

Obesity, Weight Change, Hypertension, Diuretic Use, and Risk of Gout in Men

The Health Professionals Follow-up Study

Hyon K. Choi, MD, DrPH; Karen Atkinson, MD, MPH; Elizabeth W. Karlson, MD; Gary Curhan, MD, ScD

Background: Limited prospective information exists on the relation between obesity and weight change and the risk of gout. Similarly, both hypertension and diuretic use have been considered risk factors for gout; however, their independent contributions have not been established prospectively.

Methods: We prospectively examined over a 12-year period (1986-1998) the relation between adiposity, weight change, hypertension, and diuretic use and incident gout in 47 150 male participants with no history of gout at baseline. We used a supplementary questionnaire to ascertain the American College of Rheumatology criteria for gout.

Results: During 12 years we documented 730 confirmed incident cases of gout. Compared with men with a body mass index (BMI) of 21 to 22.9, the multivariate relative risks (RRs) of gout were 1.95 (95% confidence

interval [CI], 1.44-2.65) for men with a BMI of 25 to 29.9, 2.33 (95% CI, 1.62-3.36) for men with a BMI of 30 to 34.9, and 2.97 (95% CI, 1.73-5.10) for men with a BMI of 35 or greater (*P* for trend <.001). Compared with men who had maintained their weight (± 4 lb) since age 21 years, the multivariate RR of gout for men who had gained 30 lb or more since age 21 years was 1.99 (95% CI, 1.49-2.66). In contrast, the multivariate RR for men who had lost 10 lb or more since the study baseline was 0.61 (95% CI, 0.40-0.92). The multivariate RRs of gout were 2.31 (95% CI, 1.96-2.72) for the presence of hypertension and 1.77 (95% CI, 1.42-2.20) for diuretic use.

Conclusions: Higher adiposity and weight gain are strong risk factors for gout in men, while weight loss is protective. Hypertension and diuretic use are also important independent risk factors for gout.

Arch Intern Med. 2005;165:742-748

Author Affiliations: Rheumatology Unit, Department of Medicine, Massachusetts General Hospital (Drs Choi and Atkinson), and Division of Rheumatology (Dr Karlson) and Channing Laboratory (Dr Curhan), Brigham and Women's Hospital, Harvard Medical School; and Department of Epidemiology, Harvard School of Public Health (Drs Choi and Curhan); Boston, Mass.

Financial Disclosure: None.

GOUT IS THE MOST COMMON inflammatory arthritis in adult men, affecting up to 3.4 million men in the United States.^{1,2} Although several prospective cohort studies have evaluated the association between obesity and gout,^{1,3-5} lack of data and a small number of gout cases have limited the comprehensive adjustment of relevant covariates. Specifically, no prospective information is available on the risk of gout associated with obesity after adjusting for dietary factors, which themselves may be risk factors for gout and vary with adiposity. Furthermore, most studies have analyzed the impact on the risk of gout of a single measurement of adiposity variables and hence have not assessed the importance of updating these variables over time.

A single study is available on the hazardous impact of weight gain on the risk of gout specifically in young adulthood.¹ No other prospective study has supported or refuted the finding and no prospective infor-

mation is available on the impact of weight gain later in life. Furthermore, important questions remain about the potential effect of weight loss on the incidence of gout. Since overweight and obesity are epidemic and their prevalence continues to rise,⁶ an accurate understanding of their impact on this common arthritis is essential.

Hypertension has been recognized as a risk factor for gout, and diuretic use has been shown to elevate serum uric acid levels.^{1,7,8} However, no prospective study has demonstrated the independent contributions to the risk of incident gout, primarily because of their tight association (ie, diuretics are often used to treat hypertension) and small study samples. Additionally, since hypertension is associated with other risk factors for gout (eg, adiposity, dietary/nutritional factors, alcohol intake, and chronic renal failure), it is important to adjust for them to examine hypertension as an independent risk factor for gout. Since hypertension and diuretic use are also common, a quantita-

tive assessment of their impact on the risk of gout is important.

To examine these issues, we prospectively evaluated the relations between body mass index (BMI), weight change, hypertension, and diuretic use and incident gout in a cohort of 47 150 men with no history of gout.

METHODS

STUDY POPULATION

The Health Professionals Follow-up Study is an ongoing longitudinal study of 51 529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians who were predominantly white (91%) and were aged 40 through 75 years in 1986. The participants returned a mailed questionnaire in 1986 concerning diet, medical history, and medications. Of the 49 932 men who provided complete information on diet and age, 2782 (5.6%) reported a history of gout on the baseline questionnaire. These prevalent cases at baseline were excluded from this analysis.

ASSESSMENT OF ANTHROPOMETRIC VARIABLES

Height, current weight, and weight at 21 years old were reported by men in 1986. In addition, participants reported their current weight on the biennial mailed questionnaires. Waist-to-hip ratio was assessed in 1987. We calculated BMI as the weight in kilograms divided by the square of the height in meters. Weight change since age 21 years was calculated by subtracting the current weight (updated biennially) from the weight at age 21 years. Weight change since baseline was calculated by subtracting the current weight (1988 and onward) from the weight reported in 1986. We evaluated the accuracy of self-reported anthropometric measures among 123 Health Professionals Follow-up Study participants by having trained technicians visit those participants twice (6 months apart) to measure current weight.⁹ After adjustment for age and within-person variability, the Pearson correlations between self-report and the average of the two technician measurements were 0.97 for weight, 0.95 for waist circumference, and 0.88 for hip circumference.⁹

ASSESSMENT OF HYPERTENSION AND DIURETICS

The baseline and biennial follow-up questionnaires inquired about physician-diagnosed hypertension. In this cohort, the diagnosis of hypertension is reported reliably, and self-reported blood pressure is a strong predictor of stroke.¹⁰ A study participant was considered to have hypertension from the time it was first reported on the questionnaire. Similarly, at baseline and every 2 years thereafter, the participants provided information on regular use of medications, including use of diuretics. The follow-up rate for this cohort was greater than 90% during the study period.

ASSESSMENT OF COVARIATES

To assess dietary intake, we used a semiquantitative food-frequency questionnaire that inquired about the average use of more than 130 foods and beverages, including alcohol intake, during the previous year.^{11,12} The baseline dietary questionnaire was completed in 1986, and 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.¹² The reproducibility and validity of this dietary questionnaire in this cohort have been previously reported.^{11,13} The baseline and biennial follow-up questionnaires inquired about new onset of physician-diagnosed chronic renal failure, which was used as a covariate in our analyses.

ASCERTAINMENT OF INCIDENT CASES OF GOUT

On each biennial questionnaire, participants indicated whether they had received a physician diagnosis of gout. In 2001, we mailed to those subjects with self-reported incident gout between 1986 and 1998 ($n = 1332$) a supplementary questionnaire to confirm the report and to ascertain the American College of Rheumatology survey gout criteria.¹⁴ The primary end point in this study was an incident case of gout that met 6 or more of the 11 gout criteria.¹⁴ The response rate for the supplementary gout questionnaire was 80%, and 69% of the participants with self-reported gout who returned the questionnaire met the primary end point ($n = 730$). To confirm the validity of the survey gout criteria in our cohort, we reviewed the relevant medical records from a sample of 50 of the men who had reported having gout. The concordance rate of the gout survey criteria and the medical record review was 94% (47/50).

STATISTICAL ANALYSIS

We computed person-time of follow-up for each participant from the return date of the 1986 questionnaire to the date of diagnosis of gout, death from any cause, or the end of the study period, whichever came first.

We used Cox proportional hazards modeling (PROC PHREG) to estimate the relative risk (RR) for incident gout in all multivariate analyses (SAS Institute Inc, Cary, NC). We grouped BMI values in 6 categories: less than 21, 21 to 22.9, 23 to 24.9, 25 to 29.9, 30 to 34.9, and 35 or greater. The last 3 categories were classified as overweight, obesity class 1, and obesity class 2, respectively, by the World Health Organization, Geneva, Switzerland.¹⁵ We grouped weight change values in 7 categories: more than -10 lb, -10 to -5 lb, -4 to +4 lb, +5 to +9 lb, +10 to +19 lb, +20 to +29 lb, and +30 lb or more (to convert pounds to kilograms multiply by 0.45). In addition, waist-to-hip ratios were categorized in quintiles. Presence of hypertension and use of diuretics were used as indicator exposure variables. Multivariate models were adjusted for age (continuous), total energy intake (continuous), presence of chronic renal failure (yes or no), meat intake (quintiles), seafood intake (quintiles), purine-rich vegetable intake (quintiles), dairy food intake (quintiles), alcohol intake (7 categories), animal protein intake (quintiles), and fluid intake (quintiles). Trends in BMI and weight changes were assessed in Cox proportional hazards models by using the median values for each category to minimize the influence of outliers. We calculated 95% confidence intervals (CIs) for all RRs. All *P* values are 2-sided.

We calculated the population-attributable risk,^{16,17} an estimate of the percentage of gout cases in this population that would theoretically not have occurred if the BMI had been lower than 23, assuming a causal relation between BMI and incident gout.

RESULTS

BASELINE CHARACTERISTICS

There were 730 newly diagnosed cases that met the American College of Rheumatology criteria for gout during the

Table 1. Baseline Characteristics According to Body Mass Index (BMI), Weight Gain, and Waist-to-Hip Ratio

Characteristic	Age, y*	BMI*	Weight, lb*	Weight Gain Since Age 21 y, lb*	Meat Intake, Servings/d*	Seafood Intake, Servings/d*	Dairy Intake, Servings/d*	Alcohol Intake, g/d*	Diuretic Use, %	Hypertension, %
BMI, kg/m ²										
<21	55	20	142	4	1.2	0.3	1.9	10	6	15
21-22.9	54	22	154	10	1.2	0.3	1.9	11	7	15
23-24.9	54	24	168	16	1.3	0.3	1.9	11	8	17
25-29.9	55	27	187	25	1.4	0.3	1.9	11	11	23
30-34.9	54	32	222	43	1.6	0.4	2.0	10	16	33
≥35	53	40	249	59	1.7	0.4	2.2	9	23	43
Waist-to-hip ratio										
0.70-0.88	53	23	164	11	1.9	0.3	1.9	10	6	14
0.89-0.91	54	24	169	15	1.9	0.3	1.9	11	7	16
0.92-0.94	55	25	172	19	2.0	0.3	2.0	11	9	20
0.95-0.97	56	25	178	23	2.0	0.3	2.0	12	12	23
0.98-1.39	56	26	185	29	2.0	0.3	2.0	12	14	29
Weight change since age 21 y, lb										
More than -10	54	24	167	-22	1.2	0.4	1.9	10	9	19
-10 to -5	54	24	166	-9	1.2	0.4	1.9	11	7	18
-4 to +4	54	24	165	0	1.2	0.4	1.9	11	7	16
+5 to +9	54	24	168	6	1.3	0.3	1.9	11	7	16
+10 to +19	54	25	174	13	1.3	0.3	1.9	11	8	18
+20 to +29	55	26	184	27	1.4	0.3	1.9	12	11	23
+30 or more	56	29	206	52	1.6	0.3	2.0	11	16	32
Hypertension										
Present	56	26	179	24	1.3	0.4	1.9	12	39	100
Absent	54	25	173	19	1.4	0.3	2.0	11	1	0
Diuretic use										
Present	58	26	180	27	1.4	0.4	1.9	13	100	89
Absent	54	25	174	20	1.4	0.3	1.9	11	0	14
All participants	54	25	174	20	1.4	0.3	1.9	11	10	21

Conventional conversion factor: To convert pounds to kilograms, multiply by 0.45.

*All values are means.

12-year follow-up. The baseline characteristics of the cohort according to BMI, weight gain, and waist-to-hip ratio categories are shown in **Table 1**. As expected, BMI, weight gain since age 21 years, and waist-to-hip ratio varied in the same direction. Body mass index tended to increase with increasing frequency of hypertension, with diuretic use, and with higher meat consumption. Weight gain since age 21 years and waist-to-hip ratio showed a similar relation with these variables. As expected, hypertension and diuretic use were tightly related and were more frequent with older age, higher BMI, higher weight, and weight gain. Other characteristics were similar across the categories.

BMI, WAIST-TO-HIP RATIO, AND INCIDENT GOUT

We found a graded association between BMI updated every 2 years and the risk of gout (**Table 2**). Compared with those with a BMI of 21 to 22.9, the age-adjusted RRs of gout were 1.40 (95% CI, 1.00-1.95) for a BMI of 23 to 24.9, 2.35 (95% CI, 1.74-3.17) for a BMI of 25 to 29.9, 3.26 (95% CI, 2.28-4.65) for a BMI of 30 to 34.9, and 4.41 (95% CI, 2.59-7.51) for a BMI of 35 or higher (*P* for trend <.001). After further adjusting for other risk factors for gout, these multivariate RRs were attenuated

but remained significant (*P* for trend <.001) (Table 2). When we used BMI from the 1986 baseline and at age 21 years, the multivariate RRs were attenuated further but remained significant (*P* for trend, <.001 and .002, respectively) (Table 2).

Similarly, increasing waist-to-hip ratio was associated with increasing risk of gout (Table 2). After adjusting for age, the RR for gout among men in the highest waist-to-hip ratio quintile (0.98-1.39) as compared with those in the lowest quintile (0.70-0.88) was 2.39 (95% CI, 1.83-3.13; *P* for trend <.001). After further adjustment for other risk factors, the RRs were attenuated but remained significant (Table 2).

WEIGHT CHANGE AND INCIDENT GOUT

As reflected in the person-year totals under weight change categories in **Table 3**, most men had experienced weight gain since age 21 years and only a small proportion had maintained or lost weight. In contrast, a substantially smaller proportion had gained weight since the 1986 study baseline (mean age, 54 years), and a much larger proportion had maintained or lost weight (Table 3).

There was a graded association between weight gain since age 21 years and since 1986 and the risk of gout

Table 2. Relative Risk (RR) of Gout According to Body Mass Index and Waist-to-Hip Ratio

Variable	Updated BMI						P for Trend
	<21	21-22.9	23-24.9	25-29.9	30-34.9	≥35	
Cases of gout, No.	10	48	128	361	83	19	...
Person-years	16 016	58 212	110 795	18 984	30 128	5364	...
Age-adjusted RR (95% CI)	0.79 (0.40-1.56)	1.00 (Ref)	1.40 (1.00-1.95)	2.35 (1.74-3.17)	3.26 (2.28-4.65)	4.41 (2.59-7.51)	<.001
Multivariate RR (95% CI)*	0.85 (0.43-1.68)	1.00 (Ref)	1.31 (0.94-1.83)	1.95 (1.44-2.65)	2.33 (1.62-3.36)	2.97 (1.73-5.10)	<.001
Variable	1986 BMI						P for Trend
	<21	21-22.9	23-24.9	25-29.9	30-34.9	≥35	
Cases of gout, No.	8	69	140	412	71	15	...
Person-years	18 334	70 936	136 403	206 056	28 218	4547	...
Age-adjusted RR (95% CI)	0.45 (0.22-0.94)	1.00 (Ref)	1.05 (0.78-1.40)	1.99 (1.54-2.57)	2.47 (1.77-3.45)	3.40 (1.95-5.96)	<.001
Multivariate RR (95% CI)*	0.48 (0.23-1.00)	1.00 (Ref)	0.97 (0.73-1.30)	1.65 (1.27-2.13)	1.79 (1.27-2.13)	2.30 (1.30-4.06)	<.001
Variable	BMI at Age 21 y†					P for Trend	
	<21	21-22.9	23-24.9	25-29.9	≥30		
Cases of gout, No.	141	187	174	177	22	...	
Person-years	104 624	131 239	120 593	90 742	7414	...	
Age-adjusted RR (95% CI)	0.93 (0.75-1.16)	1.00 (Ref)	1.02 (0.83-1.26)	1.38 (1.12-1.70)	2.14 (1.37-3.32)	<.001	
Multivariate RR (95% CI)*	0.92 (0.74-1.15)	1.00 (Ref)	1.00 (0.81-1.23)	1.23 (1.00-1.52)	1.66 (1.06-2.60)	.002	
Variable	1987 Waist-to-Hip Ratio					P for Trend	
	0.70-0.88	0.89-0.91	0.92-0.94	0.95-0.97	0.98-1.39		
Cases of gout, No.	81	92	96	125	173	...	
Person-years	70 845	73 424	65 592	65 944	63 189	...	
Age-adjusted RR (95% CI)	1.0 (Ref)	1.09 (0.81-1.47)	1.27 (0.94-1.71)	1.62 (1.20-2.16)	2.39 (1.83-3.13)	<.001	
Multivariate RR (95% CI)*	1.0 (Ref)	1.02 (0.76-1.38)	1.11 (0.83-1.50)	1.35 (1.01-1.79)	1.82 (1.39-2.39)	<.001	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; Ref, reference value.

*Adjusted for age, total energy intake, diuretic use, history of hypertension, history of chronic renal failure, alcohol intake, fluid intake, meat intake, seafood intake, purine-rich vegetable intake, animal protein intake, and dairy food intake.

†The number of subjects with a BMI of 35 or higher was insufficient to evaluate this category separately; therefore, subjects in this category were combined with those who had a BMI of 30 to 34.9.

Table 3. Relative Risk (RR) of Gout According to Weight Change

Variable	Weight Change Since Age 21 y, lb							P for Trend
	-10 or More	-10 to -5	-4 to +4	+ 5 to +9	+ 10 to +19	+ 20 to +29	+30 or More	
Cases of gout, No.	21	18	58	43	129	132	299	...
Person-years	22 546	14 598	56 627	48 782	105 398	84 779	121 769	...
Age-adjusted RR (95% CI)*	0.74 (0.45-1.24)	1.13 (0.67-1.92)	1.00 (Ref)	0.89 (0.60-1.32)	1.24 (0.91-1.69)	1.57 (1.15-2.14)	2.47 (1.86-3.28)	<.001
Multivariate RR (95% CI)†	0.73 (0.44-1.22)	1.16 (0.68-1.97)	1.00 (Ref)	0.86 (0.58-1.27)	1.14 (0.84-1.56)	1.39 (1.02-1.90)	1.99 (1.49-2.66)	<.001
Variable	Weight Change Since Baseline (1986), lb‡							P for Trend
	-10 or More	-10 to -5	-4 to +4	+5 to +9	+10 to +19	+20 to +29	+30 or More	
Cases of gout, No.	26	47	248	102	107	25	16	...
Person-years	20 514	25 149	154 598	59 309	44 349	10 984	4536	...
Age-adjusted RR (95% CI)§	0.68 (0.45-1.02)	1.12 (0.82-1.53)	1.00 (Ref)	1.09 (0.86-1.38)	1.49 (1.18-1.89)	1.38 (0.91-2.10)	2.09 (1.25-3.52)	<.001
Multivariate RR (95% CI)	0.61 (0.40-0.92)	1.09 (0.79-1.49)	1.00 (Ref)	1.05 (0.83-1.32)	1.36 (1.08-1.72)	1.22 (0.81-1.85)	1.72 (1.02-2.91)	<.001

Abbreviations: CI, confidence interval; Ref, reference value.

Conventional conversion factor: To convert pounds to kilograms, multiply by 0.45.

*Adjusted for age and weight at age 21 years.

†Adjusted for age, total energy intake, diuretic use, history of hypertension, history of chronic renal failure, alcohol intake, fluid intake, meat intake, seafood intake, purine-rich vegetable intake, animal protein intake, dairy food intake, and weight at age 21 years.

‡Using 591 incident cases of gout during 10 years of follow-up between 1988 and 1998.

§Adjusted for age and weight at baseline (1986).

||Adjusted for age, total energy intake, diuretic use, history of hypertension, history of chronic renal failure, alcohol intake, fluid intake, meat intake, seafood intake, purine-rich vegetable intake, animal protein intake, dairy food intake, and weight at baseline (1986).

Table 4. Relative Risk (RR) of Gout According to Presence of Hypertension and Diuretic Use

Variable	Hypertension		Diuretic Use	
	Absent	Present	Absent	Present
Cases of gout, No.	351	379	603	127
Person-years	348 061	126 733	445 296	29 498
Age-adjusted RR (95% CI)	1.00 (Ref)	3.07 (2.64-3.56)	1.00 (Ref)	3.37 (2.75-4.12)
Multivariate RR* (95% CI)	1.00 (Ref)	2.31 (1.96-2.72)	1.00 (Ref)	1.77 (1.42-2.20)

Abbreviations: CI, confidence interval; Ref, reference value.

*Adjusted for age, body mass index, total energy intake, diuretic use, history of hypertension, history of renal failure, alcohol intake, fluid intake, meat intake, seafood intake, purine-rich vegetable intake, animal protein intake, and dairy food intake.

(Table 3). After adjusting for age and weight at age 21 years, compared with men who maintained weight (± 4 lb), the RR of gout was 1.57 (95% CI, 1.15-2.14) for a weight gain of 20 to 29 lb since age 21 years and 2.47 (95% CI, 1.86-3.28) for a weight gain of 30 lb or more since age 21 years (P for trend $<.001$). After further adjusting for other risk factors, the RRs were attenuated but remained significant. The RRs of weight gain since 1986 showed similar magnitudes with a significant trend (P for trend $<.001$), although the two largest categories (ie, weight gain ≥ 20 lb) together accounted for only 4% of total person-years (Table 3).

After adjusting for baseline weight and other risk factors for gout, men who had lost 10 lb or more since the study baseline had a 39% lower risk of gout compared with men who had maintained weight (± 4 lb) (RR, 0.61; 95% CI, 0.40-0.92). Men who had lost 10 lb or more since age 21 years (accounting for 5% of total person-years) had a nonsignificantly lower risk of gout compared with men who had maintained weight (RR, 0.73; 95% CI, 0.44-1.22).

HYPERTENSION, DIURETIC USE, AND INCIDENT GOUT

After we adjusted for potential confounders, including diuretic use, the RR of gout for men with hypertension as compared with men without hypertension was 2.31 (95% CI, 1.96-2.72) (Table 4). After adjusting for the presence of hypertension in the same model, the RR for men taking a diuretic as compared with those not taking a diuretic was 1.77 (95% CI, 1.42-2.20) (Table 4). The multivariate RR for men with chronic renal failure as compared with men without chronic renal failure was 3.61 (95% CI, 1.60-8.14). When we repeated the same analysis limited to those men without diuretic exposure during follow-up, the RR associated with hypertension did not change materially (multivariate RR, 2.28; 95% CI, 1.93-2.70), and the RR associated with chronic renal failure was larger (multivariate RR, 4.60; 95% CI, 1.88-11.25).

POPULATION-ATTRIBUTABLE RISK

In our cohort, 41% of the incident gout cases were attributable to a BMI of 23 or greater. For men with a BMI of 25 or greater (overweight),¹⁵ 52% of gout risk was attributable to excess weight. For men with BMI values of 30 or greater (obesity class 1)¹⁵ and 35 or greater (obe-

sity class 2),¹⁵ 60% and 66%, respectively, of gout risk was attributable to excess weight.

COMMENT

Our objective was to evaluate prospectively the relation between obesity and weight change and the incidence of gout in a large prospective cohort of men. We validated the self-reported cases of gout using the American College of Rheumatology criteria,¹⁴ and we found that adiposity was consistently associated with risk of gout. The risk was significantly higher for a BMI of 25 or greater (overweight¹⁵), and the magnitude of the association became larger with increasing BMI, representing a clear dose-response relation. These associations were independent of other purported risk factors for gout, such as age, diuretic use, history of hypertension or chronic renal failure, and diet.

We analyzed BMI measured at 3 different time points (age 21 years, baseline, and updated every 2 years during follow-up) and found a stronger association with gout when BMI information was updated. These findings suggest that risk of gout is more strongly influenced by current BMI than by BMI earlier in life (ie, a short-term effect).

These results expand on previous studies of adiposity and gout. The Johns Hopkins Precursor Study¹ reported that an elevated BMI at age 35 years but not at baseline (mean age, 22 years) was associated with the risk of gout (RR, 1.12 for a 1-unit increase in BMI; $P = .02$). Small sample size (60 cases of incident gout) and lack of information on relevant variables limited a comprehensive adjustment of covariates, including dietary risk factors, and an evaluation of the impact of updated variables.¹ The Normative Aging Study³ showed that BMI at baseline (mean age, 52 years) was significantly associated with hyperuricemia or gout, although the study had similar limitations. In the Framingham Study,⁴ there was a significantly higher BMI among gout patients after adjusting for age but no multivariate analysis results were presented. In the present study we observed a substantial attenuation of the RRs after adjustment for confounders, emphasizing the importance of multivariate models.

We found that weight gain since young adulthood was strongly associated with the risk of gout, even after adjusting for initial weight and other risk factors. These findings agree with those from the Johns Hopkins Precursor Study.¹ We observed a clear dose-response relation, and

men who had gained 30 lb or more had a twofold increased risk of gout compared with those who had maintained their weight. Similarly, weight gain since the study baseline (mean age, 54 years) was associated with the risk of gout.

In contrast, we found that weight loss greater than 10 lb since the 1986 study baseline was associated with a substantially reduced risk of gout. To our knowledge, our study is the first to document this important potential benefit of weight loss. By demonstrating an association between weight loss and the prevention of gout together with an association between weight gain and the development of gout, the present study makes a much stronger case for a causal relation than the previous studies. Furthermore, although these findings are based on incident gout, these findings support the current recommendation for weight reduction to prevent recurrent gout attacks.^{18,19} This is relevant because weight-intervention studies typically involve more than weight reduction alone (eg, manipulating diets or exercise) in a limited number of subjects,²⁰ and therefore it is difficult to isolate the effect of weight reduction from those other interventions.

It is likely that higher BMI increases the risk of gout by increasing the serum uric acid level. Hyperuricemia has been associated with obesity via both increased production and decreased renal excretion of urate.^{18,19} Weight gain between the first and third visits was associated with rising serum uric acid levels in the Normative Aging Study.²¹ Conversely, the findings of small, open-label, interventional studies suggest that weight reduction may be associated with a decline in uric acid levels.^{20,22} Furthermore, hyperuricemia has been associated with the insulin resistance syndrome.²³⁻²⁵ While close associations have been reported between hyperuricemia and all components of the insulin resistance syndrome, including hyperinsulinemia, hypertension, dyslipidemia, and obesity, a large study demonstrated that BMI has the strongest correlation with hyperuricemia.²⁵ Renal clearance of urate has been shown to have an inverse relation with both the degree of insulin resistance²⁶ and visceral fat area as measured by abdominal computed tomography.²⁷ Factors not related to uric acid, such as chronic joint trauma due to excess weight, have been proposed as an explanation for the association between obesity and gout.^{8,19}

The population-attributable risk for incident gout due to increased BMI was substantial. In our cohort, 91% of gout cases occurred among men with a BMI of 23 or greater, which could explain 42% of all gout cases in this population, and men with higher BMIs showed higher attributable risk proportions, as expected. Since the prevalence of overweight and obesity continues to rise, having reached 66% for overweight (BMI ≥ 25) and 31% for obesity (BMI ≥ 30) in 1999-2000 according to the recent National Health and Nutrition Examination Survey,⁶ the absolute excess risk of gout due to excess weight is also expected to increase.

The presence of hypertension was strongly associated with the incidence of gout independent of diuretic use and chronic renal failure. Previous cohort studies were not able to evaluate an independent effect, possibly because of insufficient power, high correlation between hypertension

and diuretic use, and lack of dietary/nutritional data.^{1,3,4,28} A more recent report from the Meharry-Hopkins Study had the same limitations and adjusted only for baseline BMI and race in multivariate models.⁵ We observed a substantial attenuation of the RRs after adjustment for confounders. Since more than half of the gout cases in our cohort occurred among those with hypertension, the potential impact of the prevention of hypertension on the incidence of gout is substantial.

Several strengths and potential limitations of our study deserve comment. Our study included the largest number of gout cases (n = 730) to date verified by the American College of Rheumatology criteria. As in other epidemiologic studies,^{1,3-5,28} our definition of gout did not require observation of urate crystal in joint fluid examination. Fulfillment of 6 of the 11 American College of Rheumatology survey criteria (our primary outcome definition) was associated with a sensitivity of 85% and a specificity of 93%, and there was a trade-off between the two depending on the number of the criteria required for the diagnosis.¹⁴ In our study, fulfillment of 6 of the 11 criteria¹⁴ showed a high degree of concordance with medical record review, and the incidence of gout fulfilling the criteria in our cohort closely agreed with that estimated among male physicians in the Johns Hopkins Precursor Study¹ (1.5 and 1.7 per 1000 person-years, respectively). Potentially biased recall of diet was avoided in the present study because the intake data were collected before the diagnosis of gout. Our findings are most directly generalizable to men 40 years and older (the most gout-prevalent population³) with no history of gout. Whether these findings apply to women or men with existing gout remains to be studied.

In conclusion, our large prospective study indicates that increased adiposity and weight gain are strong risk factors for gout in men. In contrast, weight loss reduces the risk. Hypertension and diuretic use are also important independent risk factors for gout.

Accepted for Publication: December 15, 2004.

Correspondence: Hyon K. Choi, MD, DrPH, Rheumatology Unit, Bulfinch 165, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (hchoi@partners.org).

Funding/Support: This work was supported in part by grant DK58573 from the National Institutes of Health, Bethesda, Md, and by a grant from TAP Pharmaceuticals, Lake Forest, Ill.

Acknowledgment: The authors thank Walter Willett, MD, DrPH, for his critical review of the manuscript.

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;266:3004-3007.
2. Kramer HM, Curhan G. The association between gout and nephrolithiasis: the National Health and Nutrition Examination Survey III, 1988-1994. *Am J Kidney Dis*. 2002;40:37-42.
3. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia: risks and consequences in the Normative Aging Study. *Am J Med*. 1987;82:421-426.
4. Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham Study. *J Clin Epidemiol*. 1988;41:237-242.
5. Hochberg MC, Thomas J, Thomas DJ, Mead L, Levine DM, Klag MJ. Racial dif-

- ferences in the incidence of gout: the role of hypertension. *Arthritis Rheum.* 1995; 38:628-632.
6. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA.* 2002;288:1723-1727.
 7. Manuel MA, Steele TH. Changes in renal urate handling after prolonged thiazide treatment. *Am J Med.* 1974;57:741-746.
 8. Roubenoff R. Gout and hyperuricemia. *Rheum Dis Clin North Am.* 1990;16:539-550.
 9. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology.* 1990;1:466-473.
 10. Ascherio A, Rimm EB, Giovannucci EL, et al. A prospective study of nutritional factors and hypertension among US men. *Circulation.* 1992;86:1475-1484.
 11. 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; 135:1114-1126.
 12. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semi-quantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122:51-65.
 13. Giovannucci E, Colditz G, Stampfer MJ, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol.* 1991; 133:810-817.
 14. 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.
 15. *Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation on Obesity, 3-5 June 1997, Geneva.* Geneva, Switzerland: World Health Organization; 1998. Publication WHO/NUT/NCD/98.1.
 16. Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN. Attributable risk: advantages of a broad definition of exposure [published correction appears in *Am J Epidemiol.* 1994;140:668]. *Am J Epidemiol.* 1994;140:303-309.
 17. Rothman KJ, Greenland S. *Modern Epidemiology.* 2nd ed. Philadelphia, Pa: Lippincott-Raven; 1998.
 18. Emmerson BT. The management of gout. *N Engl J Med.* 1996;334:445-451.
 19. Fam AG. Gout, diet, and the insulin resistance syndrome. *J Rheumatol.* 2002;29: 1350-1355.
 20. Dessein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. *Ann Rheum Dis.* 2000;59:539-543.
 21. Glynn RJ, Campion EW, Silbert JE. Trends in serum uric acid levels 1961-1980. *Arthritis Rheum.* 1983;26:87-93.
 22. Yamashita S, Matsuzawa Y, Tokunaga K, Fujioka S, Tarui S. Studies on the impaired metabolism of uric acid in obese subjects: marked reduction of renal urate excretion and its improvement by a low-calorie diet. *Int J Obes.* 1986;10:255-264.
 23. Emmerson B. Hyperlipidaemia in hyperuricaemia and gout. *Ann Rheum Dis.* 1998; 57:509-510.
 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;142:288-294.
 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. *Ann Epidemiol.* 1998;8:250-261.
 26. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA.* 1991;266:3008-3011.
 27. Takahashi S, Yamamoto T, Tsutsumi Z, Moriwaki Y, Yamakita J, Higashino K. Close correlation between visceral fat accumulation and uric acid metabolism in healthy men. *Metabolism.* 1997;46:1162-1165.
 28. 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;27:1708-1712.