EXTENDED REPORT

Sugar-sweetened beverage consumption: a risk factor for prevalent gout with *SLC2A9* genotype-specific effects on serum urate and risk of gout

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ABSTRACT

Objective Consumption of high fructose corn syrup (HFCS)-sweetened beverages increases serum urate and risk of incident gout. Genetic variants in SLC2A9, that exchanges uric acid for glucose and fructose, associate with gout. We tested association between sugar (sucrose)-sweetened beverage (SSB) consumption and prevalent gout. We also tested the hypothesis that *SLC2A9* genotype and SSB consumption interact to determine gout risk.

Methods Participants were 1634 New Zealand (NZ) European Caucasian, Māori and Pacific Island people and 7075 European Caucasians from the Atherosclerosis Risk in Communities (ARIC) study. NZ samples were genotyped for *rs11942223* and ARIC for *rs6449173*. Effect estimates were multivariate adjusted.

Results SSB consumption increased gout risk. The OR for four drinks/day relative to zero was 6.89 (p=0.045), 5.19 (p=0.010) and 2.84 (p=0.043) for European Caucasian, Māori and Pacific Islanders, respectively. With each extra daily SSB serving, carriage of the gout-protective allele of *SLC2A9* associated with a 15% increase in risk (p=0.078), compared with a 12% increase in non-carriers (p=0.002). The interaction term was significant in pooled ($p_{Interaction}$=0.01) but not meta-analysed ($p_{Interaction}$=0.99) data. In ARIC, with each extra daily serving, a greater increase in serum urate protective allele carriers (0.005 ($p=8.7\times10^{-5}$) compared with 0.002 (p=0.016) mmol/L) supported the gout data ($p_{Interaction}$=0.062).

Conclusions Association of SSB consumption with prevalent gout supports reduction of SSB in management. The interaction data suggest that SLC2A9-mediated renal uric acid excretion is physiologically influenced by intake of simple sugars derived from SSB, with SSB exposure negating the gout risk discrimination of *SLC2A9*.

INTRODUCTION

A central risk factor for gout is hyperuricaemia.[1] The dominant mechanism of determining hyperuricaemia is by regulation of uric acid excretion, primarily renal, but also involving the gut.[2] Regulation of serum urate is under genetic and environmental control,[3] with 28 loci that influence serum urate levels identified as a result of genome-wide association scanning in European Caucasian.[4] The major genetic regulator is *SLC2A9*, which encodes the GLUT9 renal molecule that transports uric acid in exchange with glucose and fructose.[5 6] Variants within *SLC2A9* explain 3.70% of the phenotypic variance in serum urate levels in European Caucasian and are strongly associated with gout in European Caucasian, NZ Māori and NZ Pacific Islander sample sets.[4 7]

There is positive association between higher consumption of beverages sweetened with fructose-containing sweeteners, such as high fructose corn syrup (HFCS), and increased risk of incident gout in men and women.[8–10] For exposure to ≥2 sugar-sweetened beverages (SSB) per day, within the Health Professionals Follow-up Study there was a 1.78-fold increased risk of gout in men,[8] and in the Nurses' Health Study a 3.05-fold increased risk in women.[9] The increased risk of gout resulting from exposure to SSB is mediated, at least in part, by an effect on serum urate levels in both men and women,[10] and acute and hypercaloric ingestion of fructose raises serum urate levels.[11 12] Fructose is metabolised in the liver, initiated by the unregulated phosphorylation of fructose to fructose-1-phosphate. The subsequent depletion of ATP and increase in AMP is proposed to lead to increased serum urate via the catabolism of AMP.[9 13 14] Acute ingestion of HFCS-sweetened soft drinks increases the renal fractional excretion of uric acid (FEUA),[15] suggesting a response of renal transport to either uric acid or fructose. Given that SLC2A9 also transports fructose and glucose,[5 6] and that SLC2A9 genotype influences serum urate and FEUA response to a fructose load,[16] it is possible that fructose and glucose can both directly interfere with SLC2A9-mediated renal uric acid excretion.

There were two aims of this study. One, to replicate association between consumption of SSB and prevalent gout in a country where soft drinks are sweetened with sucrose and not HFCS. The second aim was to test for non-additive interaction between SSB consumption and *SLC2A9* genotype.

SUBJECTS AND METHODS

Subjects

Clinical and survey information was collected from 1634 individuals from 2006 to 2011 (table 1). Cases (n=925) were recruited from rheumatology clinics, workplaces and community focal points from the Auckland, Bay of Plenty, Wellington,

Table 1 Baseline demographic and clinical characteristics of study participants by ethnicity

	NZ European Caucasian		NZ Māori		NZ Pacific Islander		ARIC European Caucasian	
Individuals (n)	Obs	592	Obs	502	Obs	540	Obs	7075
Cases		412		190		323		148
Controls	–	180	–	312	–	217	–	6927
Age mean, years (range)		57.9 (17–94)		47.1 (17–81)		44.6 (17–86)		53.8 (44–65)
Cases	592	63.8 (23–94)	501	54.2 (23–81)	539	47.7 (18–81)	7075	54.5 (45–65)
Controls		44.4 (17–79)		42.7 (17–80)		39.9 (17–86)		53.8 (44–65)
Sex (% male)		68.3		51.0		75.9		47.4
Cases	590	77.8	498	80.3	539	87.9	7075	75.0
Controls		46.7		33.2		57.9		46.8
BMI mean, (range)		29.4 (19.2–62.7)		33.2 (18.1–77.0)		36.4 (19.4–71.1)		26.4 (14.4–54.6)
Cases	582	29.8 (19.2–61.7)	496	35.0 (21.7–72.7)	530	37.4 (21.5–71.1)	7073	28.0 (21.1–40.5)
Controls		28.3 (19.5–62.7)		32.1 (18.1–77.0)		34.9 (19.4–65.1)		26.3 (14.4–54.6)
Kidney disease (%)		12.8		8.6		8.5		1.2
Cases	579	17.6	486	18.5	518	12.9	6757	1.4
Controls		1.7		2.7		1.9		1.2
High blood pressure (%)		38.0		32.4		34.5		12.7
Cases	585	49.9	488	57.6	528		7037	20.3
Controls		10.2		17.1		15.6		12.6

NZ, New Zealand; Obs, Observations.

Christchurch and Dunedin areas of New Zealand (NZ), and had gout ascertained using the American Rheumatology Association Criteria.[17] Controls with no self-reported history of gout (n=709) were convenience sampled from workplaces and community focal points in the Auckland region of NZ. Ancestry was self-reported. The research was approved by the NZ Multi-Region Ethics Committee (MREC 05/10/130) and all subjects gave written informed consent.

Subjects were included from the Atherosclerosis Risk in Communities (ARIC) study and comprised 7075 controls of European Caucasian ancestry who self-reported as having not taken blood pressure-lowering medication in the previous 2 weeks (at either of exam 1 (1987–1989) or 4 (1996–1998)). Primary gout cases (n=148) were European Caucasian subjects who self-reported at Exam 4 as having physician-diagnosed gout and did not report as having taken blood pressure-lowering medication in the previous 2 weeks (at either of exam 1 or 4).

Data collection and selection of exposure groups

Collection of exposure, genetic, anthropomorphic and relevant clinical data is described in the online supplementary material.

Data analysis

Regression analysis was used to investigate relationships between the variables in this study. For continuous response variables, this involved standard linear regression; for binary response variables (ie, discrete variables with only two levels), logistic regression was used. P_{trend} was the χ^2 p value associated with the SSB variable in regression analysis. Both main effects and interaction terms were included in the models where appropriate. Coefficients with p values ≤0.05 were considered to indicate a significant association between the response and explanatory variables. For discrete explanatory variables with more than two levels, significance was achieved if at least one of the variable's model coefficients achieved a p value of ≤0.05. The adjusted OR for a single explanatory variable was obtained by using the logistic regression coefficient. An adjusted OR for the same variable was obtained by including additional variables in the logistic regression model, again taking the value of the model coefficient relating to the variable in question. In order to make ORs interpretable for multilevel discrete variables, these variables were converted to binary (two-level) form prior to analysis. Logistic regression analysis was used to assess the association between gout (binary response variable), and SSB consumption and SLC2A9 genotype (explanatory variables) and linear regression analysis was used to assess the association between serum urate levels (response variable), and SSB consumption and SLC2A9 genotype (explanatory variables). Unstandardised regression coefficients are reported. Main effects were included in the model for SSB consumption and *SLC2A9*, and for the covariates age, sex, BMI, kidney disease, high blood pressure, alcohol and fruit consumption. Individuals with missing data from any variable were excluded from analysis. An interaction term between SSB consumption (as a continuous variable) and *SLC2A9* genotype (binary: carriage and non-carriage of the serum urate-lowering and gout-protective minor allele) was also included. Results from different datasets were combined by both pooling data and adjusting for the dataset in association analysis, and Mantel–Haenszel meta-analysis with random effects. STATA software V.8.0 was used for all statistical analysis (http://www.stata.com).

RESULTS

SSB consumption and risk of gout

Table 1 presents clinical and demographic characteristics of study subjects and online supplementary table S1 presents characteristics of the sample sets according to SSB consumption. The level of SSB intake was lower in the ARIC sample; two possible explanations, at least in part, for this are: one, that the ARIC exposure data were collected 1987–1989 and the NZ exposure data 2006–2011 and two, the ARIC sample set consists of individuals 44 years of age or older, whereas the NZ samples consisted of younger individuals (table 1), who consume more SSB (see online supplementary table S1).

Testing for association of SSB consumption with gout and unadjusted ORs provided no evidence that increasing intake of

sucrose-sweetened and HFCS-sweetened beverages was associated with increasing risk of gout in any of the sample sets (table 2; p_{trend}=0.56, 0.17, 0.16 and 0.20 for the NZ European Caucasian, Māori, Pacific Islander and ARIC sample sets, respectively). Multivariate adjustment by gout risk factors BMI, age, sex, alcohol and fruit consumption, kidney disease and hypertension provided stronger evidence for association in all NZ ancestral groups (all p_{trend}<0.11; OR for gout risk for 4 SSB/day relative to 0 SSB/day in NZ European Caucasian, Māori and Pacific Islander sample sets were 6.89 (p=0.045), 5.19 (p=0.010) and 2.84 (p=0.043), respectively). In the ARIC cohort, the OR for ≥5 SSB/day of 2.31 (p=0.20) was comparable with that for the NZ European Caucasian group (OR=2.38, p=0.20). Adjustment by individual covariates (see online supplementary table S2) revealed age to be the major confounder—a combination of younger people consuming more SSBs (see online supplementary table S1: in controls the change in age per increase in SSB category were β=−3.21, $p=1.2\times10^{-4}$; β=−1.77, $p=3.7\times10^{-5}$; β=−1.40, $p=7\times10^{-3}$; β=−0.50, $p=3.6\times10^{-14}$ for NZ European Caucasian, Māori, Pacific Islander and ARIC, respectively), and NZ control sample sets having a younger age of recruitment than cases (table 1) would have obscured association between SSB and risk of gout in the unadjusted analysis.

Testing for non-additive interaction between SSB consumption, SLC2A9 genotype and risk of gout

The SLC2A9 gene was genotyped (see online supplementary table S3). Within the NZ Pacific Islanders, NZ European Caucasians and ARIC, and all datasets combined, there was a greater increase in risk of gout per increase in daily SSB consumption category in the presence of the gout protective and serum urate-lowering allele than in the group homozygous for the (major) gout risk and serum urate-increasing allele (table 3; 71% vs 11% in NZ Pacific Islander; 27% vs 16% in NZ European Caucasian; 16% vs 5% in ARIC). In NZ Māori, there appeared to be an opposing effect, with the increase in risk of gout per unit increase in SSB consumption greater in the major allele homozygous group (OR=1.19) than the minor allele-carrying group (OR=0.76). Interaction analysis of SLC2A9 genotype (presence or absence of the protective (minor) allele C[7]; *rs11942223* in NZ and *rs6449173* in ARIC) and SSB as a continuous measure did not reveal consistent evidence for non-additive interaction according to the method of combining datasets (table 3; $p_{Interaction}$=0.010 in pooled combined groups, $p_{Interaction}$=0.99 by meta-analysis of individual interaction terms from the four sample sets).There was evidence for heterogeneity in interaction terms (p_{Het}=0.025), with the Māori sample set driving the heterogeneity ($p_{Interaction}$=0.39, p_{Het}=0.17 excluding the Māori samples).

Testing for non-additive interaction between SSB consumption, SLC2A9 genotype and serum urate

Given evidence for a difference in effect according to genotype between *SLC2A9* and SSB consumption with gout as outcome, we next investigated if a similar phenomenon occurred with serum urate as outcome. In the ARIC cohort (excluding people classified with gout), there was a positive correlation between SSB consumption and serum urate levels, with a 0.003 mmol/L ($p=6.9\times10^{-6}$) increase in serum urate per change in SSB category (table 4). Each copy of the *rs6449173* minor allele (C—a perfect surrogate (r^2=1.0) for the C allele of *rs11942223* in European Caucasian) decreased serum urate by 0.025 mmol/L ($p<1\times10^{-8}$). With increasing SSB consumption in the overall cohort the presence of the normally serum urate-lowering C allele conferred a higher increase in serum urate per change in SSB category (0.005 mmol/L, $p=8.7\times10^{-5}$) compared to those without the C allele (0.002 mmol/L, p=0.016). There was a trend towards significance for non-additive interaction between *rs6449173* and SSB in determining serum urate levels ($\beta_{Interaction}$=0.003, p=0.062). Artificially sweetened soft drinks did not raise serum urate levels (β=0.000, p=0.48), nor was there any indication of a genotype-specific effect of artificially sweetened soft drinks on serum urate (β=0.000, p=0.41 in the group not carrying the C allele; β=−0.004, p=0.45 in the C allele carrier group; $\beta_{Interaction}$=−0.001, p=0.39).

DISCUSSION

We demonstrate association between sucrose-sweetened soft drink consumption and risk of gout in the Polynesian (Māori and Pacific Islanders) and European Caucasian ancestral groups of NZ, with risk independently conferred when age, gender, BMI, alcohol and fruit consumption, kidney disease and hypertension were taken into account. We also found an indication of non-additive interaction between *SLC2A9* genotype and SSB consumption in determining the risk of gout when analysing genotype-specific groups. However, the statistical support for non-additive interaction in risk of gout was inconsistent (table 3; $p_{Interaction}$=0.01 in pooled individual-level data with adjustment by dataset and $p_{Interaction}$=0.99 in meta-analysis of interaction terms from the four individual datasets). There was evidence for heterogeneity between the four sample sets meta-analyzed (p_{Het}=0.025; the NZ Māori sample set driving the heterogeneity had a significant interaction term of $p_{Interaction}$=0.018), suggesting that combination of datasets by meta-analysis may be overconservative for these data. On balance, however, we are cautious about concluding that there is evidence for non-additive interaction between *SLC2A9* genotype and SSB consumption in gout risk, our data are an indication of non-additive interactions that require further supportive evidence in additional datasets. The ARIC serum urate analysis supported the gout data—a greater genotype-specific increase of serum urate was seen for C-allele carriers than non-carriers, with no differential effect seen with the consumption of artificially sweetened beverages (table 4). There was a trend towards significant evidence for interaction between SLC2A9 genotype and SSB (but not artificially sweetened beverage) consumption in the determination of serum urate levels (table 4; $p_{Interaction}$=0.062). Collectively, these data suggest a non-additive genotype-specific interaction between SSB consumption and *SLC2A9* genotype, and imply a physiological mechanism whereby high simple sugar exposure derived from soft drinks over-rides the positive versus negative risk discrimination of the *SLC2A9* gout risk alleles by interfering with the ability of SLC2A9 to transport uric acid.

It is worthwhile directly comparing our study to those of Choi *et al*[8 9] who positively associated HFCS-sweetened beverage consumption with risk of incident gout, as the similarities and differences are illuminating. First, both the Choi *et al* studies were done in the North American population where the most common soft drink sweetener used is HFCS (HFCS-55), which is 55% fructose and 42% glucose. In NZ the sweetener used is sucrose, which is equimolar fructose and glucose. Our data, therefore, broaden the generalisability of the role of non-artificially sweetened soft drink consumption, including to an ancestral group other than European Caucasian. Second, both Choi *et al* reports studied health professionals (the Health Professionals Study (HPS) in men[8] and the Nurses Health Study (NHS) in women[9]),

Table 2 Risk of gout for sugar-sweetened beverage intake by ethnic group

	Obs (n controls, n cases)	Frequency of SSB intake (servings/day)							
		0	0.01 to 0.99*	1.0 to 1.99	2.0 to 2.99	3.0 to 3.99	4.0 to 4.99	5.0+	P_{Trend}†
NZ European Caucasian									
Unadjusted OR (95% CI)	592 (180, 412)	1.00	1.53 (0.31 to 7.49)	0.79 (0.52 to 1.21)	1.51 (0.78 to 2.93)	0.65 (0.30 to 1.41)	3.93 (0.89 to 17.26)	1.05 (0.43 to 2.64)	0.56
p Value		–	0.60	0.28	0.22	0.28	0.070	0.90	
Adjusted OR‡ (95% CI)	563	1.00	2.17 (0.38 to 12.51)	1.11 (0.60 to 2.05)	2.82 (1.08 to 7.34)	1.42 (0.47 to 4.27)	6.89 (1.05 to 45.44)	2.38 (0.64 to 8.84)	0.020
p Value		–	0.39	0.75	0.034	0.53	0.045	0.20	
NZ Māori									
Unadjusted OR (95% CI)	502 (312, 190)	1.00	1.14 (0.35 to 3.73)	0.66 (0.40 to 1.08)	0.69 (0.36 to 1.33)	1.22 (0.63 to 2.36)	1.94 (0.91 to 4.17)	1.34 (0.74 to 2.43)	0.17
p Value		–	0.83	0.10	0.27	0.56	0.088	0.33	
Adjusted OR‡ (95%CI)	463	1.00	0.32 (0.05 to 1.91)	0.76 (0.36 to 1.58)	1.28 (0.52 to 3.14)	0.89 (0.33 to 2.35)	5.19 (1.48 to 18.17)	1.44 (0.59 to 3.53)	0.11
p Value		–	0.21	0.46	0.59	0.81	0.010	0.42	
NZ Pacific Islander									
Unadjusted OR (95% CI)	536 (217, 319)	1.00	–	0.85 (0.50 to 1.45)	0.84 (0.49 to 1.42)	0.84 (0.48 to 1.47)	2.42 (1.09 to 5.33)	1.38 (0.76 to 2.50)	0.16
p Value		–	–	0.55	0.51	0.53	0.029	0.29	
Adjusted OR‡ (95% CI)	485	1.00	–	1.20 (0.59 to 2.46)	0.84 (0.42 to 1.69)	1.00 (0.47 to 2.13)	2.84 (1.04 to 7.77)	2.17 (0.98 to 4.77)	0.050
p Value		–	–	0.62	0.63	1.00	0.043	0.055	
ARIC									
Unadjusted OR (95% CI)	7059 (6911, 148)	1.00	1.71 (0.78 to 3.74)	1.54 (0.69 to 3.43)	1.48 (0.57 to 3.83)	3.79 (1.35 to 10.61)	–	2.54 (0.73 to 8.80)	0.15
p Value		–	0.18	0.29	0.43	0.011	–	0.14	
Adjusted OR‡ OR (95% CI)	6705	1.00	1.50 (0.68 to 3.30)	1.36 (0.61 to 3.05)	1.19 (0.45 to 3.12)	3.05 (1.07 to 8.66)	–	2.31 (0.65 to 8.19)	0.26
p Value		–	0.31	0.46	0.73	0.037	–	0.20	

*Selection of exposure groups is described in the Methods.
†p_{Trend} was the p value associated with the single line SSB variable in regression analysis.
‡Adjusted by age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease, high blood pressure and relatedness (ARIC only).
ARIC, Atherosclerosis Risk in Communities; NZ, New Zealand; SSB, sugar (sucrose)-sweetened beverage.

Table 3 Sugar-sweetened beverage consumption and change in gout risk, with stratification by *SLC2A9* genotype

		Obs	Δ ln gout risk, 95% CI (odds ratio)*	p	$\beta_{Interaction}$ (95% CI)†	p
NZ European Caucasian	Unstratified	563	1.20 (1.03 to to 1.40)	0.020	0.021 (−0.016 to 0.058)	0.27
	C allele non-carrier	373	1.16 (0.95 to 1.43)	0.14		
	C allele carrier	148	1.27 (0.96 to 1.67)	0.091		
NZ Māori	Unstratified	463	1.11 (0.98 to 1.27)	0.11	−0.064 (−0.12 to −0.011)	0.018
	C allele non-carrier	396	1.19 (1.03 to 1.37)	0.019		
	C allele carrier	51	0.76 (0.49 to 1.16)	0.20		
NZ Pacific Islander	Unstratified	489	1.13 (1.01 to 1.27)	0.030	0.073 (−0.018 to 0.16)	0.12
	C allele non-carrier	454	1.11 (0.99 to 1.25)	0.039		
	C allele carrier	27	1.71 (0.85 to 3.42)	0.13		
ARIC	Unstratified	6721	1.09 (0.94 to 1.27)	0.26	0.00028 (−0.0067 to 0.0072)	0.94
	G allele non-carrier‡	4082	1.05 (0.88 to 1.26)	0.58		
	G allele carrier	2639	1.16 (0.88 to 1.54)	0.29		
All Populations Combined	Unstratified	8236	1.13 (1.06 to 1.20)	1.9×10^{-4}	−0.013§ (−0.022 to −0.003)	0.010
	Minor allele non-carrier‡	5305	1.12 (1.05 to 1.21)	0.001		
	C allele carrier	2888	1.15 (0.98 to 1.34)	0.082		

*Change in gout risk per increase in consumption category adjusted by age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease, high blood pressure, relatedness and sample set where combined.
†SSB/day ordinal (ordered) variables (0, 1, 2, 3, 4, 5, 6) were created as described in the supplementary material and used as a continuous variable to derive the SSB by genotype interaction term with risk of gout as outcome.
‡ARIC genotyped with *rs11942223* surrogate *rs6449173* (major allele A, minor allele C).
§Interaction term by Mantel Haenszel meta-analysis was 0.000 (−0.033 to 0.034), p=0.99 (the p value of the Q test for heterogeneity was 0.025).
ARIC, Atherosclerosis Risk in Communities; NZ, New Zealand; Obs, Observations; SSB, sugar (sucrose)-sweetened beverage.

whereas our study was not targeted to any particular demographic. One statistic that reflects this demographic difference is the prevalence of higher SSB consumption in the NZ datasets. In the HPS, 2.3% of participants consumed ≥2 drinks/day, and in the NHS, 1.9% consumed ≥2/day. In our sample set, 18.9% of European Caucasian controls, 34.4% of Māori controls and 56.1% of Pacific Island controls consumed ≥2/day. Third, our study was on prevalent gout, not incident gout in the case of the studies of Choi *et al*[8 9] (although some incident cases may have been included in the ARIC samples (see online supplemental material)). From the incident gout studies it is possible to conclude that HFCS-sweetened beverage consumption was causative of gout, and should be targeted in primary prevention. By contrast, given our study was of cross-sectional design on prevalent gout, our results are more consistent with a contribution to established gout by SSB consumption. Collectively, this evidence strongly supports recommending reduction in SSB in primary prevention of gout,[8 9] and also in management of patients with established gout, as an adjunct to urate-lowering therapy.

One weakness in our study is the incompleteness of our dietary data, meaning we cannot address whether or not consumption of larger quantities of SSB is a marker for other dietary risk factors for hyperuricaemia and gout—a diet high in purine-rich foods, alcohol and vitamin A, and low in vitamin C and coffee.[18–22] Given our data were adjusted for alcohol consumption, we are confident that this risk factor is not a confounder in the SSB-gout association. The studies reporting association between HFCS-sweetened soft drink consumption and serum urate levels and gout in men took into account consumption of meat, seafood, purine-rich vegetables and total vitamin C,[8 10] suggesting that serum urate levels and gout risk are independently influenced by soft drink consumption. Although not a weakness in our study per se, rather a weakness inherent in case-control studies in general, it is possible that SSB consumption is a marker for a separate causal environmental risk factor. Arguing against this possibility is the biological plausibility of SSB consumption as a causal factor in gout, and some evidence for interaction with the simple sugar and uric acid transporter, SLC2A9.

Table 4 Sugar-sweetened and artificially sweetened beverage consumption and change in serum urate levels in ARIC controls, with stratification by *SLC2A9* genotype

Sweetener		Obs	Δ ln serum urate, 95% CI (mmol/L)*	p Value	$\beta_{Interaction}$, 95% CI†	p Value
HFCS	Unstratified	6574	0.003 (0.002 to 0.005)	6.9×10^{-6}	0.003 (−0.000 to 0.059)	0.062
	C allele non-carrier‡	3977	0.002 (0.000 to 0.004)	0.016		
	C allele carrier	2597	0.005 (0.003 to 0.007)	8.7×10^{-5}		
Artificial	Unstratified	6574	0.000 (−0.000 to 0.001)	0.48	−0.001 (−0.002 to 0.001)	0.39
	C allele non-carrier‡	3977	0.000 (−0.000 to 0.001)	0.41		
	C allele carrier	2597	−0.004 (−0.013 to 0.006)	0.45		

*Change per increase in consumption category (as defined for the NZ data) adjusted by age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease, high blood pressure and relatedness.
†Beverage consumption per day ordinal (ordered) variables (0, 1, 2, 3, 4, 5, 6) were created as described in the Supplementary Material and used as a continuous variable to derive the consumption by genotype interaction term with serum urate as outcome.
‡Genotyped with *rs11942223* surrogate *rs6449173* (major allele A, minor allele C)—r^2=1 with *rs11942223* in European Caucasian.
ARIC, Atherosclerosis Risk in Communities; NZ, New Zealand; HFCS, high fructose corn syrup; Obs, Observations.

SLC2A9 is expressed as two isoforms[23]—full-length (SLC2A9v1) and a variant missing 28 N-terminal residues (SLC2A9v2). SLC2A9v1 is expressed on the basolateral (blood) membrane, and SLC2A9v2 is expressed on the apical (reabsorption) membrane of the renal proximal tubule.[24] There is a positive correlation between serum urate levels and SLC2A9v2 expression, but not for SLC2A9v1.[25] If genotype at *rs11942223* correlates with expression of the different isoforms,[26] then the interaction data can be viewed in a different context, as differential reaction of two structurally distinct proteins, albeit encoded by the same gene, to increased SSB consumption; one isoform (SLC2A9v2, encoded by the major serum urate-raising allele) reacts in a simple additive fashion and the other (SLC2A9v1, encoded by the minor serum urate-lowering allele) in a not straightforward non-additive way. From the current state of knowledge and given the complexity of urate transport in the renal tubule it is difficult to propose a plausible mechanism to explain any non-additive interaction (under the assumption that this risk is mediated through a change in serum urate level). It is known that individuals of European Caucasian ancestry positive for the gout-protective C-allele at *rs11942223* exhibit a reduced change in serum urate and increased FEUA in response to an acute fructose load, with no genotype-specific effect in people of NZ Māori and Pacific Islander (Polynesian) ancestry.[16] These data are inconsistent with the observation of increased serum urate and risk of gout in C-allele carrying individuals of European Caucasian and Polynesian ancestry upon exposure to fructose-containing SSB (tables 3 and 4), suggesting that distinct biological mechanisms underlie the ref 16 observation and the interaction data reported herein. Chronic exposure to fructose-containing SSB would more likely involve other mechanisms (eg, epigenetic) that influence the expression and activity of SLC2A9.

In summary, our data support the recommendation that reduction of SSB consumption should be pursued in established gout. The collective data suggest a non-additive genotype-specific interaction between SSB consumption and *SLC2A9* genotype and imply a physiological mechanism whereby high simple sugar exposure derived from soft drinks interferes with the ability of SLC2A9 to transport uric acid.

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Contributors All authors provided a significant contribution either to conception and design, acquisition of data and/or analysis and interpretation of data. All authors provided a significant contribution to the drafting of the manuscript and to intellectual content. All authors approved the final manuscript.

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REFERENCES

1 Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med* 1987;82:421–6.
2 Sorensen LB, Levinson DJ. Origin and extrarenal elimination of uric acid in man. *Nephron* 1975;14:7–20.
3 Merriman TR, Dalbeth N. The genetic basis of hyperuricaemia and gout. *Joint Bone Spine* 2011;78:35–40.
4 Köttgen A, Albrecht E, Teumer A, *et al*. Genome-wide association analyses identify 18 new loci associated with serum urate concentrations. *Nat Genet* 2013;45:145–54.
5 Caulfield MJ, Munroe PB, O'Neill D, *et al*. SLC2A9 is a high-capacity urate transporter in humans. *PLoS Med* 2008;5:e197.
6 Witkowska K, Smith KM, Yao SY, *et al*. Human SLC2A9a and SLC2A9b isoforms mediate electrogenic transport of urate with different characteristics in the presence of hexoses. *Am J Physiol Renal Physiol* 2012;303:F527–39.
7 Hollis-Moffatt JE, Xu X, Dalbeth N, *et al*. A role for the urate transporter SLC2A9 gene in susceptibility to gout in New Zealand Māori, Pacific Island and Caucasian case-control cohorts. *Arthritis Rheum* 2009;60:3485–92.
8 Choi HK, Curhan G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *Br Med J* 2008;336:309–12.
9 Choi HK, Willett W, Curhan G. Fructose-rich beverages and risk of gout in women. *JAMA* 2010;304:2270–8.
10 Choi JW, Ford ES, Gao X, *et al*. 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.
11 Perheentupa J, Raivio K. Fructose-induced hyperuricaemia. *Lancet* 1967;2:528–31.
12 Wang DD, Sievenpiper JL, de Souza RJ, *et al*. The effects of fructose intake on serum uric acid vary among controlled dietary trials. *J Nutr* 2012;142:916–23.
13 Lanaspa MA, Tapia E, Soto V, *et al*. Uric acid and fructose: potential biological mechanisms. *Semin Nephrol* 2011;31:426–32.
14 Johnson RJ, Perez-Pozo SE, Sautin YY, *et al*. Hypothesis: could excessive fructose intake and uric acid cause type 2 diabetes? *Endocr Rev* 2009;30:96–116.
15 Le MT, Frye RF, Rivard CJ, *et al*. Effects of high-fructose corn syrup and sucrose on the pharmacokinetics of fructose and acute metabolic and hemodynamic responses in healthy subjects. *Metabolism* 2012;61:641–51.
16 Dalbeth N, House ME, Gamble GD, *et al*. Population-specific influence of *SLC2A9* genotype o the acute hyperuricemia response to a fructose load. *Ann Rheum Dis* Published Online First: 24 Jan 2013. doi:10.1136/annrheumdis-2012-202732
17 Wallace SL, Robinson H, Masi AT, *et al*. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977;20:895–900.
18 Choi HK, Atkinson K, Karlson EW, *et al*. Purine-rich foods, dairy and protein intake, and the risk of gout in men. *N Engl J Med* 2004;350:1093–103.
19 Choi HK, Atkinson K, Karlson EW, *et al*. Alcohol intake and risk of incident gout in men: a prospective study. *Lancet* 2004;363:1277–81.
20 Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study. *Arch Intern Med* 2009;169:502–7.
21 Choi WJ, Ford ES, Curhan G, *et al*. Independent association of serum retinol and β-carotene levels with hyperuricemia: a national population study. *Arthritis Care Res* 2012;64:389–96.
22 Choi HK, Willett W, Curhan G. Coffee consumption and risk of incident gout in men: a prospective study. *Arthritis Rheum* 2007;56:2049–55.
23 Augustin R, Carayannopoulos MO, Dowd LO, *et al*. Identification and characterization of human glucose transporter-like protein-9 (GLUT9): alternative splicing alters trafficking. *J Biol Chem* 2004;279:16229–36.
24 Bibert S, Hess SK, Firsov D, *et al*. Mouse GLUT9: evidences for a urate uniporter. *Am J Physiol Renal Physiol* 2009;297:F612–19.
25 Döring A, Gieger C, Mehta D, *et al*. SLC2A9 influences uric acid concentrations with pronounced sex-specific effects. *Nat Genet* 2008;40:430–6.
26 Merriman TR. Population heterogeneity in the genetic control of serum urate. *Semin Nephrol.* 2011;31:420–5.

SUPPLEMENTAL MATERIAL

Sugar-sweetened beverage consumption: A risk factor for prevalent gout that interacts with *SLC2A9* genotype in a non-additive fashion

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Subjects and Methods

Data collection

New Zealand participants were asked their normal daily sugar-sweetened beverage (SSB) intake ("How many cans or large glasses (~300 ml) of sugar-sweetened drinks, including fruit juice but excluding diet drinks, do you normally drink per day?") on a scale of 0,1,2,3,4,5 or more than 5. In the analysis, seven categories of SSB were created; 0, 0-1, 1, 2, 3, 4, 5 or more cans or large glasses of a sugar-sweetened drink per day (the 0-1 category allowed for people who voluntarily reported less than one serving per week). Although these data were not validated by diet records, they were comparable to survey data from South Australia where 11.6% of adults consumed ≥0.5 litres of soft-drink (excluding fruit juice) per day (1) - in the NZ European Caucasian control sample set 18.9% of participants reported drinking ≥2 (≥600 millilitres) SSB (including fruit juice) per day. Average SSB/day was 0.94 in NZ European Caucasian controls, 1.46 in Māori controls and 2.04 in Pacific Island controls. In questions 11, 64 and 65 of Exam One ARIC participants were asked how many "Orange or grapefruit juice; 1 glass", "Regular soft drinks, such as Coke, Pepsi, 7-Up, ginger ale; 1 glass" and "Fruit-flavored punch or non-carbonated beverages, such as lemonade, Kool-Aid or Hawaiian Punch; not diet; 1 glass", respectively, they had consumed in 9 categories ranging from "almost never" to >6/day. The consumption derived from responses to the 3 questions were combined and converted into SSB categories equivalent to those used for the NZ data. Data from artificially-sweetened soft drinks were derived from question 63, how many "Low calorie soft drinks, such as diet Coke, diet Pepsi, diet 7-Up; 1 glass" (data on artificially-sweetened soft drink consumption were not available in the NZ sample sets) and combined in categories equivalent to the SSB exposure data.

New Zealand participants were asked "How many pieces of whole fresh fruit do you usually eat per day?". Fruit consumption in ARIC, self-reported in Exam One, were combined from questions 9, 10,

12-14 (apples, oranges, peaches, apricots, plums, bananas, other fruits). NZ participants self-reported the amount of alcoholic drinks (beer, wine, spirits) consumed in the previous week. Similarly, ARIC participants self-reported weekly beer, wine and liquor consumption at Exam One (questions 96-98). Fruit and alcohol consumption were summed into a per day continuous variable.

New Zealand subjects also self-reported other metabolic medical conditions (hypertension and kidney problems). Serum urate was measured in NZ participants using the Trinder assay with a Roche Modular P (Hitachi) analyzer. From the ARIC data, urate measurements at Exam One were used, and anthropomorphic and blood pressure data were available from Exam One and kidney disease status from Exam Three (1993-1994). In the ARIC cohort, determination of gout status from Exam Four (not available at Exam One), 9 years after the exposure data were collected at Exam One, means it is likely that some cases were not diagnosed with gout when the exposure data were collected.

Genotyping of SLC2A9 single nucleotide polymorphism *rs11942223* was done using TaqMan SNP genotyping assay technology (Applied Biosystems) over the NZ samples. The ARIC samples had previously been genotyped for surrogate marker *rs6449173* using the Affymetrix 6.0 platform.

References

1. Shi Z, Dal Grande E, Taylor AW, Gill TK, Adams R, Wittert G. Association between soft drink consumption and asthma and chronic obstructive pulmonary disease among adults in Australia. *Respirology.* 2012;17:363-369.

Supplemental Table 1 Baseline characteristics by sugar-sweetened beverage intake.

	Frequency of SSB (servings/day)															
	Controls								Cases							
	0	0.1-0.9	1-1.9	2-2.9	3-3.9	4-4.9	5+	β (P)[1]	0	0.1-0.9	1-1.9	2-2.9	3-3.9	4-4.9	5+	β (P)[1]
NZ Caucasian																
Number of individuals (%)	96 (53.3%)	2 (1.1%)	48 (26.7%)	13 (7.2%)	12 (6.7%)	2 (1.1%)	7 (3.9%)	-	220 (53.4%)	7 (1.7%)	87 (21.1%)	45 (10.9%)	18 (4.4%)	18 (4.4%)	17 (4.1%)	-
Age, mean (range), years	47 (18-79)	57 (56-58)	44 (17-68)	38 (18-53)	34 (19-56)	34 (21-46)	44 (29-66)	-3.211 (1.2x10-4)	65 (23-93)	58 (47-82)	63 (23-91)	62 (27-85)	58 (23-94)	62 (38-85)	58 (28-81)	-0.842 (0.055)
Sex, % male	43.8%	50.0%	47.9%	38.5%	66.7%	50.0%	57.1%	-0.076 (0.016)	72.0%	100%	74.7%	91.1%	88.9%	88.9%	100%	-0.033 (0.016)
BMI, mean (range)	28.4 (19.6-62.7)	28.0 (25.0-31.1)	27.3 (19.5-37.1)	28.2 (22.0-37.0)	28.4 (20.9-56.3)	43.8 (29.5-58)	30.3 (23.1-39.1)	0.916 (0.037)	29.9 (19.2-60.7)	34.7 (24.4-61.4)	29.7 (20.1-42.0)	29.6 (22.0-40.1)	29.4 (22.4-36.6)	28.9 (22.3-36.8)	30.0 (21.3-37.7)	-0.167 (0.349)
Uric acid, mean (range)	0.27 (0.13-0.52)	0.27 (0.22-0.32)	0.31 (0.18-0.48)	0.30 (0.18-0.42)	0.33 (0.21-0.44)	-	0.30 (0.20-0.66)	0.012 (0.029)	0.39 (0.13-0.66)	-	0.38 (0.19-0.63)	0.44 (0.28-0.65)	0.36 (0.20-0.64)	0.42 (0.25-0.69)	0.41 (0.23-0.60)	0.006 (0.241)
Alcohol intake, mean servings/week (range)	5.9 (0-30)	6.0 (6)	6.3 (0-30)	5.4 (0-24)	4.8 (0-13)	0 (0)	13 (0-48)	0.288 (0.554)	6.5 (0-35)	8.3 (2-17)	6.9 (0-35)	8.7 (0-41)	13.6 (0-84)	8.6 (0-40)	8.5 (0-34)	0.329 (0.317)
Kidney problems, %	3.2%	0%	0%	0%	0%	0%	0%	-0.007 (0.429)	18.5%	0%	16.7%	18.2%	11.8%	22.2%	17.7%	0.008 (0.528)
High blood pressure, %	12.6%	0%	8.9%	0%	8.3%	0%	14.3%	-0.024 (0.204)	52.8%	14.3%	53.5%	48.9%	44.4%	38.9%	29.4%	-0.015 (0.375)
NZ Māori																
Number of individuals (%)	120 (38.5%)	7 (2.2%)	78 (25.0%)	37 (11.9%)	25 (8.0%)	14 (4.5%)	31 (9.9%)	-	75 (39.5%)	5 (2.6%)	32 (16.8%)	16 (8.4%)	19 (10.0%)	17 (9.0%)	26 (13.7%)	-
Age, mean (range), years	48 (18-75)	48 (40-63)	40 (18-80)	38 (18-67)	40 (17-66)	34 (20-49)	39 (17-65)	-1.768 (3.7x10-5)	59 (25-81)	54 (45-64)	52 (30-81)	51 (26-77)	52 (23-69)	49 (31-68)	50 (33-74)	-1.239 (0.003)
Sex, % male	26.3%	42.9%	26.9%	37.8%	60.0%	28.6%	48.4%	-0.039 (0.020)	69.3%	100%	81.3%	86.7%	94.4%	88.2%	88.5%	-0.026 (0.082)
BMI, mean (range)	31.6 (20.8-62.5)	35.1 (28.8-40.3)	31.9 (21.4-77.0)	31.4 (19.4-56.8)	33.5 (19.4-46.4)	33.6 (24.8-44.9)	33.3 (18.1-59.8)	0.320 (0.224)	34.8 (22.1-72.7)	36.4 (26.8-50.6)	34.2 (23.2-62.1)	32.5 (21.7-42.1)	36.5 (24.6-51.6)	36.1 (27.1-46.5)	36.3 (23.1-48.3)	0.051 (0.864)
Uric acid, mean (range)	0.32 (0.15-0.55)	0.37 (0.31-0.40)	0.32 (0.15-0.53)	0.35 (0.21-0.58)	0.39 (0.20-0.67)	0.36 (0.24-0.47)	0.36 (0.19-0.54)	0.005 (0.101)	0.40 (0.11-0.67)	0.40 (0.23-0.59)	0.41 (0.25-0.59)	0.42 (0.19-0.61)	0.46 (0.23-0.60)	0.42 (0.28-0.57)	0.42 (0.26-0.55)	0.002 (0.659)
Alcohol intake, mean servings/week (range)	3.3 (0-35)	0.6 (0-3)	6.0 (0-66)	3.8 (0-30)	7.8 (0-60)	3.9 (0-24)	3.1 (0-17)	-0.274 (0.319)	6.0 (0-120)	6.2 (0-50)	8.0 (0-50)	4.3 (0-15)	4.7 (0-24)	7.5 (0-50)	9.6 (0-96)	-0.138 (0.811)
Kidney problems, %	4.4%	0%	2.6%	0%	0%	0%	3.3%	-0.003 (0.515)	17.8%	25.0%	21.9%	12.5%	31.6%	11.8%	13.0%	0.003 (0.838)
High blood pressure, %	20.0%	42.9%	15.4%	8.1%	17.4%	0%	22.6%	-0.003 (0.782)	58.9%	60.0%	67.7%	31.3%	50.0%	58.8%	62.5%	0.014 (0.454)

Supplemental Table 1 cont Baseline characteristics by sugar-sweetened beverage intake.

NZ Pacific Island																
Number of individuals (%)	49 (22.6%)	0 (0%)	47 (21.7%)	47 (21.7%)	38 (17.5%)	10 (4.6%)	26 (12.0%)	-	71 (22.0%)	4 (1.2%)	58 (18.0%)	57 (17.7%)	46 (14.3%)	35 (10.8%)	52 (16.1%)	-
Age, mean (range), years	45 (21-85)	-	38 (18-63)	40 (17-67)	42 (18-86)	39 (19-66)	33 (18-47)	-1.403 (0.007)	51 (22-75)	46 (27-69)	49 (26-81)	48 (22-79)	47 (20-79)	48 (18-74)	42 (22-75)	-0.798 (0.018)
Sex, % male	53.1%	-	55.3%	55.3%	56.8%	50.0%	80.8%	-0.060 (0.006)	80.8%	80.0%	82.8%	93.0%	93.6%	91.7%	88.5%	-0.005 (0.594)
BMI, mean (range)	33.0 (19.4-50.3)	-	34.7 (23.4-54.8)	35.5 (20.5-65.1)	35.8 (23.4-54.9)	37.9 (31.5-42.6)	35.9 (24.7-47.9)	0.916 (0.004)	35.3 (24.0-53.5)	34.1 (21.5-42.9)	35.6 (26.3-52.5)	36.0 (27.0-54.6)	36.1 (26.0-51.6)	35.4 (24.7-52.8)	38.2 (26.1-55.0)	0.241 (0.308)
Uric acid, mean (range)	0.35 (0.26-0.48)	-	0.37 (0.20-0.55)	0.38 (0.27-0.55)	0.39 (0.17-0.57)	0.36 (0.23-0.45)	0.41 (0.26-0.57)	0.005 (0.115)	0.44 (0.18-0.70)	0.43 (0.27-0.52)	0.44 (0.17-0.64)	0.45 (0.29-0.63)	0.48 (0.26-0.68)	0.46 (0.22-0.70)	0.50 (0.20-0.65)	0.012 (0.003)
Alcohol intake, mean servings/week (range)	4.5 (0-36)	-	2.6 (0-35)	3.3 (0-27)	2.4 (0-20)	8 (0-37)	6.3 (0-48)	-0.083 (0.795)	2.4 (0-24)	6.6 (0-32)	3.1 (0-24)	3.2 (0-33)	4.9 (0-23)	3.4 (0-18)	6.6 (0-30)	0.341 (0.273)
Kidney problems, %	0%	-	0%	4.4%	2.9%	10.0%	0%	0.015 (0.015)	23.9%	20.0%	18.2%	7.6%	6.4%	8.6%	4.0%	-0.019 (0.050)
High blood pressure, %	22.9%	-	15.2%	17.4%	13.5%	20.0%	0%	-0.024 (0.108)	62.5%	20.0%	46.4%	48.2%	37.0%	44.1%	42.3%	-0.011 (0.462)
ARIC																
Number of individuals (%)	537 (7.8%)	3264 (47.1%)	2255 (32.6%)	584 (8.5%)	150 (2.2%)	16 (0.2%)	121 (1.7%)	-	7 (4.7%)	74 (50.0%)	44 (29.7%)	12 (8.1%)	7 (4.7%)	0 (0%)	4 (2.7%)	-
Age, mean (range), years	54.5 (44-65)	53.7 (44-65)	54 (44-65)	53 (44-65)	53 (45-64)	49 (45-64)	51 (44-64)	-0.503 ($3.6x10^{-14}$)	55 (45-63)	55 (45-65)	55 (46-64)	54.4 (46-63)	51 (45-61)	-	49 (45-55)	-0.699 (0.068)
Sex, % male	34.6%	45.3%	47.7%	56.7%	60.7%	62.5%	55.4%	-0.057 ($1.7x10^{-23}$)	71.4%	67.6%	81.8%	91.7%	85.7%	-	75.0%	-0.047 (0.104)
BMI, mean (range)	26.2 (14.9-44.6)	26.4 (14.4-54.6)	26.2 (16.2-54.5)	26.4 (17.3-46.5)	27.1 (18.8-53.8)	25.6 (19.4-30.7)	26.1 (17.1-41.1)	-0.100 (0.058)	30.6 (25.6-36.7)	28.1 (21.6-40.0)	27.0 (21.1-40.5)	29.0 (23.1-39.9)	28.6 (21.6-37.7)	-	27.4 (25.9-30.4)	-0.303 (0.281)
Uric acid, mean (range)	0.32 (0.12-0.57)	0.33 (0.09-0.67)	0.34 (0.03-0.71)	0.34 (0.11-0.70)	0.37 (0.07-0.55)	0.35 (0.18-0.57)	0.35 (0.15-0.63)	0.004 ($5.0x10^{-7}$)	0.44 (0.28-0.52)	0.40 (0.22-0.60)	0.42 (0.11-0.64)	0.45 (0.26-0.56)	0.51 (0.35-0.69)	-	0.41 (0.31-0.55)	0.010 (0.089)
Alcohol intake, mean servings/week (range)	3.2 (0-45)	3.5 (0-63)	3.2 (0-93)	3.5 (0-56)	2.7 (0-30)	4.0 (0-36)	4.7 (0-70)	-0.136 (0.080)	2.6 (0-17)	5.9 (0-34)	5.4 (0-43)	8.3 (0-30)	4.4 (0-12)		5.5 (0-16)	-0.544 (0.355)
Kidney problems, %	1.4%	1.0%	1.4%	1.1%	0.7%	0%	0%	-0.001 (0.435)	0%	0%	2.3%	0%	14.3%	-	0%	0.011 (0.169)
High blood pressure, %	12.7%	12.1%	13.2%	13.5%	12.0%	13.3%	8.3%	0.000 (0.994)	57.1%	16.2%	18.2%	33.3%	14.3%	-	25.0%	-0.001 (0.965)

Individual variables analysed by linear regression for association with SSB (as a continuous variable).

[1] Regression coefficients are adjusted by age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease, high blood pressure, and relatedness (ARIC only; 501/7075 were related) except when the variable was the dependent variable.

Supplemental Table 2. Individual adjustments of the odds ratios for SSB intake and risk of gout

		Frequency of SSB (servings/day)								
	Obs	0	0.01-0.99	1.00-1.99	2.00-2.99	3.00-3.99	4.00-4.99	5.00+	≥4.0[1]	P_{Trend}[2]
Unadjusted										
NZ Caucasian OR (95% CI)		1	1.53 (0.31-7.49)	0.79 (0.52-1.21)	1.51 (0.78-2.93)	0.65 (0.30-1.41)	3.93 (0.89-17.26)	1.06 (0.43-2.64)	1.70 (0.79-3.67)	
P	592	-	0.6	0.28	0.22	0.28	0.07	0.9	0.18	0.56
NZ Maori OR (95% CI)		1	1.14 (0.35-3.73)	0.66 (0.40-1.08)	0.69 (0.36-1.33)	1.22 (0.63-2.36)	1.94 (0.91-4.17)	1.34 (0.74-2.43)	1.53 (0.92-2.54)	
P	502	-	0.83	0.1	0.27	0.56	0.088	0.33	0.1	0.17
NZ Pacific Island OR (95% CI)		1	-	0.85 (0.50-1.45)	0.84 (0.49-1.42)	0.84 (048-1.47)	2.42 (1.09-5.33)	1.38 (0.76-2.50)	1.67 (0.98-2.84)	
P	536	-	-	0.55	0.51	0.53	0.029	0.29	0.06	0.16
ARIC OR (95% CI)		1	1.74 (0.80-3.80)	1.50 (0.67-3.34)	1.58 (0.62-4.03)	3.58 (1.24-10.37)	-	2.54 (0.73-8.80)	2.24 (0.65-7.76)	
P	7059	-	0.17	0.33	0.34	0.019	-	0.14	0.2	0.2
Age										
NZ Caucasian OR (95% CI)		1	1.78 (0.33-9.49)	1.02 (0.60-1.71)	2.59 (1.16-5.80)	2.08 (0.75-5.76)	6.26 (1.11-35.35)	2.19 (0.71-6.77)	3.13 (1.23-7.96)	
P	592	-	0.5	0.95	0.02	0.16	0.038	0.17	0.017	0.005
NZ Maori OR (95% CI)		1	1.46 (0.42-5.07)	1.21 (0.69-2.14)	1.38 (0.66-2.89)	2.09 (0.98-4.49)	4.94 (2.06-11.86)	2.72(1.38-5.36)	3.33 (1.84-6.03)	
P	501	-	0.55	0.51	0.4	0.058	$3.6x10^{-4}$	0.004	$7.2x10^{-5}$	$1.0x10^{-4}$
NZ Pacific Island OR (95% CI)		1	-	1.08 (0.61-1.89)	1.07 (0.61-1.88)	1.05 (0.57-1.90)	3.18 (1.37-7.35)	2.37 (1.25-4.51)	2.61 (1.47-4.65)	
P	535	-	-	0.8	0.81	0.89	0.007	0.008	0.001	0.005
ARIC OR (95% CI)		1	1.78 (0.81-3.88)	1.51 (0.68-3.38)	1.64 (0.64-4.19)	3.74 (1.29-10.85)	-	2.74 (0.79-9.55)	2.44 (0.70-8.48)	
P	7059	-	0.15	0.31	0.31	0.015	-	0.11	0.16	0.16
Sex										
NZ Caucasian OR (95% CI)		1	1.04 (0.20-5.35)	0.76 (0.48-1.19)	1.22 (0.61-2.44)	0.49 (0.22-1.09)	3.03 (0.67-13.77)	0.73 (0.28-1.87)	1.22 (0.55-2.72)	
P	590	-	0.96	0.22	0.57	0.081	0.15	0.51	0.62	0.6
NZ Maori OR (95% CI)		1	0.65 (0.18-2.42)	0.57 (0.32-1.01)	0.45 (0.22-0.96)	0.56 (0.27-1.19)	1.45 (0.61-3.49)	0.79 (0.40-1.56)	0.98 (0.55-1.75)	
P	498	-	0.52	0.056	0.038	0.13	0.4	0.51	0.95	0.49

NZ Pacific Island OR (95% CI)		1	-	0.82 (0.47-1.45)	0.73 (0.41-1.29)	0.72(0.39-1.32)	2.13 (0.92-4.92)	1.06 (0.56-2.00)	1.34 (0.76-2.37)	
P	535	-	-	0.5	0.28	0.29	0.078	0.86	0.31	0.65
ARIC OR (95% CI)		1	1.53 (0.70-3.35)	1.28 (0.57-2.86)	1.22 (0.48-3.15)	2.68 (0.92-7.80)	-	2.00 (0.57-6.99)	1.75 (0.50-6.11)	
P	7059	-	0.29	0.55	0.68	0.071	-	0.28	0.38	0.52
BMI										
NZ Caucasian OR (95% CI)		1	1.32 (0.26-6.61)	0.81 (0.53-1.25)	1.43 (0.73-2.79)	0.66 (0.30-1.43)	3.77 (0.85-16.66)	1.00 (0.40-2.52)	1.62 (0.74-3.52)	
P	582	-	0.74	0.35	0.3	0.29	0.08	0.99	0.22	0.64
NZ Maori OR (95% CI)		1	0.99 (0.30-3.27)	0.65 (0.39-1.09)	0.70 (0.36-1.36)	1.09 (0.56-2.14)	1.75 (0.81-3.79)	1.21(0.81-2.23)	1.38 (0.82-2.32)	
P	496	-	0.98	0.1	0.3	0.8	0.16	0.53	0.22	0.34
NZ Pacific Island OR (95% CI)		1	-	0.90 (0.52-1.55)	0.78 (0.45-1.34)	0.81 (0.45-1.44)	2.60 (1.14-5.93)	1.22 (0.66-2.24)	1.57 (0.91-2.71)	
P	526	-	-	0.7	0.36	0.47	0.024	0.52	0.1	0.31
ARIC OR (95% CI)		1	1.53 (0.70-3.35)	1.28 (0.57-2.86)	1.22 (0.48-4.15)	2.68 (0.92-7.80)	-	2.00 (0.57-6.99)	2.29 (0.66-7.95)	
P	7057	-	0.29	0.55	0.68	0.071	-	0.28	0.19	0.18
Alcohol Intake (continuous)										
NZ Caucasian OR (95% CI)		1	1.49 (0.30-7.30)	0.79 (0.51-1.20)	1.47 (0.76-2.86)	0.62 (0.29-1.35)	3.86 (0.88-17.00)	1.01 (0.40-2.52)	1.64 (0.76-3.55)	
P	592	-	0.63	0.27	0.25	0.23	0.074	0.99	0.21	0.66
NZ Maori OR (95% CI)		1	1.07 (0.32-3.56)	0.62 (0.37-1.03)	0.70 (0.36-1.34)	1.16 (0.59-2.27)	1.89 (0.88-4.08)	1.30 (0.71-2.37)	1.48 (0.89-2.48)	
P	502	-	0.91	0.065	0.29	0.66	0.11	0.39	0.13	0.21
NZ Pacific Island OR (95% CI)		1	-	0.87 (0.51-1.47)	0.85 (0.50-1.44)	0.83 (0.47-1.46)	2.42 (1.09-5.33)	1.34 (0.74-2.44)	1.64 (0.96-2.80)	
P	536	-	-	0.6	0.54	0.51	0.029	0.34	0.069	0.2
ARIC OR (95% CI)		1	1.72 (0.79-3.76)	1.49 (0.67-3.32)	1.54 (0.60-3.95)	3.66 (1.26-10.62)	-	2.27 (0.65-7.96)	2.01 (0.58-7.04)	
P	7059	-	0.17	0.33	0.37	0.017	-	0.2	0.27	0.24
Fruit Intake (continuous)										
NZ Caucasian OR (95% CI)		1	1.54 (0.31-7.56)	0.83 (0.54-1.28)	1.51 (0.78-2.92)	0.67 (0.31-1.44)	3.83 (0.87-16.85)	1.09 (0.44-2.72)	1.70 (0.79-3.69)	
P	589	-	0.59	0.41	0.23	0.31	0.076	0.86	0.18	0.5
NZ Maori OR (95% CI)	498	1	1.16 (0.35-3.81)	0.64 (0.38-1.06)	0.69(0.36-1.32)	1.21 (0.62-2.35)	1.93 (0.90-4.15)	1.38 (0.76-2.52)	1.56 (0.84-2.60)	0.16

P		-	0.81	0.081	0.26	0.57	0.091	0.29	0.088	
NZ Pacific Island OR (95% CI)		1	-	0.89 (0.52-1.52)	0.86 (0.51-1.47)	0.86 (0.49-1.53)	2.41 (1.09-5.33)	1.57 (0.85-2.90)	1.82 (1.06-3.14)	
P	526	-	-	0.67	0.27	0.61	0.03	0.15	0.03	0.094
ARIC OR (95% CI)		1	1.73 (0.79-3.78)	1.50 (0.67-3.35)	1.58 (0.62-4.05)	3.62 (1.25-10.50)	-	2.53 (0.73-8.78)	2.24 (0.65-7.75)	
P	7059	-	0.17	0.32	0.34	0.018	-	0.14	0.2	0.19
Kidney disease										
NZ Caucasian OR (95% CI)		1	1.87 (0.38-9.16)	0.83 (0.53-1.30)	1.51 (0.77-2.98)	0.68 (0.31-1.50)	3.83 (0.86-17.13)	1.27 (0.48-3.40)	1.91 (0.84-4.35)	
P	579	-	0.44	0.42	0.23	0.34	0.079	0.63	0.12	0.41
NZ Maori OR (95% CI)		1	0.90 (0.24-3.37)	0.65 (0.38-1.10)	0.79 (0.40-1.53)	1.16 (0.57-2.35)	2.27 (1.02-5.03)	1.28 (0.67-2.42)	1.58 (0.92-2.70)	
P	486	-	0.88	0.11	0.47	0.68	0.044	0.45	0.098	0.17
NZ Pacific Island OR (95% CI)		1	-	0.85 (0.49-1.49)	0.87 (0.50-1.52)	1.04 (0.58-1.89)	2.54 (1.13-5.71)	1.60(0.86-2.98)	1.87 (1.07-3.26)	
P	514	-	-	0.57	0.62	0.89	0.024	0.14	0.027	0.043
ARIC OR (95% CI)		1	1.72 (0.79-3.75)	1.48 (0.66-3.30)	1.57 (0.61-4.02)	3.63 (1.25-10.52)	-	2.64 (0.76-9.18)	2.31 (0.66-8.00)	
P	6745	-	0.17	0.34	0.35	0.018	-	0.13	0.19	0.18
High Blood Pressure										
NZ Caucasian OR (95% CI)		1	2.55 (0.51-12.84)	0.85 (0.53-1.36)	1.69 (0.84-3.41)	0.75 (0.33-1.73)	4.94 (1.09-22.46)	1.42 (0.55-3.71)	2.21 (0.99-4.94)	
P	585	-	0.26	0.49	0.15	0.5	0.039	0.47	0.054	0.19
NZ Maori OR (95% CI)		1	0.83 (0.22-3.10)	0.63 (0.36-1.11)	1.01 (0.50-2.06)	1.39 (0.66-2.96)	2.49 (1.06-5.84)	1.14 (0.58-2.25)	1.51 (0.85-2.68)	
P	488	-	0.78	0.11	0.98	0.39	0.036	0.7	0.16	0.16
NZ Pacific Island OR (95% CI)		1	-	1.04 (0.58-1.85)	1.02 (0.57-1.82)	1.16 (0.63-2.14)	2.91 (1.26-6.74)	2.00 (1.05-3.80)	2.26 (1.27-4.04)	
P	524	-	-	0.89	0.94	0.63	0.013	0.035	0.006	0.015
ARIC OR (95% CI)		1	1.75 (0.80-3.82)	1.50 (0.67-3.34)	1.58 (0.62-4.05)	3.60 (1.24-10.42)	-	2.61 (0.75-9.06)	2.31 (0.67-8.02)	
P	7022	-	0.16	0.33	0.34	0.018	-	0.13	0.19	0.19

1 The 4.0-4.99 and 5+ groups were collapsed and used in logistic regression with the 5 other categorical groups – data reported only for the resultant ≥4 SSB/day group (in italics).

2 P_{Trend} was the P value associated with the single line SSB variable in regression analysis.

Supplemental Table 3 Association analysis of *SLC2A9* genotype and risk of gout

	Genotype (count, freq)[1]			Minor-allele frequency	Allelic OR[2] [95% CI], *P*	Allelic OR[2] [95% CI], *P*	Hardy-Weinberg P
	TT	CT	CC				
NZ European Caucasian							
Case	291 (0.728)	104 (0.260)	10 (0.013)	0.143	0.58 [0.42-0.81],	0.59 [0.37-0.94],	0.20
Control	105 (0.618)	55 (0.324)	10 (0.059)	0.221	0.001	0.027	0.44
NZ Maori							
Case	167 (0.903)	15 (0.081)	3 (0.016)	0.057	0.84 [0.50-1.42],	0.70 [0.32-1.54],	0.001
Control	264 (0.868)	39 (0.128)	1 (0.003)	0.067	0.52	0.37	0.73
NZ Pacific Island							
Case	303 (0.956)	14 (0.044)	0 (0.000)	0.022	0.56 [0.27-1.13],	0.35 [0.15-0.83],	0.69
Control	198 (0.925)	15 (0.070)	1 (0.005)	0.040	0.11	0.016	0.24
ARIC							
Case	105 (0.709)	39 (0.264)	4 (0.027)	0.159	0.67 [0.49-0.89],	0.64 [0.47-0.89],	0.87
Control	4200 (0.606)	2414 (0.348)	313 (0.045)	0.219	0.012	0.007	0.15

1 *rs11942223* genotyped in NZ sample sets; surrogate *rs6449173* (major allele A, minor allele C) – r^2 =1 with *rs11942223* in European Caucasian used in ARIC.

2 Unadjusted.

3 Adjusted by age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease and high blood pressure.

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Gout linked to sucrose in sugary drinks

We know that regularly consuming drinks sweetened with a processed sugar called high-fructose corn syrup can lead to gout. Now a study has linked gout with drinks containing another common sugar, called sucrose.

INTRODUCTION

'Sugar' can be a fairly loose term, covering several distinct types of this common sweetener. For most people, the differences don't matter too much. But for some people the type of sugar they consume is important – for example, if they're lactose intolerant (lactose is the sugar that's found in milk).

It might also be an important distinction for people with gout. Several studies have found that regularly consuming drinks sweetened with a sugar called high-fructose corn syrup (HFCS) can lead to gout.

But when research gets reported and re-reported in the media, important details can get lost, and HFCS can just become 'sugar'. With a complex condition such as gout it's important to be clear about what might cause problems.

WHAT DID THE RESEARCHERS HOPE TO FIND?

This study looked specifically at sucrose – what most people would think of as table sugar. Before HFCS became a cheaper (and arguably sweeter) alternative for food producers, sucrose was the most common type of sugar used to sweeten foods and drinks. In this study the researchers wanted to find out whether gout was more common in people who regularly consumed drinks sweetened with sucrose.

WHO WAS STUDIED?

This study was done in New Zealand. It included white New Zealanders of European descent as well as Maori people and Pacific Island people. This gave the researchers the chance to study whether sucrose-sweetened drinks had different effects in people of different ethnic backgrounds.

HOW WAS THE STUDY CONDUCTED?

The researchers recruited some people with gout from rheumatology clinics and community centres in New Zealand. They also recruited people who didn't have gout, as a comparison group.

To give the study more weight the researchers also looked at information on people who had taken part in another study on the risk of cardiovascular disease. (Enlarging studies in this way is quite a common research method.)

The people in both parts of the study answered questions about their lifestyle, including how many sucrose-sweetened drinks they generally consumed. In total the researchers looked at about 8,700 people.

WHAT DOES THE NEW STUDY SAY?

People who consumed a lot of sucrose-sweetened drinks were more likely to have gout than those who consumed none.

People of white European origin who consumed four of these drinks a day were more than six times more likely to have gout than those who drank none of them.

Interestingly, the link between sucrose-sweetened drinks and gout wasn't as strong in the other ethnic groups. Maori people who consumed four sucrose-sweetened drinks a day were about five times more likely to have gout than those who drank none. And Pacific Island people who consumed four of these drinks daily were two to three times more likely to have the condition.

HOW RELIABLE ARE THE FINDINGS?

The researchers did their best to adjust their figures for other factors that can be linked to gout, including people's age, weight, and sex, whether they had kidney disease or high blood pressure, and how much alcohol they drank.

But they didn't have all the information on people's diets that they needed to rule out other links. For example, the researchers think it's possible that people who consume a lot of sugary drinks may be more likely to have a comparatively poor general diet. So it's possible that the higher chance of having gout was down to more than just what they drank.

WHAT DOES THIS MEAN FOR ME?

At this stage this research doesn't prove that drinks sweetened with sucrose cause gout – just that people who drink them seem more likely to have the condition. It's a subtle distinction, but researchers have to be cautious when interpreting their results.

The link does appear to be strong, though. And, whether avoiding these drinks can help prevent gout or perhaps reduce the severity of the symptoms, it's one of many good reasons to stick to water when you're thirsty.

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From: Batt C, Phipps-Green AJ, Black MA, *et al*. Sugar-sweetened beverage consumption: a risk factor for prevalent gout with SLC2A9 genotype-specific effects on serum urate and risk of gout. *Ann Rheum Dis* 2014;73:2101–106. doi: 10.1136/annrheumdis-2013-203600LaySummary