PACIFIC HEALTH DIALOG
MARCH 2014 · VOLUME 20 · NUMBER 1

RESEARCH

Sugar-Sweetened Beverages, Urate, Gout and Genetic Interaction

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ABSTRACT

The clinical manifestations of gout occur as a result of immune responses to monosodium urate crystals. Elevated serum levels of urate (hyperuricemia) are a prerequisite for the development of gout with reduced fractional renal excretion of uric acid (FEUA) an important cause. In New Zealand, Māori and Pacific Island people have inherently raised urate levels with one consequence a higher prevalence of more severe gout. One characteristic metabolic effect of fructose, present in sugar-sweetened beverages (SSB), is raised urate from hepatic processing of fructose. Here we discuss, and place in a biological context evidence, linking consumption of SSB with hyperuricemia and gout, including the first review of recent ecological and clinical studies of the impact of fructose and SSB exposure in Pacific Island people. Both increased serum urate and increased FEUA are observed in clinical studies examining the effects of an acute fructose load. In contrast, chronic exposure to increased fructose in the diet also leads to increased serum urate concentrations, but reduced FEUA. Epidemiological studies have consistently associated SSB consumption with increased serum urate levels and increased risk of gout. Non-additive interaction of SSB consumption with a genetic variant of a uric acid transporter in serum urate levels and gout risk emphasizes the causality of SSB in gout. Taken together these data demonstrate the hyperuricemic effect of SSB and fructose, with biochemical pathways reasonably well understood. The evidence that dietary fructose increases urate is strong. The evidence summarized here is of sufficient weight to recommend reduction of SSB consumption, particularly in Pacific Island and Māori people, to reduce the burden of gout.

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Introduction

Gout is the most common type of inflammatory arthritis. It results from an innate immune response to monosodium urate (MSU) crystals, with elevated serum urate (hyperuricaemia) a central cause1. In Aotearoa New Zealand, the prevalence of gout in indigenous Māori (6.1%) and more recent Pacific Island immigrants (7.6%) is double that of Europeans[2]. Compared with New Zealand Europeans, Māori and Pacific people with gout report greater pain and activity limitation and lower health-related quality of life[3]. Gout can lead to permanent joint damage. Elevated serum urate (and gout) is associated with other serious metabolic conditions such as diabetes and heart disease in New Zealand[4].

Skeletal and documentary evidence for gout in prehistoric and pre-Westernised New Zealand and the Pacific region suggests a genetic basis for the disease[5,6]. The increased prevalence of gout in NZ Māori and Pacific Island (Polynesian) people is at least in part due to higher serum urate[7] and reduced renal excretion of uric acid (FEUA), compared to Europeans[8,9]. The ability of an individual to excrete uric acid is quantitated by the FEUA - the ratio of uric acid to creatinine excreted in the urine. Renal excretion of uric acid is facilitated by the uric acid transportasome[10], which includes proteins such as the uric acid transporters GLUT9, OAT4, URAT1 and NPT1.

Historically, gout has been regarded as a disease of over-consumption, being called the disease of kings - the rich and powerful having easy access to a diet rich in urate-raising sugar, alcohol and purine rich foods such as red-meat. Whilst gout is now associated with reduced income[11], the same historical, anecdotally recognized dietary associations hold with modern epidemiological studies showing association between diet, serum urate levels and risk of gout. Seafood, red meat, alcohol and sugar-sweetened beverage (SSB) consumption increase urate and gout risk[12-15]. These food items are all modern anecdotal triggers of gout, with a case-control crossover study demonstrating alcohol and a purine-rich diet to trigger gout flares[16,17]. There are a variety of ways that these foods increase serum urate levels - purines are directly metabolized to urate (purine-rich), generation of urate through hepatic catabolism (alcohol and sugar), and direct interference with renal excretion of uric acid (alcohol[18] and perhaps sugar[12]).

Both genetic and environmental risk factors contribute to development of hyperuricaemia and gout. Here, we focus on the role of SSB and dietary fructose as key risk factors, beginning with a brief review of the role of inherited genetic variants in control of urate levels. While there are little data in Pacific populations, the findings from other populations suggest mechanisms that can be studied in Polynesian people in order to better understand the role of sugar in gout, necessary for evidence-based interventions to reduce the impact of gout.

Genetic control of urate and gout in the Pacific

A genome-wide association study (GWAS) scans the genome for common genetic variants (>5% prevalence) associated with a phenotype[19]. Genetic variants are present at conception - variants associated with phenotype, and interacting environmental exposures, can therefore be regarded as causal. A GWAS can be done using a continuous measure as outcome (eg levels of urate in the serum) using a population-based cohort, or with a binary measure as outcome (eg gout) using cases and matched controls. To date no robust GWAS has been done for gout, largely owing to the international unavailability of sufficient numbers of adequately clinically phenotyped cases that could be used for genetic studies[20].

Sixty percent of the inter-individual variance in urate levels is explained by inherited genetic variants[21]). The most recent GWAS reported 28 loci that explain ~6% of variance in serum urate in Europeans [22]. Within the 28 loci, renal uric acid excretion genes have the strongest effects, in particular SLC2A9 and ABCG2 (SLC2A9 explains 2-3% of inter-individual variance in serum urate in Europeans and ABCG2 ~1%)[22]. Other renal uric acid transport loci identified include SLC17A1 (NPT1), SLC22A12 (URAT1) and SLC22A11 (OAT4). At other loci, genes involved in glycolysis have been identified - this pathway may increase urate as a result of hepatic metabolism of alcohol and sugar. In contrast to the European results, genome-wide association studies in Asian have identified only five loci - SLC2A9, ABCG2, LRP2, SLC22A11/A12 and MAF[23,24] - all of these except LRP2 overlap with loci in the European studies.

Any genetic variants identified in Europeans represent strong candidates for influencing serum urate and risk of gout in Polynesian populations because common genetic variants associated with urate levels tend to be shared between ancestral groups[22]. Not unexpectedly, genetic association studies in gout risk have revealed commonalities and differences between European and Polynesian people in addition to differences within Polynesia (Western versus Eastern). The SLC2A9 genetic risk variant is more prevalent in Māori and Pacific Island people than in Europeans and, as in Europeans, confers a strong risk to gout with odds ratio (OR) > 225. The ABCG2 risk variant is very common in Samoan, Tongan and Niuean (Western Polynesian) people (28%) where it is a strong risk factor for gout (OR>2), similar to European[26]. However, in NZ Māori and Cook Island Māori (Eastern Polynesian), the risk variant is at a markedly lower prevalence (10%), with no evidence for association with gout (OR~1)[26]. At SLC17A1 (which encodes the phosphate-dependent renal uric acid transporter NPT1) the risk allele frequency is more common in Polynesian people than Europeans, with association evident in all population groups (OR~1.5)[27]. Finally, at the contiguous Chr11 genes, SLC22A11 (encoding OAT4) and SLC22A12 (encoding URAT1), there are several independent risk variants, two of which confer risk to gout in a heterogeneous fashion between Polynesian and European people[28]. The fact that the predisposing genetic variants at these loci are cumulatively more common in Pacific Island and Māori people will increase the population attributable risk of these variants and contribute to the reduced fractional excretion of uric acid[8,9] and increased prevalence of gout in these populations[2].

The metabolism of fructose

Fructose, known as the fruit sugar, is a simple monosaccharide that, with glucose, constitutes the sweetener sucrose commonly used in the Pacific region. In the United States high-fructose corn syrup (HFCS) is the commonly used sweetener, comprising ~55% fructose when used in beverages.

Glucose can be catabolized for energy by most tissues in the body, with metabolism regulated by negative feedback inhibition of hexokinases by glucose-6-phosphate (Figure 1). In contrast the catabolism of fructose is largely restricted to the liver. After absorption from the intestine by the fructose-specific transporter GLUT5 and GLUT2 (the latter in competition with glucose) fructose is first phosphorylated by fructokinase (with the phosphate group sourced from adenosine triphosphate (ATP)) and then cleaved by aldolase-B into two three-carbon molecules that are ultimately catalyzed by the glycolytic pathway. Unlike most hexokinases, fructokinase is not inhibited by negative feedback by downstream metabolites[29]. Thus, under a fructose metabolic load, hepatic fructokinase rapidly phosphorylates fructose, depleting ATP in the liver[30,31]. A consequence of this is an accumulation of adenosine monophosphate (AMP), which activates AMP deaminase with the eventual production of urate[32].

The metabolic consequences of fructose in causing ATP depletion and generation of urate are distinct to that of other common sugars[33]. For example, via stimulation of urate production fructose causes mitochondrial oxidative stress and stimulation of gamma-glutamyl transferase[34] and hepatic fat accumulation (fatty liver). Fructose does not induce a satiety response[35], it causes hepatic insulin resistance[36] and raises retinol binding protein-4 (RBP4) serum levels[34], linking visceral fat to insulin resistance. The differential metabolic effects of fructose, in comparison to glucose, challenge the dogma of measuring the metabolic consequences of fructose solely by its energy quotient (calorie)[33].

Acute effects of fructose on serum urate levels and renal uric acid excretion

Administration of fructose in solution (1g/kg for adults and 0.5g/kg for children) in a short time period (<15 minutes) increases serum urate levels within 60 min 37-40. One 500ml serving of the typical SSB contains up to 33g of fructose, which would be, depending on body weight, half to one third of the fructose used to demonstrate an increase in serum urate in adults in the fructose challenge studies. Given that the fructose is also dissolved in water, as is the case in soft drinks sweetened with high-fructose corn syrup or sucrose, and is in a readily absorbable form, there is a very strong basis for the hypothesis that acute ingestion of SSB raises urate levels within a 30-60 minute time period. This hypothesis was tested by Le et al.[41] in a crossover study design where 40 healthy men and women consumed 710 ml of SSB 'Dr Pepper' sweetened either with sucrose or HFCS (corresponding to 34.6g and 39.2g of fructose, respectively), over a 5 minute time period. This corresponds to a dose of 0.46-0.52 g/kg of fructose for an adult weighing 75kg. Ingestion of the HFCS-sweetened SSB resulted in a maximal increase of serum urate of 7% over baseline after 60 minutes, and the sucrose-sweetened SSB resulted in a maximal increase of 5% over baseline after 30 minutes - both increases being statistically significant. These data demonstrate an acute hyperuricemic effect of SSB ingestion. FEUA was increased after 360 min with ingestion of the HFCS-sweetened beverages by 37% over baseline, significantly different to the smaller increase of 25% over baseline resulting from ingestion of the sucrose-sweetened beverages[41], suggesting that the increased fructose in HFCS-sweetened beverages is influencing FEUA.

In a New Zealand study[37] an oral acute challenge (in a 10-minute time period) with a solution of 64g fructose and 16g glucose (0.85g fructose per kg for an adult weighing 75 kg) resulted in an 0.07 mmol/l increase in serum urate (23% of baseline) within 30 min in Europeans (n=25) and a 0.06 mmol/L increase (15% of baseline) in Polynesian participants (n=51). The acute oral fructose load increased, after 180 minutes, FEUA in Europeans (35% above baseline) but not in Polynesian people (Figure 2).

Chronic effect of fructose on serum urate and renal uric acid excretion

There have been a number of longer-term clinical trials examining the effect of isocaloric and hypercaloric chronic fructose supplementation on serum urate[42]. In addition to transient increases in urate upon acute exposure to fructose and sucrose, increased urate has been observed after chronic exposure to a high fructose or sucrose diet. One such report was a five-week crossover study of 21 men who consumed supervised isocaloric diets that differed by containing 167g of added fructose or 183g of added cornstarch[43]. At the end of each five-week period urate response to the respective fructose or cornstarch meals was measured. Beginning from a baseline of 0.312 mmol/L, there was no significant change in serum urate over 180 minutes in men who had consumed the cornstarch-supplemented diet. In contrast, the same group of men who consumed the fructose-enriched diet for five weeks exhibited a significantly higher baseline serum urate level after five weeks (0.344 mmol/L), with a significant increase in baseline to 0.355 mmol/L within 30 minutes of a fructose-enriched meal at the end of the five-week period. These data indicate that the fructose-supplemented diet induced both chronic (0.032 mmol/L or 10% over baseline) and acute increases in serum urate (an increase of 0.011 mmol/L or 3% over baseline). A more recent study examined chronic consumption (ten-weeks as 25% of total energy intake) of fructose- and glucose-sweetened beverages in 17 overweight and obese individuals per intervention[34]. The fructose-sweetened beverages resulted in an 11.9% increase in urate levels over baseline, significantly different to the 4.3% increase observed with chronic consumption of glucose-sweetened beverages.

The various studies examining the effects of fructose in isocaloric diets were meta-analysed by Wang et al[42], with no significant effect of chronic exposure to fructose on serum urate being reported. However, this analysis was flawed. Already critiqued[33], the Wang et al study is compromised by the inappropriate inclusion of two relatively large studies that dominated the weighting of the meta-analysis, and were the two largest studies included in the meta-analysis. The first study by Madero et al[44] randomized 131 obese individuals (78% women) into two energy-restricted diets (low-fructose (<20g/day) or a moderate natural fructose diet with fruit supplement (50-70g/day)) over a six-week period and reported no difference in serum urate between the groups. In both groups sugars from processed food and processed fruit were excluded. This study was designed to compare two interventions on weight loss and other metabolic features in an obese sample set, with neither intervention (low fructose or moderate fructose with additional fructose coming from fruit supplementation) necessarily expected to be detrimental to metabolic health. Indeed, both of the Madero et al[44] interventions resulted in a significant

decrease in serum urate compared to baseline (0.014 and 0.013 mmol/L, respectively). Here, the increased fructose comparison group, with fructose derived from natural fruit, was inappropriate to include in the Wang et al. meta-analysis. This is because fruit also contains numerous other confounding nutrients - for example, vitamin C, which has been ecologically associated with reduced serum urate levels[45], and cherries reduce serum urate and lower the risk of gout flares[46]. The second study is that of Huttunen et al.[47], who tested the effect of different dietary sweeteners (fructose, sucrose and xylitol) as the only sweetening agents in the diet over a 24-month period, with dental caries as the main outcome measure and urate levels as a secondary outcome measure. 127 volunteers were randomized, without any crossover, into the three arms (n=35, 33 and 48, respectively). In the fructose arm urate levels increased 4% from baseline (0.28 to 0.29 mmol/L), while 10% from baseline (0.28 to 0.31 mmol/L) in the sucrose arm. Wang et al[42] compared fructose with sucrose intake in the meta-analysis. This is inappropriate for two important reasons. Firstly, the sex composition of the fructose and sucrose groups was not presented in the original report[47]. In any study with urate response to fructose as outcome it is extremely important to match by sex - urate levels are higher in men and there is evidence that men have a more pronounced response to chronic fructose exposure (Table 1)[48]. Second, it would have been more appropriate to compare each of the fructose and sucrose intervention endpoints to baseline - this would have removed potential confounding by sex and also have obviated the questionable choice of using a fructose-containing sugar (sucrose) as the comparison group[33]. There is one other important flaw to the Wang et al study. Studies were included where the comparison group is fructose-containing glucose-containing sucrose which enhances the absorption of fructose and possibly other fructose-induced metabolic changes[33] - certainly, glucose enhances the ATP-depleting and urate producing effects of fructose[31].

The majority of feeding studies have compared sugar consumption in isocaloric studies, where total energy intake is consistent between study groups. To our knowledge, only two have been done examining hypercaloric sugar addition to the diet on urate. A crossover study design examined the addition of 35% of energy requirement of fructose (hypercaloric) in a male control group (n=8) and those with a family history of type 2 diabetes (n=16) in a one-week period[49]. In both groups there was a significant increase in urate (11.7% and 9.0% over baseline, respectively). The second report was a three-way crossover study that tested the effect of a weight maintenance diet, and addition of either fructose or glucose to this diet in 11 healthy males over a one-week period[50]. The high-fructose diet resulted in a statistically significant 10.2% increase in serum urate over the weight maintenance diet, compared to a statistically significant increase of 5.4% for the high-glucose diet. While both of these studies suggest that hypercaloric fructose does increase urate levels, the studies are potentially confounded by the effects of excess energy.

The FEUA response to a fructose load was measured in a crossover study design in men of European ancestry who had been chronically exposed to either a low- (isoenergetic, n=16)) or high-fructose (combination of isoenergetic (n=8) and hyperenergetic (n=8)) diet over a 4-6 day period[51]. The fructose load comprised 0.2g fructose/kg of free fat mass (average 11.6g fructose) per hour for 9 hours. Individuals on the high-fructose diet exhibited a reduced FEUA of 11.5% than when consuming the low-fructose diet. These data are inconsistent with the aforementioned data of Dalbeth et al[37] and Le et al[41], who reported an increase in FEUA in Europeans exposed to an acute fructose load. However, there are important differences: one, participants in the Dalbeth et al and Le et al studies had been previously eating ad libitum and had fasted overnight and, two, the acute fructose/HFCS load was ingested within a 10-minute period. Renal vascular resistance as a result of chronic effects of fructose on endothelial function[52] could explain the differences between the FEUA-effects of chronic and acute fructose exposure.

Ecological studies of sugar and fructose exposure and urate and gout

Based on the urate-increasing consequence of the hepatic biochemical pathway of fructolysis and clinical studies of the effects of acute and chronic exposure to fructose and sucrose, there is a strong literature that associates fructose exposure from sugar-sweetened beverages to raised serum urate levels and increased risk of gout (Table 1). Data collected from 14,761 multi-ethnic participants in the US Third Health and Nutrition Examination Survey (NHANES) first demonstrated that serum urate levels were associated with increasing SSB consumption[48]. For example ≥4 servings per day was associated, when compared to zero servings, with a 1.81-fold increased risk of hyperuricemia and an increase in urate of 0.025 mmol/L. In 6,721 European individuals from the Atherosclerosis Risk in Communities (ARIC) study, each SSB consumption category (equating to slightly less than one serving per day) equated to an increase of urate of 0.003 mmol/L12. Importantly there is no relationship between artificially sweetened beverages and levels of serum urate[12,48]. People drinking, for example, 3 SSBs per day will on average exhibit an increase of serum urate by ~0.01 mmol/L. This could be clinically significant for the control of gout where the target serum urate is <0.36 mmol/L. Similar effects are seen in adolescents [53,54].

Not unexpectedly, SSB consumption is also associated with an increased risk of incident and prevalent gout in European men and women, in Polynesian people and with both HFCS- and sucrose-sweetened beverages (Table 1) [12,15,55]. For example, in a combined dataset of European and Polynesian individuals, each increase in consumption category was associated with an increased risk of prevalent gout by 13%[12].

In New Zealand, 5% of European, 14.4% of Māori and 16.6% of Pacific Island participants surveyed during 2006-2011 self-reported consuming ≥4 servings of SSB per day[12]. This illustrates differing patterns of SSB consumption between ethnic groups in New Zealand. Comparison with United States survey data from the NHANES and ARIC studies collected in the 1980s and 1990s, with 1.4% and 1.9% self-reporting consuming ≥4 servings per day, illustrates changing consumption patterns over time.

Relationship between SSB consumption and genotype

The typical ecological and clinical study investigating influence of sugar on urate does not account for inherited inter-individual

differences. With the recent identification of genetic variants that control serum urate levels comes an opportunity to examine genotype effects on urate response to fructose exposure. In particular, genetic variation within the SLC2A9 gene strongly justifies inclusion in ecological and clinical studies. Not only does the variation explain a relatively large proportion of variance in urate levels (2-3%) but SLC2A9 encodes the simple sugar transporter GLUT9, which transports uric acid that is facilitated by glucose and fructose[56,57].

In an ecological study non-additive interaction between SLC2A9 and SSB in determining urate and gout risk has been reported (Table 2)[12]. Non-additive interaction is when two variables interact in an unpredictable fashion. The C allele of rs11942223 (SLC2A9) normally associates with reduced serum urate and the risk of gout. However, upon exposure to SSB both the risk of gout and levels of serum urate controlled by the C-allele increases relative to the C-allele-negative group. Increased chronic simple sugar exposure derived from SSB therefore over-rides the positive versus negative risk discrimination of the SLC2A9 risk alleles perhaps by interfering with the ability of SLC2A9/GLUT9 to transport uric acid. The effect of chronic SSB exposure in raising urate and the risk of gout could be mediated through reduced FEUA51, with genotype at SLC2A9 influencing this response in a non-additive fashion. Clinical studies examining the effect of chronic sugar exposure on urate and FEUA should include genotype at SLC2A9 as a potential interacting variable.

We have also studied the effect of genotype at uric acid transporters SLC2A9 and SLC17A1 (encodes NPT1) on the hyperuricemic and FEUA response to an acute fructose load in European and Polynesian individuals [12,37,58]. Participants in the previously described acute fructose feeding study[37] were genotyped for rs11942223 (SLC2A9) and rs1183201 (SLC17A1). SLC2A9 genotype effects on urate and FEUA response were observed only in Europeans, with the urate-lowering C allele at rs11942223 correlating with a significantly increased FEUA after fructose loading and a significantly reduced increase in serum urate[37]. No such effects were observed in Polynesian people. At SLC17A1 similar effects were observed (genotype-specific effects restricted to Europeans), although there was a genotype-specific effect on serum urate in the Western Polynesian group (people of Samoan, Tongan, Niuean and Tokelauan ancestry[58]). Whilst both rs11942223 and rs1183201 are consistently associated with the risk of gout in both European and Polynesian, it is clear that other renal or non-renal factors dominate the effects of SLC2A9 and SLC17A1 variants in acute fructose-induced influence renal uric acid excretion in Polynesian people. The identification of these factors, which possibly include interacting population-specific genetic variants, will be important in understanding the mechanism of hyperuricemia and response to fructose consumption in the Māori and Pacific Island (Polynesian) population of New Zealand, which is at high risk of gout[2].

Concluding remarks

In summary, acute exposure to sugar dissolved in water (eg soft drinks) increases serum urate and the risk of gout as a result of the generation of urate by hepatic glycolysis and perhaps by directly interfering with renal excretion of uric acid. However the medium-term effect of dietary fructose on serum urate levels and FEUA remains unclear. There is a need for large clinical trials investigating the effects of dietary fructose restriction on serum urate, particularly in people with hyperuricaemia and gout. Nevertheless, the evidence summarized here are of sufficient weight to recommend reduction of SSB consumption, particularly in Pacific Island and Māori people, to reduce the burden of gout.

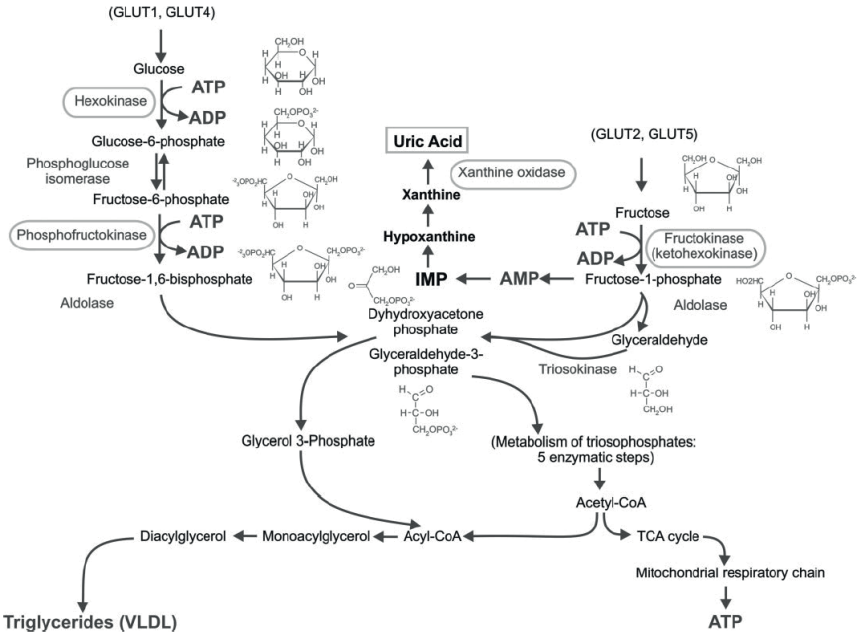

Figure 1. Fructose metabolism. Fructose is preferentially metabolized by fructokinase (KHK) to generate fructose-1-phosphate. Unlike phosphofructokinase, which is involved in glucose metabolism, fructokinase has no negative feedback system, with a consequence being that ATP is depleted, causing intracellular phosphate depletion, activation of AMP deaminase, and urate production. Fructose is lipogenic and can generate both glycerol phosphate and acyl coenzyme A, resulting in triglyceride formation that is both secreted and stored in hepatocytes. IMP, Inosine monophosphate; TCA, trichloroacetic acid. Taken from ref [29].

Figure 2. Effect of an acute fructose dose on serum urate levels and FEUA in European and Maori and Pacific Island (Polynesian) individuals
Adapted from Figure 2 of ref [37].

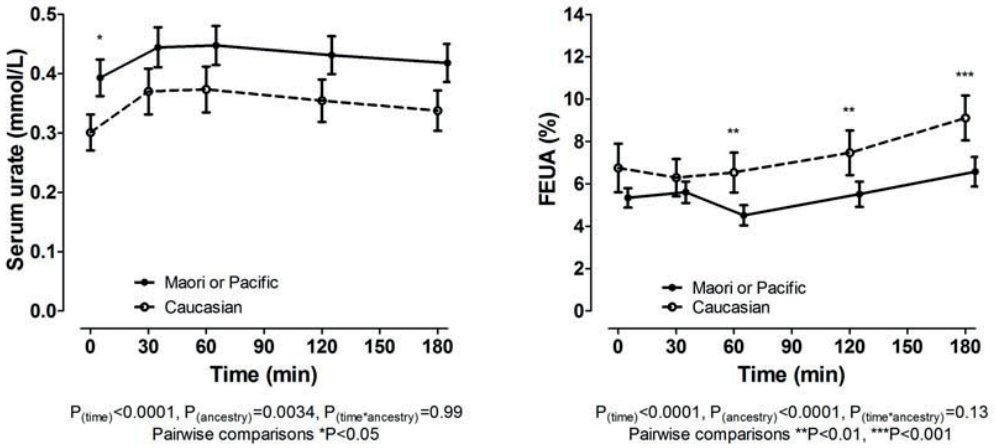

Table 1. Ecological studies associating SSB consumption with serum urate and risk of gout

Study	Survey date	n	Ancestry	Effect size	Comments
Serum urate1					
Choi et al.48	1988-1994 (NHANES)	7,085 (men)	Mixed (US)	0.006 mmol/L per consumption category. P<0.001	SSB (HFCS). Five consumption categories. Multivariate adjusted. Excluded fruit juice.
		7,676 (women)		0.002 mmol/L per consumption category, P=0.02	
		14,761		-0.002 mmol/L per consumption category. P=0.13.	Diet beverages. Five consumption categories. Multivariate adjusted.
Batt et al. 12	1987-1989 (ARIC)	7,075 (47.4% men)	European (US)	0.003 mmol/L per consumption category. P=7x10-6.	SSB (sucrose). Seven consumption categories. Multivariate adjusted. Included fruit juice.
		7,075 (47.4% men)		0.000 mmol/L per consumption category. P=0.48	Diet beverages. Seven consumption categories. Multivariate adjusted.
Gao et al.59	2001-2002 (NHANES)	4,073 (49.0% men)	Mixed (US)	0.005 mmol/L per quartile. P=9x10-4.	SSB (HFCS). Multivariate adjusted. Excluded fruit juice.
Nguyen et al. 54	1999-2004 (NHANES)	4,867 (12-18 years of age) (52.1% boys)	Mixed (US)	0.002 mmol/L per consumption category. P=0.01.	SSB (HFCS). Multivariate adjusted. Included fruit juice.
Lopez-Molina et al. 60	2008	1,134 (39.9% men)	Mexican	Intake (>1 SSB/day, %) per urate quartile: Q1 (7.7%), Q2 (16.8%), Q3 (20.5%), Q4 (24.5%). PTrend<0.001.	SSB. Not adjusted.
Lin et al. 53	2007-2009	2,727 (12-16 years of age) (48.7% boys)	Southern Taiwanese	0.007 mmol/L per consumption category. P<0.001.	SSB (sucrose/HFCS). Five consumption categories. Multivariate adjusted.
Gout					
Choi et al. 15	1986-1998	46,393 (men)	Mixed (91% European) (US). Health Professionals Follow-up Study.	Average 14% increase in risk per consumption category. P=0.002.	SSB (HFCS). Incident gout. Six consumption categories. Multivariate adjusted. Excludes fruit juice.
		46,393 (men)		Average 2% increase in risk per consumption category. P=0.99.	Diet beverages. Incident gout. Six consumption categories. Multivariate adjusted.
Choi et al. 55	1984-2006	78,906 (women)	Nurses Health Study.	Average 23% increase in risk per consumption category. P<0.001.	SSB (HFCS). Incident gout. Six consumption categories. Multivariate adjusted. Excludes fruit juice.
		78,906 (women)		Average 3% increase in risk per consumption category. P=0.27.	Diet beverages. Incident gout. Six consumption categories. Multivariate adjusted.
Batt et al.12	2006-2011	563 (68.3% men)	New Zealand European	OR=1.20 per consumption category. P=0.02.	SSB (sucrose). Prevalent gout. Seven consumption categories. Multivariate adjusted. Includes fruit juice.
		463 (51.0% men)	New Zealand Māori	OR=1.11 per consumption category. P=0.11.	
		489 (75.9% men)	New Zealand Pacific Island	OR=1.13 per consumption category. P=0.03.	

1 A study by Zgaga et al [61] reported an increase of 48 mmol/L (P=0.008) per serving of SSB in 2,076 Scottish people surveyed 1999-2006.
SSB, sugar-sweetened beverage; HFCS, high-fructose corn syrup; ARIC, Atherosclerosis Risk in Communities; NHANES, National Health and Nutrition Examination Survey.

Table 2. Non-additive interaction between *SLC2A9 rs11942223* and sugar-sweetened beverage consumption in control of urate levels and risk of gout. Adapted from ref [12].

Gout risk			Serum urate (ARIC)	
	Δ in gout risk (OR), 95% CI	P	Δ in serum urate (mmol/L)	P
Unstratified	1.13 (1.06-1.20)	2x10-4	0.003	7x10-6
C negative	1.12 (1.05-1.21)	0.001	0.002	0.02
C positive	1.15 (0.98-1.34)	0.08	0.005	9x10-6

The data show increase in gout risk (left) and serum urate (right) with exposure to one daily serving of SSB in sample sets both unstratified and stratified by the two genotype groups of *rs11942223*. $P_{interaction}$=0.01 for gout and 0.06 for urate. The main effect of the C-allele of *rs11942223* is to reduce serum urate and the risk of gout [25]. ARIC, Atherosclerosis Risk in Communities

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