

Association between Sugar-Sweetened Beverage Consumption and the Risk of Gout: A Meta-Analysis

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Objective. The aim of this study was to analyze published data for an association between consumption of sugar sweetened beverages (SSBs) and the development of gout. **Methods.** We performed a meta-analysis to examine the highest and lowest categories of SSB consumption in relation to risk of gout. **Results.** Three studies including 2,606 gout patients among 134,008 participants were included. Meta-analysis revealed a significant association between SSB consumption and gout risk (relative risk [RR]=1.986, 95% confidence interval [CI]=1.447~2.725, $p=2.2 \times 10^{-5}$). Stratification by ethnicity showed a significant association between SSB consumption and gout risk in ethnic Europeans, but not in Polynesians (RR=2.110, 95% CI=1.470~2.725, $p=5.1 \times 10^{-5}$; RR=1.624, 95% CI=0.842~3.135, $p=0.148$, respectively). SSB consumption and gout risk were associated in original data and imputed data, for both men and women, regardless of data type and sex. The association between the highest SSB consumption group and gout was stronger than the association between the middle group and gout, indicating a dose-response gradient (RR=1.986, 95% CI=1.447~2.725, $p<2.2 \times 10^{-5}$ vs. RR=1.260, 95% CI=1.043~1.522, $p<0.016$). **Conclusion.** This meta-analysis of 134,008 participants demonstrates that SSB consumption is associated with an elevated risk of gout development, particularly in the ethnic European population. Available evidence indicates a dose-response gradient of the relationship between SSB consumption and gout risk. (*J Rheum Dis* 2016;23:304-310)

Key Words. Sugar-sweetened beverages, Gout, Risk

INTRODUCTION

Gout is an inflammatory disorder characterized by hyperuricemia and urate crystal deposition, resulting in episodic gout flares, gouty arthropathy, tophi, and urolithiasis [1]. The primary cause of gout is hyperuricemia due to excess urate production or impaired renal excretion of uric acid. Increased levels of hyperuricemia correlate with greater incidence of gouty arthritis and uric acid urolithiasis [2].

Sugar-sweetened beverages (SSBs) are any beverage with added sugar, which includes soft drinks (soda), fruit drinks, iced tea, and energy and vitamin water drinks. Consumption of SSBs continues to increase worldwide due to the influence of Western lifestyle factors, and is a worldwide health concern [3]. SSBs contain low levels of

purine, but they include large amounts of fructose, the only carbohydrate known to increase uric acid levels [4]. Fructose induces uric acid production by increasing degradation of adenosine triphosphate (ATP) to adenosine monophosphate (AMP), which, in turn, induces urate production as a uric acid precursor in the liver [5].

The substantial increase in SSB consumption is associated with hyperuricemia [6], which is recognized as the most important risk factor for gout. Several studies investigated whether SSB consumption is associated with gout development [7-9]. However, the role of SSBs in the development of gout has not been quantitatively reviewed. The aim of the present study was to perform a meta-analysis to summarize the evidence for a relationship between SSB consumption and gout development [10-12].

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MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies investigating the impact of SSB intake on the development of gout using PubMed, Embase, and Cochrane databases to identify articles (up to February 2016). The following key words and subject terms were used: “sugar-sweetened beverages” (sugar-sweetened OR soda OR sugar OR soft drinks OR fructose) AND gout. All references cited by articles identified using the search terms were also reviewed to identify additional studies not indexed by the above-mentioned electronic databases. No restrictions were placed on language, ethnicity, or geographical area. Studies were considered eligible if they met the following criteria: (i) examined the association between SSB consumption and gout incidence, (ii) were original epidemiological studies with a prospective or cross-sectional design, (iii) reported the relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) for highest versus lowest category of SSB intake. The following studies were excluded: (i) reports containing overlapping data, and (ii) reviews and case reports. Data on methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus. The meta-analysis was conducted in accordance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [13]. The following information was extracted from each study: first author, year of publication, country where the study was performed, ethnicity of the study population, study design, number of cases and total, age, sex, disease duration, SSB consumption categories, follow-up period, RRs or ORs with 95% CIs for highest, middle, and lowest categories of SSB consumption, and variables used in multivariate adjustments. If the OR was reported, we calculated the RR using a statistical formula [14]. The quality of each study was scored based on the Newcastle–Ottawa Scale [15]. Studies were evaluated based on three domains as follows: the selection of study groups (0~4 points), comparability of groups (0~2 points), and ascertainment of exposure (0~3 points). The highest score is 9, and scores ranging from 6~9 range were considered to indicate high methodological quality.

Evaluation of statistical associations

We performed a meta-analysis on the highest versus

lowest SSB intake groups. Point estimates of RR and 95% CI were estimated for each study. Any variations and heterogeneity within and between studies were assessed using Cochrane’s Q-statistics [15], and the heterogeneity test was used to assess the null hypothesis that all studies evaluated the same effect. When the significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies, the random effects model was used for meta-analysis. The random effects model assumes that different studies may estimate different underlying effects and considers both intra- and inter-study variations [16]. In the present study, we used the random effects model because heterogeneity was present in most analyses. The effect of heterogeneity was quantified by using the formula: $I^2 = 100\% \times (Q - df) / Q$ [17]. I^2 provides a measure of the degree of inconsistency between studies and determines whether the percentage total variation across studies is due to heterogeneity rather than chance. I^2 values range between 0% and 100%, and I^2 values of 25%, 50%, and 75% are referred to as low, moderate, and high estimates, respectively [18]. Statistical calculations were performed using a Comprehensive Meta-Analysis computer program version 2.0 (Biosta, Englewood, NJ, USA).

Evaluation of subgroup analysis and publication bias

We performed subgroup analysis according to ethnicity, study design, data type, sex, and category, and a sensitivity test was performed to assess the influence of each individual study on the pooled odds ratio by omitting each study individually. Funnel plots are often used to detect publication bias, but require studies with different sample sizes that involve subjective judgments. Therefore, we evaluated publication bias using Egger’s linear regression test [19], which measures funnel plot asymmetry on a natural logarithm scale of ORs.

RESULTS

Studies included in the meta-analysis

Eight hundred and eighty articles were identified using electronic databases and manual searches, and 4 were selected for a full-text review on the basis of the title and abstract details [7-9,20]. One study of the four studies was excluded due to a repeated publication with same population [20]. Thus, three studies were included [7-9] (Figure 1). One of the eligible studies contained data on four different groups, and these were treated independently [7]. Thus, 6 comparisons including 3 cohort

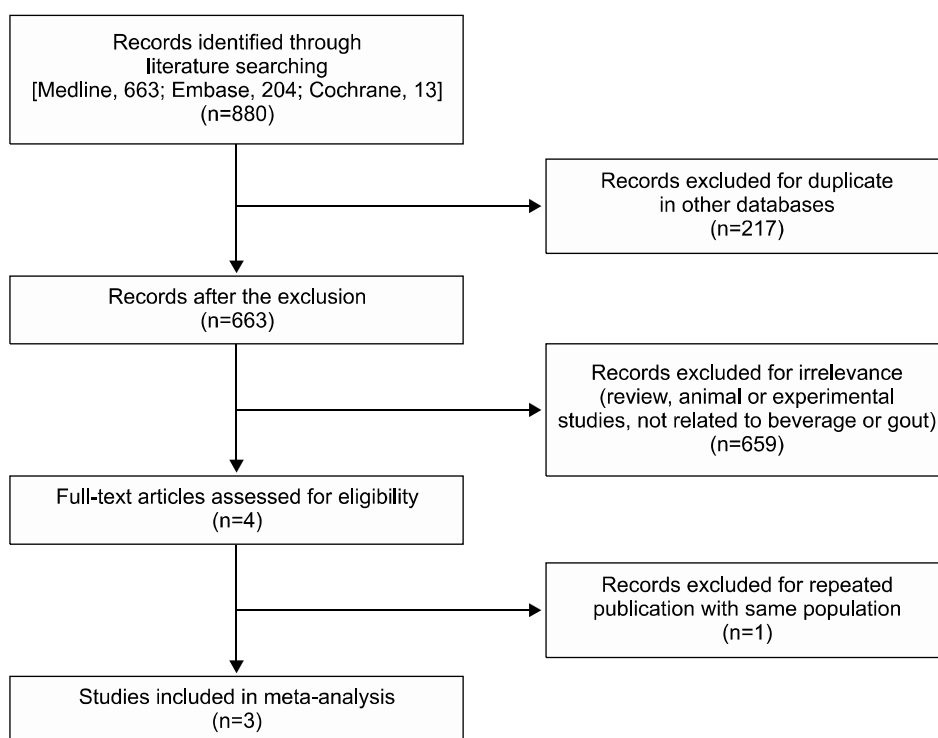


Figure 1. Flow chart for the study selection.

and 3 cross-case-control studies were considered in the meta-analysis, which included 2,606 gout patients among 134,008 participants, consisting of 4 Caucasian and 2 Polynesian populations (Table 1). Study quality was 8 for all included studies, indicating a high study quality. Definitions of the highest, middle, and lowest SSB intake in each study are as follows: ≥ 5.0 servings/d, 2.0 to 2.99 servings/d, 0 serving/d in Batt et al. study [7], and ≥ 2 servings/d, 5 to 6 servings/wk, < 1 serving/mo, respectively in Choi et al. study 2010 [8] and Choi et al. study 2008 [9]. Table 2 summarizes selected characteristics of the included studies.

1) Association between SSB consumption and gout risk

Meta-analysis of 6 studies revealed a significant association between SSB consumption and gout risk ($RR=1.986$, $95\% CI=1.447 \sim 2.725$, $p=2.2 \times 10^{-5}$) (Table 2, Figure 2). Stratification by ethnicity showed a significant association between SSB consumption and gout risk in Caucasians, but not in Polynesians ($RR=2.110$, $95\% CI=1.470 \sim 2.725$, $p=5.1 \times 10^{-5}$; $RR=1.624$, $95\% CI=0.842 \sim 3.135$, $p=0.148$, respectively) (Table 2, Figure 2). Meta-analysis showed a significant association between SSB consumption and gout risk in cohort studies, but not in cross-sectional studies (Table 2). However, meta-analysis by data type and sex showed a significant

association between SSB consumption and gout risk in original data and imputed data, and in both men and women (Table 2).

2) Dose-response association between SSB consumption and gout risk

To estimate the dose-response relationship, we measured the association between the middle group of SSB consumption and gout incidence as well as the association between the highest group of SSB consumption and gout incidence. The association between the highest group and gout was stronger than the association between the middle group and gout, indicating a dose-response gradient ($RR=1.986$, $95\% CI=1.447 \sim 2.725$, $p=2.2 \times 10^{-5}$ vs. $RR=1.260$, $95\% CI=1.043 \sim 1.522$, $p=0.016$) (Table 2). Thus, increased SSB consumption and gout risk followed a dose-response relationship.

Heterogeneity, sensitivity test, and publication bias

Between-study heterogeneities were not found during meta-analyses of SSB consumption and gout risk (Table 2). Sensitivity analysis showed that no individual study significantly affected the results, indicating robust results of this meta-analysis. Publication bias results in a disproportionate number of positive studies, and poses a problem for meta-analyses. Egger's regression test showed no evidence

Table 1. Characteristics of the individual studies included in the meta-analysis

Study [Ref]	Country	Ethnicity	Subjects' age (yr), range	Sex (%), male	Study period	Study design	Case (n)	Total (n)	RR (95% CI) for highest vs. lowest intakes	Adjustment for confounders	Study quality
Batt-1, 2014 [7]	USA	Caucasian	23 ~ 94	77.8	2006 ~ 2011	Cross-sectional	412	592	2.38* (0.64 ~ 8.84), P _{trend} = 0.020	Age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease	8
Batt-2, 2014 [7]	USA	Polynesian	23 ~ 81	80.3	2006 ~ 2011	Cross-sectional	190	502	1.44* (0.59 ~ 3.53), P _{trend} = 0.011	Age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease	8
Batt-3, 2014 [7]	USA	Polynesian	18 ~ 81	87.9	2006 ~ 2011	Cross-sectional	323	540	2.17* (0.98 ~ 4.77), P _{trend} = 0.050	Age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease	8
Batt-4, 2014 [7]	USA	Caucasian	45 ~ 65	75.0	ND	Cohort	148	7,075	2.31* (0.65 ~ 8.19), P _{trend} = 0.026	Age, sex, BMI, alcohol (continuous variable), fruit intake (continuous variable), kidney disease, high blood pressure and relatedness	8
Choi, 2010 [8]	USA	Caucasian [†]	30 ~ 55	0	1984 ~ 2006	Cohort	778	78,906	1.85 (1.08 ~ 3.16), P _{trend} = 0.002	Age, total energy intake, BMI, menopause status, use of hormonal therapy, diuretic use, history of hypertension, and intake of alcohol, total meats, seafood, dairy products, total vitamin C, SSB, and the beverages	8
Choi, 2008 [9]	Canada	Caucasian [†]	40 ~ 75	100	1986 ~ 1998	Cohort	755	46,393	2.39 (1.34 ~ 4.26), P _{trend} < 0.001	Age, total energy intake, body mass index, diuretic use, history of hypertension, and history of chronic renal failure; intake of alcohol, total meats, seafood, purine rich vegetables, dairy foods, and total vitamin C; and sweetened soft drinks, diet soft drinks, sweetened cola, and other sweetened soft drinks	8

Ref : Reference, RR: relative risk, CI: confidence interval, SSB: sugar-sweetened beverage, ND: not determined, BMI: body mass index. *Odds ratio, [†] 95%: Caucasian, [‡] 91%: Caucasian.

Table 2. Meta-analysis of studies on sugar sweetened beverages consumption and risk of gout

Variable	Population	No. of studies	Number		Test of association			Test of heterogeneity		
			Case	Total	RR	95% CI	p-value	Model	p-value	I ²
All	All	6	2,606	134,008	1.986	1.447~2.725	2.2×10^{-5}	F	0.952	0
Ethnicity	Caucasian	4	2,093	132,966	2.110	1.470~3.028	5.1×10^{-5}	F	0.934	0
	Polynesian	2	513	1,042	1.624	0.842~3.135	0.148	F	0.634	0
Study design	Cohort	3	1,981	132,374	2.098	1.441~3.055	1.1×10^{-4}	F	0.811	0
	Cross-sectional	3	925	1,634	1.736	0.964~3.124	0.066	F	0.810	0
Data type	Original	2	1,533	125,299	2.083	1.405~3.087	2.6×10^{-4}	F	0.525	0
	Imputed	4	1,073	8,709	1.819	1.067~3.100	0.028	F	0.906	0
Sex	Male	1	755	46,393	1.850	1.082~3.164	0.025	NA	NA	NA
	Female	1	778	78,906	2.390	1.340~4.261	0.003	NA	NA	NA
Dose	Highest	6	2,606	134,008	1.986	1.447~2.725	2.2×10^{-5}	F	0.952	0
	Middle	6	2,606	134,008	1.260	1.043~1.522	0.016	F	0.751	0

RR: relative risk, CI: confidence interval, F: fixed effects model, NA: not available.

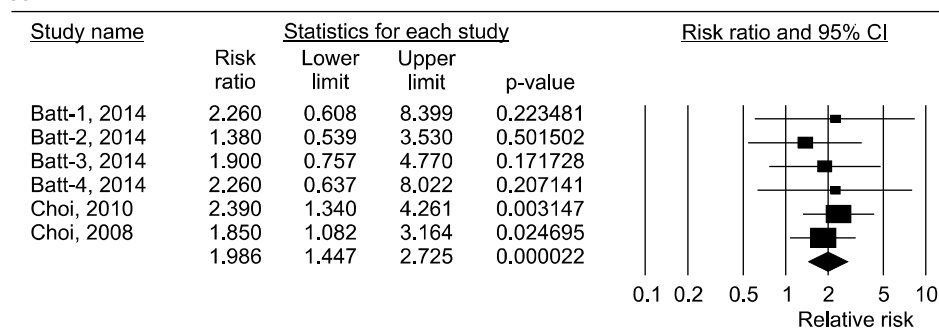
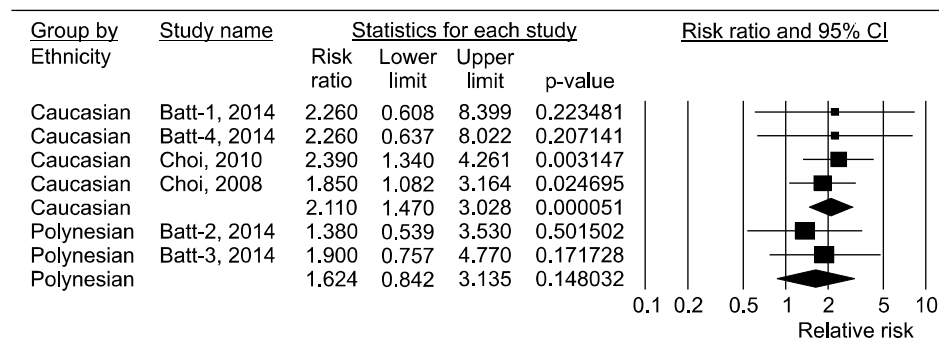
A**B**

Figure 2. Meta-analysis of the association between sugar sweetened beverages (SSBs) consumption and gout risk for the highest versus lowest groups of SSBs intake in the overall group (A) and each ethnic group (B). CI: confidence interval.

of publication bias in this meta-analysis of the relationship between total SSB intake and incidence of gout (Egger's regression test p-values=0.845), and the funnel plot suggested symmetry, indicating no evidence of a publication bias (Figure 3).

DISCUSSION

In the present study, we assessed the risk of gout associated with SSB consumption by combining data from 3

cohort and 3 cross-sectional studies, including a total of 2,606 gout patients among 134,008 participants. This meta-analysis revealed that SSB consumption significantly affected the incidence of gout. Compared to the lowest SSB intake group, individuals in the highest intake group had a 98.6% greater risk of gout development. Furthermore, there was a dose-response gradient to the relationship between SSB consumption and gout risk. Stratification by ethnicity showed a significant association between SSB consumption and gout risk in

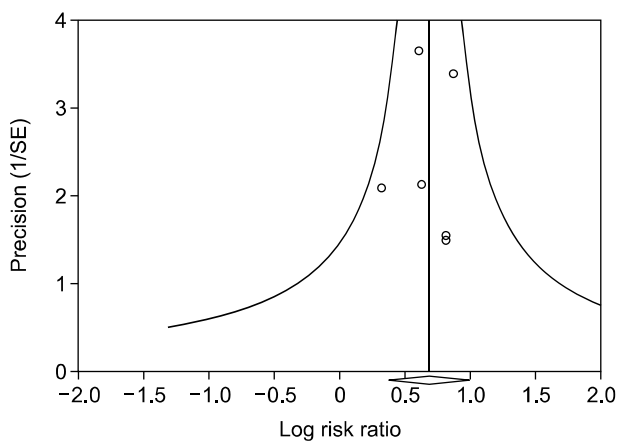


Figure 3. Funnel plot of studies that examined the association between sugar sweetened beverages consumption and gout risk (Egger's regression test p -value = 0.845). SE: standard error.

Caucasians, but not in Polynesians. It is unclear why a significant difference was observed in Caucasians but not in Polynesians. However, it may be explained by ethnic difference, and/or statistical power due to sample size. Actually, both populations showed the same direction of the ORs of the association, but the sample size was huge in Caucasians ($n=132,966$) compared to that in Polynesians ($n=1,042$). Thus, statistical power rather than ethnic difference may contribute to the difference in the association between Caucasians and Polynesians. Meta-analysis stratified by study design indicated that SSB intake increased gout incidence in the cohort studies, but not in the cross-sectional studies. The reason why a significant difference was observed in cohort studies but not in cross-sectional studies could be explained by study design, and/or also statistical power due to sample size (cohort studies, $n=132,374$ vs. cross-sectional studies, $n=1,634$). Observational cohort studies may be the best available epidemiological evidence, because human experimental studies have not yet been conducted, and well-conducted cohort studies were more likely to minimize recall and selection bias, which frequently confound cross-sectional or case-control studies [21]. The present analysis had a much larger statistical power to assess the association between SSB consumption and risk of gout by combining cohort studies with cross-sectional studies.

The plausible mechanism of our finding is that fructose contained in SSBs increases serum uric acid levels, resulting in increased risk of gout development [6]. SSBs are a major source of fructose; fructose induces uric acid production by increasing ATP degradation to AMP, which is a precursor of uric acid and serves as a substrate for uric

acid production [5]. Fructose also indirectly increases the level of serum uric acid by increasing insulin resistance and circulating insulin levels [22].

Consumption of SSBs continues to increase worldwide [22]. The rise in SSB intake has raised health concerns, because SSB consumption is associated with an increased risk of hypertension, diabetes, obesity, and metabolic syndrome [21,23-25]. Conventional dietary recommendations for gout have focused on restriction of purine intake [25]. However, low purine diets often include a high amount of carbohydrates, such as fructose-rich foods [4]. Thus the conventional low purine diet may result in fructose intake that could potentially worsen the risk of gout attacks. Because evidence shows that fructose substantially increases the risk of gout, reduction of SSB consumption should be a focus of gout management [6].

The present analysis has limitations that require consideration. First, confounders may have influenced this meta-analysis. Heterogeneity and confounding factors might have distorted the results, although no heterogeneity was found and several confounding factors were adjusted. Second, literature on the effect of SSB consumption on gout incidence is limited, and only a few studies were included in our meta-analysis. Third, our results may be affected by misclassification of SSB consumption. SSB intake was mostly assessed using number of cups of SSB consumed daily. However, cup size or SSB components may vary considerably between the different studies. The classification of SSB consumption is difficult to evaluate, which directly weakens the strength of the observed relationship. Fourth, the consumption levels of the highest and lowest groups differed among studies. For example, two cohort studies used ≥ 2 servings/d as the highest group compared with < 1 serving/mo as the lowest group, while studies from Batt et al. [7] compared the highest group of ≥ 5 servings/d with lowest group of no SSB intake. Fifth, our findings were dominated by Caucasian studies and thus might not be generalizable to other ethnic groups. Sixth, whether the difference in the content of fructose contained in SSB or other additives affected the study results needs to be considered. However, some studies presented the content of fructose contained in SSB or other additives, but others did not give the data. Thus, further meta-analysis could not be performed due to the limited data.

CONCLUSION

This meta-analysis of 134,008 participants demonstrates that SSB consumption is associated with an elevated risk of gout development, especially in Caucasians. Furthermore, there is a dose-response effect of the relationship between SSB consumption and gout risk. Future studies are necessary to elucidate the effect of SSBs on gout development to determine if SSB intake directly contributes to the pathogenesis of gout in various ethnic groups.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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