CLINICAL RESEARCH STUDY

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Gout in African Americans

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ABSTRACT

PURPOSE: African Americans have a substantially higher prevalence of risk factors for gout than Caucasians. The aim of the present study was to compare the risk for incident gout among African Americans and Caucasians.

METHODS: Incidence rates of physician-diagnosed gout among 11,559 Caucasian men and 931 African American men aged 35 to 57 years and at high cardiovascular risk, observed for 7 years as a part of the Multiple Risk Factor Intervention Trial, were analyzed. Cox regression models were used to account for potential confounding by age, body mass index, diuretic use, hypertension and diabetes status, aspirin and alcohol consumption, and kidney disease.

RESULTS: At baseline, after accounting for risk factors, African Americans had a 14% lower prevalence of hyperuricemia than Caucasians. Incidence of gout increased with increasing prevalence of risk factors in both Caucasians and African Americans. Ethnic disparities in incidence rates were most apparent among those without other risk factors for gout. In separate Cox regression models, after accounting for risk factors, African American ethnicity was associated with a hazard ratio of 0.78 (95% confidence interval [CI], 0.66-0.93) for physician-diagnosed gout and 0.88 (95% CI, 0.85-0.90) for incident hyperuricemia. Significant interactions were observed; the association was the strongest (hazard ratio 0.47; 0.37-0.60). These associations were unaffected by addition of serum urate as a covariate or by using alternate case definitions for gout.

CONCLUSIONS: After accounting for the higher prevalence of risk factors, African American ethnicity is associated with a significantly lower risk for gout and hyperuricemia compared with Caucasian ethnicity.
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KEYWORDS: African American; Disparities; Gout; Incidence; Uric acid

Little is known about the incidence of gouty arthritis (gout) among African Americans, an ethnic group that constitutes about 13% of the current US population. African Americans have a disproportionately higher frequency of risk factors for gout and hyperuricemia such as high intake of seafood, elevated blood lead levels, physical inactivity, obesity, alcohol, hypertension, diabetes, renal failure, and antihypertensive medications.[1-4] Despite these risk factors, the unadjusted mean serum urate and unadjusted prevalence of hyperuricemia and gout among African Americans are not significantly greater than among Caucasians.[5-7] Indeed, among those with no renal impairment, the age-standardized prevalence rate of gout among African Americans was nearly identical to that among Caucasians.[8] In a study that attempted to correlate incidence of gout with risk factors, Hochberg et al[9] observed higher crude incidence rates of gout in a cohort of 352 African American physicians (31 cases of gout) when compared with a separate cohort of 571 Caucasian physicians (29 cases of gout); this excess risk was explained by the higher prevalence of hypertension among

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Conflict of Interest: EK has served as a consultant to Takeda Pharmaceuticals, Inc., URL Pharmaceuticals Inc., Metabolic, Inc., and UCB Pharmaceuticals, Inc., and has received grant support from URL, ARDEA Biosciences, and Takeda. However, these entities did not sponsor this study nor did they have access to the contents before publication.

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African Americans. Other potential explanatory factors such as kidney disease, blood pressure medications such as diuretics, weight gain, and alcohol and aspirin use were not accounted for in this analysis. Whether or how such adjustment would have impacted the conclusions of that study is unclear. The present study was undertaken to test the hypothesis that the risk for incident gout associated with African American ethnicity differs from that associated with Caucasian ethnicity using a large cohort of middle-aged men with high prevalence of risk factors for gout, including hypertension, obesity, alcohol use, and aspirin use.

CLINICAL SIGNIFICANCE

- We demonstrate that the incidence and prevalence of gout and hyperuricemia in African Americans are low despite the high prevalence of risk factors.
- We hypothesize that African ancestry provides a protective effect that mitigates the other effects of other risk factors for gout.
- Identifying the biological basis of this phenomenon can help devise ways to prevent and treat gout.

METHODS

Data Source

Data were made available through the National Heart, Lung, and Blood Institute limited-access program. The Multiple Risk Factor Intervention Trial (MRFIT) participants provided informed consent for data collection and analysis. The Stanford Institutional Review Board approved the present analyses. Dr Krishnan possesses the original data and statistical codes. This study was unsponsored.

Participant Enrollment and Follow-up

From 1973 to 1975, 361,662 men at high risk for coronary artery disease aged 35 to 57 years and free of a history of hospitalization for myocardial infarction were screened in 22 clinical centers in 18 cities in the United States through the MRFIT trial. Exclusion criteria were serum creatinine level >2.0 mg/dL, diastolic blood pressure ≥115 mm Hg, serum cholesterol >9.05 mmol/L (350 mg/dL), taking medication for diabetes or previous hospitalization for a heart attack for 2 weeks or more. Those with self-reported physician diagnosis of diabetes but not on medications were not excluded. Participants were assigned randomly to special intervention (n = 6428) or usual care (n = 6438) groups. Although the study was designed to encompass 6 examinations performed annually, some participants who entered the study early in the enrollment phase were followed-up for 7 visits. Interval medical history and cardiovascular events were assessed at these visits. Vital status was assessed throughout the trial for an average of 7 years. Additional information about the MRFIT design has been published.[10-12]

Exclusions

For the present analyses, only those who identified themselves as Caucasians or African Americans were included.

Study Assessments

Questionnaires. At the baseline and follow-up visits, participants completed questionnaires on medical history and alcohol consumption. The medical history questionnaire included a self-report of gouty arthritis, defined as an affirmative answer to the question: "During the past 12 months has a doctor told you that you have gout?" No case validation for this definition is available through the MRFIT study, although it was found to have good reliability in other epidemiologic settings.[13-15]

Medications. Information on frequency of current use of aspirin, diuretics, and other blood pressure medications, and gout medications were collected at all visits. Use of allopurinol, probenecid, or colchicine was collectively categorized as "anti-gout" medicine use. Blood pressure medications were of 2 categories: diuretics and nondiuretics. Information on individual gout medications and their dose information were not available. The diuretics utilized were triamterene, spironolactone, hydrochlorothiazide, and chlorthalidone.

Laboratory Testing. Fasting blood samples were collected at each visit. Serum creatinine, lipid, and urate analyses were performed in a central laboratory using auto analyzers.[10,16] Urine testing for proteinuria and hematuria was performed at the local study center using the urine dipstick (Ames Labstix) method.[16]

Physician Evaluation. The study physician reviewed the medical history and medication history with the participants. The physical examination component included anthropometry, blood pressure measurement, and a clinical evaluation.

Assessment of Gout. The study physician assessed all participants for gout and classified participants into one of the following categories: gout present, no evidence of gout, and suspicion of gout. The MRFIT study protocol did not specify any standard criteria for this clinical assessment, and the determination was left to the clinical judgment of the individual study physician. Patients seldom presented with acute swollen joints that might have been amenable to aspiration and verification of presence of urate crystals. The primary case definition for gout was MRFIT study physician diagnosis of gout. Participants with suspected gout were not counted as cases in the present study. To assess the impact of any systematic errors associated with this case definition, we reanalyzed the data using alternate definitions for incident gout (sensitivity analyses): a) self-reported diagnosis and b) initiation of any gout medication (allopurinol, colchicine, or probenecid).

Key Case Definitions. Ethnicity was assessed by self-identification. Glomerular filtration rate was estimated as the number of mL/min/1.73 m^2 using Chronic Kidney Disease Epidemiology Collaboration equations.[17] The estimated glomerular filtration rate (eGFR) was classified as normal, mildly impaired, moderately impaired, or severely impaired as per the following cutoffs: ≥90 mL/min/1.73m^2, 60-89 mL/min/1.73 m^2, 30-59 mL/min/1.73 m^2, and <30 mL/min/1.73 m^2, respectively.[18] A reading of 3+ or more by urine dipstick for proteinuria or hematuria was used to determine presence of kidney damage. Chronic kidney disease was defined as either the presence of kidney damage or an eGFR <60 mL/min/1.73 m^2, regardless of the kidney damage status.[18]

Other Covariates. Hyperuricemia was defined as a serum urate >7.0 mg/dL (>417 micromoles/L) consistent with prior analyses.[19-22] A systolic blood pressure ≥135 mm Hg or diastolic blood pressure ≥85 mm Hg or use of any antihypertensive medication was used to identify hypertension.[23] Diabetes was defined as a fasting glucose of >126 mg/dL or use of any antidiabetic medication.[24] Metabolic syndrome was defined per the US National Cholesterol Education Program Adult Treatment Panel III criteria.[25]

Statistical Analyses

Data Analyzed. Initially, data from both arms (special intervention and usual care) were analyzed separately. Data were then pooled because there were no systematic differences or evidence of statistical interactions. Data were analyzed using survival analysis methods.[26] Each observation of a participant started at the baseline visit and ended at the time of a diagnosis of gout, death, loss to follow-up, or study end.

Incidence Rates and Ratios. Incidence rates were calculated as the number of new cases of gout per 1000 person-years of follow-up. The jackknife procedure was used to calculate 95% confidence intervals for rates that account for clustering within 2 randomization groups.

Regression Models. The primary dependent variable of interest was a physician diagnosis of gout. Analyses were repeated using alternate case definitions. The main independent variable of interest was African American ethnicity. Cox proportional hazards regressions were used to calculate hazard ratios for ethnicity based on the risk for incident gout before and after adjustment for potential confounders.[26] In these models, proportional hazards assumption was verified by examining Schoenfeld residuals. All values of covariates were updated at every visit (ie, all variables were treated as time-varying covariates).

Data were fit to unadjusted and adjusted Cox proportional hazards regression models. Multivariable models accounted for diabetes status, eGFR, aspirin use, hypertension, diuretic use (categorical), age, body mass index, and alcohol use (continuous). During calculation of 95% confidence intervals for rates and hazard ratios, clustering within the 2 randomization arms was accounted for by using appropriate methods: the jackknife procedure for rates and the robust standard Cox regressions.[27]

Table 1 Descriptive Characteristics of African Americans and Caucasians at the Time of Baseline Visit of Multiple Risk Factor Intervention Trial

	Special Intervention				Usual Care			
	Caucasians n = 5759		African Americans n = 466		Caucasians n = 5800		African Americans n = 465	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, years	46.3	5.9	45.6	5.6	46.2	6.0	45.5	6.0
Current smokers, %	69		76		69		77	
Body mass index, kg/m^2	27.7	3.4	28.1	3.8	27.7	3.5	27.7	3.6
Daily alcohol consumption, g	25.6	36.3	17.5	29.8	26.4	37.4	19.4	31.9
Systolic blood pressure, mm Hg	137.5	15.2	141.7	16.4	137.7	15.1	139.9	15.7
Diastolic blood pressure, mm Hg	92.5	9.5	96.8	10.1	92.6	9.4	96.0	9.6
Hypertensive at baseline	86		94		87		94	
Serum cholesterol, mg/dL	254.4	36.2	245.0	37.9	253.9	36.8	246.3	37.8
LDL cholesterol, mg/dL	159.9	35.4	158.8	39.2	160.4	36.2	158.8	39.0
HDL cholesterol, mg/dL	41.5	11.4	48.3	15.4	41.6	11.1	49.3	16.2
Plasma triglyceride, mg/dL	198.9	148.5	143.8	93.1	197.1	146.4	144.0	100.8
Plasma glucose, mg/dL	100	15	98	19	99	15	97	17
Serum urate, mg/dL	6.8	1.3	6.8	1.4	6.8	1.3	6.7	1.3
Serum creatinine, mg/dL	1.1	0.1	1.2	0.2	1.1	0.1	1.2	0.2
eGFR,* mL/min/1.73m^2	87	13	82	15	87	13	82	13
Chronic kidney disease, %	5.1		11.6		5.1		10.1	

*eGFR = estimated glomerular filtration rate calculated per Levey (2009)[17], HDL = high-density lipoprotein, LDL = low-density lipoprotein.

RESULTS

Baseline Characteristics

Of the 12,886 men enrolled in the MRFIT cohort, 11,559 men were Caucasian and 931 men were African American. Details of ethnicity information on the remaining 376 were not available, and thus, these men were excluded, leaving 12,490 men for the present analyses. Table 1 shows the descriptive characteristics of the cohort used in this analysis at the time of baseline visit. There were no statistical differences between ethnicities in terms of prevalence of diabetes, obesity, or mean serum concentrations of urate.

In cross-sectional analyses of baseline data, the mean serum urate concentration was similar for African Americans and Caucasians at 6.75 mg/dL and 6.79 mg/dL, respectively. After adjusting for age, body mass index, hypertension, diuretic use, alcohol use, aspirin use, and eGFR, African Americans were likely to have lower serum urate levels than Caucasians (6.60 mg/dL vs 6.80 mg/dL, $P < .001$), and a smaller proportion with hyperuricemia (32% vs 37%, $P = .002$). This represents a 17% lower prevalence of hyperuricemia in African Americans than in Caucasians.

Incidence of Gout and Hyperuricemia

Overall, there were 706 incident cases of gout over the 75,735 person-years of the study with an unadjusted incidence rate of 9.3 (95% confidence interval [CI], 8.7-10.0) per 1000 person-years. Among African Americans there were 49 incident cases of gout, whereas there were 657 incident cases among Caucasians. The corresponding incidence rates were 8.7 (95% CI, 6.6-11.5) and 9.4 (95% CI, 8.7-10.1), respectively. The difference in incidence between African Americans and Caucasians was not statistically significant before or after adjusting for age. In both racial groups, the incidence of gout increased with increasing serum urate concentration and with prevalence of gout-risk factors, including the components of metabolic syndrome (Figure 1). Table 2 shows the crude incidence rates of gout by strata of various risk factors. Notably, the rates were statistically significantly lower among African Americans without hypertension, African Americans who have a body mass index <25 kg/m^2, nonusers of diuretics, and those younger than 46 years of age. The incidence rates of hyperuricemia followed a similar pattern.

Cox Regression Models

Results of unadjusted and adjusted regression models are shown in Table 3. In unadjusted and age-adjusted regressions, African American ethnicity was associated with lower risk for gout, although this was not statistically significant. In multivariable-adjusted Cox regression models, African American ethnicity was associated with a lower risk for gout and hyperuricemia than was Caucasian ethnicity. This was statistically significant, and was driven by the adjustment for body mass index. When serum urate was added to the multivariable model of gout, the hazard ratio was essentially unchanged at 0.78 (95% CI, 0.68-0.90).

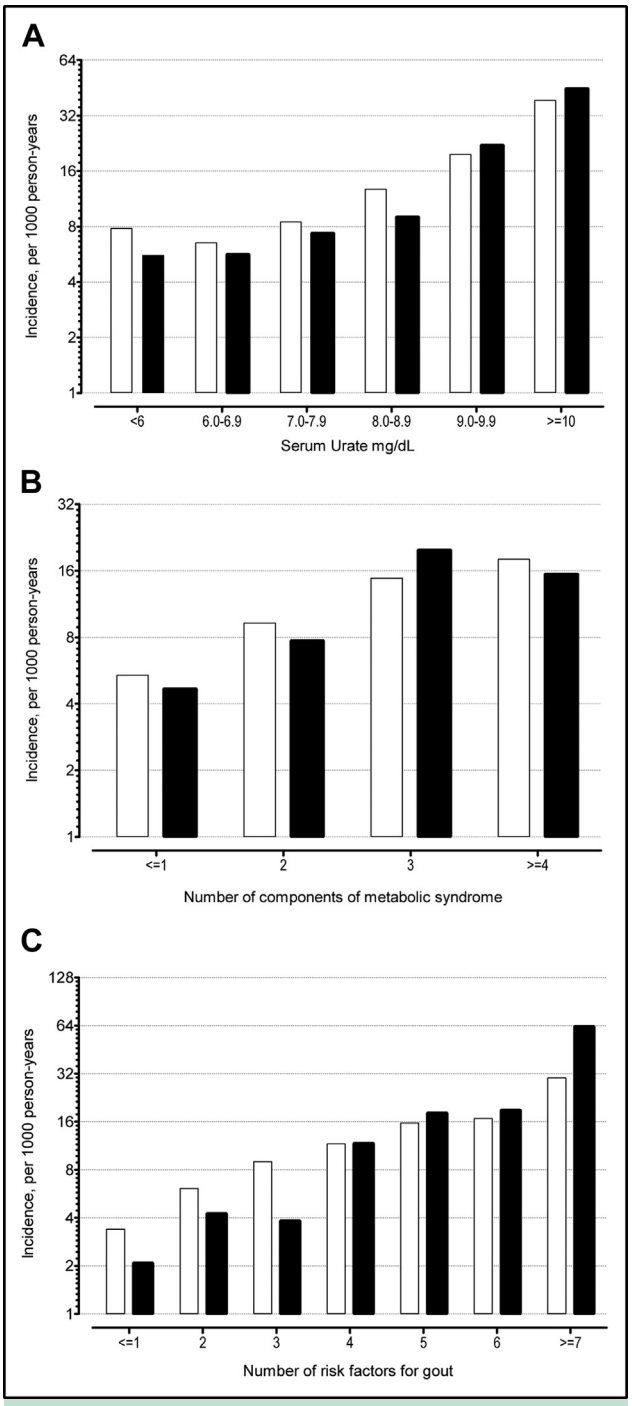

Figure 1 Comparison of incidence of gout in Caucasians (open bars) and African Americans (closed bars) by risk factor categories in the Multiple Risk Factor Intervention Trial.

On further examination, statistically significant ($P < .001$) interactions were observed between ethnicity and hypertension, diabetes, diuretic use, and body mass index. When multivariable Cox regressions were repeated for each strata (Table 4), the excess risk was statistically significant mostly among those without the risk factors, especially those

Table 2 Incidence of Physician Diagnosed Gout by Risk Factor Status: Comparison of 931 African Americans and 11,559 Caucasians in the Multiple Risk Factor Intervention Trial

	Caucasians 657 Incident Cases of Gout		African Americans 49 Incident Cases of Gout	
	Rate	95% Confidence Interval	Rate	95% Confidence Interval
Overall	8.7	(6.6-11.5)	9.4	(8.7,10.1)
Age, years				
≤46	8.3	(6.9-10.1)	6.0	(5.7-6.4)
>46	9.8	(9.6-10.1)	10.1	(6.1-18.6)
Body mass index, kg/m^2				
<25	5.6	(5.6-5.7)	1.5	(1.5-1.6)
25-30	8.9	(7.5-10.8)	8.0	(4.9-14.3)
>30	14.1	(12.1-16.7)	18.3	(11.5-30.5)
Chronic kidney disease				
Absent	8.8	(8.3-9.3)	7.5	(6.5-8.7)
Present	16.3	(15.5-17.3)	14.4	(6.1-49.6)
Diabetes				
Absent	9.2	(8.7-9.7)	8.0	(5.0-13.5)
Present	12.1	(10.3-14.5)	14.2	(11.6-17.6)
Current diuretic use				
No	7.9	(6.4-10.2)	4.9	(4.8-5.0)
Yes	11.9	(10.5-14.2)	12.5	(10-17.4)
Hypertension				
No	5.4	(4.8-6.1)	2.7	(2.2-3.3)
Yes	10.6	(10-11.3)	9.6	(6.4-15.2)
Metabolic syndrome				
Absent	7.2	(6.7-7.8)	5.9	(3.7-10.0)
Present	15.7	(15.7-15.8)	18.6	(14.5-24.8)

without hypertension. Similar results were observed for hyperuricemia as well.

Sensitivity analyses using alternate definitions of gout did not change the results. When self-reported gout was used as the case definition, the number of cases of gout was 1447 and the multivariable adjusted hazard ratio for African American ethnicity was 0.78 (95% CI, 0.62-1.00). Using either self-reported or MRFIT physician-assessed gout as the case definition, there were 1471 cases of gout and the hazard ratio was 0.80 (95% CI, 0.65-0.98). When the data were reanalyzed with the requirement for both self-reported and MRFIT physician diagnosis, the number of cases was 577 and the hazard ratio was 0.76 (95% CI, 0.67-0.86).

DISCUSSION

The present study showed that incidence of hyperuricemia and gout in a group of African Americans with high cardiovascular risk was substantially *lower* than that among Caucasians with a similar risk profile. This difference was not explained by differences in the prevalence of lifestyle or clinical risk factors for gout between these 2 groups. The reduced risk was more marked among selected subgroups of African Americans who did not have obesity or hypertension and who did not use diuretics, which increased the likelihood that the observed association may have causal underpinnings. Similar ethnic disparities also were observed with respect to the risk for incident hyperuricemia.

Table 3 Results of Multivariable Cox Regression Analyses for African American Ethnicity as a Risk Factor for Gout in the Multiple Risk Factor Intervention Trial

	Hazard Ratio for African Americans Compared with Caucasians (95% Confidence Interval)					
	Unadjusted		Age Adjusted		Final Model*	
Gout	0.94	0.63-1.40	0.95	0.64-1.41	0.78	0.66-0.93
Hyperuricemia (serum urate >7.0 mg/dL)	1.12	0.99-1.25	1.1	0.98-1.24	0.88	0.85-0.90

*Final adjusted for age, body mass index, hypertension, diabetes, alcohol use, aspirin use, and estimated glomerular filtration rate (calculated per Levey, 2009).[17]

Table 4 Multivariable Cox Regression Analyses for African American Ethnicity as a Risk factor for Gout in the Multiple Risk Factor Intervention Trial: Stratified by Presence/Absence of Individual Risk Factor

	Present		Absent	
	Hazard Ratio	95% Confidence Interval	Hazard Ratio	95% Confidence Interval
Obesity	0.66	0.55-0.79**	0.97	0.00-1.30
Hypertension	0.47	0.37-0.60**	0.80	0.65-1.00*
Diabetes	0.73	0.59-0.89**	1.10	0.68-1.78
Metabolic syndrome	0.69	0.53-0.90**	1.03	0.93-1.13
Chronic kidney disease	0.78	0.75-0.82**	0.70	0.28-1.79
Diuretics	0.56	0.47-0.67	0.95	0.89-1.02

Multivariable regressions adjusted for covariates in Table 2.
*$P < .05$.
**$P < .005$.

Prevalence rates in populations represent the net impact of incidence of new cases and exit of older cases (from mortality, migration, and disease resolution). Our incidence data are consistent with most of the incidence and prevalence data on ethnic disparities, including the one from the Meharry-Hopkins Study. In the National Health and Nutrition Examination Survey (NHANES) 2008-2009 cycle, there was no significant difference in the crude prevalence of gout and hyperuricemia between African Americans and Caucasians, although the rates were numerically higher.[6] In the NHANES 2009-2010 cycle, the age-standardized prevalence of gout was higher among African Americans, but the confidence intervals overlapped.[8] Once participants with renal impairment were excluded, however the prevalence rates were identical.[8] The US National Ambulatory Care Surveys data suggested that the proportion of outpatient visits for gout in 2002 did not differ between African Americans and Caucasians.[28] The baseline data from the Coronary Artery Risk Development in Young Adults (CARDIA) study suggest that serum urate concentrations are lower among African Americans compared with Caucasians by about 0.1 to 0.2 mg/dL.[7] After 20 years of follow-up of men in the CARDIA study cohort, there were no ethnic disparities in the risk for developing hyperuricemia. Our incidence data are not entirely consistent with some other data, such as that reported from the Atherosclerosis Risk in Communities (ARIC) study; in the ARIC cohort, African Americans were observed to have a greater incidence of gout than Caucasians.[29] In that cross-sectional study, the excess prevalence associated with African American ethnicity was mitigated when serum urate concentration was added to the statistical models. Data from the National Health Interview Survey in 1996 have been erroneously cited as suggestive of higher prevalence rates for African Americans, as the authors of the Survey report have deemed the estimates to be unreliable.[30,31]

The present study has an important implication for etiological studies of hyperuricemia and gout. Twin studies have shown that hyperuricemia is a highly heritable trait, whereas gout is not.[32] Our observations that African American ethnicity might be "protective" in terms of risk for hyperuricemia and gout (especially among those with a low prevalence of risk factors) suggest that an ethnicity-specific biological factor, rather than an environmental or lifestyle risk factor, accounts for the difference observed between African Americans and Caucasians. Such a factor could be a lower prevalence of genetic polymorphisms known to be linked with hyperuricemia[33-37] or as-yet unidentified African American-specific mutations or epigenetic factors. Important ecological evidence that supports a biological reason for low prevalence of gout in the African American population comes from numerous surveys from African countries such as South Africa, Togo, Zimbabwe, Zaire, Kenya, Ethiopia, Rwanda, and Congo, that show extremely low prevalence of gout.[38,39]

Caveats are due. There were no women in this study. Studies of ethnic disparities need to be interpreted by taking into account differences in selection of study participants from the underlying population; the more different the enrollment algorithms between the ethnicities, the higher the risk for unquantified bias. Although the MRFIT tended to randomize relatively healthier people, who were less likely to be African American,[40] it screened a very large number of participants (n = 361,662), and relatively few participants dropped out voluntarily (n = 12,679, 3.5%). Furthermore, in the present study, the baseline study suggested that the prevalence of risk factors for gout (hypertension, renal impairment, and diuretic use) tended to be higher for African Americans, suggesting that the impact of any such selection bias would be toward the null hypothesis. Finally, the case definition we used for primary analyses, physician-diagnosed gout, was not standardized, adding an element of measurement error that might have increased the statistical variance and biased the results toward the null.

In conclusion, the present analyses suggest that African American ethnicity is associated with a lower risk for gout and hyperuricemia. This may explain the relatively low prevalence of gout and hyperuricemia among this demographic segment despite a substantially higher risk profile. Further studies are needed to assess whether African Americans with gout have a different clinical profile in terms of disability erosions and tophi.

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