grape fruit juice, tomato juice and other fruit juices.

** Adjusted for age, total energy intake, body mass index, diuretic use, use of hormonal replacement, history of hypertension, and alcohol, total meats, seafood, dairy products, total vitamin C, coffee, and the beverages presented in this table and table 2.

Table 4

Relative Risk (RR) of Incident Gout According to Fructose Intake

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P Value for Trend
Free Fructose (% of energy)	<3.7	3.71-4.6	4.61-5.45	5.46-6.6	>6.6	
Cases	132	181	150	160	155	
Person-years	294841	320317	327349	329706	317937	
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.13 (0.90, 1.42)	0.91 (0.72, 1.16)	0.99 (0.78, 1.26)	1.14 (0.90, 1.45)	0.52
Multivariate RR (95% CI)*	1.0 (referent)	1.25 (0.99, 1.58)	1.07 (0.83, 1.37)	1.21 (0.93, 1.56)	1.43 (1.09, 1.88)	0.02
Multivariate RR (95% CI)**	1.0 (referent)	1.31 (1.03, 1.66)	1.15 (0.89, 1.50)	1.34 (1.01, 1.76)	1.62 (1.20, 2.19)	0.004
Total Fructose† (% of energy)	<7.5	7.51-8.97	8.97-10.2	10.3-11.9	>11.9	
Cases	154	172	149	163	140	
Person-years	300229	320963	326022	327559	3153653	
Age-BMI-alcohol adjusted RR (95% CI)	1.0 (referent)	1.01 (0.81, 1.27)	0.87 (0.69, 1.10)	0.98 (0.78, 1.24)	0.98 (0.76, 1.25)	0.80
Multivariate RR (95% CI)*	1.0 (referent)	1.14 (0.91, 1.44)	1.02 (0.80, 1.31)	1.18 (0.91, 1.53)	1.18 (0.89, 1.56)	0.27
Multivariate RR (95% CI)**	1.0 (referent)	1.23 (0.97, 1.57)	1.17 (0.90, 1.54)	1.41 (1.06, 1.88)	1.44 (1.04, 2.00)	0.03

RR = relative risk; CI = confidence interval; BMI = body mass index

Age-BMI-alcohol adjusted models were also adjusted for total energy.

*Adjusted for age, total energy intake, body mass index, menopause status, use of hormonal replacement, diuretic use, history of hypertension, intake of alcohol, total vitamin C, caffeine, and percent of energy from non-fructose carbohydrate and total protein in order to estimate effects of substituting fructose for the equivalent energy from fat.

**Adjusted for age, total energy intake, body mass index, menopause status, use of hormonal replacement, diuretic use, history of hypertension, intake of alcohol and total vitamin C, caffeine, and percentage of energy from total carbohydrate to estimate effects of fructose compared to equivalent energy from other carbohydrates.

†Free fructose + sucrose/2

Table 5

Multivariate Relative Risk of Incident Gout According to Sugar-Sweetened Soda Intake and Quintiles of Free Fructose Intake in Subgroups by Body Mass Index, Alcohol Intake, and Low-Fat Dairy Intake.

Variable	No of Cases	Sugar-Sweetened Soda Intake, RR (95% CI)*					Trend	Interaction
		<1/mo	1/mo-1/wk	2-4/wk	5-6/wk	≥1/day		
BMI								0.20
<30 kg/m^2	396	1.0 (referent)	0.98 (0.77, 1.26)	0.93 (0.70, 1.24)	1.13 (0.67, 1.90)	1.45 (0.86, 2.44)	0.10	
≥30 kg/m^2	329	2.14 (1.71, 2.67)	2.61 (1.99, 3.44)	2.50 (1.84, 3.39)	3.36 (2.02, 5.59)	6.44 (4.17, 9.94)	<0.001	
Alcohol use								0.59
No use	319	1.0 (referent)	1.05 (0.79, 1.40)	1.14 (0.84, 1.55)	1.51 (0.93, 2.47)	2.12 (1.33, 3.39)	0.04	
Use	406	1.34 (1.08, 1.67)	1.42 (1.09, 1.85)	1.16 (0.85, 1.59)	1.38 (0.79, 2.41)	2.62 (1.61, 4.28)	<0.001	
Low-fat dairy intake								0.83
<1.5 servings/day	290	1.0 (referent)	1.01 (0.75, 1.37)	0.92 (0.66, 1.28)	1.17 (0.70, 1.95)	1.95 (1.25, 3.03)	<0.001	
≥1.5 servings/day	435	0.68 (0.55, 0.86)	0.78 (0.59, 1.02)	0.78 (0.57, 1.06)	1.03 (0.61, 1.76)	1.63 (0.95, 2.77)	0.03	

		Free Fructose Intake, RR (95% CI)**						
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
BMI								0.14
<30 kg/m^2	396	1.0 (referent)	1.25 (0.90, 1.75)	1.31 (0.93, 1.84)	1.17 (0.81, 1.69)	1.50 (1.02, 2.20)	0.03	
≥30 kg/m^2	329	2.53 (1.77, 3.62)	3.00 (2.12, 4.25)	2.31 (1.56, 3.40)	3.59 (2.47, 5.22)	4.49 (3.01, 6.69)	0.04	
Alcohol use								0.59
No use	319	1.0 (referent)	1.29 (0.86, 1.94)	1.00 (0.65, 1.54)	1.39 (0.92, 2.11)	1.65 (1.07, 2.53)	0.09	
Use	406	2.14 (1.36, 3.37)	2.52 (1.60, 3.99)	2.58 (1.61, 4.14)	2.55 (1.56, 4.17)	3.42 (2.05, 5.72)	0.04	
Low-fat dairy intake		35	119	–	360	153		0.91
<1.5 servings/day	290	1.0 (referent)	1.19 (0.84, 1.69)	1.05 (0.71, 1.55)	1.12 (0.75, 1.68)	1.59 (1.07, 2.38)	0.02	
≥1.5 servings/day	435	0.71 (0.50, 1.02)	0.90 (0.64, 1.27)	0.83 (0.58, 1.19)	0.98 (0.68, 1.41)	1.12 (0.75, 1.67)	0.06	

RR = relative risk; CI = confidence interval; BMI = body mass index.

* Relative risks were adjusted for the same covariates included in the multivariate models of Table 2, except for subgroup variables themselves.

** Relative risks were adjusted for the same covariates included in the multivariate models of Table 3, except for subgroup variables themselves.