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The Epidemiology of Uric Acid and Fructose

Young Hee Rho, MD, PhD, MPH¹, Yanyan Zhu, PhD¹, and Hyon K. Choi, MD, DrPH¹

¹Section of Rheumatology and the Clinical Epidemiology Unit, Boston University School of Medicine

Abstract

During the past few decades, the mean serum uric acid levels and the prevalence of hyperuricemia in the general population appear to have increased. Correspondingly, the prevalence and incidence of gout have doubled. Potential reasons behind these trends include the increasing prevalence of obesity and metabolic syndrome, western life-style factors, increased prevalence of medical conditions (e.g. renal conditions, hypertension, and cardiovascular disorders) and use of medications that increase uric acid levels (e.g. diuretics and low-dose aspirin). The substantial increase in sugar-sweetened soft drinks and associated fructose consumption has also coincided with the secular trend of hyperuricemia and gout. Recently, several large-scale epidemiologic studies have clarified a number of these long-suspected risk factors in relation with hyperuricemia and gout. Furthermore, recent studies have illuminated the substantial comorbidities of hyperuricemia and gout, particularly metabolic-cardiovascular-renal conditions. While many prospective studies have suggested an independent association between serum uric acid levels and the future risk of cardiovascular-metabolic morbidities and mortality, only a limited number of randomized clinical trials and observational studies have recently demonstrated that the use of allopurinol can be beneficial against these outcomes. As these data are scarce and the effects of allopurinol might not be limited to lowering serum uric acid levels, the potential causal role of uric acid on these outcomes remains to be clarified with further studies.

Keywords

Uric Acid; Hyperuricemia; Gout; Epidemiology; Cardiovascular Risk

Introduction

Hyperuricemia is the precursor of gout, which is the most common inflammatory arthritis among men (1, 2). Hyperuricemia is also associated with several metabolic and cardiorenovascular conditions, including diabetes and coronary artery disease (3–8). Furthermore, hyperuricemia and gout have been linked to premature mortality in some studies (9). Serum uric acid levels and the frequency of gout have been rising during the last decades (10–23), coinciding with a worsening trend of risk factor profiles, such as obesity, metabolic syndrome, and life-style factors. Another notable change is that sugar-sweetened

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Correspondence to: Hyon K. Choi, MD, DrPH, Professor of Medicine, Section of Rheumatology and the Clinical Epidemiology Unit, 650 Albany Street, Suite 200, Boston, MA 02118, 895 W. 10th Avenue, Tel: +1 617-638-5490; Fax: +1 617-638 5239, hchoius@bu.edu.

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soft drinks and associated fructose consumption have also increased substantially over the last few decades (24–26).

In this review, we sought to summarize available epidemiologic data related to serum uric acid levels and their trends. We also discuss determinants of uric acid levels from an epidemiologic perspective, with a special focus on the data on fructose and soft drink consumption and their link to serum uric acid and associated conditions. Finally, we provide an update on comorbidities and potential outcomes of hyperuricemia, particularly metabolic-cardiovascular-renal conditions. While our focus throughout this review is on uric acid, we extend our discussion to its direct end-result, gout, wherever the relevant data are available.

Epidemiology of Uric Acid

According to the Third US National Health and Nutritional Examination Survey (NHANES III, 1988–1994) study (Table 1), the estimated mean serum uric acid concentration of the US population was 5.33 mg/dL (95% CI (5.29–5.37 mg/dL)). Overall, men had higher serum concentrations (6.06 mg/dL) than women (4.66 mg/dL) by approximately 1.4mg/dL. The mean serum uric acid concentrations did not appear to differ significantly across race/ethnicity in this nationally representative study (Table 1). While overall mean serum uric acid concentrations increased with age from 5.21 mg/dL (95% CI, 5.11–5.30mg/dL) in individuals aged 20–29 to 5.72 mg/dL (95% CI, 5.61–5.84 mg/dL) in individuals aged 80 years or older, this trend is limited to women, and is primarily driven by post-menopausal increase in serum uric acid levels (Table 2). Similar gender differences in serum uric acid levels has been reported in a Taiwanese national survey (the Nutrition and Health Survey in Taiwan [NAHSIT], 1993–96) where the mean serum uric acid concentration was 6.77 mg/dL for men, and 5.32 mg/dL for women (11).

Almost one-third of the entire US population had serum uric acid concentration >6mg/dL (49.1 million) (a widely-accepted target level of urate lowering therapy for gout (27)), whereas 11.9% had serum uric acid level >7mg/dL (19.9 million). Using the NHANES III laboratory definition of hyperuricemia (serum uric acid level > 7.0 mg/dL in men and > 5.7 mg/dL in women) (28), the prevalence of hyperuricemia in the NHANES III is 18.2%, which translates into 30.5 million of the US population (Table 1). African-Americans had the highest proportion of hyperuricemia (22.5%), followed by Caucasians (18.0%), others (16.3%), and Mexican Americans (15.2%) (Table 1). The Taiwanese NAHSIT study has shown a prevalence of 42.1% in males (serum uric acid level $\geq$ 7.0 mg/dL) and 27.4% in females (serum uric acid level $\geq$ 6.0 mg/dL) (11). Relative lack of obesity and alcohol consumption in that population suggested potential genetic or other environmental influences (11).

The serum uric acid levels have increased over the past few decades in both men (10, 12, 16, 17, 23, 29) and women (10, 17, 23, 29), according to population studies of various demographic groups (Table 3). For example, the Framingham study compared the serum uric acid levels from 1954–1958 with 1972–1976 and found a mean increase of 5.0 to 5.7 mg/dL in men and 3.9 to 4.7 mg/dL in women during the observation period (10). Similarly, The Normative Aging Study of middle-aged Caucasian men investigated the period between 1961–1980 and found the mean levels increased from below 5.5 to above 6.5mg/dL in men (12). The Coronary Artery Risk Development in Young Adults (CARDIA), which consists of African-American and Caucasian young adults aged between 24.1 to 25.6 years at baseline, found that the serum uric acid levels rose from 5.3 to 5.8 mg/dL in African-American men and 3.8 to 4.0 mg/dL in African-American women, and from 5.5 to 5.7 mg/dL in Caucasian men and 3.9 to 4.0 mg/dL in Caucasian women during 1985 to 1996 (17). A Japanese study based on young males from a university population showed an increase of

serum uric acid from 5.5 to 5.76 mg/dL between 1991 and 2002 (16). Finally, a recent abstract reported that serum uric acid level increased by 0.15 mg/dL between NHANES III (1988–1994) and NHANES 2007–2008 (21), suggesting that the increasing trend continued in the new millennium in the US. The same NHANES data comparison found a consistent increase in the prevalence of hyperuricemia during the same period (23) (Table 3). Similarly increasing trends have been reported in Japanese (16) and Chinese populations (20), although their background prevalences were lower (Table 3). Taken together, these data suggest that serum uric acid levels have increased during the past few decades. Speculation behind this increasing trend has included the increasing burden of obesity, metabolic syndrome (12, 16, 17), various life-style factors including increased alcohol consumption (12), increased prevalence of associated medical conditions (e.g. renal conditions, hypertension, and cardiovascular disorders), and increased use of medications that increase uric acid levels (low-dose aspirin or diuretics) (10).

This increasing trend of uric acid levels and hyperuricemia in turn has translated into an increasing disease frequency of gout in several populations (Table 3), including the US (14, 19, 30–32), UK (13) and Maori (33–35) populations. The incidence of gout appeared to increase in the US, from 45/100,000 during 1977–78 to 62.3/100,000 during 1995–96 in Rochester, Minnesota (36). A comparison analysis of NHANES data found an increase in the prevalence of gout from 2.7% (NHANES III) to 3.9% (NHANES 2007–2008) (21). The increase in prevalence of gout in the Maori populations, already known to have a higher prevalence than European populations (33), is notable, as it has increased from 27 per 1000 people to 64 per 1000 people during 1958 – 1992 (18, 33–35). A multicenter study of general practices in the United Kingdom found that the prevalence of gout in 1991 had increased 3-fold compared to the 1970s (13). Similarly, the prevalence of gout has been increasing in urban African communities (37).

Epidemiologic Evidence for Determinants of Serum Uric Acid and Gout

Demographics

Although hyperuricemia and gout have historically been considered conditions of men, and most research has focused on men, growing evidence suggests a substantial disease burden of gout among older women (14, 38). The difference in serum uric acid levels between genders (10) is likely due to the increased renal urate clearance by estrogen in women, particularly before menopause (39). A Japanese study showed a combination of estrogen and progesterone resulting in a significant drop in serum uric acid among hyperuricemic women, whereas there was no drop among controls (40). Similarly, the Heart and Estrogen-Progestin Replacement Study (HERS) reported that one year of estrogen plus progesterone therapy resulted in a slight drop in serum uric acid levels, as compared with placebo (0.2 mg/dL at one year of follow-up) (41). Finally, an NHANES III study found that menopause was associated with increased serum uric acid levels and postmenopausal hormone replacement therapy with decreased uric acid levels (42), and the Nurses' Health Study (NHS) showed consistent findings with the risk of incident gout among 92,535 women (43).

Age appears to have an influence only among women, as serum uric acid levels steadily increase with age (Tables 1, 2) (42, 44–46). In the aforementioned NHANES analysis, the increase attenuated substantially after adjusting for menopausal status, but remained significant, suggesting that menopause explains a substantial portion, but not all, of the age-associated increase among women (42). The remaining age-associated increase was explained by other age-related factors such as renal function, diuretic use and hypertension (42).

Serum uric acid levels appear to vary among race or ethnicity. African Americans have been observed to have higher serum uric acid levels than Caucasian Americans (47). This was previously linked to the increased prevalence of hypertension among African Americans (48). Also serum uric acid levels appear to be higher in aboriginal people, as observed in the Maori (18) and Taiwanese (11) aborigines, suggesting a genetic influence.

Lifestyle Factors

Lifestyle factors have an important role on the development of hyperuricemia and gout (Table 4). Various purine-rich foods and high protein intake had long been thought to be risk factors for gout (49, 50). Previous metabolic experiments in animals and humans demonstrated the urate-raising effect of the artificial short-term loading of purified purines (51–54), whereas the possibility that the consumption of dairy products has a role in protecting against gout has been raised by previous studies (55, 56). Furthermore, the role of the Western diet has been supported by epidemiologic studies of Japanese (57) and Filipino (58) immigrants, which showed that US immigrants had higher serum urate levels than their offshore counterparts. More recently, NHANES III analyses showed that serum uric acid levels increased with increasing total meat or seafood intake, and decreased with increasing dairy intake. Furthermore, alcohol consumption increased serum uric acid levels, particularly with beer and liquor (59). These findings were replicated in the prospective analysis of the Health Professionals Follow-Up Study (HPFS, n=47,150), showing the same pattern of associations with the risk of incident gout (1, 60).

Adiposity is one of the strongest risk factors for hyperuricemia and gout (2, 12, 38, 61–64). Adiposity likely increases uric acid levels both by decreasing renal excretion of urate and in part by increasing urate production (49, 50, 65). Prospective cohort studies have found a strong relation between higher adiposity (or weight gain) and both hyperuricemia and an increased risk of incident gout (2, 12, 22, 61–64). A recent study also documented that weight reduction leads to a considerable reduction of serum urate (22). Similarly, in the Swedish Bariatric Surgery Outcome study, gastric surgery-induced weight reduction was associated with a substantially lower odds of hyperuricemia (66). Finally, the HPFS Study reported that men who had lost weight had a significantly lower risk of incident gout (63). These data collectively indicate that adiposity is a prominent determinant for hyperuricaemia and gout.

Coffee consumption may lower serum uric acid levels and the risk of gout (67, 68) in the long term via various mechanisms (69–72). For example, caffeine (1, 3, 7-trimethyl-xanthine) is a methyl-xanthine and may be a competitive inhibitor of xanthine oxidase, as demonstrated in rats (67, 69). Long-term intake of coffee and caffeine intake may also lower insulin levels (72) and increase insulin sensitivity (73). An NHANES III study and two Japanese studies found that serum uric acid levels decreased with increasing coffee intake (74–76). The HPFS (68) and NHS (67) studies also found that coffee consumption decreased the risk of gout.

Previous studies have found that high doses of vitamin C supplementation lower serum uric acid via a uricosuric effect (77–81). A double-blinded placebo-controlled randomized trial among 184 non-smoking participants showed that supplementation with 500 mg/day of vitamin C for 2 months reduced serum urate levels by 0.5 mg/dL (95% CI 0.3 to 0.6) (82). Several observational studies from Taiwan (83) and from the US (80, 84) extended the evidence for the inverse link between Vitamin C intake and the lower risk of hyperuricemia or gout.

Medical Conditions and Medications

There are many medical conditions that can elevate serum uric acid levels and the risk of gout, including hypertension, renal insufficiency, congestive heart failure and other conditions associated with severe tissue hypoxia, proliferative and inflammatory disorders associated with increased cell turnover (85). Nevertheless, large-scale epidemiologic quantification of potential impact from these conditions has been limited to several relatively common conditions, such as hypertension (or high blood pressure) and renal insufficiency (63, 64). Similarly, there are many substances and medications that can elevate serum uric acid levels and the risk of gout; however, large-scale epidemiologic data have been limited to several agents such as diuretics (63) and postmenopausal hormone therapy (42, 43).

Fructose, Hyperuricemia and Gout

Trends in Fructose Consumption

The consumption of fructose in the US has increased considerably since the introduction of high fructose corn syrup (HFCS) in 1967 (25). HFCS is a product made from corn, and usually has a composition of 42% fructose (HFCS-42) or 55% fructose (HFCS-55) (86). HFCS has several commercial advantages over crystalline sugar (sucrose), its predecessor sweetener, such as convenience to transport and use (as it is a transferable and easily mixable liquid), less dependence on foreign sources (as opposed to sugar cane, which is a tropical product) (86), and possibly being sweeter than sugar (24, 86). These properties, combined with strong marketing efforts (87) made the consumption of HFCS-containing beverages dramatically increase during the past several decades. The popularity of soft drinks in schools soared (88) and soft drinks have become the beverage of choice in the US (89). During 1977–1997 the consumption of soft drinks has increased by 61% in the US (26), which contributed to increased total caloric intake during the same periods (90).

Fructose and Serum Uric Acid

The substantial increase in soft drink and fructose consumption coincided with the increasing trend of serum uric acid (12, 17, 23, 29) and doubling of the disease burden of gout (14, 36) over the past few decades in the US (85, 91, 92)(Figure 1). Fructose is known to induce uric acid production by increasing ATP degradation to AMP, a uric acid precursor (85, 93, 94) and thus, within minutes after fructose infusion, serum uric acid levels rise (94). Furthermore, *de novo* purine synthesis is accelerated, further potentiating uric acid production.

An NHANES III study showed that fructose-rich beverages, both artificial (such as soft drinks) and natural (such as orange juice), were associated with increased serum uric acid levels (95). Furthermore, nutrient fructose consumption was also positively associated with increased serum uric acid levels (difference between >75mg/day vs. <10mg/day, 0.88mg/dL). In contrast, “diet” soft drinks were not associated with serum uric acid, further supporting the notion that increased fructose consumption leads to hyperuricemia. The HPFS study found consistent links about the impact of these beverages and nutrient fructose with the outcome of gout among men (92).

Sugar Sweetened Soft Drinks, Obesity, the Metabolic Syndrome, and Diabetes

The epidemic secular trend of obesity in recent years has also coincided with the increasing use of HFCS in beverages (24). Experimental studies in animal models and from short-term feeding trials among humans have suggested that higher fructose intake contributes to insulin resistance, impaired glucose tolerance, and hyperinsulinemia (90, 96, 97). In contrast, glucose intake had no similar adverse effects (96). Furthermore, prospective studies

have reported that soft drink consumption is associated with increased risk of obesity, insulin resistance, metabolic syndrome, and diabetes (90, 98, 99). A meta-analysis based on 310,819 participants from 11 studies has also concluded that consumption of soft drinks was associated with the development of metabolic syndrome and type 2 diabetes (100). Nevertheless, these epidemiologic studies did not include the specific effects of the fructose nutrient. It remains conceivable that positive energy balance often associated with increased fructose consumption has contributed to excess adiposity (90, 101).

In addition, fructose consumption has been linked to an increased risk of hypertension and chronic renal disease. According to the NHANES III data, adolescents who drank more sugar-sweetened beverages was associated with increased systolic blood pressure (102). The NHANES 2003–2006 data similarly has shown that an increased fructose intake of $\geq 74\text{g/day}$ was associated with a 30% increased risk for having a blood pressure of $\geq 140/90$ mmHg than those who had a fructose intake of $<74\text{g/day}$ (103). However, prospective studies using the HPFS and NHS cohorts have failed to show a significant effect of fructose intake on the risk of hypertension (104).

Similar conflicting findings have been found in chronic renal disease. Data from the NHANES 1999–2004 revealed that an intake of 2+ sugary drinks / day was associated with albuminuria (OR 1.40, 95% CI(1.13–1.74)) (105). However, the Atherosclerosis Risk in Communities Study (ARIC) showed that while increased consumption of sugar-sweetened soda consumption led to an increased prevalence of chronic kidney disease, it was not associated with an increase of incident chronic kidney disease (106). From these studies, it appears that fructose consumption is associated with prevalent, but not incident hypertension or chronic kidney disease. Why such patterns appear is not clear and the association of fructose consumption, hypertension and chronic kidney disease remains controversial.

Potential Outcomes and Associated Conditions of Hyperuricemia

Metabolic Syndrome and Diabetes

The metabolic syndrome affects more than 50 million Americans (107), and increases the risk for atherosclerotic cardiovascular disease and type 2 diabetes, as well as mortality (108). Insulin may enhance renal urate reabsorption via stimulation of urate-anion exchanger (109) and/or the Na^+ -dependent anion co-transporter in brush border membranes of the renal proximal tubule (85). Higher insulin levels are known to reduce renal excretion of uric acid (110–112). A close association between serum urate levels and individual components of the metabolic syndrome has been reported (64, 113). In a representative sample of adult US men and women (NHANES III), the prevalence of the metabolic syndrome according to the same criteria increased substantially with increasing levels of serum urate from 19% for serum urate levels less than 6 mg/dL to 71% for levels of 10 mg/dL or greater (5). Correspondingly, the prevalence of the metabolic syndrome was 63% among US adults with gout versus 25% among individuals without gout. It has been suggested that hyperuricemia should be regarded as an intrinsic part (114) or surrogate marker (50, 115) for the metabolic syndrome.

Expanding on the strong associations between hyperuricemia, gout, and the metabolic syndrome, several prospective studies have reported an independent association between serum uric acid levels and the future risk of type 2 diabetes (116–119). Similarly, data from the MRFIT (Multiple Risk Factor Intervention Trial) showed that male participants with gout had a 26% increased risk for incident type 2 diabetes (4).

Cardiovascular Disease, Renal Diseases, and Mortality

Many, but not all, prospective studies reported an independent association between serum urate levels and the future risk of cardiovascular-renal outcomes and mortality and these data have been well-summarized in several reviews and meta-analysis studies (8, 85, 120–123). More recently, gout has been also linked to these outcomes, as recently reviewed (9).

A randomized clinical trial (124) and two large cohort studies (125, 126) recently showed that the use of allopurinol, a hypo-uricemic agent, could be beneficial to cardiovascular outcomes or all-cause mortality. Another previous randomized trial found reno-protective effects of allopurinol (127). Although these allopurinol benefits are correlated well with reduced uric acid levels in these studies, it is conceivable that the effect of allopurinol to lower BP may be due to the lowering of xanthine oxidase–induced oxidants, or other effects of allopurinol (124). Thus, the potential causal role of serum uric acid on these outcomes remains to be clarified further by future studies. In particular, additional randomized trial data on the effect of various urate-lowering medications (e.g. with or without xanthine oxidase inhibitor related properties) on the prevention or treatment of these outcomes would be valuable.

Conclusion

During the past few decades, the mean serum uric acid levels and the prevalence of hyperuricemia in the general population appear to have increased. Potential reasons behind these trends include the increasing prevalence of obesity and metabolic syndrome, western life-style factors, increased prevalence of medical conditions, and medication use that increase uric acid levels. In addition, the substantial increase in sugar-sweetened soft drinks and fructose consumption coincides with the secular trend of hyperuricemia and gout. These exposures appear to have several solid biologic rationales and are supported by epidemiologic data in relation to development of hyperuricemia and of gout. While sugar-sweetened beverages, a major source of fructose, are also associated with an increased risk of hypertension, and diabetes, it remains unclear whether the associations are caused by fructose *per se*, or through some other mechanism (128). Nevertheless, given their demonstrated adverse health associations and the lack of any health benefit, the evidence appears to favor minimization of sugar-sweetened beverage intake.

References

1. 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):1093–1103. [PubMed: 15014182]
2. 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):3004–3007. [PubMed: 1820473]
3. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation*. 2007; 116(8):894–900. [PubMed: 17698728]
4. Choi HK, De Vera MA, Krishnan E. Gout and the risk of type 2 diabetes among men with a high cardiovascular risk profile. *Rheumatology (Oxford)*. 2008; 47(10):1567–1570. [PubMed: 18710901]
5. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am J Med*. 2007; 120(5):442–447. [PubMed: 17466656]
6. Choi HK, Ford ES. Haemoglobin A1c, fasting glucose, serum C-peptide and insulin resistance in relation to serum uric acid levels--the Third National Health and Nutrition Examination Survey. *Rheumatology (Oxford)*. 2008; 47(5):713–717. [PubMed: 18390895]
7. Choi HK, Ford ES, Li C, Curhan G. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2007; 57(1):109–115. [PubMed: 17266099]

8. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2010; 62(2): 170–180. [PubMed: 20191515]
9. Kim SY, De Vera MA, Choi HK. Gout and mortality. *Clin Exp Rheumatol*. 2008; 26 Suppl 51(5):S115–S119. [PubMed: 19026153]
10. Brand FN, McGee DL, Kannel WB, Stokes J 3rd, Castelli WP. Hyperuricemia as a risk factor of coronary heart disease: The Framingham Study. *Am J Epidemiol*. 1985; 121(1):11–18. [PubMed: 3964986]
11. Chang HY, Pan WH, Yeh WT, Tsai KS. Hyperuricemia and gout in Taiwan: results from the Nutritional and Health Survey in Taiwan (1993–96). *J Rheumatol*. 2001; 28(7):1640–1646. [PubMed: 11469473]
12. Glynn RJ, Campion EW, Silbert JE. Trends in serum uric acid levels 1961–1980. *Arthritis Rheum*. 1983; 26(1):87–93. [PubMed: 6824508]
13. Harris CM, Lloyd DC, Lewis J. The prevalence and prophylaxis of gout in England. *J Clin Epidemiol*. 1995; 48(9):1153–1158. [PubMed: 7636517]
14. 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]
15. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR Jr, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990–1999. *Ann Rheum Dis*. 2005; 64(2):267–272. [PubMed: 15647434]
16. Ogura T, Matsuura K, Matsumoto Y, Mimura Y, Kishida M, Otsuka F, et al. Recent trends of hyperuricemia and obesity in Japanese male adolescents, 1991 through 2002. *Metabolism*. 2004; 53(4):448–453. [PubMed: 15045690]
17. Rathmann W, Haastert B, Icks A, Giani G, Roseman JM. Ten-year change in serum uric acid and its relation to changes in other metabolic risk factors in young black and white adults: the CARDIA study. *Eur J Epidemiol*. 2007; 22(7):439–445. [PubMed: 17484024]
18. Roddy E, Zhang W, Doherty M. The changing epidemiology of gout. *Nat Clin Pract Rheumatol*. 2007; 3(8):443–449. [PubMed: 17664951]
19. Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. *J Rheumatol*. 2004; 31(8):1582–1587. [PubMed: 15290739]
20. Zeng QY, Chen R, Darmawan J, Xiao ZY, Chen SB, Wigley R, et al. Rheumatic diseases in China. *Arthritis Res Ther*. 2008; 10(1):R17. [PubMed: 18237382]
21. Zhu, Y.; Pandva, B.; Choi, HK. American College of Rheumatology (ACR). Atlanta: 2010. Increasing Gout Prevalence in the US over the Last Two Decades: The National Health and Nutrition Examination Survey (NHANES). #2154; 2010;
22. Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. *Rheumatology (Oxford)*. 2010
23. Zhu, Y.; Pandva, B.; Choi, HK. American College of Rheumatology (ACR). Atlanta: 2010. Prevalence of Hyperuricemia in the US General Population: The National Health and Nutrition Examination Survey (NHANES) 1999–2008. #1363; 2010;
24. 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(4):537–543. [PubMed: 15051594]
25. Johnson RJ, Segal MS, Sautin Y, Nakagawa T, Feig DI, Kang DH, et al. Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease. *Am J Clin Nutr*. 2007; 86(4):899–906. [PubMed: 17921363]
26. Putnam JJ, Allshouse JE. Food Consumption, Prices and Expenditures, 1970–97. US Department of Agriculture Economic Research Service Statistical Bulletin. 1999; (No. 965)
27. Zhang W, Doherty M, Bardin T, Pascual E, Barskova V, Conaghan P, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis*. 2006; 65(10):1312–1324. [PubMed: 16707532]

28. 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.
29. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 2005; 52(1):283–289. [PubMed: 15641075]
30. Adams PF, Hardy AM. Current estimates from the National Health Interview Survey, 1998. *Vital Health Stat* 10. 1989; 173:1–250. [PubMed: 2596038]
31. Benson V, Marano MA. Current estimates from the National Health Interview Survey, 1992. *Vital Health Stat* 10. 1994; (189):1–269. [PubMed: 8154108]
32. Adams PF, Hendershot GE, Marano MA. Current Estimates from the National Health Interview Survey, 1996. *Vital Health Stat.* 1999; 10(200)
33. Lennane GA, Rose BS, Isdale IC. Gout in the Maori. *Ann Rheum Dis.* 1960; 19:120–125. [PubMed: 14415696]
34. Prior IA, Rose BS. Uric acid, gout and public health in the South Pacific. *N Z Med J.* 1966; 65(405):295–300. [PubMed: 5220372]
35. Klemp P, Stansfield SA, Castle B, Robertson MC. Gout is on the increase in New Zealand. *Ann Rheum Dis.* 1997; 56(1):22–26. [PubMed: 9059136]
36. Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE. Epidemiology of gout: is the incidence rising? *J Rheumatol.* 2002; 29(11):2403–2406. [PubMed: 12415600]
37. Cassim B, Mody GM, Deenadayalu VK, Hammond MG. Gout in black South Africans: a clinical and genetic study. *Ann Rheum Dis.* 1994; 53(11):759–762. [PubMed: 7826138]
38. 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):1069–1076. [PubMed: 20131266]
39. Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. *Br Med J.* 1973; 1(5851):449–451. [PubMed: 4689833]
40. Sumino H, Ichikawa S, Kanda T, Nakamura T, Sakamaki T. Reduction of serum uric acid by hormone replacement therapy in postmenopausal women with hyperuricaemia. *Lancet.* 1999; 354(9179):650. [PubMed: 10466673]
41. Simon JA, Lin F, Vittinghoff E, Bittner V. The relation of postmenopausal hormone therapy to serum uric acid and the risk of coronary heart disease events: the Heart and Estrogen-Progestin Replacement Study (HERS). *Ann Epidemiol.* 2006; 16(2):138–145. [PubMed: 16039873]
42. Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women--the Third National Health and Nutrition Examination Survey. *Arthritis Res Ther.* 2008; 10(5):R116. [PubMed: 18822120]
43. Hak AE, Curhan GC, Grodstein F, Choi HK. Menopause, postmenopausal hormone use and risk of incident gout. *Ann Rheum Dis.* 2010; 69(7):1305–1309. [PubMed: 19592386]
44. Mikkelsen WM, Dodge HJ, Valkenburg H. The Distribution of Serum Uric Acid Values in a Population Unselected as to Gout or Hyperuricemia: Tecumseh, Michigan 1959–1960. *Am J Med.* 1965; 39:242–251. [PubMed: 14320691]
45. O'Sullivan JB. Gout in a New England town. A prevalence study in Sudbury, Massachusetts. *Ann Rheum Dis.* 1972; 31(3):166–169. [PubMed: 5032448]
46. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med.* 1999; 131(1):7–13. [PubMed: 10391820]
47. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. *National Health and Nutrition Examination Survey.* *JAMA.* 2000; 283(18):2404–2410. [PubMed: 10815083]
48. 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):628–632. [PubMed: 7748218]
49. Emmerson BT. The management of gout. *N Engl J Med.* 1996; 334(7):445–451. [PubMed: 8552148]

50. Fam AG. Gout, diet, and the insulin resistance syndrome. *J Rheumatol.* 2002; 29(7):1350–1355. [PubMed: 12136887]
51. Zollner N. Influence of various purines on uric acid metabolism. *Bibl Nutr Dieta.* 1973; 19:34–43. [PubMed: 4600927]
52. Zollner N, Griebisch A. Diet and gout. *Adv Exp Med Biol.* 1974; 41:435–442. [PubMed: 4832568]
53. Clifford AJ, Riumallo JA, Young VR, Scrimshaw NS. Effect of Oral Purines on Serum and Urinary Uric Acid of Normal, Hyperuricemic and Gouty Humans. *J Nutr.* 1976; 106:428–434.
54. Clifford AJ, Story DL. Levels of Purines in Foods and Their Metabolic Effects in Rats. *J Nutr.* 1976; 106:435–442.
55. 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(3):665–669. [PubMed: 2000819]
56. Loenen HM, Eshuis H, Lowik MR, Schouten EG, Hulshof KF, Odink J, et al. Serum uric acid correlates in elderly men and women with special reference to body composition and dietary intake (Dutch Nutrition Surveillance System). *J Clin Epidemiol.* 1990; 43(12):1297–1303. [PubMed: 2254766]
57. 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(7–8):345–364. [PubMed: 4436426]
58. Torralba TP, Bayani-Sioson PS. The Filipino and gout. *Semin Arthritis Rheum.* 1975; 4(4):307–320. [PubMed: 1135632]
59. Choi HK, Curhan G. Beer, liquor, and wine consumption and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 2004; 51(6):1023–1029. [PubMed: 15593346]
60. 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):1277–1281. [PubMed: 15094272]
61. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med.* 1987; 82(3):421–426. [PubMed: 3826098]
62. Abbott RD, Brand FN, Kannel WB, Castelli WP. Gout and coronary heart disease: the Framingham Study. *J Clin Epidemiol.* 1988; 41(3):237–242. [PubMed: 3339376]
63. 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):742–748. [PubMed: 15824292]
64. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: the CARDIA study. Coronary Artery Risk Development in Young Adults. *Ann Epidemiol.* 1998; 8(4):250–261. [PubMed: 9590604]
65. Emmerson BT. Alteration of urate metabolism by weight reduction. *Aust N Z J Med.* 1973; 3(4):410–412. [PubMed: 4519128]
66. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med.* 2004; 351(26):2683–2693. [PubMed: 15616203]
67. Choi HK, Curhan G. Coffee consumption and risk of incident gout in women: the Nurses' Health Study. *Am J Clin Nutr.* 2010
68. Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men: a prospective study. *Arthritis Rheum.* 2007; 56(6):2049–2055. [PubMed: 17530645]
69. Kela U, Vijayvargiya R, Trivedi CP. Inhibitory effects of methylxanthines on the activity of xanthine oxidase. *Life Sci.* 1980; 27(22):2109–2119. [PubMed: 6894176]
70. Petrie HJ, Chown SE, Belfie LM, Duncan AM, McLaren DH, Conquer JA, et al. Caffeine ingestion increases the insulin response to an oral-glucose-tolerance test in obese men before and after weight loss. *Am J Clin Nutr.* 2004; 80(1):22–28. [PubMed: 15213023]
71. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA.* 2005; 294(1):97–104. [PubMed: 15998896]

72. Wu T, Willett WC, Hankinson SE, Giovannucci E. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. *Diabetes Care*. 2005; 28(6):1390–1396. [PubMed: 15920057]
73. Arnlov J, Vessby B, Riserus U. Coffee consumption and insulin sensitivity. *JAMA*. 2004; 291(10):1199–1201. [PubMed: 15010440]
74. Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey. *Arthritis Rheum*. 2007; 57(5):816–821. [PubMed: 17530681]
75. Pham NM, Yoshida D, Morita M, Yin G, Toyomura K, Ohnaka K, et al. The relation of coffee consumption to serum uric Acid in Japanese men and women aged 49–76 years. *J Nutr Metab*. 2010; 2010
76. Kiyohara C, Kono S, Honjo S, Todoroki I, Sakurai Y, Nishiwaki M, et al. Inverse association between coffee drinking and serum uric acid concentrations in middle-aged Japanese males. *Br J Nutr*. 1999; 82(2):125–130. [PubMed: 10743484]
77. Berger L, Gerson CD, Yu TF. The effect of ascorbic acid on uric acid excretion with a commentary on the renal handling of ascorbic acid. *Am J Med*. 1977; 62(1):71–76. [PubMed: 835593]
78. Sutton JL, Basu TK, Dickerson JW. Effect of large doses of ascorbic acid in man on some nitrogenous components of urine. *Human Nutrition Applied Nutrition*. 1983; 37(2):136–140. [PubMed: 6863023]
79. Stein HB, Hasan A, Fox IH. Ascorbic acid-induced uricosuria. A consequence of megavitamin therapy. *Ann Intern Med*. 1976; 84(4):385–388. [PubMed: 1259282]
80. Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study. *Arch Intern Med*. 2009; 169(5):502–507. [PubMed: 19273781]
81. Mitch WE, Johnson MW, Kirshenbaum JM, Lopez RE. Effect of large oral doses of ascorbic acid on uric acid excretion by normal subjects. *Clin Pharmacol Ther*. 1981; 29(3):318–321. [PubMed: 7471601]
82. Huang HY, Appel LJ, Choi MJ, Gelber AC, Charleston J, Norkus EP, et al. The effects of vitamin C supplementation on serum concentrations of uric acid: results of a randomized controlled trial. *Arthritis Rheum*. 2005; 52(6):1843–1847. [PubMed: 15934094]
83. Lyu LC, Hsu CY, Yeh CY, Lee MS, Huang SH, Chen CL. A case-control study of the association of diet and obesity with gout in Taiwan. *American Journal of Clinical Nutrition*. 2003; 78(4):690–701. [PubMed: 14522726]
84. Gao X, Curhan G, Forman JP, Ascherio A, Choi HK. Vitamin C intake and serum uric acid concentration in men. *J Rheumatol*. 2008; 35(9):1853–1858. [PubMed: 18464304]
85. Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. *Ann Intern Med*. 2005; 143(7):499–516. [PubMed: 16204163]
86. White JS. Straight talk about high-fructose corn syrup: what it is and what it ain't. *Am J Clin Nutr*. 2008; 88(6):1716S–1721S. [PubMed: 19064536]
87. Murray R, Frankowski B, Taras H. Are soft drinks a scapegoat for childhood obesity? *J Pediatr*. 2005; 146(5):586–590. [PubMed: 15870659]
88. Ralston, K.; Lin, BH. Food Assistance Research Brief—Competitive Foods: Soft Drinks vs. Milk; Food Assistance and Nutrition Research Report No (FANRR34-7). 2003. p. 3[cited; Available from: <http://www.ers.usda.gov/publications/fanrr34/fanrr34-7/fanrr34-7.pdf>
89. Clauson, A. How Americans Quench Their Thirsts. 2005. [cited; Available from: <http://www.ers.usda.gov/AmberWaves/September05/Findings/HowAmericans.htm>
90. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA*. 2004; 292(8):927–934. [PubMed: 15328324]
91. Apovian CM. Sugar-sweetened soft drinks, obesity, and type 2 diabetes. *JAMA*. 2004; 292(8):978–979. [PubMed: 15328331]
92. Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ*. 2008; 336(7639):309–312. [PubMed: 18244959]

93. Gibson T, Rodgers AV, Simmonds HA, Court-Brown F, Todd E, Meilton V. A controlled study of diet in patients with gout. *Annals of the Rheumatic Diseases*. 1983; 42(2):123–127. [PubMed: 6847259]
94. Fox IH, Kelley WN. Studies on the mechanism of fructose-induced hyperuricemia in man. *Metabolism: Clinical and Experimental*. 1972; 21(8):713–721. [PubMed: 5047915]
95. 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(1):109–116. [PubMed: 18163396]
96. Beck-Nielsen H, Pedersen O, Lindskov HO. Impaired cellular insulin binding and insulin sensitivity induced by high-fructose feeding in normal subjects. *Am J Clin Nutr*. 1980; 33(2):273–278. [PubMed: 6986758]
97. Thorburn AW, Storlien LH, Jenkins AB, Khouri S, Kraegen EW. Fructose-induced in vivo insulin resistance and elevated plasma triglyceride levels in rats. *Am J Clin Nutr*. 1989; 49(6):1155–1163. [PubMed: 2658534]
98. Dhingra R, Sullivan L, Jacques PF, Wang TJ, Fox CS, Meigs JB, et al. Soft drink consumption and risk of developing cardiometabolic risk factors and the metabolic syndrome in middle-aged adults in the community. *Circulation*. 2007; 116(5):480–488. [PubMed: 17646581]
99. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugarsweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001; 357(9255):505–508. [PubMed: 11229668]
100. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar Sweetened Beverages and Risk of Metabolic Syndrome and Type 2 Diabetes: A Meta-analysis. *Diabetes Care*. 2010
101. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. *Am J Clin Nutr*. 2002; 76(5):911–922. [PubMed: 12399260]
102. Nguyen S, Choi HK, Lustig RH, Hsu CY. Sugar-sweetened beverages, serum uric acid, and blood pressure in adolescents. *J Pediatr*. 2009; 154(6):807–813. [PubMed: 19375714]
103. Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol*. 2010; 21(9):1543–1549. [PubMed: 20595676]
104. Forman JP, Choi H, Curhan GC. Fructose and vitamin C intake do not influence risk for developing hypertension. *J Am Soc Nephrol*. 2009; 20(4):863–871. [PubMed: 19144761]
105. Shoham DA, Durazo-Arvizu R, Kramer H, Luke A, Vupputuri S, Kshirsagar A, et al. Sugary soda consumption and albuminuria: results from the National Health and Nutrition Examination Survey, 1999–2004. *PLoS One*. 2008; 3(10) e3431.
106. Bombardier AS, Derbail VK, Shoham DA, Anderson CA, Steffen LM, Rosamond WD, et al. Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. *Kidney Int*. 2010; 77(7): 609–616. [PubMed: 20032963]
107. 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):356–359. [PubMed: 11790215]
108. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care*. 2005; 28(7):1769–1778. [PubMed: 15983333]
109. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, et al. Molecular identification of a renal urate anion exchanger that regulates blood urate levels. *Nature*. 2002; 417(6887):447–452. [PubMed: 12024214]
110. 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(21):3008–3011. [PubMed: 1820474]
111. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens*. 1996; 9(8):746–752. [PubMed: 8862220]
112. Ter Maaten JC, Voorburg A, Heine RJ, Ter Wee PM, Donker AJ, Gans RO. Renal handling of urate and sodium during acute physiological hyperinsulinaemia in healthy subjects. *Clin Sci (Lond)*. 1997; 92(1):51–58. [PubMed: 9038591]

113. Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. The Normative Aging Study. *Am J Epidemiol*. 1995; 142(3):288–294. [PubMed: 7631632]
114. Emmerson B. Hyperlipidaemia in hyperuricaemia and gout. *Ann Rheum Dis*. 1998; 57(9):509–510. [PubMed: 9849306]
115. Snaith ML. Gout: diet and uric acid revisited. *Lancet*. 2001; 358(9281):525. [PubMed: 11520519]
116. 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 In Press.
117. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care*. 2008; 31(2):361–362. [PubMed: 17977935]
118. Kramer CK, von Muhlen D, Jassal SK, Barrett-Connor E. Serum uric acid levels improve prediction of incident type 2 diabetes in individuals with impaired fasting glucose: the Rancho Bernardo Study. *Diabetes Care*. 2009; 32(7):1272–1273. [PubMed: 19366963]
119. Niskanen L, Laaksonen DE, Lindstrom J, Eriksson JG, Keinänen-Kiukaanniemi S, Ilanne-Parikka P, et al. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish Diabetes Prevention Study. *Diabetes Care*. 2006; 29(3):709–711. [PubMed: 16505534]
120. Grayson PC, Kim SY, Lavalley M, Choi HK. Hyperuricemia and incident hypertension: A systematic review and meta-analysis. *Arthritis Care Res (Hoboken)*. 2010
121. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and risk of stroke: a systematic review and meta-analysis. *Arthritis Rheum*. 2009; 61(7):885–892. [PubMed: 19565556]
122. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med*. 2009; 169(4):342–350. [PubMed: 19237717]
123. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*. 2003; 41(6):1183–1190. [PubMed: 12707287]
124. Noman A, Ang DS, Ogston S, Lang CC, Struthers AD. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet*. 2010; 375(9732):2161–2167. [PubMed: 20542554]
125. Thanassoulis G, Brophy JM, Richard H, Pilote L. Gout, allopurinol use, and heart failure outcomes. *Arch Intern Med*. 2010; 170(15):1358–1364. [PubMed: 20696962]
126. Luk AJ, Levin GP, Moore EE, Zhou XH, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricaemic patients. *Rheumatology (Oxford)*. 2009; 48(7):804–806. [PubMed: 19447769]
127. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis*. 2006; 47(1):51–59. [PubMed: 16377385]
128. Curhan GC, Forman JP. Sugar-sweetened beverages and chronic disease. *Kidney Int*. 2010; 77(7):569–570. [PubMed: 20224584]
129. Currie WJ. Prevalence and incidence of the diagnosis of gout in Great Britain. *Ann Rheum Dis*. 1979; 38(2):101–106. [PubMed: 312625]
130. 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(5):1480–1487. [PubMed: 18469274]
131. Gao X, Qi L, Qiao N, Choi HK, Curhan G, Tucker KL, et al. Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. *Hypertension*. 2007; 50(2):306–312. [PubMed: 17592072]
132. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol*. 2010; 22(2):165–172. [PubMed: 20035225]
133. Wilder MH. Prevalence of Chronic Skin and Musculoskeletal Conditions, United States, 1969. *Vital Health Stat*. 1974; 10(92)
134. Bonham GS. Prevalence of Chronic Skin and Musculoskeletal Conditions, United States, 1976. *Vital Health Stat*. 1981; 10(124)

135. Dawson DA, Adams PF. Current Estimates From the National Health Interview Survey, United States, 1986. *Vital Health Stat.* 1987; 10(164)

Figure 1. The relationship between high fructose corn syrup (HFCS) consumption and gout prevalence in the US

The HFCS consumption estimates are based on data from reference (26), whereas gout prevalences are based on data from references (32, 133–135) (National Health Interview Survey [NHIS]). The gout prevalence for 1970 is based on the data from 1969.

Table 1

Prevalence of Hyperuricemia, Number of US Adults with Hyperuricemia, and Mean Serum Uric Acid Levels, NHANES III (1988–1994)

	Prevalence of Hyperuricemia **, % (95% CI)	US Adults with Hyperuricemia ** (in millions)	Prevalence of Hyperuricemia (>6mg/dL), % (95% CI)	US Adults with Hyperuricemia (>6mg/dL) (in millions)	Mean Serum Uric Acid Level, mg/dL (95% CI)
Overall *	18.2 (17.1 to 19.3)	30.5	29.4 (28.0 to 30.7)	49.1	5.33 (5.29 to 5.37)
Gender					
Men	19.2 (17.8 to 20.5)	15.3	47.3 (45.2 to 49.4)	37.9	6.06 (6.01 to 6.11)
Women	17.3 (16.0 to 18.7)	15.1	12.9 (11.7 to 14.0)	11.2	4.66 (4.60 to 4.72)
Race or Ethnicity					
White	18.0 (16.8 to 19.3)	23.2	29.0 (27.3 to 30.8)	37.4	5.32 (5.27 to 5.37)
African American	22.5 (20.4 to 24.5)	3.9	31.8 (30.1 to 33.5)	5.5	5.41 (5.33 to 5.49)
Mexican American	15.2 (13.4 to 17.0)	1.3	28.8 (26.3 to 31.2)	2.4	5.26 (5.18 to 5.33)
Others	16.3 (12.7 to 19.9)	2.1	29.6 (25.8 to 33.5)	3.8	5.35 (5.22 to 5.47)
Age Category (y)					
Men					
20–29	17.5 (13.8 to 21.3)	3.2	50.8 (46.7 to 55.0)	9.3	6.10 (5.98 to 6.23)
30–39	16.6 (13.7 to 19.5)	3.3	42.9 (38.5 to 47.3)	8.5	5.96 (5.84 to 6.08)
40–49	19.5 (16.2 to 22.9)	3.1	46.1 (41.9 to 50.4)	7.2	6.04 (5.95 to 6.14)
50–59	21.0 (17.4 to 24.6)	2.2	48.4 (42.8 to 53.9)	5.0	6.05 (5.90 to 6.20)
60–69	21.2 (17.5 to 24.9)	1.9	48.2 (43.3 to 53.1)	4.2	6.12 (5.98 to 6.26)
70–79	24.6 (20.8 to 28.3)	1.3	51.2 (46.9 to 55.5)	2.8	6.22 (6.10 to 6.35)
80+	23.9 (18.6 to 29.1)	0.5	48.0 (43.3 to 52.7)	0.9	6.13 (5.97 to 6.30)
Women					
20–29	8.9 (5.7 to 12.1)	1.6	5.4 (3.4 to 7.4)	1.0	4.32 (4.23 to 4.41)
30–39	9.8 (7.3 to 12.3)	2.0	6.0 (4.0 to 7.9)	1.2	4.33 (4.22 to 4.44)
40–49	12.5 (9.2 to 15.7)	2.0	8.5 (6.1 to 10.9)	1.4	4.44 (4.30 to 4.58)
50–59	22.0 (18.7 to 25.3)	2.4	16.2 (13.5 to 18.8)	1.8	4.95 (4.84 to 5.05)
60–69	29.2 (25.6 to 32.9)	3.0	24.0 (20.1 to 27.9)	2.5	5.21 (5.09 to 5.33)
70–79	35.6 (31.7 to 39.6)	2.7	29.9 (26.4 to 33.4)	2.2	5.28 (5.15 to 5.41)
80+	39.2 (35.3 to 43.1)	1.4	32.4 (29.0 to 35.8)	1.1	5.50 (5.37 to 5.64)

* Data are presented incorporating sample weights and adjusted for clusters and strata of the complex sample design of NHANES III.

**Hyperuricemia was defined as serum uric acid level > 7.0 mg/dL in men and > 5.7 mg/dL in women.

Table 2

Serum Uric Acid Trends by Age, NHANES III (1988–1994)

	Age Category (yrs)	20–29	30–39	40–49	50–59	60–69	≥ 70	P*
Men	Participants Number	1532	1368	1158	814	1120	1420	-
	Unadjusted difference mg/dl (95% CI)	0 (referent)	-0.14 (-0.31, 0.03)	-0.06 (-0.24, 0.12)	-0.05 (-0.27, 0.17)	0.02 (-0.18, 0.22)	0.10 (-0.05, 0.25)	0.174
Women	Participants Number	1737	1740	1288	952	1101	1608	-
	Unadjusted difference mg/dl (95% CI)	0 (referent)	0.01 (-0.1, 0.15)	0.12 (-0.04, 0.27)	0.62 (0.47, 0.78)	0.88 (0.75, 1.02)	1.03 (0.91, 1.15)	<0.001

* P value for linear trend.

Table 3

Secular Trends of Uric Acid Concentrations and Gout Prevalence

	Study	Follow-up Time	Age	Longitudinal Trend ^a
Mean Uric Acid	Framingham Study (10) (4 th exam n=5019 13 th exam n=3596)	US: 1954–1958 (4 th exam) 1972–1976 (13 th exam)	Range: 30–62y at 1948	Men: 5.0 → 5.7mg/dL Women: 3.9 → 4.7mg/dL
	Normative Age Study (12) (n=1,141)	US: 1961 – 1980	Mean: 42y (baseline)	Men: 5.5 → 6.5mg/dL
	CARDIA ^b Study (17) (n=2611)	US: 1985–6 – 1995–6	<i>African American</i> Men: 24y Women: 24y <i>White</i> Men: 26y Women: 26y (baseline)	<i>African American</i> Men: 5.3 → 5.8mg/dL Women: 3.8 → 4.0mg/dL <i>White</i> Men: 5.5 → 5.7mg/dL Women: 3.9 → 4.0mg/dL
	NHANES ^c Study (21) (n=18825 / 5707)	US: 1988–1994 (NHANES III) NHANES 2007–2008	Range: ≥ 20y	Overall mean change: 0.15mg/dL
	Okayama Study (16) (n=17155)	Japan: 1991–2002	Range: 18–19y	Men: 5.5 → 5.76 mg/dL
Hyperuricemia	NHANES Study (23, 29) (n= 14809 / 24693)	US: 1988–1994 (NHANES III) NHANES 1999–2008	Mean: 45y (1988–1994) Mean: 47y (1999–2008)	Men: 19% → 21% (>7.0mg/dL) Women: 17% → 19% (>5.7mg/dL)
	Okayama Study (16) (n=17155)	Japan: 1991–2002	Range: 18–19y	Men: 3.5% → 4.5% (≥ 7.6mg/dL)
	Zeng et al. (20) ^d (n=502 / 7888)	China: 1980–2003	Range: ≥ 20y	Men: 1.4% → 13.8% (≥7.0mg/dL) Women: 1.3% → 6.1% (≥6.0mg/dL)
Gout	NHIS ^e Study (14)	US: 1988, 1992, 1996	Range: ≥ 18y	0.85% → 0.84% → 0.94%
	Wallace et al. (19) (n= ~ 8 million)	US: 1900 – 1999	-	0.29% → 0.52% ^f
	NHANES Study (21) (n= 14809 / 5707)	US: 1988–1994 (NHANES III) NHANES 1999–2008	Range: ≥ 20y	2.7% → 3.9%
	Harris et al. (13) (n= 300376)	UK: 1975– 1993	-	0.30% → 0.95%
	Mikuls et al. (15, 129) (UK GPRD ^g)	UK: mid 1970s, 1999	-	0.26% → 1.39%
	Zeng et al. (20) (n=1722/1818)	China: 1992 – 1999	Range: ≥ 16y	0.17% → 0.26%
	Zeng et al. (20) (n=3000/ 5707)	Taiwan: 1992 – 1996	Range: ≥ 20y	0.67% → 1.98%
	Roddy et al. (18) (n=186/747/ 342)	Maori: 1958, 1966, 1992	“Adult population”, ≥ 20y, ≥ 15y	0.27% → 0.60% → 0.64%

^a Mean of percentage unless specified otherwise.^b CARDIA: Coronary Artery Risk Development in Young Adults.^c NHANES: National Health and Nutritional Examination Survey.^d Measured at different cities of China. The results are based on the data reported in Zeng et al.'s review article, not original studies.^e NHIS: National Health Interview Survey.

^fGout or “clinically significant” hyperuricemia.

^gGPRD: General Practice Research Database.

Table 4

Lifestyle Risk Factors of Hyperuricemia and Gout*

Risk Factors	Direction of Risk		References
	Risk of Hyperuricemia	Risk of Gout	
Adiposity			(2, 63, 130)
BMI	↑	↑	
Waist-to-Hip Ratio	↑	↑	
Weight Gain	↓	↓	
Weight Loss	↓	↓	
Purine-rich Foods			(1, 29)
Meats	↑	↑	
Seafoods	↑	↑	
Purine-rich Vegetables/Nuts		↔	
Alcohol	↑	↑	(59, 60)
Fructose	↑	↑	(92, 95, 102, 131)
Sugar-Sweetened Beverages	↑	↑	
Sweet Fruits/Fruit Juices	↑	↑	
Coffee/Decaffeinated Coffee	↓	↓	(68, 74)
Dairy Products			(1, 29)
Low-fat Dairy Products	↓	↓	
High-fat Dairy Products		↔	
Vitamin C Supplements	↓	↓	(77, 79–82)

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