Published in final edited form as:

Arthritis Rheumatol. 2020 January ; 72(1): 157–165. doi:10.1002/art.41067.

Population Impact Attributable to Modifiable Risk Factors for Hyperuricemia

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Abstract

Objective: To examine modifiable risk factors in relation to the presence of hyperuricemia and estimate the proportion of hyperuricemia cases that could be prevented through risk factor modification in the general population compared with estimates of the variance explained.

Methods: Using data from 14,624 adults representative of the non-institutionalized civilian US population, we calculated adjusted prevalence ratios for hyperuricemia, population attributable risks (PAR), and the variance explained according to the following four factors: body mass index (BMI ≥ 25 kg/m²), alcohol intake, non-adherence to a DASH-style diet, and diuretic use.

Results: BMI, alcohol intake, adherence to a DASH-style diet, and diuretic use were all associated with serum urate levels and the presence of hyperuricemia in a dose-response manner. The corresponding PARs of hyperuricemia cases for overweight/obesity (prevalence, 60%), non-adherence to a DASH-style diet (prevalence, 82%), alcohol use (prevalence, 48%), and diuretic use (prevalence, 8%) were 44% (95% CI, 41 to 48%), 9% (3% to 16%), 8% (5% to 11%), and 12% (11% to 14%), respectively, whereas the corresponding variances explained were 8.9%, 0.1%, 0.5%, and 5.0%. Our simulation study showed the variance nearing zero with exposure prevalence's nearing 100%.

Conclusion: In these nationally representative US adults, four modifiable risk factors (BMI, the DASH diet, alcohol use, and diuretic use) could individually account for a notable proportion of hyperuricemia cases. However, the corresponding serum urate variance explained by these risk factors was very small and paradoxically masked their high prevalences, providing real-life empirical evidence for its limitations in assessing common risk factors.

INTRODUCTION

Once considered a condition associated with a lifestyle of excess and overindulgence (“disease of kings”), gout is now the most common form of inflammatory arthritis worldwide (“disease of commoners”), with its prevalence rising in many countries.(1–3) Paralleling the introduction of high-fructose corn syrup in the 1970s, increased consumption of sugar-sweetened beverages,(4) expanding portion sizes,(5) and the rising obesity epidemic (4,6–8) in the US, both the incidence and prevalence of gout have more than doubled.(2,6,9,10) Similarly, gout was previously rare in rural African communities where traditional agricultural diets were consumed, but the prevalence in these regions is also now increasing, most notably in urban communities.(2,11,12) Increased serum urate levels (SU; the causal precursor of gout) have been reported among Japanese immigrants who moved to the US, whereas an elevated SU was not observed among those who continued to live in Japan.(11,13) Moreover, the Tokelau Island migrant study found that the incidence of developing gout between 1968 and 1982 was 9.0 times higher in the migrant men living in urban New Zealand than in the non-migrant men living in their isolated atoll homeland, with consistent serum urate level changes among men under 55.(14) Finally, contemporary epidemiology data from Canada, Europe, New Zealand, and China all suggest that gout incidence and prevalence are increasing,(3,15–17) correlating with their obesity trends.(2,7)

These historical descriptions and epidemiologic data are at odds with a recent report that 0.3% of SU variance in the US is explained by dietary components, particularly when compared with the variance explained by common genome-wide genes (i.e., GWAS-based heritability estimate = 23.9%).(18) However, as the variance explained depends on the level of spread of the exposure (its variability) without incorporating the exposure’s prevalence in the population, it can be highly misleading as a measure of relative importance among risk factors.(19–21) This is particularly relevant when a risk factor is ubiquitous (and thus its variability is near-zero), in which case this approach leads to almost-none of the variance being explained, although almost all cases are related to the factor.(20) The dietary exposures in the US (an extreme “Western lifestyle” country) would likely fall into this case with most people having unhealthy, gout-prone diets. For example, an analysis of the NHANES showed an overwhelming level of non-compliance to the Dietary Approaches to Stop Hypertension (DASH) diet, a dietary pattern associated with a lower SU level(18,22) and risk of gout.(23) Less than 1% of the US population with hypertension was fully adherent to the DASH diet and only 20% met half of the DASH nutrient targets.(24,25)

To properly examine the theoretical population impact attributable to key modifiable risk factors (i.e., obesity, alcohol intake, diet, and diuretic use) for hyperuricemia in the US population, thereby overcoming the critical limitations of the variance explained,(18) we calculated the population attributable risk percent (PAR%) for each risk factor, assuming exposures are causal.(26,27) The same approach has been used to estimate the population impact of lifestyle factors for myocardial infarction,(28) hypertension,(29) and type-2 diabetes,(30) as well as for genetic factors discovered from GWAS studies for hyperuricemia(31,32) and gout.(33) We also estimated the variance explained(18) for the same risk factors for illustration purposes.

MATERIALS AND METHODS

Study Population

The NHANES III consisted of a representative sample of the non-institutionalized civilian US population between 1988 and 1994, which was selected by using a multistage, stratified sampling design.(34) We analyzed this NHANES data for comparison purposes as it was the same data used by the recent study that reported the extremely low SU variance explained by dietary components.(18) Our analysis was limited to adult participants (≥ 20 years) who attended the medical examination and included the 14,624 participants with complete information for the target risk factors and covariates. We repeated our analyses among 14,187 participants after excluding those who self-reported gout or were taking allopurinol or uricosuric agents (n=437). As this was a secondary analysis of aggregated data, this study was exempt from institutional review board approval.

Uric Acid Measurement

SU was measured by oxidization with the specific enzyme uricase to form allantoin and H₂O₂ (Hitachi Model 737 Multichannel Analyzer, Boehringer Mannheim Diagnostics, Indianapolis, IN).(34) Values are reported in micromoles per liter and milligrams per deciliter.

Assessment of Modifiable Risk Factors

Usual food intakes were determined from responses to the food frequency questionnaire administered to participants to assess their usual consumption over the past month. We constructed a DASH diet score based on individual dietary components that are emphasized or minimized in the DASH diet,(23,35) focusing on eight components: high intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains, and low intake of sodium, sweetened beverages, and red and processed meats.(23,36) For each of the components, individuals were classified into quintiles according to their intake ranking. We then summed the component scores to obtain an overall DASH diet score ranging from 8 to 40. This DASH score has been successfully used in studies of serum urate levels,(18) gout, (23) CVD,(35) and kidney stones,(37) and this same quintile approach for dietary exposures has been used in PAR studies of cardiovascular-metabolic endpoints.(28–30)

The NHANES III collected information on body measurements (including height and weight), medication use (including urate-lowering drugs and diuretics), and medical conditions. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters.

Statistical Analysis

The risk factors of interest were categorized as follows; BMI (<25.0 kg/m², 25.0–29.9 kg/m², 30.0–34.9 kg/m², and ≥ 35.0 kg/m²), DASH diet score (quintiles), alcohol intake (0, 0.01 to 0.09, 0.1 to 0.49, 0.5 to 0.99, and ≥ 1.0 serving/day),(38) and diuretic use (yes vs. no). We evaluated the relation between these modifiable risk factors and SU level using linear regression. We also estimated adjusted prevalence ratios for hyperuricemia (serum urate > 417 micromol/L among men [7.0 mg/dL] and serum urate > 340 micromol/L among

women [5.7 mg/dL] following the NHANES III laboratory definition(34)). We chose prevalence ratios (as opposed to odds ratios) in our primary analysis, given the relatively common frequency of hyperuricemia, as the odds ratio would overestimate the magnitude of the association when used as an approximation of relative risk. We examined the potential impact of an alternative definition of hyperuricemia (serum urate level > 417 micromol/L [7.0 mg/dL]) regardless of sex(39)). For all difference estimates and prevalence ratios, we calculated 95% confidence intervals (CI). All P values are two-sided.

For each risk factor, we calculated the PAR,(28,30) which is an estimate of the percentage of hyperuricemia cases in this population that would have been avoided if the risk factor exposure belonged to the corresponding lowest-risk group (BMI <25 kg/m², no alcohol intake, adherence to a DASH-style diet, and no diuretic use), assuming a causal relation between the risk factor and hyperuricemia.(26,27) The evidence for causality of these four factors on serum urate levels and gout are summarized in the Supplemental Table and below. The PAR formula that we used was:

$$\sum_{i=0}^k pd_i \left(\frac{RR_i - 1}{RR_i} \right) = 1 - \sum_{i=0}^k \frac{pd_i}{RR_i}$$

where pd_i = proportion of cases falling into i th exposure level; RR_i = relative risk comparing i th exposure level with unexposed group ($i = 0$). (26) The PARs for individual risk factors accounted for covariates, using regression approaches.(40) The individual (adjusted) PARs provided the following information: 1) the theoretical fraction of cases avoided by eliminating each individual factor from the US population; and 2) the relative importance among these factors. Adherence to a DASH-style diet was defined as the top quintile of DASH score, corresponding to a 50% compliance with the DASH nutrient targets among hypertensive patients in a previous NHANES analysis (N=4,556)(24,25) and to a 36% compliance in the current study population (N=14,624). Furthermore, we also explored the impact of changing the definition of adherence to 25%, 50%, and 75% compliance levels, corresponding to the top half, decile, and percentile of the DASH score in the current study population. Finally we calculated the variance explained by each factor for comparison purposes, indicated by the partial R² obtained from linear regression models.(18)

Simulation Analyses

We conducted simulation analyses to evaluate the impact on PAR and variance explained when varying the prevalence of exposure by varying the proportion of target exposure group individuals in the study population. Using the parameters and variables from the current study population, including the adjusted prevalence ratios and covariates, we evaluated alcohol consumption (a lifestyle factor) and diuretic use (a drug) as examples (Table 2).

RESULTS

Characteristics

The population's mean age was 47 years. The mean SU was 319 micromol/L (5.36 mg/dL) (361 micromol/L among men [6.07 mg/dL] and 281 micromol/L among women [4.72 mg/

dLJ) and 20% were hyperuricemic (21% of men and 19% of women). The prevalence and distribution of risk factor categories are shown in Table 1.

Population Attributable Risk vs. Variance Explained

The most important risk factor for hyperuricemia was BMI, with prevalence ratios of 1.85 (95% confidence interval [CI], 1.69 to 2.03), 2.72 (2.48 to 3.00), and 3.53 (3.19 to 3.91), respectively, for individuals with a BMI of 25.0 to 29.9 kg/m², 30.0 to 34.9 kg/m², and 35 kg/m² or greater compared with those of BMI <25.0 kg/m² (Table 1). In this population, 44% (95% CI, 41 to 48%) of hyperuricemia cases was attributed to overweight or obesity (i.e., having a BMI ≥ 25 kg/m²) alone, whereas the SU variance explained by BMI as a categorical variable and as a continuous variable was 8.3% and 8.9%, respectively (Table 2).

The remaining three factors (i.e., a DASH-style diet, alcohol intake, and diuretic use) were also associated with the presence of hyperuricemia (Table 1). Those with a DASH-style diet score in the lowest quintile had a 22% higher prevalence of hyperuricemia compared with those in the highest quintile (prevalence ratio 1.22 [95% CI, 1.09 to 1.37]). In this population, 9% (95% CI, 3% to 16%) of hyperuricemia cases could be prevented through adherence to a DASH-style diet (i.e., DASH-style diet score in the top quintile), whereas the corresponding variance explained was 0.1% (Table 2). When we used the top half, decile, and percentile of the DASH diet score as the reference group, the PARs were 6%, 14% and 40%, respectively (see Supplemental Figure), whereas the corresponding variance explained remained at 0.1%. The adjusted serum urate level difference between the extreme deciles and percentiles were 0.16 mg/dL and 0.44 mg/dL; the adjusted prevalence ratios between the extreme deciles and percentiles were 1.32 (95% CI, 1.08 to 1.61) and 2.11 (95% CI, 1.18 to 3.76).

A dose-response relation was observed for alcohol intake categories, with those in the highest category (≥ 1 serving per day) showing the greatest prevalence ratio for hyperuricemia (prevalence ratio 1.40 [1.23 to 1.58]). In this population, 8% (95% CI, 5% to 11%) of hyperuricemia cases could be prevented through abstaining from alcohol consumption, whereas the corresponding SU variance explained as a categorical variable and as a continuous variable was 0.9% and 0.5%, respectively. The PAR of beer alone was 7%; when we used 0 – 0.09 serving/day as the reference, the PAR remained the same (8%). Diuretic use showed an increased risk of gout (prevalence ratio 2.24 [2.08 to 2.41]), with a PAR of 12% (95% CI, 11% to 14%) and a SU variance explained of 5%.

Exclusion of individuals with a self-reported lifetime history of physician-diagnosed gout or those who were taking medication to treat hyperuricemia did not materially alter our results (PARs for overweight/obesity, non-adherence to a DASH-style diet, alcohol use, and diuretic use = 46%, 8%, 8%, and 12%, respectively). Similarly, an alternative definition of hyperuricemia (serum uric acid level > 417 micromol/L [7.0 mg/dL] regardless of sex) did not materially alter these results (corresponding PARs = 44%, 9%, 11%, and 16%, respectively).

Simulation Study for Varying Prevalence of Alcohol Use and Diuretic Use.

In our simulation study where the prevalence of diuretic use increased from 8% (our study population prevalence, see Table 1) to 100%, the PAR continued to increase as the prevalence increased, whereas the peak variance (6.3%) was observed at a prevalence of approximately 30% (Figure 1). The variance progressively declined after the prevalence reached 50%, and approached zero when the prevalence was near 100%. Similarly, as the prevalence of alcohol use (at least 1 serving per day) increased from 6% to near 100%, the PAR continued to increase, whereas the variance explained peaked at 1%, when the prevalence was approximately 50% (Figure 2). As the prevalence increased further, the variance progressively declined and approached zero when the prevalence was nearly 100%.

DISCUSSION

In this national sample of US men and women, we found that overweight/obesity, gout-prone diet, alcohol consumption, and diuretic use could individually account for a substantial proportion of hyperuricemia cases. In contrast, the SU variance explained by these risk factors was very small. In particular, the SU variance explained by the DASH diet in the US was very small (0.1%), similar to the recent report (0.3%) based on five US cohorts.(18)

How can dietary changes over time (together with a Western lifestyle) be associated with obesity(7,8) and gout epidemics,(1,6) yet also paradoxically appear extremely insignificant according to the variance measure? This occurs because the variance measure does not incorporate how common the exposure is (i.e., its prevalence). As such, the proportion of the population variance explained can be highly misleading as a measure of which risk factor is more important,(19) as previous papers and textbooks have cautioned (i.e., the fallacy of employing the “proportion of population variance explained” as a measure of effect).(19–21,41) In a previous illustration of a population where 90% of individuals were smokers, (2,42) the proportion of variance explained by smoking in lung cancer was estimated to be <1% (with PAR of 90%). Similarly, in our simulation analyses specifically using the context of hyperuricemia, a 90% prevalence of diuretic or alcohol use (of 1 serving/day) corresponded to 1.6% and <1% of variance explained, respectively (Figures 1 and 2). These variance data would appear highly counterintuitive, as one would expect a very high level of contribution from these exposures with an extremely high prevalence in the population, provided they have a strong causal effect. This is directly due to a low level of variability in exposure (e.g., 90% are diuretic users or alcohol users) and the variance explained does not account for the high prevalence itself. Heuristically, this would be a case of “*the most important causes of disease are invisible because they are everywhere.*”(2,20,42,43)

In contrast, the PAR correctly reflected the high level of exposure contribution by incorporating both its effect size as well as the high prevalence (Figures 1 and 2). This is highly relevant to the potential population impact of dietary factors, as less than 1% of the US population is fully adherent to the DASH diet, and only 20% meet half of the DASH nutrient targets.(24,25,44) These data collectively indicate there is substantial room for improvement in dietary factors to help prevent hyperuricemia and gout, as well as hypertension and related cardiovascular outcomes.(24)

Furthermore, the continually worsening obesity epidemic in the US is largely driven by diet (including larger portion sizes(5)) and lifestyle changes that have occurred since the 1970's (7,8,42,45) and have coincided with the rising prevalence of hyperuricemia and gout.(6,42) The current study also found that the most important risk factor for hyperuricemia among the four modifiable risk factors was BMI, with a population attributable risk of 44%. As diet as the calorie source (together with physical activity [calorie output]) plays a critical role in the risk of obesity as well as the subsequent risk of hyperuricemia and gout (indirect effect mediated by obesity, see Figure 3), the net total effect of 'diet' would be greater than the PAR estimated for the isocaloric DASH diet alone (direct effect, measured independently of BMI), as in the current and previous studies.(18) To that end, the large PAR associated with BMI suggests large indirect effects of diet and exercise, through BMI, on the risk of hyperuricemia at the population level. Indeed, a previous prospective study of exercise found that running distance and fitness performance are both associated with a lower risk of gout; however, when BMI was adjusted in the model, the association disappeared, suggesting the total effect of exercise was entirely through the indirect effect (through BMI).(46) Although there are multiple layers of evidence for the direct effect of isocaloric diet as discussed below, its expected impact is likely smaller than the indirect effect through BMI.(47)

Obesity increases gout risk by raising the serum urate level, both through decreased renal urate excretion and increased urate production.(48–53) Mendelian randomization studies have found obesity is causally associated with serum urate levels in the general population; (54,55) weight loss through bariatric surgery or through lifestyle intervention leads to reductions in serum urate.(56) In terms of diet and alcohol, prompted by the strong biologic mechanism and plausibility of intake of purine, fructose, and alcohol, prior metabolic loading experiments of purine,(57–60) fructose,(61–64) and alcohol(65) have confirmed their serum urate-raising effect,(57–64) whereas dairy products showed urate-lowering effects in three experimental studies, including two randomized trials.(66–68) The DASH diet discourages purine-rich red meat as well as fructose-rich foods, while advocating dairy products, healthy protein, and vegetables/fruits.(23,35) Indeed, a DASH diet trial analysis found that the DASH diet lowers serum uric acid levels compared with a typical American diet (i.e., control diet), particularly among those with hyperuricemia (i.e., by 0.4mg/dL overall, by 1.0 mg/dL in those with a baseline serum urate level ≥ 6 mg/dL, and by 1.3 mg/dL in those with a baseline serum urate level ≥ 7 mg/dL).(22) These experimental/trial data, together with consistent epidemiologic data (prospective cohort studies,(23,69–71) ecologic studies,(1) immigration studies,(11,13) as well as food consumption/obesity epidemic correlating trends(1,2,4,6–10)) all support a casual role of 'diet' on hyperuricemia (directly or mediated by obesity as a calorie source) at the population level. Regarding diuretics, the increase in serum urate level caused by diuretics has been documented within a few days after the initiation of diuretics.(72–74) To that end, urate-lowering anti-hypertensive agents (e.g., calcium channel blockers or losartan) could be preferred, if hyperuricemia relevant.(74) These findings provide support for our assumptions that these associations are causal.

Strengths and limitations of our study deserve comment. This study was performed in a nationally representative sample of US women and men; thus, the findings are likely to be generalizable to the US adult population. Our individual (adjusted) PARs estimate the

fraction of cases avoided by eliminating each of the individual factors from the US population and allows for the relative importance among these factors; however, simply adding the individual PAR of each risk factor would be fallacious, because it would imply that every case of disease has a single factor and that two or more factors cannot together contribute to the same case of disease. Measurement errors inherent to diet and alcohol exposures (unlike BMI, diuretic use, or genes) would have underestimated their association with SU levels. Furthermore, the relatively small effect size was likely also due to exposure status saturation in the US population, which makes it difficult to detect differences between the quintiles of individual DASH food components (that constitutes to the DASH score) or the quintiles of the resulting diet score (see Supplemental Text for further detailed explanations). Together, these mechanisms likely contributed to the observed small variance explained by the dietary scores. When a larger contrast with more stringent cut-offs was examined, the adjusted prevalence ratio increased as high as 2.11. This dose-response relationship provides further support for a causal role of the DASH diet. If there were no such dose-response relation, PAR would not have increased, even with more stringent choice of cut-offs. As opposed to prospective studies, a cross-sectional study design tends to leave uncertainty regarding the temporal sequence of exposure-outcome relations and is also vulnerable to recall bias. However, if some participants modified lifestyle factors based on previously measured hyperuricemia, it would lead to an underestimation of the association between the corresponding factor and SU levels, making our findings conservative. Furthermore, given the absence of existing conventional recommendations for the DASH diet for hyperuricemia and gout at the time of study execution, it is unlikely that some participants changed their adherence to the DASH diet based on previously identified hyperuricemia or gout. Moreover, exclusion of individuals with a self-reported lifetime history of physician-diagnosed gout or those who were taking medication to treat hyperuricemia did not materially alter our results. Finally, in the NHANES III, the health examination component including SU measurement (outcome) was performed after the household interview that inquired about dietary intake during the past month (exposure).

In conclusion, this nationally representative study indicates that modifiable risk factors (BMI, the DASH diet, alcohol use and diuretic use) all have an important place in the *primary* prevention of hyperuricemia. Public health efforts to promote a healthy diet and prevent obesity would also help reduce the frequency of hyperuricemia and eventually the risk of gout in the general population. These include promoting individual behavioral changes as well as broader policy changes targeting the obesogenic food environment (e.g., the implementation of a sugary beverage tax, menu labeling initiatives, and reforms to federal nutrition assistance programs).(75) Our findings also provide real-life empirical evidence that when the exposure is common, the variance explained has a severe limitation as a measure of the relative importance among risk factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This research was supported by the National Institutes of Health [R01AR065944]. The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. NM is supported by a Fellowship Award, and SKR is supported by a Doctoral Foreign Study Award, both from the Canadian Institutes of Health Research. CY is supported by the National Institutes of Health Ruth L. Kirschstein Institutional National Research Service Award [T32-AR-007258].

REFERENCES

1. Kuo CF, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. *Nature reviews. Rheumatology* 2015;11:649–62. [PubMed: 26150127]
2. Rai S, Zhang Y, Hu FB, Pearce N, Choi HK. The Paradox of Ubiquitous Risk Factors for Gout. Vol. 2019: BMJ; 2018.
3. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis* 2015;74:661–7. [PubMed: 24431399]
4. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *Am J Clin Nutr* 2004;79:537–43. [PubMed: 15051594]
5. Young LR, Nestle M. The contribution of expanding portion sizes to the US obesity epidemic. *Am J Public Health* 2002;92:246–9. [PubMed: 11818300]
6. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population. *Arthritis Rheum* 2011;63:3136–41. [PubMed: 21800283]
7. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017;390:2627–2642. [PubMed: 29029897]
8. Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet* 2011;378:815–25. [PubMed: 21872750]
9. Arromdee E, Michet CJ, Crowson CS, O’Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? *J Rheumatol* 2002;29:2403–6. [PubMed: 12415600]
10. 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* 2007;58:26–35.
11. Johnson RJ, Rideout BA. Uric acid and diet—insights into the epidemic of cardiovascular disease. *N Engl J Med* 2004;350:1071–3. [PubMed: 15014177]
12. Cassim B, Mody GM, Deenadayalu VK, Hammond MG. Gout in black South Africans: a clinical and genetic study. *Ann Rheum Dis* 1994;53:759–62. [PubMed: 7826138]
13. Kagan A, Harris BR, Winkelstein W Jr., Johnson KG, Kato H, Syme SL, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: demographic, physical, dietary and biochemical characteristics. *J Chronic Dis* 1974;27:345–64. [PubMed: 4436426]
14. Prior IA, Welby TJ, Ostbye T, Salmond CE, Stokes YM. Migration and gout: the Tokelau Island migrant study. *British Medical Journal Clinical Research Ed.* 1987;295:457–61. [PubMed: 3117170]
15. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. *Ann Rheum Dis* 1997;56:22–6. [PubMed: 9059136]
16. Miao Z, Li C, Chen Y, Zhao S, Wang Y, Wang Z, et al. Dietary and lifestyle changes associated with high prevalence of hyperuricemia and gout in the Shandong coastal cities of Eastern China. *J Rheumatol* 2008;35:1859–64. [PubMed: 18634142]
17. Rai SK, Antonio Aviña-Zubieta J, McCormick N, De Vera MA, Shojania K, Sayre EC, et al. The rising prevalence and incidence of gout in British Columbia, Canada: Population-based trends from 2000 to 2012. *Seminars in Arthritis and Rheumatism* 2017;46:451–456. [PubMed: 28040245]

18. Major TJ, Topless RK, Dalbeth N, Merriman TR. Evaluation of the diet wide contribution to serum urate levels: meta-analysis of population based cohorts. *BMJ* 2018;363:k3951. [PubMed: 30305269]
19. Greenland S, Schlesselman JJ, Criqui MH. The fallacy of employing standardized regression coefficients and correlations as measures of effect. *Am J Epidemiol* 1986;123:203–8. [PubMed: 3946370]
20. Pearce N Epidemiology in a changing world: variation, causation and ubiquitous risk factors. *Int J Epidemiol* 2011;40:503–12. [PubMed: 21247886]
21. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. Second Edition ed Philadelphia: Lippincott Williams & Wilkins; 2008.
22. Juraschek SP, Gelber AC, Choi HK, Appel LJ, Miller ER 3rd., Effects of the Dietary Approaches To Stop Hypertension (DASH) Diet and Sodium Intake on Serum Uric Acid. *Arthritis & rheumatology* 2016.
23. Rai SK, Fung TT, Lu N, Keller SF, Curhan GC, Choi HK. The Dietary Approaches to Stop Hypertension (DASH) diet, Western diet, and risk of gout in men: prospective cohort study. *BMJ* 2017;357:j1794. [PubMed: 28487277]
24. Steinberg D, Bennett GG, Svetkey L. The DASH Diet, 20 Years Later. *JAMA* 2017;317:1529–1530. [PubMed: 28278326]
25. Mellen PB, Gao SK, Vitolins MZ, Goff DC Jr., Deteriorating dietary habits among adults with hypertension: DASH dietary concordance, NHANES 1988–1994 and 1999–2004. *Arch Intern Med* 2008;168:308–14. [PubMed: 18268173]
26. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. *Am J Public Health* 1998;88:15–9. [PubMed: 9584027]
27. Greenland S, Robins JM. Conceptual problems in the definition and interpretation of attributable fractions. *Am J Epidemiol* 1988;128:1185–97. [PubMed: 3057878]
28. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary prevention of coronary heart disease in women through diet and lifestyle. *New England Journal of Medicine*. 2000;343:16–22. [PubMed: 10882764]
29. Forman JP, Stampfer MJ, Curhan GC. Diet and lifestyle risk factors associated with incident hypertension in women. *JAMA* 2009;302:401–11. [PubMed: 19622819]
30. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *New England Journal of Medicine*. 2001;345:790–7. [PubMed: 11556298]
31. Yamagishi K, Tanigawa T, Kitamura A, Kottgen A, Folsom AR, Iso H, et al. The rs2231142 variant of the ABCG2 gene is associated with uric acid levels and gout among Japanese people. *Rheumatology (Oxford)* 2010;49:1461–5. [PubMed: 20421215]
32. Nakayama A, Matsuo H, Nakaoka H, Nakamura T, Nakashima H, Takada Y, et al. Common dysfunctional variants of ABCG2 have stronger impact on hyperuricemia progression than typical environmental risk factors. *Scientific reports* 2014;4:5227. [PubMed: 24909660]
33. Woodward OM, Kottgen A, Coresh J, Boerwinkle E, Guggino WB, Kottgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci U S A* 2009;106:10338–42. [PubMed: 19506252]
34. Centers for Disease Control and Prevention. *NHANES III 1988–94 Reference Manuals and Reports (on CD-ROM)*. Hyattsville, Md: National Center for Health Statistics 1996.
35. Fung TT, Chiuve SE, McCullough ML, Rexrode KM, Logroscino G, Hu FB. Adherence to a DASH-style diet and risk of coronary heart disease and stroke in women. *Arch Intern Med* 2008;168:713–20. [PubMed: 18413553]
36. Karanja NM, Obarzanek E, Lin PH, McCullough ML, Phillips KM, Swain JF, et al. Descriptive characteristics of the dietary patterns used in the Dietary Approaches to Stop Hypertension Trial. DASH Collaborative Research Group. *Journal of the American Dietetic Association* 1999;99:S19–27. [PubMed: 10450290]
37. Taylor EN, Fung TT, Curhan GC. DASH-style diet associates with reduced risk for kidney stones. *Journal of the American Society of Nephrology : JASN* 2009;20:2253–9. [PubMed: 19679672]

38. Choi HK, Curhan G. Beer, Liquor, Wine, and Serum Uric Acid Level - The Third National Health and Nutrition Examination Survey. *Arthritis Rheum* 2004;51:1023–9. [PubMed: 15593346]
39. Choi JW, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum* 2008;59:109–16. [PubMed: 18163396]
40. Benichou J A review of adjusted estimators of attributable risk. *Stat Methods Med Res* 2001;10:195–216. [PubMed: 11446148]
41. Rose G, Khaw KT, Marmot M. *Rose's Strategy of Preventative Medicine*. Oxford: Oxford University Press; 2008.
42. Rai SK, Zhang Y, Hu BF, Pearce N, Choi HK. The Fatalistic Public Health Implication of Flawed Methodology. Vol. 2019: *BMJ*; 2018.
43. Rose G Sick individuals and sick populations. *Int J Epidemiol* 2001;30:427–32; discussion 433–4. [PubMed: 11416056]
44. Kim H, Andrade FC. Diagnostic status of hypertension on the adherence to the Dietary Approaches to Stop Hypertension (DASH) diet. *Prev Med Rep* 2016;4:525–531. [PubMed: 27747149]
45. Hu BF. Genetic Predictors of Obesity In: Hu BF, ed. *Obesity Epidemiology*. New York City: Oxford University Press; 2008.
46. Williams PT. Effects of diet, physical activity and performance, and body weight on incident gout in ostensibly healthy, vigorously active men. *Am J Clin Nutr* 2008;87:1480–7. [PubMed: 18469274]
47. 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. *Annals of the Rheumatic Diseases* 2000;59:539–43. [PubMed: 10873964]
48. Fam AG. Gout, diet, and the insulin resistance syndrome. *The Journal of rheumatology* 2002;29:1350–5. [PubMed: 12136887]
49. Emmerson BT. The management of gout. *N Engl J Med* 1996;334:445–51. [PubMed: 8552148]
50. Emmerson BT. Alteration of urate metabolism by weight reduction. *Aust N Z J Med* 1973;3:410–2. [PubMed: 4519128]
51. Modan M, Halkin H, Fuchs Z, Lusky A, Chetrit A, Segal P, et al. Hyperinsulinemia--a link between glucose intolerance, obesity, hypertension, dyslipoproteinemia, elevated serum uric acid and internal cation imbalance. *Diabete Metab* 1987;13:375–80. [PubMed: 3308568]
52. 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;266:3008–11. [PubMed: 1820474]
53. 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;10:255–64. [PubMed: 3771090]
54. Lyngdoh T, Vuistiner P, Marques-Vidal P, Rousson V, Waeber G, Vollenweider P, et al. Serum uric acid and adiposity: deciphering causality using a bidirectional Mendelian randomization approach. *PLoS One* 2012;7:e39321.
55. Oikonen M, Wendelin-Saarenhovi M, Lyytikainen LP, Siitonen N, Loo BM, Julia A, et al. Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. *Atherosclerosis* 2012;223:497–503. [PubMed: 22749515]
56. Nielsen SM, Bartels EM, Henriksen M, Wæhrens EE, Gudbergesen H, Bliddal H, et al. Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies. *Annals of the rheumatic diseases* 2017;76:1870–1882. [PubMed: 28866649]
57. Clifford AJ, Riunallo JA, Young VR, Scrimshaw NS. Effects of oral purines on serum and urinary uric acid of normal, hyperuricaemic and gouty humans. *J Nutr* 1976;106:428–50.
58. Clifford AJ, Story DL. Levels of purines in foods and their metabolic effects in rats. *J Nutr* 1976;106:435–42.
59. Zollner N Influence of various purines on uric acid metabolism. *Bibl Nutr Dieta* 1973;34–43. [PubMed: 4600927]

60. Zollner N, Griebisch A. Diet and gout. *Adv Exp Med Biol* 1974;41:435–42. [PubMed: 4832568]
61. Stirpe F, Della Corte E, Bonetti E, Abbondanza A, Abbati A, De Stefano F. Fructose-induced hyperuricaemia. *Lancet* 1970;2:1310–1. [PubMed: 4098798]
62. Emmerson BT. Effect of oral fructose on urate production. *Ann Rheum Dis* 1974;33:276–80. [PubMed: 4843132]
63. Perheentupa J, Raivio K. Fructose-induced hyperuricaemia. *Lancet* 1967;2:528–31. [PubMed: 4166890]
64. Dalbeth N, House ME, Gamble GD, Horne A, Pool B, Purvis L, et al. Population-specific influence of SLC2A9 genotype on the acute hyperuricaemic response to a fructose load. *Ann Rheum Dis* 2013;72:1868–1873. [PubMed: 23349133]
65. Gibson T, Rodgers AV, Simmonds HA, Toseland P. Beer drinking and its effect on uric acid. *Br J Rheumatol* 1984;23:203–9. [PubMed: 6743968]
66. Garrel DR, Verdy M, PetitClerc C, Martin C, Brule D, Hamet P. Milk- and soy-protein ingestion: acute effect on serum uric acid concentration. *Am J Clin Nutr* 1991;53:665–9. [PubMed: 2000819]
67. Ghadirian P, Shatenstein B, Verdy M, Hamet P. The influence of dairy products on plasma uric acid in women. *Eur J Epidemiol* 1995;11:275–81. [PubMed: 7493659]
68. Dalbeth N, Wong S, Gamble GD, Horne A, Mason B, Pool B, et al. Acute effect of milk on serum urate concentrations: a randomised controlled crossover trial. *Ann Rheum Dis*;69:1677–82.
69. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *The New England journal of medicine* 2004;350:1093–103. [PubMed: 15014182]
70. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ (Clinical research ed.)* 2008;336:309–312.
71. Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA* 2010;304:2270–8. [PubMed: 21068145]
72. Leary WP, Reyes AJ, Wynne RD, van der Byl K. Renal excretory actions of furosemide, of hydrochlorothiazide and of the vasodilator flosequinan in healthy subjects. *J. Int. Med. Res.* 1990;18:120–41. [PubMed: 2340945]
73. Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. *J Rheumatol* 2006;33:1341–5. [PubMed: 16758506]
74. Choi HK, Soriano LC, Zhang Y, Rodriguez LA. Antihypertensive drugs and risk of incident gout among patients with hypertension: population based case-control study. *BMJ* 2012;344:d8190. [PubMed: 22240117]
75. Gortmaker SL, Swinburn BA, Levy D, Carter R, Mabry PL, Finegood DT, et al. Changing the future of obesity: science, policy, and action. *Lancet* 2011;378:838–47. [PubMed: 21872752]

1.
Population Attributable Risk vs Variance Explained According to the Prevalence of Diuretic Use

2.

Population Attributable Risk vs Variance Explained According to the Prevalence of Alcohol Use

3. Causal Pathways of Modifiable Factors (Diet and Physical Activity) on Developing Hyperuricemia (HU). Input (diet) and output (physical activity) of calories are the modifiable determinants of overweight/obesity, which leads to HU (indirect effect mediated by overweight/obesity). The other causal pathway for HU is a direct effect, not mediated by overweight/obesity (e.g., isocaloric DASH diet or Western diet not affecting weight). The total effect of these lifestyle modifications is the combination of indirect and direct effects. Consistent with the large role of overweight/obesity on the risk of HU, published papers suggest that the indirect effect of these lifestyle factors (through overweight/obesity) is larger than their direct effect.(46,47) CVD = cardiovascular disease, T2D = type-2 diabetes, CKD = chronic kidney disease.

Table 1.

Multivariable serum urate level difference and prevalence ratio for hyperuricemia according to modifiable risk factors in the NHANES III

Risk Factor	N of Individuals (%)	N of hyperuricemia	Multivariable prevalence ratios for hyperuricemia (95% CI)*	Multivariable serum urate level difference, mg/dL (95% CI)*
Body Mass Index (kg/m²)				
<25.0	5,789 (40)	607	1.0	0.0
25.0–29.9	5,133 (35)	1,090	1.85 (1.69 to 2.03)	0.48 (0.44 to 0.53)
30.0–34.9	2,378 (16)	729	2.72 (2.48 to 3.00)	0.84 (0.78 to 0.89)
35.0	1,324 (9)	508	3.53 (3.19 to 3.91)	1.11 (1.04 to 1.19)
DASH Diet Score				
1 st Quintile	2,602 (18)	544	1.0	0.0
2 nd Quintile	2,908 (20)	612	1.08 (0.98 to 1.19)	0.01 (–0.06 to 0.07)
3 rd Quintile	3,499 (24)	706	1.11 (1.00 to 1.22)	0.04 (–0.02 to 0.10)
4 th Quintile	3,075 (21)	593	1.16 (1.05 to 1.29)	0.07 (0.01 to 0.14)
5 th Quintile	2,540 (17)	544	1.22 (1.09 to 1.37)	0.13 (0.05 to 0.20)
Alcohol Use (serving/day)				
0	7,564 (52)	1,555	1.0	0.0
0.01 to 0.09	1,428 (10)	237	0.95 (0.85 to 1.07)	0.00 (–0.07 to 0.07)
0.1 to 0.49	3,398 (23)	637	1.18 (1.09 to 1.28)	0.16 (0.11 to 0.21)
0.5 to 0.99	1,313 (9)	284	1.37 (1.23 to 1.53)	0.32 (0.25 to 0.40)
1	921 (6)	221	1.40 (1.23 to 1.58)	0.37 (0.29 to 0.46)
Diuretic Use				
No	13,388 (92)	2,280	1.0	0.0
Yes	1,236 (8)	654	2.24 (2.08 to 2.41)	1.07 (1.00 to 1.15)

Abbreviations: CI, confidence interval. DASH, Dietary Approaches to Stop Hypertension.

* Mutually adjusted for the other risk factors in the table.

Table 2.

Population attributable risk of hyperuricemia and serum urate variance explained for serum urate level according to modifiable risk factors in the NHANES III

Modifiable Risk Factors	Exposure prevalence, %	PAR for hyperuricemia (95% CI), %	Serum urate variance explained, %	Serum urate variance explained, %*
BMI >25 kg/m ²	60	44 (41 to 48)	8.3	8.9
DASH Diet Score (Bottom 4 Quintiles)	82	9 (3 to 16)	0.1	0.1
Alcohol Use	48	8 (5 to 11)	0.9	0.5
Diuretic Use	8	12 (11 to 14)	5.0	5.0

Abbreviations: BMI, body mass index. CI, confidence interval. DASH, Dietary Approaches to Stop Hypertension. PAR%, Population attributable risk percent.

* Calculated based on continuous variables except for diuretic use.