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FRUCTOSE INTAKE AND RISK OF GOUT AND HYPERURICEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE COHORT STUDIES

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Complete List of Authors:	Jamnik, Joseph; University of Toronto Faculty of Medicine, Nutritional Sciences Rehman, Sara; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Blanco Mejia, Sonia; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital de Souza, Russell; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital; McMaster University Faculty of Health Sciences, Department of Clinical Epidemiology and Biostatistics Khan, Tauseef ; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Leiter, Lawrence; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Wolever, Thomas M. S.; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Kendall, Cyril; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Jenkins, David; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Sievenpiper, John; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital
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Fructose Intake and Risk of Gout and Hyperuricemia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Joseph Jamnik[1], Sarah Rehman[1,2], Sonia Blanco Meja[1,2], Russefll J de Souza[2,3], Tauseef A Khan[1,2], Lawrence A Leiter[1,2,4-6], Thomas MS Wolever[1,2,4-6], Cyril WC Kendall[1,2,7], David JA Jenkins[1,2,4-6], John L Sievenpiper[1,2,5,6]

[1]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada; [3]Department of Clinical Epidemiology and Biostatistics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada, [4]Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, [5]Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada; [6]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada, [7]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Corresponding Author:

Dr. John L Sievenpiper MD, PhD, FRCPC, Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital, 6137-61 Queen Street East, Toronto, ON, M5C 2T2, CANADA, Tel: 416 867 7475, Fax: 416 867 7495, email: john.sievenpiper@medportal.ca

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ABSTRACT

Background: The prevalence of hyperuricemia and gout has increased in recent decades. The role of dietary fructose in the development of these conditions remains unclear.

Objective: To conduct a systematic review and meta-analysis of prospective cohort studies investigating the association fructose consumption with incident gout and hyperuricemia.

Data sources: We searched MEDLINE, EMBASE, and the Cochrane Library (through September 2015).

Eligibility criteria: We included prospective cohort studies that assessed fructose consumption and incident gout or hyperuricemia.

Data extraction: Two independent reviewers extracted relevant data and assessed study quality using the Newcastle-Ottawa Scale.

Synthesis methods: We pooled natural-log transformed risk ratios (RRs) using the generic inverse variance method. Inter-study heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). The overall quality of the evidence was assessed using the Grading of recommendations assessment, development, and evaluation (GRADE) approach.

Results: Two studies involving 125,299 participants and 1,533 cases of incident gout assessed the association between fructose consumption and incident gout. No eligible studies assessed incident hyperuricemia as an outcome. Fructose consumption was associated with an increase in the risk of gout (RR=1.62, 95% CI 1.28 to 2.03, p<0.0001) with no evidence of inter-study heterogeneity (I^2=0%, p=0.33) when comparing the highest (>11.8 to >11.9% total energy) and lowest (<6.9 to <7.5% total energy) quantiles of consumption.

Limitations: Despite a dose-response gradient, the overall quality of evidence as assessed by GRADE was low, due to indirectness. There were only two prospective cohort studies involving

predominantly white health professionals that assessed incident gout, and none assessed hyperuricemia.

Conclusions: Fructose consumption was associated with an increased risk of developing gout in predominantly white health professionals. More prospective studies are necessary to understand better the role of fructose and its food sources in the development of gout and hyperuricemia.

Protocol Registration: clinicaltrials.gov identifier, NCT01608620.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review and meta-analysis assessed the overall quality of the evidence using the Grading of recommendations assessment, development, and evaluation (GRADE) approach.
- Large prospective cohort studies that were of high quality and had a long duration of follow-up were included
- The pooled results showed good consistency (low between-study heterogeneity) and evidence of a dose response gradient.
- Only two 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 is a systemic rheumatic condition characterized by urate crystal deposition and accumulation around joints. Individuals with gout often experience acute and recurring attacks of arthritis that can affect several joints (1). Hyperuricemia or excessive circulating concentrations of urate, the final product of purine metabolism, is a major risk factor for gout and plays a major role in the pathogenesis of this condition (2). Chronic hyperuricemia and gout also represent potential risk factors for cardiovascular disease (CVD)(3). According to the National Health and Nutritional Examination Survey 2007-2008, hyperuricemia affects greater than 20% of the U.S. population, while approximately 4% of American adults have gout (4). The prevalence of both hyperuricemia and gout has increased in recent decades (4-6), suggesting potential environmental triggers. Several lifestyle and dietary factors have been implicated in the development of these conditions, including elevated body mass index (BMI) (7), alcohol consumption (8), and high dietary intakes of meat and seafood (9, 10). Recent research has also implicated fructose intake in the pathogenesis of hyperuricemia and gout (11, 12).

Fructose is a monosaccharide found commonly in plants. It is also a major constituent of high-fructose corn syrup (HFCS) in sugar-sweetened beverages (SSBs) (13). Ecological evidence has shown that the increasing prevalence of hyperuricemia and gout in developed countries has paralleled the increase in consumption of total fructose and HFCS (14). The phosphorylation of fructose, unlike the monosaccharide glucose, is understood to facilitate ATP depletion and result in an elevation of circulating uric acid levels (11, 15, 16). Animal studies and select trials of acute ingestion of fructose-sweetened beverages have shown that fructose can lead to higher blood concentrations of uric acid (17, 18). However, a meta-analysis of isocaloric substitution trials did not support this association between fructose and serum uric acid (19). The

role of fructose from all dietary sources as a risk factor for incident hyperuricemia and ultimately gout, therefore, remains unclear. The objective of this study was to conduct a systematic review and meta-analysis of prospective cohort studies investigating total fructose consumption and its association with incident hyperuricemia and gout.

METHODS

This meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (20) and reported following the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE) (21). The study protocol was registered at ClinicalTrials.gov (NCT01608620).

Study Selection

We performed a comprehensive search of MEDLINE, EMBASE and the Cochrane Library databases from conception through 22 September 2015. The following search terms were used: “fructose”, “sucrose”, “sugar”, honey”, “HFCS”, “gout”, “hyperuricemia”, and “uric acid”. No language restrictions were imposed on the search. The complete search strategy is reported in **S1 Table**. The electronic search was supplemented by a manual review of article reference lists. Abstracts were considered, and authors were contacted for missing information. We only included prospective cohort studies which assessed the association between total dietary fructose intake and incident hyperuricemia or gout.

Data Extraction

Studies were reviewed and excluded based on an evaluation of titles and abstracts. Articles that passed this initial screening were then reviewed in full by two independent reviewers (JJ, and SR). The following data were extracted from each using a standardized

proforma: authorship, year of publication, cohort name, country, sample size, subject characteristics, duration of follow-up, method of dietary assessment, fructose exposure levels, number of incident hyperuricemia/gout cases, covariates included in statistical models, and risk ratios (RR) of hyperuricemia or gout per quantile of fructose intake with 95% confidence intervals (95% CIs).

Study Quality

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for Cohort Studies. The NOS for Cohort Studies is a rating scale where points are awarded to studies based on cohort selection, comparability of groups and assessment of outcomes (22). Any given study can have a maximum of 9 points. In this analysis, studies that received ≥6 points were considered of high quality. Differences in grading between reviewers were resolved by consensus.

Grading of Recommendations Assessment, Development and Evaluation

The grading of recommendations assessment, development and evaluation (GRADE) approach was used to assess the overall quality and strength of evidence (23-35). By this approach, the quality of the totality of evidence can be graded as 'very low', 'low', 'moderate' or 'high'. Evidence derived from observational studies receive an initial grade of 'low', while evidence derived from randomized trials receive an initial grade of 'high' (25). Scores can be either upgraded or downgraded depending on a number of factors. Scores for observational analyses can be upgraded for 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(31). Conversely, scores can be downgraded for risk of bias (weight of studies show risk of bias as assessed by low NOS <6) (26), inconsistency (substantial unexplained inter-study heterogeneity), I^2>50% (29), indirectness (presence of

factors that limit the generalizability of the results) (30), 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 to 1.1]) (28), and publication bias (evidence of small-study effects) (27).

Statistical Analysis

Data analysis was done using Review Manager (RevMan, v5.3; The Nordic Cochrane Centre, The Cochrane Collaboration). Risk Ratios (RRs) of extreme quantiles of fructose intake for incident hyperuricemia/gout were natural-log transformed and pooled using the generic inverse variance method(36). Although random-effects models are preferred to fixed effects models because of their conservative nature in the presence of residual inter-study heterogeneity, we used fixed effects models as there were too few studies to estimate tau-squared reliably. Inter-study heterogeneity was assessed and quantified using the Cochran Q and I^2 statistics, respectively (37). The I^2 statistic represents the percentage of total variation across studies that is due to between-study heterogeneity, and $I^2 \geq 50\%$ was considered evidence for substantial heterogeneity (20). We could not explore sources of heterogeneity by sensitivity analyses or *a priori* subgroup analyses owing to too few studies. Publication bias also could not be assessed owing to too few studies.

RESULTS

Search Results

Results of the systematic search and article selection process are shown in **Figure 1**. Of the 2,195 studies initially identified in the literature search, 2,171 were excluded on the basis of title and abstract review. The remaining 24 articles were reviewed in full, and 22 were subsequently excluded. A total of 2 prospective cohort studies were included in this analysis (38,

39). Both of these studies pertained to fructose intake and incident gout. We did not identify any prospective studies that assessed total fructose intake and its association with incident hyperuricemia.

Study Characteristics

The characteristics of the two prospective cohort studies included in this analysis are presented in **Table 1.** Both studies investigated cohorts based in the United States and comprised of older, predominantly white (91% and 95%), health professionals. Choi et al. 2008 (38) consisted of 46,393 male dentists, optometrists, osteopaths, pharmacists, and veterinarians; aged 40-75, from the Health professionals follow-up study. Choi et al. 2010 (39) investigated a cohort of 78,906 female nurses aged 30-55, from the Nurses' Health Study. The follow-up rate for both cohorts exceeded 90%. The women's cohort had a follow-up duration of 22 years (39), while the male cohort was followed for 12 years (38). Both studies received 6 points on the Newcastle-Ottawa Scale, indicating that they were of high quality. All 125,299 participants across both studies were free of gout at baseline, and a total of 1,533 confirmed cases of incident gout (755 male, 778 female) were identified.

Methods for collecting dietary and health information were similar between studies. Validated food frequency questionnaires (FFQs) of over 130 different foods and beverages were completed every four years. Corresponding nutrient values were derived from US Department of Agriculture Sources and supplemented by manufacturers. Total fructose intake, defined as fructose plus half the intake of sucrose, was assessed in both studies. Median fructose intake was ~7.2% of total energy in the lowest quantiles of intake and ~ 11.9% of total energy in the highest quantiles of intake (38, 39). In the prospective study of the Health Professionals Follow-up

Study, the main dietary sources of total monosaccharide fructose were orange juice (15.9%), SSBs (15.5%), apples (14.5%), raisins (5.2%), and oranges (3.2%) (38).

Information regarding weight, medications, and medical conditions (including gout) was collected at baseline and every two years following for the duration of both studies. Participants that reported physician-diagnosed incident gout were sent a supplementary questionnaire based on the American College of Rheumatology gout survey criteria (40). To meet the endpoint of the study, participants needed ≥6 symptoms out of a possible 11. The response rate of the supplementary survey was approximately 80% for both cohorts. Both studies adjusted for the critical confounders of age, BMI, total energy intake and alcohol consumption (each study was conducted in a single sex, so adjustment for sex was not necessary). Additional adjustments were made for diuretic use, history of hypertension, history of renal failure, menopause status, use of hormone therapy; caffeine intake and total vitamin C; as well as the percentage of energy from total carbohydrates (38, 39).

Funding sources were assessed for all of the included prospective cohort studies. All reported funding from agency alone (add in references for Choi et al 2008, and 2010).

Total Fructose Intake on Incident Gout

Figure 2 depicts the relationship between total fructose intake and incident gout. We identified a significant overall association between fructose intake and increased the risk of incident gout with a pooled risk ratio of 1.62 (95% CI 1.28 to 2.03) with no evidence of significant inter-study heterogeneity (I^2=0%, p=0.33). The pooled risk estimates came from the most adjusted models including the adjustment for energy from total carbohydrate intake(38, 39). This adjustment enables the effects of fructose compared with isocaloric exchange for other carbohydrates on gout could be estimated. Both studies included in our analysis also presented

results adjusted for energy from non-fructose carbohydrate and total protein to facilitate the comparison of isocaloric substitution of fructose for fat. This model resulted in more modest effect estimates (RR 1.34, 95% CI 1.05 to 1.72) (see **S1 Figure**). Pooled analysis of the least-adjusted models (adjusted for age, total energy intake, BMI and alcohol consumption in both studies) did not result in a significant association between fructose intake and gout (RR 1.10, 95% CI 0.88 to 1.39) (see **S2 Figure**).

Total Fructose intake on Incident Hyperuricemia

The lack of prospective studies investigating the association between total fructose intake and incident hyperuricemia yielded by our strategy precluded testing the effect of total fructose intake on incident hyperuricemia.

Study Quality

S2 Table shows the NOS for assessing the quality of cohort studies. All studies were considered to be high quality (NOS≥6).

GRADE assessment

The overall strength and quality of the evidence for the effect of fructose intake on incident gout was assessed by GRADE. Despite grading up for an observed dose-response gradient in the studies, evidence of serious indirectness resulted in the evidence being downgraded to low quality, the default level for observational studies **(S3 Table)**.

DISCUSSION

Statement of Principle Findings

We present the results of a systematic review and meta-analysis of prospective cohort studies investigating the association between total fructose intake and risk of developing

hyperuricemia and gout. We identified a total of two prospective studies that assessed the relationship between fructose and gout (38, 39), and no prospective studies pertaining to fructose and hyperuricemia. The two studies that assessed gout included a total of 125,299 subjects free of gout at baseline, and 1,533 identified cases of incident gout over an average of 17 years of follow-up. The results of our pooled analysis indicated that total fructose consumption was positively associated with an increased risk of developing gout by 62% when comparing extreme quantiles of fructose intake.

Strengths and Weaknesses of the Study

There are many strengths of our analysis pertaining to fructose and gout. The studies that were included were relatively large (125,299 subjects and 1,533 cases of incident gout) and both had follow-up durations in excess of 10 years (12 and 22 years). The methodologies of these two studies, including the validated FFQ used for dietary assessment and the evaluation of incident gout, were remarkably similar, and there was no evidence of inter-study heterogeneity. In both studies, repeated administration of FFQs facilitated the analyses of long-term intakes of fructose, not simply diets at baseline. Furthermore, both studies included in the analysis of gout had NOS scores ≥6, indicating that they were of high quality. We also assessed the overall strength of evidence from both studies combined using the GRADE approach. However, there are many notable limitations. We were unable to test the pooled relationship between fructose intake and incident hyperuricemia due to the lack of any prospective studies investigating this association. With regards to fructose and incident gout, we only identified two prospective studies. This meant that we were unable to assess publication bias or perform sensitivity, *a priori* subgroup, and dose-response analyses using the pooled data. Furthermore, although the number of subjects included in both studies were relatively large, both cohorts were recruited in the United States,

meaning that our analysis has low generalizability to other populations. Indeed, various genetic risk factors for gout have been identified (41) with some ethnic groups particularly susceptible to gout (6), therefore, the results might not apply to other populations. Finally, although both studies included in this analysis adjusted for a number of potentially important confounders, the observational design of these studies precludes the inference of causation due to the possibility of residual confounders that remain unaccounted.

Findings in Relation to Other Studies

The results of our meta-analysis support the notion that elevated fructose intake is a risk factor for the development of gout. A recent cross-sectional analysis identified a link between intake of SSBs and prevalent gout (42), and a systematic review of risk factors associated with gout identified fructose intake among many other dietary factors (43). Furthermore, the prevalence of gout has been found to be significantly higher in males than females in many diverse populations (44-46). Of the two studies included in our analysis of fructose and gout, one was conducted in males from the Health Professionals Follow-up Study (38), and the other was carried out in females from the Nurses' Health Study (39). In agreement with worldwide prevalence estimates, males in the Health Professionals Follow-up Study developed gout at a higher rate than females from the Nurses' Health Study. This potentially contributed to the lower effect size observed in the analysis of the Nurses' Health Study despite a larger sample size and similar levels of fructose intake compared to the Health Professional Follow-up Study analysis. Although the exact mechanisms that result in differences in the rates of developing gout between the sexes have not yet been fully elucidated, the protective and uricosuric effects of female sex hormones are thought to play a role (47, 48).

Hyperuricemia is a major risk factor for gout and is understood to be instrumental in its development (1). Emerging evidence has also implicated hyperuricemia in the development of the metabolic syndrome, hypertension and CVD (3), although these associations have not been consistently reported in studies that include only hyperuricemic individuals without gout (49, 50). We found no prospective studies investigating fructose intake and incident hyperuricemia to support the observed association between fructose and gout. Some cross-sectional analyses and clinical trials that have supported the association between HFCS-sweetened beverage intake and increased levels of circulating uric acid (51-54); however, analysis of NHANES data did not support the link between fructose intake and increased risk of hyperuricemia (55). Furthermore, prospective evidence has shown that intake of SSBs, which is known to be a large contributor to total fructose intake in western populations (56), is not associated with an increased risk of incident hyperuricemia (52). These inconsistent findings highlight the need for more long-term prospective studies investigating fructose intake from all sources in order to gain a better understanding of the effects of fructose intake on risk of hyperuricemia.

Meaning of study: possible explanations and implications for clinicians and policymakers

Mechanistically, the phosphorylation of fructose is thought to lead to ATP depletion and the subsequent accumulation of AMP (57). The lack of free phosphate results in the conversion of AMP to IMP, a uric acid precursor, by AMP deaminase (39). High fructose levels and this associated decrease in ATP has been shown to lead to a compensatory effect of increasing purine nucleotide synthesis (15), which can subsequently lead to the further overproduction of uric acid in the presence of additional fructose. Additionally, fructose-induced hyperinsulinemia and insulin resistance (39, 58) may lead to higher levels of circulating uric acid through the reduction of uric acid excretion (59). Results of our pooled analysis suggest that fructose may indeed act as

a risk factor for the development of gout; however, the lack of prospective studies assessing hyperuricemia as an outcome limits our ability to attribute this association with gout to the mechanism proposed above.

Current dietary guidelines recommend a reduction in added or free sugars that include fructose intake (especially from SSBs) while also not discouraging the consumption of sugars from whole fruits and vegetables (60). While SSBs represent the largest contributor to total fructose intake in the United States, fruits and fruit products are also a significant contributor (56). Furthermore, the 2012 American College of Rheumatology Guidelines for Management of Gout recommends limited consumption of HFCS-sweetened soft drinks and energy drinks, but does not mention whether fructose from other sources should be limited (61). It is clear that more prospective research investigating the effects of fructose intake and important food sources of fructose (SSBs, fruits and fruit products, grain-based products, dairy products, etc.) on both incident gout and hyperuricemia are necessary to better inform policymakers as they develop improved dietary guidelines for both the management and prevention of these chronic conditions.

Conclusions

Our systematic review and meta-analysis of prospective cohort studies supports the association between fructose intake and increased risk of developing gout. The strength of evidence for the association between fructose consumption and risk of gout was low, as assessed by GRADE. It means that further research is likely to have a significant impact on our confidence in the effect estimate and is likely to change the estimate(25). Indeed, only two studies involving predominantly while health professionals were included in our analysis. Nevertheless, our results are consistent with a growing body of literature implicating fructose as

a risk factor for developing gout. We were unable to identify any prospective studies investigating the effects of fructose intake on risk of developing hyperuricemia. Given that gout is on the rise and has recently been shown to affect approximately 4% of the American population (4, 5), it is crucial that the dietary factors that may confer risk of developing gout are fully elucidated and understood. It is, therefore, imperative that more prospective studies assess the intake of fructose and its food sources in relation to gout and hyperuricemia in diverse populations to determine if and, ultimately, to what extent fructose may mediate the risk of hyperuricemia and gout.

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Ethical Approval

Not required.

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: R.J. de Souza, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

Analysis and interpretation of the data: J. Jamnik, S. Rehman, S. Blanco Mejia, R.J. de Souza, T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

Drafting of the article: J. Jamnik, S. Rehman, J.L. Sievenpiper.

Critical revision of the article for important intellectual content: J. Jamnik, S. Rehman,, S. Blanco Mejia, R.J. de Souza, T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper .

Final approval of the article: J. Jamnik, S. Rehman,, S. Blanco Mejia, R.J. de Souza, T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

Statistical expertise: R.J. de Souza

Obtaining of funding: R.J. de Souza, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

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

Collection and assembly of data: J. Jamnik, S. Rehman, S. Blanco Mejia, R.J. de Souza

Guarantor: J.L. Sievenpiper

Competing Interests

RJdS has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated, unrestricted grant). He has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and received travel support from WHO to attend group meetings. He is the lead author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of saturated fatty acids and trans fatty acids with health outcomes. **TMSW** is a part owner and the President of Glycemic Index Laboratories, Toronto, Canada and has authored several popular diet books on the glycemic index for which he has received royalties from Phillipa Sandall Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for CIHR, CDA Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University,

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Guidelines Expert Committees of the CDA, EASD, and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of ASN. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of 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. His wife is an employee of Unilever Canada. No relevant competing interests were declared by **JJ, SR, SBM, TAK and LL**.

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Data sharing statement

No additional data available.

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Table 1. Characteristics of Prospective Cohort Studies Investigating Total Dietary Fructose Intake and Incident Gout.

Study, year [ref]	Country	Participants	Age Range	Duration	Dietary Assessment	Divisions	Total Incidence	Exposure Range (total fructose)	Method of outcome measure	Funding source[1]	Adjustments
Choi *et al*, 2008 Males [38]	USA	46,393 M	40 – 75	12 years	Food frequency questionnaire (repeated every 4 years)	Quintiles	755	<6.9 - >11.8 (% energy)	Self-report and supplementary questionnaire	Agency	Age, total energy intake, BMI, diuretic use, hypertension, renal failure, alcohol, vitamin C, percentage of energy from carbohydrates
Choi *et al*, 2010 Females [39]	USA	78,906 F	30 - 55	22 years	Food frequency questionnaire (repeated every 4 years)	Quintiles	778	<7.5 - >11.9 (% energy)	Self-report and supplementary questionnaire	Agency	Age, total energy intake, BMI, menopause, hormone therapy, diuretic use, hypertension, alcohol, vitamin C, caffeine, percentage of energy from carbohydrates

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

FIGURE LEGENDS

Figure 1. Summary of Evidence Search and Selection.

Flow of the literature search for the effect of fructose intake on incident gout and hyperuricemia. Of the 2,195 studies initially identified, 2,171 were excluded on the basis of title and abstract review. The remaining 24 studies were reviewed in full. A total of two prospective cohort studies met inclusion criteria and qualified for further analysis.

Figure 2. Fructose Intake and the Relative Risk of Gout.

Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from most-adjusted multivariate models accounting for percentage of energy from total carbohydrates were used. The diamond represents the pooled effect estimate. Inter-study heterogeneity was tested using Cochran's Q and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as risk ratios (RR) with 95% confidence intervals.

Figure 1. Summary of Evidence Search and Selection.

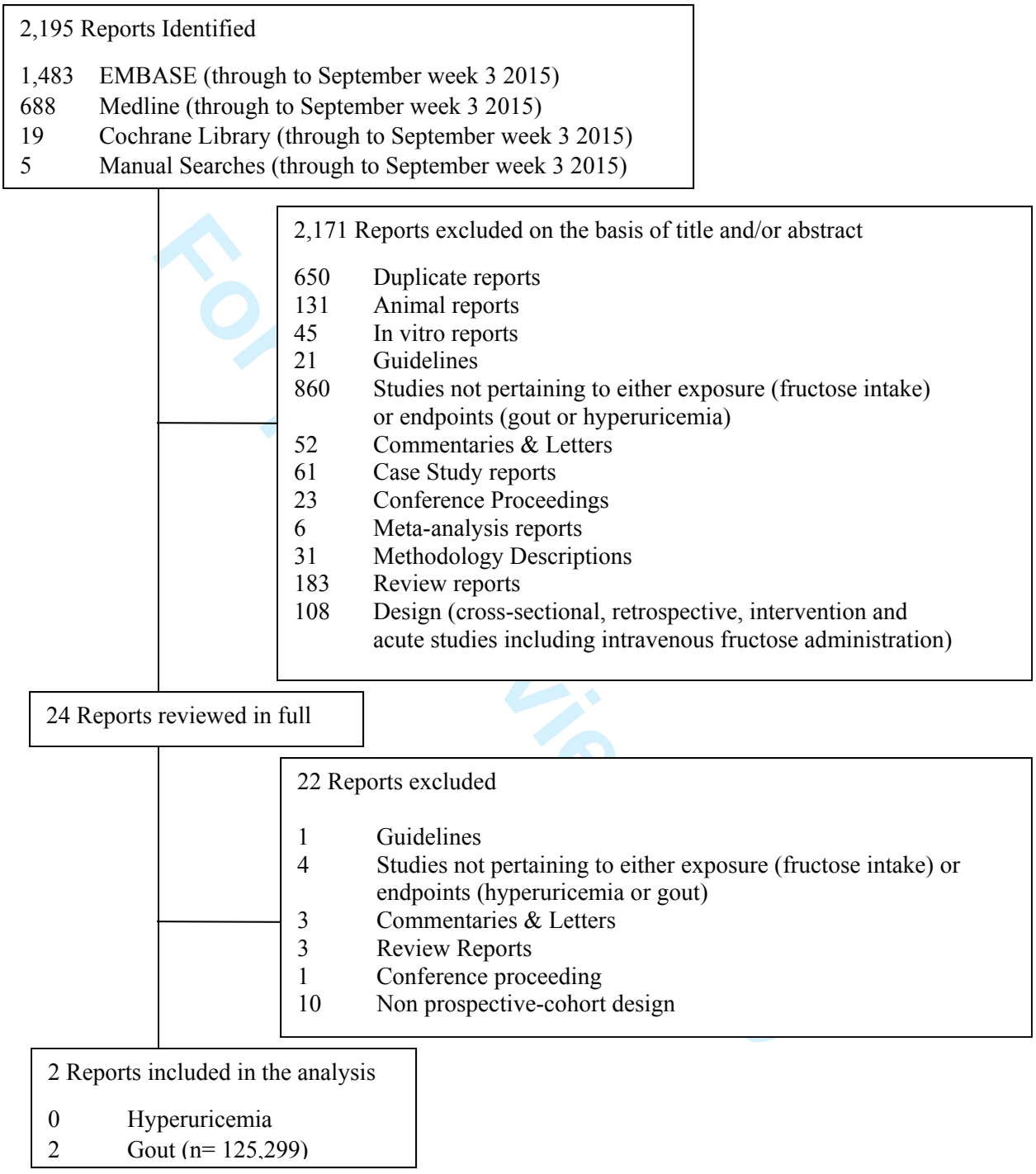
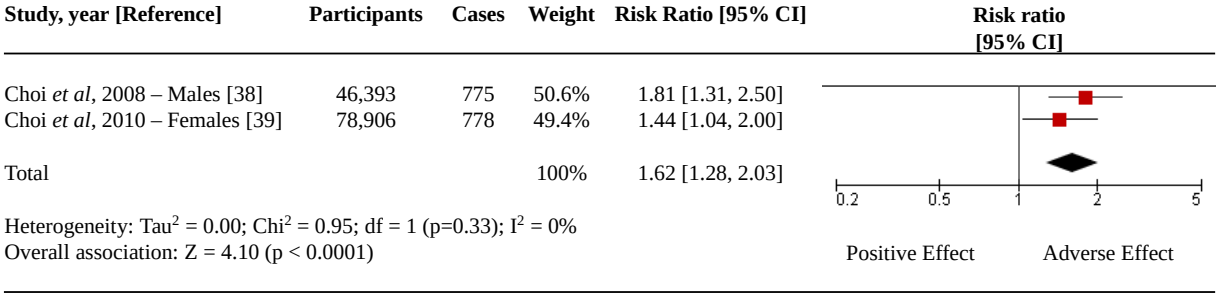


Figure 2. Fructose Intake and the Relative Risk of Gout.



MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4-5
2	Hypothesis statement	4-5
3	Description of study outcome(s)	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 & 15
8	Search strategy, including time period included in the synthesis and key words	5
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)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	5 & 8
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
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)	5-6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-7
22	Assessment of heterogeneity	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	7
24	Provision of appropriate tables and graphics	5-11
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	9-10
26	Table giving descriptive information for each study included	8
27	Results of sensitivity testing (eg, subgroup analysis)	10 & 12
28	Indication of statistical uncertainty of findings	9-10

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	12
30	Justification for exclusion (eg, exclusion of non-English language citations)	N/A
31	Assessment of quality of included studies	12
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
34	Guidelines for future research	15
35	Disclosure of funding source	Submitted online

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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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Submitted online

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Supporting Information

S1 Table. Search Strategy for Studies Assessing Fructose Intake and Risk of Incident Gout and Hyperuricemia.

Database (# of hits)	Search Terms
EMBASE (1,483) & MEDLINE (688) & Cochrane (19)	1. fructose/ 2. fructose*.mp. 3. sucrose/ 4. sucrose*.mp. 5. sugar* 6. (honey or honeys).mp. 7. HFCS.mp. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. Gout/ 10. (gout or gouty).mp. 11. hyperuricemia/ 12. (hyperuricemia or hyperuricaemia).mp. 13. uric acid/ 14. uric*.mp. 15. 9 or 10 or 11 or 12 or 13 or 14 16. 8 and 15

For all databases, the original search date was October 5th, 2012; updated search was performed on: September 22nd, 2015.

S2 table. Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Cohort Studies

Study	Selection[1]	Outcome[2]	Comparability[3]	Total[4]
Choi et al, 2008 Males [38]	2	2	2	6
Choi et al, 2010 Females [39]	2	2	2	6

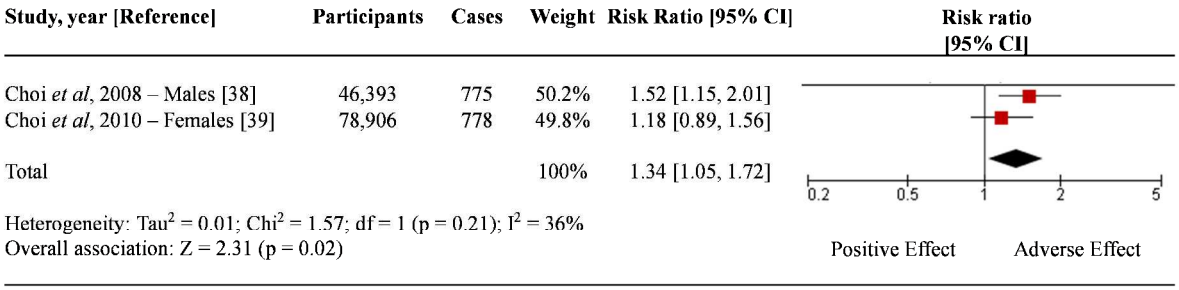
[1]Maximum 4 stars awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment, and demonstration outcome not present at baseline
[2]Maximum 3 stars awarded for follow-up length, adequacy of follow-up, and outcome assessment
[3]Maximum 2 stars awarded for controlling for main confounders
[4]Studies receiving ≥6 points were considered high quality; a maximum of 9 points could be awarded

S3 Table. GRADE Assessment.

Quality assessment							
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Overall Quality (Very Low ⊕; Low ⊕⊕; Moderate ⊕⊕⊕; High ⊕⊕⊕⊕)**
Total fructose intake on incident gout (follow-up median 17 years)							
125,299 (2 studies) 17 years	No serious risk of bias[1]	No serious inconsistency[2]	Serious[3]	No serious imprecision	Undetected[5]	Dose response gradient[6]	⊕⊕ **LOW**[1,2,3,4,5] due to indirectness, dose-response gradient

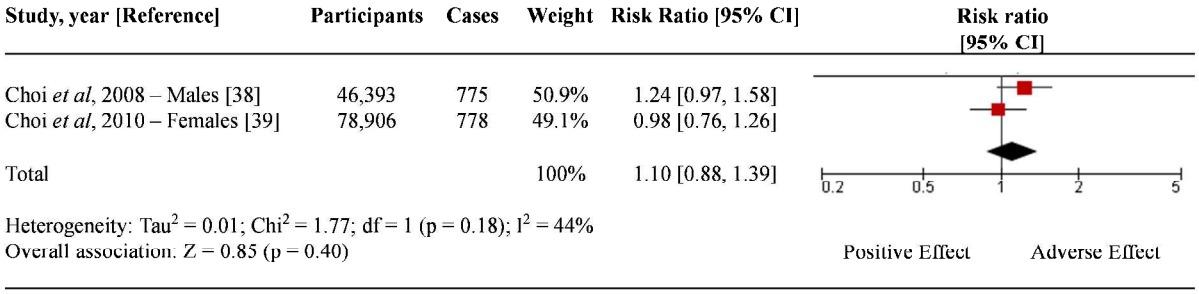
[1] No serious risk of bias as both studies included had NOS=6.
[2] No evidence of significant inter-study heterogeneity (I^2=0%, p=0.33).
[3] Serious indirectness as evidence is based on only 2 cohorts in predominantly white health professionals and may not be representative of different populations.
[4] Publication bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 studies).
[5] An approximate dose-response gradient was observed in both studies where most increasing quintiles of fructose consumption corresponded with an increased risk of gout.

S1 Figure. Fructose Intake and the Relative Risk of Gout in Multivariate Models Adjusted for Percentage of Energy from Non-Fructose Carbohydrates and Protein.



Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from most-adjusted multivariate models accounting for percentage of energy from non-fructose carbohydrates and protein were used. The diamond represents the pooled effect estimate. Inter-study heterogeneity was tested using Cochran's Q and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as risk ratios (RR) with 95% confidence intervals.

S2 Figure. Fructose Intake and Risk of Gout in Least-Adjusted Models.



Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from least-adjusted models were used. The diamond represents the pooled effect estimate. Inter-study heterogeneity was tested using Cochran's Q and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as risk ratios (RR) with 95% confidence intervals.

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FRUCTOSE INTAKE AND RISK OF GOUT AND HYPERURICEMIA: A SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE COHORT STUDIES

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Complete List of Authors:	Jamnik, Joseph; University of Toronto Faculty of Medicine, Nutritional Sciences Rehman, Sara; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Blanco Mejia, Sonia; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital de Souza, Russell; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital; McMaster University Faculty of Health Sciences, Department of Clinical Epidemiology and Biostatistics Khan, Tauseef ; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Leiter, Lawrence; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Wolever, Thomas M. S.; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Kendall, Cyril; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Jenkins, David; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital Sievenpiper, John; University of Toronto Faculty of Medicine, Nutritional Sciences; Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital
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Keywords:	Fructose, Gout, Hyperuricemia, systematic review

Fructose Intake and Risk of Gout and Hyperuricemia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies

Joseph Jamnik[1], Sarah Rehman[1,2], Sonia Blanco Meja[1,2], Russefll J de Souza[2,3], Tauseef A Khan[1,2], Lawrence A Leiter[1,2,4-6], Thomas MS Wolever[1,2,4-6], Cyril WC Kendall[1,2,7], David JA Jenkins[1,2,4-6], John L Sievenpiper[1,2,5,6]

[1]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada; [3]Department of Clinical Epidemiology and Biostatistics, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada, [4]Department of Medicine, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, [5]Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada; [6]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada, [7]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Corresponding Author:

Dr. John L Sievenpiper MD, PhD, FRCPC, Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital, 6137-61 Queen Street East, Toronto, ON, M5C 2T2, CANADA,

Tel: 416 867 7475, Fax: 416 867 7495, email: john.sievenpiper@utoronto.ca

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ABSTRACT

Background: The prevalence of hyperuricemia and gout has increased in recent decades. The role of dietary fructose in the development of these conditions remains unclear.

Objective: To conduct a systematic review and meta-analysis of prospective cohort studies investigating the association fructose consumption with incident gout and hyperuricemia.

Design: MEDLINE, EMBASE, and the Cochrane Library were searched (through September 2015). We included prospective cohort studies that assessed fructose consumption and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and assessed study quality using the Newcastle-Ottawa Scale. We pooled natural-log transformed risk ratios (RRs) using the generic inverse variance method. Inter-study heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). The overall quality of the evidence was assessed using the Grading of recommendations assessment, development, and evaluation (GRADE) approach.

Results: Two studies involving 125,299 participants and 1,533 cases of incident gout assessed the association between fructose consumption and incident gout over an average of 17 years of follow-up. No eligible studies assessed incident hyperuricemia as an outcome. Fructose consumption was associated with an increase in the risk of gout (RR=1.62, 95% CI 1.28 to 2.03, p<0.0001) with no evidence of inter-study heterogeneity (I^2=0%, p=0.33) when comparing the highest (>11.8 to >11.9% total energy) and lowest (<6.9 to <7.5% total energy) quantiles of consumption.

Limitations: Despite a dose-response gradient, the overall quality of evidence as assessed by GRADE was low, due to indirectness. There were only two prospective cohort studies involving predominantly white health professionals that assessed incident gout, and none assessed hyperuricemia.

Conclusions: Fructose consumption was associated with an increased risk of developing gout in predominantly white health professionals. More prospective studies are necessary to understand better the role of fructose and its food sources in the development of gout and hyperuricemia.

Protocol Registration: clinicaltrials.gov identifier, NCT01608620.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review and meta-analysis assessed the overall quality of the evidence using the Grading of recommendations assessment, development, and evaluation (GRADE) approach.
- Large prospective cohort studies that were of high quality and had a long duration of follow-up were included
- The pooled results showed good consistency (low between-study heterogeneity) and evidence of a dose response gradient.
- Only two 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 is a systemic rheumatic condition characterized by monosodium urate crystal deposition and accumulation around joints. Individuals with gout often experience acute and recurring attacks of arthritis that can affect several joints [1]. Hyperuricemia or excessive circulating concentrations of urate, the final product of purine metabolism, is a major risk factor for gout and plays a major role in the pathogenesis of this condition [2]. Chronic hyperuricemia and gout also represent potential risk factors for cardiovascular disease (CVD)[3]. According to the National Health and Nutritional Examination Survey 2007-2008, hyperuricemia affects greater than 20% of the U.S. population, while approximately 4% of American adults have gout [4]. The prevalence of both hyperuricemia and gout has increased in recent decades [4-6], suggesting potential environmental triggers. Several lifestyle and dietary factors have been implicated in the development of these conditions, including elevated body mass index (BMI) [7], alcohol consumption [8], and high dietary intakes of meat and seafood [9 10]. Recent research has also implicated fructose intake in the pathogenesis of hyperuricemia and gout [11 12].

Fructose is a monosaccharide found commonly in plants. It is also a major constituent of high-fructose corn syrup (HFCS) in sugar-sweetened beverages (SSBs) [13]. Ecological evidence has shown that the increasing prevalence of hyperuricemia and gout in developed countries has paralleled the increase in consumption of total fructose and HFCS [14]. The phosphorylation of fructose, unlike the monosaccharide glucose, is understood to facilitate ATP depletion and result in an elevation of circulating uric acid levels [11 15 16]. Animal studies and select trials of acute ingestion of fructose-sweetened beverages have shown that fructose can lead to higher blood concentrations of uric acid [17 18]. However, a meta-analysis of isocaloric substitution trials did not support this association between fructose and serum uric acid [19]. The role of fructose from all

dietary sources as a risk factor for incident hyperuricemia and ultimately gout, therefore, remains unclear. Furthermore, there is a notable lack of meta-analyses of prospective studies assessing the role of dietary fructose in the development of disorders of purine metabolism. The objective of this study was to conduct a systematic review and meta-analysis of prospective cohort studies investigating total fructose consumption and its association with incident hyperuricemia and gout.

METHODS

This meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [20] and reported following the Meta-analysis of Observational Studies in Epidemiology guidelines (MOOSE) [21]. The study protocol was registered at ClinicalTrials.gov (NCT01608620).

Study Selection

We performed a comprehensive search of MEDLINE, EMBASE and the Cochrane Library databases from conception through 22 September 2015. The following search terms were used: “fructose”, “sucrose”, “sugar”, honey”, “HFCS”, “gout”, “hyperuricemia”, and “uric acid”. No language restrictions were imposed on the search. The complete search strategy is reported in **S1 Table**. The electronic search was supplemented by a manual review of article reference lists. Abstracts were considered, and authors were contacted for missing information. We only included prospective cohort studies which assessed the association between total dietary fructose intake and incident hyperuricemia or gout. Studies were considered eligible if cases of gout were ascertained using self-report of a physician diagnosis, while the assessment of hyperuricemia required serum uric acid measurements above study-specific predefined thresholds.

Data Extraction

Studies were reviewed and excluded based on an evaluation of titles and abstracts. Articles that passed this initial screening were then reviewed in full by two independent reviewers (JJ, and SR). The following data were extracted from each using a standardized *proforma*: authorship, year of publication, cohort name, country, sample size, subject characteristics, duration of follow-up, method of dietary assessment, fructose exposure levels, number of incident hyperuricemia/gout cases, covariates included in statistical models, and risk ratios (RR) of hyperuricemia or gout per quantile of fructose intake with 95% confidence intervals (95% CIs).

Study Quality

Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for Cohort Studies. The NOS for Cohort Studies is a rating scale where points are awarded to studies based on cohort selection, comparability of groups and assessment of outcomes [22]. Any given study can have a maximum of 9 points. In this analysis, studies that received ≥6 points were considered of high quality. Differences in grading between reviewers were resolved by consensus.

Grading of Recommendations Assessment, Development and Evaluation

The grading of recommendations assessment, development and evaluation (GRADE) approach was used to assess the overall quality and strength of evidence [23-35]. By this approach, the quality of the totality of evidence can be graded as 'very low', 'low', 'moderate' or 'high'. Evidence derived from observational studies receive an initial grade of 'low', while evidence derived from randomized trials receive an initial grade of 'high' [25]. Scores can be either upgraded or downgraded depending on a number of factors. Scores for observational analyses can be upgraded for 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[31]. Conversely, scores can be downgraded for risk of bias (weight of studies show risk of bias as assessed by low NOS <6) [26], inconsistency (substantial unexplained inter-study heterogeneity), I^2>50% [29], indirectness (presence of factors that limit the generalizability of the results) [30], 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 to 1.1]) [28], and publication bias (evidence of small-study effects) [27].

Statistical Analysis

Data analysis was done using Review Manager (RevMan, v5.3; The Nordic Cochrane Centre, The Cochrane Collaboration). Risk Ratios (RRs) of extreme quantiles of fructose intake for incident hyperuricemia/gout were natural-log transformed and pooled using the generic inverse variance method[36]. Although random-effects models are preferred to fixed effects models because of their conservative nature in the presence of residual inter-study heterogeneity, we used fixed effects models as there were too few studies to estimate tau-squared reliably. Inter-study heterogeneity was assessed and quantified using the Cochran Q and I^2 statistics, respectively [37]. The I^2 statistic represents the percentage of total variation across studies that is due to between-study heterogeneity, and $I^2 \geq 50\%$ was considered evidence for substantial heterogeneity [20]. We could not explore sources of heterogeneity by sensitivity analyses or *a priori* subgroup analyses owing to too few studies. Publication bias also could not be assessed owing to too few studies.

RESULTS

Search Results

Results of the systematic search and article selection process are shown in **Figure 1**. Of the 2,195 studies initially identified in the literature search, 2,171 were excluded on the basis of title and abstract review. The remaining 24 articles were reviewed in full, and 22 were subsequently excluded. A total of 2 prospective cohort studies were included in this analysis [38 39]. Both of these studies pertained to fructose intake and incident gout. We did not identify any prospective studies that assessed total fructose intake and its association with incident hyperuricemia.

Study Characteristics

The characteristics of the two prospective cohort studies included in this analysis are presented in **Table 1.** Both studies investigated cohorts based in the United States and comprised of older, predominantly white (91% and 95%), health professionals. Choi et al. 2008 [38] consisted of 46,393 male dentists, optometrists, osteopaths, pharmacists, and veterinarians; aged 40-75, from the Health Professionals Follow-up Study. Choi et al. 2010 [39] investigated a cohort of 78,906 female nurses aged 30-55, from the Nurses' Health Study. The follow-up rate for both cohorts exceeded 90%. The women's cohort had a follow-up duration of 22 years [39], while the male cohort was followed for 12 years [38]. Both studies received 6 points on the Newcastle-Ottawa Scale, indicating that they were of high quality. All 125,299 participants across both studies were free of gout at baseline, and a total of 1,533 confirmed cases of incident gout (755 male, 778 female) were identified.

Methods for collecting dietary and health information were similar between studies. Validated food frequency questionnaires (FFQs) of over 130 different foods and beverages were completed every four years. Corresponding nutrient values were derived from US Department of Agriculture Sources and supplemented by manufacturers. Total fructose intake, defined as

fructose plus half the intake of sucrose, was assessed in both studies. Median fructose intake was ~7.2% of total energy in the lowest quantiles of intake and ~ 11.9% of total energy in the highest quantiles of intake [38 39]. In the prospective study of the Health Professionals Follow-up Study, the main dietary sources of total monosaccharide fructose were orange juice (15.9%), SSBs (15.5%), apples (14.5%), raisins (5.2%), and oranges (3.2%) [38].

Information regarding weight, medications, and medical conditions (including gout) was collected at baseline and every two years following for the duration of both studies. Participants that reported physician-diagnosed incident gout were sent a supplementary questionnaire based on the American College of Rheumatology gout survey criteria [40]. To meet the endpoint of the study, participants needed ≥6 symptoms out of a possible 11. The response rate of the supplementary survey was approximately 80% for both cohorts. Both studies adjusted for the critical confounders of age, BMI, total energy intake and alcohol consumption (each study was conducted in a single sex, so adjustment for sex was not necessary). Additional adjustments were made for diuretic use, history of hypertension, history of renal failure, menopause status, use of hormone therapy; caffeine intake and total vitamin C; as well as the percentage of energy from total carbohydrates [38 39].

Funding sources were assessed for all of the included prospective cohort studies. All reported funding from agency alone [38 39].

Total Fructose Intake on Incident Gout

Figure 2 depicts the relationship between total fructose intake and incident gout. We identified a significant overall association between fructose intake and increased the risk of incident gout with a pooled risk ratio of 1.62 (95% CI 1.28 to 2.03) with no evidence of significant inter-study heterogeneity (I^2=0%, p=0.33). The pooled risk estimates came from the

most adjusted models including the adjustment for energy from total carbohydrate intake[38 39]. This model allows for the effects of fructose compared with isocaloric exchange for other carbohydrates to be estimated. Both studies included in our analysis also presented results adjusted for energy from non-fructose carbohydrate and total protein to facilitate the comparison of isocaloric substitution of fructose for fat. This model resulted in more modest effect estimates (RR 1.34, 95% CI 1.05 to 1.72) (see **S1 Figure**). Pooled analysis of the least-adjusted models (adjusted for age, total energy intake, BMI and alcohol consumption in both studies) did not result in a significant association between fructose intake and gout (RR 1.10, 95% CI 0.88 to 1.39) (see **S2 Figure**).

Total Fructose intake on Incident Hyperuricemia

The lack of prospective studies investigating the association between total fructose intake and incident hyperuricemia yielded by our strategy precluded testing the effect of total fructose intake on incident hyperuricemia.

Study Quality

S2 Table shows the NOS for assessing the quality of cohort studies. All studies were considered to be high quality (NOS≥6).

GRADE assessment

The overall strength and quality of the evidence for the effect of fructose intake on incident gout was assessed by GRADE. Despite grading up for an observed dose-response gradient in the studies, evidence of serious indirectness resulted in the evidence being downgraded to low quality, the default level for observational studies **(S3 Table)**.

DISCUSSION

Statement of Principle Findings

We present the results of a systematic review and meta-analysis of prospective cohort studies investigating the association between total fructose intake and risk of developing hyperuricemia and gout. We identified a total of two prospective studies that assessed the relationship between fructose and gout [38 39], and no prospective studies pertaining to fructose and hyperuricemia. The two studies that assessed gout included a total of 125,299 subjects free of gout at baseline, and 1,533 identified cases of incident gout over an average of 17 years of follow-up. The results of our pooled analysis indicated that total fructose consumption was positively associated with an increased risk of developing gout by 62% when comparing extreme quantiles of fructose intake.

Strengths and Weaknesses of the Study

There are many strengths of our analysis pertaining to fructose and gout. The studies that were included were relatively large (125,299 subjects and 1,533 cases of incident gout) and both had follow-up durations in excess of 10 years (12 and 22 years). The methodologies of these two studies, including the validated FFQ used for dietary assessment and the evaluation of incident gout, were remarkably similar, and there was no evidence of inter-study heterogeneity. In both studies, repeated administration of FFQs facilitated the analyses of long-term intakes of fructose, not simply diets at baseline. Furthermore, both studies included in the analysis of gout had NOS scores ≥6, indicating that they were of high quality. We also assessed the overall strength of evidence from both studies combined using the GRADE approach. However, there are many notable limitations. We were unable to test the pooled relationship between fructose intake and incident hyperuricemia due to the lack of any prospective studies investigating this association. With regards to fructose and incident gout, we only identified two prospective studies. This

meant that we were unable to assess publication bias or perform sensitivity, *a priori* subgroup, and dose-response analyses using the pooled data. Furthermore, although the number of subjects included in both studies were relatively large, both cohorts were recruited in the United States, meaning that our analysis has low generalizability to other populations. Indeed, various genetic risk factors for gout have been identified [41] with some ethnic groups particularly susceptible to gout [6], therefore, the results might not apply to other populations. Finally, although both studies included in this analysis adjusted for a number of potentially important confounders, the observational design of these studies precludes the inference of causation due to the possibility of residual confounders that remain unaccounted.

Findings in Relation to Other Studies

The results of our meta-analysis support the notion that elevated fructose intake is a risk factor for the development of gout. A recent cross-sectional analysis identified a link between intake of SSBs and prevalent gout [42], and a systematic review [43] of risk factors associated with gout identified fructose intake among other established dietary risk factors including alcohol, meat and seafood consumption. Dietary factors associated with a lower risk of gout include dairy, folate and coffee intake [43]. Both studies included in our meta-analysis identified a significant association between SSB consumption and increased risk of gout, while similar associations not observed for diet soft drink consumption [38 39].

The prevalence of gout has been found to be significantly higher in males than females in many diverse populations [44-46]. Of the two studies included in our analysis of fructose and gout, one was conducted in males from the Health Professionals Follow-up Study [38], and the other was carried out in females from the Nurses' Health Study [39]. In agreement with worldwide prevalence estimates, males in the Health Professionals Follow-up Study developed gout at a

higher rate than females from the Nurses' Health Study. This potentially contributed to the lower effect size observed in the analysis of the Nurses' Health Study despite a larger sample size and similar levels of fructose intake compared to the Health Professional Follow-up Study analysis. Although the exact mechanisms that result in differences in the rates of developing gout between the sexes have not yet been fully elucidated, the protective and uricosuric effects of female sex hormones are thought to play a role [47 48].

Hyperuricemia is a major risk factor for gout and is understood to be instrumental in its development [1]. Emerging evidence has also implicated hyperuricemia in the development of the metabolic syndrome, hypertension and CVD [3], although these associations have not been consistently reported in studies that include only hyperuricemic individuals without gout [49 50]. We found no prospective studies investigating fructose intake and incident hyperuricemia to support the observed association between fructose and gout. Some cross-sectional analyses and clinical trials that have supported the association between HFCS-sweetened beverage intake and increased levels of circulating uric acid [51-54]; however, analysis of NHANES data did not support the link between fructose intake and increased risk of hyperuricemia [55]. Furthermore, prospective evidence has shown that intake of SSBs, which is known to be a large contributor to total fructose intake in western populations [56], is not associated with an increased risk of incident hyperuricemia [52]. These inconsistent findings highlight the need for more long-term prospective studies investigating fructose intake from all sources in order to gain a better understanding of the effects of fructose intake on risk of hyperuricemia.

Meaning of study: possible explanations and implications for clinicians and policymakers

Mechanistically, the phosphorylation of fructose is thought to lead to ATP depletion and the subsequent accumulation of AMP [57]. The lack of free phosphate results in the conversion of

AMP to IMP, a uric acid precursor, by AMP deaminase [39]. High fructose levels and this associated decrease in ATP has been shown to lead to a compensatory effect of increasing purine nucleotide synthesis [15], which can subsequently lead to the further overproduction of uric acid in the presence of additional fructose. Additionally, fructose-induced hyperinsulinemia and insulin resistance [39 58] may lead to higher levels of circulating uric acid through the reduction of uric acid excretion [59]. Results of our pooled analysis suggest that fructose may indeed act as a risk factor for the development of gout; however, the lack of prospective studies assessing hyperuricemia as an outcome limits our ability to attribute this association with gout to the mechanism proposed above. It remains possible that fructose intake increases the risk of developing gout through undetermined mechanisms independent of any effects on serum urate levels, although this is unlikely given both the link between fructose and uric acid production [57], and the established role of elevated serum urate in the development of gout [2].

Current dietary guidelines recommend a reduction in added or free sugars that include fructose intake (especially from SSBs) while also not discouraging the consumption of sugars from whole fruits and vegetables [60]. While SSBs represent the largest contributor to total fructose intake in the United States, fruits and fruit products are also a significant contributor [56]. Furthermore, the 2012 American College of Rheumatology Guidelines for Management of Gout recommends limited consumption of HFCS-sweetened soft drinks and energy drinks, but does not mention whether fructose from other sources should be limited [61]. It is clear that more prospective research investigating the effects of fructose intake and important food sources of fructose (SSBs, fruits and fruit products, grain-based products, dairy products, etc.) on both incident gout and hyperuricemia are necessary to better inform policymakers as they develop

improved dietary guidelines for both the management and prevention of these chronic conditions.

Conclusions

Our systematic review and meta-analysis of prospective cohort studies supports the association between fructose intake and increased risk of developing gout. The strength of evidence for the association between fructose consumption and risk of gout was low, as assessed by GRADE. It means that further research is likely to have a significant impact on our confidence in the effect estimate and is likely to change the estimate[25]. Indeed, only two studies involving predominantly while health professionals were included in our analysis. Nevertheless, our results are consistent with a growing body of literature implicating fructose as a risk factor for developing gout. We were unable to identify any prospective studies investigating the effects of fructose intake on risk of developing hyperuricemia. Given that gout is on the rise and has recently been shown to affect approximately 4% of the American population [4 5], it is crucial that the dietary factors that may confer risk of developing gout are fully elucidated and understood. It is, therefore, imperative that more prospective studies assess the intake of fructose and its food sources in relation to gout and hyperuricemia in diverse populations to determine if and, ultimately, to what extent fructose may mediate the risk of hyperuricemia and gout.

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Ethical Approval

Not required.

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: R.J. de Souza, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

Analysis and interpretation of the data: J. Jamnik, S. Rehman, S. Blanco Mejia, R.J. de Souza, T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

Drafting of the article: J. Jamnik, S. Rehman, J.L. Sievenpiper.

Critical revision of the article for important intellectual content: J. Jamnik, S. Rehman,, S. Blanco Mejia, R.J. de Souza, T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper .

Final approval of the article: J. Jamnik, S. Rehman,, S. Blanco Mejia, R.J. de Souza, T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

Statistical expertise: R.J. de Souza

Obtaining of funding: R.J. de Souza, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.

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

Collection and assembly of data: J. Jamnik, S. Rehman, S. Blanco Mejia, R.J. de Souza

Guarantor: J.L. Sievenpiper

Competing Interests

RJdS has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated, unrestricted grant). He has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and received travel support from WHO to attend group meetings. He is the lead author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of

saturated fatty acids and trans fatty acids with health outcomes. **TMSW** is a part owner and the President of Glycemic Index Laboratories, Toronto, Canada and has authored several popular diet books on the glycemic index for which he has received royalties from Phillipa Sandall Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for CIHR, CDA Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University, Canadian Society for Nutritional Sciences, National Sports and Conditioning Association, Faculty of Public Health and Nutrition—Autonomous University of Nuevo Leon, Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes. **CWCK** has received research support from the Advanced Foods and Material Network, Agrifoods and Agriculture Canada, the Almond Board of California, the American Pistachio Growers, Barilla, the California Strawberry Commission, the Calorie Control Council, CIHR, the Canola Council of Canada, the Coca-Cola Company (investigator initiated, unrestricted grant), Hain Celestial, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Companies Ltd., Orafti, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. He has received travel funding, consultant fees and/or honoraria from Abbott Laboratories, the Almond Board of California, the American Peanut Council, the American Pistachio Growers, Barilla, Bayer, the Canola Council of Canada, the Coca-Cola Company, Danone, General Mills, the International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Loblaw Companies Ltd., the Nutrition Foundation of Italy, Oldways Preservation Trust, Orafti, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is

on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European Association for the Study of Diabetes (EASD) and has served on the scientific advisory board for the Almond Board of California, the International Tree Nut Council, Oldways Preservation Trust, Paramount Farms and Pulse Canada. **DJAJ** has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever, Barilla, the Almond Board of California, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has been on the speaker's panel, served on the scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca- Cola Company, Saskatchewan Pulse Growers, Sanitarium Company, Orafti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi- Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of

Canada, the Nutritional Fundamentals for Health, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra- Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association. His wife is a director and partner of Glycemic Index Laboratories, and his sister received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. **JLS** has received research support from the CIHR, American Society of Nutrition (ASN), Canadian Diabetes Association (CDA), Banting & Best Diabetes Centre (BBDC), Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted), Dr. Pepper Snapple Group (investigator initiated, unrestricted), Pulse Canada, and the International Tree Nut Council Nutrition Research and Education Foundation. He has received travel funding, speaker fees, and/or honoraria from American Heart Association (AHA), American College of Physicians (ACP), ASN, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), CDA, CNS, University of South Carolina, University of Alabama at Birmingham, Oldways Preservation Trust, Nutrition Foundation of Italy (NFI), Calorie Control Council, Diabetes and Nutrition Study Group of the EASD, International Life Sciences Institute

(ILSI), Abbott Laboratories, Pulse Canada, Canadian Sugar Institute, Dr. Pepper Snapple Group, The Coca-Cola Company, Corn Refiners Association, World Sugar Research Organization, Dairy Farmers of Canada, and Società Italiana di Nutrizione Umana (SINU), III World Congress of Public Health Nutrition, C3 Collaborating for Health, White Wave Foods, Rippe Lifestyle, mdBriefcase, Tate & Lyle, Federation of European Nutrition Societies (FENS), New York Academy of Sciences, International Diabetes Federation. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is on Clinical Practice Guidelines Expert Committees of the CDA, EASD, and Canadian Cardiovascular Society (CCS), as well as an expert writing panel of ASN. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of 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. His wife is an employee of Unilever Canada. No relevant competing interests were declared by **JJ, SR, SBM, TAK and LL**.

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Data Sharing Statement

No additional data available.

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Table 1. Characteristics of Prospective Cohort Studies Investigating Total Dietary Fructose Intake and Incident Gout.

Study, year [ref]	Country	Participants	Age Range	Duration	Dietary Assessment	Divisions	Total Incidence	Exposure Range (total fructose)	Method of outcome measure	Funding source[1]	Adjustments
Choi *et al*, 2008 Males [38]	USA	46,393 M	40 – 75	12 years	Food frequency questionnaire (repeated every 4 years)	Quintiles	755	<6.9 - >11.8 (% energy)	Self-report and supplementary questionnaire	Agency	Age, total energy intake, BMI, diuretic use, hypertension, renal failure, alcohol, vitamin C, percentage of energy from carbohydrates
Choi *et al*, 2010 Females [39]	USA	78,906 F	30 - 55	22 years	Food frequency questionnaire (repeated every 4 years)	Quintiles	778	<7.5 - >11.9 (% energy)	Self-report and supplementary questionnaire	Agency	Age, total energy intake, BMI, menopause, hormone therapy, diuretic use, hypertension, alcohol, vitamin C, caffeine, percentage of energy from carbohydrates

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

FIGURE LEGENDS

Figure 1. Summary of Evidence Search and Selection.

Flow of the literature search for the effect of fructose intake on incident gout and hyperuricemia. Of the 2,195 studies initially identified, 2,171 were excluded on the basis of title and abstract review. The remaining 24 studies were reviewed in full. A total of two prospective cohort studies met inclusion criteria and qualified for further analysis.

Figure 2. Fructose Intake and the Relative Risk of Gout.

Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from most-adjusted multivariate models accounting for percentage of energy from total carbohydrates were used. The diamond represents the pooled effect estimate. Inter-study heterogeneity was tested using Cochran's Q and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as risk ratios (RR) with 95% confidence intervals.

Figure 1. Summary of Evidence Search and Selection.

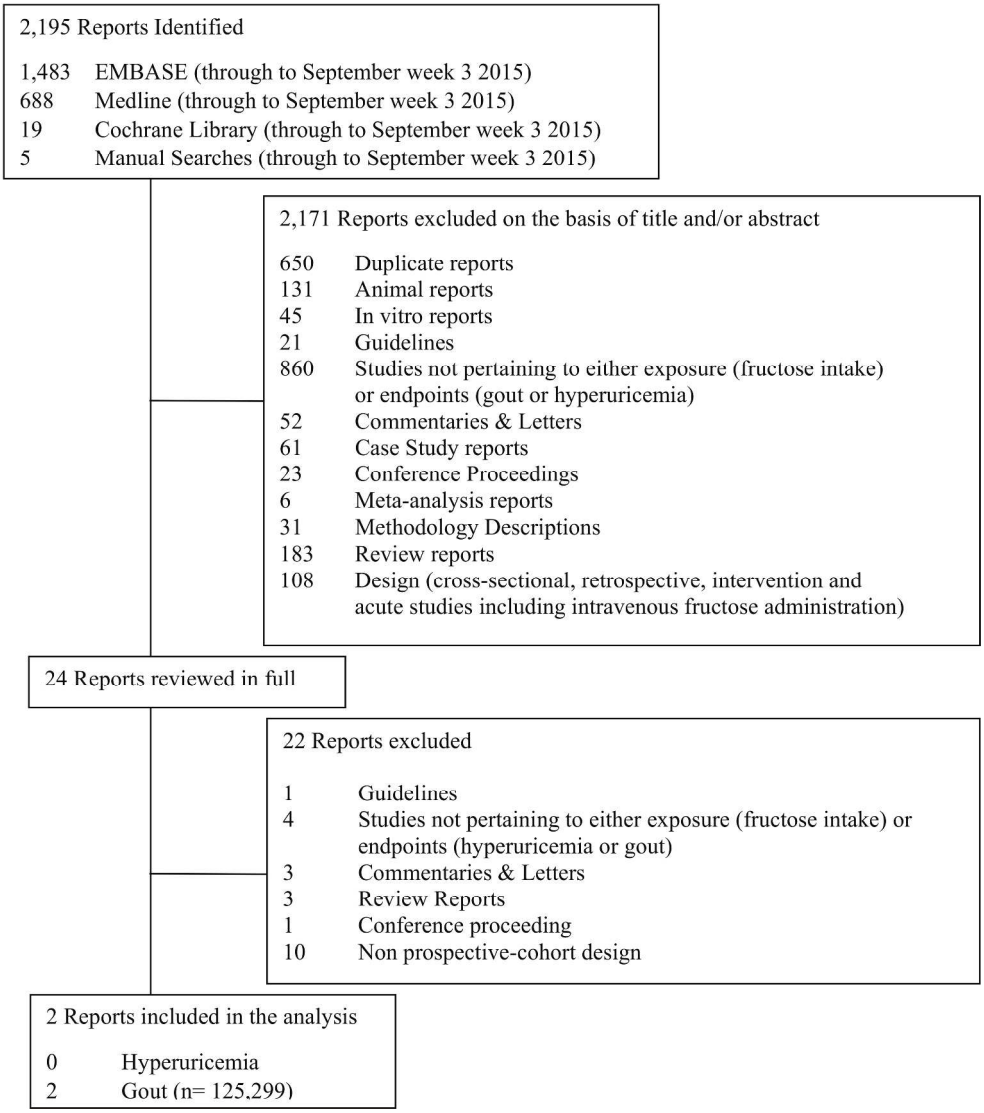


Figure 1. Summary of Evidence Search and Selection
Figure 1
281x328mm (300 x 300 DPI)

Figure 2. Fructose Intake and the Relative Risk of Gout.

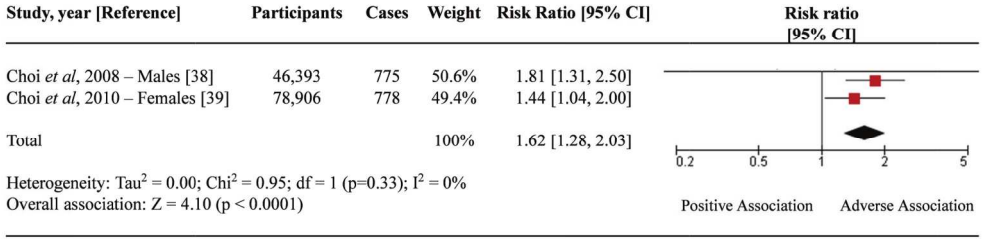


Figure 2. Fructose Intake and the Relative Risk of Gout
Figure 2
326x98mm (300 x 300 DPI)

Supporting Information

S1 Table. Search Strategy for Studies Assessing Fructose Intake and Risk of Incident Gout and Hyperuricemia.

Database (# of hits)	Search Terms
EMBASE (1,483) & MEDLINE (688) & Cochrane (19)	1. fructose/ 2. fructose*.mp. 3. sucrose/ 4. sucrose*.mp. 5. sugar* 6. (honey or honeys).mp. 7. HFCS.mp. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. Gout/ 10. (gout or gouty).mp. 11. hyperuricemia/ 12. (hyperuricemia or hyperuricaemia).mp. 13. uric acid/ 14. uric*.mp. 15. 9 or 10 or 11 or 12 or 13 or 14 16. 8 and 15

For all databases, the original search date was October 5th, 2012; updated search was performed on: September 22nd, 2015.

S2 table. Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Cohort Studies

Study	Selection[1]	Outcome[2]	Comparability[3]	Total[4]
Choi et al, 2008 Males [38]	2	2	2	6
Choi et al, 2010 Females [39]	2	2	2	6

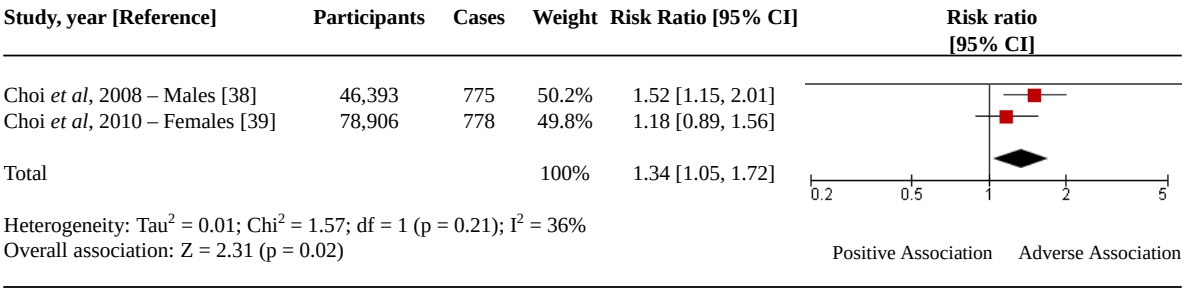
[1]Maximum 4 stars awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment, and demonstration outcome not present at baseline
[2]Maximum 3 stars awarded for follow-up length, adequacy of follow-up, and outcome assessment
[3]Maximum 2 stars awarded for controlling for main confounders
[4]Studies receiving ≥6 points were considered high quality; a maximum of 9 points could be awarded

S3 Table. GRADE Assessment.

Quality assessment							
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations**	**Overall Quality (Very Low ⊕; Low ⊕⊕; Moderate ⊕⊕⊕; High ⊕⊕⊕⊕)**
Total fructose intake on incident gout (follow-up median 17 years)							
125,299 (2 studies) 17 years	No serious risk of bias[1]	No serious inconsistency[2]	Serious[3]	No serious imprecision	Undetected[5]	Dose response gradient[6]	⊕⊕ **LOW**[1,2,3,4,5] due to indirectness, dose-response gradient

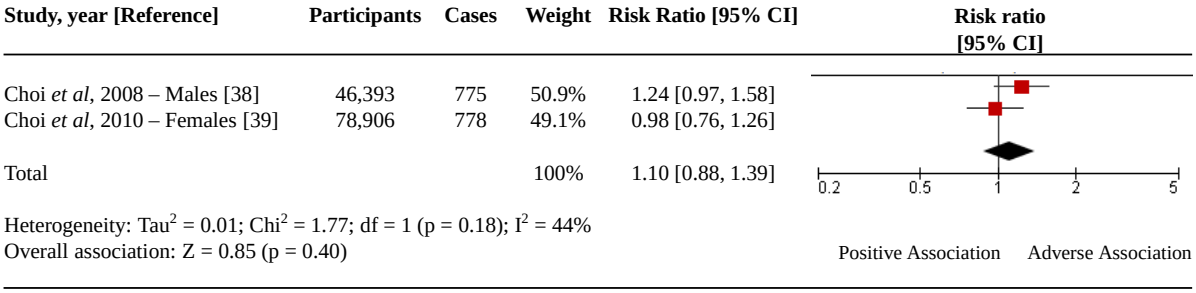
[1] No serious risk of bias as both studies included had NOS=6.
[2] No evidence of significant inter-study heterogeneity (I^2=0%, p=0.33).
[3] Serious indirectness as evidence is based on only 2 cohorts in predominantly white health professionals and may not be representative of different populations.
[4] Publication bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 studies).
[5] An approximate dose-response gradient was observed in both studies where most increasing quintiles of fructose consumption corresponded with an increased risk of gout.

S1 Figure. Fructose Intake and the Relative Risk of Gout in Multivariate Models Adjusted for Percentage of Energy from Non-Fructose Carbohydrates and Protein.



Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from most-adjusted multivariate models accounting for percentage of energy from non-fructose carbohydrates and protein were used. The diamond represents the pooled effect estimate. Inter-study heterogeneity was tested using Cochran's Q and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as risk ratios (RR) with 95% confidence intervals.

S2 Figure. Fructose Intake and Risk of Gout in Least-Adjusted Models.



Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from least-adjusted models were used. The diamond represents the pooled effect estimate. Inter-study heterogeneity was tested using Cochran's Q and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant heterogeneity). All results are presented as risk ratios (RR) with 95% confidence intervals.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4-5
2	Hypothesis statement	4-5
3	Description of study outcome(s)	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 & 15
8	Search strategy, including time period included in the synthesis and key words	5
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)	5
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	5 & 8
14	Method of addressing articles published in languages other than English	5
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	5
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
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)	5-6
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	6-7
22	Assessment of heterogeneity	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	7
24	Provision of appropriate tables and graphics	5-11
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	9-10
26	Table giving descriptive information for each study included	8
27	Results of sensitivity testing (eg, subgroup analysis)	10 & 12
28	Indication of statistical uncertainty of findings	9-10

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	12
30	Justification for exclusion (eg, exclusion of non-English language citations)	N/A
31	Assessment of quality of included studies	12
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	13
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	15
34	Guidelines for future research	15
35	Disclosure of funding source	Submitted online

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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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Submitted online

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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