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Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies

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ABSTRACT

Objective: Sugar-sweetened beverages (SSBs) are associated with hyperuricemia and gout. Whether other important food sources of sugars share this association is unclear.

Design: To assess the relation of important food-sources of fructose-containing sugars with incident gout and hyperuricemia, we conducted a systematic review and meta-analysis of prospective cohort studies.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library (through September 13, 2017). We included prospective cohort studies that investigated the relationship between food sources of sugar and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and assessed risk of bias. We pooled natural-log transformed risk ratios (RRs) using the generic inverse variance method with random effects model and expressed as RR with 95% confidence intervals (CIs). The overall certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: We identified three studies (154,289 participants, 1,761 cases of gout), comparing the highest with the lowest level of exposure for SSBs, fruit juice and fruits. No reports were found reporting incident hyperuricemia. Fruit juice and SSB intake showed an adverse association (fruit juice, RR = 1.76, 95% CI 1.19 to 2.60; SSB, RR = 2.07, 95% CI 1.40 to 3.06), when comparing the highest to lowest intake of the most adjusted models. There was no significant association between fruit intake and gout (RR 0.82, 95% CI 0.61 to 1.11). Strongest evidence was for the adverse association in SSB (moderate quality), and the weakest evidence was for the adverse association in fruit juice (very low quality) and the no effect in fruit intake (very low quality).

Conclusion: The adverse association of SSB is also seen for fruit juice consumption but does not extend to fruit intake. Further research is likely to improve our estimates.

Protocol registration: ClinicalTrials.gov identifier: NCT02702375

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review and meta-analysis assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
- Large prospective cohort studies that were of high quality and had a long duration of follow-up were included.
- Most of the pooled results showed good consistency (low between study heterogeneity) and sugar sweetened beverages showed evidence of a dose-response gradient.
- Only three prospective cohort studies with low external generalizability were available for inclusion.
- The observational design of the prospective cohort studies did not allow for causal inferences to be drawn.

INTRODUCTION

Gout and associated hyperuricemia were both associated with the development of hypertension, insulin resistance syndrome [1], and cardiovascular disease (CVD) [2]. Different diets have been shown to be associated with the development and severity of gout [3]. Foods that increase net ATP degradation including alcohol and high purine meats are risk factors for gout [1]. Ingestion of large amounts of the monosaccharide fructose can increase uric acid production during its metabolism in the liver through unregulated phosphorylation of ATP into AMP [1] as demonstrated in randomized controlled trials [4, 5]. Similarly, in cohort studies, high intake of fructose-containing sugars in the form of sugar-sweetened beverages (SSBs) is associated with incident gout [6]. It is unclear whether the association seen for SSBs holds for other important food-sources of fructose-containing sugars, such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based products and sweets and desserts. As dietary guidelines and public health policy move from nutrient-based recommendations toward food and dietary-based recommendations [3, 4, 7], it is important to understand the contribution of these different food sources of fructose-containing sugars to the association of incident gout. To address this gap, we conducted a systematic review and meta-analysis of prospective cohort studies of the relation of important food sources of fructose-containing sugars with incident gout and hyperuricemia.

METHOD

Design

We followed the Cochrane Handbook for Systematic Reviews of Interventions [8] for the conduct of our systematic review and meta-analysis and reported our results according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [9] and preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) [10] guidelines. The study protocol was registered at ClinicalTrials.gov (identifier, NCT02702375).

Search strategy

We conducted systematic searches in MEDLINE, EMBASE and Cochrane through September 13, 2017 with no language restriction (**supplementary table 1**). Targeted manual searches served to supplement the database search; these included finding related papers from references of review papers, included studies, perusing articles with data from major prospective cohorts that usually report dietary data, and speaking to experts in the field.

Study selection

We included prospective cohort studies of ≥1 year duration that assessed the association of important food sources of fructose-containing sugars including non-alcoholic beverages (SSBs), cereal grain and grain based products, fruit and fruit-based products, dairy and dairy-based products, and sweets, chocolate and desserts with incident gout or hyperuricemia in participants free from gout or hyperuricemia at the start of the study. One year duration was chosen as it allows for the development of diseases such as hyperuricemia and gout.

Data extraction

Two independent reviewers (SAC and QL) extracted relevant data from included studies onto standardized pro forma. Extracted data included sample size, subject characteristics, sources of fructose-containing sugars, exposure levels, duration of follow-up, number of gout or hyperuricemia cases, model adjustments, and the risk ratio with 95% confidence intervals (95% CI) per quantile of

intake. The main outcome was incident gout or hyperuricemia expressed as risk ratios (RR) with 95% confidence intervals (95% CI). Discrepancies were resolved by consensus.

Risk of bias

The same two independent reviewers (SAC and QL) assessed each study for risk of bias. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Points were awarded based on cohort selection, comparability of groups and assessment of outcomes, for a maximum total of 9 points [11]. Studies with ≥6 points were considered high quality [11]. Difference between reviewers was resolved by consensus.

Statistical analyses

Primary pooled analyses were conducted using Review Manager (RevMan) 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analysis and the assessments of dose response were performed using Stata 14 (StataCorp, College Station, TX, USA). Natural log-transformed RR for incident gout or hyperuricemia, comparing extreme quantiles (the highest exposure versus the lowest exposure or reference group), were pooled separately for each food source of fructose-containing sugars using the generic inverse variance method with DerSimonian and Laird random effects models and expressed as RRs with 95% CI. Inter-study heterogeneity was assessed with the Cochran Q statistic with significance set at $p<0.10$ and quantified with the I^2 statistic, where $I^2 \geq 50\%$ represented evidence of substantial heterogeneity [8]. We explored sources of heterogeneity by sensitivity analyses. Sensitivity analyses, where each study was systematically removed, and effect size was recalculated in the remaining studies, were carried out to explore the impact of individual studies on the pooled risk. As ≥10 cohort comparisons were not available, *a priori*

subgroup analyses were not performed. Linear and non-linear dose-response analyses were assessed by using generalized least squares trend estimation models (GLST) and spline curve modeling (MKSPLINE procedure), respectively [12]. Publication bias was not assessed as the number of cohort comparisons was less than 10.

Grading of the evidence

The overall quality and the strength of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [13-25]. The evidence was graded as high, moderate, low, or very low quality, with observational studies starting with an initial grade of 'low'. This then can be downgraded based on 5 pre-specified criteria or upgraded based on 3 pre-specified criteria. Criteria to downgrade included risk of bias (weight of studies showed risk of bias as assessed by low NOS <6), inconsistency (substantial unexplained inter-study heterogeneity i.e. I^2>50%), indirectness (presence of factors that limit the generalizability of the results), imprecision in the pooled risk estimate (the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for benefit or harm (RR 0.9–1.1)), and publication bias (evidence of small-study effects). Conversely, criteria to upgrade included a large magnitude of effect (RR>2 or RR<0.5 in the absence of plausible confounders), dose–response gradient or reasonable evidence of attenuation of the pooled effect estimate by confounders.

RESULTS

Search results

Figure 1 shows the flow of the systematic search and study selection. Of the 309 reports identified by the literature search, three reports with data from three prospective cohort studies met our inclusion

criteria [26-28]: Nurses' Health Study (NHS) [27], Health Professionals Follow-up Study (HPFS) [26] and the National Runner's Health Study [28]. All three reports reported the association of food sources of fructose-containing sugars on incident gout, but none on incident hyperuricemia. These reports involved a total of 154,289 participants with 1,761 incident cases of gout. Two reports each reported data on fruit intake [n= 75,383; 983 cases] [26, 28], fruit juice [n= 125,299; 1,533 cases] [26, 27] and SSBs [n=125,299; 1,533 cases] [26, 27]. We did not identify prospective cohort studies reporting the association of other food sources of fructose-containing sugars (e.g. cereal grain and grain-based products, sweets and desserts, dairy and dairy based products and chocolate) with incident gout.

Study characteristics

Table 1 lists the characteristics of the included prospective cohort studies. All studies were performed in the USA. The median age of the included participants ranged from 30 to 75. The median follow-up periods was 17 years (range, 12 to 22 years) for SSB, 18.7 years (12 to 22 years) for fruit juice and 9.9 years (7.74 to 12 years) for fruit. Dietary intake assessments were done with self-reported, validated food frequency questionnaires (FFQs) in all studies. Quantiles of exposure depended on the food source. Lowest and highest median quantiles of exposure were <1 servings/month and ≥14 servings/week respectively for SSB; ≤1 servings/month and ≥14 servings/week respectively for fruit juice; and ≤0.4 servings/week (range, <0-0.5 servings/week) and ≥8 servings/day (range, ≥2-14 servings/day), respectively for fruit. The ascertainment of incident gout in both HPFS and NHS cohorts [26, 27] was through self-report, followed by supplementary surveys of the subjects based on the American College of Rheumatology gout survey criteria [29] to confirm that the diagnosis. The authors defined individuals with gout that met ≥6 of the 11 criteria for gout. In addition, in a sub-sample the

self-reported diagnoses were validated with medical records. As for the NRHS cohort [28], incident gout was self-reported based upon physician diagnosis.

Supplementary table 2 shows the complete list of adjusted confounding variables for the most adjusted models for each of the included prospective cohorts. The median number of variables in the most adjusted models was 14 (range, 6 to 14). All studies adjusted for primary and secondary confounders such as age, body mass index (BMI) and history of hypertension. Each of the three cohorts were single-sex studies, so adjustment for sex was not necessary. The NHS cohort study authored by Choi *et al.* 2010 [27] and NRHS study by Williams *et al.* [28] were agency funded, while the HPFS paper authored by Choi *et al.* 2008 [26] was funded by both agency and industry.

Study Quality

Supplementary table 3 shows the study quality assessments by the NOS scale. There was no evidence of serious risk of bias. Only NRHS cohort scored <6 on the NOS scale, which denotes lower quality [28].

Fruit intake on incident gout

Figure 2 shows the relationship between fruit intake and incident gout. When comparing the highest to the lowest intake, no association was shown for fruit intake on incident gout (RR = 0.82, 95% CI 0.61 to 1.11). There was evidence of significant interstudy heterogeneity (I^2 = 94%, p<0.001).

Fruit juice intake on incident gout

Figure 2 shows the relationship between fruit juice intake and incident gout. When comparing the highest to lowest intake, a protective association was shown for fruit juice intake on incident gout (RR 1.76, 95% CI 1.19 to 2.60]). There was no evidence of significant interstudy heterogeneity (I^2 = 0%, p = 0.53).

SSB intake on incident gout

Figure 2 shows the relationship between SSB intake and incident gout. When comparing the highest with the lowest intake, an adverse association was shown for SSB intake on incident gout (RR=2.07 [95% CI 1.40 to 3.06]). There was no evidence of significant interstudy heterogeneity (I^2 = 0%, p = 0.52).

Additional analysis

Sensitivity analysis (the systematic removal of each study), publication bias and subgroup analyses could not be performed due to the small number of studies included in each analysis (n=2).

Dose-response analysis

A random-effect GLST model showed a significant dose-response relationship between SSB intake and incident gout per serving/week (RR = 1.05, 95% CI 1.03 to 1.07, p<0.001) (**supplementary figure 2**), but not for fruit juice intake (RR = 1.03, 95% CI 1.0 to 1.07, p = 0.06) (**supplementary figure 1**). There was no evidence for departure from linear dose response gradient or dose thresholds for SSB intake while using the MKSPLINE procedure (p = 0.196) (**supplementary figure 2**). In contrast, fruit juice intake showed a significant departure from linearity (p = 0.02), and visual inspection of the graph

(**supplementary figure 1**) indicated a plateau for risk increase after ≥5 servings per day. Dose-response modeling was not possible for fruit intake due to lack of data.

GRADE assessment

Table 2 shows the GRADE assessment of individual food sources of fructose-containing sugars. The certainty of evidence of an adverse association from both fruit and fruit juice was rated as very low, with downgrades to the lowest level for indirectness for fruit intake, and for inconsistency, indirectness and imprecision for fruit juice intake. The quality of evidence of an adverse association of SSB intake with incident gout was rated as moderate, with a downgrade of one level for indirectness but upgrade of two levels for a large magnitude effect and significant dose-response.

DISCUSSION

We conducted a systematic review and meta-analysis of studies investigating the relation of important food sources of fructose-containing sugars with incident gout. We identified three prospective cohort studies [26-28] comprising of 154,289 participants and 1,761 cases of incident gout. The pooled analyses revealed that there was moderate quality evidence that SSB intake was associated with 207% increase in risk of incident gout when comparing the highest with the lowest intake. Similarly, there was low quality evidence that fruit juice intake was associated with a 14% increase in risk of incident gout, but fruit intake did not show any significant association with incident gout (low quality evidence). There was no data available of other important food sources of fructose-containing sugars.

Findings in the context of the literature

Our results are consistent with previous research that indicate that intake of certain food sources of fructose-containing sugars are associated with the risk of gout. Our previous systematic review and meta-analysis of prospective cohort studies that assessed fructose intake, found a harmful relationship between fructose consumption and gout [6]. While that study indicated that fructose moiety might possibly drive the association with gout, all the fructose data was derived from SSB intake. Another systematic review of the literature identified numerous dietary factors associated with the risk of gout including meat, alcohol, seafood and SSBs, but also that lower risk was associated with the intake of dairy, folate and coffee [3].

SSBs are one of the main source of fructose-containing added sugars in the western diet comprising around 30% of intake of added sugars in the USA [30] and around 24% in Canada [31]. Excess intake of fructose can increase uric acid though an unregulated phosphofructose kinase pathway that uses substantial amounts of ATP [32] to convert fructose into fructose-1-phosphate in the liver [33]. Mechanistically, net ATP degradation leads to accumulation of AMP, which is subsequently degraded to uric acid. Additionally, fructose can increase de novo purine synthesis, which further produces uric acid [1]. This increase in uric acid can lead to gout. Since we were unable to investigate the relationship between food sources of fructose-containing sugars and hyperuricemia, we cannot validate this mechanism. It is possible, that fructose increases the risk of gout independently of serum uric acid levels. However, since the link between fructose and serum uric acid [34-37], and the link between serum uric acid and the development of gout have been independently established [1], it is unlikely that fructose increases the risk of gout without using uric acid as an intermediate.

We identified adverse association of fruit juices intake with incident gout. The two studies that contributed to this result [26, 27] were both performed in the Harvard cohorts which do not differentiate between fruit drinks and pure fruit juice, the former being largely similar to SSBs i.e. mainly sugar and water. This is supported by studies investigating pure fruit juice and fruit drinks which have shown divergent response for cardiometabolic disease [38, 39].

We did not see any association between fruit intake and incident gout but the effect estimates in the two studies were in opposite direction. The NRHS [28] cohort showed a 51% reduction in risk of gout when with high intake of fruit whereas the HPFS [26] cohort showed a 63% increased risk — both studies were performed in men. These discordant results highlight the differences in the studies. NHPS cohort [26] only measured oranges and apples, fruit high in fructose, while NRHS [28] cohort assessed all fruit and its increasing intake, as the authors admit, might represent a healthier dietary intake. It is possible that higher intake of fruits in NRHS might be associated with high intake of dairy or coffee, which have been associated with lowering the risk of gout [3] and not measured in NRHS. Additionally, the highest fruit intake contained less fructose than the SSB and fruit juice food sources of fructose-containing sugars. Therefore, the exposure may not have been high enough to see consistent affects. Furthermore, case-control and cross-sectional studies have shown a protective effect of fruit intake with gout [40, 41]. The harmful association for oranges, which are rich in vitamin C, in HPFS [26] cohort is at odds with its own result in another paper, in which the author demonstrated a protective association of vitamin C intake with gout [42]. Fruits are rich in fructose; however, fruit intake has consistently shown a benefit for cardiometabolic risk factors, cardiometabolic diseases and all cause-mortality [43-49] even though the fructose in fruit can increase uric acid levels. More data might clarify this association.

We could not find any prospective studies looking at the association of food sources of fructose-containing sugars and hyperuricemia even though hyperuricemia is the most important risk factor for gout [3, 50]. Hyperuricemia is also a risk factor for hypertension [51], metabolic syndrome, diabetes [52], and CVD [53]. Several cross-sectional analyses have investigated the link between SSB consumption and serum uric acid levels, showing a positive relationship [34-37]. In contrast, the analysis of the National Health and Nutrition Examination Survey (NHANES) showed no link between dietary fructose and risk of hyperuricemia [54], indicating that perhaps different food sources of fructose-containing sugars may have different effects on serum uric acid. This point is reinforced by another analysis of NHANES data that showed a relationship of SSB intake with higher serum uric acid concentration, but not with fruit juice [55]. Future studies investigating food sources of sugars and risk of hyperuricemia may help to elucidate some of the above inconsistent findings.

Strengths and limitations

Our analysis has many strengths. First, we employed a comprehensive systematic search across major databases and the quantitative synthesis of results. Second, the studies we included had a substantial number of participants and cases of gout (154,289 participants and 1,761 gout cases) leading to increased precision. Additionally, the median follow-up duration was greater than 10 years, which allowed for enough time from exposure for the development of disease. Another strength is the use of validated measures of intake like food frequency questionnaires. The two Harvard cohorts [26, 27] administered FFQ multiple times, and validated them on a subsample, allowing for more accurate and robust long-term intakes compared to the NRHS [28] cohort, which only measured dietary intakes at

baseline. In our analysis, we made use of GRADE to evaluate the quality and strength of our analysis and evaluate our confidence in the estimates.

There are some notable limitations to our systematic review and meta-analysis. First, while we included the most adjusted multivariable models for this analysis, there is always potential for unmeasured and residual confounding, since the studies included were observational in nature. This explains why GRADE starts at "low quality" for observational studies. Second, there was evidence of indirectness in some of the relationships. All studies were conducted in the USA, and two of the three studies were in health professionals. The two Harvard [26, 27] cohorts included only middle aged or older people who worked in health care and who were predominately white and the NRHS [28] cohort included only middle to old aged physically active men. Thus, the specific nature of the included studies' population limits the generalizability of our results to other populations and geographical locations; however, the biological process of diet and gout are still likely to be similar to other populations. While, genome wide association studies have found numerous genes that increase one's risk for gout [56] and some ethnic groups may be more susceptible than others [1] though it is not known if the association of fructose intake with gout is modified by genes. Third, sources of heterogeneity remained unexplained; with only three studies, we were unable to assess publication bias or perform sensitivity or a priori subgroup analysis. Thus for these reasons, data pertaining to SSB and fruit juice intake and incident gout received a GRADE of moderate and very low, respectively, indicating that further studies in this regard is likely to impact our certainty in the effect estimate and may change the estimate for SSB and that our certainty in the estimate for fruit juice is very uncertain; therefore, caution should be used when interpreting these results. Similarly, for fruit,

which received a GRADE of very low, so we are very uncertain in these results and caution should be used in the interpretation of these results.

Implications

Dietary guidelines have shifted their focus from nutrients based recommendations to food and dietary pattern-based recommendations [57], since it has been recognized that one does not eat nutrients in isolation, but as a part of food. Interactions between nutrients in food are complex and important components of disease risk [57]. Our findings support this view in relation to food sources of fructose-containing sugars and their relationship with gout. Our findings also have implications for recommendations for the prevention of gout. Conventional dietary recommendations for gout have focused on restriction of purine intake; however, low-purine diets are often high in carbohydrates, including fructose-rich foods [58]. We have shown an adverse association between fruit juice and SSBs, supporting the recommendations to limit their intakes. Since we did not have data relating to children, hyperuricemia or other food sources of fructose-containing sugars, we cannot extend our conclusion to these groups of individuals or these foods.

Conclusion

Our systematic review and meta-analysis of prospective cohort studies showed an adverse association between SSBs and fruit juice with risk of gout, while there was no association with fruit intake. The strength of the evidence was moderate for SSB intake and very low for fruit juice and fruit intake, as assessed by GRADE. For SSBs, the true association is likely to be close to the estimate, but there is a possibility that it is substantially different. For fruit juice and fruit intake, the true association are likely to be substantially different from the estimate and future research will very likely impact our

confidence in the effect estimates and likely to change them [59]. Our results are consistent with the literature that certain food sources of fructose-containing sugars especially SSBs are a risk factor for the development of gout. We were unable to identify studies assessing food sources of fructose-containing sugars and hyperuricemia, indicating a gap in the literature. Given that incident gout is rising [7, 60-65], and that gout and hyperuricemia are both associated with metabolic syndrome, myocardial infarction, diabetes and premature death [1, 2, 66], it is becoming increasingly important to identify and understand risk factors for developing gout. It is imperative for additional prospective studies to assess the intake of various food sources of fructose-containing sugars and their relationship with gout and hyperuricemia in diverse populations. This will help identify to what extent does our foods mediate the risk for hyperuricemia and gout and will further inform health care professionals, policymakers, and aid in the development of improved dietary guidelines for the prevention and management of gout and hyperuricemia.

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analysis, and interpretation of the data; and preparation, review, approval of the manuscript or decision to publish.

Data Sharing

There is no additional unpublished data available from the study.

Competing Interests

TA Khan has received research support from the Canadian Institutes of health Research (CIHR) and an unrestricted travel donation from Bee Maid Honey Ltd. **RJ de Souza** has served as an external resource person to the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health (guidelines for trans fats and saturated fats), and received renumeration from WHO for travel and accommodation. He also received compensation for contract research conducted for the Institute of Nutrition, Metabolism, and Diabetes at the Canadian Institutes of Health Research (CIHR), Health Canada and WHO. He has received research grants from the Canadian Foundation for Dietetic Research and CIHR, and lecture fees from McMaster Children's Hospital. **TMS Wolever** and his wife are part owners and employees of Glycemic Index Laboratories. **CWC Kendall** has received research support from the Advanced Foods and Materials Network, Agricultural Bioproducts Innovation Program through the Pulse Research Network, Agriculture and Agri-Food Canada, Almond Board of California, Barilla, Calorie Control Council, CIHR, Canola Council of Canada, The International Tree Nut Council Nutrition Research & Education Foundation, Kellogg, Loblaw Companies Ltd., Pulse Canada, Saskatchewan Pulse Growers and Unilever. He has received consultant fees from American Pistachio Growers; speaker fees from American Peanut Council, Tate & Lyle and The WhiteWave Foods Company; and travel funding from Sabra Dipping Company, Tate &

Lyle, International Tree Nut Council Research & Education Foundation, California Walnut Commission, Sun-Maid, The Peanut Institute, General Mills, Oldways Foundation and International Nut and Dried Fruit Council Foundation. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European Association for the Study of Diabetes (EASD). He is a member of the International Carbohydrate Quality Consortium (ICQC), Secretary of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. **JL Sievenpiper** has received research support from the CIHR, Canadian Diabetes Association (CDA), PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), American Society for Nutrition (ASN), Calorie Control Council, INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, and The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers). He has received speaker fees and/or honoraria from the CDA, CNS, Dr. Pepper Snapple Group, Dairy Farmers of Canada, Nutrition Foundation of Italy (NFI), C3 Collaborating for Health, Sprim Brasil, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, The Ginger Network LLC, International Sweeteners Association, and Pulse Canada. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of the CDA, European Association for the study of Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the ASN. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive

Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada. No competing interests were declared by **Q Liu, S Ayoub-Charette, F Au-Yeung, S Blanco Mejia, LA Leiter**. There are no patents, products in development or marketed products to declare.

Authors' contributions

All authors had full access to all of the data (including statistical reports and tables) in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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TABLES AND FIGURES

Figure 1 Summary of evidence search and selection. Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia. Of the 280 studies initially identified, 265 were excluded based on title and/or abstract. The remainder were read in full by two independent reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort studies.

Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-adjusted multivariate models accounting for food sources of fructose-containing sugars intake were used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using the Cochran Q statistic and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit juices.

Table 1 Characteristics of prospective cohort studies investigating food sources of fructose-containing sugar intake and incident gout.

Study, year (Reference)	Cohort	Country	Participants	Incident Cases	Age (years, range)	Follow-up (mean, range)	Dietary Assessment	Frequency of Administration	Quantiles	Exposure (servings/week, median, range)	Serving size	Outcome assessment	Funding Source*
Sugar sweetened beverage (SSB)													
HPFS (Choi *et al.*, 2008) (26)	Health Professionals Follow-Up Study	USA	46,393 (M)	755	52.5 (40-75)	12 years	Validated SFFQ	4 times	Quintiles	¼ - ≥14	Not reported	Record linkage	Agency and Industry
NHS (Choi *et al.*, 2010) (27)	Nurses Health Study	USA	78,906 (F)	778	49 (30-55)	22 years	Validated SFFQ	4 times	Sextiles	¼ - ≥14	Not reported	Self-reported	Agency
Fruit juice													
NHS (Choi *et al.*, 2008) (26)	Health Professionals Follow-Up Study	USA	46,393 (M)	755	52.5 (40-75)	12 years	Validated SFFQ	4 times	Quintiles	¼ - ≥14	Not reported	Record linkage	Agency
HPFS (Choi *et al.*, 2010) (27)	Nurses Health Study	USA	78,906 (F)	778	49 (30-55)	22 years	Validated SFFQ	4 times	Sextiles	¼ - ≥14	Not reported	Self-reported	Agency and industry
Fruit													
NRHS Williams, 2008) (28)	National Runner's Health Study	USA	28,990 (M)	228	44.9	7.7 years (5.9-9.6)	Validated SFFQ	1 (baseline)	Quartiles	¼ – 2 (0 – ≥2)	Not reported	Self-reported	Agency
NHS (Choi *et al.*, 2008) (26)	Health Professionals Follow-Up Study	USA	46,393 (M)	755	52.5 (40-75)	12 years	Validated SFFQ	4 times	Quintiles	<¼ - ≥14	Not reported	Record linkage	Agency

Abbreviations: SFFQ = Semi quantitative Food-Frequency Questionnaire; M=males; F=females.

*Agency funding is that from government, university or not-for-profit health agency sources.

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684 **Table 2** GRADE assessment of individual food source of fructose-containing sugars.

Quality assessment								Study event rates (%)	Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations		Relative Risk (95% CI)	Importance
Sugar sweetened beverages intake on incident gout (follow-up median 17 years)										
2	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	No serious imprecision	Undetected[2]	Large magnitude of effect[3] Dose-response[4]	1533/125299 (1.22%)	2.08 [1.40, 3.07]	⊕⊕⊕◯ **Moderate** [1,2,3,4] Due to downgrade for indirectness and upgrade for large magnitude effect and dose-response
Fruit juice intake on incident gout (follow-up median 17 years)										
2	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirectness [1]	No serious imprecision	Undetected[2]	None	1532/125299 (1.22%)	1.73 [1.17, 2.57]	⊕◯◯◯ **Very low**[1,2] Due to downgrade for indirectness
Fruit intake on incident gout (follow-up median 9.87 years)										
2	Observational studies	No serious risk of bias	Very serious inconsistency[5]	Serious indirectness [1]	Serious[6]	Undetected[2]	None	982/75383 (1.3%)	0.89 [0.27, 2.87]	⊕◯◯◯ **Very low**[1,2,5,6] Due to downgrade for inconsistency, indirectness and imprecision

685 [1]Downgrade for indirectness, as the study population is specific to a group of the population like professionals, nurses or runners.

[2]No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effect (<10 cohort included in our meta-analysis).

[3]Upgrade for a large magnitude of effect (RR>2.0).

[4]Upgrade for a dose response gradient, as the GLST dose-response analysis revealed a significant linear relationship between sugar sweetened beverage intake and incident gout (P=0.0001).

[5]Downgrade for very serious inconsistency, as the two studies included had opposite associations and there was evidence of substantial inter-study heterogeneity (I^2=94%, p<0.0001). Due to the small number of studies included in the analysis, subgroup analysis was not performed.

[6]Downgrade for serious imprecision, as the lower bound of the 95% CI (RR, 0.27) includes clinically important benefit (RR<0.9), while the upper bound of the 95% CI (RR, 2.87) crosses the minimally important difference of 10% (RR>1.1).

Figure 1 Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia.

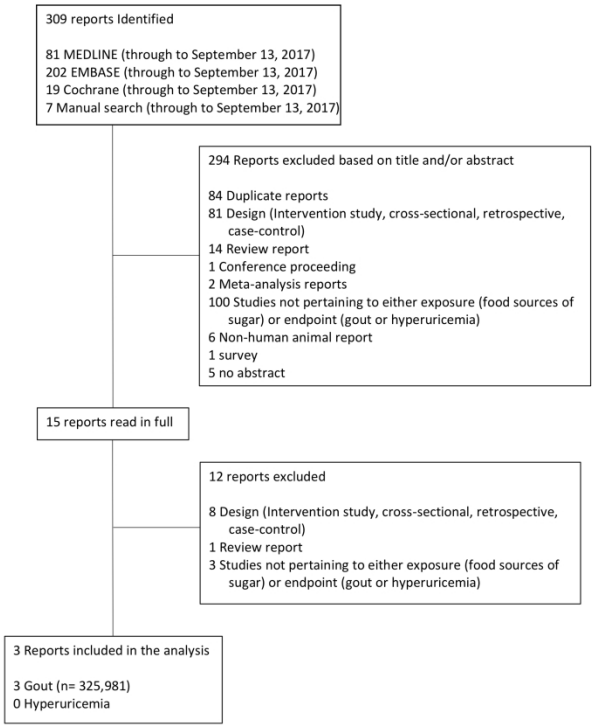


Figure 1. Summary of evidence search and selection. Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia. Of the 280 studies initially identified, 265 were excluded based on title and/or abstract. The remainder were read in full by two independent reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort studies.

279x361mm (300 x 300 DPI)

Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout.

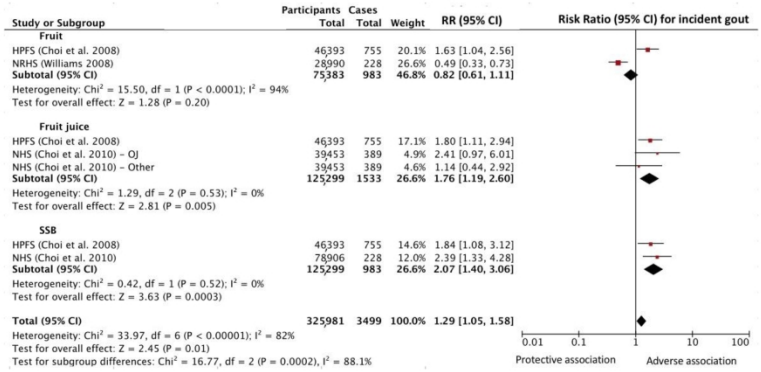


Figure 2. Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-adjusted multivariate models accounting for food sources of fructose-containing sugars intake were used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using the Cochran Q statistic and quantified using the I2 statistic (I2 ≥ 50% indicative of significant heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit juices.

279x361mm (300 x 300 DPI)

Supplementary material

SUPPLEMENTARY TABLES

SUPPLEMENTARY FIGURES

Supplementary table 1. Search terms

Database and search terms

MEDLINE	EMBASE	Cochrane
1. sugar*.mp.	1. sugar*.mp.	1. sugar*.mp.
2.exp fructose/	2. exp sugar/	2. exp fructose/
3. fructose.mp.	3. exp fructose/	3. fructose.mp.
4. HFCS.mp.	4. fructose.mp.	4. HFCS.mp.
5. exp high fructose Corn Syrup/	5. HFCS.mp.	5. exp Nutritive Sweeteners/
6. sucrose.mp.	6. exp high fructose Corn Syrup/	6. sucrose.mp.
7. exp dietary Sucrose/	7. sucrose.mp.	7. exp dietary sucrose/
8. sugar sweetened beverage*.mp.	8. exp dietary Sucrose/	8. sugar sweetened beverage*.mp.
9. ssb.mp.	9. sugar sweetened beverage*.mp.	9. ssb.mp.
10. soda.mp.	10. SSB.mp.	10. soda.mp.
11. soft drink*.mp.	11. soda.mp.	11. soft drink*.mp.
12. exp carbonated beverages/	12. soft drink*.mp.	12. exp carbonated beverages/
13. carbonated beverages.mp.	13. exp soft drink/	13. non alcoholic beverage*.mp.
14. non alcoholic beverage*.mp.	14. exp carbonated beverages/	14. nonalcoholic beverage*.mp.
15. nonalcoholic beverage*.mp.	15. carbonated beverages.mp.	15. exp energy drinks/
16. exp energy drinks/	16. non alcoholic beverage*.mp.	16. energy drink*.mp.
17. energy drink*.mp.	17. nonalcoholic beverage*.mp.	17. smoothie*.mp.
18. smoothie*.mp.	18. exp energy drinks/	18. ((fruit or vegetable) and juice*).mp.
19. exp "fruit and vegetable juices"/	19. energy drink*.mp.	19. fruit.mp.
20. fruit.mp.	20. smoothie*.mp.	20. exp fruit/
21. exp fruit/	21. exp "fruit and vegetable juices"/	21. exp honey/
22. exp honey/	22. fruit.mp.	22. y*g*rt.mp.
23. y*g*rt.mp.	23. exp fruit/	23. exp yogurt/
24. exp yogurt/	24. exp honey/	24. ice cream*.mp.
25. ice cream*.mp.	25. y*g*rt.mp.	25. icecream*.mp.
26. icecream*.mp.	26. exp yoghurt/	26. exp ice cream/
27. exp ice cream/	27. ice cream*.mp.	27. cereal*.mp.
28. exp edible grain/	28. icecream*.mp.	28. dessert*.mp.
29. cereal*.mp.	29. exp ice cream/	29. sweets.mp.
30. dessert*.mp.	30. cereal*.mp.	30. confection*.mp.
31. sweets.mp.	31. dessert*.mp.	31. pastries.mp.
32. confection*.mp.	32. sweets.mp.	32. biscuit*.mp.
33. pastries.mp.	33. confection*.mp.	33. cookie*.mp.
34. biscuit*.mp.	34. exp bakery product/	34. cake*.mp.
35. cookie*.mp.	35. pastries.mp.	35. candy.mp.
36. cake*.mp.	36. biscuit*.mp.	36. candies.mp.
37. candy.mp.	37. cookie*.mp.	37. exp candy/
38. candies*.mp.	38. cake*.mp.	38. (chocolate adj2 milk).mp.
39. exp candy/	39. candy.mp.	39. cohort.mp.
40. (chocolate adj2 milk).mp.	40. candies*.mp.	40. exp Prospective Studies/
41. chocolate.mp	41. chocolate.mp	41. chocolate.mp
42. exp chocolate/	42. exp chocolate/	42. cacao.mp
43. cacao.mp	43. cacao.mp	43. exp cacao/
44. exp cacao/	44. exp cacao/	44. (prospective adj2 (cohort or study)).mp.
45. cohort.mp.	45. (chocolate adj2 milk).mp.	45. exp follow-up studies/
46. exp prospective study/	46. cohort.mp.	46. exp multivariate analysis/
47. (prospective adj2 (cohort or study)).mp.	47. exp prospective study/	47. exp proportional hazards models/
48. exp multivariate analysis/	48. (prospective adj2 (cohort or study)).mp.	48. follow up study.mp.
49. exp follow up studies/	49. exp multivariate analysis/	49. (longitudinal adj2 study).mp.
50. exp proportional hazards models/	50. exp proportional hazards models/	50. gout/

51. follow-up study.mp.	51. follow-up study.mp.	51. gout*.mp
52. (longitudinal adj2 study).mp.	52. (longitudinal adj2 study).mp.	52. uric acid*.mp
53. gout/	53. gout/	53. hyperuricemia*.mp
54. gout*.mp.	54. gout*.mp.	54. hyperuricemia/
55. uric acid*.mp.	55. uric acid*.mp.	55. hyperuricaemia*.mp
56. hyperuricemia*.mp.	56. hyperuricemia*.mp.	56. uric.mp
57. hyperuricemia/	57. hyperuricemia/	57. or/1-43
58. hyperuricaemia*.mp.	58. hyperuricaemia*.mp.	58. or/44-49
59. uric.mp.	59. uric.mp.	59. or/50-56
60. or/1-44	60. or/1-45	60. and/57-59
61. or/45-52	61. or/46-52	
62. or/53-59	62. or/53-59	
63. and/60-62	63. and/60-62	

Database	Total
MEDLINE: September 13, 2017	81
EMBASE: September 13, 2017	202
Cochrane: September 13, 2017	19
Manual search	7
Total	309

For all databases, the original search was September 13, 2017.

Supplementary table 2. Analysis of confounding variables among 3 studies of food sources of sugar intake and incident gout

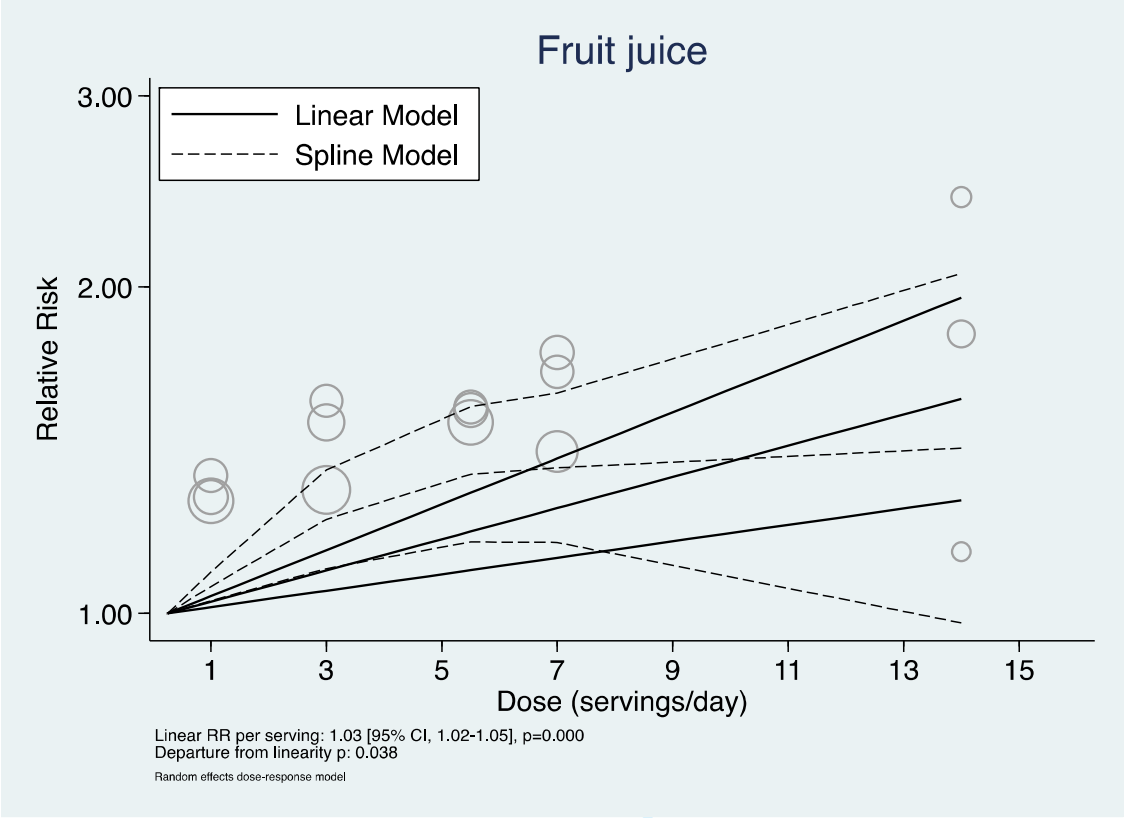
Study	HPFS (Choi *et al.*, 2008)	NRHS (Williams, 2008)	NHS (Choi *et el.*, 2010)
Number of variables in fully adjusted model	14	6	14
Number of multivariable models presented	2	1	3
Timing of measurement of confounding variables	2y	BL*	2y
Pre-specified primary confounding variable			
Age	✓	✓	✓
Pre-specified secondary confounding variables			
Marker of overweight/obesity (Body mass index, weight, waist circumference, waste to hip ratio)	✓		✓
Sex	M §	M §	F ‡
History of gout/hyperuricemia			
Diabetes			
Physical activity			
Lipid medication/dyslipidemia			
Animal protein intake	✓		✓
Hypertension or blood pressure medication including diuretics	✓		✓
Other confounding variables			
Lifestyle factors			
Weekly intake of:			
Alcohol	✓	✓	✓
Seafood	✓		✓
Purine from vegetables	✓		✓
Dairy food	✓		✓
Vitamin C	✓		✓
Coffee		✓	
Meat		✓	
Fish			✓∇
Diet soda	✓∇		✓∇
Sugar-sweetened cola	✓∇		✓∇
Other soda	✓∇		✓∇
Orange or apple juice	✓∇		✓∇
Other fruit juice			✓∇
Orange or apple	✓∇		
Total energy	✓		✓
Weekly intake of aspirin		✓	
Medical history			
History of Hypertension	✓	✓	✓
History of chronic Renal failure	✓		
Menopause status			✓
Use of hormonal therapy			✓

HPFS=Health Professionals Follow-Up Study, NHS=Nurses Health Study
*Denotes confounders measured only at baseline years.
† Indicates confounders measured every 2 years.
‡ Indicates the study includes only female subjects
§ Indicates the study includes only male subjects
∇ Indicates the confounder was present in some, but not all, models.

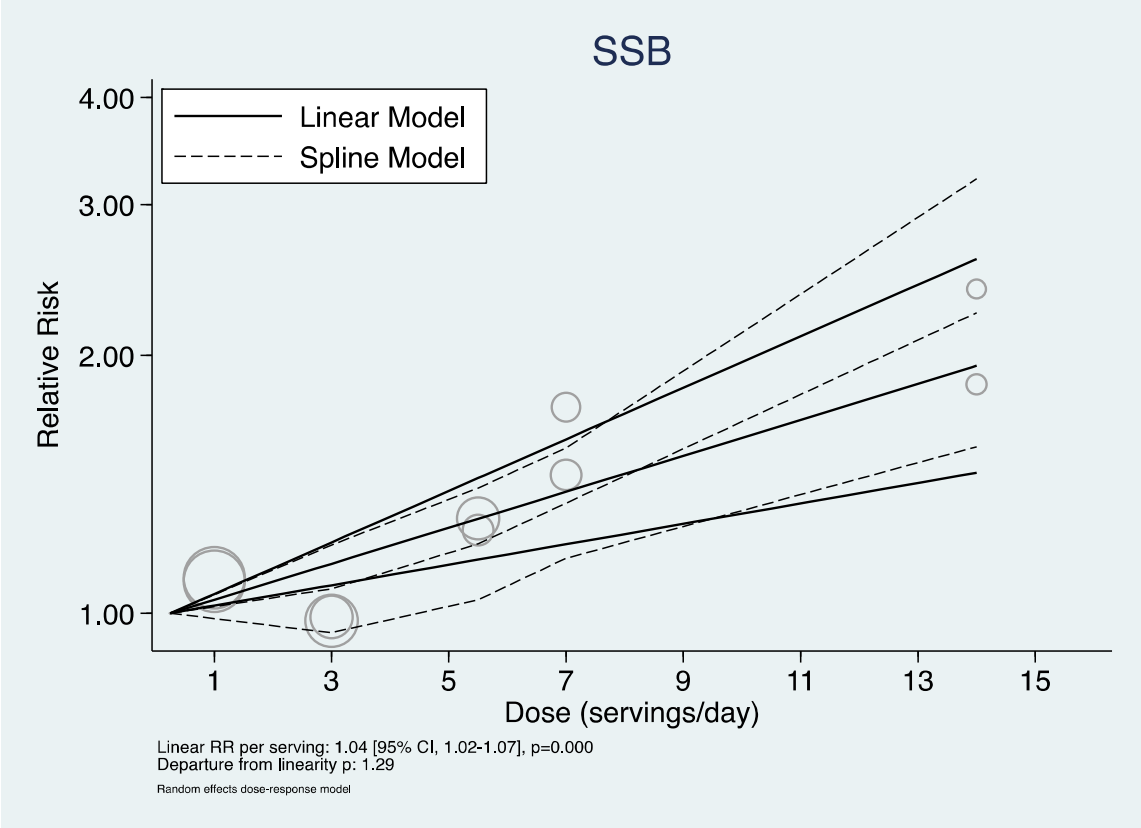
Supplementary table 3. Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies

Study	Selection*	Outcome†	Comparability‡	total§
Choi *et al.*, 2008	2	3	1	6
Williams, 2008	2	2	1	5
Choi *et al.*, 2010	2	3	1	6

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline.
†Maximum 3 points awarded for follow-up length, adequacy of follow-up and outcome assessment.
‡Maximum 2 points awarding for controlling for the pre-specified primary confounding variable (age) and >6 of the secondary confounding variables (sex, body mass index, history of gout or hyperuricemia, diabetes, alcohol, physical activity, lipid medication/dyslipidemia, animal protein intake, hypertension or blood pressure medication including diuretics).
§A maximum of 9 points could be awarded.



supplementary figure 2. Linear and non-linear dose-response relationship between fruit juice intake and incident gout per serving/week. Linear dose response data were modeled using the generalized least squares trend estimation models (GLST). Dashed lines represent the pointwise 95% confidence interval for the fitted linear trend (solid line). Each study was centered to the baseline reference dose for the estimation of increasing dose risk. Non-linear dose response data were modeled with the fixed-effect restricted cubic spline models with 3 knots using the spline curve modeling (MKSPLINE procedure). Dashed lines represent the pointwise 95% confidence interval for the fitted linear trend (solid line). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.



Supplementary figure 1. Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week. Linear dose response data were modeled using the generalized least squares trend estimation models (GLST). Dashed lines represent the pointwise 95% confidence interval for the fitted linear trend (solid line). Each study was centered to the baseline reference dose for the estimation of increasing dose risk. Non-linear dose response data were modeled with the fixed-effect restricted cubic spline models with 3 knots using the spline curve modeling (MKSPLINE procedure). Dashed lines represent the pointwise 95% confidence interval for the fitted linear trend (solid line). Each study was centered to the baseline reference dose for the estimation of increasing dose risk.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	4, 5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, supplementary table 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7, 8, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-9
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9, supplementary table 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9, supplementary table 3
22	Assessment of heterogeneity	6, 7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6, 7
24	Provision of appropriate tables and graphics	Tables 1, 2, Figs 1, 2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 2
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	-

28	Indication of statistical uncertainty of findings	11, table 2

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, 16
30	Justification for exclusion (eg, exclusion of non-English language citations)	5
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	17, 18

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies

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Primary Subject Heading:	Nutrition and metabolism

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Keywords:	uric acid, systematic review and meta-analysis, gout, sugars, fructose, food sources of fructose containing sugars

Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies

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ABSTRACT

Objective: Sugar-sweetened beverages (SSBs) are associated with hyperuricemia and gout. Whether other important food sources of sugars share this association is unclear.

Design: To assess the relation of important food-sources of fructose-containing sugars with incident gout and hyperuricemia, we conducted a systematic review and meta-analysis of prospective cohort studies.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library (through September 13, 2017). We included prospective cohort studies that investigated the relationship between food sources of sugar and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and assessed risk of bias. We pooled natural-log transformed risk ratios (RRs) using the generic inverse variance method with random effects model and expressed as RR with 95% confidence intervals (CIs). The overall quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: We identified three studies (154,289 participants, 1,761 cases of gout), comparing the highest with the lowest level of exposure for SSBs, fruit juice and fruits. No reports were found reporting incident hyperuricemia. Fruit juice and SSB intake showed an adverse association (fruit juice, RR = 1.77, 95% CI 1.20 to 2.61; SSB, RR = 2.08, 95% CI 1.40 to 3.08), when comparing the highest to lowest intake of the most adjusted models. There was no significant association between fruit intake and gout (RR 0.85, 95% CI 0.63 to 1.14). Strongest evidence was for the adverse association in SSB (moderate quality), and the weakest evidence was for the adverse association in fruit juice (very low quality) and the no effect in fruit intake (very low quality).

Conclusion: The adverse association of SSB is also seen for fruit juice consumption but does not extend to fruit intake. Further research is likely to improve our estimates.

Protocol registration: ClinicalTrials.gov identifier: NCT02702375

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review and meta-analysis assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
- Large prospective cohort studies that were of high quality and had a long duration of follow-up were included.
- Most of the pooled results showed good consistency (low between study heterogeneity) and sugar sweetened beverages showed evidence of a dose-response gradient.
- Only three prospective cohort studies with low external generalizability were available for inclusion.
- The observational design of the prospective cohort studies did not allow for causal inferences to be drawn.

INTRODUCTION

Gout and associated hyperuricemia are both associated with the development of hypertension, insulin resistance syndrome [1], and cardiovascular disease (CVD) [2]. Different diets have been shown to be associated with the development and severity of gout [3]. Foods that increase net ATP degradation including alcohol and high purine meats, are risk factors for gout [1]. Ingestion of large amounts of the monosaccharide fructose can increase uric acid production during its metabolism in the liver through unregulated phosphorylation of ATP into AMP [1] as demonstrated in randomized controlled trials [4, 5]. Similarly, in cohort studies, high intake of fructose-containing sugars in the form of sugar-sweetened beverages (SSBs) is associated with incident gout [6]. It is unclear whether the association seen for SSBs holds for other important food-sources of fructose-containing sugars, such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based products and sweets and desserts. As dietary guidelines and public health policy move from nutrient-based recommendations toward food and dietary-based recommendations [3, 4, 7], it is important to understand the contribution of these different food sources of fructose-containing sugars to the association of incident gout. To address this gap, we conducted a systematic review and meta-analysis of prospective cohort studies of the relation of important food sources of fructose-containing sugars with incident gout and hyperuricemia.

METHOD

Design

We followed the Cochrane Handbook for Systematic Reviews of Interventions [8] for the conduct of our systematic review and meta-analysis and reported our results according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [9] and preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) [10] guidelines. The study protocol was registered at ClinicalTrials.gov (identifier, NCT02702375).

Search strategy

We conducted systematic searches in MEDLINE, EMBASE and Cochrane through September 13, 2017 with no language restriction (**supplementary table 1**). Targeted manual searches served to supplement the database search; these included finding related papers from references of review papers, included studies, perusing articles with data from major prospective cohorts that usually report dietary data, and speaking to experts in the field.

Study selection

We included prospective cohort studies of ≥one-year duration that assessed the association of important food sources of fructose-containing sugars including non-alcoholic beverages (SSBs), cereal grain and grain based products, fruit and fruit-based products, dairy and dairy-based products, and sweets, chocolate and desserts with incident gout or hyperuricemia in participants free from gout or hyperuricemia at the start of the study. One-year duration was chosen as it allows for the development of diseases such as hyperuricemia and gout.

Data extraction

Two independent reviewers (SAC and QL) extracted relevant data from included studies onto standardized pro forma. Extracted data included sample size, subject characteristics, sources of fructose-containing sugars, exposure levels, duration of follow-up, number of gout or hyperuricemia cases, model adjustments, and the risk ratio with 95% confidence intervals (95% CI) per quantile of

intake. The main outcome was incident gout or hyperuricemia expressed as risk ratios (RR) with 95% confidence intervals (95% CI). Discrepancies were resolved by consensus.

Risk of bias

The same two independent reviewers (SAC and QL) assessed each study for risk of bias. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Points were awarded based on cohort selection, comparability of groups and assessment of outcomes, for a maximum total of 9 points [11]. Studies with ≥6 points were considered high quality [11]. Difference between reviewers was resolved by consensus.

Statistical analyses

Primary pooled analyses were conducted using Review Manager (RevMan) 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analysis and the assessments of dose response were performed using Stata 14 (StataCorp, College Station, TX, USA). Natural log-transformed RR for incident gout or hyperuricemia, comparing extreme quantiles (the highest exposure versus the lowest exposure or reference group), were pooled separately for each food source of fructose-containing sugars using the generic inverse variance method with DerSimonian and Laird random effects models and expressed as RRs with 95% CI. To overcome a unit-of-analysis error for studies appearing more than once in the same analysis, we divided participants equally among the multiple comparisons and readjusted the log-standard errors [8]. Inter-study heterogeneity was assessed with the Cochran Q statistic with significance set at $p<0.10$ and quantified with the I^2 statistic, where $I^2 \geq 50\%$ represented evidence of substantial heterogeneity [8]. Interaction between food sources was assessed using Cochrane Q statistic for between group interaction while adjusting

log-standard errors for units-of-analysis. We explored sources of heterogeneity by sensitivity analyses. Sensitivity analyses, where each study was systematically removed, and effect size was recalculated in the remaining studies, were carried out to explore the impact of individual studies on the pooled risk. As ≥10 cohort comparisons were not available, *a priori* subgroup analyses were not performed. Linear and non-linear dose-response analyses were assessed using generalized least squares trend estimation models (GLST) and fixed-effects restricted cubic spline model with 3 knots, respectively [12]. Publication bias was not assessed as the number of cohort comparisons was less than 10.

Grading of the evidence

The overall quality and the strength of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [13-25]. The evidence was graded as high, moderate, low, or very low quality, with observational studies starting with an initial grade of 'low'. This then can be downgraded based on 5 pre-specified criteria or upgraded based on 3 pre-specified criteria. Criteria to downgrade included risk of bias (weight of studies showed risk of bias as assessed by low NOS <6), inconsistency (substantial unexplained inter-study heterogeneity i.e. I^2>50%), indirectness (presence of factors that limit the generalizability of the results), imprecision in the pooled risk estimate (the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for benefit or harm (RR 0.9–1.1)), and publication bias (evidence of small-study effect). Conversely, criteria to upgrade included a large magnitude of effect (RR>2 or RR<0.5 in the absence of plausible confounders), dose–response gradient or reasonable evidence of attenuation of the pooled effect estimate by confounders.

Patient and public involvement

Patients and the public were not involved in the study.

RESULTS

Search results

Figure 1 shows the flow of the systematic search and study selection. Of the 309 reports identified by the literature search, three reports with data from three prospective cohort studies met our inclusion criteria [26-28]: Nurses' Health Study (NHS) [27], Health Professionals Follow-up Study (HPFS) [26] and the National Runner's Health Study [28]. All three reports reported the association of food sources of fructose-containing sugars on incident gout, but none on incident hyperuricemia. These reports involved a total of 154,289 participants with 1,761 incident cases of gout. Two reports each reported data on fruit intake [n= 75,383; 983 cases] [26, 28], fruit juice [n= 125,299; 1,533 cases] [26, 27] and SSBs [n=125,299; 983 cases] [26, 27]. We did not identify prospective cohort studies reporting the association of other food sources of fructose-containing sugars (e.g. cereal grain and grain-based products, sweets and desserts, dairy and dairy based products and chocolate) with incident gout fitting our inclusion criteria.

Study characteristics

Table 1 lists the characteristics of the included prospective cohort studies. All studies were performed in the USA. The median age of the included participants ranged from 30 to 75. The median follow-up period was 17 years (range, 12 to 22 years) for SSB, 18.7 years (12 to 22 years) for fruit juice and 9.9 years (7.74 to 12 years) for fruit. Dietary intake assessments were done with self-reported, validated food frequency questionnaires (FFQs) in all studies. Quantiles of exposure depended on the food source. Medians for the lowest and highest quantiles of exposure were <1 servings/month and ≥14

servings/week respectively for SSB; ≤1 servings/month and ≥14 servings/week respectively for fruit juice; and ≤0.4 servings/week (range, <0-0.5 servings/week) and ≥8 servings/day (range, ≥2-14 servings/day), respectively for fruit. The ascertainment of incident gout in both HPFS and NHS cohorts [26, 27] was through self-report, followed by supplementary surveys of the subjects based on the American College of Rheumatology gout survey criteria [29] to confirm that the diagnosis. The authors defined individuals with gout that met ≥6 of the 11 criteria for gout. In addition, in a sub-sample the self-reported diagnoses were validated with medical records. As for the NRHS cohort [28], incident gout was self-reported based upon physician diagnosis.

Supplementary table 2 shows the complete list of adjusted confounding variables for the most adjusted models for each of the included prospective cohorts. The median number of variables in the most adjusted models was 14 (range, 6 to 14). All studies adjusted for primary and secondary confounders such as age, body mass index (BMI) and history of hypertension. Each of the three cohorts were single-sex studies, so adjustment for sex was not necessary. The NHS cohort study authored by Choi *et al.* 2010 [27] and NRHS study by Williams *et al.* [28] were agency funded, while the HPFS paper authored by Choi *et al.* 2008 [26] was funded by both agency and industry.

Study Quality

Supplementary table 3 shows the study quality assessments by the NOS scale. There was no evidence of serious risk of bias. Only NRHS cohort scored <6 on the NOS scale, which denotes lower quality [28].

Fruit intake on incident gout

Figure 2 shows the relationship between food sources of fructose-containing sugars intake and incident gout. There was significant interaction between the food sources (p=0.02). When comparing the highest to the lowest fruit intake, no association was shown for fruit intake on incident gout (RR = 0.85, [95% CI 0.63 to 1.14]). There was evidence of significant interstudy heterogeneity (I^2 = 93%, p<0.001).

Fruit juice intake on incident gout

Figure 2 shows the relationship between fruit juice intake and incident gout. When comparing the highest to lowest intake, an adverse association was shown for fruit juice intake on incident gout (RR 1.77, [95% CI 1.20 to 2.61]). There was no evidence of significant interstudy heterogeneity (I^2 = 0% [95% CI 0% to 90%], p = 0.54).

SSB intake on incident gout

Figure 2 shows the relationship between SSB intake and incident gout. When comparing the highest with the lowest intake, an adverse association was shown for SSB intake on incident gout (RR=2.08 [95% CI 1.40 to 3.08]). There was no evidence of significant interstudy heterogeneity (I^2 = 0%, p = 0.52).

Additional analysis

Sensitivity analysis (the systematic removal of each study), publication bias and subgroup analyses could not be performed due to the small number of studies included in each analysis (n=2).

Dose-response analysis

A random-effect GLST model showed a significant dose-response relationship between fruit juice intake and incident gout per serving/week (RR = 1.03, 95% CI 1.02 to 1.05, p<0.001) (**supplementary figure 1**), and for SSB intake (RR = 1.04, 95% CI 1.02 to 1.07, p<0.001) (**supplementary figure 2**). Fruit juice intake showed a significant departure from linearity (p = 0.038), and visual inspection of the graph (**supplementary figure 1**) indicated a plateau for risk increase after ≥5 servings per day. There was no evidence for departure from linear dose response gradient or dose thresholds for SSB intake while using the restricted cubic spline model (p = 1.29) (**supplementary figure 2**). Dose-response modeling was not conduced for fruit intake due to lack of data.

GRADE assessment

Table 2 shows the GRADE assessment of individual food sources of fructose-containing sugars. The quality of evidence of an adverse association from both fruit and fruit juice was rated as very low, with downgrades to the lowest level for indirectness for fruit intake, and for inconsistency, indirectness and imprecision for fruit juice intake. The quality of evidence of an adverse association of SSB intake with incident gout was rated as moderate, with a downgrade of one level for indirectness but upgrade of two levels for a large magnitude effect and significant dose-response association.

DISCUSSION

We conducted a systematic review and meta-analysis of studies investigating the relation of important food sources of fructose-containing sugars with incident gout. We identified three prospective cohort studies [26-28] comprising of 154,289 participants and 1,761 cases of incident gout. The pooled analyses revealed that there was moderate quality evidence that SSB intake was

associated with 208% increase in risk of incident gout when comparing the highest with the lowest intake. Similarly, there was low quality evidence that fruit juice intake was associated with a 77% increase in risk of incident gout, but fruit intake did not show any significant association with incident gout (low quality evidence). There was no data available of other important food sources of fructose-containing sugars.

Findings in the context of the literature

Our results are consistent with previous research which indicate that intake of certain food sources of fructose-containing sugars are associated with the risk of gout. Our previous systematic review and meta-analysis of prospective cohort studies that assessed fructose intake, found a harmful relationship between fructose consumption and gout [6]. While that study indicated that fructose moiety might possibly drive the association with gout, all the fructose data was derived from SSB intake. Another systematic review of the literature identified numerous dietary factors associated with the risk of gout including meat, alcohol, seafood and SSBs, but also that lower risk was associated with the intake of dairy, folate and coffee [3].

SSBs are a major source of fructose-containing added sugars in the western diet comprising around 30% of intake of added sugars in the USA [30] and around 24% in Canada [31]. Excess intake of fructose can increase uric acid though an unregulated phosphofructose kinase pathway that uses substantial amounts of ATP [32] to convert fructose into fructose-1-phosphate in the liver [33]. Mechanistically, net ATP degradation leads to accumulation of AMP, which is subsequently degraded to uric acid. Additionally, fructose can increase de novo purine synthesis, which further produces uric acid [1]. This increase in uric acid can lead to the development of gout. Since we were unable to

investigate the relationship between food sources of fructose-containing sugars and hyperuricemia, we cannot validate this mechanism. It is possible, that fructose increases the risk of gout independently of serum uric acid levels. However, since the link between fructose and serum uric acid [34-37], and the link between serum uric acid and the development of gout have been independently established [1], it is unlikely that fructose increases the risk of gout without using uric acid as an intermediate.

We identified adverse association of fruit juices intake with incident gout. The two studies that contributed to this result [26, 27] were both performed in two Harvard cohorts which do not differentiate between fruit drinks and pure fruit juice, the former being largely similar to SSBs i.e. mainly sugar and water. This is supported by studies investigating pure fruit juice and fruit drinks which have shown divergent response for cardiometabolic disease [38, 39].

We did not see any association between fruit intake and incident gout but the effect estimates in the two studies were in opposite direction. The NRHS [28] cohort showed a 51% reduction in risk of gout when with high intake of fruit whereas the HPFS [26] cohort showed a 63% increased risk — both studies were performed in men. These discordant results highlight the differences in the studies. NHPS cohort [26] only measured oranges and apples, fruit high in fructose, while NRHS [28] cohort assessed all fruit and its increasing intake, as the authors admit, might represent a healthier dietary intake. It is possible that higher intake of fruits in NRHS might be associated with high intake of dairy or coffee, which have been associated with lowering the risk of gout [3] and not measured in NRHS. Furthermore, case-control and cross-sectional studies have shown a protective effect of total fruit intake with gout albeit in Asian populations [40, 41], their relevance to the included studies,

conducted in a largely Caucasian population, might be limited. The harmful association for oranges, which are rich in vitamin C, in HPFS [26] cohort is at odds with its own result in another paper, in which the authors demonstrated a protective association of vitamin C intake with gout [42]. Fruits are rich in fructose; however, fruit intake has consistently shown a benefit for cardiometabolic risk factors, cardiometabolic diseases and all cause-mortality [43-49] even though the fructose in fruit can increase uric acid levels. More data might clarify this association.

We could not find any prospective studies looking at the association of food sources of fructose-containing sugars and hyperuricemia even though hyperuricemia is the most important risk factor for gout [3, 50]. Hyperuricemia is also a risk factor for hypertension , metabolic syndrome, diabetes , and CVD [51]. Several cross-sectional analyses have investigated the link between SSB consumption and serum uric acid levels, showing a positive relationship [34-37]. In contrast, the analysis of the National Health and Nutrition Examination Survey (NHANES) showed no link between dietary fructose and risk of hyperuricemia, indicating that perhaps different food sources of fructose-containing sugars may have different effects on serum uric acid. This point is reinforced by another analysis of NHANES data that showed a relationship of SSB intake with higher serum uric acid concentration, but not with fruit juice [52]. Future studies investigating food sources of sugars and risk of hyperuricemia may help to elucidate some of the above inconsistent findings.

We were not been able to find prospective cohort studies investigating the association of other food sources of fructose-containing sugars and the risk of gout. However, cross-sectional studies suggest that cereal and yogurt may be associated with lower serum uric acid [53]. More research is needed to clarify the relationship between other food sources of fructose-containing sugars and the risk of gout.

Strengths and limitations

Our analysis has many strengths. First, we employed a comprehensive systematic search across major databases and the quantitative synthesis of results. Second, the studies we included had a substantial number of participants and cases of gout (154,289 participants and 1,761 gout cases) leading to increased precision. Additionally, the median follow-up duration was greater than 10 years, which allowed for enough time from exposure for the development of disease. Another strength is the use of validated measures of intake like food frequency questionnaires. The two Harvard cohorts [26, 27] administered FFQ multiple times, and validated them on a subsample, allowing for more accurate and robust long-term intakes compared to the NRHS [28] cohort, which only measured dietary intakes at baseline. In our analysis, we made use of GRADE to evaluate the quality and strength of our analysis and evaluate our confidence in the estimates.

There are some notable limitations to our systematic review and meta-analysis. First, while we included the most adjusted multivariable models for this analysis, there is always potential for unmeasured and residual confounding, since the studies included were observational in nature. This explains why GRADE starts at “low quality” for observational studies. Second, there was evidence of indirectness in some of the relationships. All studies were conducted in the USA, and two of the three studies were in health professionals. The two Harvard [26, 27] cohorts included only middle aged or older people who worked in health care and who were predominately white and the NRHS [28] cohort included only middle to old aged physically active men. Thus, the specific nature of the included studies’ population limits the generalizability of our results to other populations and geographical locations; however, the biological process of diet and gout are still likely to be similar to

other populations. While, genome wide association studies have found numerous genes that increase one's risk for gout [54] and some ethnic groups may be more susceptible than others [1], it is not known if the association of fructose intake with gout is modified by genes. Third, sources of heterogeneity remained unexplained; with only three studies, we were unable to assess publication bias or perform sensitivity or a priori subgroup analysis. Thus for these reasons, data pertaining to SSB and fruit juice intake and incident gout received a GRADE of moderate and very low quality, respectively, indicating that further studies in this regard is likely to impact our certainty in the effect estimate and may change the estimate for SSB and that our certainty in the estimate for fruit juice is very uncertain; therefore, caution should be used when interpreting these results. Similarly, for fruit, which received a GRADE of very low, so we are very uncertain in these results and caution should be used in the interpretation of these results.

Implications

Dietary guidelines have shifted their focus from nutrients based recommendations to food and dietary pattern-based recommendations [55], since it has been recognized that one does not eat nutrients in isolation, but as a part of food. Interactions between nutrients in food are complex and important components of disease risk [55]. Our findings support this view in relation to food sources of fructose-containing sugars and their relationship with gout. Our findings also have implications for recommendations for the prevention of gout. Conventional dietary recommendations for gout have focused on restriction of purine intake; however, low-purine diets are often high in carbohydrates, including fructose-rich foods [56]. We have shown an adverse association between fruit juice and SSBs, supporting the recommendations to limit their intakes. Since we did not have data relating to

children, hyperuricemia or other food sources of fructose-containing sugars, we cannot extend our conclusion to these groups of individuals or these foods.

Conclusion

Our systematic review and meta-analysis of prospective cohort studies showed an adverse association between SSBs and fruit juice with risk of gout, while there was no association with fruit intake. The strength of the evidence was moderate for SSB intake and very low for fruit juice and fruit intake, as assessed by GRADE. For SSBs, the true association is likely to be close to the estimate, but there is a possibility that it is substantially different. For fruit juice and fruit intake, the true association are likely to be substantially different from the estimate and future research will very likely impact our confidence in the effect estimates and likely to change them [57]. Our results are consistent with the literature that certain food sources of fructose-containing sugars especially SSBs are a risk factor for the development of gout. We were unable to identify studies assessing food sources of fructose-containing sugars and hyperuricemia, indicating a gap in the literature. Given that incident gout is rising [7, 58-63], and that gout and hyperuricemia are both associated with metabolic syndrome, myocardial infarction, diabetes and premature death [1, 2, 64], it is becoming increasingly important to identify and understand risk factors for developing gout. It is imperative for additional prospective studies to assess the intake of various food sources of fructose-containing sugars and their relationship with gout and hyperuricemia in diverse populations. This will help identify to what extent does our foods mediate the risk for hyperuricemia and gout and will further inform health care professionals, policymakers, and aid in the development of improved dietary guidelines for the prevention and management of gout and hyperuricemia.

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Data Sharing

There is no additional unpublished data available from the study.

Competing Interests

TA Khan has received research support from the Canadian Institutes of health Research (CIHR) and an unrestricted travel donation from Bee Maid Honey Ltd. **RJ de Souza** has served as an external resource person to the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health (guidelines for trans fats and saturated fats), and received renumeration from WHO for travel and accommodation. He also received compensation for contract research conducted for the Institute of Nutrition, Metabolism, and Diabetes at the Canadian Institutes of Health Research (CIHR), Health Canada and WHO. He has received research grants from the

Canadian Foundation for Dietetic Research and CIHR, and lecture fees from McMaster Children's Hospital. **TMS Wolever** and his wife are part owners and employees of Glycemic Index Laboratories. **CWC Kendall** has received research support from the Advanced Foods and Materials Network, Agricultural Bioproducts Innovation Program through the Pulse Research Network, Agriculture and Agri-Food Canada, Almond Board of California, Barilla, Calorie Control Council, CIHR, Canola Council of Canada, The International Tree Nut Council Nutrition Research & Education Foundation, Kellogg, Loblaw Companies Ltd., Pulse Canada, Saskatchewan Pulse Growers and Unilever. He has received consultant fees from American Pistachio Growers; speaker fees from American Peanut Council, Tate & Lyle and The WhiteWave Foods Company; and travel funding from Sabra Dipping Company, Tate & Lyle, International Tree Nut Council Research & Education Foundation, California Walnut Commission, Sun-Maid, The Peanut Institute, General Mills, Oldways Foundation and International Nut and Dried Fruit Council Foundation. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European Association for the Study of Diabetes (EASD). He is a member of the International Carbohydrate Quality Consortium (ICQC), Secretary of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. **JL Sievenpiper** has received research support from the CIHR, Canadian Diabetes Association (CDA), PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), American Society for Nutrition (ASN), Calorie Control Council, INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, and The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers). He has received speaker fees and/or honoraria from the CDA, CNS, Dr. Pepper Snapple Group, Dairy Farmers of Canada, Nutrition Foundation of Italy (NFI), C3 Collaborating for Health, Sprim Brasil,

WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, The Ginger Network LLC, International Sweeteners Association, and Pulse Canada. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice Guidelines Expert Committees of the CDA, European Association for the study of Diabetes (EASD), and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the ASN. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada. No competing interests were declared by **Q Liu, S Ayoub-Charette, F Au-Yeung, S Blanco Mejia, LA Leiter**. There are no patents, products in development or marketed products to declare.

Authors' contributions

All authors had full access to all of the data (including statistical reports and tables) in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: J.L. Sievenpiper.

Analysis and interpretation of the data: Q. Liu, S. Ayoub-Charette, T.A.Khan, F. Au-Yeung, S. Blanco Mejia, R.J. de Souza, T.M.S. Wolever, L.A. Leiter, C.W.C. Kendall, J.L. Sievenpiper.

Drafting of the article: Q. Liu, T.A. Khan, J.L. Sievenpiper.

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Statistical expertise: T.A. Khan, R.J. de Souza

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Administrative, technical, or logistic support: S. Blanco Mejia

Collection and assembly of data: Q. Liu, S. Ayoub-Charette, F. Au-Yeung

Guarantor: J.L. Sievenpiper

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TABLES AND FIGURES

Figure 1 Summary of evidence search and selection. Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia. Of the 309 studies initially identified, 294 were excluded based on title and/or abstract. The remainder were read in full by two independent reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort studies.

Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-adjusted multivariate models accounting for food sources of fructose-containing sugars intake were used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using the Cochran Q statistic and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit juices. * The number of cases and participants are divided equally between the multiple entries of the study to ensure total count gives unique individuals. To overcome a unit-of-analysis error for studies appearing more than once in the same analysis, we readjusted the log-standard errors to participants equally among the multiple comparisons and.

Table 1 Characteristics of prospective cohort studies investigating food sources of fructose-containing sugar intake and incident gout.

Study, year (Reference)	Cohort	Country	Participants	Incident Cases	Age (mean years, range)	Follow-up (mean, range)	Dietary Assessment	Food source of fructose-containing sugars	Frequency of Administration	Quantiles	Exposure (servings/ week, median, range)	Serving size	Outcome assessment	Funding Source*
Choi *et al.*, 2008 (26)	HPFS NHS	USA	46,393 (M)	755	52.5 (40-75)	12 years	Validated SFFQ	SSBs Fruit Juice Fruit	4 times	Quintiles	¼ - ≥14	Not reported	Record linkage	Agency and Industry
Choi *et al.*, 2010 (27)	NHS	USA	78,906 (F)	778	49 (30-55)	22 years	Validated SFFQ	SSBs Fruit Juice	4 times	Sextiles	¼ - ≥14	Not reported	Self-reported	Agency
Williams, 2008 (28)	NRHS	USA	28,990 (M)	228	44.9	7.7 years (5.9-9.6)	Validated SFFQ	Fruit	1 (baseline)	Quartiles	¼ – 2 (0 – ≥2)	Not reported	Self-reported	Agency

Abbreviations: HPFS = Health Professionals Follow-Up Study; NHS = Nurses Health Study; NRHS =National Runner's Health Study; M=males; F=females; SFFQ = Semi quantitative Food-Frequency Questionnaire; SSBs = Sugar Sweetened Beverages.

*Agency funding is that from government, university or not-for-profit health agency sources.

Table 2 GRADE assessment of individual food source of fructose-containing sugars.

Quality assessment								Study event rates (%)	Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations		Relative Risk (95% CI)	Importance
Sugar sweetened beverages intake on incident gout (follow-up median 17 years)										
2	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	No serious imprecision	Undetected[2]	Large magnitude of effect[3] Dose-response[4]	1533/125299 (1.22%)	2.08 [1.40, 3.07]	⊕⊕⊕◯ **Moderate** [1,2,3,4] Due to downgrade for indirectness and upgrade for large magnitude effect and dose-response
Fruit juice intake on incident gout (follow-up median 17 years)										
2	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirectness [1]	No serious imprecision	Undetected[2]	None	1533/125299 (1.22%)	1.73 [1.17, 2.57]	⊕◯◯◯ **Very low**[1,2] Due to downgrade for indirectness
Fruit intake on incident gout (follow-up median 9.87 years)										
2	Observational studies	No serious risk of bias	Very serious inconsistency[5]	Serious indirectness [1]	Serious[6]	Undetected[2]	None	983/75383 (1.3%)	0.89 [0.27, 2.87]	⊕◯◯◯ **Very low**[1,2,5,6] Due to downgrade for inconsistency, indirectness and imprecision

[1]Downgrade for indirectness, as the study population is specific to a group of the population like professionals, nurses or runners.

[2]No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effect (<10 cohort included in our meta-analysis).

[3]Upgrade for a large magnitude of effect (RR>2.0).

[4]Upgrade for a dose response gradient, as the GLST dose-response analysis revealed a significant linear relationship between sugar sweetened beverage intake and incident gout (P=0.0001).

[5]Downgrade for very serious inconsistency, as the two studies included had opposite associations and there was evidence of substantial inter-study heterogeneity (I^2=94%, p<0.0001). Due to the small number of studies included in the analysis, subgroup analysis was not performed.

[6]Downgrade for serious imprecision, as the lower bound of the 95% CI (RR, 0.27) includes clinically important benefit (RR<0.9), while the upper bound of the 95% CI (RR, 2.87) crosses the minimally important difference of 10% (RR>1.1).

Figure 1 Summary of evidence search and selection

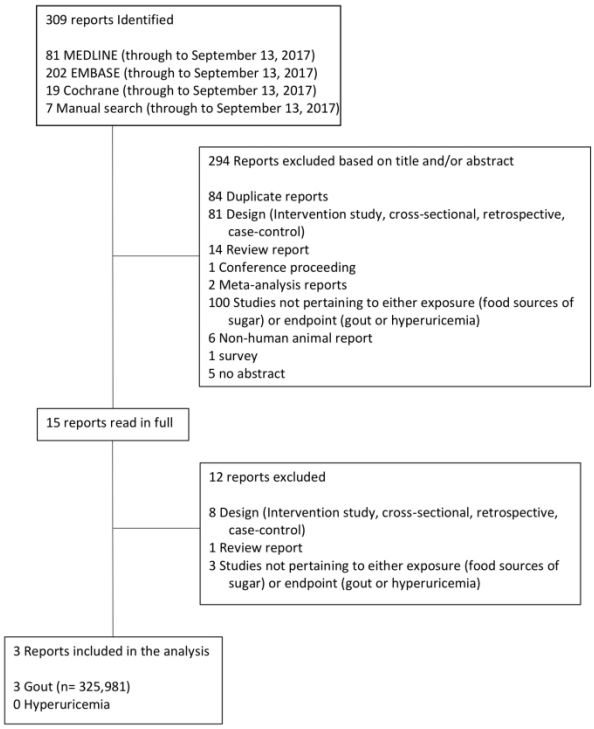

Figure 1. Summary of evidence search and selection

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Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout.

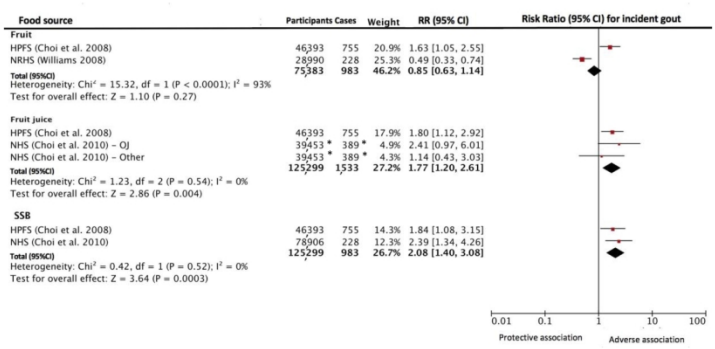

Figure 2. Relation between intake of fruit, fruit juice and SSB incident gout.

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Supplementary material

SUPPLEMENTARY TABLES

SUPPLEMENTARY FIGURES

Supplementary table 1. Search terms

Database and search terms

MEDLINE	EMBASE	Cochrane
1. sugar*.mp.	1. sugar*.mp.	1. sugar*.mp.
2.exp fructose/	2. exp sugar/	2. exp fructose/
3. fructose.mp.	3. exp fructose/	3. fructose.mp.
4. HFCS.mp.	4. fructose.mp.	4. HFCS.mp.
5. exp high fructose Corn Syrup/	5. HFCS.mp.	5. exp Nutritive Sweeteners/
6. sucrose.mp.	6. exp high fructose Corn Syrup/	6. sucrose.mp.
7. exp dietary Sucrose/	7. sucrose.mp.	7. exp dietary sucrose/
8. sugar sweetened beverage*.mp.	8. exp dietary Sucrose/	8. sugar sweetened beverage*.mp.
9. ssb.mp.	9. sugar sweetened beverage*.mp.	9. ssb.mp.
10. soda.mp.	10. SSB.mp.	10. soda.mp.
11. soft drink*.mp.	11. soda.mp.	11. soft drink*.mp.
12. exp carbonated beverages/	12. soft drink*.mp.	12. exp carbonated beverages/
13. carbonated beverages.mp.	13. exp soft drink/	13. non alcoholic beverage*.mp.
14. non alcoholic beverage*.mp.	14. exp carbonated beverages/	14. nonalcoholic beverage*.mp.
15. nonalcoholic beverage*.mp.	15. carbonated beverages.mp.	15. exp energy drinks/
16. exp energy drinks/	16. non alcoholic beverage*.mp.	16. energy drink*.mp.
17. energy drink*.mp.	17. nonalcoholic beverage*.mp.	17. smoothie*.mp.
18. smoothie*.mp.	18. exp energy drinks/	18. ((fruit or vegetable) and juice*).mp.
19. exp "fruit and vegetable juices"/	19. energy drink*.mp.	19. fruit.mp.
20. fruit.mp.	20. smoothie*.mp.	20. exp fruit/
21. exp fruit/	21. exp "fruit and vegetable juices"/	21. exp honey/
22. exp honey/	22. fruit.mp.	22. y*g*rt.mp.
23. y*g*rt.mp.	23. exp fruit/	23. exp yogurt/
24. exp yogurt/	24. exp honey/	24. ice cream*.mp.
25. ice cream*.mp.	25. y*g*rt.mp.	25. icecream*.mp.
26. icecream*.mp.	26. exp yoghurt/	26. exp ice cream/
27. exp ice cream/	27. ice cream*.mp.	27. cereal*.mp.
28. exp edible grain/	28. icecream*.mp.	28. dessert*.mp.
29. cereal*.mp.	29. exp ice cream/	29. sweets.mp.
30. dessert*.mp.	30. cereal*.mp.	30. confection*.mp.
31. sweets.mp.	31. dessert*.mp.	31. pastries.mp.
32. confection*.mp.	32. sweets.mp.	32. biscuit*.mp.
33. pastries.mp.	33. confection*.mp.	33. cookie*.mp.
34. biscuit*.mp.	34. exp bakery product/	34. cake*.mp.
35. cookie*.mp.	35. pastries.mp.	35. candy.mp.
36. cake*.mp.	36. biscuit*.mp.	36. candies.mp.
37. candy.mp.	37. cookie*.mp.	37. exp candy/
38. candies*.mp.	38. cake*.mp.	38. (chocolate adj2 milk).mp.
39. exp candy/	39. candy.mp.	39. cohort.mp.
40. (chocolate adj2 milk).mp.	40. candies*.mp.	40. exp Prospective Studies/
41. chocolate.mp	41. chocolate.mp	41. chocolate.mp
42. exp chocolate/	42. exp chocolate/	42. cacao.mp
43. cacao.mp	43. cacao.mp	43. exp cacao/
44. exp cacao/	44. exp cacao/	44. (prospective adj2 (cohort or study)).mp.
45. cohort.mp.	45. (chocolate adj2 milk).mp.	45. exp follow-up studies/
46. exp prospective study/	46. cohort.mp.	46. exp multivariate analysis/
47. (prospective adj2 (cohort or study)).mp.	47. exp prospective study/	47. exp proportional hazards models/
48. exp multivariate analysis/	48. (prospective adj2 (cohort or study)).mp.	48. follow up study.mp.
49. exp follow up studies/	49. exp multivariate analysis/	49. (longitudinal adj2 study).mp.
50. exp proportional hazards models/	50. exp proportional hazards models/	50. gout/

51. follow-up study.mp.	51. follow-up study.mp.	51. gout*.mp
52. (longitudinal adj2 study).mp.	52. (longitudinal adj2 study).mp.	52. uric acid*.mp
53. gout/	53. gout/	53. hyperuricemia*.mp
54. gout*.mp.	54. gout*.mp.	54. hyperuricemia/
55. uric acid*.mp.	55. uric acid*.mp.	55. hyperuricaemia*.mp
56. hyperuricemia*.mp.	56. hyperuricemia*.mp.	56. uric.mp
57. hyperuricemia/	57. hyperuricemia/	57. or/1-43
58. hyperuricaemia*.mp.	58. hyperuricaemia*.mp.	58. or/44-49
59. uric.mp.	59. uric.mp.	59. or/50-56
60. or/1-44	60. or/1-45	60. and/57-59
61. or/45-52	61. or/46-52	
62. or/53-59	62. or/53-59	
63. and/60-62	63. and/60-62	

Database	Total
MEDLINE: September 13, 2017	81
EMBASE: September 13, 2017	202
Cochrane: September 13, 2017	19
Manual search	7
Total	309

For all databases, the original search was September 13, 2017.

Supplementary table 2. Analysis of confounding variables among 3 studies of food sources of sugar intake and incident gout

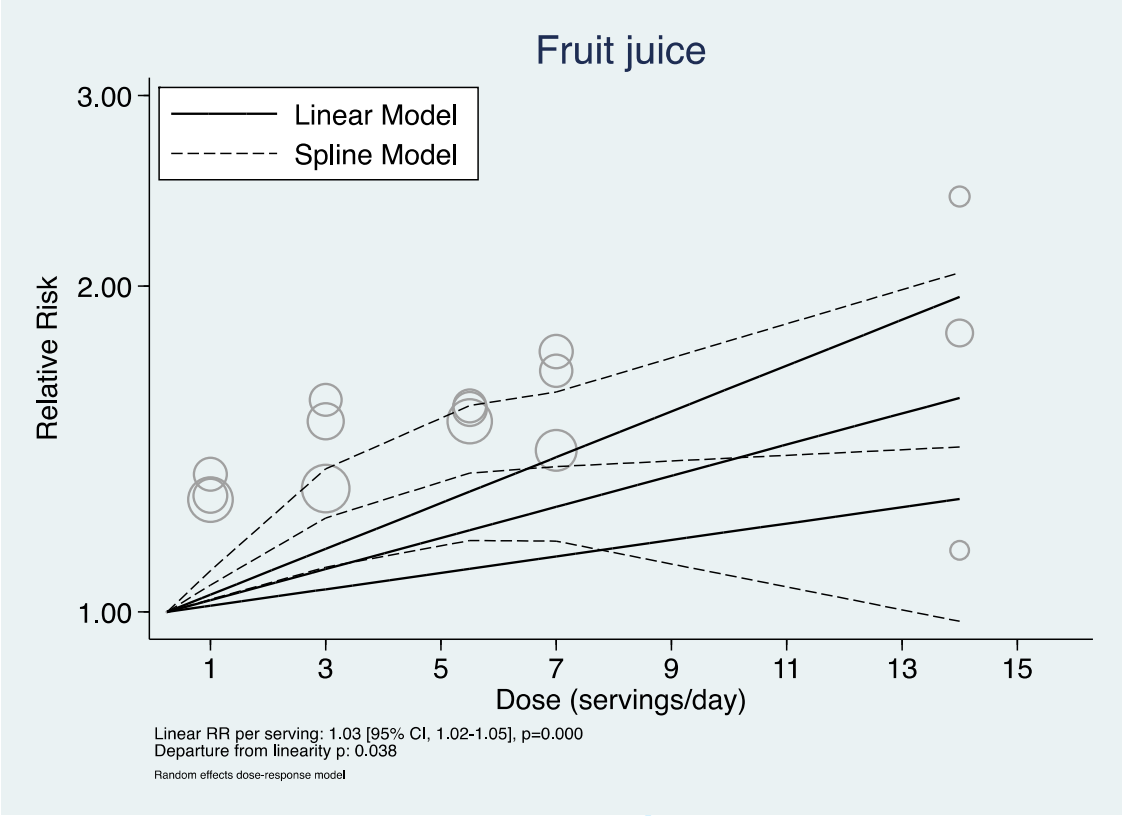
Study	HPFS (Choi *et al.*, 2008)	NRHS (Williams, 2008)	NHS (Choi *et el.*, 2010)
Number of variables in fully adjusted model	14	6	14
Number of multivariable models presented	2	1	3
Timing of measurement of confounding variables	2y	BL*	2y
Pre-specified primary confounding variable			
Age	✓	✓	✓
Pre-specified secondary confounding variables			
Marker of overweight/obesity (Body mass index, weight, waist circumference, waste to hip ratio)	✓		✓
Sex	M §	M §	F ‡
History of gout/hyperuricemia			
Diabetes			
Physical activity			
Lipid medication/dyslipidemia			
Animal protein intake	✓		✓
Hypertension or blood pressure medication including diuretics	✓		✓
Other confounding variables			
Lifestyle factors			
Weekly intake of:			
Alcohol	✓	✓	✓
Seafood	✓		✓
Purine from vegetables	✓		✓
Dairy food	✓		✓
Vitamin C	✓		✓
Coffee		✓	
Meat		✓	
Fish			✓∇
Diet soda	✓∇		✓∇
Sugar-sweetened cola	✓∇		✓∇
Other soda	✓∇		✓∇
Orange or apple juice	✓∇		✓∇
Other fruit juice			✓∇
Orange or apple	✓∇		
Total energy	✓		✓
Weekly intake of aspirin		✓	
Medical history			
History of Hypertension	✓	✓	✓
History of chronic Renal failure	✓		
Menopause status			✓
Use of hormonal therapy			✓

HPFS=Health Professionals Follow-Up Study, NHS=Nurses Health Study
*Denotes confounders measured only at baseline years.
† Indicates confounders measured every 2 years.
‡ Indicates the study includes only female subjects
§ Indicates the study includes only male subjects
∇ Indicates the confounder was present in some, but not all, models.

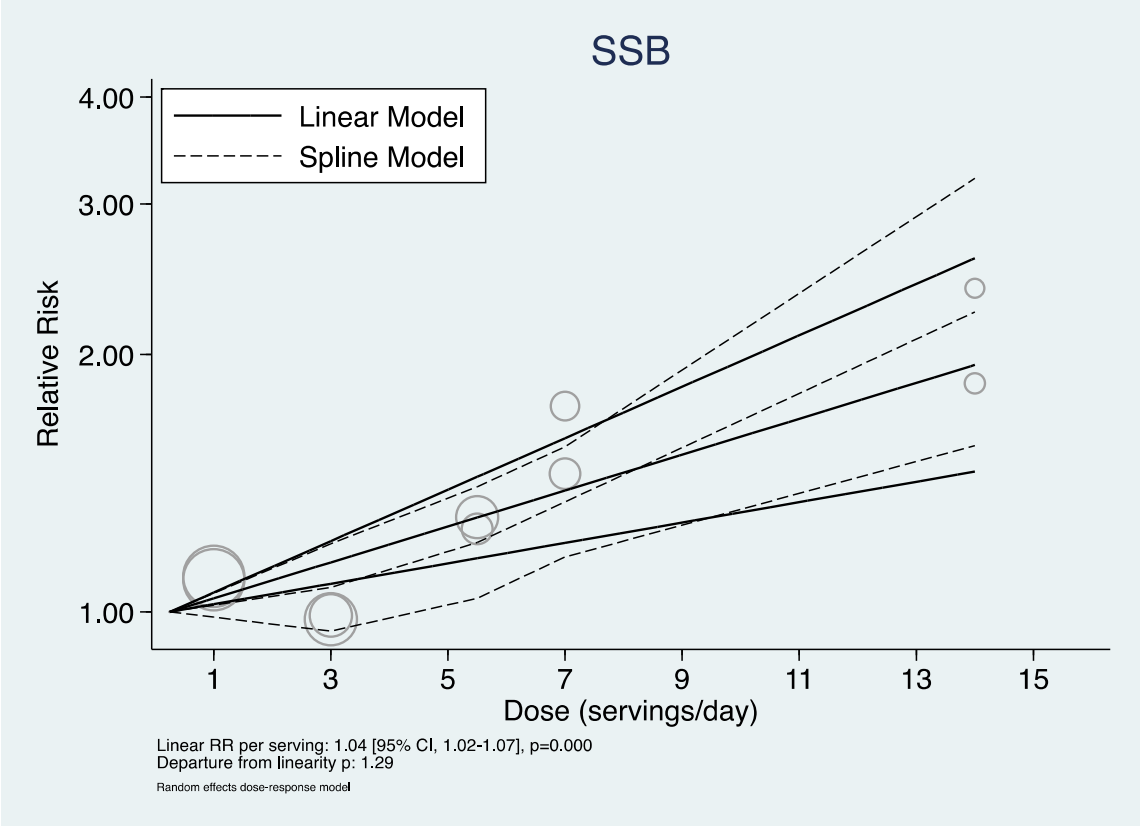
Supplementary table 3. Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies

Study	Selection*	Outcome†	Comparability‡	total§
Choi *et al.*, 2008	2	3	1	6
Williams, 2008	2	2	1	5
Choi *et al.*, 2010	2	3	1	6

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline.
†Maximum 3 points awarded for follow-up length, adequacy of follow-up and outcome assessment.
‡Maximum 2 points awarding for controlling for the pre-specified primary confounding variable (age) and >6 of the secondary confounding variables (sex, body mass index, history of gout or hyperuricemia, diabetes, alcohol, physical activity, lipid medication/dyslipidemia, animal protein intake, hypertension or blood pressure medication including diuretics).
§A maximum of 9 points could be awarded.



Supplementary figure 1. Linear and non-linear dose-response relationship between fruit juice intake and incident gout per serving/week. Linear dose response data (solid lines) were modeled using the generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines) were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval for the fitted trend are shown above and below the solid line. Each study was centered to its own baseline reference dose when estimating increasing dose risk.



Supplementary figure 2. Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week. Linear dose response data (solid lines) were modeled using the generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines) were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval for the fitted trend are shown above and below the solid line. Each study was centered to its own baseline reference dose when estimating increasing dose risk.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	4, 5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, supplementary table 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7, 8, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-9
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9, supplementary table 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9, supplementary table 3
22	Assessment of heterogeneity	6, 7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6, 7
24	Provision of appropriate tables and graphics	Tables 1, 2, Figs 1, 2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 2
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	-

28	Indication of statistical uncertainty of findings	11, table 2

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, 16
30	Justification for exclusion (eg, exclusion of non-English language citations)	5
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	17, 18

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies

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Primary Subject Heading:	Nutrition and metabolism

Secondary Subject Heading:	Rheumatology, Diabetes and endocrinology
Keywords:	uric acid, systematic review and meta-analysis, gout, sugars, fructose, food sources of fructose containing sugars

Important food sources of fructose-containing sugars and incident gout: A systematic review and meta-analysis of prospective cohort studies

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Supplemental Material: 3 Tables and 2 Figures
Abstract Word Count: 298
Manuscript Word Count: 3,835
Key Words: sugars, fructose, food sources of fructose containing sugars, gout, uric acid and systematic review, meta-analysis

ABSTRACT

Objective: Sugar-sweetened beverages (SSBs) are associated with hyperuricemia and gout. Whether other important food sources of sugars share this association is unclear.

Design: To assess the relation of important food-sources of fructose-containing sugars with incident gout and hyperuricemia, we conducted a systematic review and meta-analysis of prospective cohort studies.

Methods: We searched MEDLINE, EMBASE and the Cochrane Library (through September 13, 2017). We included prospective cohort studies that investigated the relationship between food sources of sugar and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and assessed the risk of bias. We pooled natural-log transformed risk ratios (RRs) using the generic inverse variance method with random effects model and expressed as RR with 95% confidence intervals (CIs). The overall certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Results: We identified three studies (154,289 participants, 1,761 cases of gout), comparing the highest with the lowest level of exposure for SSBs, fruit juice and fruits. No reports were found reporting incident hyperuricemia. Fruit juice and SSB intake showed an adverse association (fruit juice, RR = 1.77, 95% CI 1.20 to 2.61; SSB, RR = 2.08, 95% CI 1.40 to 3.08), when comparing the highest to lowest intake of the most adjusted models. There was no significant association between fruit intake and gout (RR 0.85, 95% CI 0.63 to 1.14). Strongest evidence was for the adverse association in SSB (moderate certainty), and the weakest evidence was for the adverse association in fruit juice (very low certainty) and the no effect in fruit intake (very low certainty).

Conclusion: There is an adverse association of SSB and fruit juice consumption with gout which does not extend to fruit intake. Further research is likely to improve our estimates.

Protocol registration: ClinicalTrials.gov identifier: NCT02702375

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review and meta-analysis assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
- Large prospective cohort studies that were of high quality and had a long duration of follow-up were included.
- Most of the pooled results showed good consistency (low between study heterogeneity) and sugar sweetened beverages showed evidence of a dose-response gradient.
- Only three prospective cohort studies with low external generalizability were available for inclusion.
- The observational design of the prospective cohort studies did not allow for causal inferences to be drawn.

INTRODUCTION

Gout and associated hyperuricemia are both associated with the development of hypertension, insulin resistance syndrome [1], and cardiovascular disease (CVD) [2]. Different diets have been shown to be associated with the development and severity of gout [3]. Foods that increase net ATP degradation including alcohol and high purine meats, are risk factors for gout [1]. Ingestion of large amounts of the monosaccharide fructose can increase uric acid production during its metabolism in the liver through unregulated phosphorylation of ATP into AMP [1] as demonstrated in randomized controlled trials [4, 5]. Similarly, in cohort studies, high intake of fructose-containing sugars in the form of sugar-sweetened beverages (SSBs) is associated with incident gout [6]. It is unclear whether the association seen for SSBs holds for other important food-sources of fructose-containing sugars, such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based products and sweets and desserts. As dietary guidelines and public health policy move from nutrient-based recommendations toward food and dietary-based recommendations [3, 4, 7], it is important to understand the contribution of these different food sources of fructose-containing sugars to the association of incident gout. To address this gap, we conducted a systematic review and meta-analysis of prospective cohort studies of the relation of important food sources of fructose-containing sugars with incident gout and hyperuricemia.

METHOD

Design

We followed the Cochrane Handbook for Systematic Reviews of Interventions [8] for the conduct of our systematic review and meta-analysis and reported our results according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [9] and preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA) [10] guidelines. The study protocol was registered at ClinicalTrials.gov (identifier, NCT02702375).

Search strategy

We conducted systematic searches in MEDLINE, EMBASE and Cochrane through September 13, 2017 with no language restriction (**supplementary table 1**). Targeted manual searches served to supplement the database search; these included finding related papers from references of selected papers and review articles, perusing articles with data from major prospective cohorts that usually report dietary data, and speaking to experts in the field.

Study selection

We included prospective cohort studies of ≥1 year duration that assessed the association of important food sources of fructose-containing sugars including non-alcoholic beverages (SSBs), cereal grain and grain-based products, fruit and fruit-based products, dairy and dairy-based products, and sweets, chocolate and desserts with incident gout or hyperuricemia in participants free from gout or hyperuricemia at the start of the study. One-year duration was chosen as it allows sufficient time for the development of disease.

Data extraction

Two independent reviewers (SAC and QL) extracted relevant data from included studies onto standardized pro forma. Extracted data included sample size, subject characteristics, sources of fructose-containing sugars, exposure levels, duration of follow-up, number of gout or hyperuricemia cases, model adjustments, and the risk ratio with 95% confidence intervals (95% CI) per quantile of

intake. The main outcome was incident gout or hyperuricemia expressed as risk ratios (RR) with 95% confidence intervals (95% CI). Discrepancies were resolved by consensus.

Risk of bias

The same two independent reviewers (SAC and QL) assessed each study for risk of bias. Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Points were awarded based on cohort selection, comparability of groups and assessment of outcomes, for a maximum total of 9 points [11]. Studies with ≥6 points were considered high quality [11]. Difference between reviewers was resolved by consensus.

Statistical analyses

Primary pooled analyses were conducted using Review Manager (RevMan) 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analysis and the assessments of dose response were performed using Stata 14 (StataCorp, College Station, TX, USA). Natural log-transformed RR for incident gout or hyperuricemia, comparing extreme quantiles (the highest exposure versus the lowest exposure or reference group), were pooled separately for each food source of fructose-containing sugars using the generic inverse variance method with DerSimonian and Laird random effects models and expressed as RRs with 95% CI. To overcome a unit-of-analysis error for studies appearing more than once in the same analysis, we divided participants equally among the multiple comparisons and readjusted the log-standard errors [8]. Inter-study heterogeneity was assessed with the Cochran Q statistic with significance set at $p<0.10$ and quantified with the I^2 statistic, where $I^2 \geq 50\%$ represented evidence of substantial heterogeneity [8]. Interaction between food sources was assessed using Cochran Q statistic for between group interaction. We explored

sources of heterogeneity by sensitivity analyses. Influence analyses, where each study was systematically removed, and effect size was recalculated in the remaining studies, were carried out to explore the influence of individual studies on the pooled risk. As ≥10 cohort comparisons were not available, *a priori* subgroup analyses were not performed. Linear and non-linear dose-response analyses were assessed using generalized least squares trend estimation models (GLST) and fixed-effects restricted cubic spline model with 3 knots, respectively [12]. Publication bias was not assessed as the number of cohort comparisons was less than 10.

Grading of the evidence

The overall certainty and the strength of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [13-25]. The evidence was graded as high, moderate, low, or very low certainty, with observational studies starting with an initial grade of 'low'. This then can be downgraded based on 5 pre-specified criteria or upgraded based on 3 pre-specified criteria. Criteria to downgrade included risk of bias (weight of studies showed risk of bias as assessed by low NOS <6), inconsistency (substantial unexplained inter-study heterogeneity i.e. I^2>50%), indirectness (presence of factors that limit the generalizability of the results), imprecision in the pooled risk estimate (the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for benefit or harm (RR 0.9–1.1)), and publication bias (evidence of small-study effect). Conversely, criteria to upgrade included a large magnitude of effect (RR>2 or RR<0.5 in the absence of plausible confounders), dose–response gradient or reasonable evidence of attenuation of the pooled effect estimate by confounders.

Patient and public involvement

The study was performed using published data. No patients or the public were involved in the study.

RESULTS

Search results

Figure 1 shows the flow of the systematic search and study selection. Of the 309 reports identified by the literature search, three reports with data from three prospective cohort studies met our inclusion criteria [26-28]: Nurses' Health Study (NHS) [27], Health Professionals Follow-up Study (HPFS) [26] and the National Runner's Health Study [28]. All three reports reported the association of food sources of fructose-containing sugars on incident gout, but none on incident hyperuricemia. These reports involved a total of 154,289 participants with 1,761 incident cases of gout. Two reports each reported data on fruit intake [n= 75,383; 983 cases] [26, 28], fruit juice [n= 125,299; 1,533 cases] [26, 27] and SSBs [n=125,299; 983 cases] [26, 27]. We did not identify prospective cohort studies reporting the association of other food sources of fructose-containing sugars (e.g. cereal grain and grain-based products, sweets and desserts, dairy and dairy based products and chocolate) with incident gout fitting our inclusion criteria.

Study characteristics

Table 1 lists the characteristics of the included prospective cohort studies. All studies were performed in the USA. The median age of the included participants ranged from 30 to 75 years. The median follow-up period was 17 years (range, 12 to 22 years) for SSB, 18.7 years (12 to 22 years) for fruit juice and 9.9 years (7.74 to 12 years) for fruit. Dietary intake assessments were done with self-reported, validated food frequency questionnaires (FFQs) in all studies. Quantiles of exposure depended on the food source. Medians for the lowest and highest quantiles of exposure were <1 servings/month and

≥14 servings/week respectively for SSB; ≤1 servings/month and ≥14 servings/week respectively for fruit juice; and ≤0.4 servings/week (range, <0-0.5 servings/week) and ≥8 servings/day (range, ≥2-14 servings/day), respectively for fruit. The ascertainment of incident gout in both HPFS and NHS cohorts [26, 27] was through self-report, followed by supplementary surveys of the subjects based on the American College of Rheumatology gout survey criteria [29] to confirm that the diagnosis. The authors defined individuals with gout that met ≥6 of the 11 criteria for gout. In addition, in a sub-sample the self-reported diagnoses were validated with medical records. As for the NRHS cohort [28], incident gout was self-reported based upon physician diagnosis.

Supplementary table 2 shows the complete list of adjusted confounding variables for the most adjusted models for each of the included prospective cohorts. The median number of variables in the most adjusted models was 14 (range, 6 to 14). All studies adjusted for primary and secondary confounders such as age, body mass index (BMI) and history of hypertension. Each of the three cohorts were single-sex studies, so adjustment for sex was not necessary. The NHS cohort study authored by Choi *et al.* 2010 [27] and NRHS study by Williams *et al.* [28] were agency funded, while the HPFS paper authored by Choi *et al.* 2008 [26] was funded by both agency and industry.

Study Quality

Supplementary table 3 shows the study quality assessments by the NOS scale. There was no evidence of serious risk of bias. Only NRHS cohort scored <6 on the NOS scale, which denotes lower quality [28].

Fruit intake on incident gout

Figure 2 shows the relationship between food sources of fructose-containing sugars intake and incident gout. There was significant interaction between the food sources (p=0.02). When comparing the highest to the lowest fruit intake, no association was shown for fruit intake on incident gout (RR = 0.85, [95% CI 0.63 to 1.14]). There was evidence of significant interstudy heterogeneity (I^2 = 93%, p<0.001).

Fruit juice intake on incident gout

Figure 2 shows the relationship between fruit juice intake and incident gout. When comparing the highest to lowest intake, an adverse association was shown for fruit juice intake on incident gout (RR 1.77, [95% CI 1.20 to 2.61]). There was no evidence of significant interstudy heterogeneity (I^2 = 0% [95% CI 0% to 90%], p = 0.54).

SSB intake on incident gout

Figure 2 shows the relationship between SSB intake and incident gout. When comparing the highest with the lowest intake, an adverse association was shown for SSB intake on incident gout (RR=2.08 [95% CI 1.40 to 3.08]). There was no evidence of significant interstudy heterogeneity (I^2 = 0%, p = 0.52).

Additional analysis

Influence analysis (the systematic removal of each study), publication bias and subgroup analyses could not be performed due to the small number of studies included in each analysis (n=2).

Dose-response analysis

A random-effect GLST model showed a significant dose-response relationship between fruit juice intake and incident gout per serving/week (RR = 1.03, 95% CI 1.02 to 1.05, p<0.001) (**supplementary figure 1**), and for SSB intake (RR = 1.04, 95% CI 1.02 to 1.07, p<0.001) (**supplementary figure 2**). Fruit juice intake showed a significant departure from linearity (p = 0.038), and visual inspection of the graph (**supplementary figure 1**) indicated a plateau for risk increase after ≥5 servings per day. There was no evidence for departure from linear dose response gradient or dose thresholds for SSB intake while using the restricted cubic spline model (p = 1.29) (**supplementary figure 2**). Dose-response modeling was not conduced for fruit intake due to lack of data.

GRADE assessment

Table 2 shows the GRADE assessment of individual food sources of fructose-containing sugars. The certainty of the evidence for an adverse association from both fruit and fruit juice was rated as very low, with downgrades to the lowest level for indirectness for fruit juice intake, and for inconsistency, indirectness and imprecision for fruit intake. The certainty of the evidence for an adverse association of SSB intake with incident gout was rated as moderate, with a downgrade of one level for indirectness but upgrade of two levels for a large magnitude effect and significant dose-response association.

DISCUSSION

We conducted a systematic review and meta-analysis of studies investigating the relation of important food sources of fructose-containing sugars with incident gout. We identified three prospective cohort studies [26-28] comprising of 154,289 participants and 1,761 cases of incident gout. The pooled analyses revealed that there was a moderate certainty of evidence that SSB intake

was associated with 208% increase in risk of incident gout when comparing the highest with the lowest intake. Similarly, there was a low certainty of evidence that fruit juice intake was associated with a 77% increase in risk of incident gout, but fruit intake did not show any significant association with incident gout (low certainty of evidence). There was no data available of other important food sources of fructose-containing sugars.

Findings in the context of the literature

Our results are consistent with previous research which indicate that the intake of certain food sources of fructose-containing sugars is associated with the risk of gout. Our previous systematic review and meta-analysis of prospective cohort studies found a harmful relationship between fructose consumption and gout [6]. While that study indicated that fructose moiety might possibly drive the association with gout, all the fructose data in the included studies was derived from SSB intake. Another systematic review of the literature identified numerous dietary factors associated with the risk of gout including meat, alcohol, seafood and SSBs, but also that lower risk was associated with the intake of dairy, folate and coffee [3].

SSBs are a major source of fructose-containing added sugars in the western diet comprising around 30% of intake of added sugars in the USA [30] and around 24% in Canada [31]. Excess intake of fructose can increase uric acid though an unregulated phosphofructose kinase pathway that uses substantial amounts of ATP [32] to convert fructose into fructose-1-phosphate in the liver [33]. Mechanistically, net ATP degradation leads to accumulation of AMP, which is subsequently degraded to uric acid. Additionally, fructose can increase de novo purine synthesis, which further produces uric acid [1]. This increase in uric acid can lead to the development of gout. Since we were unable to

investigate the relationship between food sources of fructose-containing sugars and hyperuricemia, we cannot validate this mechanism. It is possible, that fructose increases the risk of gout independently of serum uric acid levels. However, since the link between fructose and serum uric acid [34-37], and the link between serum uric acid and the development of gout have been independently established [1], it is unlikely that fructose increases the risk of gout without using uric acid as an intermediate.

We identified adverse association of fruit juices intake with incident gout. The two studies that contributed to this result [26, 27] were both performed in two Harvard cohorts which do not differentiate between fruit drinks and pure fruit juice, the former being largely similar to SSBs i.e. mainly sugar and water. This difference between pure fruit juice and fruit drink is supported by studies investigating pure fruit juice and fruit drinks that show divergent response for cardiometabolic disease [38, 39].

We did not see any association between fruit intake and incident gout but the individual effect estimates from the two studies were in opposite direction. The NRHS [28] cohort showed a 51% reduction in the risk of gout with high intake of fruit whereas the HPFS [26] cohort showed a 63% increased risk; both studies were performed in men. These discordant results highlight the differences in the studies. HPFS cohort [26] only measured oranges and apples, fruit high in fructose, while NRHS [28] cohort assessed all fruit which might represent a healthier dietary intake. It is also possible that higher intake of fruits in NRHS might be associated with high intake of dairy or coffee, which have been associated with lowering the risk of gout [3]. As the data on dairy and coffee was not reported by NRHS, this remains a speculation. The harmful association for oranges, which are rich in vitamin C,

in HPFS [26] cohort is at odds with another study from the same cohort, in which the authors demonstrated a protective association of vitamin C intake with gout [40]. While fruits are rich in fructose which can increase uric acid levels, fruit intake has consistently shown a benefit for cardiometabolic risk factors, cardiometabolic diseases and all cause-mortality [41-47]. Several case-control and cross-sectional studies have shown a protective effect of total fruit intake with gout albeit only in Asian populations [48, 49], their relevance to the included studies, conducted in a largely Caucasian population, might be limited. More data from different populations might clarify the association between fruit intake and gout.

We could not find any prospective studies looking at the association of food sources of fructose-containing sugars and hyperuricemia even though hyperuricemia is the most important risk factor for gout [3, 50]. Hyperuricemia is also a risk factor for hypertension , metabolic syndrome, diabetes , and CVD [51]. Several cross-sectional analyses have investigated the link between SSB consumption and serum uric acid levels, showing a positive relationship [34-37]. In contrast, the analysis of the National Health and Nutrition Examination Survey (NHANES) showed no link between dietary fructose and risk of hyperuricemia, indicating that perhaps different food sources of fructose-containing sugars may have different effects on serum uric acid. This point is reinforced by another analysis of NHANES data that showed a relationship of SSB intake with higher serum uric acid concentration, but not with fruit juice [52]. Future studies investigating food sources of sugars and risk of hyperuricemia may help to elucidate some of the above inconsistent findings.

We were not been able to find prospective cohort studies investigating the association of other food sources of fructose-containing sugars and the risk of gout though cross-sectional studies suggest that

cereal and yogurt may be associated with lower serum uric acid [53]. More research is needed to assess the relationship between other food sources of fructose-containing sugars and the risk of gout.

Strengths and limitations

Our analysis has many strengths. First, we employed a comprehensive systematic search across major databases and the quantitative synthesis of results. Second, the studies we included had a substantial number of participants and cases of gout (154,289 participants and 1,761 gout cases) providing increased precision. Additionally, the median follow-up duration was greater than 10 years, which allowed for enough time from exposure for the development of disease. Another strength is the use of validated measures of intake like food frequency questionnaires. The two Harvard cohorts [26, 27] administered FFQ multiple times, and validated them on a subsample, allowing for more accurate and robust long-term intakes compared to the NRHS [28] cohort, which only measured dietary intakes at baseline. In our analysis, we made use of GRADE to evaluate the certainty and strength of our analysis and evaluate our confidence in the estimates.

There are some notable limitations to our systematic review and meta-analysis. First, while we included the most adjusted multivariable models for this analysis, there is always potential for unmeasured and residual confounding, since the studies included were observational in nature. This explains why GRADE starts at “low certainty” for observational studies. Second, there was evidence of indirectness in some of the relationships. All studies were conducted in the USA, and two of the three studies were conducted in health professionals. The two Harvard [26, 27] cohorts included only middle aged or older people who worked in health care and who were predominately white and the NRHS [28] cohort included only middle to old aged physically active men. Thus, the specific nature of

the included studies' population limits the generalizability of our results to other populations and geographical locations; however, the biological process of diet and gout are still likely to be similar to other populations. While, genome wide association studies have found numerous genes that increase one's risk for gout [54] and some ethnic groups may be more susceptible than others [1], it is not known if the association of fructose intake with gout is modified by genes. Third, sources of heterogeneity remained unexplained; with only three studies, we were unable to assess publication bias or perform sensitivity analysis though an a priori subgroup analysis. Thus, for these reasons, data pertaining to SSB and fruit juice intake and incident gout received a GRADE of moderate and very low certainty, respectively, indicating that further studies in this regard is likely to impact our certainty in the effect estimate and may change the estimate for SSB and that our certainty in the estimate for fruit juice is very uncertain; therefore, caution should be used when interpreting these results. Similarly, for fruit, which received a GRADE of very low, so we are very uncertain in these results and caution should be used in the interpretation of these results.

Implications

Dietary guidelines have shifted their focus from nutrient-based recommendations to food and dietary pattern-based recommendations [55], since it has been recognized that one does not eat nutrients in isolation but as a part of foods. Interactions between nutrients in food are complex and the whole food matrix works as a whole to increase or decrease disease risk [55]. Our findings support this view of food matrix affect independent of a single-nutrient in relation to food sources of fructose-containing sugars and their relationship with gout.

Our findings also have implications for recommendations for the prevention of gout. Conventional dietary recommendations for gout have focused on restriction of purine intake; however, low-purine diets are often high in carbohydrates, including fructose-rich foods [56]. We have shown an adverse association between fruit juice and SSBs, supporting the recommendations to limit their intakes. Since we did not have data relating to children, hyperuricemia or other food sources of fructose-containing sugars, we cannot extend our conclusion to these groups of individuals or these foods.

Conclusion

Our systematic review and meta-analysis of prospective cohort studies showed an adverse association between SSBs and fruit juice with the risk of gout, while there was no association with fruit intake. The strength of the evidence was moderate for SSB intake and very low for fruit juice and fruit intake, as assessed by GRADE. For SSBs, the true association is likely to be close to the estimate, but there is a possibility that it is substantially different. For fruit juice and fruit intake, the true association are likely to be substantially different from the estimate and future research will very likely impact our confidence in the effect estimates and likely to change them [57]. Our results are consistent with the literature that certain food sources of fructose-containing sugars especially SSBs are a risk factor for the development of gout. We were unable to identify studies assessing food sources of fructose-containing sugars and hyperuricemia, indicating a gap in the literature. Given that incident gout is rising in many countries [7, 58-63], and that gout and hyperuricemia are both associated with metabolic syndrome, myocardial infarction, diabetes and premature death [1, 2, 64], it is becoming increasingly important to identify and understand risk factors for developing gout. It is imperative for additional prospective studies to assess the intake of various food sources of fructose-containing sugars and their relationship with gout and hyperuricemia in diverse populations. This will help

identify to what extent does our foods mediate the risk for hyperuricemia and gout and will further inform health care professionals, policymakers, and aid in the development of improved dietary guidelines for the prevention and management of gout and hyperuricemia.

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Data Sharing

There is no additional unpublished data available from the study.

Competing Interests

TA Khan has received research support from the Canadian Institutes of health Research (CIHR), an unrestricted travel donation from Bee Maid Honey Ltd and has been an invited speaker at the Calorie Control Council annual meeting. **RJ de Souza** has served as an external resource person to the World

Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health (guidelines for trans fats and saturated fats), and received renumeration from WHO for travel and accommodation. He also received compensation for contract research conducted for the Institute of Nutrition, Metabolism, and Diabetes at the Canadian Institutes of Health Research (CIHR), Health Canada and WHO. He has received research grants from the Canadian Foundation for Dietetic Research and CIHR, and lecture fees from McMaster Children's Hospital. **TMS Wolever** and his wife are part owners and employees of Glycemic Index Laboratories. **CWC Kendall** has received research support from the Advanced Foods and Materials Network, Agricultural Bioproducts Innovation Program through the Pulse Research Network, Agriculture and Agri-Food Canada, Almond Board of California, Barilla, Calorie Control Council, CIHR, Canola Council of Canada, The International Tree Nut Council Nutrition Research & Education Foundation, Kellogg, Loblaw Companies Ltd., Pulse Canada, Saskatchewan Pulse Growers and Unilever. He has received consultant fees from American Pistachio Growers; speaker fees from American Peanut Council, Tate & Lyle and The WhiteWave Foods Company; and travel funding from Sabra Dipping Company, Tate & Lyle, International Tree Nut Council Research & Education Foundation, California Walnut Commission, Sun-Maid, The Peanut Institute, General Mills, Oldways Foundation and International Nut and Dried Fruit Council Foundation. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European Association for the Study of Diabetes (EASD). He is a member of the International Carbohydrate Quality Consortium (ICQC), Secretary of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and a Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. **JL Sievenpiper** has received research support from the CIHR, Canadian Diabetes Association (CDA), PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), American Society for Nutrition (ASN), Calorie Control Council, INC International Nut and Dried Fruit Council

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Authors' contributions

All authors had full access to all of the data (including statistical reports and tables) in this study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

Conception and design: J.L. Sievenpiper.

Analysis and interpretation of the data: Q. Liu, S. Ayoub-Charette, T.A.Khan, F. Au-Yeung, S. Blanco Mejia, R.J. de Souza, L.A. Leiter, C.W.C. Kendall, T.M.S. Wolever, J.L. Sievenpiper.

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TABLES AND FIGURES

Figure 1 Summary of evidence search and selection. Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia. Of the 309 studies initially identified, 294 were excluded based on title and/or abstract. The remainder were read in full by two independent reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort studies.

Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-adjusted multivariate models accounting for food sources of fructose-containing sugars intake were used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using the Cochran Q statistic and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit juices. * The number of cases and participants are divided equally between the multiple entries of the study to ensure total count gives unique individuals. To overcome a unit-of-analysis error for studies appearing more than once in the same analysis, we readjusted the log-standard errors to participants equally among the multiple comparisons and.

Table 1 Characteristics of prospective cohort studies investigating food sources of fructose-containing sugar intake and incident gout.

Study, year (Reference)	Cohort	Country	Participants	Incident Cases	Age (mean years, range)	Follow-up (mean, range)	Dietary Assessment	Food source of fructose-containing sugars	Frequency of Administration of SFFQ	Quantiles	Exposure (servings/ week, mean, range)	Serving size	Outcome assessment	Funding Source*
Choi *et al.*, 2008 (26)	HPFS	USA	46,393 (M)	755	52.5 (40 to 75)	12 years	Validated SFFQ	SSBs Fruit Juice Fruit	4	Quintiles	¼ to ≥14	Not reported	Record linkage	Agency and Industry
Choi *et al.*, 2010 (27)	NHS	USA	78,906 (F)	778	49 (30 to 55)	22 years	Validated SFFQ	SSBs Fruit Juice	4	Sextiles	¼ to ≥14	Not reported	Self-reported	Agency
Williams, 2008 (28)	NRHS	USA	28,990 (M)	228	44.9	7.7 years (5.9 to 9.6)	Validated SFFQ	Fruit	1 (baseline)	Quartiles	¼ to 2 (0 to ≥2)	Not reported	Self-reported	Agency

Abbreviations: HPFS = Health Professionals Follow-Up Study; NHS = Nurses Health Study; NRHS =National Runner's Health Study; M=males; F=females; SFFQ = Semi quantitative Food-Frequency Questionnaire; SSBs = Sugar Sweetened Beverages.

*Agency funding is that from government, university or not-for-profit health agency sources.

684 **Table 2** GRADE assessment of individual food source of fructose-containing sugars.

Certainty assessment								Study event rates (%)	Effect	Certainty
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations		Relative Risk (95% CI)	
Sugar sweetened beverages intake on incident gout (follow-up median 17 years)										
2	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	No serious imprecision	Undetected[2]	Large magnitude of effect[3] Dose-response[4]	1,533/125,299 (1.22%)	2.08 [1.40, 3.07]	⨁⨁⨁◯ **Moderate** [1,2,3,4] Due to downgrade for indirectness and upgrade for large magnitude effect and dose-response
Fruit juice intake on incident gout (follow-up median 17 years)										
2	Observational studies	No serious risk of bias	No serious inconsistency	Serious indirectness[1]	No serious imprecision	Undetected[2]	None	1,533/125,299 (1.22%)	1.73 [1.17, 2.57]	⨁◯◯◯ **Very low**[1,2] Due to downgrade for indirectness
Fruit intake on incident gout (follow-up median 9.87 years)										
2	Observational studies	No serious risk of bias	Very serious inconsistency[5]	Serious indirectness[1]	Serious[6]	Undetected[2]	None	983/75,383 (1.3%)	0.89 [0.27, 2.87]	⨁◯◯◯ **Very low**[1,2,5,6] Due to downgrade for inconsistency, indirectness and imprecision

685 [1]Downgrade for indirectness, as the study population is specific to a group of the population like professionals, nurses or runners.

686 [2]No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry

687 and small study effect (<10 cohort included in our meta-analysis).

688 [3]Upgrade for a large magnitude of effect (RR>2.0).

[4]Upgrade for a dose response gradient, as the GLST dose-response analysis revealed a significant linear relationship between sugar sweetened beverage intake and incident gout (P=0.0001).

[5]Downgrade for very serious inconsistency, as the two studies included had opposite associations and there was evidence of substantial inter-study heterogeneity (I^2=94%, p<0.0001). Due to the small number of studies included in the analysis, subgroup analysis was not performed.

[6]Downgrade for serious imprecision, as the lower bound of the 95% CI (RR, 0.27) includes clinically important benefit (RR<0.9), while the upper bound of the 95% CI (RR, 2.87) crosses the minimally important difference of 10% (RR>1.1).

Figure 1 Summary of evidence search and selection

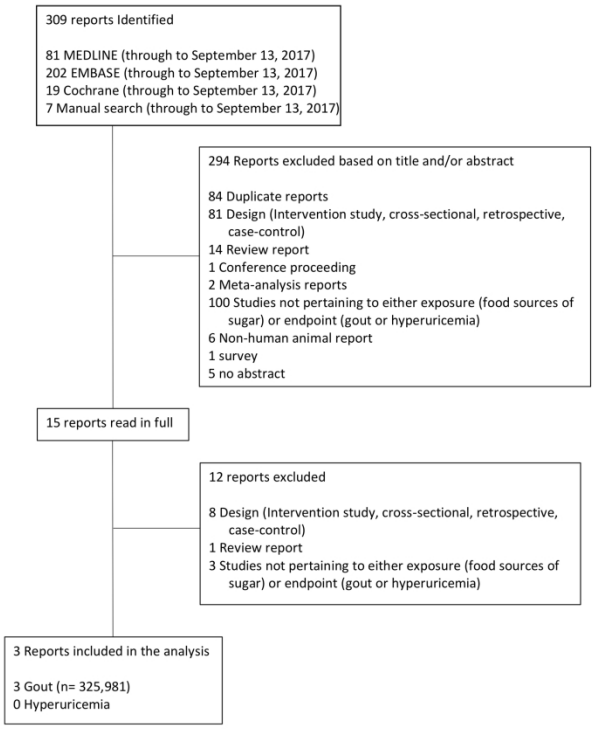


Figure 1 Summary of evidence search and selection

215x279mm (300 x 300 DPI)

Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout.

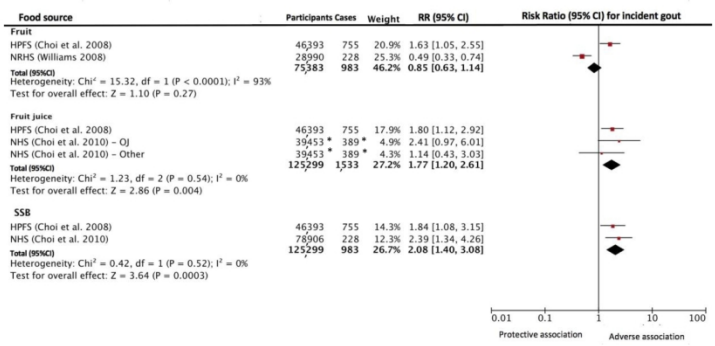


Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout.

215x279mm (300 x 300 DPI)

Supplementary material

SUPPLEMENTARY TABLES

SUPPLEMENTARY FIGURES

Supplementary table 1. Search terms

Database and search terms

MEDLINE
1. sugar*.mp.
2.exp fructose/
3. fructose.mp.
4. HFCS.mp.
5. exp high fructose Corn Syrup/
6. sucrose.mp.
7. exp dietary Sucrose/
8. sugar sweetened beverage*.mp.
9. ssb.mp.
10. soda.mp.
11. soft drink*.mp.
12. exp carbonated beverages/
13. carbonated beverages.mp.
14. non alcoholic beverage*.mp.
15. nonalcoholic beverage*.mp.
16. exp energy drinks/
17. energy drink*.mp.
18. smoothie*.mp.
19. exp "fruit and vegetable juices"/
20. fruit.mp.
21. exp fruit/
22. exp honey/
23. y*g*rt.mp.
24. exp yogurt/
25. ice cream*.mp.
26. icecream*.mp.
27. exp ice cream/
28. exp edible grain/
29. cereal*.mp.
30. dessert*.mp.
31. sweets.mp.
32. confection*.mp.
33. pastries.mp.
34. biscuit*.mp.
35. cookie*.mp.
36. cake*.mp.
37. candy.mp.
38. candies*.mp.
39. exp candy/
40. (chocolate adj2 milk).mp.
41. chocolate.mp
42. exp chocolate/
43. cacao.mp
44. exp cacao/
45. cohort.mp.
46. exp prospective study/
47. (prospective adj2 (cohort or study)).mp.
48. exp multivariate analysis/
49. exp follow up studies/
50. exp proportional hazards models/
51. follow-up study.mp.
52. (longitudinal adj2 study).mp.
53. gout/
54. gout*.mp.
55. uric acid*.mp.

EMBASE
1. sugar*.mp.
2. exp sugar/
3. exp fructose/
4. fructose.mp.
5. HFCS.mp.
6. exp high fructose Corn Syrup/
7. sucrose.mp.
8. exp dietary Sucrose/
9. sugar sweetened beverage*.mp.
10. SSB.mp.
11. soda.mp.
12. soft drink*.mp.
13. exp soft drink/
14. exp carbonated beverages/
15. carbonated beverages.mp.
16. non alcoholic beverage*.mp.
17. nonalcoholic beverage*.mp.
18. exp energy drinks/
19. energy drink*.mp.
20. smoothie*.mp.
21. exp "fruit and vegetable juices"/
22. fruit.mp.
23. exp fruit/
24. exp honey/
25. y*g*rt.mp.
26. exp yoghurt/
27. ice cream*.mp.
28. icecream*.mp.
29. exp ice cream/
30. cereal*.mp.
31. dessert*.mp.
32. sweets.mp.
33. confection*.mp.
34. exp bakery product/
35. pastries.mp.
36. biscuit*.mp.
37. cookie*.mp.
38. cake*.mp.
39. candy.mp.
40. candies*.mp.
41. chocolate.mp
42. exp chocolate/
43. cacao.mp
44. exp cacao/
45. (chocolate adj2 milk).mp.
46. cohort.mp.
47. exp prospective study/
48. (prospective adj2 (cohort or study)).mp.
49. exp multivariate analysis/
50. exp proportional hazards models/
51. follow-up study.mp.
52. (longitudinal adj2 study).mp.
53. gout/
54. gout*.mp.
55. uric acid*.mp.

Cochrane
1. sugar*.mp.
2. exp fructose/
3. fructose.mp.
4. HFCS.mp.
5. exp Nutritive Sweeteners/
6. sucrose.mp.
7. exp dietary sucrose/
8. sugar sweetened beverage*.mp.
9. ssb.mp.
10. soda.mp.
11. soft drink*.mp.
12. exp carbonated beverages/
13. non alcoholic beverage*.mp.
14. nonalcoholic beverage*.mp.
15. exp energy drinks/
16. energy drink*.mp.
17. smoothie*.mp.
18. ((fruit or vegetable) and juice*).mp.
19. fruit.mp.
20. exp fruit/
21. exp honey/
22. y*g*rt.mp.
23. exp yogurt/
24. ice cream*.mp.
25. icecream*.mp.
26. exp ice cream/
27. cereal*.mp.
28. dessert*.mp.
29. sweets.mp.
30. confection*.mp.
31. pastries.mp.
32. biscuit*.mp.
33. cookie*.mp.
34. cake*.mp.
35. candy.mp.
36. candies.mp.
37. exp candy/
38. (chocolate adj2 milk).mp.
39. cohort.mp.
40. exp Prospective Studies/
41. chocolate.mp
42. cacao.mp
43. exp cacao/
44. (prospective adj2 (cohort or study)).mp.
45. exp follow-up studies/
46. exp multivariate analysis/
47. exp proportional hazards models/
48. follow up study.mp.
49. (longitudinal adj2 study).mp.
50. gout/
51. gout*.mp
52. uric acid*.mp
53. hyperuricemia*.mp
54. hyperuricemia/
55. hyperuricaemia*.mp

56. hyperuricemia*.mp.	56. hyperuricemia*.mp.	56. uric.mp
57. hyperuricemia/	57. hyperuricemia/	57. or/1-43
58. hyperuricaemia*.mp.	58. hyperuricaemia*.mp.	58. or/44-49
59. uric.mp.	59. uric.mp.	59. or/50-56
60. or/1-44	60. or/1-45	60. and/57-59
61. or/45-52	61. or/46-52	
62. or/53-59	62. or/53-59	
63. and/60-62	63. and/60-62	

Database	Total
MEDLINE: September 13, 2017	81
EMBASE: September 13, 2017	202
Cochrane: September 13, 2017	19
Manual search	7
Total	309

For all databases, the original search was September 13, 2017.

Supplementary table 2. Analysis of confounding variables among 3 studies of food sources of sugar intake and incident gout

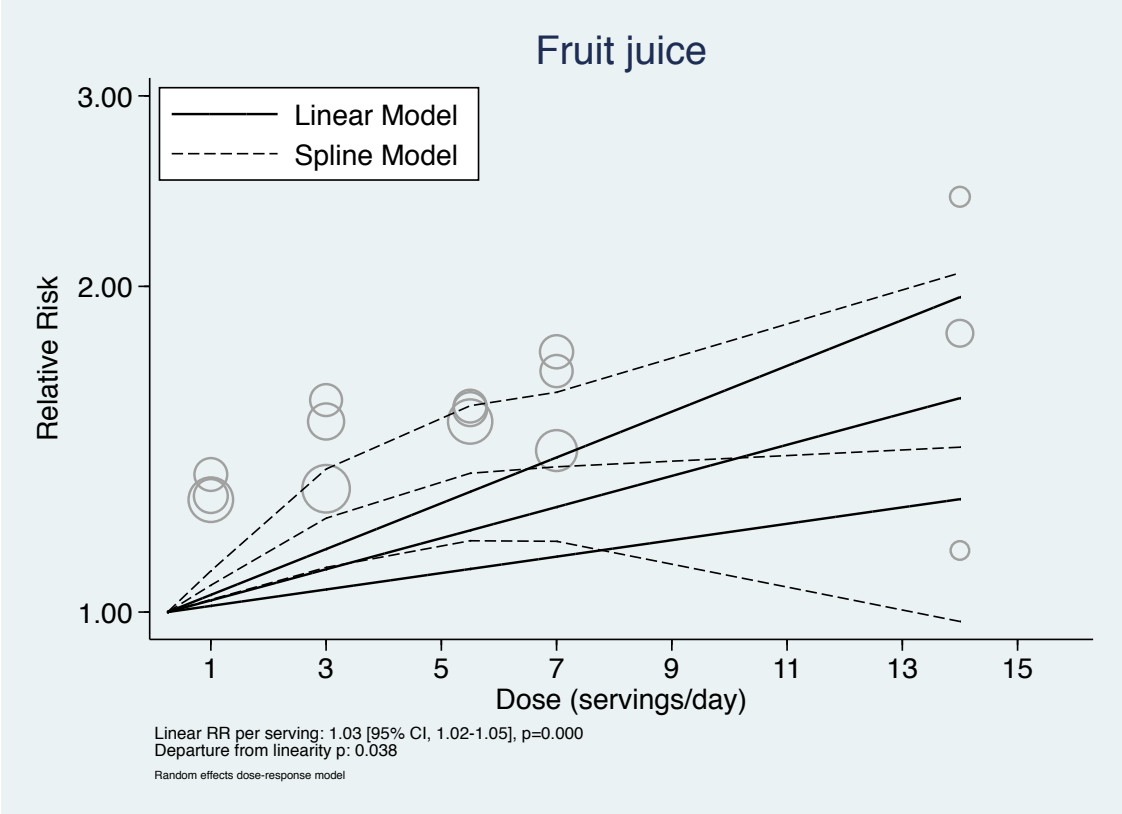
Study	HPFS (Choi *et al.*, 2008)	NRHS (Williams, 2008)	NHS (Choi *et el.*, 2010)
Number of variables in fully adjusted model	14	6	14
Number of multivariable models presented	2	1	3
Timing of measurement of confounding variables	2y	BL*	2y
Pre-specified primary confounding variable			
Age	✓	✓	✓
Pre-specified secondary confounding variables			
Marker of overweight/obesity (Body mass index, weight, waist circumference, waste to hip ratio)	✓		✓
Sex	M §	M §	F ‡
History of gout/hyperuricemia			
Diabetes			
Physical activity			
Lipid medication/dyslipidemia			
Animal protein intake	✓		✓
Hypertension or blood pressure medication including diuretics	✓		✓
Other confounding variables			
Lifestyle factors			
Weekly intake of:			
Alcohol	✓	✓	✓
Seafood	✓		✓
Purine from vegetables	✓		✓
Dairy food	✓		✓
Vitamin C	✓		✓
Coffee		✓	
Meat		✓	
Fish			✓∇
Diet soda	✓∇		✓∇
Sugar-sweetened cola	✓∇		✓∇
Other soda	✓∇		✓∇
Orange or apple juice	✓∇		✓∇
Other fruit juice			✓∇
Orange or apple	✓∇		
Total energy	✓		✓
Weekly intake of aspirin		✓	
Medical history			
History of Hypertension	✓	✓	✓
History of chronic Renal failure	✓		
Menopause status			✓
Use of hormonal therapy			✓

HPFS=Health Professionals Follow-Up Study, NHS=Nurses Health Study
*Denotes confounders measured only at baseline years.
† Indicates confounders measured every 2 years.
‡ Indicates the study includes only female subjects
§ Indicates the study includes only male subjects
∇ Indicates the confounder was present in some, but not all, models.

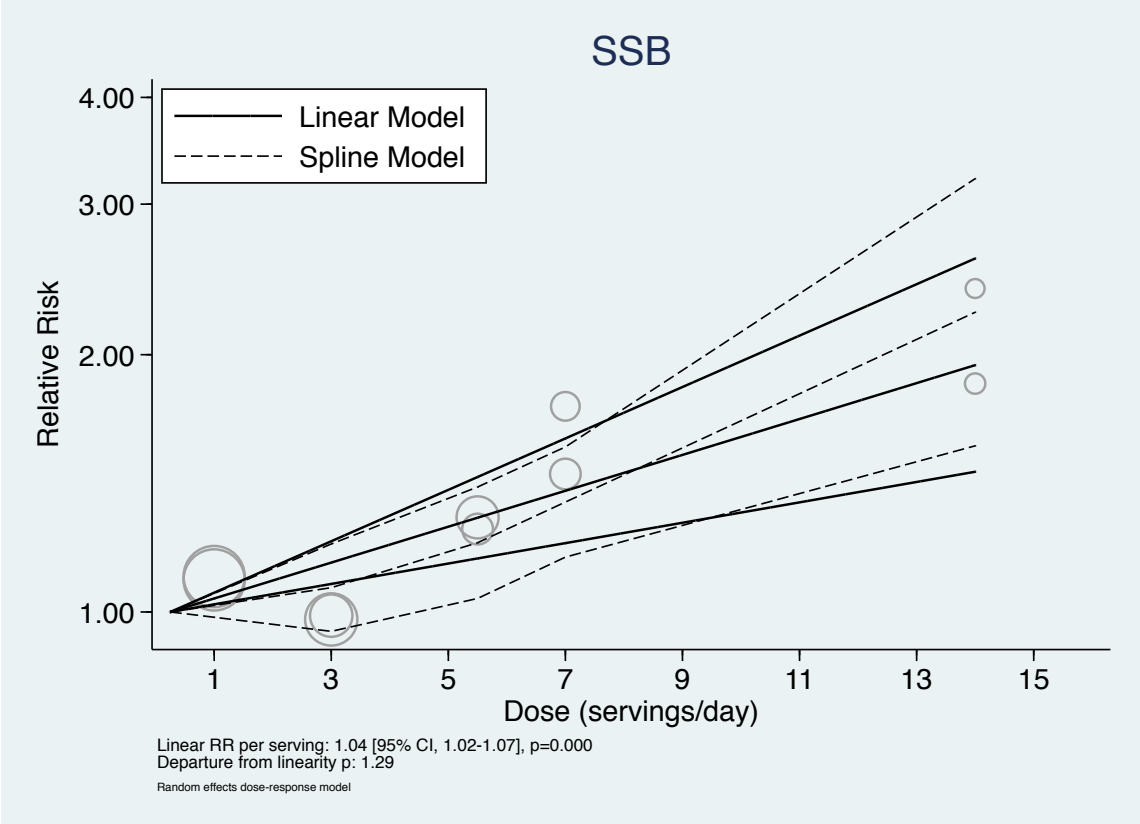
Supplementary table 3. Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies

Study	Selection*	Outcome†	Comparability‡	total§
Choi *et al.*, 2008	2	3	1	6
Williams, 2008	2	2	1	5
Choi *et al.*, 2010	2	3	1	6

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline.
†Maximum 3 points awarded for follow-up length, adequacy of follow-up and outcome assessment.
‡Maximum 2 points awarding for controlling for the pre-specified primary confounding variable (age) and >6 of the secondary confounding variables (sex, body mass index, history of gout or hyperuricemia, diabetes, alcohol, physical activity, lipid medication/dyslipidemia, animal protein intake, hypertension or blood pressure medication including diuretics).
§A maximum of 9 points could be awarded.



Supplementary figure 1. Linear and non-linear dose-response relationship between fruit juice intake and incident gout per serving/week. Linear dose response data (solid lines) were modeled using the generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines) were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval for the fitted trend are shown above and below the solid line. Each study was centered to its own baseline reference dose when estimating increasing dose risk.



Supplementary figure 2. Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week. Linear dose response data (solid lines) were modeled using the generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines) were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval for the fitted trend are shown above and below the solid line. Each study was centered to its own baseline reference dose when estimating increasing dose risk.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	-
3	Description of study outcome(s)	4, 5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, supplementary table 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7, 8, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-9
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9, supplementary table 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9, supplementary table 3
22	Assessment of heterogeneity	6, 7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6, 7
24	Provision of appropriate tables and graphics	Tables 1, 2, Figs 1, 2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 2
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	-

28	Indication of statistical uncertainty of findings	11, table 2

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, 16
30	Justification for exclusion (eg, exclusion of non-English language citations)	5
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	17, 18

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.