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

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2 1 **Important food sources of fructose-containing sugars and incident gout:**
3 2 **A systematic review and meta-analysis of prospective cohort studies**
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56 35 systematic review and meta-analysis
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1
2 36 **ABSTRACT**

3
4 37 **Objective:** Sugar-sweetened beverages (SSBs) are associated with hyperuricemia and gout. Whether
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6
7 38 other important food sources of sugars share this association is unclear.

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9 39 **Design:** To assess the relation of important food-sources of fructose-containing sugars with incident
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12 40 gout and hyperuricemia, we conducted a systematic review and meta-analysis of prospective cohort
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14 41 studies.

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16 42 **Methods:** We searched MEDLINE, EMBASE and the Cochrane Library (through September 13, 2017).
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19 43 We included prospective cohort studies that investigated the relationship between food sources of
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22 44 sugar and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and
23
24 45 assessed risk of bias. We pooled natural-log transformed risk ratios (RRs) using the generic inverse
25
26 46 variance method with random effects model and expressed as RR with 95% confidence intervals (CIs).
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29 47 The overall certainty of the evidence was assessed using the Grading of Recommendations
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31 48 Assessment, Development and Evaluation (GRADE) system.

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33
34 49 **Results:** We identified three studies (154,289 participants, 1,761 cases of gout), comparing the
35
36 50 highest with the lowest level of exposure for SSBs, fruit juice and fruits. No reports were found
37
38
39 51 reporting incident hyperuricemia. Fruit juice and SSB intake showed an adverse association (fruit
40
41 52 juice, RR = 1.76, 95% CI 1.19 to 2.60; SSB, RR = 2.07, 95% CI 1.40 to 3.06), when comparing the highest
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43
44 53 to lowest intake of the most adjusted models. There was no significant association between fruit
45
46 54 intake and gout (RR 0.82, 95% CI 0.61 to 1.11). Strongest evidence was for the adverse association in
47
48 55 SSB (moderate quality), and the weakest evidence was for the adverse association in fruit juice (very
49
50
51 56 low quality) and the no effect in fruit intake (very low quality).

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53 57 **Conclusion:** The adverse association of SSB is also seen for fruit juice consumption but does not
54
55
56 58 extend to fruit intake. Further research is likely to improve our estimates.

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2 59 **Protocol registration:** ClinicalTrials.gov identifier: NCT02702375
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7 61 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 9 62 - This systematic review and meta-analysis assessed the certainty of the evidence using the
10
11 Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
12 63
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14 64 - Large prospective cohort studies that were of high quality and had a long duration of follow-up
15
16 were included.
17 65
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19 66 - Most of the pooled results showed good consistency (low between study heterogeneity) and
20
21 sugar sweetened beverages showed evidence of a dose-response gradient.
22 67
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24 68 - Only three prospective cohort studies with low external generalizability were available for
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26 inclusion.
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29 70 - The observational design of the prospective cohort studies did not allow for causal inferences
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31 to be drawn.
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1 2 82 **INTRODUCTION**

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4 83 Gout and associated hyperuricemia were both associated with the development of hypertension,
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7 84 insulin resistance syndrome [1], and cardiovascular disease (CVD) [2]. Different diets have been
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9 85 shown to be associated with the development and severity of gout [3]. Foods that increase net ATP
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12 86 degradation including alcohol and high purine meats are risk factors for gout [1]. Ingestion of large
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14 87 amounts of the monosaccharide fructose can increase uric acid production during its metabolism in
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17 88 the liver through unregulated phosphorylation of ATP into AMP [1] as demonstrated in randomized
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19 89 controlled trials [4, 5]. Similarly, in cohort studies, high intake of fructose-containing sugars in the
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22 90 form of sugar-sweetened beverages (SSBs) is associated with incident gout [6]. It is unclear whether
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24 91 the association seen for SSBs holds for other important food-sources of fructose-containing sugars,
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26
27 92 such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based
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29 93 products and sweets and desserts. As dietary guidelines and public health policy move from nutrient-
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31 94 based recommendations toward food and dietary-based recommendations [3, 4, 7], it is important to
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34 95 understand the contribution of these different food sources of fructose-containing sugars to the
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36 96 association of incident gout. To address this gap, we conducted a systematic review and meta-analysis
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39 97 of prospective cohort studies of the relation of important food sources of fructose-containing sugars
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41 98 with incident gout and hyperuricemia.

43 99 44 45 46 100 **METHOD**

47 48 101 **Design**

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51 102 We followed the Cochrane Handbook for Systematic Reviews of Interventions [8] for the conduct of
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53 103 our systematic review and meta-analysis and reported our results according to the Meta-analysis of
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56 104 Observational Studies in Epidemiology (MOOSE) guidelines [9] and preferred Reporting Items for
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2 105 Systematic Reviews and Meta-Analysis (PRISMA) [10] guidelines. The study protocol was registered at
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4 106 ClinicalTrials.gov (identifier, NCT02702375).
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7 107 8 9 108 **Search strategy**

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12 109 We conducted systematic searches in MEDLINE, EMBASE and Cochrane through September 13, 2017
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14 110 with no language restriction (**supplementary table 1**). Targeted manual searches served to
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16 111 supplement the database search; these included finding related papers from references of review
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18 112 papers, included studies, perusing articles with data from major prospective cohorts that usually
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20 113 report dietary data, and speaking to experts in the field.
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24 114 25 26 115 **Study selection**

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29 116 We included prospective cohort studies of ≥ 1 year duration that assessed the association of important
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31 117 food sources of fructose-containing sugars including non-alcoholic beverages (SSBs), cereal grain and
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33 118 grain based products, fruit and fruit-based products, dairy and dairy-based products, and sweets,
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35 119 chocolate and desserts with incident gout or hyperuricemia in participants free from gout or
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37 120 hyperuricemia at the start of the study. One year duration was chosen as it allows for the
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40 121 development of diseases such as hyperuricemia and gout.
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45 46 122 47 48 123 **Data extraction**

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50 124 Two independent reviewers (SAC and QL) extracted relevant data from included studies onto
51
52 125 standardized pro forma. Extracted data included sample size, subject characteristics, sources of
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54 126 fructose-containing sugars, exposure levels, duration of follow-up, number of gout or hyperuricemia
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56 127 cases, model adjustments, and the risk ratio with 95% confidence intervals (95% CI) per quantile of
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1
2 128 intake. The main outcome was incident gout or hyperuricemia expressed as risk ratios (RR) with 95%
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4 129 confidence intervals (95% CI). Discrepancies were resolved by consensus.

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9 131 **Risk of bias**

11
12 132 The same two independent reviewers (SAC and QL) assessed each study for risk of bias. Risk of bias
13
14 133 was assessed using the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Points were
15
16 134 awarded based on cohort selection, comparability of groups and assessment of outcomes, for a
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19 135 maximum total of 9 points [11]. Studies with ≥ 6 points were considered high quality [11]. Difference
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22 136 between reviewers was resolved by consensus.

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26 138 **Statistical analyses**

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29 139 Primary pooled analyses were conducted using Review Manager (RevMan) 5.3 (The Nordic Cochrane
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31 140 Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analysis and the assessments
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33
34 141 of dose response were performed using Stata 14 (StataCorp, College Station, TX, USA). Natural log-
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36 142 transformed RR for incident gout or hyperuricemia, comparing extreme quantiles (the highest
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39 143 exposure versus the lowest exposure or reference group), were pooled separately for each food
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41 144 source of fructose-containing sugars using the generic inverse variance method with DerSimonian and
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44 145 Laird random effects models and expressed as RRs with 95% CI. Inter-study heterogeneity was
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46 146 assessed with the Cochran Q statistic with significance set at $p < 0.10$ and quantified with the I^2
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48 147 statistic, where $I^2 \geq 50\%$ represented evidence of substantial heterogeneity [8]. We explored sources
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51 148 of heterogeneity by sensitivity analyses. Sensitivity analyses, where each study was systematically
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53 149 removed, and effect size was recalculated in the remaining studies, were carried out to explore the
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56 150 impact of individual studies on the pooled risk. As ≥ 10 cohort comparisons were not available, *a priori*

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2 151 subgroup analyses were not performed. Linear and non-linear dose-response analyses were assessed
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4 152 by using generalized least squares trend estimation models (GLST) and spline curve modeling
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7 153 (MKSPLINE procedure), respectively [12]. Publication bias was not assessed as the number of cohort
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9 154 comparisons was less than 10.
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14 156 **Grading of the evidence**

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17 157 The overall quality and the strength of the evidence was assessed using the Grading of
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19 158 Recommendations Assessment, Development and Evaluation (GRADE) system [13-25]. The evidence
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21 159 was graded as high, moderate, low, or very low quality, with observational studies starting with an
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24 160 initial grade of 'low'. This then can be downgraded based on 5 pre-specified criteria or upgraded
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26 161 based on 3 pre-specified criteria. Criteria to downgrade included risk of bias (weight of studies
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29 162 showed risk of bias as assessed by low NOS <6), inconsistency (substantial unexplained inter-study
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31 163 heterogeneity i.e. $I^2 > 50\%$), indirectness (presence of factors that limit the generalizability of the
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34 164 results), imprecision in the pooled risk estimate (the 95% CI for risk estimates are wide or cross a
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36 165 minimally important difference of 10% for benefit or harm (RR 0.9–1.1)), and publication bias
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39 166 (evidence of small-study effects). Conversely, criteria to upgrade included a large magnitude of effect
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41 167 (RR > 2 or RR < 0.5 in the absence of plausible confounders), dose–response gradient or reasonable
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44 168 evidence of attenuation of the pooled effect estimate by confounders.
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48 170 **RESULTS**

51 171 **Search results**

53 172 **Figure 1** shows the flow of the systematic search and study selection. Of the 309 reports identified by
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56 173 the literature search, three reports with data from three prospective cohort studies met our inclusion
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2 174 criteria [26-28]: Nurses' Health Study (NHS) [27], Health Professionals Follow-up Study (HPFS) [26] and
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4 175 the National Runner's Health Study [28]. All three reports reported the association of food sources of
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7 176 fructose-containing sugars on incident gout, but none on incident hyperuricemia. These reports
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9 177 involved a total of 154,289 participants with 1,761 incident cases of gout. Two reports each reported
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12 178 data on fruit intake [n= 75,383; 983 cases] [26, 28], fruit juice [n= 125,299; 1,533 cases] [26, 27] and
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14 179 SSBs [n=125,299; 1,533 cases] [26, 27]. We did not identify prospective cohort studies reporting the
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17 180 association of other food sources of fructose-containing sugars (e.g. cereal grain and grain-based
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19 181 products, sweets and desserts, dairy and dairy based products and chocolate) with incident gout.
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24 183 **Study characteristics**

26 184 **Table 1** lists the characteristics of the included prospective cohort studies. All studies were performed
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28
29 185 in the USA. The median age of the included participants ranged from 30 to 75. The median follow-up
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31 186 periods was 17 years (range, 12 to 22 years) for SSB, 18.7 years (12 to 22 years) for fruit juice and 9.9
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34 187 years (7.74 to 12 years) for fruit. Dietary intake assessments were done with self-reported, validated
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36 188 food frequency questionnaires (FFQs) in all studies. Quantiles of exposure depended on the food
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39 189 source. Lowest and highest median quantiles of exposure were <1 servings/month and ≥14
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41 190 servings/week respectively for SSB; ≤1 servings/month and ≥14 servings/week respectively for fruit
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44 191 juice; and ≤0.4 servings/week (range, <0-0.5 servings/week) and ≥8 servings/day (range, ≥2-14
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46 192 servings/day), respectively for fruit. The ascertainment of incident gout in both HPFS and NHS cohorts
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48 193 [26, 27] was through self-report, followed by supplementary surveys of the subjects based on the
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51 194 American College of Rheumatology gout survey criteria [29] to confirm that the diagnosis. The authors
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53 195 defined individuals with gout that met ≥6 of the 11 criteria for gout. In addition, in a sub-sample the
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2 196 self-reported diagnoses were validated with medical records. As for the NRHS cohort [28], incident
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4 197 gout was self-reported based upon physician diagnosis.
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9 199 **Supplementary table 2** shows the complete list of adjusted confounding variables for the most
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11 200 adjusted models for each of the included prospective cohorts. The median number of variables in the
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14 201 most adjusted models was 14 (range, 6 to 14). All studies adjusted for primary and secondary
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16 202 confounders such as age, body mass index (BMI) and history of hypertension. Each of the three
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19 203 cohorts were single-sex studies, so adjustment for sex was not necessary. The NHS cohort study
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21 204 authored by Choi *et al.* 2010 [27] and NRHS study by Williams *et al.* [28] were agency funded, while
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23
24 205 the HPFS paper authored by Choi *et al.* 2008 [26] was funded by both agency and industry.
25

26 206 27 28 29 207 **Study Quality**

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31 208 **Supplementary table 3** shows the study quality assessments by the NOS scale. There was no evidence
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34 209 of serious risk of bias. Only NRHS cohort scored <6 on the NOS scale, which denotes lower quality
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36 210 [28].
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38 211 39 40 41 212 **Fruit intake on incident gout**

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43 213 **Figure 2** shows the relationship between fruit intake and incident gout. When comparing the highest
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46 214 to the lowest intake, no association was shown for fruit intake on incident gout (RR = 0.82, 95% CI
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48 215 0.61 to 1.11). There was evidence of significant interstudy heterogeneity ($I^2 = 94%$, $p < 0.001$).
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50 51 216 52 53 217 **Fruit juice intake on incident gout**

1
2 218 **Figure 2** shows the relationship between fruit juice intake and incident gout. When comparing the
3
4 219 highest to lowest intake, a protective association was shown for fruit juice intake on incident gout (RR
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6 220 1.76, 95% CI 1.19 to 2.60]). There was no evidence of significant interstudy heterogeneity ($I^2 = 0\%$, $p =$
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SSB intake on incident gout

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

Additional analysis

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

Dose-response analysis

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

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2 240 (supplementary figure 1) indicated a plateau for risk increase after ≥ 5 servings per day. Dose-
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4 241 response modeling was not possible for fruit intake due to lack of data.
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7 242 8 9 243 **GRADE assessment**

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12 244 **Table 2** shows the GRADE assessment of individual food sources of fructose-containing sugars. The
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14 245 certainty of evidence of an adverse association from both fruit and fruit juice was rated as very low,
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16 246 with downgrades to the lowest level for indirectness for fruit intake, and for inconsistency,
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18
19 247 indirectness and imprecision for fruit juice intake. The quality of evidence of an adverse association
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21 248 of SSB intake with incident gout was rated as moderate, with a downgrade of one level for
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24 249 indirectness but upgrade of two levels for a large magnitude effect and significant dose-response.
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26 250 27 28 29 251 **DISCUSSION**

30
31 252 We conducted a systematic review and meta-analysis of studies investigating the relation of
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34 253 important food sources of fructose-containing sugars with incident gout. We identified three
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36 254 prospective cohort studies [26-28] comprising of 154,289 participants and 1,761 cases of incident
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39 255 gout. The pooled analyses revealed that there was moderate quality evidence that SSB intake was
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41 256 associated with 207% increase in risk of incident gout when comparing the highest with the lowest
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44 257 intake. Similarly, there was low quality evidence that fruit juice intake was associated with a 14%
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46 258 increase in risk of incident gout, but fruit intake did not show any significant association with incident
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48 259 gout (low quality evidence). There was no data available of other important food sources of fructose-
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51 260 containing sugars.
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53 261 54 55 56 262 **Findings in the context of the literature**

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2 263 Our results are consistent with previous research that indicate that intake of certain food sources of
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4 264 fructose-containing sugars are associated with the risk of gout. Our previous systematic review and
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6
7 265 meta-analysis of prospective cohort studies that assessed fructose intake, found a harmful
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9 266 relationship between fructose consumption and gout [6]. While that study indicated that fructose
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11
12 267 moiety might possibly drive the association with gout, all the fructose data was derived from SSB
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14 268 intake. Another systematic review of the literature identified numerous dietary factors associated
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16
17 269 with the risk of gout including meat, alcohol, seafood and SSBs, but also that lower risk was associated
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19 270 with the intake of dairy, folate and coffee [3].
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24 272 SSBs are one of the main source of fructose-containing added sugars in the western diet comprising
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27 273 around 30% of intake of added sugars in the USA [30] and around 24% in Canada [31]. Excess intake of
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29 274 fructose can increase uric acid through an unregulated phosphofructose kinase pathway that uses
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31 275 substantial amounts of ATP [32] to convert fructose into fructose-1-phosphate in the liver [33].
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33
34 276 Mechanistically, net ATP degradation leads to accumulation of AMP, which is subsequently degraded
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36 277 to uric acid. Additionally, fructose can increase de novo purine synthesis, which further produces uric
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39 278 acid [1]. This increase in uric acid can lead to gout. Since we were unable to investigate the
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41 279 relationship between food sources of fructose-containing sugars and hyperuricemia, we cannot
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44 280 validate this mechanism. It is possible, that fructose increases the risk of gout independently of serum
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46 281 uric acid levels. However, since the link between fructose and serum uric acid [34-37], and the link
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48
49 282 between serum uric acid and the development of gout have been independently established [1], it is
50
51 283 unlikely that fructose increases the risk of gout without using uric acid as an intermediate.
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53 284

1
2 285 We identified adverse association of fruit juices intake with incident gout. The two studies that
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4 286 contributed to this result [26, 27] were both performed in the Harvard cohorts which do not
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6
7 287 differentiate between fruit drinks and pure fruit juice, the former being largely similar to SSBs i.e.
8
9 288 mainly sugar and water. This is supported by studies investigating pure fruit juice and fruit drinks
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11
12 289 which have shown divergent response for cardiometabolic disease [38, 39].
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15
16 291 We did not see any association between fruit intake and incident gout but the effect estimates in the
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18
19 292 two studies were in opposite direction. The NRHS [28] cohort showed a 51% reduction in risk of gout
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22 293 when with high intake of fruit whereas the HPFS [26] cohort showed a 63% increased risk — both
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24 294 studies were performed in men. These discordant results highlight the differences in the studies.
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26 295 NHPS cohort [26] only measured oranges and apples, fruit high in fructose, while NRHS [28] cohort
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29 296 assessed all fruit and its increasing intake, as the authors admit, might represent a healthier dietary
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31 297 intake. It is possible that higher intake of fruits in NRHS might be associated with high intake of dairy
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34 298 or coffee, which have been associated with lowering the risk of gout [3] and not measured in NRHS.
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36 299 Additionally, the highest fruit intake contained less fructose than the SSB and fruit juice food sources
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39 300 of fructose-containing sugars. Therefore, the exposure may not have been high enough to see
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41 301 consistent affects. Furthermore, case-control and cross-sectional studies have shown a protective
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44 302 effect of fruit intake with gout [40, 41]. The harmful association for oranges, which are rich in vitamin
45
46 303 C, in HPFS [26] cohort is at odds with its own result in another paper, in which the author
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49 304 demonstrated a protective association of vitamin C intake with gout [42]. Fruits are rich in fructose;
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51 305 however, fruit intake has consistently shown a benefit for cardiometabolic risk factors,
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53 306 cardiometabolic diseases and all cause-mortality [43-49] even though the fructose in fruit can
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56 307 increase uric acid levels. More data might clarify this association.
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4 309 We could not find any prospective studies looking at the association of food sources of fructose-
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7 310 containing sugars and hyperuricemia even though hyperuricemia is the most important risk factor for
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9 311 gout [3, 50]. Hyperuricemia is also a risk factor for hypertension [51], metabolic syndrome, diabetes
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12 312 [52], and CVD [53]. Several cross-sectional analyses have investigated the link between SSB
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14 313 consumption and serum uric acid levels, showing a positive relationship [34-37]. In contrast, the
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17 314 analysis of the National Health and Nutrition Examination Survey (NHANES) showed no link between
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19 315 dietary fructose and risk of hyperuricemia [54], indicating that perhaps different food sources of
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22 316 fructose-containing sugars may have different effects on serum uric acid. This point is reinforced by
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24 317 another analysis of NHANES data that showed a relationship of SSB intake with higher serum uric acid
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27 318 concentration, but not with fruit juice [55]. Future studies investigating food sources of sugars and
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29 319 risk of hyperuricemia may help to elucidate some of the above inconsistent findings.
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32 321 **Strengths and limitations**

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36 322 Our analysis has many strengths. First, we employed a comprehensive systematic search across major
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39 323 databases and the quantitative synthesis of results. Second, the studies we included had a substantial
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41 324 number of participants and cases of gout (154,289 participants and 1,761 gout cases) leading to
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44 325 increased precision. Additionally, the median follow-up duration was greater than 10 years, which
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46 326 allowed for enough time from exposure for the development of disease. Another strength is the use
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49 327 of validated measures of intake like food frequency questionnaires. The two Harvard cohorts [26, 27]
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51 328 administered FFQ multiple times, and validated them on a subsample, allowing for more accurate and
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53 329 robust long-term intakes compared to the NRHS [28] cohort, which only measured dietary intakes at
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2 330 baseline. In our analysis, we made use of GRADE to evaluate the quality and strength of our analysis
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4 331 and evaluate our confidence in the estimates.
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9 333 There are some notable limitations to our systematic review and meta-analysis. First, while we
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11 334 included the most adjusted multivariable models for this analysis, there is always potential for
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14 335 unmeasured and residual confounding, since the studies included were observational in nature. This
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16 336 explains why GRADE starts at “low quality” for observational studies. Second, there was evidence of
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19 337 indirectness in some of the relationships. All studies were conducted in the USA, and two of the three
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21 338 studies were in health professionals. The two Harvard [26, 27] cohorts included only middle aged or
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24 339 older people who worked in health care and who were predominately white and the NRHS [28]
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26 340 cohort included only middle to old aged physically active men. Thus, the specific nature of the
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29 341 included studies’ population limits the generalizability of our results to other populations and
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31 342 geographical locations; however, the biological process of diet and gout are still likely to be similar to
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34 343 other populations. While, genome wide association studies have found numerous genes that increase
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36 344 one’s risk for gout [56] and some ethnic groups may be more susceptible than others [1] though it is
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39 345 not known if the association of fructose intake with gout is modified by genes. Third, sources of
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41 346 heterogeneity remained unexplained; with only three studies, we were unable to assess publication
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44 347 bias or perform sensitivity or a priori subgroup analysis. Thus for these reasons, data pertaining to SSB
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46 348 and fruit juice intake and incident gout received a GRADE of moderate and very low, respectively,
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49 349 indicating that further studies in this regard is likely to impact our certainty in the effect estimate and
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51 350 may change the estimate for SSB and that our certainty in the estimate for fruit juice is very
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53 351 uncertain; therefore, caution should be used when interpreting these results. Similarly, for fruit,
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2 352 which received a GRADE of very low, so we are very uncertain in these results and caution should be
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4 353 used in the interpretation of these results.
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9 355 **Implications**

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11 356 Dietary guidelines have shifted their focus from nutrients based recommendations to food and

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14 357 dietary pattern-based recommendations [57], since it has been recognized that one does not eat

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16 358 nutrients in isolation, but as a part of food. Interactions between nutrients in food are complex and

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19 359 important components of disease risk [57]. Our findings support this view in relation to food sources

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21 360 of fructose-containing sugars and their relationship with gout. Our findings also have implications for

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24 361 recommendations for the prevention of gout. Conventional dietary recommendations for gout have

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26 362 focused on restriction of purine intake; however, low-purine diets are often high in carbohydrates,

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29 363 including fructose-rich foods [58]. We have shown an adverse association between fruit juice and

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31 364 SSBs, supporting the recommendations to limit their intakes. Since we did not have data relating to

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34 365 children, hyperuricemia or other food sources of fructose-containing sugars, we cannot extend our

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36 366 conclusion to these groups of individuals or these foods.
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41 368 **Conclusion**

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43 369 Our systematic review and meta-analysis of prospective cohort studies showed an adverse association

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46 370 between SSBs and fruit juice with risk of gout, while there was no association with fruit intake. The

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48 371 strength of the evidence was moderate for SSB intake and very low for fruit juice and fruit intake, as

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51 372 assessed by GRADE. For SSBs, the true association is likely to be close to the estimate, but there is a

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53 373 possibility that it is substantially different. For fruit juice and fruit intake, the true association are likely

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56 374 to be substantially different from the estimate and future research will very likely impact our
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2 375 confidence in the effect estimates and likely to change them [59]. Our results are consistent with the
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4 376 literature that certain food sources of fructose-containing sugars especially SSBs are a risk factor for
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7 377 the development of gout. We were unable to identify studies assessing food sources of fructose-
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9 378 containing sugars and hyperuricemia, indicating a gap in the literature. Given that incident gout is
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11 379 rising [7, 60-65], and that gout and hyperuricemia are both associated with metabolic syndrome,
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14 380 myocardial infarction, diabetes and premature death [1, 2, 66], it is becoming increasingly important
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16 381 to identify and understand risk factors for developing gout. It is imperative for additional prospective
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19 382 studies to assess the intake of various food sources of fructose-containing sugars and their
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21 383 relationship with gout and hyperuricemia in diverse populations. This will help identify to what extent
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24 384 does our foods mediate the risk for hyperuricemia and gout and will further inform health care
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26 385 professionals, policymakers, and aid in the development of improved dietary guidelines for the
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29 386 prevention and management of gout and hyperuricemia.
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3
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7 399

9 400 **Data Sharing**

12 401 There is no additional unpublished data available from the study.

14 402

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1
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4 421 Sun-Maid, The Peanut Institute, General Mills, Oldways Foundation and International Nut and Dried
5
6
7 422 Fruit Council Foundation. He is on the Clinical Practice Guidelines Expert Committee for Nutrition
8
9 423 Therapy of the European Association for the Study of Diabetes (EASD). He is a member of the
10
11
12 424 International Carbohydrate Quality Consortium (ICQC), Secretary of the Diabetes and Nutrition Study
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16
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37
38
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41 436 Canada. He has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and
42
43
44 437 Tate & Lyle. He is a member of the European Fruit Juice Association Scientific Expert Panel. He is on
45
46 438 the Clinical Practice Guidelines Expert Committees of the CDA, European Association for the study of
47
48
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50
51 440 ASN. He serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and
52
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54
55
56 442 America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive
57
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1
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5
6
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8
9 446 **Mejia, LA Leiter**. There are no patents, products in development or marketed products to declare.
10

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12 447

14 448 **Authors' contributions**

15
16 449 All authors had full access to all of the data (including statistical reports and tables) in this study and
17
18 450 take full responsibility for the integrity of the data and the accuracy of the data analysis.

19
20 451 **Conception and design:** J.L. Sievenpiper.

21
22 452 **Analysis and interpretation of the data:** Q. Liu, S. Ayoub-Charette, T.A.Khan, F. Au-Yeung, S. Blanco
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42 463 **Guarantor:** J.L. Sievenpiper
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9 616 [eng.htm](http://www.statcan.gc.ca/pub/82-625-x/2014001/article/11896-eng.htm).
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2 642 **TABLES AND FIGURES**
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5
6 644 **Figure 1** Summary of evidence search and selection. Flow of the literature search for the effect of
7 645 food sources of sugar intake on incident gout and hyperuricemia. Of the 280 studies initially
8 646 identified, 265 were excluded based on title and/or abstract. The remainder were read in full by two
9 647 independent reviewers; after, 12 were further excluded. Included in this analysis were three
10 648 prospective cohort studies.
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14
15 650 **Figure 2** Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-
16 651 adjusted multivariate models accounting for food sources of fructose-containing sugars intake were
17 652 used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using
18 653 the Cochran Q statistic and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant
19 654 heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit
20 655 juices.
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2 674 **Table 1** Characteristics of prospective cohort studies investigating food sources of fructose-containing sugar intake and incident

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4 675 gout.

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

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33 677 Abbreviations: SFFQ = Semi quantitative Food-Frequency Questionnaire; M=males; F=females.

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35 678 *Agency funding is that from government, university or not-for-profit health agency sources.

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

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

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

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2 686 ²No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry
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4 687 and small study effect (<10 cohort included in our meta-analysis).

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6 688 ³Upgrade for a large magnitude of effect (RR>2.0).

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8 689 ⁴Upgrade for a dose response gradient, as the GLST dose-response analysis revealed a significant linear relationship between sugar
9 690 sweetened beverage intake and incident gout (P=0.0001).
10

11 691 ⁵Downgrade for very serious inconsistency, as the two studies included had opposite associations and there was evidence of substantial
12 inter-study heterogeneity ($I^2=94%$, $p<0.0001$). Due to the small number of studies included in the analysis, subgroup analysis was not
13 692 performed.
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17 694 ⁶Downgrade for serious imprecision, as the lower bound of the 95% CI (RR, 0.27) includes clinically important benefit (RR<0.9), while the
18 695 upper bound of the 95% CI (RR, 2.87) crosses the minimally important difference of 10% (RR>1.1).
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Figure 1 Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia.

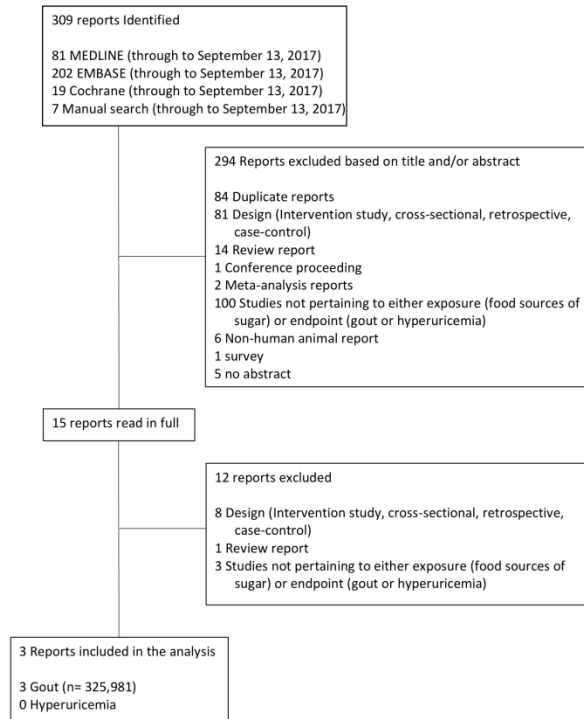


Figure 1. Summary of evidence search and selection. Flow of the literature search for the effect of food sources of sugar intake on incident gout and hyperuricemia. Of the 280 studies initially identified, 265 were excluded based on title and/or abstract. The remainder were read in full by two independent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

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

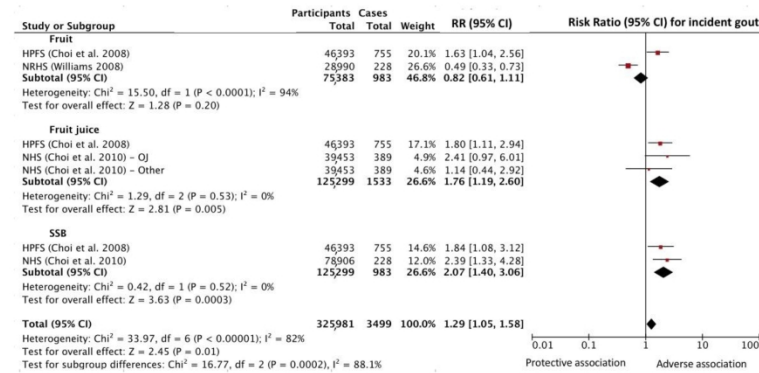


Figure 2. Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-adjusted multivariate models accounting for food sources of fructose-containing sugars intake were used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using the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

279x361mm (300 x 300 DPI)

Supplementary material

SUPPLEMENTARY TABLES

Supplementary table 1 Search terms

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

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

SUPPLEMENTARY FIGURES

Supplementary figure 1 Linear and non-linear dose-response relationship between fruit juice intake and incident gout per serving/week

Supplementary figure 2 Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week

Supplementary table 1. Search terms

Database and search terms

MEDLINE

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

EMBASE

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

Cochrane

1. sugar*.mp.
2. exp fructose/
3. fructose.mp.
4. HFCS.mp.
5. exp Nutritive Sweeteners/
6. sucrose.mp.
7. exp dietary sucrose/
8. sugar sweetened beverage*.mp.
9. ssb.mp.
10. soda.mp.
11. soft drink*.mp.
12. exp carbonated beverages/
13. non alcoholic beverage*.mp.
14. nonalcoholic beverage*.mp.
15. exp energy drinks/
16. energy drink*.mp.
17. smoothie*.mp.
18. ((fruit or vegetable) and juice*).mp.
19. fruit.mp.
20. exp fruit/
21. exp honey/
22. y*g*rt.mp.
23. exp yogurt/
24. ice cream*.mp.
25. icecream*.mp.
26. exp ice cream/
27. cereal*.mp.
28. dessert*.mp.
29. sweets.mp.
30. confection*.mp.
31. pastries.mp.
32. biscuit*.mp.
33. cookie*.mp.
34. cake*.mp.
35. candy.mp.
36. candies.mp.
37. exp candy/
38. (chocolate adj2 milk).mp.
39. cohort.mp.
40. exp Prospective Studies/
41. chocolate.mp
42. cacao.mp
43. exp cacao/
44. (prospective adj2 (cohort or study)).mp.
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46. exp multivariate analysis/
47. exp proportional hazards models/
48. follow up study.mp.
49. (longitudinal adj2 study).mp.
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9 57. hyperuricemia/ 57. hyperuricemia/ 57. or/1-43
10 58. hyperuricaemia*.mp. 58. hyperuricaemia*.mp. 58. or/44-49
11 59. uric.mp. 59. uric.mp. 59. or/50-56
12 60. or/1-44 60. or/1-45 60. and/57-59
13 61. or/45-52 61. or/46-52
14 62. or/53-59 62. or/53-59
15 63. and/60-62 63. and/60-62

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

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

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

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

HPFS=Health Professionals Follow-Up Study, NHS=Nurses Health Study

*Denotes confounders measured only at baseline years.

† Indicates confounders measured every 2 years.

‡ Indicates the study includes only female subjects

§ Indicates the study includes only male subjects

∇ Indicates the confounder was present in some, but not all, models.

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

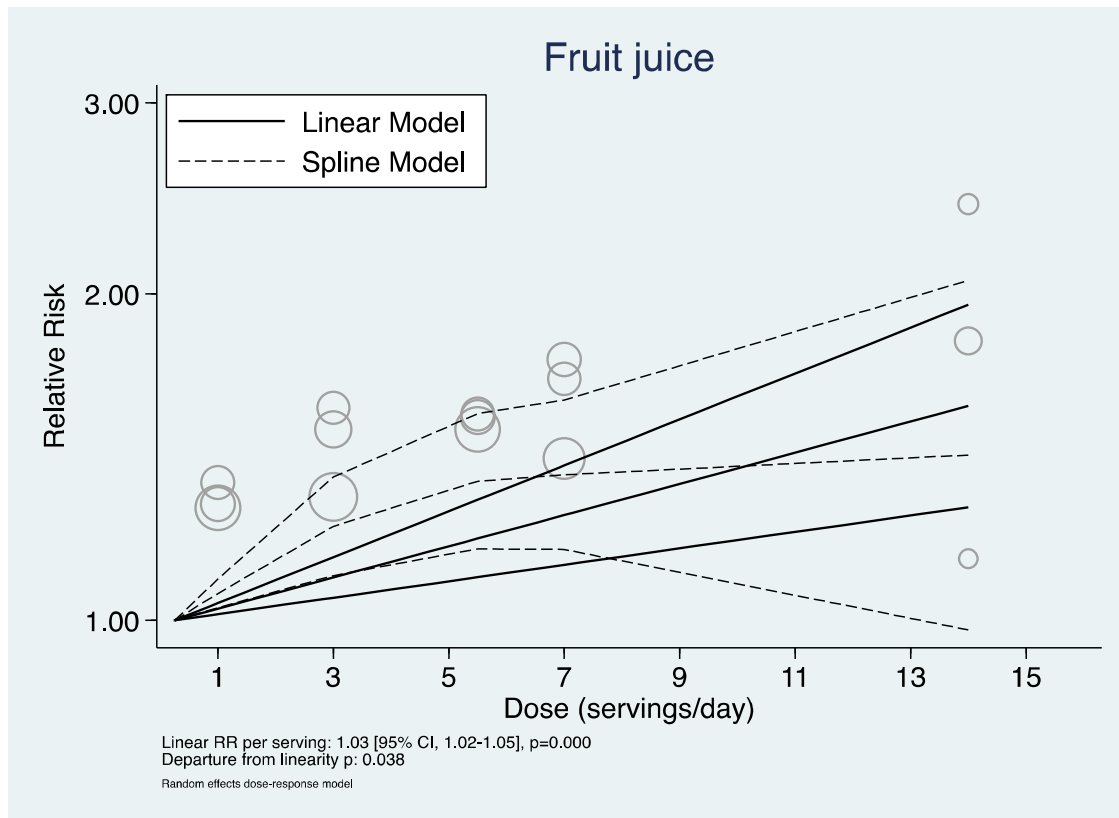
Study	Selection*	Outcome†	Comparability‡	total§
Choi <i>et al.</i> , 2008	2	3	1	6
Williams, 2008	2	2	1	5
Choi <i>et al.</i> , 2010	2	3	1	6

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline.

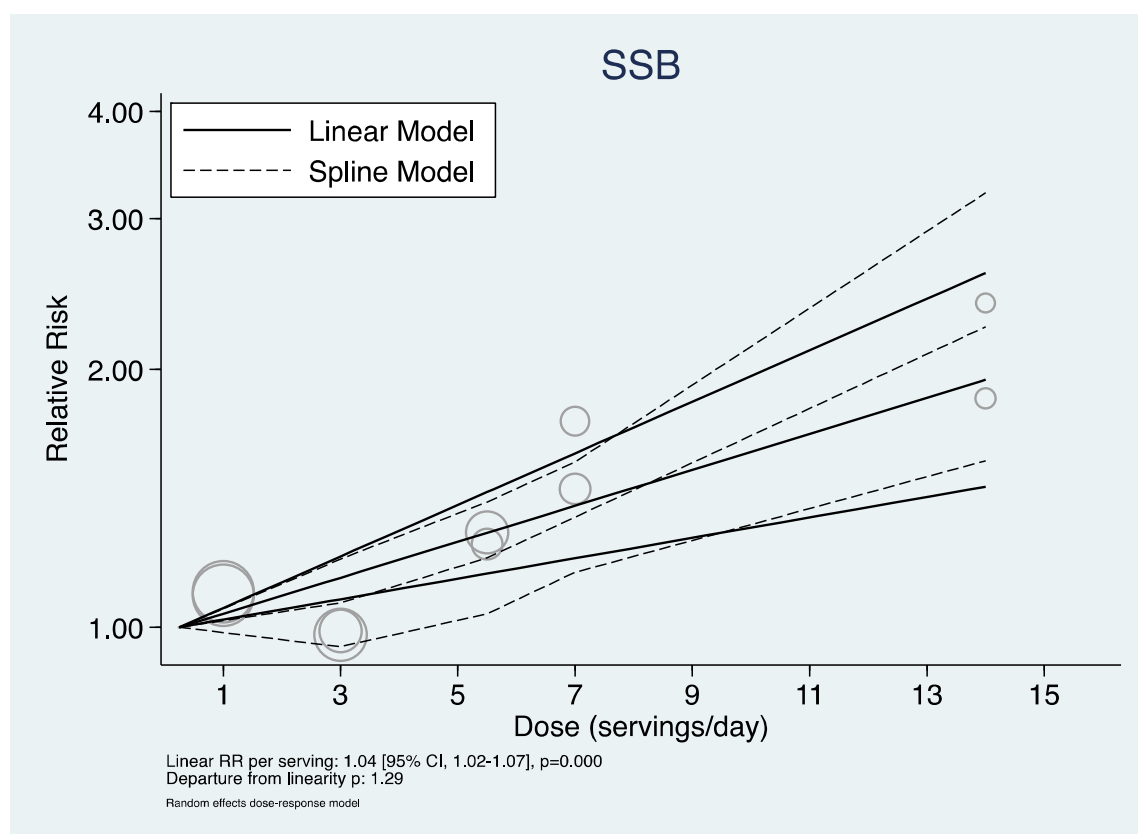
†Maximum 3 points awarded for follow-up length, adequacy of follow-up and outcome assessment.

‡Maximum 2 points awarded for controlling for the pre-specified primary confounding variable (age) and >6 of the secondary confounding variables (sex, body mass index, history of gout or hyperuricemia, diabetes, alcohol, physical activity, lipid medication/dyslipidemia, animal protein intake, hypertension or blood pressure medication including diuretics).

§A maximum of 9 points could be awarded.



28 **supplementary figure 2.** Linear and non-linear dose-response relationship between fruit juice intake
29 and incident gout per serving/week. Linear dose response data were modeled using the generalized least
30 squares trend estimation models (GLST). Dashed lines represent the pointwise 95% confidence interval
31 for the fitted linear trend (solid line). Each study was centered to the baseline reference dose for the
32 estimation of increasing dose risk. Non-linear dose response data were modeled with the fixed-effect
33 restricted cubic spline models with 3 knots using the spline curve modeling (MKSPLINE procedure).
34 Dashed lines represent the pointwise 95% confidence interval for the fitted linear trend (solid line). Each
35 study was centered to the baseline reference dose for the estimation of increasing dose risk.
36



28 **Supplementary figure 1.** Linear and non-linear dose-response relationship between SSB intake and
 29 incident gout per serving/week. Linear dose response data were modeled using the generalized least
 30 squares trend estimation models (GLST). Dashed lines represent the pointwise 95% confidence interval
 31 for the fitted linear trend (solid line). Each study was centered to the baseline reference dose for the
 32 estimation of increasing dose risk. Non-linear dose response data were modeled with the fixed-effect
 33 restricted cubic spline models with 3 knots using the spline curve modeling (MKSPLINE procedure).
 34 Dashed lines represent the pointwise 95% confidence interval for the fitted linear trend (solid line). Each
 35 study was centered to the baseline reference dose for the estimation of increasing dose risk.
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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
2	Hypothesis statement	-
3	Description of study outcome(s)	4, 5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5, supplementary table 1
9	Effort to include all available studies, including contact with authors	5
10	Databases and registries searched	5
11	Search software used, name and version, including special features used (eg, explosion)	6
12	Use of hand searching (eg, reference lists of obtained articles)	5
13	List of citations located and those excluded, including justification	7, 8, Fig 1
14	Method of addressing articles published in languages other than English	-
15	Method of handling abstracts and unpublished studies	5
16	Description of any contact with authors	-
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-9
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	5
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	5
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9, supplementary table 2
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9, supplementary table 3
22	Assessment of heterogeneity	6, 7
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	6, 7
24	Provision of appropriate tables and graphics	Tables 1, 2, Figs 1, 2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figs 2
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	-

28	Indication of statistical uncertainty of findings	11, table 2
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Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, 16
30	Justification for exclusion (eg, exclusion of non-English language citations)	5
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	17, 18

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

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024171.R1
Article Type:	Research
Date Submitted by the Author:	31-Oct-2018
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Primary Subject Heading:	Nutrition and metabolism

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



1
2 1 **Important food sources of fructose-containing sugars and incident gout:**
3 2 **A systematic review and meta-analysis of prospective cohort studies**
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7 6

8 5 **Sabrina Ayoub-Charette^{1,2}, Qi Liu^{1,2}, Tauseef Ahmad Khan^{1,2}, Fei Au-Yeung^{1,2}, Sonia Blanco Mejia^{1,2},**
9
10 6 **Russell J de Souza^{1,2,4}, Thomas MS Wolever^{1,2,3,5}, Lawrence A Leiter^{1,2,3,5}, Cyril WC Kendall^{1,2,6}, John L.**
11
12 7 **Sievenpiper^{1,2,3,5}**
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55 35 systematic review, meta-analysis
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1
2 36 **ABSTRACT**

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4 37 **Objective:** Sugar-sweetened beverages (SSBs) are associated with hyperuricemia and gout. Whether
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6
7 38 other important food sources of sugars share this association is unclear.

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9 39 **Design:** To assess the relation of important food-sources of fructose-containing sugars with incident
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12 40 gout and hyperuricemia, we conducted a systematic review and meta-analysis of prospective cohort
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14 41 studies.

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16 42 **Methods:** We searched MEDLINE, EMBASE and the Cochrane Library (through September 13, 2017).
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19 43 We included prospective cohort studies that investigated the relationship between food sources of
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22 44 sugar and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and
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24 45 assessed risk of bias. We pooled natural-log transformed risk ratios (RRs) using the generic inverse
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26 46 variance method with random effects model and expressed as RR with 95% confidence intervals (CIs).
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29 47 The overall quality of the evidence was assessed using the Grading of Recommendations Assessment,
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31 48 Development and Evaluation (GRADE) system.

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34 49 **Results:** We identified three studies (154,289 participants, 1,761 cases of gout), comparing the
35
36 50 highest with the lowest level of exposure for SSBs, fruit juice and fruits. No reports were found
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39 51 reporting incident hyperuricemia. Fruit juice and SSB intake showed an adverse association (fruit
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41 52 juice, RR = 1.77, 95% CI 1.20 to 2.61; SSB, RR = 2.08, 95% CI 1.40 to 3.08), when comparing the highest
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44 53 to lowest intake of the most adjusted models. There was no significant association between fruit
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46 54 intake and gout (RR 0.85, 95% CI 0.63 to 1.14). Strongest evidence was for the adverse association in
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48 55 SSB (moderate quality), and the weakest evidence was for the adverse association in fruit juice (very
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51 56 low quality) and the no effect in fruit intake (very low quality).

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53 57 **Conclusion:** The adverse association of SSB is also seen for fruit juice consumption but does not
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56 58 extend to fruit intake. Further research is likely to improve our estimates.

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2 59 **Protocol registration:** ClinicalTrials.gov identifier: NCT02702375
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7 61 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 9 62 - This systematic review and meta-analysis assessed the quality of the evidence using the
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11 Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
12 63
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14 64 - Large prospective cohort studies that were of high quality and had a long duration of follow-up
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16 were included.
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19 66 - Most of the pooled results showed good consistency (low between study heterogeneity) and
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21 sugar sweetened beverages showed evidence of a dose-response gradient.
22 67
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24 68 - Only three prospective cohort studies with low external generalizability were available for
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26 inclusion.
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29 70 - The observational design of the prospective cohort studies did not allow for causal inferences
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31 to be drawn.
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1 2 82 **INTRODUCTION**

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4 83 Gout and associated hyperuricemia are both associated with the development of hypertension,
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7 84 insulin resistance syndrome [1], and cardiovascular disease (CVD) [2]. Different diets have been
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9 85 shown to be associated with the development and severity of gout [3]. Foods that increase net ATP
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12 86 degradation including alcohol and high purine meats, are risk factors for gout [1]. Ingestion of large
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14 87 amounts of the monosaccharide fructose can increase uric acid production during its metabolism in
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17 88 the liver through unregulated phosphorylation of ATP into AMP [1] as demonstrated in randomized
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19 89 controlled trials [4, 5]. Similarly, in cohort studies, high intake of fructose-containing sugars in the
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22 90 form of sugar-sweetened beverages (SSBs) is associated with incident gout [6]. It is unclear whether
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24 91 the association seen for SSBs holds for other important food-sources of fructose-containing sugars,
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26
27 92 such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based
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29 93 products and sweets and desserts. As dietary guidelines and public health policy move from nutrient-
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31 94 based recommendations toward food and dietary-based recommendations [3, 4, 7], it is important to
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34 95 understand the contribution of these different food sources of fructose-containing sugars to the
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36 96 association of incident gout. To address this gap, we conducted a systematic review and meta-analysis
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39 97 of prospective cohort studies of the relation of important food sources of fructose-containing sugars
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41 98 with incident gout and hyperuricemia.

43 99 44 45 46 100 **METHOD**

47 48 101 **Design**

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51 102 We followed the Cochrane Handbook for Systematic Reviews of Interventions [8] for the conduct of
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53 103 our systematic review and meta-analysis and reported our results according to the Meta-analysis of
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56 104 Observational Studies in Epidemiology (MOOSE) guidelines [9] and preferred Reporting Items for
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2 105 Systematic Reviews and Meta-Analysis (PRISMA) [10] guidelines. The study protocol was registered at
3
4 106 ClinicalTrials.gov (identifier, NCT02702375).

9 108 **Search strategy**

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12 109 We conducted systematic searches in MEDLINE, EMBASE and Cochrane through September 13, 2017
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14 110 with no language restriction (**supplementary table 1**). Targeted manual searches served to
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16 111 supplement the database search; these included finding related papers from references of review
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18 112 papers, included studies, perusing articles with data from major prospective cohorts that usually
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20 113 report dietary data, and speaking to experts in the field.
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26 115 **Study selection**

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29 116 We included prospective cohort studies of \geq one-year duration that assessed the association of
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31 117 important food sources of fructose-containing sugars including non-alcoholic beverages (SSBs), cereal
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33 118 grain and grain based products, fruit and fruit-based products, dairy and dairy-based products, and
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35 119 sweets, chocolate and desserts with incident gout or hyperuricemia in participants free from gout or
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37 120 hyperuricemia at the start of the study. One-year duration was chosen as it allows for the
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40 121 development of diseases such as hyperuricemia and gout.
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46 123 **Data extraction**

47
48 124 Two independent reviewers (SAC and QL) extracted relevant data from included studies onto
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50 125 standardized pro forma. Extracted data included sample size, subject characteristics, sources of
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52 126 fructose-containing sugars, exposure levels, duration of follow-up, number of gout or hyperuricemia
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54 127 cases, model adjustments, and the risk ratio with 95% confidence intervals (95% CI) per quantile of
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2 128 intake. The main outcome was incident gout or hyperuricemia expressed as risk ratios (RR) with 95%
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4 129 confidence intervals (95% CI). Discrepancies were resolved by consensus.
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9 131 **Risk of bias**

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12 132 The same two independent reviewers (SAC and QL) assessed each study for risk of bias. Risk of bias
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14 133 was assessed using the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Points were
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17 134 awarded based on cohort selection, comparability of groups and assessment of outcomes, for a
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19 135 maximum total of 9 points [11]. Studies with ≥ 6 points were considered high quality [11]. Difference
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22 136 between reviewers was resolved by consensus.
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26 138 **Statistical analyses**

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29 139 Primary pooled analyses were conducted using Review Manager (RevMan) 5.3 (The Nordic Cochrane
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31 140 Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analysis and the assessments
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33
34 141 of dose response were performed using Stata 14 (StataCorp, College Station, TX, USA). Natural log-
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36 142 transformed RR for incident gout or hyperuricemia, comparing extreme quantiles (the highest
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39 143 exposure versus the lowest exposure or reference group), were pooled separately for each food
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41 144 source of fructose-containing sugars using the generic inverse variance method with DerSimonian and
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44 145 Laird random effects models and expressed as RRs with 95% CI. To overcome a unit-of-analysis error
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46 146 for studies appearing more than once in the same analysis, we divided participants equally among the
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49 147 multiple comparisons and readjusted the log-standard errors [8]. Inter-study heterogeneity was
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51 148 assessed with the Cochran Q statistic with significance set at $p < 0.10$ and quantified with the I^2
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53 149 statistic, where $I^2 \geq 50\%$ represented evidence of substantial heterogeneity [8]. Interaction between
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56 150 food sources was assessed using Cochran Q statistic for between group interaction while adjusting
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2 151 log-standard errors for units-of-analysis. We explored sources of heterogeneity by sensitivity analyses.
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4 152 Sensitivity analyses, where each study was systematically removed, and effect size was recalculated in
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7 153 the remaining studies, were carried out to explore the impact of individual studies on the pooled risk.
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9 154 As ≥ 10 cohort comparisons were not available, *a priori* subgroup analyses were not performed. Linear
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12 155 and non-linear dose-response analyses were assessed using generalized least squares trend
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14 156 estimation models (GLST) and fixed-effects restricted cubic spline model with 3 knots, respectively
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17 157 [12]. Publication bias was not assessed as the number of cohort comparisons was less than 10.
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21 159 **Grading of the evidence**

24 160 The overall quality and the strength of the evidence was assessed using the Grading of
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26 161 Recommendations Assessment, Development and Evaluation (GRADE) system [13-25]. The evidence
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29 162 was graded as high, moderate, low, or very low quality, with observational studies starting with an
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31 163 initial grade of 'low'. This then can be downgraded based on 5 pre-specified criteria or upgraded
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33
34 164 based on 3 pre-specified criteria. Criteria to downgrade included risk of bias (weight of studies
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36 165 showed risk of bias as assessed by low NOS < 6), inconsistency (substantial unexplained inter-study
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39 166 heterogeneity i.e. $I^2 > 50\%$), indirectness (presence of factors that limit the generalizability of the
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41 167 results), imprecision in the pooled risk estimate (the 95% CI for risk estimates are wide or cross a
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44 168 minimally important difference of 10% for benefit or harm (RR 0.9–1.1)), and publication bias
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46 169 (evidence of small-study effect). Conversely, criteria to upgrade included a large magnitude of effect
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48 170 (RR > 2 or RR < 0.5 in the absence of plausible confounders), dose–response gradient or reasonable
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51 171 evidence of attenuation of the pooled effect estimate by confounders.
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53 172 **Patient and public involvement**

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2 174 Patients and the public were not involved in the study.

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5 6 7 176 **RESULTS**

8 9 177 **Search results**

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12 178 **Figure 1** shows the flow of the systematic search and study selection. Of the 309 reports identified by
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14 179 the literature search, three reports with data from three prospective cohort studies met our inclusion
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16 180 criteria [26-28]: Nurses' Health Study (NHS) [27], Health Professionals Follow-up Study (HPFS) [26] and
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18
19 181 the National Runner's Health Study [28]. All three reports reported the association of food sources of
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21 182 fructose-containing sugars on incident gout, but none on incident hyperuricemia. These reports
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24 183 involved a total of 154,289 participants with 1,761 incident cases of gout. Two reports each reported
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26 184 data on fruit intake [n= 75,383; 983 cases] [26, 28], fruit juice [n= 125,299; 1,533 cases] [26, 27] and
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29 185 SSBs [n=125,299; 983 cases] [26, 27]. We did not identify prospective cohort studies reporting the
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31 186 association of other food sources of fructose-containing sugars (e.g. cereal grain and grain-based
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34 187 products, sweets and desserts, dairy and dairy based products and chocolate) with incident gout
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36 188 fitting our inclusion criteria.

37 38 39 189 40 41 190 **Study characteristics**

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43
44 191 **Table 1** lists the characteristics of the included prospective cohort studies. All studies were performed
45
46 192 in the USA. The median age of the included participants ranged from 30 to 75. The median follow-up
47
48 193 period was 17 years (range, 12 to 22 years) for SSB, 18.7 years (12 to 22 years) for fruit juice and 9.9
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51 194 years (7.74 to 12 years) for fruit. Dietary intake assessments were done with self-reported, validated
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53 195 food frequency questionnaires (FFQs) in all studies. Quantiles of exposure depended on the food
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56 196 source. Medians for the lowest and highest quantiles of exposure were <1 servings/month and ≥14

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2 197 servings/week respectively for SSB; ≤ 1 servings/month and ≥ 14 servings/week respectively for fruit
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4 198 juice; and ≤ 0.4 servings/week (range, $< 0-0.5$ servings/week) and ≥ 8 servings/day (range, $\geq 2-14$
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7 199 servings/day), respectively for fruit. The ascertainment of incident gout in both HPFS and NHS cohorts
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9 200 [26, 27] was through self-report, followed by supplementary surveys of the subjects based on the
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11
12 201 American College of Rheumatology gout survey criteria [29] to confirm that the diagnosis. The authors
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14 202 defined individuals with gout that met ≥ 6 of the 11 criteria for gout. In addition, in a sub-sample the
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17 203 self-reported diagnoses were validated with medical records. As for the NRHS cohort [28], incident
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19 204 gout was self-reported based upon physician diagnosis.
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24 206 **Supplementary table 2** shows the complete list of adjusted confounding variables for the most
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26 207 adjusted models for each of the included prospective cohorts. The median number of variables in the
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28
29 208 most adjusted models was 14 (range, 6 to 14). All studies adjusted for primary and secondary
30
31 209 confounders such as age, body mass index (BMI) and history of hypertension. Each of the three
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33
34 210 cohorts were single-sex studies, so adjustment for sex was not necessary. The NHS cohort study
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36 211 authored by Choi *et al.* 2010 [27] and NRHS study by Williams *et al.* [28] were agency funded, while
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38
39 212 the HPFS paper authored by Choi *et al.* 2008 [26] was funded by both agency and industry.
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41 213 42 43 214 **Study Quality**

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46 215 **Supplementary table 3** shows the study quality assessments by the NOS scale. There was no evidence
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48 216 of serious risk of bias. Only NRHS cohort scored < 6 on the NOS scale, which denotes lower quality
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51 217 [28].
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53 218 54 55 219 **Fruit intake on incident gout**

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2 220 **Figure 2** shows the relationship between food sources of fructose-containing sugars intake and
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4 221 incident gout. There was significant interaction between the food sources ($p=0.02$). When comparing
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6
7 222 the highest to the lowest fruit intake, no association was shown for fruit intake on incident gout (RR =
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9 223 0.85, [95% CI 0.63 to 1.14]). There was evidence of significant interstudy heterogeneity ($I^2 = 93\%$,
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12 224 $p<0.001$).

13 14 225 15 16 226 **Fruit juice intake on incident gout**

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19 227 **Figure 2** shows the relationship between fruit juice intake and incident gout. When comparing the
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21
22 228 highest to lowest intake, an adverse association was shown for fruit juice intake on incident gout (RR
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24 229 1.77, [95% CI 1.20 to 2.61]). There was no evidence of significant interstudy heterogeneity ($I^2 = 0\%$
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26 230 [95% CI 0% to 90%], $p = 0.54$).

27 28 29 231 30 31 232 **SSB intake on incident gout**

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34 233 **Figure 2** shows the relationship between SSB intake and incident gout. When comparing the highest
35
36 234 with the lowest intake, an adverse association was shown for SSB intake on incident gout (RR=2.08
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38
39 235 [95% CI 1.40 to 3.08]). There was no evidence of significant interstudy heterogeneity ($I^2 = 0\%$, $p =$
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41 236 0.52).

42 43 237 44 45 46 238 **Additional analysis**

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48 239 Sensitivity analysis (the systematic removal of each study), publication bias and subgroup analyses
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51 240 could not be performed due to the small number of studies included in each analysis ($n=2$).

52 53 241 54 55 56 242 **Dose-response analysis**

1
2 243 A random-effect GLST model showed a significant dose-response relationship between fruit juice
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4 244 intake and incident gout per serving/week (RR = 1.03, 95% CI 1.02 to 1.05, $p < 0.001$) (**supplementary**
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7 245 **figure 1**), and for SSB intake (RR = 1.04, 95% CI 1.02 to 1.07, $p < 0.001$) (**supplementary figure 2**). Fruit
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9 246 juice intake showed a significant departure from linearity ($p = 0.038$), and visual inspection of the
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12 247 graph (**supplementary figure 1**) indicated a plateau for risk increase after ≥ 5 servings per day. There
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14 248 was no evidence for departure from linear dose response gradient or dose thresholds for SSB intake
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17 249 while using the restricted cubic spline model ($p = 1.29$) (**supplementary figure 2**). Dose-response
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19 250 modeling was not conducted for fruit intake due to lack of data.
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24 252 **GRADE assessment**

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26 253 **Table 2** shows the GRADE assessment of individual food sources of fructose-containing sugars. The
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28
29 254 quality of evidence of an adverse association from both fruit and fruit juice was rated as very low,
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31 255 with downgrades to the lowest level for indirectness for fruit intake, and for inconsistency,
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34 256 indirectness and imprecision for fruit juice intake. The quality of evidence of an adverse association
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36 257 of SSB intake with incident gout was rated as moderate, with a downgrade of one level for
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39 258 indirectness but upgrade of two levels for a large magnitude effect and significant dose-response
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41 259 association.
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46 261 **DISCUSSION**

47
48 262 We conducted a systematic review and meta-analysis of studies investigating the relation of
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51 263 important food sources of fructose-containing sugars with incident gout. We identified three
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53 264 prospective cohort studies [26-28] comprising of 154,289 participants and 1,761 cases of incident
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56 265 gout. The pooled analyses revealed that there was moderate quality evidence that SSB intake was
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2 266 associated with 208% increase in risk of incident gout when comparing the highest with the lowest
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4 267 intake. Similarly, there was low quality evidence that fruit juice intake was associated with a 77%
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7 268 increase in risk of incident gout, but fruit intake did not show any significant association with incident
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9 269 gout (low quality evidence). There was no data available of other important food sources of fructose-
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12 270 containing sugars.

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16 17 272 **Findings in the context of the literature**

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19 273 Our results are consistent with previous research which indicate that intake of certain food sources of
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21
22 274 fructose-containing sugars are associated with the risk of gout. Our previous systematic review and
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24 275 meta-analysis of prospective cohort studies that assessed fructose intake, found a harmful
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26 276 relationship between fructose consumption and gout [6]. While that study indicated that fructose
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29 277 moiety might possibly drive the association with gout, all the fructose data was derived from SSB
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31 278 intake. Another systematic review of the literature identified numerous dietary factors associated
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34 279 with the risk of gout including meat, alcohol, seafood and SSBs, but also that lower risk was associated
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36 280 with the intake of dairy, folate and coffee [3].

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40
41 282 SSBs are a major source of fructose-containing added sugars in the western diet comprising around
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43
44 283 30% of intake of added sugars in the USA [30] and around 24% in Canada [31]. Excess intake of
45
46 284 fructose can increase uric acid through an unregulated phosphofructose kinase pathway that uses
47
48 285 substantial amounts of ATP [32] to convert fructose into fructose-1-phosphate in the liver [33].

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51 286 Mechanistically, net ATP degradation leads to accumulation of AMP, which is subsequently degraded
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53 287 to uric acid. Additionally, fructose can increase de novo purine synthesis, which further produces uric
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56 288 acid [1]. This increase in uric acid can lead to the development of gout. Since we were unable to

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2 289 investigate the relationship between food sources of fructose-containing sugars and hyperuricemia,
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4 290 we cannot validate this mechanism. It is possible, that fructose increases the risk of gout
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7 291 independently of serum uric acid levels. However, since the link between fructose and serum uric acid
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9 292 [34-37], and the link between serum uric acid and the development of gout have been independently
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11 293 established [1], it is unlikely that fructose increases the risk of gout without using uric acid as an
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14 294 intermediate.

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19 296 We identified adverse association of fruit juices intake with incident gout. The two studies that
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21 297 contributed to this result [26, 27] were both performed in two Harvard cohorts which do not
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24 298 differentiate between fruit drinks and pure fruit juice, the former being largely similar to SSBs i.e.
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26 299 mainly sugar and water. This is supported by studies investigating pure fruit juice and fruit drinks
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29 300 which have shown divergent response for cardiometabolic disease [38, 39].
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33
34 302 We did not see any association between fruit intake and incident gout but the effect estimates in the
35
36 303 two studies were in opposite direction. The NRHS [28] cohort showed a 51% reduction in risk of gout
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39 304 when with high intake of fruit whereas the HPFS [26] cohort showed a 63% increased risk — both
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41 305 studies were performed in men. These discordant results highlight the differences in the studies.
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43 306 NHPS cohort [26] only measured oranges and apples, fruit high in fructose, while NRHS [28] cohort
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46 307 assessed all fruit and its increasing intake, as the authors admit, might represent a healthier dietary
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48 308 intake. It is possible that higher intake of fruits in NRHS might be associated with high intake of dairy
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51 309 or coffee, which have been associated with lowering the risk of gout [3] and not measured in NRHS.
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53 310 Furthermore, case-control and cross-sectional studies have shown a protective effect of total fruit
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56 311 intake with gout albeit in Asian populations [40, 41], their relevance to the included studies,
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2 312 conducted in a largely Caucasian population, might be limited. The harmful association for oranges,
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4 313 which are rich in vitamin C, in HPFS [26] cohort is at odds with its own result in another paper, in
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6
7 314 which the authors demonstrated a protective association of vitamin C intake with gout [42]. Fruits are
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9 315 rich in fructose; however, fruit intake has consistently shown a benefit for cardiometabolic risk
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12 316 factors, cardiometabolic diseases and all cause-mortality [43-49] even though the fructose in fruit can
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14 317 increase uric acid levels. More data might clarify this association.
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19 319 We could not find any prospective studies looking at the association of food sources of fructose-
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22 320 containing sugars and hyperuricemia even though hyperuricemia is the most important risk factor for
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24 321 gout [3, 50]. Hyperuricemia is also a risk factor for hypertension , metabolic syndrome, diabetes , and
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26 322 CVD [51]. Several cross-sectional analyses have investigated the link between SSB consumption and
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28
29 323 serum uric acid levels, showing a positive relationship [34-37]. In contrast, the analysis of the National
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31 324 Health and Nutrition Examination Survey (NHANES) showed no link between dietary fructose and risk
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34 325 of hyperuricemia, indicating that perhaps different food sources of fructose-containing sugars may
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36 326 have different effects on serum uric acid. This point is reinforced by another analysis of NHANES data
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39 327 that showed a relationship of SSB intake with higher serum uric acid concentration, but not with fruit
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41 328 juice [52]. Future studies investigating food sources of sugars and risk of hyperuricemia may help to
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44 329 elucidate some of the above inconsistent findings.
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48 331 We were not been able to find prospective cohort studies investigating the association of other food
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51 332 sources of fructose-containing sugars and the risk of gout. However, cross-sectional studies suggest
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53 333 that cereal and yogurt may be associated with lower serum uric acid [53]. More research is needed to
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56 334 clarify the relationship between other food sources of fructose-containing sugars and the risk of gout.
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Strengths and limitations

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

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

1
2 358 other populations. While, genome wide association studies have found numerous genes that increase
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4 359 one's risk for gout [54] and some ethnic groups may be more susceptible than others [1], it is not
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7 360 known if the association of fructose intake with gout is modified by genes. Third, sources of
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9 361 heterogeneity remained unexplained; with only three studies, we were unable to assess publication
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11 362 bias or perform sensitivity or a priori subgroup analysis. Thus for these reasons, data pertaining to SSB
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14 363 and fruit juice intake and incident gout received a GRADE of moderate and very low quality,
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16
17 364 respectively, indicating that further studies in this regard is likely to impact our certainty in the effect
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19 365 estimate and may change the estimate for SSB and that our certainty in the estimate for fruit juice is
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21
22 366 very uncertain; therefore, caution should be used when interpreting these results. Similarly, for fruit,
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24 367 which received a GRADE of very low, so we are very uncertain in these results and caution should be
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27 368 used in the interpretation of these results.

31 370 **Implications**

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34 371 Dietary guidelines have shifted their focus from nutrients based recommendations to food and
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36 372 dietary pattern-based recommendations [55], since it has been recognized that one does not eat
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39 373 nutrients in isolation, but as a part of food. Interactions between nutrients in food are complex and
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41 374 important components of disease risk [55]. Our findings support this view in relation to food sources
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44 375 of fructose-containing sugars and their relationship with gout. Our findings also have implications for
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46 376 recommendations for the prevention of gout. Conventional dietary recommendations for gout have
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48
49 377 focused on restriction of purine intake; however, low-purine diets are often high in carbohydrates,
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51 378 including fructose-rich foods [56]. We have shown an adverse association between fruit juice and
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53 379 SSBs, supporting the recommendations to limit their intakes. Since we did not have data relating to

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2 380 children, hyperuricemia or other food sources of fructose-containing sugars, we cannot extend our
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4 381 conclusion to these groups of individuals or these foods.
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7 382 8 9 383 **Conclusion**

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11 384 Our systematic review and meta-analysis of prospective cohort studies showed an adverse association
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14 385 between SSBs and fruit juice with risk of gout, while there was no association with fruit intake. The
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16 386 strength of the evidence was moderate for SSB intake and very low for fruit juice and fruit intake, as
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19 387 assessed by GRADE. For SSBs, the true association is likely to be close to the estimate, but there is a
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21 388 possibility that it is substantially different. For fruit juice and fruit intake, the true association are likely
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24 389 to be substantially different from the estimate and future research will very likely impact our
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26 390 confidence in the effect estimates and likely to change them [57]. Our results are consistent with the
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29 391 literature that certain food sources of fructose-containing sugars especially SSBs are a risk factor for
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31 392 the development of gout. We were unable to identify studies assessing food sources of fructose-
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34 393 containing sugars and hyperuricemia, indicating a gap in the literature. Given that incident gout is
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36 394 rising [7, 58-63], and that gout and hyperuricemia are both associated with metabolic syndrome,
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39 395 myocardial infarction, diabetes and premature death [1, 2, 64], it is becoming increasingly important
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41 396 to identify and understand risk factors for developing gout. It is imperative for additional prospective
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44 397 studies to assess the intake of various food sources of fructose-containing sugars and their
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46 398 relationship with gout and hyperuricemia in diverse populations. This will help identify to what extent
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49 399 does our foods mediate the risk for hyperuricemia and gout and will further inform health care
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51 400 professionals, policymakers, and aid in the development of improved dietary guidelines for the
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53 401 prevention and management of gout and hyperuricemia.
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28
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30
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33

34 462

36 463 **Authors' contributions**

37
38 464 All authors had full access to all of the data (including statistical reports and tables) in this study and
39
40 465 take full responsibility for the integrity of the data and the accuracy of the data analysis.

41
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11 480
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2 644 **TABLES AND FIGURES**
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6 646 **Figure 1** Summary of evidence search and selection. Flow of the literature search for the effect of food
7 647 sources of sugar intake on incident gout and hyperuricemia. Of the 309 studies initially identified, 294
8 648 were excluded based on title and/or abstract. The remainder were read in full by two independent
9 649 reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort
10 650 studies.
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17 652 **Figure 2** Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-
18 653 adjusted multivariate models accounting for food sources of fructose-containing sugars intake were
19 654 used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using
20 655 the Cochran Q statistic and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant
21 656 heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit juices.
22 657 * The number of cases and participants are divided equally between the multiple entries of the study
23 658 to ensure total count gives unique individuals. To overcome a unit-of-analysis error for studies
24 659 appearing more than once in the same analysis, we readjusted the log-standard errors to participants
25 660 equally among the multiple comparisons and.
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Table 1 Characteristics of prospective cohort studies investigating food sources of fructose-containing sugar intake and incident gout.

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

Abbreviations: HPFS = Health Professionals Follow-Up Study; NHS = Nurses Health Study; NRHS =National Runner’s Health Study; M=males;

F=females; SFFQ = Semi quantitative Food-Frequency Questionnaire; SSBs = Sugar Sweetened Beverages.

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

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

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

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

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

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

1
2 694 ⁴Upgrade for a dose response gradient, as the GLST dose-response analysis revealed a significant linear relationship between sugar
3
4 695 sweetened beverage intake and incident gout (P=0.0001).

5
6 696 ⁵Downgrade for very serious inconsistency, as the two studies included had opposite associations and there was evidence of substantial
7
8 697 inter-study heterogeneity ($I^2=94%$, $p<0.0001$). Due to the small number of studies included in the analysis, subgroup analysis was not
9
10 698 performed.

11 699 ⁶Downgrade for serious imprecision, as the lower bound of the 95% CI (RR, 0.27) includes clinically important benefit (RR<0.9), while the
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13 700 upper bound of the 95% CI (RR, 2.87) crosses the minimally important difference of 10% (RR>1.1).
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Figure 1 Summary of evidence search and selection

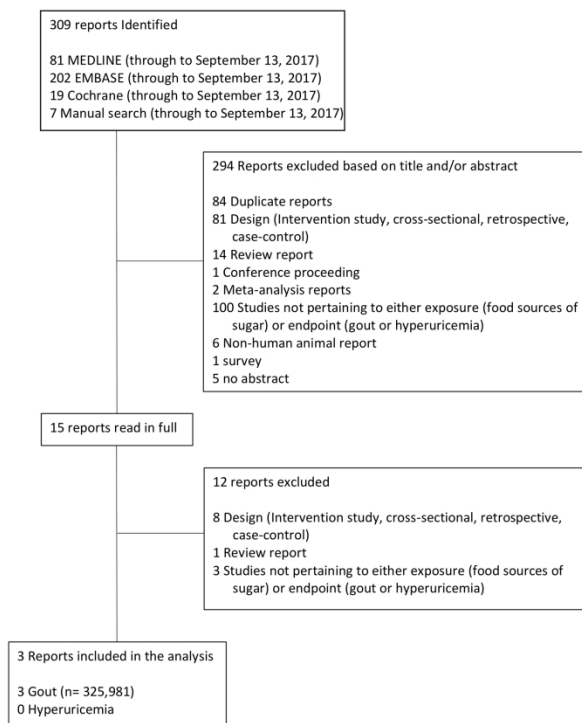


Figure 1. Summary of evidence search and selection

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

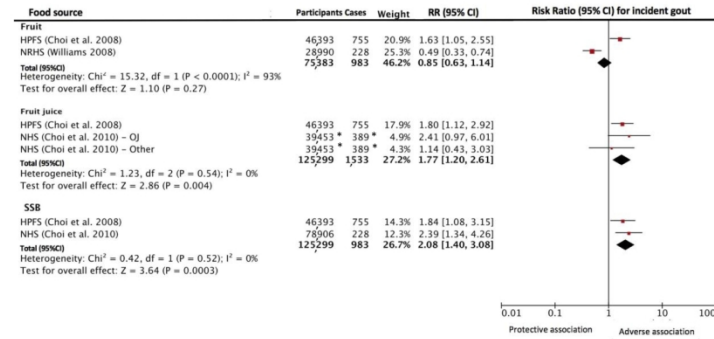


Figure 2. Relation between intake of fruit, fruit juice and SSB incident gout.

215x279mm (300 x 300 DPI)

Supplementary material

SUPPLEMENTARY TABLES

Supplementary table 1 Search terms

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

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

SUPPLEMENTARY FIGURES

Supplementary figure 1 Linear and non-linear dose-response relationship between fruit juice intake and incident gout per serving/week

Supplementary figure 2 Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week

Supplementary table 1. Search terms

Database and search terms

MEDLINE

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

EMBASE

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

Cochrane

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

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3 51. follow-up study.mp. 51. follow-up study.mp. 51. gout*.mp
4 52. (longitudinal adj2 study).mp. 52. (longitudinal adj2 study).mp. 52. uric acid*.mp
5 53. gout/ 53. gout/ 53. hyperuricemia*.mp
6 54. gout*.mp. 54. gout*.mp. 54. hyperuricemia/
7 55. uric acid*.mp. 55. uric acid*.mp. 55. hyperuricaemia*.mp
8 56. hyperuricemia*.mp. 56. hyperuricemia*.mp. 56. uric.mp
9 57. hyperuricemia/ 57. hyperuricemia/ 57. or/1-43
10 58. hyperuricaemia*.mp. 58. hyperuricaemia*.mp. 58. or/44-49
11 59. uric.mp. 59. uric.mp. 59. or/50-56
12 60. or/1-44 60. or/1-45 60. and/57-59
13 61. or/45-52 61. or/46-52
14 62. or/53-59 62. or/53-59
15 63. and/60-62 63. and/60-62

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

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

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

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

HPFS=Health Professionals Follow-Up Study, NHS=Nurses Health Study

*Denotes confounders measured only at baseline years.

† Indicates confounders measured every 2 years.

‡ Indicates the study includes only female subjects

§ Indicates the study includes only male subjects

∇ Indicates the confounder was present in some, but not all, models.

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

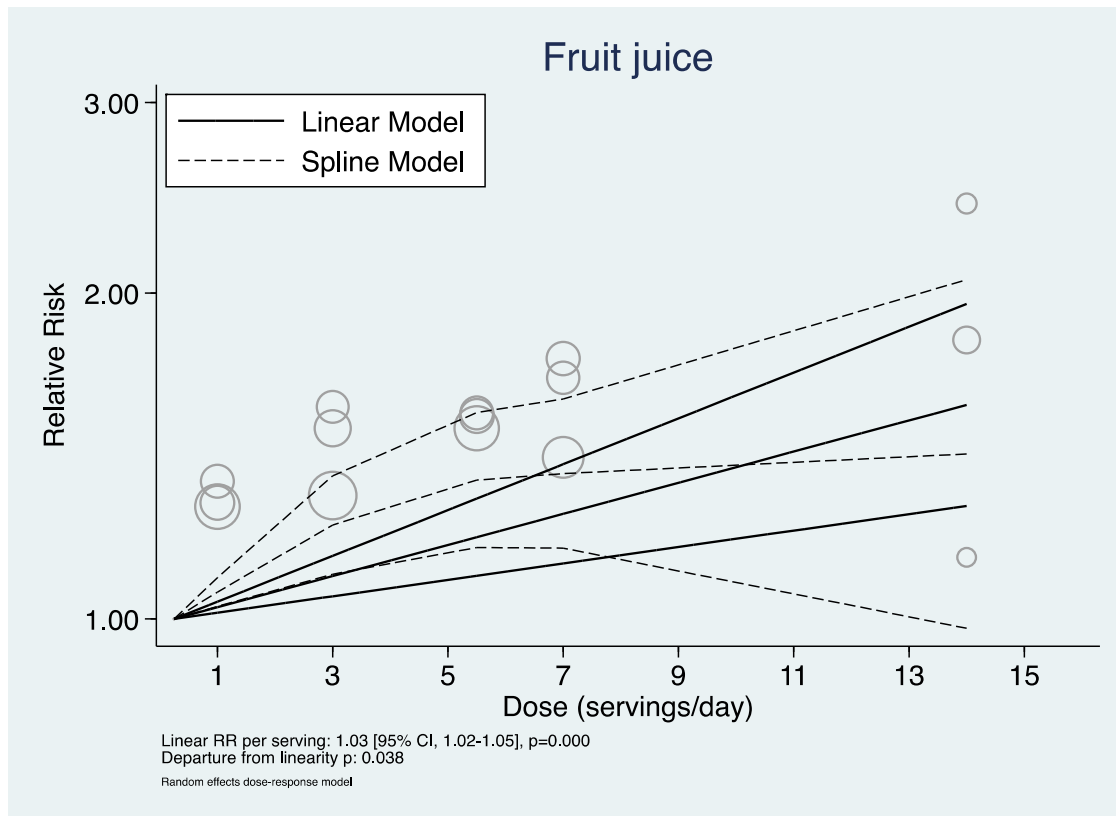
Study	Selection*	Outcome†	Comparability‡	total§
Choi <i>et al.</i> , 2008	2	3	1	6
Williams, 2008	2	2	1	5
Choi <i>et al.</i> , 2010	2	3	1	6

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline.

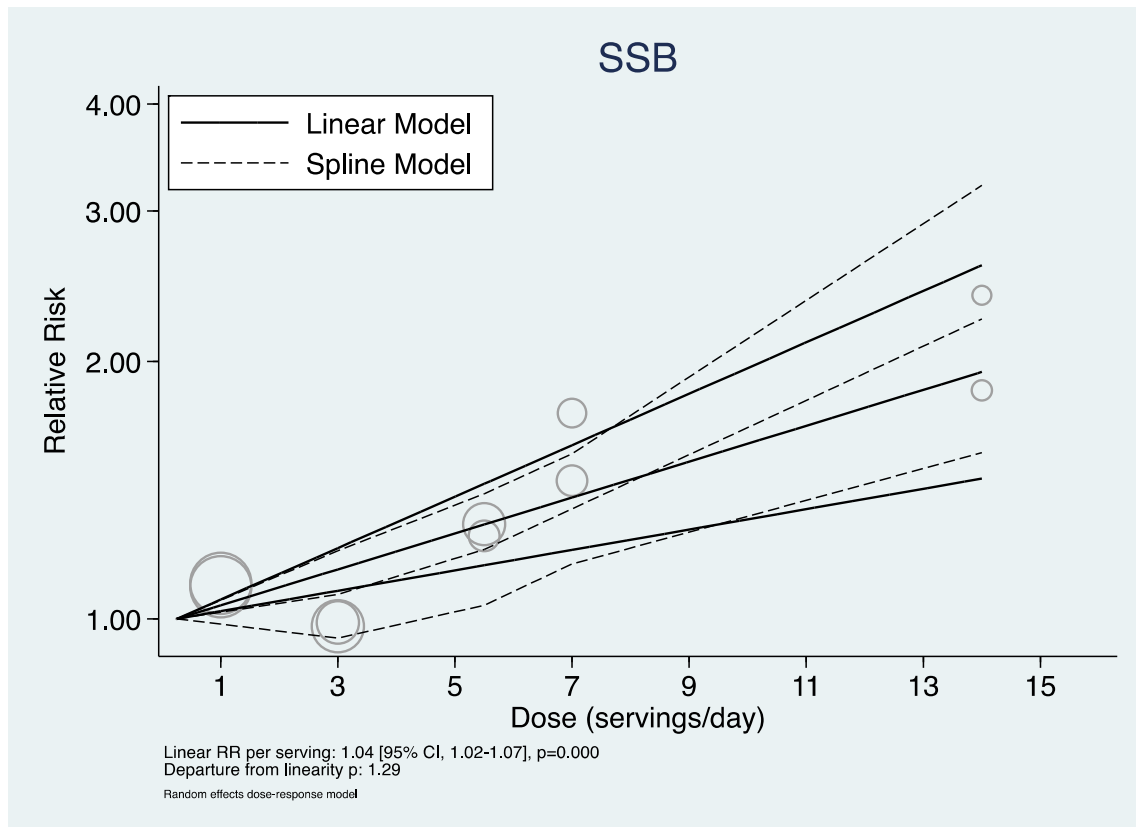
†Maximum 3 points awarded for follow-up length, adequacy of follow-up and outcome assessment.

‡Maximum 2 points awarded for controlling for the pre-specified primary confounding variable (age) and >6 of the secondary confounding variables (sex, body mass index, history of gout or hyperuricemia, diabetes, alcohol, physical activity, lipid medication/dyslipidemia, animal protein intake, hypertension or blood pressure medication including diuretics).

§A maximum of 9 points could be awarded.



28 **Supplementary figure 1.** Linear and non-linear dose-response relationship between fruit juice intake
29 and incident gout per serving/week. Linear dose response data (solid lines) were modeled using the
30 generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines)
31 were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval
32 for the fitted trend are shown above and below the solid line. Each study was centered to its own
33 baseline reference dose when estimating increasing dose risk.
34



28 **Supplementary figure 2.** Linear and non-linear dose-response relationship between SSB intake and
 29 incident gout per serving/week. Linear dose response data (solid lines) were modeled using the
 30 generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines)
 31 were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval
 32 for the fitted trend are shown above and below the solid line. Each study was centered to its own
 33 baseline reference dose when estimating increasing dose risk.
 34

MOOSE Checklist for Meta-analyses of Observational Studies

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

28	Indication of statistical uncertainty of findings	11, table 2
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Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, 16
30	Justification for exclusion (eg, exclusion of non-English language citations)	5
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	17, 18

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

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-024171.R2
Article Type:	Research
Date Submitted by the Author:	02-Jan-2019
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Primary Subject Heading:	Nutrition and metabolism

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



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2 1 **Important food sources of fructose-containing sugars and incident gout:**
3 2 **A systematic review and meta-analysis of prospective cohort studies**
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8 5 **Sabrina Ayoub-Charette^{1,2}, Qi Liu^{1,2}, Tauseef Ahmad Khan^{1,2}, Fei Au-Yeung^{1,2}, Sonia Blanco Mejia^{1,2},**
9
10 6 **Russell J de Souza^{1,2,4}, Thomas MS Wolever^{1,2,3,5}, Lawrence A Leiter^{1,2,3,5}, Cyril WC Kendall^{1,2,6}, John L.**
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12 7 **Sievenpiper^{1,2,3,5}**
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28 16 of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.
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48 28

49 29 **Number of Figures:** 2

50 30 **Number of Tables:** 2

51 31 **Supplemental Material:** 3 Tables and 2 Figures

52 32 **Abstract Word Count:** 298

53 33 **Manuscript Word Count:** 3,835

54 34 **Key Words:** sugars, fructose, food sources of fructose containing sugars, gout, uric acid and
55 35 systematic review, meta-analysis
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1
2 36 **ABSTRACT**

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4 37 **Objective:** Sugar-sweetened beverages (SSBs) are associated with hyperuricemia and gout. Whether
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7 38 other important food sources of sugars share this association is unclear.

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9 39 **Design:** To assess the relation of important food-sources of fructose-containing sugars with incident
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12 40 gout and hyperuricemia, we conducted a systematic review and meta-analysis of prospective cohort
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14 41 studies.

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16 42 **Methods:** We searched MEDLINE, EMBASE and the Cochrane Library (through September 13, 2017).
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19 43 We included prospective cohort studies that investigated the relationship between food sources of
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22 44 sugar and incident gout or hyperuricemia. Two independent reviewers extracted relevant data and
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24 45 assessed the risk of bias. We pooled natural-log transformed risk ratios (RRs) using the generic inverse
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26 46 variance method with random effects model and expressed as RR with 95% confidence intervals (CIs).
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29 47 The overall certainty of the evidence was assessed using the Grading of Recommendations
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31 48 Assessment, Development and Evaluation (GRADE) system.

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34 49 **Results:** We identified three studies (154,289 participants, 1,761 cases of gout), comparing the
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36 50 highest with the lowest level of exposure for SSBs, fruit juice and fruits. No reports were found
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39 51 reporting incident hyperuricemia. Fruit juice and SSB intake showed an adverse association (fruit
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41 52 juice, RR = 1.77, 95% CI 1.20 to 2.61; SSB, RR = 2.08, 95% CI 1.40 to 3.08), when comparing the highest
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44 53 to lowest intake of the most adjusted models. There was no significant association between fruit
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46 54 intake and gout (RR 0.85, 95% CI 0.63 to 1.14). Strongest evidence was for the adverse association in
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49 55 SSB (moderate certainty), and the weakest evidence was for the adverse association in fruit juice
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51 56 (very low certainty) and the no effect in fruit intake (very low certainty).

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53 57 **Conclusion:** There is an adverse association of SSB and fruit juice consumption with gout which does
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56 58 not extend to fruit intake. Further research is likely to improve our estimates.

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2 59 **Protocol registration:** ClinicalTrials.gov identifier: NCT02702375
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7 61 **STRENGTHS AND LIMITATIONS OF THIS STUDY**
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- 9 62 - This systematic review and meta-analysis assessed the certainty of the evidence using the
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11 Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.
12 63
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14 64 - Large prospective cohort studies that were of high quality and had a long duration of follow-up
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16 were included.
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19 66 - Most of the pooled results showed good consistency (low between study heterogeneity) and
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21 sugar sweetened beverages showed evidence of a dose-response gradient.
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24 68 - Only three prospective cohort studies with low external generalizability were available for
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26 inclusion.
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29 70 - The observational design of the prospective cohort studies did not allow for causal inferences
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31 to be drawn.
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1 2 82 **INTRODUCTION**

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4 83 Gout and associated hyperuricemia are both associated with the development of hypertension,
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6
7 84 insulin resistance syndrome [1], and cardiovascular disease (CVD) [2]. Different diets have been
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9 85 shown to be associated with the development and severity of gout [3]. Foods that increase net ATP
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12 86 degradation including alcohol and high purine meats, are risk factors for gout [1]. Ingestion of large
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14 87 amounts of the monosaccharide fructose can increase uric acid production during its metabolism in
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17 88 the liver through unregulated phosphorylation of ATP into AMP [1] as demonstrated in randomized
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19 89 controlled trials [4, 5]. Similarly, in cohort studies, high intake of fructose-containing sugars in the
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22 90 form of sugar-sweetened beverages (SSBs) is associated with incident gout [6]. It is unclear whether
23
24 91 the association seen for SSBs holds for other important food-sources of fructose-containing sugars,
25
26
27 92 such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based
28
29 93 products and sweets and desserts. As dietary guidelines and public health policy move from nutrient-
30
31 94 based recommendations toward food and dietary-based recommendations [3, 4, 7], it is important to
32
33
34 95 understand the contribution of these different food sources of fructose-containing sugars to the
35
36 96 association of incident gout. To address this gap, we conducted a systematic review and meta-analysis
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38
39 97 of prospective cohort studies of the relation of important food sources of fructose-containing sugars
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41 98 with incident gout and hyperuricemia.

43 99 44 45 46 100 **METHOD**

47 48 101 **Design**

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51 102 We followed the Cochrane Handbook for Systematic Reviews of Interventions [8] for the conduct of
52
53 103 our systematic review and meta-analysis and reported our results according to the Meta-analysis of
54
55
56 104 Observational Studies in Epidemiology (MOOSE) [9] and preferred Reporting Items for Systematic

1
2 105 Reviews and Meta-Analysis (PRISMA) [10] guidelines. The study protocol was registered at
3
4 106 ClinicalTrials.gov (identifier, NCT02702375).
5
6

7 107 8 9 108 **Search strategy**

10
11
12 109 We conducted systematic searches in MEDLINE, EMBASE and Cochrane through September 13, 2017
13
14 110 with no language restriction (**supplementary table 1**). Targeted manual searches served to
15
16 111 supplement the database search; these included finding related papers from references of selected
17
18 112 papers and review articles, perusing articles with data from major prospective cohorts that usually
19
20 113 report dietary data, and speaking to experts in the field.
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22
23

24 114 25 26 115 **Study selection**

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28
29 116 We included prospective cohort studies of ≥ 1 year duration that assessed the association of important
30
31 117 food sources of fructose-containing sugars including non-alcoholic beverages (SSBs), cereal grain and
32
33 118 grain-based products, fruit and fruit-based products, dairy and dairy-based products, and sweets,
34
35 119 chocolate and desserts with incident gout or hyperuricemia in participants free from gout or
36
37 120 hyperuricemia at the start of the study. One-year duration was chosen as it allows sufficient time for
38
39
40 121 the development of disease.
41
42
43

44 122 45 46 123 **Data extraction**

47
48 124 Two independent reviewers (SAC and QL) extracted relevant data from included studies onto
49
50 125 standardized pro forma. Extracted data included sample size, subject characteristics, sources of
51
52 126 fructose-containing sugars, exposure levels, duration of follow-up, number of gout or hyperuricemia
53
54 127 cases, model adjustments, and the risk ratio with 95% confidence intervals (95% CI) per quantile of
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1
2 128 intake. The main outcome was incident gout or hyperuricemia expressed as risk ratios (RR) with 95%
3
4 129 confidence intervals (95% CI). Discrepancies were resolved by consensus.

7 130

9 131 **Risk of bias**

11
12 132 The same two independent reviewers (SAC and QL) assessed each study for risk of bias. Risk of bias
13
14 133 was assessed using the Newcastle-Ottawa Scale (NOS) for prospective cohort studies. Points were
15
16 134 awarded based on cohort selection, comparability of groups and assessment of outcomes, for a
17
18
19 135 maximum total of 9 points [11]. Studies with ≥ 6 points were considered high quality [11]. Difference
20
21
22 136 between reviewers was resolved by consensus.

24 137

26 138 **Statistical analyses**

28
29 139 Primary pooled analyses were conducted using Review Manager (RevMan) 5.3 (The Nordic Cochrane
30
31 140 Centre, The Cochrane Collaboration, Copenhagen, Denmark). Sensitivity analysis and the assessments
32
33
34 141 of dose response were performed using Stata 14 (StataCorp, College Station, TX, USA). Natural log-
35
36 142 transformed RR for incident gout or hyperuricemia, comparing extreme quantiles (the highest
37
38
39 143 exposure versus the lowest exposure or reference group), were pooled separately for each food
40
41 144 source of fructose-containing sugars using the generic inverse variance method with DerSimonian and
42
43
44 145 Laird random effects models and expressed as RRs with 95% CI. To overcome a unit-of-analysis error
45
46 146 for studies appearing more than once in the same analysis, we divided participants equally among the
47
48
49 147 multiple comparisons and readjusted the log-standard errors [8]. Inter-study heterogeneity was
50
51 148 assessed with the Cochran Q statistic with significance set at $p < 0.10$ and quantified with the I^2
52
53 149 statistic, where $I^2 \geq 50\%$ represented evidence of substantial heterogeneity [8]. Interaction between
54
55
56 150 food sources was assessed using Cochran Q statistic for between group interaction. We explored

1
2 151 sources of heterogeneity by sensitivity analyses. Influence analyses, where each study was
3
4 152 systematically removed, and effect size was recalculated in the remaining studies, were carried out to
5
6
7 153 explore the influence of individual studies on the pooled risk. As ≥ 10 cohort comparisons were not
8
9 154 available, *a priori* subgroup analyses were not performed. Linear and non-linear dose-response
10
11 155 analyses were assessed using generalized least squares trend estimation models (GLST) and fixed-
12
13
14 156 effects restricted cubic spline model with 3 knots, respectively [12]. Publication bias was not assessed
15
16
17 157 as the number of cohort comparisons was less than 10.
18

21 159 **Grading of the evidence**

24 160 The overall certainty and the strength of the evidence was assessed using the Grading of
25
26 161 Recommendations Assessment, Development and Evaluation (GRADE) system [13-25]. The evidence
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28
29 162 was graded as high, moderate, low, or very low certainty, with observational studies starting with an
30
31 163 initial grade of 'low'. This then can be downgraded based on 5 pre-specified criteria or upgraded
32
33
34 164 based on 3 pre-specified criteria. Criteria to downgrade included risk of bias (weight of studies
35
36 165 showed risk of bias as assessed by low NOS < 6), inconsistency (substantial unexplained inter-study
37
38
39 166 heterogeneity i.e. $I^2 > 50\%$), indirectness (presence of factors that limit the generalizability of the
40
41 167 results), imprecision in the pooled risk estimate (the 95% CI for risk estimates are wide or cross a
42
43
44 168 minimally important difference of 10% for benefit or harm (RR 0.9–1.1)), and publication bias
45
46 169 (evidence of small-study effect). Conversely, criteria to upgrade included a large magnitude of effect
47
48 170 (RR > 2 or RR < 0.5 in the absence of plausible confounders), dose–response gradient or reasonable
49
50
51 171 evidence of attenuation of the pooled effect estimate by confounders.
52

53 172 **Patient and public involvement**

1
2 174 The study was performed using published data. No patients or the public were involved in the study.
3

4 175

7 176 RESULTS

9 177 Search results

11
12 178 **Figure 1** shows the flow of the systematic search and study selection. Of the 309 reports identified by
13
14 179 the literature search, three reports with data from three prospective cohort studies met our inclusion
15
16 180 criteria [26-28]: Nurses' Health Study (NHS) [27], Health Professionals Follow-up Study (HPFS) [26] and
17
18
19 181 the National Runner's Health Study [28]. All three reports reported the association of food sources of
20
21 182 fructose-containing sugars on incident gout, but none on incident hyperuricemia. These reports
22
23
24 183 involved a total of 154,289 participants with 1,761 incident cases of gout. Two reports each reported
25
26 184 data on fruit intake [n= 75,383; 983 cases] [26, 28], fruit juice [n= 125,299; 1,533 cases] [26, 27] and
27
28
29 185 SSBs [n=125,299; 983 cases] [26, 27]. We did not identify prospective cohort studies reporting the
30
31 186 association of other food sources of fructose-containing sugars (e.g. cereal grain and grain-based
32
33
34 187 products, sweets and desserts, dairy and dairy based products and chocolate) with incident gout
35
36 188 fitting our inclusion criteria.
37

38
39 189

41 190 Study characteristics

42
43 191 **Table 1** lists the characteristics of the included prospective cohort studies. All studies were performed
44
45
46 192 in the USA. The median age of the included participants ranged from 30 to 75 years. The median
47
48 193 follow-up period was 17 years (range, 12 to 22 years) for SSB, 18.7 years (12 to 22 years) for fruit juice
49
50
51 194 and 9.9 years (7.74 to 12 years) for fruit. Dietary intake assessments were done with self-reported,
52
53 195 validated food frequency questionnaires (FFQs) in all studies. Quantiles of exposure depended on the
54
55
56 196 food source. Medians for the lowest and highest quantiles of exposure were <1 servings/month and

1
2 197 ≥14 servings/week respectively for SSB; ≤1 servings/month and ≥14 servings/week respectively for
3
4 198 fruit juice; and ≤0.4 servings/week (range, <0-0.5 servings/week) and ≥8 servings/day (range, ≥2-14
5
6
7 199 servings/day), respectively for fruit. The ascertainment of incident gout in both HPFS and NHS cohorts
8
9 200 [26, 27] was through self-report, followed by supplementary surveys of the subjects based on the
10
11
12 201 American College of Rheumatology gout survey criteria [29] to confirm that the diagnosis. The authors
13
14 202 defined individuals with gout that met ≥6 of the 11 criteria for gout. In addition, in a sub-sample the
15
16
17 203 self-reported diagnoses were validated with medical records. As for the NRHS cohort [28], incident
18
19 204 gout was self-reported based upon physician diagnosis.
20
21
22 205

23
24 206 **Supplementary table 2** shows the complete list of adjusted confounding variables for the most
25
26 207 adjusted models for each of the included prospective cohorts. The median number of variables in the
27
28
29 208 most adjusted models was 14 (range, 6 to 14). All studies adjusted for primary and secondary
30
31 209 confounders such as age, body mass index (BMI) and history of hypertension. Each of the three
32
33
34 210 cohorts were single-sex studies, so adjustment for sex was not necessary. The NHS cohort study
35
36 211 authored by Choi *et al.* 2010 [27] and NRHS study by Williams *et al.* [28] were agency funded, while
37
38
39 212 the HPFS paper authored by Choi *et al.* 2008 [26] was funded by both agency and industry.
40

41 213 42 43 214 **Study Quality**

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45
46 215 **Supplementary table 3** shows the study quality assessments by the NOS scale. There was no evidence
47
48 216 of serious risk of bias. Only NRHS cohort scored <6 on the NOS scale, which denotes lower quality
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50
51 217 [28].
52

53 218 54 55 219 **Fruit intake on incident gout**

1
2 220 **Figure 2** shows the relationship between food sources of fructose-containing sugars intake and
3
4 221 incident gout. There was significant interaction between the food sources ($p=0.02$). When comparing
5
6
7 222 the highest to the lowest fruit intake, no association was shown for fruit intake on incident gout (RR =
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9 223 0.85, [95% CI 0.63 to 1.14]). There was evidence of significant interstudy heterogeneity ($I^2 = 93\%$,
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11
12 224 $p<0.001$).

13 14 225 15 16 226 **Fruit juice intake on incident gout**

17
18
19 227 **Figure 2** shows the relationship between fruit juice intake and incident gout. When comparing the
20
21
22 228 highest to lowest intake, an adverse association was shown for fruit juice intake on incident gout (RR
23
24 229 1.77, [95% CI 1.20 to 2.61]). There was no evidence of significant interstudy heterogeneity ($I^2 = 0\%$
25
26 230 [95% CI 0% to 90%], $p = 0.54$).

27 28 29 231 30 31 232 **SSB intake on incident gout**

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33
34 233 **Figure 2** shows the relationship between SSB intake and incident gout. When comparing the highest
35
36 234 with the lowest intake, an adverse association was shown for SSB intake on incident gout (RR=2.08
37
38
39 235 [95% CI 1.40 to 3.08]). There was no evidence of significant interstudy heterogeneity ($I^2 = 0\%$, $p =$
40
41 236 0.52).

42 43 237 44 45 46 238 **Additional analysis**

47
48 239 Influence analysis (the systematic removal of each study), publication bias and subgroup analyses
49
50
51 240 could not be performed due to the small number of studies included in each analysis ($n=2$).

52 53 241 54 55 56 242 **Dose-response analysis**

1
2 243 A random-effect GLST model showed a significant dose-response relationship between fruit juice
3
4 244 intake and incident gout per serving/week (RR = 1.03, 95% CI 1.02 to 1.05, $p < 0.001$) (**supplementary**
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6
7 245 **figure 1**), and for SSB intake (RR = 1.04, 95% CI 1.02 to 1.07, $p < 0.001$) (**supplementary figure 2**). Fruit
8
9 246 juice intake showed a significant departure from linearity ($p = 0.038$), and visual inspection of the
10
11
12 247 graph (**supplementary figure 1**) indicated a plateau for risk increase after ≥ 5 servings per day. There
13
14 248 was no evidence for departure from linear dose response gradient or dose thresholds for SSB intake
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16
17 249 while using the restricted cubic spline model ($p = 1.29$) (**supplementary figure 2**). Dose-response
18
19 250 modeling was not conducted for fruit intake due to lack of data.
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21
22 251

24 252 **GRADE assessment**

25
26 253 **Table 2** shows the GRADE assessment of individual food sources of fructose-containing sugars. The
27
28
29 254 certainty of the evidence for an adverse association from both fruit and fruit juice was rated as very
30
31 255 low, with downgrades to the lowest level for indirectness for fruit juice intake, and for inconsistency,
32
33
34 256 indirectness and imprecision for fruit intake. The certainty of the evidence for an adverse association
35
36 257 of SSB intake with incident gout was rated as moderate, with a downgrade of one level for
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39 258 indirectness but upgrade of two levels for a large magnitude effect and significant dose-response
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41 259 association.
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44 260

46 261 **DISCUSSION**

47
48 262 We conducted a systematic review and meta-analysis of studies investigating the relation of
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51 263 important food sources of fructose-containing sugars with incident gout. We identified three
52
53 264 prospective cohort studies [26-28] comprising of 154,289 participants and 1,761 cases of incident
54
55
56 265 gout. The pooled analyses revealed that there was a moderate certainty of evidence that SSB intake
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1
2 266 was associated with 208% increase in risk of incident gout when comparing the highest with the
3
4 267 lowest intake. Similarly, there was a low certainty of evidence that fruit juice intake was associated
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6
7 268 with a 77% increase in risk of incident gout, but fruit intake did not show any significant association
8
9 269 with incident gout (low certainty of evidence). There was no data available of other important food
10
11
12 270 sources of fructose-containing sugars.

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16 272 **Findings in the context of the literature**

18
19 273 Our results are consistent with previous research which indicate that the intake of certain food
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21
22 274 sources of fructose-containing sugars is associated with the risk of gout. Our previous systematic
23
24 275 review and meta-analysis of prospective cohort studies found a harmful relationship between
25
26 276 fructose consumption and gout [6]. While that study indicated that fructose moiety might possibly
27
28
29 277 drive the association with gout, all the fructose data in the included studies was derived from SSB
30
31 278 intake. Another systematic review of the literature identified numerous dietary factors associated
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34 279 with the risk of gout including meat, alcohol, seafood and SSBs, but also that lower risk was associated
35
36 280 with the intake of dairy, folate and coffee [3].

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41 282 SSBs are a major source of fructose-containing added sugars in the western diet comprising around
42
43
44 283 30% of intake of added sugars in the USA [30] and around 24% in Canada [31]. Excess intake of
45
46 284 fructose can increase uric acid through an unregulated phosphofructose kinase pathway that uses
47
48 285 substantial amounts of ATP [32] to convert fructose into fructose-1-phosphate in the liver [33].
49
50
51 286 Mechanistically, net ATP degradation leads to accumulation of AMP, which is subsequently degraded
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53 287 to uric acid. Additionally, fructose can increase de novo purine synthesis, which further produces uric
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55
56 288 acid [1]. This increase in uric acid can lead to the development of gout. Since we were unable to

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1
2 289 investigate the relationship between food sources of fructose-containing sugars and hyperuricemia,
3
4 290 we cannot validate this mechanism. It is possible, that fructose increases the risk of gout
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6
7 291 independently of serum uric acid levels. However, since the link between fructose and serum uric acid
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9 292 [34-37], and the link between serum uric acid and the development of gout have been independently
10
11 293 established [1], it is unlikely that fructose increases the risk of gout without using uric acid as an
12
13
14 294 intermediate.

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16 295
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18
19 296 We identified adverse association of fruit juices intake with incident gout. The two studies that
20
21 297 contributed to this result [26, 27] were both performed in two Harvard cohorts which do not
22
23
24 298 differentiate between fruit drinks and pure fruit juice, the former being largely similar to SSBs i.e.
25
26 299 mainly sugar and water. This difference between pure fruit juice and fruit drink is supported by
27
28
29 300 studies investigating pure fruit juice and fruit drinks that show divergent response for cardiometabolic
30
31 301 disease [38, 39].

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33 302
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35
36 303 We did not see any association between fruit intake and incident gout but the individual effect
37
38 304 estimates from the two studies were in opposite direction. The NRHS [28] cohort showed a 51%
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40
41 305 reduction in the risk of gout with high intake of fruit whereas the HPFS [26] cohort showed a 63%
42
43 306 increased risk; both studies were performed in men. These discordant results highlight the differences
44
45
46 307 in the studies. HPFS cohort [26] only measured oranges and apples, fruit high in fructose, while NRHS
47
48 308 [28] cohort assessed all fruit which might represent a healthier dietary intake. It is also possible that
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50
51 309 higher intake of fruits in NRHS might be associated with high intake of dairy or coffee, which have
52
53 310 been associated with lowering the risk of gout [3]. As the data on dairy and coffee was not reported
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55
56 311 by NRHS, this remains a speculation. The harmful association for oranges, which are rich in vitamin C,

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2 312 in HPFS [26] cohort is at odds with another study from the same cohort, in which the authors
3
4 313 demonstrated a protective association of vitamin C intake with gout [40]. While fruits are rich in
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6
7 314 fructose which can increase uric acid levels, fruit intake has consistently shown a benefit for
8
9 315 cardiometabolic risk factors, cardiometabolic diseases and all cause-mortality [41-47]. Several case-
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11
12 316 control and cross-sectional studies have shown a protective effect of total fruit intake with gout albeit
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14 317 only in Asian populations [48, 49], their relevance to the included studies, conducted in a largely
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16
17 318 Caucasian population, might be limited. More data from different populations might clarify the
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19 319 association between fruit intake and gout.

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23
24 321 We could not find any prospective studies looking at the association of food sources of fructose-
25
26 322 containing sugars and hyperuricemia even though hyperuricemia is the most important risk factor for
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28
29 323 gout [3, 50]. Hyperuricemia is also a risk factor for hypertension , metabolic syndrome, diabetes , and
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31 324 CVD [51]. Several cross-sectional analyses have investigated the link between SSB consumption and
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33
34 325 serum uric acid levels, showing a positive relationship [34-37]. In contrast, the analysis of the National
35
36 326 Health and Nutrition Examination Survey (NHANES) showed no link between dietary fructose and risk
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38
39 327 of hyperuricemia, indicating that perhaps different food sources of fructose-containing sugars may
40
41 328 have different effects on serum uric acid. This point is reinforced by another analysis of NHANES data
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43
44 329 that showed a relationship of SSB intake with higher serum uric acid concentration, but not with fruit
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46 330 juice [52]. Future studies investigating food sources of sugars and risk of hyperuricemia may help to
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48 331 elucidate some of the above inconsistent findings.

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53 333 We were not been able to find prospective cohort studies investigating the association of other food
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56 334 sources of fructose-containing sugars and the risk of gout though cross-sectional studies suggest that

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2 335 cereal and yogurt may be associated with lower serum uric acid [53]. More research is needed to
3
4 336 assess the relationship between other food sources of fructose-containing sugars and the risk of gout.
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7 337
8
9 338 **Strengths and limitations**
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11
12 339 Our analysis has many strengths. First, we employed a comprehensive systematic search across major
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14 340 databases and the quantitative synthesis of results. Second, the studies we included had a substantial
15
16 341 number of participants and cases of gout (154,289 participants and 1,761 gout cases) providing
17
18 342 increased precision. Additionally, the median follow-up duration was greater than 10 years, which
19
20 343 allowed for enough time from exposure for the development of disease. Another strength is the use
21
22 344 of validated measures of intake like food frequency questionnaires. The two Harvard cohorts [26, 27]
23
24 345 administered FFQ multiple times, and validated them on a subsample, allowing for more accurate and
25
26 346 robust long-term intakes compared to the NRHS [28] cohort, which only measured dietary intakes at
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28 347 baseline. In our analysis, we made use of GRADE to evaluate the certainty and strength of our analysis
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30 348 and evaluate our confidence in the estimates.
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37
38 350 There are some notable limitations to our systematic review and meta-analysis. First, while we
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40 351 included the most adjusted multivariable models for this analysis, there is always potential for
41
42 352 unmeasured and residual confounding, since the studies included were observational in nature. This
43
44 353 explains why GRADE starts at “low certainty” for observational studies. Second, there was evidence of
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46 354 indirectness in some of the relationships. All studies were conducted in the USA, and two of the three
47
48 355 studies were conducted in health professionals. The two Harvard [26, 27] cohorts included only
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50 356 middle aged or older people who worked in health care and who were predominately white and the
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52 357 NRHS [28] cohort included only middle to old aged physically active men. Thus, the specific nature of
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1
2 358 the included studies' population limits the generalizability of our results to other populations and
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4 359 geographical locations; however, the biological process of diet and gout are still likely to be similar to
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6
7 360 other populations. While, genome wide association studies have found numerous genes that increase
8
9 361 one's risk for gout [54] and some ethnic groups may be more susceptible than others [1], it is not
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11
12 362 known if the association of fructose intake with gout is modified by genes. Third, sources of
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14 363 heterogeneity remained unexplained; with only three studies, we were unable to assess publication
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16
17 364 bias or perform sensitivity analysis though an a priori subgroup analysis. Thus, for these reasons, data
18
19 365 pertaining to SSB and fruit juice intake and incident gout received a GRADE of moderate and very low
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21
22 366 certainty, respectively, indicating that further studies in this regard is likely to impact our certainty in
23
24 367 the effect estimate and may change the estimate for SSB and that our certainty in the estimate for
25
26 368 fruit juice is very uncertain; therefore, caution should be used when interpreting these results.
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29 369 Similarly, for fruit, which received a GRADE of very low, so we are very uncertain in these results and
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31 370 caution should be used in the interpretation of these results.
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34 371 35 36 372 **Implications**

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38
39 373 Dietary guidelines have shifted their focus from nutrient-based recommendations to food and dietary
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41 374 pattern-based recommendations [55], since it has been recognized that one does not eat nutrients in
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44 375 isolation but as a part of foods. Interactions between nutrients in food are complex and the whole
45
46 376 food matrix works as a whole to increase or decrease disease risk [55]. Our findings support this view
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48 377 of food matrix affect independent of a single-nutrient in relation to food sources of fructose-
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50
51 378 containing sugars and their relationship with gout.
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1
2 380 Our findings also have implications for recommendations for the prevention of gout. Conventional
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4 381 dietary recommendations for gout have focused on restriction of purine intake; however, low-purine
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6
7 382 diets are often high in carbohydrates, including fructose-rich foods [56]. We have shown an adverse
8
9 383 association between fruit juice and SSBs, supporting the recommendations to limit their intakes. Since
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11
12 384 we did not have data relating to children, hyperuricemia or other food sources of fructose-containing
13
14 385 sugars, we cannot extend our conclusion to these groups of individuals or these foods.
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17 386

19 387 **Conclusion**

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22 388 Our systematic review and meta-analysis of prospective cohort studies showed an adverse association
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24 389 between SSBs and fruit juice with the risk of gout, while there was no association with fruit intake.

25
26 390 The strength of the evidence was moderate for SSB intake and very low for fruit juice and fruit intake,
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29 391 as assessed by GRADE. For SSBs, the true association is likely to be close to the estimate, but there is a
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31 392 possibility that it is substantially different. For fruit juice and fruit intake, the true association are likely
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33
34 393 to be substantially different from the estimate and future research will very likely impact our
35
36 394 confidence in the effect estimates and likely to change them [57]. Our results are consistent with the
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38
39 395 literature that certain food sources of fructose-containing sugars especially SSBs are a risk factor for
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41 396 the development of gout. We were unable to identify studies assessing food sources of fructose-
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43
44 397 containing sugars and hyperuricemia, indicating a gap in the literature. Given that incident gout is
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46 398 rising in many countries [7, 58-63], and that gout and hyperuricemia are both associated with
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48
49 399 metabolic syndrome, myocardial infarction, diabetes and premature death [1, 2, 64], it is becoming
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51 400 increasingly important to identify and understand risk factors for developing gout. It is imperative for
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53 401 additional prospective studies to assess the intake of various food sources of fructose-containing
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56 402 sugars and their relationship with gout and hyperuricemia in diverse populations. This will help
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1
2 403 identify to what extent does our foods mediate the risk for hyperuricemia and gout and will further
3
4 404 inform health care professionals, policymakers, and aid in the development of improved dietary
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6
7 405 guidelines for the prevention and management of gout and hyperuricemia.
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10 406

11 12 407 **Funding Statement**

13
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15
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17
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22
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27
28
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30
31 415 aspect of the present study, including design and conduct of the study; collection, management,
32
33
34 416 analysis, and interpretation of the data; and preparation, review, approval of the manuscript or
35
36 417 decision to publish.
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40 41 419 **Data Sharing**

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43 420 There is no additional unpublished data available from the study.
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48 422 **Competing Interests**

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50
51 423 **TA Khan** has received research support from the Canadian Institutes of health Research (CIHR), an
52
53 424 unrestricted travel donation from Bee Maid Honey Ltd and has been an invited speaker at the Calorie
54
55
56 425 Control Council annual meeting. **RJ de Souza** has served as an external resource person to the World
57
58

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2 426 Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and
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4 427 Health (guidelines for trans fats and saturated fats), and received remuneration from WHO for travel
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37
38
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40
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44 443 European Association for the Study of Diabetes (EASD). He is a member of the International
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46 444 Carbohydrate Quality Consortium (ICQC), Secretary of the Diabetes and Nutrition Study Group (DNSG)
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48
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18
19 456 hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle. He is a
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21
22 457 member of the European Fruit Juice Association Scientific Expert Panel. He is on the Clinical Practice
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24 458 Guidelines Expert Committees of the CDA, European Association for the study of Diabetes (EASD), and
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27 459 Canadian Cardiovascular Society (CCS), as well as an expert writing panel of the ASN. He serves as an
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29 460 unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical
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34 462 member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of
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38
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46 467

48 468 **Authors' contributions**

50 469 All authors had full access to all of the data (including statistical reports and tables) in this study and
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52 470 take full responsibility for the integrity of the data and the accuracy of the data analysis.

54 471 **Conception and design:** J.L. Sievenpiper.

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24 484 **Guarantor:** J.L. Sievenpiper

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2 639 **TABLES AND FIGURES**
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6 641 **Figure 1** Summary of evidence search and selection. Flow of the literature search for the effect of food
7 642 sources of sugar intake on incident gout and hyperuricemia. Of the 309 studies initially identified, 294
8 643 were excluded based on title and/or abstract. The remainder were read in full by two independent
9 644 reviewers; after, 12 were further excluded. Included in this analysis were three prospective cohort
10 645 studies.
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15 647 **Figure 2** Relation between intake of fruit, fruit juice and SSB incident gout. Estimates from most-
16 648 adjusted multivariate models accounting for food sources of fructose-containing sugars intake were
17 649 used. The diamond represents the pooled effect estimate. Interstudy heterogeneity was tested using
18 650 the Cochran Q statistic and quantified using the I^2 statistic ($I^2 \geq 50\%$ indicative of significant
19 651 heterogeneity). All results are presented as RR with 95% CI. OJ = orange juice. Other = other fruit juices.
20 652 * The number of cases and participants are divided equally between the multiple entries of the study
21 653 to ensure total count gives unique individuals. To overcome a unit-of-analysis error for studies
22 654 appearing more than once in the same analysis, we readjusted the log-standard errors to participants
23 655 equally among the multiple comparisons and.
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Table 1 Characteristics of prospective cohort studies investigating food sources of fructose-containing sugar intake and incident gout.

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

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

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

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

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

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

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

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

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2 689 ⁴Upgrade for a dose response gradient, as the GLST dose-response analysis revealed a significant linear relationship between sugar
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4 690 sweetened beverage intake and incident gout (P=0.0001).

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6 691 ⁵Downgrade for very serious inconsistency, as the two studies included had opposite associations and there was evidence of substantial
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8 692 inter-study heterogeneity ($I^2=94%$, $p<0.0001$). Due to the small number of studies included in the analysis, subgroup analysis was not
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10 693 performed.

11 694 ⁶Downgrade for serious imprecision, as the lower bound of the 95% CI (RR, 0.27) includes clinically important benefit (RR<0.9), while the
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13 695 upper bound of the 95% CI (RR, 2.87) crosses the minimally important difference of 10% (RR>1.1).
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Figure 1 Summary of evidence search and selection

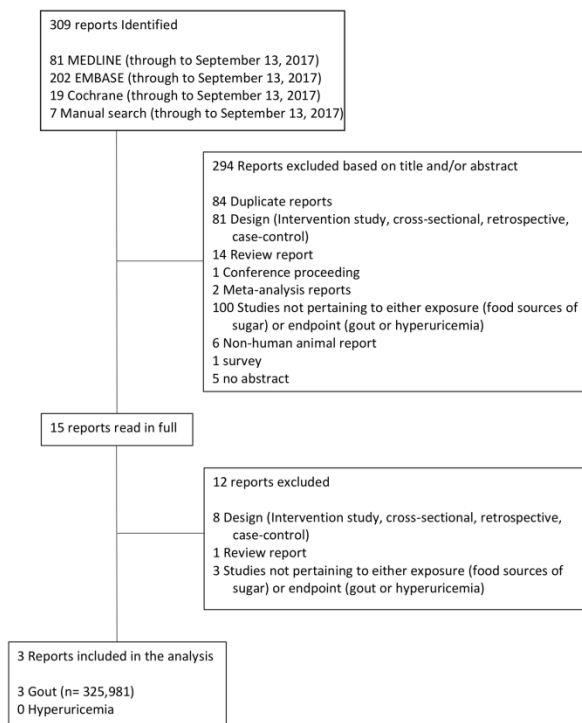


Figure 1 Summary of evidence search and selection

215x279mm (300 x 300 DPI)

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

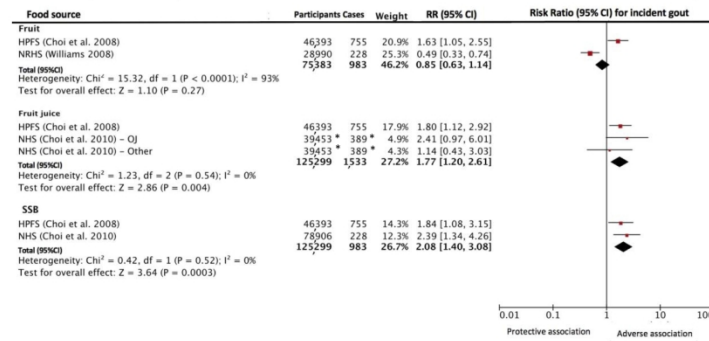


Figure 2 Relation between intake of fruit, fruit juice and SSB incident gout.

215x279mm (300 x 300 DPI)

Supplementary material**SUPPLEMENTARY TABLES****Supplementary table 1** Search terms**Supplementary table 2** Analysis of confounding variables among 3 studies of food sources of sugar intake and incident gout**Supplementary table 3** Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies**SUPPLEMENTARY FIGURES****Supplementary figure 1** Linear and non-linear dose-response relationship between fruit juice intake and incident gout per serving/week**Supplementary figure 2** Linear and non-linear dose-response relationship between SSB intake and incident gout per serving/week**Supplementary table 1.** Search terms

Database and search terms**MEDLINE**

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

EMBASE

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

Cochrane

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

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3 56. hyperuricemia*.mp. 56. hyperuricemia*.mp. 56. uric.mp
4 57. hyperuricemia/ 57. hyperuricemia/ 57. or/1-43
5 58. hyperuricaemia*.mp. 58. hyperuricaemia*.mp. 58. or/44-49
6 59. uric.mp. 59. uric.mp. 59. or/50-56
7 60. or/1-44 60. or/1-45 60. and/57-59
8 61. or/45-52 61. or/46-52
9 62. or/53-59 62. or/53-59
10 63. and/60-62 63. and/60-62

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

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18 For all databases, the original search was September 13, 2017.
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Supplementary table 2. Analysis of confounding variables among 3 studies of food sources of sugar intake and incident gout

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

HPFS=Health Professionals Follow-Up Study, NHS=Nurses Health Study

*Denotes confounders measured only at baseline years.

† Indicates confounders measured every 2 years.

‡ Indicates the study includes only female subjects

§ Indicates the study includes only male subjects

∇ Indicates the confounder was present in some, but not all, models.

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

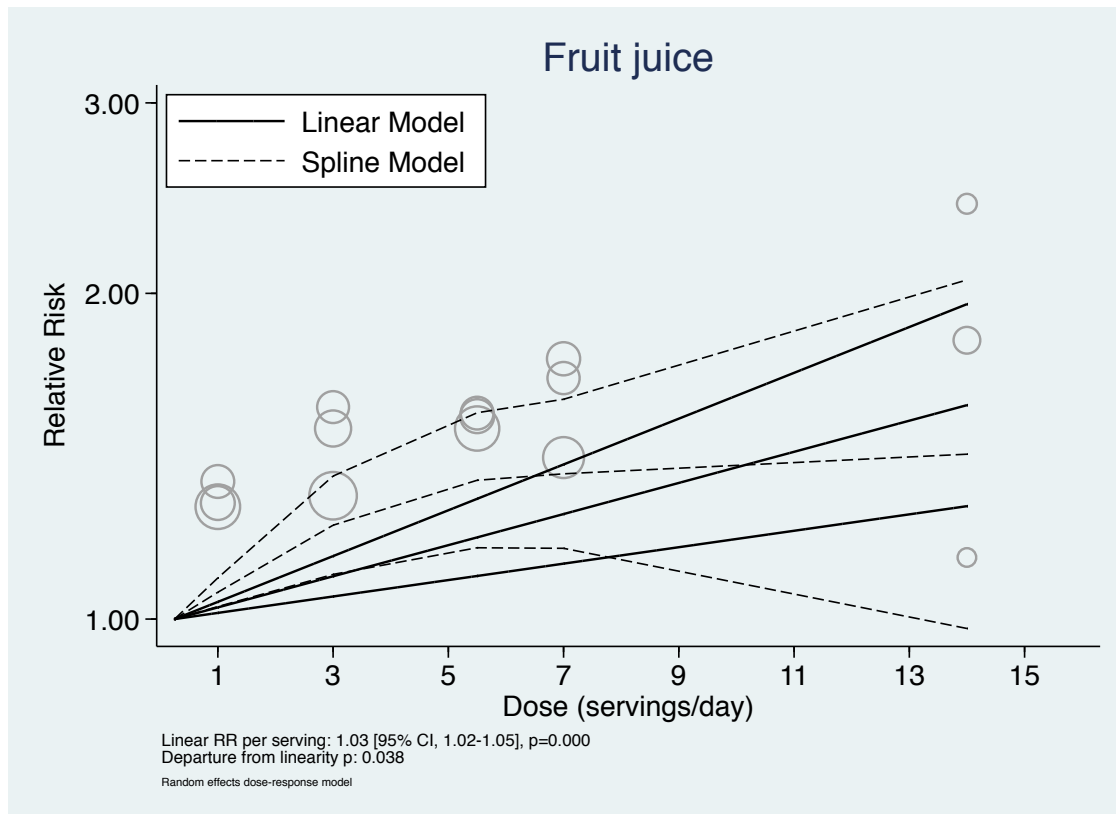
Study	Selection*	Outcome†	Comparability‡	total§
Choi <i>et al.</i> , 2008	2	3	1	6
Williams, 2008	2	2	1	5
Choi <i>et al.</i> , 2010	2	3	1	6

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, exposure assessment and demonstration outcome not present at baseline.

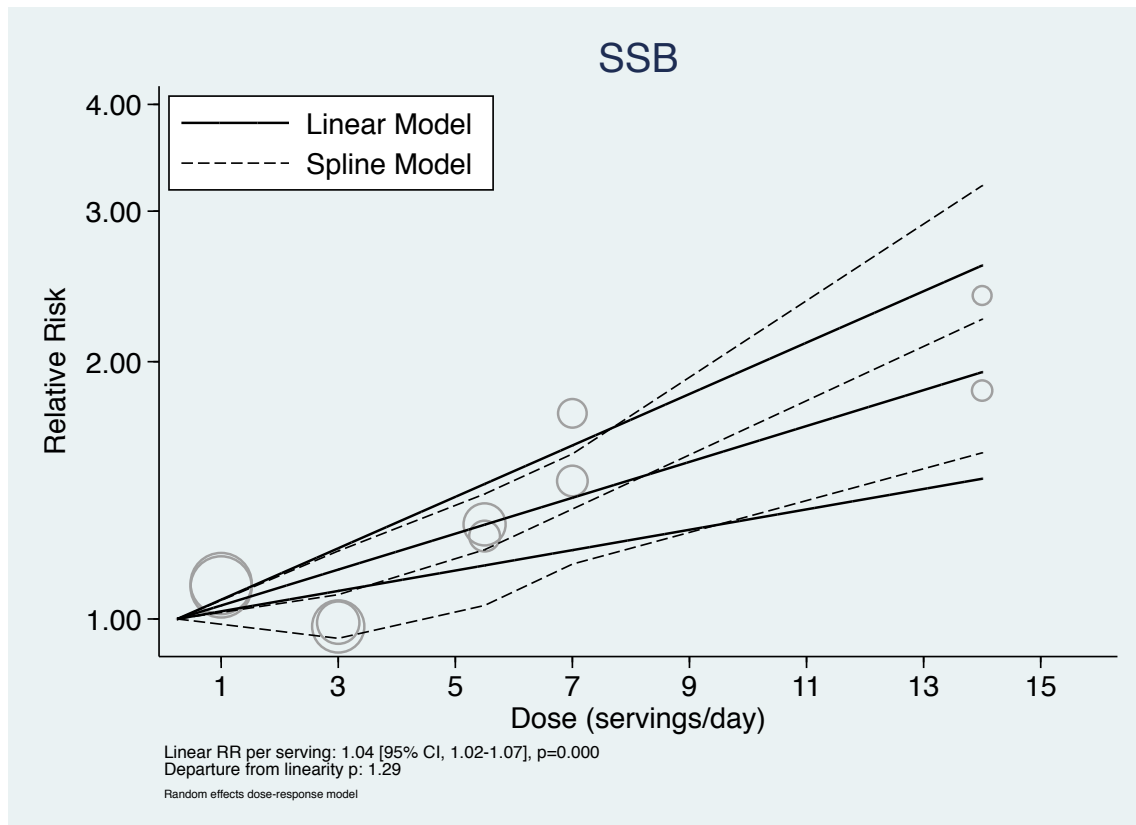
†Maximum 3 points awarded for follow-up length, adequacy of follow-up and outcome assessment.

‡Maximum 2 points awarded for controlling for the pre-specified primary confounding variable (age) and >6 of the secondary confounding variables (sex, body mass index, history of gout or hyperuricemia, diabetes, alcohol, physical activity, lipid medication/dyslipidemia, animal protein intake, hypertension or blood pressure medication including diuretics).

§A maximum of 9 points could be awarded.



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



28 **Supplementary figure 2.** Linear and non-linear dose-response relationship between SSB intake and
29 incident gout per serving/week. Linear dose response data (solid lines) were modeled using the
30 generalized least squares trend estimation models (GLST). Non-linear dose response data (dashed lines)
31 were modeled with fixed-effects restricted cubic spline models with 3 knots. 95% confidence interval
32 for the fitted trend are shown above and below the solid line. Each study was centered to its own
33 baseline reference dose when estimating increasing dose risk.
34

MOOSE Checklist for Meta-analyses of Observational Studies

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

28	Indication of statistical uncertainty of findings	11, table 2
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Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	10, 16
30	Justification for exclusion (eg, exclusion of non-English language citations)	5
31	Assessment of quality of included studies	16
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	11-17
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 17
34	Guidelines for future research	16, 17
35	Disclosure of funding source	17, 18

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