Published in final edited form as:

Am J Med. 2012 July ; 125(7): 717.e9–717.e17. doi:10.1016/j.amjmed.2011.11.018.

Incident Gout in Women and Association with Obesity in the Atherosclerosis Risk in Communities (ARIC) Study

Janet W. Maynard, MD, MHS¹, Mara A. McAdams DeMarco, MS², Alan N. Baer, MD¹, Anna Köttgen, MD, MPH^{2,3}, Aaron R. Folsom, MD, MPH⁴, Josef Coresh, MD, PhD², and Allan C. Gelber, MD, MPH, PhD^{1,2}

¹Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

²Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

³Renal Division, Freiburg University Hospital, Freiburg, Germany

⁴Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN

Abstract

Background—We hypothesized that women with early- and mid-adult life obesity, as well as high mid-adult life waist-to-hip ratios, and high weight gain during adulthood, experience a greater incidence of gout.

Methods—We examined the incidence of gout in the Atherosclerosis Risk in Communities (ARIC) Study, a population-based biracial cohort comprised of individuals aged 45–65 years of age at baseline (1987–1989). A total of 6,263 women without prior history of gout were identified. We examined the association of BMI and obesity at cohort entry and at age 25 years, waist-to-hip ratio and weight change, with gout incidence (1996–1998).

Results—Over 9 years of follow-up, 103 women developed gout. The cumulative incidence of gout, by age 70 years, according to BMI category at baseline of <25, 25–29.9, 30–34.9, and 35 kg/m², was 1.9, 3.6, 7.9, and 11.8%, respectively (P <0.001). Obese women (BMI ≥30) at baseline had an adjusted 2.4-fold greater risk of developing gout than non-obese women (95% confidence interval (CI) 1.53, 3.68). This association was attenuated after further adjustment for urate levels. Further, early adult obesity in women was associated with a 2.8-fold increased risk of gout compared to non-obese women (95% CI 1.33, 6.09), which remained statistically significant after baseline urate adjustment. There was a graded association between each anthropometric measure, including weight gain, with incident gout (each P for trend <0.001). The results were similar in black and white women.

© 2011 Elsevier Inc. All rights reserved.

Address correspondence to: Allan C. Gelber, MD, MPH, PhD, 5200 Eastern Avenue, Mason F. Lord Building, Center Tower, Suite 4100, Baltimore, MD 21224, Phone: (410) 550-2018, Fax: (410) 550-2072, agelber@jhmi.edu.

Conflict of Interest Statement: None of the authors has a potential conflict of interest with the statements made in this manuscript.

All authors had access to the data and all had a role in writing the manuscript.

Financial Disclosure: Alan Baer and Mara McAdams Demarco received grant funding from the Takeda Pharmaceuticals North America, Inc. in support of their effort on this project.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conclusions—In a large cohort of African American and Caucasian women, obesity in early and mid-adulthood, and weight gain during this interval, were each independent risk factors for incident gout in women.

Keywords

Gout; Women; Obesity; Weight; Arthritis

INTRODUCTION

Gout is a highly prevalent form of inflammatory arthritis (1) and the management of this condition occurs principally by primary care providers (2). Patients suffer from abrupt episodes of incapacitating joint pain and poor quality of life (3, 4). Typically, gout is viewed as a disease of men, in whom prevalence is more than twice that of women (1). The majority of previous studies focused on gout in men (5–10). Several cohorts evaluated predictive factors, including weight and race, entirely in men (5, 6, 9). However, women also suffer from gout.

Over the past 20 years, the incidence of gout has increased. One study showed that the age- and gender-adjusted incidence of primary gout has doubled in Olmsted County, Minnesota (11). The prevalence of gout in American women is also increasing (1, 12). While a number of recent studies have investigated the epidemiology of gout in women (13–16), none have examined the association of weight change from early to mid-adult life, waist-to-hip ratio (WHR), nor studied the epidemiology of gout in a biracial population-based setting.

Understanding the impact of anthropometric measures on the risk of gout is especially important given the rising incidence of obesity (17, 18). Notably, whereas studies of incident cardiovascular disease suggest that WHR is more predictive of coronary heart disease than other anthropometric measures, (19), no previous studies have investigated WHR and incident gout risk in women. We hypothesized that women with early- and mid-adult life obesity, as well as high mid-adult life waist-to-hip ratios, and high weight gain during adulthood, experience a greater incidence of gout than women without these profiles. We examined these hypotheses in the Atherosclerosis Risk in Communities (ARIC) Study, which included 6,263 women of both African American and white race, including 106 women who developed gout over 9 years of follow-up.

METHODS

Study population

The ARIC study is an ongoing, NIH-sponsored, prospective population-based cohort of 15,792 persons (55% female) aged 45–64 years. Participants were selected by probability sampling from four US communities (Forsyth County, NC; Jackson, MS; the northwestern suburbs of Minneapolis, MN; and Washington County, MD). A baseline examination occurred between 1987 and 1989, with three follow-up visits, thereafter, administered three years apart (visit 2: 1990–1992; visit 3: 1993–1995; visit 4: 1996–1998) (20, 21). Institutional Review Boards of the participating institutions approved the study protocols. All participants provided written informed consent. The present report consists of the female ARIC participants who self-reported white or black race and indicated their gout status at visit 4 (n=6,406). In addition, 143 women with prevalent gout were excluded, leaving 6,263 women in the final analyses (Figure 1).

Assessment of gout

A woman was considered to have gout if she responded affirmatively to the query: “Has a doctor ever told you that you had gout?” administered at ARIC visit 4 (1996–1998). The age of gout onset was derived from the subsequent question: “How old were you when you were first told that you had gout?” Prevalent gout was defined as gout which occurred at a younger age than the participant’s age at the ARIC baseline assessment (1987–89). Incident gout was defined as development of gout between visit 1 (1987–89) and visit 4 (1996–1998). Our previous research indicates that self-report of a physician diagnosis of gout is both a reliable (3-year reliability kappa=0.73) and sensitive (sensitivity=84%) measure of gout (22).

Assessment of anthropometric measures

At the baseline visit, anthropometric data were obtained. Weight and height were measured in a scrub suit using a standard protocol (23). BMI was calculated as the weight in kilograms (kg) divided by the square of the height in meters (m). At enrollment, participants self-reported their weight at age 25 years; the validity of self-reported weight in early adult life has been validated in the Nurses’ Health Study II Cohort (24). Weight change was calculated by subtracting the participants’ self-reported weight at age 25 from measured body weight at baseline. Waist (umbilical level) and hip (maximum buttocks) circumferences were measured to the nearest centimeter while standing (23).

First, baseline BMI was dichotomized as those obese (BMI ≥ 30 kg/m²) versus those not obese (BMI < 30 kg/m²). In additional analyses, BMI at baseline was grouped into four categories: normal weight (BMI < 25 kg/m²), overweight (BMI 25–29.9 kg/m²), class I obesity (BMI 30–34.9 kg/m²), and class II or III obesity (BMI ≥ 35 kg/m²) (25). Baseline waist-to-hip ratios (WHR) were categorized as: tertile 1 (WHR < 0.900), tertile 2 (WHR 0.901–0.967), and tertile 3 (WHR ≥ 0.968). BMI at age 25 years was grouped into three categories only: normal weight (BMI < 25 kg/m²), overweight (BMI 25–29.9 kg/m²), and obese (BMI ≥ 30 kg/m²). Weight change was divided into tertiles: tertile 1 (weight gain < 6.8 kg), tertile 2 (weight gain 6.8–16.2 kg), and tertile 3 (weight gain ≥ 16.3 kg).

Assessment of covariates

Central laboratories performed analyses on baseline fasting serum and plasma specimens (26). Prevalent diabetes mellitus was defined as a fasting glucose level of 126 mg/dL or greater, nonfasting glucose level of 200 mg/dL or greater, reported physician-diagnosis of diabetes, or medication use for diabetes at baseline assessment (27). Participants were considered to have prevalent hypertension if they had a systolic value of ≥ 140 mm Hg, a diastolic value ≥ 90 mm Hg (28), or use of a medication to treat hypertension. Participants brought all prescription medications used in the two weeks prior to the visit.

Serum creatinine was measured using a modified kinetic Jaffé reaction. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (29, 30). Serum creatinine concentration was corrected for interlaboratory differences and calibrated to the Cleveland Clinic measurement by subtraction of 0.24 mg/dL (31, 32). We classified participants into three groups on the basis of thresholds of eGFR: ≥ 90 , 60–89, or 30–59 ml/min/1.73m². There were no participants (with or without gout) with an eGFR < 30 . Serum urate concentrations were measured with the uricase method at baseline and at visit 2 in mg/dL. The reliability coefficient of serum urate was 0.91; the coefficient of variation was 7.2% in a sample of 40 individuals with repeated measures taken at least 1 week apart (33).

Diet was assessed with an interviewer-administered 66-item semiquantitative food-frequency questionnaire (FFQ) (34). The reproducibility of the Willett questionnaire in this cohort has been previously reported (35). We focused on animal protein, organ meat, shellfish, and alcohol intake as dietary covariates of interest (7, 8). Reported intake of animal protein was analyzed in grams per day. Reported organ meat consumption was dichotomized to at least twice per month or less than twice per month, while shellfish consumption was dichotomized as greater versus less than once weekly. Alcohol intake was reported as number of drinks (10 grams) per day.

At baseline, women completed an interviewer-administered questionnaire regarding menopausal status and leisure time activity (36). A physical activity index was then derived which ranged from 1 (low activity) to 5 (high activity). The physical activity index was grouped into tertiles: tertile 1 (1–2.25), tertile 2 (2.30–2.75) and tertile 3 (2.80–5). Menopause was categorized as pre- or post-menopausal.

Statistical analysis

The distributions of baseline variables among women with and without gout were compared using chi-squared or t-tests, as appropriate. Kaplan-Meier cumulative incidence plots examined time to development of gout, according to baseline BMI categories. The log-rank test was used to compare the cumulative incidence by category of baseline BMI, waist-to-hip ratio, BMI categories at age 25 years, and weight change. Using Cox proportional hazards analysis, we examined the independent association of the five anthropometrics with gout incidence.

Separate models were examined for each anthropometric measure to estimate the relative risk (RR) of incident gout according to: 1) baseline obesity, 2) baseline BMI categories, 3) baseline WHR, 4) BMI categories at age 25 years, and 5) weight change from age 25 years to cohort entry. Each model was first adjusted for age, then adjusted for additional potential confounders (age, menopausal status, race, prevalent diabetes status, hypertension status, diuretic use, alcohol intake, organ meat intake, and eGFR), as in prior studies (9, 14, 37). A third set of models adjusted for baseline urate levels to determine if the relationship between the various anthropometric measures and incident gout were mediated by serum urate.

Furthermore, to evaluate whether the association of baseline BMI categories was independent of each of the other anthropometric measures, we additionally adjusted for one of the following anthropometric variables (WHR, weight at age 25 years, and weight change between baseline and age 25 years). This process was repeated to evaluate the association of WHR and BMI categories at age 25 years with incident gout, while simultaneously adjusting for another anthropometric variable.

A sensitivity analysis evaluated whether changing the gout case definition altered the results. In this analysis, gout cases were defined as participants who self-reported gout and were either using a medication recognized primarily to treat gout (colchicine, probenecid, or allopurinol) or had an ICD-9 code for gout (274.0, 274.1, 274.8, or 274.9) in a hospital discharge summary. Lastly, we performed stratified analyses to determine whether race modified the association of obesity with incident gout. We tested whether an interaction was statistically significant using the two-sided P value derived from the Wald test of the interaction term. All analyses were conducted using Stata IC, version 10.0.

RESULTS

There were 6,263 women included in this study (Figure 1), 106 of whom developed gout over 9 years of follow-up. Overall, the cumulative incidence of gout was 4.6% (95% CI

3.7%, 5.6%) by age 70 years. Older age, black race, greater BMI at baseline and at age 25, higher WHR, greater weight gain, hypertension, diuretic use, diabetes, and decreased GFR at baseline were each associated with incident gout in the ARIC women (Table 1). Only 13.3% of the participants with gout were of normal weight, compared to 40.3% of participants without gout ($P<0.001$). The baseline characteristics of this cohort, stratified by gender and sex, have been previously presented (38).

Obesity, BMI, Waist-to-Hip Ratio, and Incident Gout

The cumulative incidence of gout by age 70 years in the ARIC women increased with successively higher categories of BMI at baseline (Figure 2; log rank $P<0.001$). As such, the cumulative incidence of gout, according to BMI category at baseline of <25 , 25–29.9, 30–34.9, and ≥ 35 kg/m², were 1.9, 3.6, 7.9, and 11.8%, respectively (Table 2). Similarly, the cumulative incidence of gout increased with increasing categories of the other anthropometric variables, in a similar manner (log rank $p<0.001$ for each).

Obese women at baseline were more than three-fold more likely to develop gout than non-obese women (RR 3.49; 95% CI 2.37, 5.14) (Table 3). This association persisted after adjustment for age, menopausal status, race, dietary intake of organ meat and alcohol, and co-morbid conditions. The risk of gout increased with each increase in BMI category (P for trend <0.001). Notably, further adjustment for urate levels attenuated the association between baseline obesity and BMI category with gout and was no longer statistically significant, indicating that the association of obesity at baseline with the development of gout was mediated in part by level of serum uric acid.

Similarly, body fat distribution represented by WHR, was associated with the development of gout. Women with a WHR in the highest tertile had a more than two-fold increase in risk of gout (RR 2.78; 95% CI 1.65, 4.70) compared to those in the leanest tertile, even after adjustment for potential confounders (Table 3). The association between WHR and gout was similarly attenuated though remained significant after adjusting for urate levels.

Early Adult Weight, Weight Change and Incident Gout

The prevalence of obesity among the women in the ARIC study at age 25 years was 3.0%. Compared to individuals with a BMI of <25 kg/m² at age 25 years, a greater than 2-fold increase in gout incidence was observed for women with a BMI of 25–29.9, and for women with a BMI of ≥ 30 kg/m², which persisted after adjustment for other risk factors, including urate levels (Table 3).

On average, women in the cohort gained weight between age 25 years and baseline evaluation in ARIC. Only six participants (5.3%) who developed gout lost weight over this interval, compared to 440 participants (7.1%) without gout. The mean weight gain for women without gout was 14.4kg (SD 12.8kg) compared to 20.6kg (SD 15.3kg) for women with gout ($P<0.001$). Women with the highest tertile of weight gain (≥ 16.3 kg) had a four-fold increase in risk of incident gout compared with individuals in the lowest tertile (RR 4.20; 95% CI 2.26, 7.79; Table 3). This association retained statistical significance after adjustment for confounders. However, weight change was no longer related to incident gout after adjustment for urate levels.

Independent Effect of Anthropometric Variables

When BMI at baseline was adjusted for one of the three other anthropometric measures, the risk of incident gout was minimally altered and remained statistically significant (Table 4). This pattern persisted when baseline waist-to-hip ratio and BMI at age 25 years were similarly adjusted for the other parameters. Of note, women who were overweight in early

adulthood remained at heightened risk to develop gout, even after taking into account their weight gain to middle adult life.

Sensitivity Analyses

In a sensitivity analysis, in which the gout case definition was restricted to individuals who self-reported gout and were taking either a medication used primarily to treat gout or had an ICD-9 hospital discharge diagnosis for gout (n=54), the results were minimally attenuated and remained statistically significant. The results did not differ by race in stratified analyses (interaction term $p=0.50$).

DISCUSSION

Among the women in the ARIC cohort, mid- and early-adult obesity, high mid-adult WHR, and weight gain were each associated with an increased risk of developing gout. Furthermore, even ARIC participants who were categorized as overweight had an increased risk of incident gout. The magnitude of the association between BMI and gout increased with increasing categories of BMI, indicative of a dose-response association. These associations were independent of other measured risk factors for gout. Importantly, the relationship between mid-adult obesity and gout was mediated by elevated urate levels. In contrast, early adult obesity was still associated with gout risk even after controlling for mid-adult urate levels.

Our findings extend previous reports (15, 16, 39–41) by evaluating gout incidence in a large, population-based cohort of women. Most previous studies were performed in white, male, health professionals (7–9) or white females from either one profession (e.g. nursing) (15, 16) or geographic region (14). In contrast, we examined a population-based cohort of 6,270 women, of which 106 developed incident gout over 9 years of follow-up. Our approach included detailed anthropometric data. In addition, 25.4% of our cohort was black, while most previous cohorts were comprised primarily of white participants (15, 16, 39–41), or examined female gout in the hospital or referral setting (39, 41). Notably, in a recent report examining the Framingham cohort (14), obesity in mid-life was related to gout risk among women. Similar findings were noted in the prospective CLUE cohort in Hagerstown, Maryland (42). However, both these cohorts were overwhelmingly white in demographic composition and did not focus on other anthropometric risk factors.

Hypertension and diabetes are associated with gout and likely contribute to hyperuricemia (14, 39, 41, 43). Prior study in the ARIC cohort has shown that most coronary heart disease risk factors, including BMI and WHR, are associated with increased serum urate (44). Increased urate production and decreased renal excretion both contribute to hyperuricemia in the setting of obesity (45, 46). Our data suggest that elevated urate levels mediate the association between gout and mid-adult obesity and with weight gain.

Study Strengths and Limitations

A number of limitations warrant attention. Our definition of gout did not require observation of monosodium urate crystals in joint fluid or fulfillment of the ACR criteria for gout (48). However, in population-based studies, access to synovial fluid analysis is logistically challenging. Previous epidemiological studies have used gout ICD-9 codes (43) and self-reported gout status (13, 49), including important genetic analyses from the ARIC cohort (50, 51). Self-reported gout ascertainment could lead to misclassification. Nonetheless, the findings remain consistent, even in sensitivity analyses utilizing a stricter case definition of gout, emphasizing the robustness of our findings. Ascertainment of gout was conditional on survival to and participation in visit 4, when gout status was ascertained. In addition,

diagnostic suspicion bias is possible. Though weight at age 25 was self-reported, this is a valid measure for epidemiological studies (24, 52). Several strengths include the relatively large number of female gout cases with detailed anthropometric measurements. ARIC included many important covariates, including eGFR and dietary intake, which enabled adjustment for confounding. Additionally, the population-based study composition of ARIC offers a racially and geographically diverse population in which to study gout epidemiology in women.

In conclusion, in the large population-based ARIC study, obesity and weight gain were associated with greater risk of gout incidence among women. The increased risk of gout associated with obesity is observed in both whites and blacks. The cumulative incidence of gout by age 70 years was 4.6% supporting recent data that gout is a common form of inflammatory arthritis in women. Physicians need recognize that obesity in both early- and mid- adulthood, and central adiposity, are each independent risk factors for the development of gout in women. These findings further imply that among women, excess body weight and weight gain from young to mid-adult life, are optimal targets to identify in the primary prevention of gout.

Acknowledgments

We thank the staff and participants of the ARIC Study for their important contributions.

Funding Source: The ARIC Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. In addition, Dr. Maynard was supported by NIH 1KL2RR025006. Ms. McAdams Demarco was supported NIH NHLBI 5T32HL007024. Drs. Janet Maynard, Allan Gelber and Alan Baer were supported by the Donald B. and Dorothy Stabler Foundation. Dr. Allan Gelber was also supported by the Ira T. Fine Discovery Fund. Dr. Anna Kottgen was supported by the Emmy Noether Program of the German Research Foundation.

References

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008; 58(1):26–35. [PubMed: 18163497]
2. Pal B, Foxall M, Dysart T, Carey F, Whittaker M. How is gout managed in primary care? A review of current practice and proposed guidelines. *Clin Rheumatol.* 2000; 19(1):21–5. [PubMed: 10752494]
3. Singh JA. Quality of life and quality of care for patients with gout. *Curr Rheumatol Rep.* 2009; 11(2):154–60. [PubMed: 19296889]
4. Roddy E, Zhang W, Doherty M. Is gout associated with reduced quality of life? A case-control study. *Rheumatology (Oxford).* 2007; 46(9):1441–4. [PubMed: 17586863]
5. 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(5):628–32. [PubMed: 7748218]
6. Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC. Incidence and risk factors for gout in white men. *JAMA.* 1991; 266(21):3004–7. [PubMed: 1820473]
7. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet.* 2004; 363(9417):1277–81. [PubMed: 15094272]
8. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med.* 2004; 350(11):1093–103. [PubMed: 15014182]
9. 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(7): 742–8. [PubMed: 15824292]

10. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ*. 2008; 336(7639):309–12. [PubMed: 18244959]
11. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? *J Rheumatol*. 2002; 29(11):2403–6. [PubMed: 12415600]
12. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008; 58(1):15–25. [PubMed: 18163481]
13. Cea Soriano L, Rothenbacher D, Choi HK, Garcia Rodriguez LA. Contemporary epidemiology of gout in the UK general population. *Arthritis Res Ther*. 2011; 13(2):R39. [PubMed: 21371293]
14. Bhole V, de Vera M, Rahman MM, Krishnan E, Choi H. Epidemiology of gout in women: Fifty-two-year followup of a prospective cohort. *Arthritis Rheum*. 2010; 62(4):1069–76. [PubMed: 20131266]
15. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA*. 2010; 304(20):2270–8. [PubMed: 21068145]
16. Choi HK, Curhan G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. *Am J Clin Nutr*. 2010; 92(4):922–7. [PubMed: 20739424]
17. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002; 287(3):356–9. [PubMed: 11790215]
18. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA*. 2002; 288(14):1723–7. [PubMed: 12365955]
19. Canoy D, Boekholdt SM, Wareham N, Luben R, Welch A, Bingham S, et al. Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk cohort: a population-based prospective study. *Circulation*. 2007; 116(25):2933–43. [PubMed: 18071080]
20. The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989; 129(4):687–702. [PubMed: 2646917]
21. Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, et al. Differences between respondents and nonrespondents in a multicenter community-based study vary by gender ethnicity. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *J Clin Epidemiol*. 1996; 49(12):1441–46. [PubMed: 8970495]
22. McAdams MA, Maynard JW, Baer AN, Kottgen A, Clipp S, Coresh J, et al. Reliability and sensitivity of the self-report of physician-diagnosed gout in the campaign against cancer and heart disease and the atherosclerosis risk in the community cohorts. *J Rheumatol*. 2011; 38(1):135–41. [PubMed: 21123328]
23. Idem. Operations manual no. 2: cohort component procedures, version 1.0. Chapel Hill: University of North Carolina School of Public Health; 1987.
24. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer M, Willett W. The validity of recalled weight among younger women. *Int J Obes Relat Metab Disord*. 1995; 19(8):570–2. [PubMed: 7489028]
25. Obesity: Preventing and Managing the Global Epidemic: Report of a WHO Consultation on Obesity; 3–5 June 1997; Geneva. Geneva, Switzerland: World Health Organization; p. 2998Publication WHO/NUT/NCD/98.1
26. Center ARICC. Operations manual no. 10: clinical chemistry determinations, version 1.0. Chapel Hill: University of North Carolina School of Public Health; 1987.
27. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med*. 2010; 362(9): 800–11. [PubMed: 20200384]
28. Idem. Operations manual no. 11: sitting blood pressure, version 1.0. Chapel Hill: University of North Carolina School of Public Health; 1987.
29. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150(9):604–12. [PubMed: 19414839]

30. Astor BC, Arnett DK, Brown A, Coresh J. Association of kidney function and hemoglobin with left ventricular morphology among African Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am J Kidney Dis.* 2004; 43(5):836–45. [PubMed: 15112174]
31. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol.* 2003; 41(1):47–55. [PubMed: 12570944]
32. Coresh J, Astor BC, McQuillan G, Kusek J, Greene T, Van Lente F, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. *Am J Kidney Dis.* 2002; 39(5):920–9. [PubMed: 11979335]
33. Eckfeldt JH, Chambless LE, Shen YL. Short-term, within-person variability in clinical chemistry test results. Experience from the Atherosclerosis Risk in Communities Study. *Arch Pathol Lab Med.* 1994; 118(5):496–500. [PubMed: 8192558]
34. 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(1):51–65. [PubMed: 4014201]
35. Stevens J, Metcalf PA, Dennis BH, Tell GS, Shimakawa T. Reliability of a food frequency questionnaire by ethnicity, gender, age, and education. *Nutrition Research.* 1996; 16(5):735–45.
36. Richardson MT, Ainsworth BE, Wu HC, Jacobs DR Jr, Leon AS. Ability of the Atherosclerosis Risk in Communities (ARIC)/Baecke Questionnaire to assess leisure-time physical activity. *Int J Epidemiol.* 1995; 24(4):685–93. [PubMed: 8550264]
37. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med.* 1987; 82(3):421–6. [PubMed: 3826098]
38. Mellen PB, Bleyer AJ, Erlinger TP, Evans GW, Nieto FJ, Wagenknecht LE, et al. Serum uric acid predicts incident hypertension in a biethnic cohort: the atherosclerosis risk in communities study. *Hypertension.* 2006; 48(6):1037–42. [PubMed: 17060502]
39. Puig JG, Michan AD, Jimenez ML, Perez de Ayala C, Mateos FA, Capitan CF, et al. Female gout. Clinical spectrum and uric acid metabolism. *Arch Intern Med.* 1991; 151(4):726–32. [PubMed: 2012455]
40. Bhole V, Choi JW, Kim SW, de Vera M, Choi H. Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am J Med.* 2010; 123(10):957–61. [PubMed: 20920699]
41. Lally EV, Ho G Jr, Kaplan SR. The clinical spectrum of gouty arthritis in women. *Arch Intern Med.* 1986; 146(11):2221–5. [PubMed: 3778053]
42. McAdams DeMarco, Mara A.; Maynard, Janet W.; Huizinga, Mary Margaret; Baer, Alan N.; Köttgen, Anna; Gelber, Allan C.; Coresh, Josef. Younger age at gout onset is related to obesity in a community-based cohort. *Arthritis Care Res (Hoboken).* 2011 Aug; 63(8):1108–1114.10.1002/acr.20479 [PubMed: 21485022]
43. Harrold LR, Yood RA, Mikuls TR, Andrade SE, Davis J, Fuller J, et al. Sex differences in gout epidemiology: evaluation and treatment. *Ann Rheum Dis.* 2006; 65(10):1368–72. [PubMed: 16644784]
44. Moriarty JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. *Ann Epidemiol.* 2000; 10(3):136–43. [PubMed: 10813506]
45. Matsuura F, Yamashita S, Nakamura T, Nishida M, Nozaki S, Funahashi T, et al. Effect of visceral fat accumulation on uric acid metabolism in male obese subjects: visceral fat obesity is linked more closely to overproduction of uric acid than subcutaneous fat obesity. *Metabolism.* 1998; 47(8):929–33. [PubMed: 9711987]
46. Fam AG. Gout, diet, and the insulin resistance syndrome. *J Rheumatol.* 2002; 29(7):1350–5. [PubMed: 12136887]
47. Roubenoff R. Gout and hyperuricemia. *Rheum Dis Clin North Am.* 1990; 16(3):539–50. [PubMed: 2217957]
48. 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(3):895–900. [PubMed: 856219]

49. Gelber AC, Klag MJ, Mead LA, Thomas J, Thomas DJ, Pearson TA, et al. Gout and risk for subsequent coronary heart disease. The Meharry-Hopkins Study. *Arch Intern Med.* 1997; 157(13): 1436–40. [PubMed: 9224221]
50. Dehghan A, Kottgen A, Yang Q, Hwang SJ, Kao WL, Rivadeneira F, et al. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. *Lancet.* 2008; 372(9654):1953–61. [PubMed: 18834626]
51. Yang Q, Kottgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. *Circ Cardiovasc Genet.* 2010; 3(6):523–30. [PubMed: 20884846]
52. McAdams MA, Van Dam RM, Hu FB. Comparison of self-reported and measured BMI as correlates of disease markers in US adults. *Obesity (Silver Spring).* 2007; 15(1):188–96. [PubMed: 17228047]

Figure 1.
Flowchart of ARIC participants

Figure 2. Cumulative Incidence of Gout in Women According to Baseline BMI Category in the ARIC Study

Table 1

Baseline (1987–89) Characteristics among 6,263 Women in ARIC According to Gout Status

Risk Factor	Women with gout (n=106)	Women without gout (n=6,157)	P value
Age, yr (mean $\pm$ SD)	54.6 $\pm$ 5.9	53.5 $\pm$ 5.6	<0.03
Black race	56 (52.8)	1,531 (24.9)	<0.001
Serum Urate, mg/dL (mean $\pm$ SD)	7.4 $\pm$ 2.2	5.3 $\pm$ 2.2	<0.001
Anthropometric Risk Factors			
Baseline BMI Categories			<0.001
<25	14 (13.3)	2,479 (40.3)	
25–29.9	31 (29.5)	1,969 (32.0)	
30–34.9	28 (26.7)	1,058 (17.2)	
35	32 (30.5)	649 (10.5)	
Baseline Waist-to-Hip Ratio in Tertiles			<0.001
<0.900	32 (30.2)	3,343 (54.3)	
0.901–0.967	29 (27.4)	1,729 (28.1)	
0.968	45 (42.5)	1,082 (17.6)	
BMI Categories at Age 25 Years			<0.001
<25	64 (62.8)	5,355 (87.8)	
25–29.9	29 (28.4)	568 (9.3)	
30	9 (8.8)	178 (2.9)	
Weight Change From Age 25 Years to Baseline in Tertiles			<0.001
<6.8kg	12 (11.9)	1,331 (21.8)	
6.8 to 16.2kg	28 (27.7)	1,962 (32.2)	
16.3kg	61 (60.4)	2,806 (46.0)	
Comorbidities			
Hypertension	68 (64.2)	1,884 (30.7)	<0.001
Diuretic use	50 (47.2)	1,142 (18.6)	<0.001
Diabetes mellitus	23 (21.6)	516 (8.5)	<0.001
eGFR (ml/min/1.73m ²) (mean $\pm$ SD)	89.0 $\pm$ 21.1	93.6 $\pm$ 15.4	0.02
Baseline Urate (mg/dL) (mean $\pm$ SD)	7.43 $\pm$ 2.16	5.33 $\pm$ 1.30	<0.001
Leisure Time Physical Activity in Tertiles			0.14
1–2.25	58 (54.7)	2,918 (47.5)	
2.30–2.75	24 (22.6)	1,938 (31.5)	
2.80–5	24 (22.6)	1,292 (21.0)	
Dietary Risk Factors			
Protein (grams/day) (mean $\pm$ SD)	55.1 $\pm$ 23.0	51.7 $\pm$ 22.6	0.14
Organ meat (>2 serving/month)	19 (18.1)	729 (11.9)	0.07
Shellfish (>1 serving/week)	8 (7.6)	505 (8.2)	0.83
Alcohol (drinks/day)	0.27 $\pm$ 0.78	0.29 $\pm$ 0.71	0.73
Postmenopausal	68 (70.9)	3,523 (65.5)	0.28

Abbreviations: SD (standard deviation), BMI (body mass index), eGFR (estimated glomerular filtration rate) Values are shown as number (percent) unless otherwise indicated. Analyses performed with chi-squared or t-test as appropriate. Sample size ranged from 6,137–6,270 due to missing values among the various risk factors.

Table 2

Cumulative Incidence of Gout According to Increasing Categories of Baseline BMI, Waist-to-Hip Ratio Tertiles, BMI Categories at Age 25 Years, and Weight Change Tertiles Among Women in the ARIC Study

Cumulative Incidence at Age 70 years		95% Confidence Interval
Baseline BMI Categories		
BMI<25	0.02	(0.01, 0.03)
BMI 25–29.9	0.03	(0.02, 0.05)
BMI 30–34.9	0.08	(0.05, 0.12)
BMI >35	0.12	(0.08, 0.17)
Baseline Waist-to-Hip Ratio in Tertiles		
<0.900	0.02	(0.02, 0.04)
0.901–0.967	0.04	(0.03, 0.06)
0.968	0.10	(0.07, 0.13)
BMI Categories at Age 25 Years		
<25	0.03	(0.02, 0.04)
25–29.9	0.15	(0.10, 0.22)
30	0.13	(0.06, 0.27)
Weight Change between Baseline and Age 25 Years in Tertiles		
<6.8kg	0.02	(0.01, 0.03)
6.8 to 16.2kg	0.04	(0.03, 0.06)
16.3kg	0.07	(0.05, 0.09)

Abbreviations: BMI (body mass index); CI (confidence interval)

Table 3

Relative Risk of Gout Among Women in the ARIC Study According to Body Mass Index at Baseline (1987–89) and at Age 25 Years, Waist-to-Hip Ratio, and Weight Change

Risk factor	Model 1	Model 2	Model 3			
	RR	95% CI	RR	95% CI		
Baseline Obesity						
BMI<30	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
BMI 30	3.49	2.37, 5.14	2.37	1.53, 3.68	1.38	0.88, 2.17
Baseline BMI Categories						
<25	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
25–29.9	2.72	1.44, 5.11	1.63	0.84, 3.18	1.12	0.57, 2.22
30–34.9	4.64	2.44, 8.82	2.76	1.40, 5.44	2.24	0.60, 2.55
35	8.69	4.63, 16.28	3.90	1.95, 7.82	1.82	0.90, 3.69
<i>P for trend</i>	<0.001		<0.001		0.06	
Baseline Waist-to-Hip Ratio in Tertiles						
<0.900	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
0.901–0.967	1.65	0.99–2.74	1.56	0.91, 2.69	1.11	0.64, 1.92
0.968	3.87	2.43–6.14	2.78	1.65, 4.70	1.74	1.02, 2.95
<i>P for trend</i>	<0.001		<0.001		0.04	
BMI Categories at Age 25 Years						
<25	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
25–29.9	4.23	2.73, 6.56	3.36	2.09, 5.41	2.75	1.71, 4.42
30	4.30	2.14, 8.64	2.84	1.33, 6.09	2.20	1.03, 4.70
<i>P for trend</i>	<0.001		<0.001		<0.001	
Weight Change between Baseline and Age 25 Years						
<6.8kg	1.00	(Ref)	1.00	(Ref)	1.00	(Ref)
6.8 to 16.2kg	2.10	1.07, 4.12	1.54	0.77, 3.08	1.14	0.57, 2.29
16.3kg	4.20	2.26, 7.79	2.05	1.06, 3.96	0.95	0.48, 1.89
<i>P for trend</i>	<0.001		0.03		0.72	

Abbreviations: BMI (body mass index), RR (relative risk), CI (confidence interval), Ref (reference)

Model 1: Adjusted for age (years)

Model 2: Adjusted for age (years), menopausal status (pre or post), race (black or white), diabetes (yes or no), hypertension (yes or no), diuretic use (yes or no), alcohol intake (drinks per day), organ meat intake (≥ 2 servings per month or < 2 servings per month), and eGFR (categorical)

Model 3: Adjusted for covariates in model 2 and urate (continuous)

Statistically significant ($p < 0.05$) values in **bold**

Table 4

Adjusted Relative Risk of Incident Gout Among Women in the ARIC, in with Further Adjustment for One Other Anthropometric Measure

	Model 1^{\$} Additionally Adjusted for Baseline Weight RR (95% CI)	Model 2[^] Additionally Adjusted for Waist-to-Hip Ratio RR (95% CI)	Model 3^{&} Additionally Adjusted for Weight at Age 25 Years RR (95% CI)	Model 4[@] Additionally Adjusted for Weight Change RR (95% CI)
Baseline BMI Categories				
<25	---	1.00 (Ref.)	1.00 (Ref)	1.00 (Ref)
25–29.9	---	1.46 (0.74, 2.88)	1.45 (0.75, 2.88)	1.56 (0.74, 3.30)
30–34.9	---	2.24 (1.10, 4.57)	2.21 (1.10, 4.45)	3.06 (1.32, 7.13)
35	---	2.10 (1.38, 6.14)	2.55 (1.19, 5.47)	4.69 (1.96, 11.22)
Baseline Waist-to-Hip Ratio in Tertiles				
<0.900	1.00 (Ref.)	---	1.00 (Ref)	1.00 (Ref)
0.901–0.967	1.25 (0.71, 2.19)	---	1.31 (0.75, 2.29)	1.38 (0.79, 2.41)
0.968	1.91 (1.08, 3.36)	---	2.17 (1.26, 3.72)	2.40 (1.39, 4.15)
BMI Categories at Age 25 Years				
<25	1.00 (Ref)	1.00 (Ref)	---	1.00 (Ref)
25–29.9	2.47 (1.46, 4.16)	3.37 (2.08, 5.46)	---	3.37 (2.08, 5.46)
30	1.97 (0.86, 4.50)	3.23 (1.50, 6.96)	---	3.23 (1.50, 6.96)

Abbreviations: BMI (body mass index), RR (relative risk), CI (confidence interval), Ref (reference)

Model 1^{\$}: Adjusted for covariates* and baseline weight

Model 2[^]: Adjusted for covariates* and baseline waist-to-hip ratio

Model 3[&]: Adjusted for covariates* and weight at age 25 years

Model 4[@]: Adjusted for covariates* and weight change

* Covariates: age (years), menopausal status (pre or post), race (black or white), diabetes (yes or no), hypertension (yes or no), diuretic use (yes or no), alcohol intake (drinks per day), organ meat intake (>2 servings per month or 2 servings per month), and eGFR (categorical)