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Coffee Consumption and Risk of Incident Gout in Men

A Prospective Study

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Objective. **Coffee is one of the most widely consumed beverages in the world and may affect the risk of gout via various mechanisms. We prospectively evaluated the relationship between coffee intake and the risk of incident gout in a large cohort of men.**

Methods. **Over a 12-year period, we studied 45,869 men with no history of gout at baseline. Intake of coffee, decaffeinated coffee, tea, and total caffeine was assessed every 4 years through validated questionnaires. We used a supplementary questionnaire to ascertain whether participants met the American College of Rheumatology survey criteria for gout.**

Results. **We documented 757 confirmed incident cases of gout. Increasing coffee intake was inversely associated with the risk of gout. The multivariate relative risks (RRs) for incident gout according to coffee consumption categories (0, <1, 1–3, 4–5, and ≥6 cups per day) were 1.00, 0.97, 0.92, 0.60 (95% confidence interval [95% CI] 0.41–0.87), and 0.41 (95% CI 0.19–0.88), respectively (*P* for trend = 0.009). For decaffeinated coffee, the multivariate RRs according to consumption categories (0, <1, 1–3, and ≥4 cups per day) were 1.00, 0.83, 0.67 (95% CI 0.54–0.82), and 0.73 (95% CI 0.46–1.17), respectively (*P* for trend = 0.002). Total caffeine from all sources and tea intake were not associated with the risk of gout.**

Conclusion. **These prospective data suggest that long-term coffee consumption is associated with a lower risk of incident gout.**

Gout is the most common inflammatory arthritis in adult males (1–4). The overall disease burden of gout remains substantial and may be growing (5). Identifying the risk factors for gout that are modifiable with available measures is an important first step in the prevention and management of this common and excruciatingly painful condition (2–4). Coffee consumption may affect the risk of gout via various mechanisms including reducing serum uric acid levels (6) and influencing insulin resistance (7–14). Coffee is one of the most widely consumed beverages in the world. For example, more than 50% of Americans drink coffee, and the average per capita intake is ~2 cups per day (14,15). Given this widespread use, information about the health effects of coffee are important for public health as well as for an individual to help make an informed choice regarding coffee consumption.

Several potential mechanisms suggest that coffee consumption may affect the risk of gout. Caffeine (1,3,7-trimethyl xanthine) is a methyl xanthine and may be a competitive inhibitor of xanthine oxidase, as demonstrated in rats (16). This potential property of caffeine may exert a protective effect against gout similar to that of allopurinol. Furthermore, caffeine stimulates thermogenesis and increases energy expenditure (17–19), which may facilitate weight management, thus potentially leading to a lower risk of gout. However, in humans, acute administration of caffeine decreases insulin sensitivity and impairs glucose tolerance (7–11), which may lead to an increased risk of hyperuricemia and gout. Because of these complex physiologic effects of caffeine and be-

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cause tolerance to the humoral and hemodynamic effects of caffeine typically develops with long-term use (20), it is difficult to extrapolate findings from short-term metabolic studies to long-term use of caffeine (14).

Components of coffee other than caffeine may affect the risk of gout by influencing insulin resistance and circulating insulin levels (12–14). Higher long-term coffee intake is associated with lower insulin levels (12) and increased insulin sensitivity (21). Furthermore, several studies and a recent meta-analysis consistently found that coffee consumption was inversely associated with the risk of type 2 diabetes (13,14,22,23). Because there is a strong positive relationship between serum insulin resistance and hyperuricemia (5,24–27), and insulin reduces the renal excretion of urate (26,28,29), decreased insulin resistance and insulin levels from coffee consumption may lead to a lower risk of hyperuricemia and gout. Indeed, a Japanese cross-sectional study of 2,240 men showed a significant inverse association between coffee consumption and serum uric acid levels (6). Furthermore, a study of a nationally representative sample of US adults showed that coffee consumption was associated with a lower serum level of uric acid and a lower frequency of hyperuricemia (30). To examine these issues, we prospectively evaluated the relationship between intake of coffee, decaffeinated coffee, tea, and total caffeine and the incidence of gout in a cohort of 45,869 men with no history of gout.

SUBJECTS AND 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 were ages 40–75 years in 1986. The participants returned a mailed questionnaire in 1986 concerning diet, medical history, and medications. Of the 48,642 men who provided complete information on coffee, 2,773 (5.7%) reported a history of gout on the baseline questionnaire. These prevalent cases at baseline were excluded from this analysis.

Assessment of coffee and dietary intake. To assess dietary intake including coffee intake, we used a validated food-frequency questionnaire that inquired about the average use of >130 foods and beverages during the previous year (2–4,31,32). The baseline dietary questionnaire was completed in 1986 and was updated every 4 years. On all questionnaires, participants were asked how often on average during the previous year they had consumed coffee and tea. Consumption of decaffeinated coffee and different types of caffeinated soft drinks was also assessed. We assessed the total intake of caffeine by summing the caffeine content for a specific amount of each food during the previous year (1 cup for coffee or tea, one 12-ounce bottle or can for carbonated beverages, and 1 ounce for chocolate) multiplied by a weight proportional to the frequency of its use. The participants could choose from 9 frequency responses (never, 1–3 per month, 1 per week, 2–4 per week, 5–6 per week, 1 per day, 2–3 per day, 4–5 per day, and ≥6 per day). Using the US Department of Agriculture food composition sources, we estimated that the caffeine content was 137 mg per cup of coffee, 47 mg per cup of tea, 46 mg per bottle or can of cola beverage, and 7 mg per serving of chocolate candy.

Food and nutrient intakes assessed by this dietary questionnaire have been validated previously against two 1-week diet records in this cohort (31,33). Specifically, high correlations were recorded for coffee and other caffeinated beverage intake ($r = 0.93$ for coffee, $r = 0.77$ for tea, and $r = 0.84$ for cola). Other relevant dietary data (i.e., intake of meats, seafood, purine-rich vegetables, dairy foods, alcohol, and total vitamin C) have been similarly validated, as previously described in detail (2,3,33,34).

Assessment of nondietary factors. At baseline and every 2 years thereafter, the participants provided information on weight, regular use of medications (including diuretics), and medical conditions (including self-reported physician-diagnosed chronic renal failure and hypertension) (4). Body mass index (BMI) was calculated by dividing the updated weight in kilograms by the square of the baseline height in meters. The followup rate for this cohort was >90% during the study period.

Ascertainment of incident cases of gout. We ascertained incident cases of gout by the American College of Rheumatology (ACR) survey gout criteria, as previously described (2–4). Briefly, on each biennial questionnaire, participants indicated whether they had received a physician diagnosis of gout. To those participants with self-reported incident gout diagnosed in 1986 onward, we mailed a supplementary questionnaire to confirm the report and to ascertain the fulfillment of the ACR survey gout criteria (2–4,35). The primary end point in this study was an incident case of gout that met ≥6 of the 11 gout criteria (2–4,35). 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 having gout. The concordance rate of confirming the report of gout between the gout survey criteria and the medical record review was 94% (47 of 50) (2–4).

Statistical analysis. We computed person-time of followup 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 followup.

To represent long-term coffee and caffeine intake patterns of individual subjects, we used cumulative average intakes based on the information from 1986, 1990, and 1994 dietary questionnaires (2–4,36,37). For example, the incidence of gout from 1986 through 1990 was related to the coffee intake reported on the 1986 questionnaire, and incidence from 1990 through 1994 was related to the average intake reported on the 1986 and 1990 questionnaires. Secondary analyses using only information from baseline questionnaires (in 1986) yielded similar results.

We used Cox proportional hazards modeling (PROC PHREG) to estimate the relative risk (RR) for incident gout in all multivariate analyses (SAS Institute, Cary, NC). For these

Table 1. Baseline characteristics according to coffee consumption level (1986)*

Variable	Coffee consumption level, cups/day					All participants (n = 45,869)†
	0 (n = 13,731)	<1 (n = 10,258)	1–3 (n = 16,892)	4–5 (n = 3,716)	≥6 (n = 1,272)	
Age, years	54	55	54	53	52	54 ± 10
Body mass index, kg/m^2	24.7	24.8	24.9	25.2	25.0	24.8 ± 5
Diuretic use, %	10	10	10	8	5	9
History of hypertension, %	22	21	21	17	15	21
History of chronic renal failure, %	0.1	0.1	0.1	0.1	0.0	0.1
Alcohol intake, gm/day	8	10	13	14	16	11 ± 15
Total meat intake, servings/day	1.2	1.3	1.4	1.6	1.7	1.4 ± 0.7
Seafood intake, servings/day	0.4	0.4	0.4	0.4	0.3	0.4 ± 0.3
Low-fat dairy foods intake, servings/day	1.1	1.0	0.9	0.9	0.9	1.0 ± 1.6
High-fat dairy foods intake, servings/day	1.0	1.1	1.3	1.6	1.8	1.2 ± 1.3
Total caffeine intake, mg/day	46	99	320	668	880	232 ± 228
Tea, cups/day	0.4	0.5	0.4	0.3	0.4	0.4 ± 0.8
Decaffeinated coffee, cups/day	0.7	0.9	0.6	0.3	0.3	0.4 ± 0.8

* Except where indicated otherwise, values are the mean. All data except for age were directly standardized to the age distribution of each study sample.
† Mean ± SD.

analyses, coffee consumption was categorized into 5 groups: never, <1 cup per day, 1–3 cups per day, 4–5 cups per day, and ≥6 cups per day (14). Caffeine intake was categorized into quintiles (12,14). Multivariate models were adjusted for age (continuous), total energy intake (continuous), alcohol consumption (7 categories), BMI (5 categories), use of diuretics (thiazide or furosemide) (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 total vitamin C (quintiles) (2–4). Trends in gout risk across categories of coffee or caffeine 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 BMI (<25 kg/m^2 versus ≥25 kg/m^2), by alcohol use (yes or no), by history of hypertension (yes or no), and by total meat intake (≤1.2 servings/day [median value] versus >1.2 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 (95% CIs). All *P* values are 2-sided.

RESULTS

During 12 years of followup, we documented 757 newly diagnosed cases meeting ACR criteria for gout. The characteristics of the cohort according to coffee consumption levels at baseline are shown in Table 1. With increasing coffee consumption, the frequency of a history of hypertension and diuretic use tended to decrease, but intakes of alcohol, meat, and high-fat dairy foods tended to increase (Table 1).

Increasing coffee intake was inversely associated with the risk of gout (Table 2). The multivariate RRs for incident gout according to coffee consumption categories (0, <1, 1–3, 4–5, and ≥6 cups per day) were 1.00, 0.97, 0.92, 0.60 (95% CI 0.41–0.87), and 0.41 (95% CI 0.19–0.88), respectively (*P* for trend = 0.009). These RRs did not change materially after additional adjustment for smoking (multivariate RR for ≥6 cups per day: 0.41 [95% CI 0.19–0.89]). When we restricted our analysis to men who did not use diuretics (n = 601 gout cases), the corresponding multivariate RRs were 1.00, 1.01, 0.90, 0.49 (95% CI 0.31–0.80), and 0.30 (95% CI 0.12–0.75) (*P* for trend = 0.008).

There was a modest inverse association between decaffeinated coffee consumption and incidence of gout (Table 2). The multivariate RRs according to decaffeinated coffee consumption categories (0, <1, 1–3, and ≥4 cups per day) were 1.00, 0.83, 0.67 (95% CI 0.54–0.82), and 0.73 (95% CI 0.46–1.17), respectively (*P* for trend = 0.002). Tea consumption was not associated with risk for gout (*P* for trend = 0.62) (Table 2).

There was no significant association between total caffeine intake and risk for gout (Table 3). To evaluate the impact of non-coffee sources of caffeine, we examined the association between caffeine intake and risk for gout among non–coffee users and observed a null result (multivariate RR comparing extreme quintiles: 1.08 [95% CI 0.62–1.87]). Furthermore, when we additionally adjusted for caffeine intake in the multivariate model in Table 2, the inverse association with coffee intake did not change materially (multivariate RR for ≥6 cups per day 0.44 [95% CI 0.19–0.99]).

Table 2. Relative risk of incident gout according to coffee, tea, and decaffeinated coffee consumption level*

Consumption level	No. of cases	Person-years	Age/BMI/alcohol-adjusted RR (95% CI)†	Multivariate RR (95% CI)‡
Coffee, cups/day				
0	174	110,745	1.0	1.0
<1	198	116,691	0.95 (0.77–1.17)	0.97 (0.78–1.20)
1–3	336	174,488	0.96 (0.79–1.16)	0.92 (0.75–1.11)
4–5	38	27,192	0.65 (0.45–0.93)	0.60 (0.41–0.87)
≥6	7	7,310	0.44 (0.21–0.95)	0.41 (0.19–0.88)
P for trend	–	–	0.03	0.009
Decaffeinated coffee, cups/day				
0	314	170,748	1.0	1.0
<1	263	158,190	0.88 (0.75–1.04)	0.83 (0.70–0.99)
1–3	153	95,660	0.76 (0.62–0.92)	0.67 (0.54–0.82)
≥4	20	9,900	0.87 (0.55–1.38)	0.73 (0.46–1.17)
P for trend	–	–	0.03	0.002
Tea, cups/day				
0	236	146,198	1.0	1.0
<1	385	217,341	1.14 (0.97–1.35)	1.09 (0.92–1.30)
1–3	126	66,949	1.22 (0.98–1.52)	1.06 (0.85–1.33)
≥4	7	4,347	1.01 (0.47–2.14)	0.82 (0.38–1.75)
P for trend	–	–	0.49	0.62

* The number of gout cases do not add up to the total because of missing data. RR = relative risk; 95% CI = 95% confidence interval.
† Age/body mass index (BMI)/alcohol–adjusted models were also adjusted for total energy.
‡ Adjusted for age, total energy intake, BMI, diuretic use, history of hypertension, history of renal failure, and intake of alcohol, total meats, seafood, purine-rich vegetables, dairy foods, total vitamin C, and the beverages presented in this table.

We conducted stratified analyses to determine whether the association between coffee consumption and gout varied according to BMI, alcohol use, history of hypertension, and total meat intake. RRs from these stratified analyses consistently suggested inverse associations similar to those from main analyses, and there was no significant interaction between these variables and coffee intake (all P for interaction > 0.05).

DISCUSSION

Our objective was to prospectively evaluate the potential association between coffee intake and the risk of gout in a large cohort of men. Using the ACR criteria for gout (35), we found that the risk of incident gout decreased with increasing coffee intake. The risk of gout was 40% lower with coffee intake of 4–5 cups per day and 59% lower with ≥6 cups per day, compared with no use. We also found a modest inverse association with decaffeinated coffee consumption. These associations were independent of dietary and other risk factors for gout such as BMI, age, hypertension, diuretic use, alcohol consumption, and chronic renal failure. The current study provides the first prospective data about the inverse association between coffee intake and risk of gout.

The modest inverse association with decaffeinated coffee suggests that components of coffee other than caffeine may primarily contribute to the observed

Table 3. Relative risk of incident gout according to caffeine intake*

Quintile of caffeine intake, mg/day	No. of cases	Person-years	Age/BMI/alcohol-adjusted RR (95% CI)†	Multivariate RR (95% CI)‡
<34	125	87,072	1.0	1.0
34–114	138	88,763	0.99 (0.78–1.27)	0.92 (0.72–1.17)
115–220	178	87,938	1.21 (0.96–1.52)	1.09 (0.86–1.38)
221–379	164	88,007	1.00 (0.78–1.27)	0.94 (0.74–1.20)
≥380	152	88,672	0.90 (0.70–1.16)	0.83 (0.64–1.08)
P for trend	–	–	0.22	0.19

* See Table 2 for definitions.
† Age/BMI/alcohol-adjusted models were also adjusted for total energy.
‡ Adjusted for age, total energy intake, BMI, diuretic use, history of hypertension, history of renal failure, and intake of alcohol, total meats, seafood, purine-rich vegetables, total vitamin C, and dairy foods.

inverse association between coffee intake and the risk of gout. This inference was consistent with the absence of an association with total caffeine intake and the null association with tea intake, which is another major source of caffeine. These results are closely in line with those of the Japanese cross-sectional study (6) and the Third National Health and Nutrition Examination Survey study (30), both of which found coffee consumption, but not tea consumption, to be inversely associated with serum uric acid levels. Furthermore, these results agree with the recent data about the relationship between these beverages and serum insulin level (12), which is a strong correlate of serum uric acid level (26,28,29). Notably, both caffeinated and decaffeinated coffee were found to be inversely associated with C peptide levels (a marker of endogenous insulin levels), but tea intake or total caffeine intake after adjusting for coffee intake was not (12).

Coffee is the major source of the phenol chlorogenic acid, a strong antioxidant. Previous studies have suggested that plasma glucose concentrations are reduced by chlorogenic acid (38), which may combine with other antioxidants in coffee to decrease oxidative stress (12). Antioxidants may improve insulin sensitivity (39,40) and decrease insulin levels in rats (41). Chlorogenic acid also acts as a competitive inhibitor of glucose absorption in the intestine (42). Indeed, decaffeinated coffee seemed to delay intestinal absorption of glucose and increase glucagon-like peptide 1 concentrations in an intervention study in humans (43). Glucagon-like peptide 1 is well known for its beneficial effects on glucose-induced insulin secretion and insulin action (44). Tea also contains many different types of antioxidants; however, the antioxidant capacity per serving and total contributions are substantially higher in coffee than in tea (12,45–47). Furthermore, the effect of caffeine may also depend on other components of coffee. It has also been speculated that noncaffeine xanthines contained in coffee may inhibit xanthine oxidase, thus contributing to lower serum uric acid levels (6).

Caffeine (1,3,7-trimethyl xanthine) is metabolized by demethylation, and the major human pathway results in paraxanthine (1,7-dimethyl xanthine), leading to the principal urinary metabolites of l-methyl xanthine, 1-methyl uric acid, and an acetylated uracil derivative. Caffeine and other methyl xanthines were shown to competitively inhibit xanthine oxidase in in vitro and in vivo studies of rats (16). Similarly, caffeine may reduce the risk of gout via xanthine oxidase inhibition in humans. However, because administration of caffeine lowers insulin sensitivity in humans (7–11), this action of caffeine may increase the risk of gout, although these effects may not persist during chronic caffeine consumption (9). Of note, complete tolerance can develop after several days of caffeine use with respect to humoral and hemodynamic variables such as blood pressure, heart rate, plasma renin activity, plasma catecholamines, or urinary catecholamines (20,48). Reflecting these opposing possibilities of the effect of caffeine on the risk of gout, our results suggest that long-term intake of caffeine per se may not be a significant net contributor to the risk of gout.

Several strengths and potential limitations of this study deserve comment. Our study was substantially larger than previous studies concerning gout (1,49–54), and dietary data including coffee intake information were prospectively collected and validated. Potential biased recall of diet was avoided in this study because the intake data were collected before the diagnosis of gout. Because coffee consumption was self-reported by questionnaire, some misclassification of exposure is inevitable. However, self-reported coffee consumption has been extensively validated in subsamples of this cohort, 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 coffee use over time, but also decreases measurement error. The validity of gout ascertainment in this cohort has been documented by the high degree of concordance with medical record review (2–4). Furthermore, the incidence 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 versus 1.7 per 1,000 person-years, respectively).

The restriction to health professionals in our cohort is both a strength and a limitation. The cohort of well-educated men minimizes the potential for confounding associated with socioeconomic status, and we were able to obtain high-quality data with minimal loss to followup. Although the absolute rates of gout and distribution of coffee intake may not be representative of a random sample of US men, the biologic effects of coffee intake on gout should be similar. Our findings are most directly generalizable to men ages 40 years and older (the most gout-prevalent population [49]) with no history of gout. Given the potential influence of female hormones on the risk of gout in women (55) and an increased role of dietary impact on uric acid levels among patients with existing gout (56), prospective studies of these populations would be valuable.

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 long-term coffee consumption is associated with a lower risk of gout.

AUTHOR CONTRIBUTIONS

Dr. Choi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Choi, Willett, Curhan.
Acquisition of data. Choi, Willett, Curhan.
Analysis and interpretation of data. Choi, Willett, Curhan.
Manuscript preparation. Choi, Willett, Curhan.
Statistical analysis. Choi.

ROLE OF THE STUDY SPONSOR

TAP Pharmaceuticals had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

REFERENCES

1. Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC. Incidence and risk factors for gout in white men. JAMA 1991;266:3004–7.
2. Choi HK, Atkinson K, Karlson EW, Willett WC, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. New Engl J Med 2004;350:1093–103.
3. Choi HK, Atkinson K, Karlson EW, Willett WC, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. Lancet 2004;363:1277–81.
4. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165: 742–8.
5. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med 2005;143:499–516.
6. Kiyohara C, Kono S, Honjo S, Todoroki I, Sakurai Y, Nishiwaki M, et al. Inverse association between coffee drinking and serum uric acid concentrations in middle-aged Japanese males. Br J Nutr 1999;82:125–30.
7. Petrie HJ, Chown SE, Belfie LM, Duncan AM, McLaren DH, Conquer JA, et al. Caffeine ingestion increases the insulin response to an oral-glucose-tolerance test in obese men before and after weight loss. Am J Clin Nutr 2004;80:22–8.
8. Greer F, Hudson R, Ross R, Graham T. Caffeine ingestion decreases glucose disposal during a hyperinsulinemic-euglycemic clamp in sedentary humans. Diabetes 2001;50:2349–54.
9. Keijzers GB, De Galan BE, Tack CJ, Smits P. Caffeine can decrease insulin sensitivity in humans. Diabetes Care 2002;25: 364–9.
10. Thong FS, Derave W, Kiens B, Graham TE, Urso B, Wojtaszewski JF, et al. Caffeine-induced impairment of insulin action but not insulin signaling in human skeletal muscle is reduced by exercise. Diabetes 2002;51:583–90.
11. Thong FS, Graham TE. Caffeine-induced impairment of glucose tolerance is abolished by β-adrenergic receptor blockade in humans. J Appl Physiol 2002;92:2347–52.
12. Wu T, Willett WC, Hankinson SE, Giovannucci E. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. Diabetes Care 2005;28:1390–6.
13. Van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. JAMA 2005;294:97–104.
14. Salazar-Martinez E, Willett WC, Ascherio A, Manson JE, Leitzmann MF, Stampfer MJ, et al. Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med 2004;140:1–8.
15. Lundsberg LS. Caffeine consumption. In: Spiller GA, editor. Caffeine. Boca Raton (FL): CRC Press; 1998. p. 199–224.
16. Kela U, Vijayvargiya R, Trivedi CP. Inhibitory effects of methylxanthines on the activity of xanthine oxidase. Life Sci 1980;27: 2109–19.
17. Dulloo AG, Geissler CA, Horton T, Collins A, Miller DS. Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers. Am J Clin Nutr 1989;49:44–50.
18. Astrup A, Toubro S, Cannon S, Hein P, Breum L, Madsen J. Caffeine: a double-blind, placebo-controlled study of its thermogenic, metabolic, and cardiovascular effects in healthy volunteers. Am J Clin Nutr 1990;51:759–67.
19. Bracco D, Ferrarra JM, Arnaud MJ, Jequier E, Schutz Y. Effects of caffeine on energy metabolism, heart rate, and methylxanthine metabolism in lean and obese women. Am J Physiol 1995;269: 671–8.
20. Robertson D, Wade D, Workman R, Woosley RL, Oates JA. Tolerance to the humoral and hemodynamic effects of caffeine in man. J Clin Invest 1981;67:1111–7.
21. Arnlov J, Vessby B, Riserus U. Coffee consumption and insulin sensitivity. JAMA 2004;291:1199–201.
22. Van Dam RM, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. Lancet 2002;360:1477–8.
23. Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. JAMA 2004;291:1213–9.
24. Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. The Normative Aging Study. Am J Epidemiol 1995;142:288–94.
25. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. Coronary Artery Risk Development in Young Adults. Ann Epidemiol 1998;8:250–61.
26. Emmerson B. Hyperlipidaemia in hyperuricaemia and gout. Ann Rheum Dis 1998;57:509–10.
27. Fam AG. Gout, diet, and the insulin resistance syndrome. J Rheumatol 2002;29:1350–5.
28. Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, Gans RO. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. Clin Sci (Lond) 1997;92:51–8.
29. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. Am J Hypertens 1996;9:746–52.
30. Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: The Third National Health and Nutrition Examination Survey. Arthritis Rheum. In press.
31. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135: 1114–26.
32. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
33. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, et al. Reproducibility and validity of food intake

measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
34. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B6, and the risk of kidney stones in men. J Urol 1996;155:1847–51.
35. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895–900.
36. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997;337:1491–9.
37. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Speizer FE, et al. Dietary protein and risk of ischemic heart disease in women. Am J Clin Nutr 1999;70:221–7.
38. Arion WJ, Canfield WK, Ramos FC, Schindler PW, Burger HJ, Hemmerle H, et al. Chlorogenic acid and hydroxynitrobenzaldehyde: new inhibitors of hepatic glucose 6-phosphatase. Arch Biochem Biophys 1997;339:315–22.
39. Jacob S, Henriksen EJ, Schiemann AL, Simon I, Clancy DE, Tritschler HJ, et al. Enhancement of glucose disposal in patients with type 2 diabetes by α-lipoic acid. Arzneimittelforschung 1995; 45:872–4.
40. Bruce CR, Carey AL, Hawley JA, Febbraio MA. Intramuscular heat shock protein 72 and heme oxygenase-1 mRNA are reduced in patients with type 2 diabetes: evidence that insulin resistance is associated with a disturbed antioxidant defense mechanism. Diabetes 2003;52:2338–45.
41. Thirunavukkarasu V, Anuradha CV. Influence of α-lipoic acid on lipid peroxidation and antioxidant defence system in blood of insulin-resistant rats. Diabetes Obes Metab 2004;6:200–7.
42. Clifford MN. Chlorogenic acid and other cinnamates - nature, occurrence, dietary burden, absorption and metabolism. J Sci Food Agric 2000;80:1033–43.
43. Johnston KL, Clifford MN, Morgan LM. Coffee acutely modifies gastrointestinal hormone secretion and glucose tolerance in humans: glycemic effects of chlorogenic acid and caffeine. Am J Clin Nutr 2003;78:728–33.
44. Drucker DJ. Glucagon-like peptides. Diabetes 1998;47:159–69.
45. Svilaas A, Sakhi AK, Andersen LF, Svilaas T, Strom EC, Jacobs DR Jr, et al. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. J Nutr 2004; 134:562–7.
46. Richelle M, Tavazzi I, Offord E. Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. J Agric Food Chem 2001;49:3438–42.
47. Pellegrini N, Serafini M, Colombi B, Del Rio D, Salvatore S, Bianchi M, et al. Total antioxidant capacity of plant foods, beverages and oils consumed in Italy assessed by three different in vitro assays. J Nutr 2003;133:2812–9.
48. Brown CR, Benowitz NL. Caffeine and cigarette smoking: behavioral, cardiovascular, and metabolic interactions. Pharmacol Biochem Behav 1989;34:565–70.
49. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421–6.
50. Shadick NA, Kim R, Weiss S, Liang MH, Sparrow D, Hu H. Effect of low level lead exposure on hyperuricemia and gout among middle aged and elderly men: the Normative Aging Study. J Rheumatol 2000;27:1708–12.
51. Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham Study. J Clin Epidemiol 1988;41:237–42.
52. Hochberg MC, Thomas J, Thomas DJ, Mead L, Levine DM, Klag MJ. Racial differences in the incidence of gout: the role of hypertension. Arthritis Rheum 1995;38:628–32.
53. Sharpe CR. A case-control study of alcohol consumption and drinking behaviour in patients with acute gout. Can Med Assoc J 1984;131:563–7.
54. Gibson T, Rodgers AV, Simmonds HA, Court-Brown F, Todd E, Meilton V. A controlled study of diet in patients with gout. Ann Rheum Dis 1983;42:123–7.
55. Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. Br Med J 1973;1:449–51.
56. Gibson T, Hannan SF, Hatfield PJ, Simmonds HA, Cameron JS, Potter CS, et al. The effect of acid loading on renal excretion of uric acid and ammonium in gout. Adv Exp Med Biol 1977;76B: 46–56.