

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

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6 2 **META-ANALYSIS OF PROSPECTIVE COHORT STUDIES**  
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29 **ABSTRACT**

30 **Background:** The prevalence of hyperuricemia and gout has increased in recent decades.

31 The role of dietary fructose in the development of these conditions remains unclear.

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

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

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

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

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

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

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

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3 52 predominantly white health professionals that assessed incident gout, and none assessed  
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5 53 hyperuricemia.  
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8 **Conclusions:** Fructose consumption was associated with an increased risk of developing gout in  
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10 55 predominantly white health professionals. More prospective studies are necessary to understand  
11  
12 56 better the role of fructose and its food sources in the development of gout and hyperuricemia.  
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15 57 **Protocol Registration:** clinicaltrials.gov identifier, NCT01608620.  
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19  
20 59 **STRENGTHS AND LIMITATIONS OF THIS STUDY**  
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- 22 60
- 23 • This systematic review and meta-analysis assessed the overall quality of the evidence  
24 using the Grading of recommendations assessment, development, and evaluation  
25 (GRADE) approach.  
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27 62
  - 28 • Large prospective cohort studies that were of high quality and had a long duration of  
29 follow-up were included  
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31 64
  - 32 • The pooled results showed good consistency (low between-study heterogeneity) and  
33 evidence of a dose response gradient.  
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35 66
  - 36 • Only two prospective cohort studies with low external generalizability were available for  
37 inclusion.  
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39 68
  - 40 • The observational design of the prospective cohort studies did not allow for causal  
41 inferences to be drawn.  
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## 71 INTRODUCTION

72 Gout is a systemic rheumatic condition characterized by urate crystal deposition and  
73 accumulation around joints. Individuals with gout often experience acute and recurring attacks of  
74 arthritis that can affect several joints (1). Hyperuricemia or excessive circulating concentrations  
75 of urate, the final product of purine metabolism, is a major risk factor for gout and plays a major  
76 role in the pathogenesis of this condition (2). Chronic hyperuricemia and gout also represent  
77 potential risk factors for cardiovascular disease (CVD)(3). According to the National Health and  
78 Nutritional Examination Survey 2007-2008, hyperuricemia affects greater than 20% of the U.S.  
79 population, while approximately 4% of American adults have gout (4). The prevalence of both  
80 hyperuricemia and gout has increased in recent decades (4-6), suggesting potential  
81 environmental triggers. Several lifestyle and dietary factors have been implicated in the  
82 development of these conditions, including elevated body mass index (BMI) (7), alcohol  
83 consumption (8), and high dietary intakes of meat and seafood (9, 10). Recent research has also  
84 implicated fructose intake in the pathogenesis of hyperuricemia and gout (11, 12).

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

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

## 99 **METHODS**

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

### 104 **Study Selection**

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

### 113 **Data Extraction**

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

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3 117 *proforma*: authorship, year of publication, cohort name, country, sample size, subject  
4  
5  
6 118 characteristics, duration of follow-up, method of dietary assessment, fructose exposure levels,  
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8 119 number of incident hyperuricemia/gout cases, covariates included in statistical models, and risk  
9  
10 120 ratios (RR) of hyperuricemia or gout per quantile of fructose intake with 95% confidence  
11  
12 121 intervals (95% CIs).

## 122 **Study Quality**

123 Study quality was assessed using the Newcastle-Ottawa Scale (NOS) for Cohort Studies.

124 The NOS for Cohort Studies is a rating scale where points are awarded to studies based on  
125 cohort selection, comparability of groups and assessment of outcomes (22). Any given study can  
126 have a maximum of 9 points. In this analysis, studies that received  $\geq 6$  points were considered of  
127 high quality. Differences in grading between reviewers were resolved by consensus.

## 128 **Grading of Recommendations Assessment, Development and Evaluation**

129 The grading of recommendations assessment, development and evaluation (GRADE)  
130 approach was used to assess the overall quality and strength of evidence (23-35). By this  
131 approach, the quality of the totality of evidence can be graded as 'very low', 'low', 'moderate' or  
132 'high'. Evidence derived from observational studies receive an initial grade of 'low', while  
133 evidence derived from randomized trials receive an initial grade of 'high' (25). Scores can be  
134 either upgraded or downgraded depending on a number of factors. Scores for observational  
135 analyses can be upgraded for a large magnitude of effect ( $RR > 2$  or  $RR < 0.5$  in the absence of  
136 plausible confounders), dose-response gradient, or reasonable evidence of attenuation of the  
137 pooled effect estimate by confounders(31). Conversely, scores can be downgraded for risk of  
138 bias (weight of studies show risk of bias as assessed by low NOS  $< 6$ ) (26), inconsistency  
139 (substantial unexplained inter-study heterogeneity),  $I^2 > 50\%$  (29), indirectness (presence of



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3 140 factors that limit the generalizability of the results) (30), imprecision in the pooled risk estimate  
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5 141 (the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for  
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8 142 benefit or harm [RR 0.9 to 1.1]) (28), and publication bias (evidence of small-study effects) (27).  
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## 10 143 **Statistical Analysis**

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13 144 Data analysis was done using Review Manager (RevMan, v5.3; The Nordic Cochrane  
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15 145 Centre, The Cochrane Collaboration). Risk Ratios (RRs) of extreme quantiles of fructose intake  
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17 146 for incident hyperuricemia/gout were natural-log transformed and pooled using the generic  
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20 147 inverse variance method(36). Although random-effects models are preferred to fixed effects  
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22 148 models because of their conservative nature in the presence of residual inter-study heterogeneity,  
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24 149 we used fixed effects models as there were too few studies to estimate tau-squared reliably. Inter-  
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27 150 study heterogeneity was assessed and quantified using the Cochran Q and  $I^2$  statistics,  
28  
29 151 respectively (37). The  $I^2$  statistic represents the percentage of total variation across studies that is  
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31 152 due to between-study heterogeneity, and  $I^2 \geq 50\%$  was considered evidence for substantial  
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33 153 heterogeneity (20). We could not explore sources of heterogeneity by sensitivity analyses or *a*  
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35 154 *priori* subgroup analyses owing to too few studies. Publication bias also could not be assessed  
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38 155 owing to too few studies.  
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## 42 43 157 **RESULTS**

### 44 158 **Search Results**

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48 159 Results of the systematic search and article selection process are shown in **Figure 1**. Of  
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50 160 the 2,195 studies initially identified in the literature search, 2,171 were excluded on the basis of  
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52 161 title and abstract review. The remaining 24 articles were reviewed in full, and 22 were  
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55 162 subsequently excluded. A total of 2 prospective cohort studies were included in this analysis (38,  
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3 163 39). Both of these studies pertained to fructose intake and incident gout. We did not identify any  
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6 164 prospective studies that assessed total fructose intake and its association with incident  
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8 165 hyperuricemia.

### 10 166 **Study Characteristics**

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13 167 The characteristics of the two prospective cohort studies included in this analysis are  
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15 168 presented in **Table 1**. Both studies investigated cohorts based in the United States and comprised  
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17 169 of older, predominantly white (91% and 95%), health professionals. Choi et al. 2008 (38)  
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19 170 consisted of 46,393 male dentists, optometrists, osteopaths, pharmacists, and veterinarians; aged  
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21 171 40-75, from the Health professionals follow-up study. Choi et al. 2010 (39) investigated a cohort  
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23 172 of 78,906 female nurses aged 30-55, from the Nurses' Health Study. The follow-up rate for both  
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25 173 cohorts exceeded 90%. The women's cohort had a follow-up duration of 22 years (39), while the  
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27 174 male cohort was followed for 12 years (38). Both studies received 6 points on the Newcastle-  
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29 175 Ottawa Scale, indicating that they were of high quality. All 125,299 participants across both  
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31 176 studies were free of gout at baseline, and a total of 1,533 confirmed cases of incident gout (755  
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33 177 male, 778 female) were identified.

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36 178 Methods for collecting dietary and health information were similar between studies.  
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38 179 Validated food frequency questionnaires (FFQs) of over 130 different foods and beverages were  
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40 180 completed every four years. Corresponding nutrient values were derived from US Department of  
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42 181 Agriculture Sources and supplemented by manufacturers. Total fructose intake, defined as  
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44 182 fructose plus half the intake of sucrose, was assessed in both studies. Median fructose intake was  
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46 183 ~7.2% of total energy in the lowest quantiles of intake and ~ 11.9% of total energy in the highest  
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48 184 quantiles of intake (38, 39). In the prospective study of the Health Professionals Follow-up  
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3 185 Study, the main dietary sources of total monosaccharide fructose were orange juice (15.9%),  
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5 186 SSBs (15.5%), apples (14.5%), raisins (5.2%), and oranges (3.2%) (38).  
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8 187 Information regarding weight, medications, and medical conditions (including gout) was  
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10 188 collected at baseline and every two years following for the duration of both studies. Participants  
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12 189 that reported physician-diagnosed incident gout were sent a supplementary questionnaire based  
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14 190 on the American College of Rheumatology gout survey criteria (40). To meet the endpoint of the  
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16 191 study, participants needed  $\geq 6$  symptoms out of a possible 11. The response rate of the  
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18 192 supplementary survey was approximately 80% for both cohorts. Both studies adjusted for the  
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20 193 critical confounders of age, BMI, total energy intake and alcohol consumption (each study was  
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22 194 conducted in a single sex, so adjustment for sex was not necessary). Additional adjustments were  
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24 195 made for diuretic use, history of hypertension, history of renal failure, menopause status, use of  
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26 196 hormone therapy; caffeine intake and total vitamin C; as well as the percentage of energy from  
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28 197 total carbohydrates (38, 39).  
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34 198 Funding sources were assessed for all of the included prospective cohort studies. All  
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36 199 reported funding from agency alone (add in references for Choi et al 2008, and 2010).  
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### 39 200 **Total Fructose Intake on Incident Gout**

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41 201 **Figure 2** depicts the relationship between total fructose intake and incident gout. We  
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43 202 identified a significant overall association between fructose intake and increased the risk of  
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45 203 incident gout with a pooled risk ratio of 1.62 (95% CI 1.28 to 2.03) with no evidence of  
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47 204 significant inter-study heterogeneity ( $I^2=0\%$ ,  $p=0.33$ ). The pooled risk estimates came from the  
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49 205 most adjusted models including the adjustment for energy from total carbohydrate intake(38, 39).  
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51 206 This adjustment enables the effects of fructose compared with isocaloric exchange for other  
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53 207 carbohydrates on gout could be estimated. Both studies included in our analysis also presented  
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3 208 results adjusted for energy from non-fructose carbohydrate and total protein to facilitate the  
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6 209 comparison of isocaloric substitution of fructose for fat. This model resulted in more modest  
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8 210 effect estimates (RR 1.34, 95% CI 1.05 to 1.72) (see **S1 Figure**). Pooled analysis of the least-  
9  
10 211 adjusted models (adjusted for age, total energy intake, BMI and alcohol consumption in both  
11  
12 212 studies) did not result in a significant association between fructose intake and gout (RR 1.10,  
13  
14 213 95% CI 0.88 to 1.39) (see **S2 Figure**).

### 214 **Total Fructose intake on Incident Hyperuricemia**

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

### 218 **Study Quality**

219 **S2 Table** shows the NOS for assessing the quality of cohort studies. All studies were  
220 considered to be high quality (NOS $\geq$ 6).

### 221 **GRADE assessment**

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

## 227 **DISCUSSION**

### 228 **Statement of Principle Findings**

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

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3 231 hyperuricemia and gout. We identified a total of two prospective studies that assessed the  
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5 232 relationship between fructose and gout (38, 39), and no prospective studies pertaining to fructose  
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8 233 and hyperuricemia. The two studies that assessed gout included a total of 125,299 subjects free  
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10 234 of gout at baseline, and 1,533 identified cases of incident gout over an average of 17 years of  
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12 235 follow-up. The results of our pooled analysis indicated that total fructose consumption was  
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14 236 positively associated with an increased risk of developing gout by 62% when comparing extreme  
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16 237 quantiles of fructose intake.  
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### 20 238 **Strengths and Weaknesses of the Study**

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22 239 There are many strengths of our analysis pertaining to fructose and gout. The studies that  
23  
24 240 were included were relatively large (125,299 subjects and 1,533 cases of incident gout) and both  
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26 241 had follow-up durations in excess of 10 years (12 and 22 years). The methodologies of these two  
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28 242 studies, including the validated FFQ used for dietary assessment and the evaluation of incident  
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30 243 gout, were remarkably similar, and there was no evidence of inter-study heterogeneity. In both  
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32 244 studies, repeated administration of FFQs facilitated the analyses of long-term intakes of fructose,  
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34 245 not simply diets at baseline. Furthermore, both studies included in the analysis of gout had NOS  
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36 246 scores  $\geq 6$ , indicating that they were of high quality. We also assessed the overall strength of  
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38 247 evidence from both studies combined using the GRADE approach. However, there are many  
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40 248 notable limitations. We were unable to test the pooled relationship between fructose intake and  
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42 249 incident hyperuricemia due to the lack of any prospective studies investigating this association.  
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44 250 With regards to fructose and incident gout, we only identified two prospective studies. This  
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46 251 meant that we were unable to assess publication bias or perform sensitivity, *a priori* subgroup,  
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48 252 and dose-response analyses using the pooled data. Furthermore, although the number of subjects  
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50 253 included in both studies were relatively large, both cohorts were recruited in the United States,  
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3 254 meaning that our analysis has low generalizability to other populations. Indeed, various genetic  
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5 255 risk factors for gout have been identified (41) with some ethnic groups particularly susceptible to  
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8 256 gout (6), therefore, the results might not apply to other populations. Finally, although both  
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10 257 studies included in this analysis adjusted for a number of potentially important confounders, the  
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12 258 observational design of these studies precludes the inference of causation due to the possibility of  
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14  
15 259 residual confounders that remain unaccounted.

### 17 260 **Findings in Relation to Other Studies**

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20 261 The results of our meta-analysis support the notion that elevated fructose intake is a risk  
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22 262 factor for the development of gout. A recent cross-sectional analysis identified a link between  
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24 263 intake of SSBs and prevalent gout (42), and a systematic review of risk factors associated with  
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26 264 gout identified fructose intake among many other dietary factors (43). Furthermore, the  
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28 265 prevalence of gout has been found to be significantly higher in males than females in many  
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30 266 diverse populations (44-46). Of the two studies included in our analysis of fructose and gout, one  
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32 267 was conducted in males from the Health Professionals Follow-up Study (38), and the other was  
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34 268 carried out in females from the Nurses' Health Study (39). In agreement with worldwide  
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36 269 prevalence estimates, males in the Health Professionals Follow-up Study developed gout at a  
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38 270 higher rate than females from the Nurses' Health Study. This potentially contributed to the lower  
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40 271 effect size observed in the analysis of the Nurses' Health Study despite a larger sample size and  
41  
42 272 similar levels of fructose intake compared to the Health Professional Follow-up Study analysis.  
43  
44 273 Although the exact mechanisms that result in differences in the rates of developing gout between  
45  
46 274 the sexes have not yet been fully elucidated, the protective and uricosuric effects of female sex  
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48 275 hormones are thought to play a role (47, 48).

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3 276           Hyperuricemia is a major risk factor for gout and is understood to be instrumental in its  
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6 277   development (1). Emerging evidence has also implicated hyperuricemia in the development of  
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8 278   the metabolic syndrome, hypertension and CVD (3), although these associations have not been  
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10 279   consistently reported in studies that include only hyperuricemic individuals without gout (49,  
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12 280   50). We found no prospective studies investigating fructose intake and incident hyperuricemia to  
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14 281   support the observed association between fructose and gout. Some cross-sectional analyses and  
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16 282   clinical trials that have supported the association between HFCS-sweetened beverage intake and  
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18 283   increased levels of circulating uric acid (51-54); however, analysis of NHANES data did not  
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20 284   support the link between fructose intake and increased risk of hyperuricemia (55). Furthermore,  
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22 285   prospective evidence has shown that intake of SSBs, which is known to be a large contributor to  
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24 286   total fructose intake in western populations (56), is not associated with an increased risk of  
25  
26 287   incident hyperuricemia (52). These inconsistent findings highlight the need for more long-term  
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28 288   prospective studies investigating fructose intake from all sources in order to gain a better  
29  
30 289   understanding of the effects of fructose intake on risk of hyperuricemia.

### 31 290 **Meaning of study: possible explanations and implications for clinicians and policymakers**

32 291           Mechanistically, the phosphorylation of fructose is thought to lead to ATP depletion and  
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34 292   the subsequent accumulation of AMP (57). The lack of free phosphate results in the conversion  
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36 293   of AMP to IMP, a uric acid precursor, by AMP deaminase (39). High fructose levels and this  
37  
38 294   associated decrease in ATP has been shown to lead to a compensatory effect of increasing purine  
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40 295   nucleotide synthesis (15), which can subsequently lead to the further overproduction of uric acid  
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42 296   in the presence of additional fructose. Additionally, fructose-induced hyperinsulinemia and  
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44 297   insulin resistance (39, 58) may lead to higher levels of circulating uric acid through the reduction  
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46 298   of uric acid excretion (59). Results of our pooled analysis suggest that fructose may indeed act as  
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3 299 a risk factor for the development of gout; however, the lack of prospective studies assessing  
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6 300 hyperuricemia as an outcome limits our ability to attribute this association with gout to the  
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8 301 mechanism proposed above.  
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10 302 Current dietary guidelines recommend a reduction in added or free sugars that include  
11  
12 303 fructose intake (especially from SSBs) while also not discouraging the consumption of sugars  
13  
14 304 from whole fruits and vegetables (60). While SSBs represent the largest contributor to total  
15  
16 305 fructose intake in the United States, fruits and fruit products are also a significant contributor  
17  
18 306 (56). Furthermore, the 2012 American College of Rheumatology Guidelines for Management of  
19  
20 307 Gout recommends limited consumption of HFCS-sweetened soft drinks and energy drinks, but  
21  
22 308 does not mention whether fructose from other sources should be limited (61). It is clear that more  
23  
24 309 prospective research investigating the effects of fructose intake and important food sources of  
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26 310 fructose (SSBs, fruits and fruit products, grain-based products, dairy products, etc.) on both  
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28 311 incident gout and hyperuricemia are necessary to better inform policymakers as they develop  
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30 312 improved dietary guidelines for both the management and prevention of these chronic  
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32 313 conditions.  
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### 39 314 **Conclusions**

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41 315 Our systematic review and meta-analysis of prospective cohort studies supports the  
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43 316 association between fructose intake and increased risk of developing gout. The strength of  
44  
45 317 evidence for the association between fructose consumption and risk of gout was low, as assessed  
46  
47 318 by GRADE. It means that further research is likely to have a significant impact on our  
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49 319 confidence in the effect estimate and is likely to change the estimate(25). Indeed, only two  
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51 320 studies involving predominantly health professionals were included in our analysis.  
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53 321 Nevertheless, our results are consistent with a growing body of literature implicating fructose as  
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3 322 a risk factor for developing gout. We were unable to identify any prospective studies  
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5  
6 323 investigating the effects of fructose intake on risk of developing hyperuricemia. Given that gout  
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8 324 is on the rise and has recently been shown to affect approximately 4% of the American  
9  
10 325 population (4, 5), it is crucial that the dietary factors that may confer risk of developing gout are  
11  
12 326 fully elucidated and understood. It is, therefore, imperative that more prospective studies assess  
13  
14 327 the intake of fructose and its food sources in relation to gout and hyperuricemia in diverse  
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16 328 populations to determine if and, ultimately, to what extent fructose may mediate the risk of  
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18 329 hyperuricemia and gout.  
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30  
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32  
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### 34 335 **Contributions**

35  
36 336 All authors had full access to all of the data (including statistical reports and tables) in  
37  
38 337 this study and take full responsibility for the integrity of the data and the accuracy of the data  
39  
40 338 analysis.  
41

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43 339 Conception and design: R.J. de Souza, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.  
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45  
46 340 Analysis and interpretation of the data: J. Jamnik, S. Rehman, S. Blanco Mejia, R.J. de Souza,  
47

48 341 T.A. Khan, L.A. Leiter, T.M.S. Wolever, C.W.C. Kendall, D.J.A. Jenkins, J.L. Sievenpiper.  
49

50 342 Drafting of the article: J. Jamnik, S. Rehman, J.L. Sievenpiper.  
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10 346 Final approval of the article: J. Jamnik, S. Rehman,, S. Blanco Mejia, R.J. de Souza, T.A. Khan,  
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28  
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31 355 Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated,  
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36  
37 358 author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of  
38  
39 359 saturated fatty acids and trans fatty acids with health outcomes. **TMSW** is a part owner and the  
40  
41 360 President of Glycemic Index Laboratories, Toronto, Canada and has authored several popular  
42  
43 361 diet books on the glycemic index for which he has received royalties from Phillipa Sandall  
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45 362 Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel  
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47 363 funding, or research support from or served on the scientific advisory board for CIHR, CDA  
48  
49 364 Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal  
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51 365 Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University,  
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3 366 Canadian Society for Nutritional Sciences, National Sports and Conditioning Association,  
4  
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6  
7  
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35  
36 382 on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European  
37  
38 383 Association for the Study of Diabetes (EASD) and has served on the scientific advisory board for  
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9  
10 438 ILSI North America. He is a member of the International Carbohydrate Quality Consortium  
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### 456 **Data sharing statement**

457 No additional data available.

458

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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 <sup>†</sup>	Adjustments
Choi <i>et al</i> , 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 <i>et al</i> , 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

<sup>†</sup>Agency funding is that from government, university or not-for-profit health agency sources.

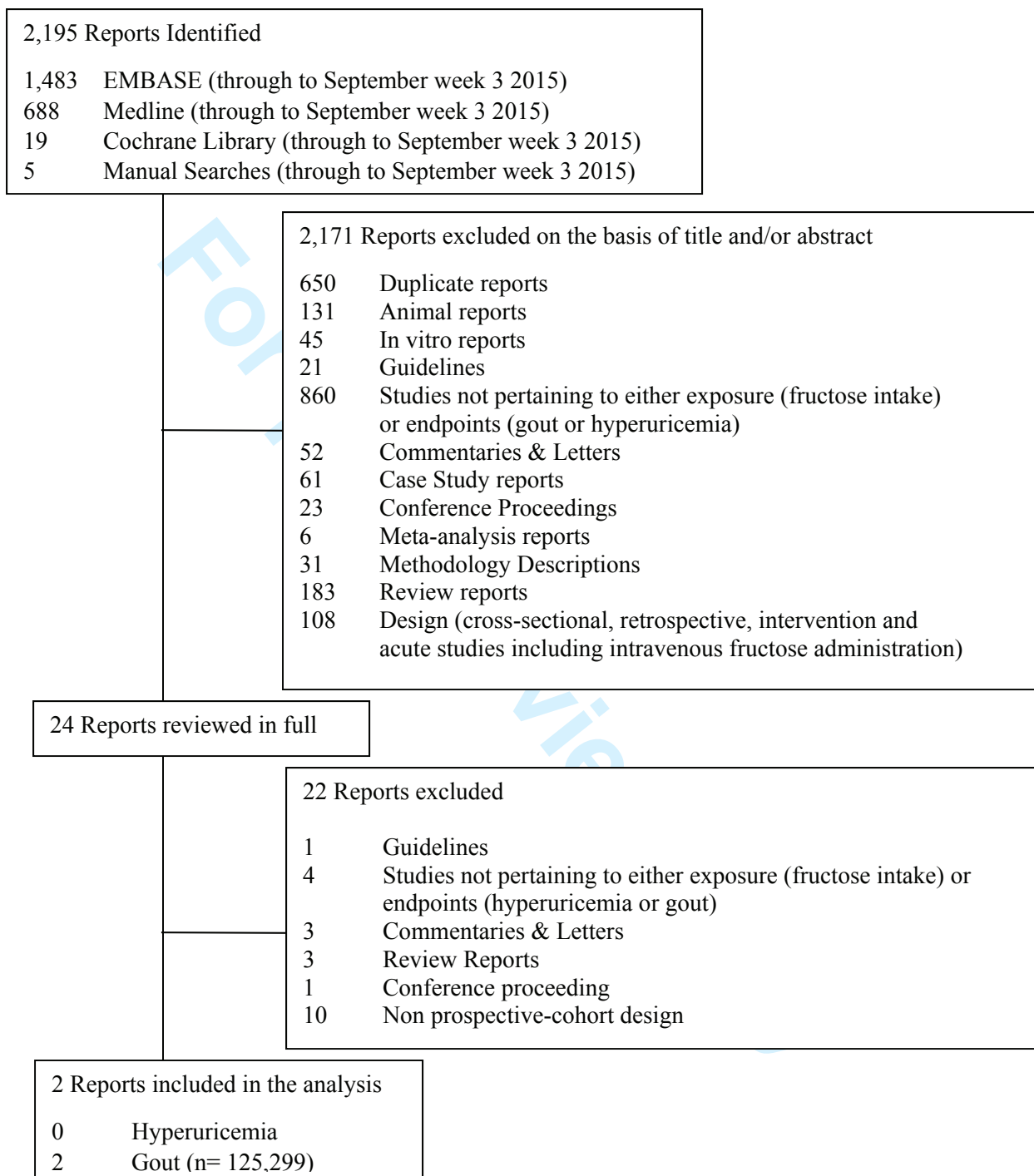
## FIGURE LEGENDS

### **Figure 1.** Summary of Evidence Search and Selection.

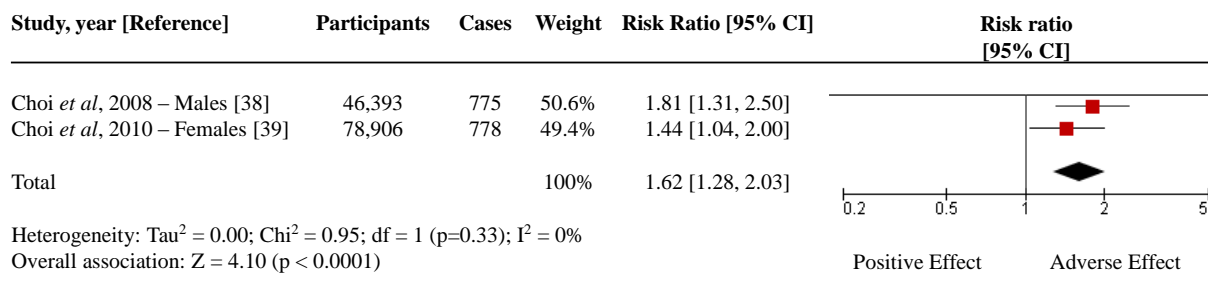
Flow of the literature search for the effect of fructose intake on incident gout and hyperuricemia. Of the 2,195 studies initially identified, 2,171 were excluded on the basis of title and abstract review. The remaining 24 studies were reviewed in full. A total of two prospective cohort studies met inclusion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



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## 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.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United States. August 2012.



# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

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# PRISMA 2009 Checklist

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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
	1. fructose/
	2. fructose*.mp.
	3. sucrose/
	4. sucrose*.mp.
	5. sugar*
	6. (honey or honeys).mp.
	7. HFCS.mp.
EMBASE (1,483)	8. 1 or 2 or 3 or 4 or 5 or 6 or 7
&	9. Gout/
MEDLINE (688)	10. (gout or gouty).mp.
&	11. hyperuricemia/
Cochrane (19)	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 5<sup>th</sup>, 2012; updated search was performed on: September 22nd, 2015.

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

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

<sup>1</sup>Maximum 4 stars awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment, and demonstration outcome not present at baseline

<sup>2</sup>Maximum 3 stars awarded for follow-up length, adequacy of follow-up, and outcome assessment

<sup>3</sup>Maximum 2 stars awarded for controlling for main confounders

<sup>4</sup>Studies receiving  $\geq 6$  points were considered high quality; a maximum of 9 points could be awarded

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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 ⊕⊕⊕⊕)
<b>Total fructose intake on incident gout (follow-up median 17 years)</b>							
125,299 (2 studies) 17 years	No serious risk of bias <sup>1</sup>	No serious inconsistency <sup>2</sup>	Serious <sup>3</sup>	No serious imprecision	Undetected <sup>5</sup>	Dose response gradient <sup>6</sup>	⊕⊕ <b>LOW</b> <sup>1,2,3,4,5</sup> due to indirectness, dose-response gradient

<sup>1</sup> No serious risk of bias as both studies included had NOS=6.

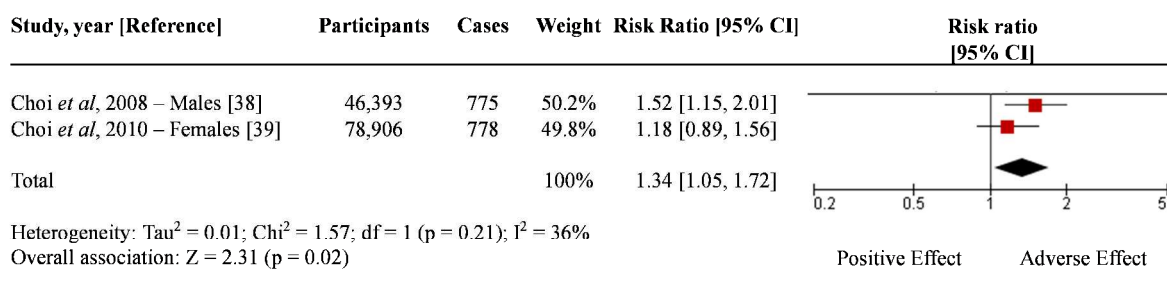
<sup>2</sup> No evidence of significant inter-study heterogeneity ( $I^2=0\%$ ,  $p=0.33$ ).

<sup>3</sup> Serious indirectness as evidence is based on only 2 cohorts in predominantly white health professionals and may not be representative of different populations.

<sup>4</sup> Publication bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 studies).

<sup>5</sup> 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.

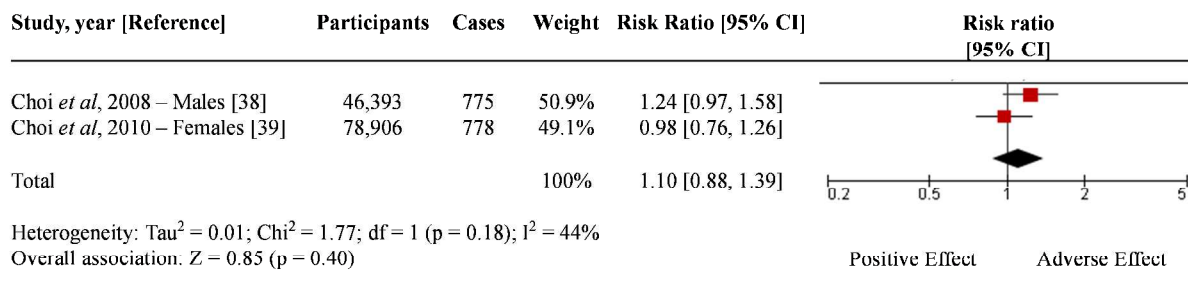


Forest plot of prospective cohort studies investigating the relationship between total fructose intake and incident gout. Estimates from most-adjusted multivariate models accounting for percentage of energy from non-fructose carbohydrates and protein were used. The diamond represents the pooled effect 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.

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**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.

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-013191.R1
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<b>Primary Subject Heading</b>:	Nutrition and metabolism
Secondary Subject Heading:	Rheumatology, Evidence based practice, Epidemiology
Keywords:	Fructose, Gout, Hyperuricemia, systematic review

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4 1 **FRUCTOSE INTAKE AND RISK OF GOUT AND HYPERURICEMIA: A SYSTEMATIC REVIEW AND**  
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6 2 **META-ANALYSIS OF PROSPECTIVE COHORT STUDIES**  
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14 6 **JA Jenkins<sup>1,2,4-6</sup>, John L Sievenpiper<sup>1,2,5,6</sup>**  
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49 23 **Number of Figures:** 2

50 24 **Number of Tables:** 1

51 25 **Supplemental Material:** 3 tables and 2 figures

52 26 **Abstract Word Count:** 290

53 27 **Manuscript Word Count:** 3,544

54 28 **Key words:** Fructose, gout, hyperuricemia, systematic review  
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29 **ABSTRACT**

30 **Background:** The prevalence of hyperuricemia and gout has increased in recent decades.

31 The role of dietary fructose in the development of these conditions remains unclear.

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

34 **Design:** MEDLINE, EMBASE, and the Cochrane Library were searched (through September  
35 2015). We included prospective cohort studies that assessed fructose consumption and incident  
36 gout or hyperuricemia. Two independent reviewers extracted relevant data and assessed study  
37 quality using the Newcastle-Ottawa Scale. We pooled natural-log transformed risk ratios (RRs)  
38 using the generic inverse variance method. Inter-study heterogeneity was assessed (Cochran Q  
39 statistic) and quantified ( $I^2$  statistic). The overall quality of the evidence was assessed using the  
40 Grading of recommendations assessment, development, and evaluation (GRADE) approach.

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

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

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4 52 **Conclusions:** Fructose consumption was associated with an increased risk of developing gout in  
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6 53 predominantly white health professionals. More prospective studies are necessary to understand  
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8 54 better the role of fructose and its food sources in the development of gout and hyperuricemia.  
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10 55 **Protocol Registration:** clinicaltrials.gov identifier, NCT01608620.  
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## 13 14 15 57 **STRENGTHS AND LIMITATIONS OF THIS STUDY** 16

- 17 58 • This systematic review and meta-analysis assessed the overall quality of the evidence  
18 59 using the Grading of recommendations assessment, development, and evaluation  
19 60 (GRADE) approach.  
20  
21 61 • Large prospective cohort studies that were of high quality and had a long duration of  
22 62 follow-up were included  
23  
24 63 • The pooled results showed good consistency (low between-study heterogeneity) and  
25 64 evidence of a dose response gradient.  
26  
27 65 • Only two prospective cohort studies with low external generalizability were available for  
28 66 inclusion.  
29  
30 67 • The observational design of the prospective cohort studies did not allow for causal  
31 68 inferences to be drawn.  
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## 69 INTRODUCTION

70 Gout is a systemic rheumatic condition characterized by monosodium urate crystal  
71 deposition and accumulation around joints. Individuals with gout often experience acute and  
72 recurring attacks of arthritis that can affect several joints <sup>1</sup>. Hyperuricemia or excessive  
73 circulating concentrations of urate, the final product of purine metabolism, is a major risk factor  
74 for gout and plays a major role in the pathogenesis of this condition <sup>2</sup>. Chronic hyperuricemia  
75 and gout also represent potential risk factors for cardiovascular disease (CVD)<sup>3</sup>. According to the  
76 National Health and Nutritional Examination Survey 2007-2008, hyperuricemia affects greater  
77 than 20% of the U.S. population, while approximately 4% of American adults have gout <sup>4</sup>. The  
78 prevalence of both hyperuricemia and gout has increased in recent decades <sup>4-6</sup>, suggesting  
79 potential environmental triggers. Several lifestyle and dietary factors have been implicated in the  
80 development of these conditions, including elevated body mass index (BMI) <sup>7</sup>, alcohol  
81 consumption <sup>8</sup>, and high dietary intakes of meat and seafood <sup>9 10</sup>. Recent research has also  
82 implicated fructose intake in the pathogenesis of hyperuricemia and gout <sup>11 12</sup>.

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

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3 92 dietary sources as a risk factor for incident hyperuricemia and ultimately gout, therefore, remains  
4  
5 93 unclear. Furthermore, there is a notable lack of meta-analyses of prospective studies assessing  
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8 94 the role of dietary fructose in the development of disorders of purine metabolism. The objective  
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10 95 of this study was to conduct a systematic review and meta-analysis of prospective cohort studies  
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12 96 investigating total fructose consumption and its association with incident hyperuricemia and  
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15 97 gout.  
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## 19 20 99 **METHODS**

21  
22 100 This meta-analysis was conducted in accordance with the Cochrane Handbook for  
23  
24 101 Systematic Reviews of Interventions<sup>20</sup> and reported following the Meta-analysis of  
25  
26 102 Observational Studies in Epidemiology guidelines (MOOSE)<sup>21</sup>. The study protocol was  
27  
28  
29 103 registered at ClinicalTrials.gov (NCT01608620).  
30

### 31 32 104 **Study Selection**

33  
34 105 We performed a comprehensive search of MEDLINE, EMBASE and the Cochrane  
35  
36 106 Library databases from conception through 22 September 2015. The following search terms were  
37  
38 107 used: “fructose”, “sucrose”, “sugar”, “honey”, “HFCS”, “gout”, “hyperuricemia”, and “uric acid”.  
39  
40 108 No language restrictions were imposed on the search. The complete search strategy is reported in  
41  
42  
43 109 **S1 Table**. The electronic search was supplemented by a manual review of article reference lists.  
44  
45 110 Abstracts were considered, and authors were contacted for missing information. We only  
46  
47 111 included prospective cohort studies which assessed the association between total dietary fructose  
48  
49 112 intake and incident hyperuricemia or gout. Studies were considered eligible if cases of gout were  
50  
51 113 ascertained using self-report of a physician diagnosis, while the assessment of hyperuricemia  
52  
53 114 required serum uric acid measurements above study-specific predefined thresholds.  
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## 115 **Data Extraction**

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

## 124 **Study Quality**

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

## 130 **Grading of Recommendations Assessment, Development and Evaluation**

131 The grading of recommendations assessment, development and evaluation (GRADE)  
132 approach was used to assess the overall quality and strength of evidence<sup>23-35</sup>. By this approach,  
133 the quality of the totality of evidence can be graded as 'very low', 'low', 'moderate' or 'high'.  
134 Evidence derived from observational studies receive an initial grade of 'low', while evidence  
135 derived from randomized trials receive an initial grade of 'high'<sup>25</sup>. Scores can be either upgraded  
136 or downgraded depending on a number of factors. Scores for observational analyses can be  
137 upgraded for a large magnitude of effect (RR >2 or RR <0.5 in the absence of plausible

1  
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3 138 confounders), dose-response gradient, or reasonable evidence of attenuation of the pooled effect  
4  
5 139 estimate by confounders<sup>31</sup>. Conversely, scores can be downgraded for risk of bias (weight of  
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7  
8 140 studies show risk of bias as assessed by low NOS <6)<sup>26</sup>, inconsistency (substantial unexplained  
9  
10 141 inter-study heterogeneity),  $I^2 > 50\%$ <sup>29</sup>, indirectness (presence of factors that limit the  
11  
12 142 generalizability of the results)<sup>30</sup>, imprecision in the pooled risk estimate (the 95% CI for risk  
13  
14 143 estimates are wide or cross a minimally important difference of 10% for benefit or harm [RR 0.9  
15  
16 144 to 1.1])<sup>28</sup>, and publication bias (evidence of small-study effects)<sup>27</sup>.

## 145 **Statistical Analysis**

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

## 159 **RESULTS**

### 160 **Search Results**

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3 161 Results of the systematic search and article selection process are shown in **Figure 1**. Of  
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5 162 the 2,195 studies initially identified in the literature search, 2,171 were excluded on the basis of  
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8 163 title and abstract review. The remaining 24 articles were reviewed in full, and 22 were  
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10 164 subsequently excluded. A total of 2 prospective cohort studies were included in this analysis<sup>38 39</sup>.  
11  
12 165 Both of these studies pertained to fructose intake and incident gout. We did not identify any  
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14 166 prospective studies that assessed total fructose intake and its association with incident  
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16  
17 167 hyperuricemia.

### 168 **Study Characteristics**

169 The characteristics of the two prospective cohort studies included in this analysis are  
170 presented in **Table 1**. Both studies investigated cohorts based in the United States and comprised  
171 of older, predominantly white (91% and 95%), health professionals. Choi et al. 2008<sup>38</sup> consisted  
172 of 46,393 male dentists, optometrists, osteopaths, pharmacists, and veterinarians; aged 40-75,  
173 from the Health Professionals Follow-up Study. Choi et al. 2010<sup>39</sup> investigated a cohort of  
174 78,906 female nurses aged 30-55, from the Nurses' Health Study. The follow-up rate for both  
175 cohorts exceeded 90%. The women's cohort had a follow-up duration of 22 years<sup>39</sup>, while the  
176 male cohort was followed for 12 years<sup>38</sup>. Both studies received 6 points on the Newcastle-  
177 Ottawa Scale, indicating that they were of high quality. All 125,299 participants across both  
178 studies were free of gout at baseline, and a total of 1,533 confirmed cases of incident gout (755  
179 male, 778 female) were identified.

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



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3 184 fructose plus half the intake of sucrose, was assessed in both studies. Median fructose intake was  
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5 185 ~7.2% of total energy in the lowest quantiles of intake and ~ 11.9% of total energy in the highest  
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8 186 quantiles of intake<sup>38 39</sup>. In the prospective study of the Health Professionals Follow-up Study, the  
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10  
11 187 main dietary sources of total monosaccharide fructose were orange juice (15.9%), SSBs (15.5%),  
12  
13 188 apples (14.5%), raisins (5.2%), and oranges (3.2%)<sup>38</sup>.

14  
15 189 Information regarding weight, medications, and medical conditions (including gout) was  
16  
17 190 collected at baseline and every two years following for the duration of both studies. Participants  
18  
19 191 that reported physician-diagnosed incident gout were sent a supplementary questionnaire based  
20  
21 192 on the American College of Rheumatology gout survey criteria<sup>40</sup>. To meet the endpoint of the  
22  
23 193 study, participants needed  $\geq 6$  symptoms out of a possible 11. The response rate of the  
24  
25 194 supplementary survey was approximately 80% for both cohorts. Both studies adjusted for the  
26  
27 195 critical confounders of age, BMI, total energy intake and alcohol consumption (each study was  
28  
29 196 conducted in a single sex, so adjustment for sex was not necessary). Additional adjustments were  
30  
31 197 made for diuretic use, history of hypertension, history of renal failure, menopause status, use of  
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33 198 hormone therapy; caffeine intake and total vitamin C; as well as the percentage of energy from  
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35 199 total carbohydrates<sup>38 39</sup>.

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41 200 Funding sources were assessed for all of the included prospective cohort studies. All  
42  
43 201 reported funding from agency alone<sup>38 39</sup>.

#### 44 45 46 202 **Total Fructose Intake on Incident Gout**

47  
48 203 **Figure 2** depicts the relationship between total fructose intake and incident gout. We  
49  
50 204 identified a significant overall association between fructose intake and increased the risk of  
51  
52 205 incident gout with a pooled risk ratio of 1.62 (95% CI 1.28 to 2.03) with no evidence of  
53  
54 206 significant inter-study heterogeneity ( $I^2=0\%$ ,  $p=0.33$ ). The pooled risk estimates came from the  
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3 207 most adjusted models including the adjustment for energy from total carbohydrate intake<sup>38 39</sup>.  
4  
5 208 This model allows for the effects of fructose compared with isocaloric exchange for other  
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7  
8 209 carbohydrates to be estimated. Both studies included in our analysis also presented results  
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10 210 adjusted for energy from non-fructose carbohydrate and total protein to facilitate the comparison  
11  
12 211 of isocaloric substitution of fructose for fat. This model resulted in more modest effect estimates  
13  
14 212 (RR 1.34, 95% CI 1.05 to 1.72) (see **S1 Figure**). Pooled analysis of the least-adjusted models  
15  
16 213 (adjusted for age, total energy intake, BMI and alcohol consumption in both studies) did not  
17  
18 214 result in a significant association between fructose intake and gout (RR 1.10, 95% CI 0.88 to  
19  
20 215 1.39) (see **S2 Figure**).

### 216 **Total Fructose intake on Incident Hyperuricemia**

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

### 220 **Study Quality**

221 **S2 Table** shows the NOS for assessing the quality of cohort studies. All studies were  
222 considered to be high quality (NOS $\geq$ 6).

### 223 **GRADE assessment**

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

228

### 229 **DISCUSSION**

## 230 **Statement of Principle Findings**

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

## 240 **Strengths and Weaknesses of the Study**

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

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3 253 meant that we were unable to assess publication bias or perform sensitivity, *a priori* subgroup,  
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5 254 and dose-response analyses using the pooled data. Furthermore, although the number of subjects  
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8 255 included in both studies were relatively large, both cohorts were recruited in the United States,  
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10 256 meaning that our analysis has low generalizability to other populations. Indeed, various genetic  
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12 257 risk factors for gout have been identified<sup>41</sup> with some ethnic groups particularly susceptible to  
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14 258 gout<sup>6</sup>, therefore, the results might not apply to other populations. Finally, although both studies  
15  
16 259 included in this analysis adjusted for a number of potentially important confounders, the  
17  
18 260 observational design of these studies precludes the inference of causation due to the possibility of  
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20 261 residual confounders that remain unaccounted.

### 24 262 **Findings in Relation to Other Studies**

26 263 The results of our meta-analysis support the notion that elevated fructose intake is a risk  
27  
28 264 factor for the development of gout. A recent cross-sectional analysis identified a link between  
29  
30 265 intake of SSBs and prevalent gout<sup>42</sup>, and a systematic review<sup>43</sup> of risk factors associated with  
31  
32 266 gout identified fructose intake among other established dietary risk factors including alcohol,  
33  
34 267 meat and seafood consumption. Dietary factors associated with a lower risk of gout include  
35  
36 268 dairy, folate and coffee intake<sup>43</sup>. Both studies included in our meta-analysis identified a  
37  
38 269 significant association between SSB consumption and increased risk of gout, while similar  
39  
40 270 associations not observed for diet soft drink consumption<sup>38 39</sup>.

41 271 The prevalence of gout has been found to be significantly higher in males than females in  
42  
43 272 many diverse populations<sup>44-46</sup>. Of the two studies included in our analysis of fructose and gout,  
44  
45 273 one was conducted in males from the Health Professionals Follow-up Study<sup>38</sup>, and the other was  
46  
47 274 carried out in females from the Nurses' Health Study<sup>39</sup>. In agreement with worldwide  
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49 275 prevalence estimates, males in the Health Professionals Follow-up Study developed gout at a  
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3 276 higher rate than females from the Nurses' Health Study. This potentially contributed to the lower  
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5 277 effect size observed in the analysis of the Nurses' Health Study despite a larger sample size and  
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8 278 similar levels of fructose intake compared to the Health Professional Follow-up Study analysis.  
9  
10  
11 279 Although the exact mechanisms that result in differences in the rates of developing gout between  
12  
13 280 the sexes have not yet been fully elucidated, the protective and uricosuric effects of female sex  
14  
15 281 hormones are thought to play a role<sup>47 48</sup>.

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17  
18 282 Hyperuricemia is a major risk factor for gout and is understood to be instrumental in its  
19  
20 283 development<sup>1</sup>. Emerging evidence has also implicated hyperuricemia in the development of the  
21  
22 284 metabolic syndrome, hypertension and CVD<sup>3</sup>, although these associations have not been  
23  
24 285 consistently reported in studies that include only hyperuricemic individuals without gout<sup>49 50</sup>.  
25  
26  
27 286 We found no prospective studies investigating fructose intake and incident hyperuricemia to  
28  
29 287 support the observed association between fructose and gout. Some cross-sectional analyses and  
30  
31 288 clinical trials that have supported the association between HFCS-sweetened beverage intake and  
32  
33 289 increased levels of circulating uric acid<sup>51-54</sup>; however, analysis of NHANES data did not support  
34  
35 290 the link between fructose intake and increased risk of hyperuricemia<sup>55</sup>. Furthermore, prospective  
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38 291 evidence has shown that intake of SSBs, which is known to be a large contributor to total  
39  
40 292 fructose intake in western populations<sup>56</sup>, is not associated with an increased risk of incident  
41  
42 293 hyperuricemia<sup>52</sup>. These inconsistent findings highlight the need for more long-term prospective  
43  
44  
45 294 studies investigating fructose intake from all sources in order to gain a better understanding of  
46  
47  
48 295 the effects of fructose intake on risk of hyperuricemia.

#### 296 **Meaning of study: possible explanations and implications for clinicians and policymakers**

297 Mechanistically, the phosphorylation of fructose is thought to lead to ATP depletion and  
298 the subsequent accumulation of AMP<sup>57</sup>. The lack of free phosphate results in the conversion of

1  
2  
3 299 AMP to IMP, a uric acid precursor, by AMP deaminase<sup>39</sup>. High fructose levels and this  
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5  
6 300 associated decrease in ATP has been shown to lead to a compensatory effect of increasing purine  
7  
8 301 nucleotide synthesis<sup>15</sup>, which can subsequently lead to the further overproduction of uric acid in  
9  
10 302 the presence of additional fructose. Additionally, fructose-induced hyperinsulinemia and insulin  
11  
12 303 resistance<sup>39 58</sup> may lead to higher levels of circulating uric acid through the reduction of uric acid  
13  
14 304 excretion<sup>59</sup>. Results of our pooled analysis suggest that fructose may indeed act as a risk factor  
15  
16 305 for the development of gout; however, the lack of prospective studies assessing hyperuricemia as  
17  
18 306 an outcome limits our ability to attribute this association with gout to the mechanism proposed  
19  
20 307 above. It remains possible that fructose intake increases the risk of developing gout through  
21  
22 308 undetermined mechanisms independent of any effects on serum urate levels, although this is  
23  
24 309 unlikely given both the link between fructose and uric acid production<sup>57</sup>, and the established role  
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26 310 of elevated serum urate in the development of gout<sup>2</sup>.

27  
28  
29 311 Current dietary guidelines recommend a reduction in added or free sugars that include  
30  
31 312 fructose intake (especially from SSBs) while also not discouraging the consumption of sugars  
32  
33 313 from whole fruits and vegetables<sup>60</sup>. While SSBs represent the largest contributor to total fructose  
34  
35 314 intake in the United States, fruits and fruit products are also a significant contributor<sup>56</sup>.  
36  
37 315 Furthermore, the 2012 American College of Rheumatology Guidelines for Management of Gout  
38  
39 316 recommends limited consumption of HFCS-sweetened soft drinks and energy drinks, but does  
40  
41 317 not mention whether fructose from other sources should be limited<sup>61</sup>. It is clear that more  
42  
43 318 prospective research investigating the effects of fructose intake and important food sources of  
44  
45 319 fructose (SSBs, fruits and fruit products, grain-based products, dairy products, etc.) on both  
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47 320 incident gout and hyperuricemia are necessary to better inform policymakers as they develop  
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321 improved dietary guidelines for both the management and prevention of these chronic  
322 conditions.

### 323 **Conclusions**

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

338

### 339 **Acknowledgements**

340 We wish to thank Teruko Kishibe for her help in the development of search terms used.

341

### 342 **Ethical Approval**

343 Not required.

## 344 **Contributions**

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

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356 Statistical expertise: R.J. de Souza

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

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

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

360 Guarantor: J.L. Sievenpiper

361

## 362 **Competing Interests**

363 **RJdS** has received research support from the CIHR, the Calorie Control Council, the

364 Canadian Foundation for Dietetic Research and the Coca-Cola Company (investigator initiated,  
365 unrestricted grant). He has served as an external resource person to WHO's Nutrition Guidelines

366 Advisory Group and received travel support from WHO to attend group meetings. He is the lead

367 author of 2 systematic reviews and meta-analyses commissioned by WHO of the relation of



1  
2  
3 368 saturated fatty acids and trans fatty acids with health outcomes. **TMSW** is a part owner and the  
4  
5 369 President of Glycemic Index Laboratories, Toronto, Canada and has authored several popular  
6  
7  
8 370 diet books on the glycemic index for which he has received royalties from Phillipa Sandall  
9  
10 371 Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel  
11  
12 372 funding, or research support from or served on the scientific advisory board for CIHR, CDA  
13  
14 373 Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal  
15  
16 374 Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University,  
17  
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21  
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27  
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29  
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37  
38 385 Laboratories, the Almond Board of California, the American Peanut Council, the American  
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42 387 Danone, General Mills, the International Tree Nut Council Nutrition Research and Education  
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44 388 Foundation, Kellogg, Loblaw Companies Ltd., the Nutrition Foundation of Italy, Oldways  
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46 389 Preservation Trust, Orafiti, Paramount Farms, the Peanut Institute, PepsiCo, Pulse Canada, Sabra  
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49 390 Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate and Lyle, and Unilever. He is  
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3 391 on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the European  
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5 392 Association for the Study of Diabetes (EASD) and has served on the scientific advisory board for  
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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 <sup>1</sup>	Adjustments
Choi <i>et al</i> , 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 <i>et al</i> , 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

<sup>1</sup>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.

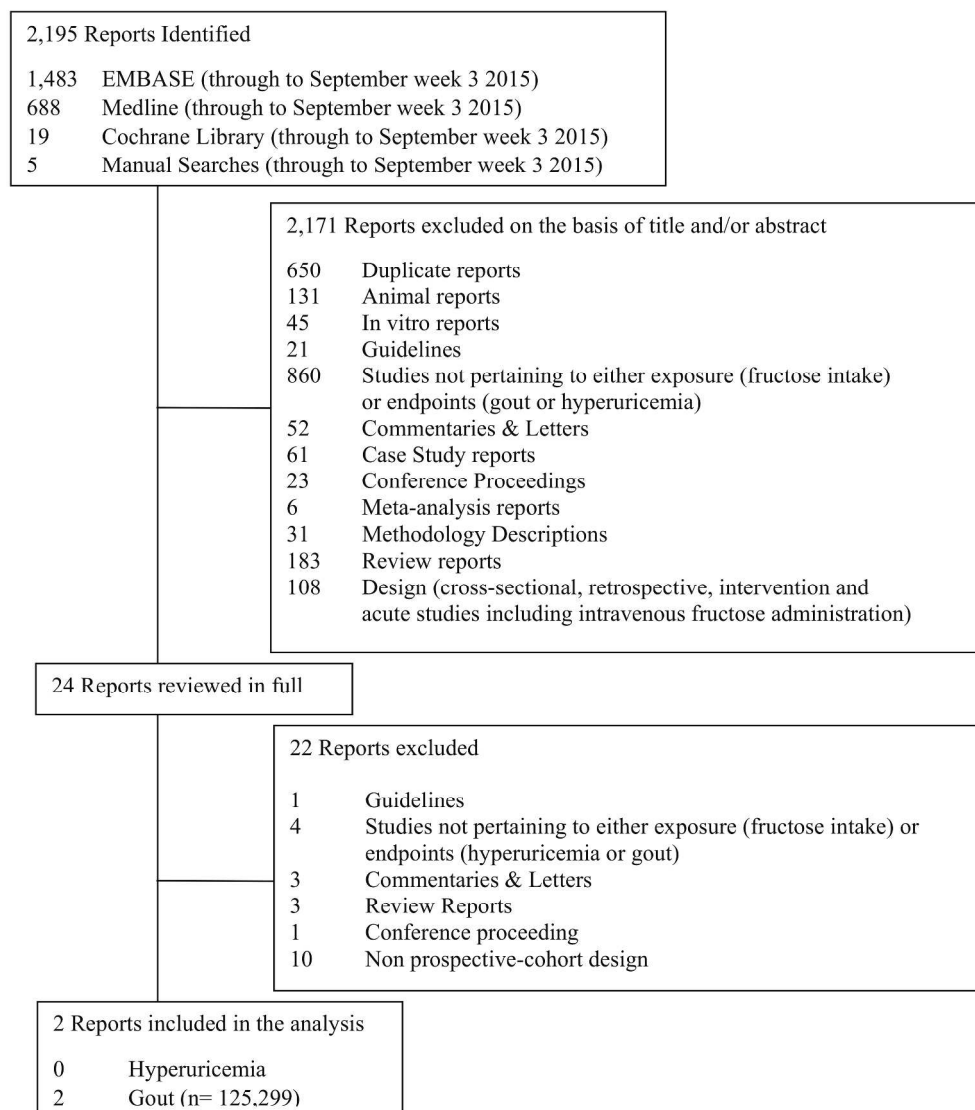
**Figure 1.** Summary of Evidence Search and Selection.

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.

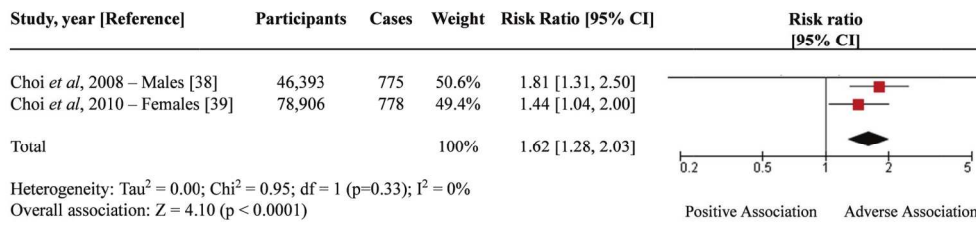


Figure 2. Fructose Intake and the Relative Risk of Gout  
 Figure 2  
 326x98mm (300 x 300 DPI)

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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 5<sup>th</sup>, 2012; updated search was performed on: September 22nd, 2015.

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

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

<sup>1</sup>Maximum 4 stars awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment, and demonstration outcome not present at baseline

<sup>2</sup>Maximum 3 stars awarded for follow-up length, adequacy of follow-up, and outcome assessment

<sup>3</sup>Maximum 2 stars awarded for controlling for main confounders

<sup>4</sup>Studies receiving  $\geq 6$  points were considered high quality; a maximum of 9 points could be awarded

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**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 ⊕⊕⊕⊕)
<b>Total fructose intake on incident gout (follow-up median 17 years)</b>							
125,299 (2 studies) 17 years	No serious risk of bias <sup>1</sup>	No serious inconsistency <sup>2</sup>	Serious <sup>3</sup>	No serious imprecision	Undetected <sup>5</sup>	Dose response gradient <sup>6</sup>	⊕⊕ <b>LOW</b> <sup>1,2,3,4,5</sup> due to indirectness, dose-response gradient

<sup>1</sup> No serious risk of bias as both studies included had NOS=6.

<sup>2</sup> No evidence of significant inter-study heterogeneity ( $I^2=0\%$ ,  $p=0.33$ ).

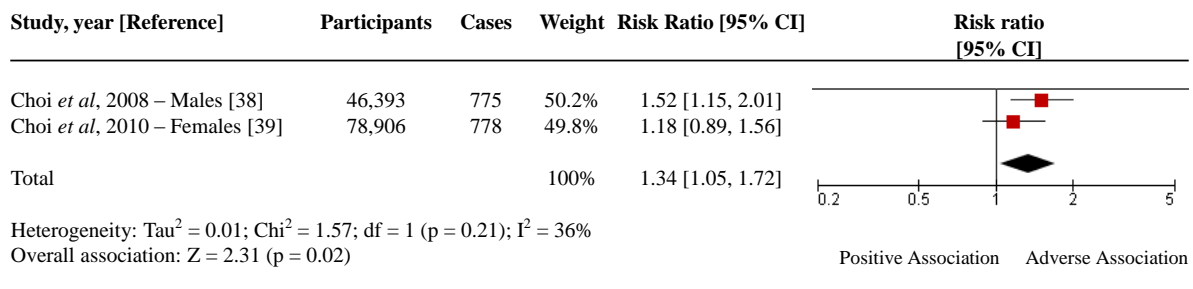
<sup>3</sup> Serious indirectness as evidence is based on only 2 cohorts in predominantly white health professionals and may not be representative of different populations.

<sup>4</sup> Publication bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 studies).

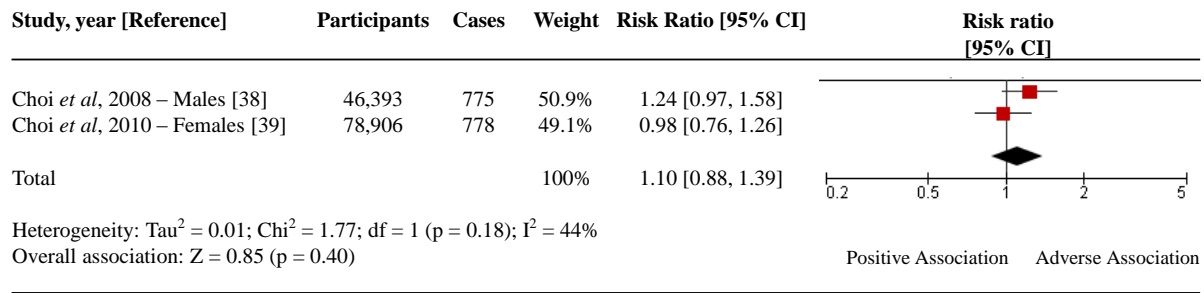
<sup>5</sup> An approximate dose-response gradient was observed in both studies where most increasing quintiles of fructose consumption corresponded with an increased risk of gout.



**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.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United States. August 2012.



# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
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
<b>INTRODUCTION</b>			
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
<b>METHODS</b>			
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

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# PRISMA 2009 Checklist

Page 1 of 2

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
<b>RESULTS</b>			
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
<b>DISCUSSION</b>			
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
<b>FUNDING</b>			
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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