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Article

Soft drink raises plasma uric acid in comparison to fruit: results from a four-week, randomized controlled trial

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Abstract: High fructose and sugar-sweetened soft drink (SSSD) intakes are associated with elevated blood uric acid concentrations and increased risk of gout and cardiovascular disease. Fruits are naturally high in fructose but their effect on cardiometabolic risk is unknown. We examined the effect on serum uric acid and cardiometabolic risk factors of consuming fructose from either fruit or SSSD in overweight adults. 48 healthy, overweight (BMI≥ 28 kg/m^2) men (n=21) and women (n=20) were randomised to either a fruit (n = 19) or SSSSD (n = 22) intervention for 4 weeks. The fruit group received 6 items of fresh and dried fruit per day and the SSSD group received 955ml of SSSD per day with treatments matched for energy and fructose content. Serum uric acid concentrations were significantly reduced in men in the fruit group compared to the SSSD group (difference 57.2 μmol/L [95% CI: 16.4, 98.0], p= 0.008) but there was no difference amongst women (1.3 μmol/L [95%CI: -9.5, 6.9], p= 0.295). There differences in weight change or other cardiometabolic risk factors. These findings suggest no need to restrict fruit intake in individuals with elevated serum uric acid concentrations, such as those with gout.

Keywords: urate; uric acid; cardiometabolic risk; fruit; sugar; sugar-sweetened soft drink; sugar-sweetened; beverage; dietary intake; dietary intervention; gout

1. Introduction

Fruit is high in micronutrients, antioxidants and dietary fibre, and has a relatively low energy density. Thus, it is not surprising that a greater intake of fruit is associated with a reduced risk of several chronic diseases [1]. Despite this apparent benefit, alongside table sugar, honey and high fructose corn syrup, fruit is also an important source of the sugar fructose, increasing intakes of which have been implicated in the simultaneous increase in obesity and its related diseases worldwide [2]. In particular, higher fructose intakes have been linked with hyperuricaemia [3-5] and risk of gout [6]. A meta-analysis of randomized controlled trials has recently confirmed that hypercaloric fructose feeding, in excess of 35% of energy intake or 215g per day, leads to an increase in serum uric acid [7].

Hyperuricemia (serum uric acid concentrations of >= 420 μmol/l in men and >= 360 μmol/l in women) is the most important risk factor for gout, which is a painful form of inflammatory arthritis characterised by the deposition of crystallized uric acid in joints [8]. Gout affects more men than women and its prevalence is also increasing, with gout-related hospital admissions between 1999 and 2009 rising by more than 5% per year in New Zealand and by more than 7% per year in England [9]. Hyperuricaemia has also been shown to be associated with increased cardiovascular disease risk and to predict the development of hypertension, myocardial infarction and stroke [8].

Whether or not the fructose from fruit plays a part in the etiology of hyperuricemia and gout is unclear. Generally, observational studies of varied design have indicated a reduced risk of incident gout [10] or experiencing gout attacks [11] with higher fruit consumption. Contrary to these findings, in an analysis of the Health Professionals Follow-up Study (n 46 393 men), higher fruit juice and fruit

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intakes were associated with an *increased* risk of incident gout after a 12 y follow-up [6]. Acute feeding studies in humans involving fruit or fruit juice have also produced mixed results, with an immediate rise in serum uric acid seen after consuming apples [12] or apple juice [13]; a lowered plasma urate level after cherry consumption, and no effect of grapes, strawberries or kiwifruit on plasma urate [14]. Finally, in a 6-week weight reduction trial, energy-restricted diets providing either a relatively high intake of fructose from fruit (50-70 g/d) or a low amount of fructose (< 10-20 g/d) led to significantly lowered serum uric acid concentrations, although no difference was seen between the diets and the reductions in serum uric acid could have been explained by the weight achieved in both interventions [15].

In the present study, we sought to compare the effect of consuming, in addition to an *ad libitum* diet, fructose from either whole fruit or sugar sweetened soft drink (SSSD) on plasma uric acid over four weeks, matched for both energy and fructose content. We hypothesized that due to its more favourable nutritional properties, fruit would have a more favourable effect on serum uric acid concentrations and other cardiometabolic risk factors than SSSD.

2. Materials and Methods

2.1. Subjects

Overweight men and women were recruited using a local newspaper advertisement and University of Otago, Dunedin, New Zealand email lists. Two-hundred and sixty-seven (267) respondents were assessed via an online survey or telephone interview, 48 of whom appeared to meet inclusion criteria: body mass index (BMI) ≥ 28 kg/m^2; aged between 20 and 75 y; no established diabetes, liver or kidney disease, gout or a history of other major chronic illnesses; no diagnosed mental disorders; not currently taking medications affecting blood pressure, blood lipids, blood glucose or mood/mental state; not currently pregnant or breastfeeding; no intolerance to study fruit or fructose; able to remain in Dunedin for the duration of the intervention period; and willing to consume either fruit or SSSD for four weeks. Of the 48 respondents invited to attend a screening visit to confirm their eligibility and obtain written informed consent, seven did not meet inclusion criteria. A total of 41 participants were randomized to consume either fruit (n = 19) or SSSD (n = 22). Following randomization, but prior to receiving their allocated beverage, three participants withdrew from the study. One participant in the fruit group moved away from Dunedin midway through the intervention and was lost to follow-up, resulting in a final total of 37 participants (n = 18 fruit; n = 19 SSSD) completing the study. This study was approved by University of Otago Human Ethics Committee (Ref: 12/197). The trial was registered with the Australian New Zealand Clinical Trials Registry: ACTRN12612000874819; http://www.anzctr.org.au.

2.2. Experimental protocol

Computer-generated block randomization was stratified by sex, performed before recruitment, and concealed from researchers in sealed, numbered envelopes. After establishing a participant's eligibility at the screening visit, and obtaining written informed consent, the next envelope was opened, and the participant's group allocation revealed. Due to the nature of the study the researcher responsible for delivering the interventions, and participants, could not be blinded to group allocation.

Approximately one to two weeks after their initial screening visit, participants attended a baseline visit at the Department of Human Nutrition Clinic, University of Otago, Dunedin, New Zealand. Between screening and baseline, and during the final week of the intervention, participants completed a 3-day weighed diet record, recorded on non-consecutive days and including a weekend day. Electronic scales were provided along with written instructions, and a trained researcher verbally explained how to complete the diet records. The researcher was available by email or telephone to answer questions that arose during completion of the diet record. Dietary intakes of macronutrients, fructose; vitamin C; potassium and dietary fiber were determined using Kaiculator dietary assessment software (University of Otago, Dunedin, NZ), which uses the New Zealand food

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composition database [16]. Participants were informed of their group allocation at baseline. Those randomized to fruit were provided with one Cavendish banana (128 g), three Braeburn or Jazz apples (149 g each) and two 14 g boxes of Sunmaid seedless raisins per day. Those assigned to soft drink were provided with one 355 mL can and one 600 mL bottle of sugar sweetened soft drink (either Coca-Cola or Sprite) per day. The interventions were matched for both energy (fruit: 1800 kJ/d; soft drink: 1767 kJ/d) and fructose (fruit: 51.8 g/d; soft drink: 51.7 g/d) content. Participants collected fruit and soft drink weekly, and were asked to record daily consumption in a log booklet, and to return empty beverage containers and any unconsumed fruit/beverages on a weekly basis.

Participants attended baseline and follow-up visits after an overnight (10-12 h) fast. Anthropometric measurements were made by one trained researcher, during which participants wore light clothing and no shoes. Weight to the nearest 0.1 kg, body fat percentage to the nearest 0.1% and BMI to the nearest 0.1 kg/m^2 were measured in duplicate using a calibrated Tanita Wedderburn bioimpedence analyzer. Height was measured using a Seca fixed stadiometer, and waist circumference was measured underneath clothing with a non-stretching anthropometric tape according to the International Society for the Advancement of Kinanthropometry protocols [17]. Height and waist circumference were measured to the nearest 0.1 cm in duplicate, or in triplicate if measurements differed by > 0.5 cm or > 1%, respectively. Seated blood pressure was measured after a 5-min rest in triplicate using an Omron digital blood pressure monitor in mm Hg. Fasting blood samples (8 mL) were drawn by a research nurse using ethylenediaminetetraacetic acid (EDTA)-treated vacutainers. Blood samples were kept at < 4ºC for approximately 1 h, then centrifuged at 1650 g for 15 min. Plasma samples were then frozen in polyethelene cryovials at -80ºC until analysis.

2.3. Laboratory analysis

Plasma insulin was measured using a specific electrochemiluminescence immunoassay for the Elecsys analyzer (Roche Diagnostics, Mannheim, Germany), with a coefficient of variation (CV) of 1.1%. Plasma uric acid (CV: 0.9%), total cholesterol (CV: 1.0%), triglyceride (CV: 0.9%) and glucose (CV: 0.8%) concentrations were measured enzymatically with kits and calibrators supplied by Roche Diagnostics on a Cobas Mira analyzer (Roche Diagnostics). High-density lipoprotein (CV: 1.5%) was measured in the supernatant after precipitation of apolipoprotein B-containing lipoproteins with phosphotungstate/magnesium chloride solution [18]. Low-density lipoprotein (LDL) was calculated using the Friedewald equation [19]. High sensitivity C-reactive protein was measured using a latex-enhanced immunoturbidimetric method (Roche Diagnostics) with a CV of 6.4%.

2.4. Statistical analysis

Using an estimated change in mean plasma uric acid of 50 μmol/L (SD of 75 μmol/L) and a correlation between repeated measures of 0.75[20], it was estimated that 15 participants per group would be required for analysis of covariance (ANCOVA) with one baseline and one follow-up measurement, at 80% power and alpha = 0.05. To allow for attrition, n = 40 was the overall recruitment goal. Change in serum uric acid, body composition and clinical measures from baseline to week 4 were compared within treatment groups using Students t-tests. Data were checked for normality and equal variance, with non-normal data compared using Mann-Whitney tests, and data with unequal variance compared using Welch's t-tests. The effect of treatment on serum uric acid, body composition and clinical measures was analyzed by ANCOVA with baseline values as a covariate. Other participant characteristics likely to affect outcomes (baseline BMI and age) and a potential interaction effect (sex by group) were included as covariates individually, and those with a P-value <0.25 were retained in the final model. All analyses were conducted using Stata 11.1 (Stata Corporation 2010, College Station, Texas, United States), and a two-sided 0.05 level of significance was used in all cases.

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3. Results

Table 1 summarizes baseline characteristics of participants randomized to treatment. Thirty-seven participants completed the study, 19 in the fruit group and 18 in the soft drink group. Nine women completed each intervention. Participants had a mean age of 33.2 years and 54% were obese with mean BMI of 31.4 kg/m^2. The prevalence of hyperuricaemia was 43% in men and 20% in women.

Table 1. Baseline demographic and clinical measures of participants randomized to fruit or soft drink[1]

	Fruit (n 19)	**SSSD (n 22)**
Female, n (%)	9 (47.4)	11 (50.0)
Age, years	34.7 (12.5)	33.2 (12.8)
Weight, kg	91.0 (21.4)	94.5 (15.2)
Height, cm	170.8 (9.4)	170.8 (9.9)
BMI, kg/m^2	31.0 (5.3)	32.2 (3.4)
Waist circumference, cm	97.3 (17.2)	99.4 (11.4)
Body fat, %	34.4 (8.4)	35.7 (7.6)
Self-reported physical activity, n (%)		
Inactive	3 (15.8)	4 (20.0)
Moderately active	6 (31.6)	6 (30.0)
Active	10 (52.6)	10 (50.0)
Plasma uric acid, μmol/L	334.2 (66.5)	385.5 (79.7)
Systolic blood pressure, mm Hg	122 (15)	120 (13)
Diastolic blood pressure, mm Hg	70 (11)	69 (9)
Triglycerides, mmol/L	1.29 (0.65)	1.19 (0.45)
LDL-cholesterol, mmol/L	2.93 (0.97)	3.19 (0.89)
HDL-cholesterol, mmol/L	1.26 (0.22)	1.32 (0.37)
Total cholesterol, mmol/L	4.78 (1.10)	5.05 (0.97)
Plasma insulin, mIU/ml	12.67 (10.32)	11.61 (4.70)
Plasma glucose, mmol/L	5.44 (0.60)	5.29 (0.37)

[1]Data are means (SD) unless otherwise indicated; SSSD = sugar-sweetened soft drink

There were no significant differences in total energy, carbohydrate, total sugars and glucose intakes between treatments (**Table 2**). However, sucrose intake was higher in the SSSD group, and fructose intake was higher in the fruit group amongst women only. The fruit group also consumed significantly more dietary fiber during treatment.

153 **Table 2.** Change in dietary intake from baseline to week 4 and difference between treatments

	Fruit[1]		SSSD[1]		Overall difference between the treatments[2]	
		within treatment P-value		within treatment P-value		between treatment P-value
Energy (kJ)						
Males	-879 (6639)	0.7192	218 (3592)	0.8683	-1031 (-3899, 1837)	0.467
Females	930 (1461)	0.1148	891 (2723)	0.3555	-93 (-2881, 2694)	0.946
Carbohydrate (g)						
Males	41 (148)	0.4629	14 (162)	0.8197	-11 (-89, 65)	0.754
Females	48 (42)	0.0148	36 (88)	0.2605	-2 (-76, 72)	0.959
Total sugars (g)						
Males	52 (80)	0.1052	64 (63)	0.024	-40 (-83, 3)	0.068
Females	52 (34)	0.0033	51 (63)	0.0407	-13 (-54, 27)	0.506
Sucrose (g)						
Males	-4 (36)	0.7471	32 (43)	0.073	-54 (-79, -29)	<0.001
Females	0 (23)	0.9577	32 (31)	0.0138	-34 (-57, -10)	0.006
Fructose (g)						
Males	29 (16)	0.0012	21 (19)	0.019	8 (-3, 20)	0.139
Females	31 (7)	<0.001	11 (15)	0.0706	12 (0, 24)	0.044
Glucose (g)						
Males	22 (5)	0.003	20 (6)	0.0143	3 (-4, 11)	0.538
Females	23 (3)	<0.001	9 (5)	0.1107	5 (-5, 15)	0.33
Vitamin C (mg)						
Males	-6 (64)	0.8073	63 (269)	0.5305	-68 (-212, 76)	0.339
Females	28 (61)	0.2378	-25 (91)	0.4253	55 (-85, 195)	0.426
Dietary fiber (g)						
Males	-2 (18)	0.817	-7 (11)	0.1272	9 (1, 16)	0.004
Females	6 (5)	0.0066	-3 (8)	0.3982	12 (5, 19)	0.002
Alcohol (g)						
Males	-6 (10)	0.0989	9 (11)	0.0568	-11 (-23, 0)	0.054
Females	3 (12)	0.5799	6 (13)	0.2467	-4 (-14, 7)	0.459

154 [1] Values are mean change (SD); P-values for significance of changes were derived by paired Students t-tests; [2] ANCOVA was used to obtain estimate with adjustment for
155 baseline values with a sex by treatment interaction effect; SSSD = sugar-sweetened soft drink

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On average participants in the fruit group consumed 92% of the fruit provided (5.5 items per day) and participants in the soft drink group consumed 94% of the beverages provided (900 ml per day).

There were no overall significant differences in the effects of treatment on uric acid concentrations, body composition or other cardiometabolic variables (**Table 3**). However, there was a significant sex by treatment interaction for serum uric acid. Amongst men uric acid was 57 μmol/L higher in those in the SSSD group (P=0.008) but there was no effect in women. In a multivariate adjusted model SSSD treatment (P=0.001), baseline BMI (P<0.001) and increased alcohol intake (P=0.032) were associated with higher uric acid while female sex (P=0.002) was associated with lower uric acid (**Table 4**).

Table 3. Change in body composition and clinical measures from baseline to week 4 and difference between treatments

	Fruit[1]		SSSD[1]		Overall difference between treatments[2]	
		Within treatment P-value		Within treatment P-value		Between treatment P-value
Weight, kg	0.03 (1.02)	0.909	0.24 (1.67)	0.544	0.26 (-0.67, 1.18)	0.579
Waist circumference, cm	0.72 (1.83)	0.114	1.48 (1.62)	<0.001	0.79 (-0.33, 1.91)	0.161
Body fat, %	-0.18 (1.06)	0.474	0.27 (1.28)	0.364	0.46 (-0.32, 1.24)	0.235
Plasma uric acid (μmol/L)						
All participants	-6.00 (37.75)	0.509	4.37 (49.15)	0.703	14.09 (-17.77, 45.96)	0.375
Males	-14.67 (31.89)	0.205	22.80 (39.42)	0.101	57.17 (16.35, 98.00)[3]	0.008
Females	2.67 (42.92)	0.857	-16.11 (52.82)	0.387	-1.33 (-6.88, 9.53)[3]	0.295
Systolic blood pressure, mm Hg	2.17 (9.54)	0.349	0.63 (6.62)	0.682	-2.18 (-7.16, 2.80)	0.381
Diastolic blood pressure, mm Hg	4.11 (11.50)	0.148	0.32 (8.33)	0.871	-4.96 (-10.84, 0.92)	0.272
Triglycerides, mmol/L	0.04 (0.36)	0.679	0.12 (0.10)	0.242	0.07 (-0.18, 0.32)	0.571
LDL-cholesterol, mmol/L	0.03 (0.36)	0.764	0.08 (0.42)	0.418	0.08 (-0.18, 0.34)	0.526
HDL-cholesterol, mmol/L	-0.04 (0.17)	0.388	-0.04 (0.15)	0.224	0.004 (-0.08, 0.09)	0.932
Total cholesterol, mmol/L	0.01 (0.41)	0.945	0.09 (0.53)	0.468	0.12 (-0.19, 0.43)	0.438
Plasma insulin, mIU/ml	0.02 (0.71)	0.990	1.94 (5.97)	0.173	1.54 (-2.48, 5.56)	0.443
Fasting glucose, mmol/L	0.02 (0.39)	0.865	0.02 (0.32)	0.769	-0.05 (-0.27, 0.17)	0.632
CRP, mg/L	0.74 (0.39)	0.073	0.21 (0.69)	0.771	0.10 (-1.54, 1.74)	0.902

[1]Values are mean change (SD); P-values for significance of changes were derived by paired Students t-tests; [2]ANCOVA was used to obtain estimate with adjustment for baseline values; [3]ANCOVA was used to obtain estimate with adjustment for baseline uric acid and an interaction effect between treatment and sex; SSSD = sugar-sweetened soft drink

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Table 4. Multivariate analysis of covariance of the effect of treatment and confounding variables on uric acid at week 4

	β (SE)	P-value	R^2
Model 1		<0.0001	0.756
SSSD	14.10 (15.70)	0.375	
Model 2		<0.0001	0.817
SSSD	57.17 (20.04)	0.008	
Female	-20.61 (24.64)	0.409	
Model 3		<0.0001	0.871
SSSD	65.50 (17.28)	0.001	
Female	-38.21 (21.63)	0.087	
Baseline BMI	5.20 (1.45)	0.001	
Model 4		<0.0001	0.893
SSSD	58.3 (15.5)	0.001	
Female	-65.0 (19.5)	0.002	
Baseline BMI	6.7 (1.3)	<0.001	
Alcohol intake (g)	1.0 (0.5)	0.032	

Model 1 covariate = baseline uric acid; Model 2 covariates = baseline uric acid, sex by group interaction term; Model 3 covariates = baseline uric acid, sex by group interaction term, baseline BMI; Model 4 covariates = baseline uric acid, sex by group interaction term, baseline BMI, change in alcohol intake during intervention period; SSSD = sugar-sweetened soft drink.

4. Discussion

In this 4-week parallel intervention study, we found that while SSSD resulted in a non-significant rise in plasma uric acid levels among men, intake of an equivalent amount of fruit did not, with the difference between treatments being statistically significant. Despite the effect of SSSD on uric acid there was no evidence of an effect on other cardiometabolic risk factors. Although fructose was likely the causal factor behind the observed rise in uric acid, our study has revealed that fructose intake from whole fruit appears to be handled differently by the body than that from SSSDs. This finding is important as fruit provides many beneficial dietary components, and restriction of fruit intake due to its high fructose content would therefore reduce these components in the diet unnecessarily.

A particular strength of this study is that a physiologically relevant quantity of fructose (~50 g/d) was provided to participants in whole fruit or SSSD, factors often neglected in studies of this kind [7,21]. While intake of both fruit (6 items) and soft drink (1 liter, equivalent to 3 x 12 oz cans) could be considered at the upper end of the normal range, the amount of fructose they provided was lower than that consumed on a daily basis by the average American (75 g) [22]. An additional strength of the current study is that the difference in plasma uric acid of 57 μmol/L between treatments amongst males is not only statistically significant, but is also large enough to be of clinical importance in the etiology of gout. In the Normative Aging Study, where a cohort of 2,046 initially healthy men was followed for 14.9 y, the yearly incidence of gout was more than four times higher in the group with a prior mean serum uric acid level of 384 μmol/L compared with those with a mean of 443 μmol/L: a 59 μmol/L difference [23].

While this was not a mechanistic study, potential reasons for the difference in uric acid between male groups should be explored. Firstly, it is not surprising that no difference in plasma uric acid was seen between female intervention groups, as high plasma uric acid levels and gout are characteristically more prevalent among men [8]. During the intervention period, fiber intake was significantly higher among men and women consuming fruit (by 9-12 g/d), while total energy intake

appeared higher (~1000 kJ/d) among males consuming soft drinks. Thus, it is possible that fruit, due to its high fiber content, was more satiating and therefore conferred a reduced overall energy intake among men, leading to a lower plasma uric acid level. If continued longer, this difference in energy intake between male groups may have resulted in a significant difference in weight gain. The intrinsic fiber content of fruit may also have slowed the digestion rate of fructose, producing portal fructose concentrations that did not exceed the capacity of the liver to metabolize fructose via routes other than those resulting in uric acid production [24,25]. In addition, the fruit was consumed on average over 4 occasions per day (1.5 items/occasion) compared with 1.5 occasions for soft drink, further reducing the bolus dose of fructose consumed. When fructose is consumed in conjunction with glucose, as is the case in sugar-sweetened soft drinks, its absorption is enhanced [24] and it is unable to be metabolized down the glycogenic pathway, which is occupied by glucose [26]. A further possibility is that the higher vitamin C content of fruit reduced the effect of fructose on plasma uric acid levels. In a meta-analysis of 13 vitamin C supplementation studies reporting serum uric acid levels, a statistically significant mean reduction in serum uric acid of 21 μmol/L was observed with a median supplementary intake of 500 mg/d vitamin C [27]. In this study, however, fruits with low vitamin C contents were chosen, and the difference in vitamin C intakes, although not significantly different, appeared higher in men receiving the SSSD treatment. Alcohol consumption is also associated with increased serum uric acid [28]. Alcohol appears to decrease urate excretion and increase synthesis. In addition, beer has a high purine (a substrate for uric acid synthesis) content and this may augment the uric acid raising effects of alcohol [29]. Our findings show that alcohol had a modest effect on raising uric acid concentrations in addition to the effect of treatment.

Several factors limit the interpretation of the current study. While it is important to note that a meaningful difference in plasma uric acid in men was observed *without* an evidence of a difference in weight gain, this study was underpowered to detect such a difference. In addition, it is possible that the intervention was not of sufficient duration to see an effect of soft drink consumption on other cardiometabolic risk factors also thought to be elevated by high fructose intakes and associated with hyperuricaemia [2,24]. A further, appropriately powered, longer-term study in overweight men is therefore warranted.

Although not statistically significantly different, the male SSSD consumers had a greater overall increase in intake of energy, alcohol and sucrose than those consuming fruit. Although it may be argued that these factors lead to the higher plasma uric acid levels observed in the SSSD group our multivariate analysis did not find that energy intake predicted uric acid. Higher alcohol amongst the SSSD consumers made a small contribution to the effect of treatment on serum uric acid whereas differences in sucrose intake did not explain the effect on uric acid. Nevertheless, our aim was to compare the effect of consuming fructose in the form of whole fruit or SSSD on plasma uric acid in addition to an *ad libitum* diet. We hypothesized that although the fruit and SSSD we provided were matched for both energy and fructose content, the beneficial nutritional components in fruit, including factors such as its greater satiating effect, would prevent an increase in raise plasma uric acid levels in comparison to soft drink. Therefore, it is reasonable to conclude from the current study that while a relatively high consumption of SSSD results in increased plasma uric acid levels among overweight men, replacing soft drink with an equivalent amount of fruit will not. Further our findings do not provide any evidence that fruit intake should be limited.

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References

1. Boeing, H.; Bechthold, A.; Bub, A.; Ellinger, S.; Haller, D.; Kroke, A.; Leschik-Bonnet, E.; Muller, M.J.; Oberritter, H.; Schulze, M., *et al.* Critical review: vegetables and fruit in the prevention of chronic diseases. *European journal of nutrition* **2012**, *51*, 637-663.
2. Johnson, R.J.; Segal, M.S.; Sautin, Y.; Nakagawa, T.; Feig, D.I.; Kang, D.H.; Gersch, M.S.; Benner, S.; Sanchez-Lozada, L.G. 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*, 899-906.
3. Choi, J.W.J.; Ford, E.S.; Gao, X.; Choi, H.K. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis and rheumatism* **2008**, *59*, 109-116.
4. Gao, X.; Qi, L.; Qiao, N.; Choi, H.K.; Curhan, G.; Tucker, K.L.; Ascherio, A. Intake of added sugar and sugar-sweetened drink and serum uric acid concentration in US men and women. *Hypertension* **2007**, *50*, 306-312.
5. Lin, W.T.; Huang, H.L.; Huang, M.C.; Chan, T.F.; Ciou, S.Y.; Lee, C.Y.; Chiu, Y.W.; Duh, T.H.; Lin, P.L.; Wang, T.N., *et al.* Effects on uric acid, body mass index and blood pressure in adolescents of consuming beverages sweetened with high-fructose corn syrup. *International Journal of Obesity* **2013**, *37*, 532-539.
6. Choi, H.K.; Curhan, G. Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ (Clinical research ed)* **2008**, *336*, 309-312.
7. Wang, D.D.; Sievenpiper, J.L.; de Souza, R.J.; Chiavaroli, L.; Ha, V.; Cozma, A.I.; Mirrahimi, A.; Yu, M.E.; Carleton, A.J.; Di Buono, M., *et al.* The effects of fructose intake on serum uric acid vary among controlled dietary trials. *The Journal of nutrition* **2012**, *142*, 916-923.
8. Smith, E.U.R.; Diaz-Torne, C.; Perez-Ruiz, F.; March, L.M. Epidemiology of gout: an update. *Best practice & research Clinical rheumatology* **2010**, *24*, 811-827.
9. Robinson, P.C.; Merriman, T.R.; Herbison, P.; Highton, J. Hospital admissions associated with gout and their comorbidities in New Zealand and England 1999-2009. *Rheumatology (Oxford, England)* **2013**, *52*, 118-126.
10. Tsai, Y.-T.; Liu, J.-P.; Tu, Y.-K.; Lee, M.-S.; Chen, P.-R.; Hsu, H.-C.; Chen, M.-F.; Chien, K.-L. Relationship between dietary patterns and serum uric acid concentrations among ethnic Chinese adults in Taiwan. *Asia Pacific journal of clinical nutrition* **2012**, *21*, 263-270.
11. Zhang, Y.; Neogi, T.; Chen, C.; Chaisson, C.; Hunter, D.J.; Choi, H.K. Cherry consumption and decreased risk of recurrent gout attacks. *Arthritis and rheumatism* **2012**, *64*, 4004-4011.
12. Lotito, S.B.; Frei, B. The increase in human plasma antioxidant capacity after apple consumption is due to the metabolic effect of fructose on urate, not apple-derived antioxidant flavonoids. *Free Radic Biol Med* **2004**, *37*, 251-258.
13. Godycki-Cwirko, M.; Krol, M.; Krol, B.; Zwolinska, A.; Kolodziejczyk, K.; Kasielski, M.; Padula, G.; Grębocki, J.; Kazimierska, P.; Miatkowski, M., *et al.* Uric Acid but Not Apple Polyphenols Is Responsible for the Rise of Plasma Antioxidant Activity after Apple Juice Consumption in Healthy Subjects. *Journal of the American College of Nutrition* **2010**, *29*, 397-406.
14. Jacob, R.A.; Spinozzi, G.M.; Simon, V.A.; Kelley, D.S.; Prior, R.L.; Hess-Pierce, B.; Kader, A.A. Consumption of cherries lowers plasma urate in healthy women. *The Journal of nutrition* **2003**, *133*, 1826-1829.
15. Madero, M.; Arriaga, J.C.; Jalal, D.; Rivard, C.; McFann, K.; Perez-Mendez, O.; Vazquez, A.; Ruiz, A.; Lanaspa, M.A.; Jimenez, C.R., *et al.* The effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters: a randomized controlled trial. *Metabolism* **2011**, *60*, 1551-1559.

16. Plant & Food Research; Ministry of Health (NZ). New Zealand Food Composition Database. Ministry of Health (NZ) and the New Zealand Institute for Plant and Food Research: 2013.
17. Stewart, A.; Marfell-Jones, M.; Olds, T.; Ridder, H. *International standards for anthropometric assessment*. ISAK: Lower Hutt, New Zealand, 2011.
18. Assmann, G.; Schriewer, H.; Schmitz, G.; Hagele, E.O. Quantification of high-density-lipoprotein cholesterol by precipitation with phosphotungstic acid/MgCl2. *Clinical chemistry* **1983**, *29*, 2026-2030.
19. Friedewald, W.T.; Levy, R.I.; Fredrickson, D.S. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry* **1972**, *18*, 499-502.
20. McAuley, K.A.; Smith, K.J.; Taylor, R.W.; McLay, R.T.; Williams, S.M.; Mann, J.I. Long-term effects of popular dietary approaches on weight loss and features of insulin resistance. *Int J Obes* **2006**, *30*, 342-349.
21. White, J.S. Challenging the fructose hypothesis: new perspectives on fructose consumption and metabolism. *Advances in nutrition (Bethesda, Md)* **2013**, *4*, 246-256.
22. Vos, M.B.; Kimmons, J.E.; Gillespie, C.; Welsh, J.; Blanck, H.M. Dietary fructose consumption among US children and adults: the Third National Health and Nutrition Examination Survey. *Medscape journal of medicine* **2008**, *10*, 160.
23. Campion, E.W.; Glynn, R.J.; DeLabry, L.O. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *The American journal of medicine* **1987**, *82*, 421-426.
24. Tappy, L.; Le, K.A. Metabolic effects of fructose and the worldwide increase in obesity. *Physiological reviews* **2010**, *90*, 23-46.
25. Ludwig, D.S. Examining the health effects of fructose. *JAMA* **2013**, *310*, 33-34.
26. Hudgins, L.C.; Parker, T.S.; Levine, D.M.; Hellerstein, M.K. A dual sugar challenge test for lipogenic sensitivity to dietary fructose. *The Journal of clinical endocrinology and metabolism* **2011**, *96*, 861-868.
27. Juraschek, S.P.; Miller, E.R., 3rd; Gelber, A.C. Effect of oral vitamin C supplementation on serum uric acid: a meta-analysis of randomized controlled trials. *Arthritis care & research (Hoboken)* **2011**, *63*, 1295-1306.
28. Choi, H.K.; Curhan, G. Beer, liquor, and wine consumption and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis and rheumatism* **2004**, *51*, 1023-1029.
29. Gibson, T.; Rodgers, A.V.; Simmonds, H.A.; Toseland, P. Beer drinking and its effect on uric acid. *British journal of rheumatology* **1984**, *23*, 203-209.