Important Food Sources of Fructose-Containing Sugars and Incident Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies

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Background—Sugar-sweetened beverages are associated with hypertension. We assessed the relation of important food sources of fructose-containing sugars with incident hypertension using a systematic review and meta-analysis of prospective cohort studies.

Methods and Results—We searched MEDLINE, EMBASE, and Cochrane (through December week 2, 2018) for eligible studies. For each food source, natural log-transformed risk ratios (RRs) for incident hypertension were pooled using pair-wise meta-analysis and linear and nonlinear dose-response meta-analyses. Certainty in our evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation. We identified 26 reports, including 15 prospective cohorts (930 677 participants; 363 459 cases). Sugar-sweetened beverages showed harmful ($RR_{per\text{-}355\text{-}mL}$, 1.10 [95% CI, 1.08, 1.12]) whereas fruit ($RR_{per\text{-}240\text{-}g}$, 0.94 [95% CI, 0.96, 0.99]) and yogurt showed protective associations ($RR_{per\text{-}125\text{-}g}$, 0.95 [95% CI, 0.94, 0.97]) with incident hypertension throughout the dose range. One hundred percent fruit juice showed a protective association only at moderate doses ($RR_{at\text{-}100\text{-}mL}$, 0.97 [95% CI, 0.94, 0.99]). The pair-wise protective association of dairy desserts was not supported by linear dose-response analysis. Fruit drinks or sweet snacks were not associated with hypertension. Certainty of the evidence was "low" for sugar-sweetened beverages, 100% fruit juice, fruit, and yogurt and "very low" for fruit drinks, sweet snacks, and dairy desserts.

Conclusions—The harmful association between sugar-sweetened beverages and hypertension does not extend to other important food sources of fructose-containing sugars. Further research is needed to improve our estimates and better understand the dose-response relationship between food sources of fructose-containing sugars and hypertension.

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Key Words: dairy • fruit • fruit juice • hypertension • SSBs • yogurt

Hypertension is a major risk factor for developing cardiovascular disease (coronary heart disease and stroke).[1] The global prevalence of hypertension has been increasing in the past decades.[2] The World Health Organization attributes the increasing prevalence of hypertension to certain individual behavioural risk factors, including unhealthy dietary choices.[2] Fructose and fructose-containing sugars have been implicated as a dietary contributor to the development of hypertension.[3–5] The suggested mechanism is thought to involve uric acid, whereby high intakes of

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Accompanying Data S1, S2, Tables S1 through S6, and Figures S1 through S13 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010977

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Clinical Perspective

What Is New?

- Fructose intake is purported to elevate blood pressure.
- Dietary guidelines and public health policy are moving from nutrient- to food- and dietary pattern–based recommendations.
- We examined the relation of important food sources of fructose-containing sugars with incident hypertension.

What Are the Clinical Implications?

- We identified the following associations of food intake with incident hypertension: harmful: sugar-sweetened beverages; protective: fruit, yogurt, and 100% fruit juice (moderate dose only); and no association: dairy desserts, fruit drinks, and sweet snacks.
- Overall, this systematic review and meta-analysis of 26 reports, including 15 unique prospective cohorts, showed that only sugar-sweetened beverages as a food source of fructose-containing sugars have a harmful association with incident hypertension.

fructose raise uric acid, which, in turn, activates the renin-angiotensin system and inhibits the nitric oxide system, leading to hypertension.[4–6]

Sugar-sweetened beverages (SSBs) are a major source of fructose in the North American diet.[7] Although systematic reviews and meta-analyses of prospective cohort studies have shown a consistent association between SSBs and incident hypertension,[8] the same has not been shown for the fructose-containing sugars they contain independent of food form, both in prospective cohort studies and in controlled feeding trials.[9,10] It is also unclear whether the association observed for SSBs holds for other important food sources of fructose-containing sugars, such as fruit and fruit-based products, grains and grain-based products, dairy and dairy-based products, and sweets and desserts. As dietary guidelines and public health policy move from nutrient-based recommendations toward food- and dietary pattern–based recommendations,[11–13] it is important to understand the contribution of these different food sources of sugars to the risk of hypertension. To address this gap, we conducted a systematic review and meta-analysis of prospective cohort studies of the relation of important food sources of fructose-containing sugars and incident hypertension.

Methods

The authors declare that the methods have been made publicly available with the registered study protocol (ClinicalTrials.gov; identifier, NCT02702375), and that all supporting data are available within the article and the online Supporting Information.

Design

We followed the *Cochrane Handbook for Systematic Reviews of Interventions*[14] for the conduct of our systematic review and meta-analysis and reported our results according to the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15,16]

Search Strategy

We conducted systematic searches in MEDLINE, EMBASE, and Cochrane Library databases through December 13, 2018 with no language restriction (Table S1). Targeted manual searches served to supplement database searches; these included finding related articles from references of review articles, perusing articles with data from major prospective cohorts that usually report dietary data and speaking to experts in the field. Our search terms reflect the most-consumed food sources of fructose-containing sugars in the North American diet[17,18] (eg, "fructose," "sugar-sweetened beverage," "fruit," "yogurt," "ice cream," and "sweets") as well as our study design (eg, "prospective study") and outcome of interest (eg, "hypertension").

Study Selection

We included all prospective cohort studies of ≥1 year duration that assessed the association of important food sources of fructose-containing sugars, including nonalcoholic beverages (eg, SSBs), grain and grain-based products, fruit and fruit-based products, dairy and dairy-based products, and sweets and desserts with incident hypertension in participants free of hypertension at the start of the study. If several studies provided results on the same outcome and used overlapping groups of individuals, we included the study with the longest follow-up. Abstracts and unpublished studies were not included.

Data Extraction

Two independent reviewers (Q.L., S.A.C.) extracted relevant data using a standardized proforma. The main outcome was incident hypertension expressed as risk ratios (RRs) with 95% CIs. Data on the amount of food source consumption, distribution of cases and person-years, and RRs and 95% CIs were extracted. Translation of articles published in languages other than English was done online or by colleagues fluent in the languages. Disagreements were

reconciled by consensus. Authors were contacted for missing data.

Risk of Bias

The same 2 independent reviewers (Q.L., S.A.C.) assessed each study for risk of bias using the Newcastle–Ottawa Scale (NOS) for prospective cohort studies.[19] NOS points were awarded based on cohort selection, adequacy of outcome measures, and comparability of cohorts regarding design or analysis.[19] A maximum of 9 points could have been awarded, with 6 points as a minimum threshold for the study to be considered higher quality.[12] Differences were resolved by consensus.

Statistical Analyses

Primary pooled pair-wise analyses were conducted using Review Manager (RevMan 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), whereas the dose-response meta-analyses, subgroup analyses, and publication bias analyses were performed using Stata software (version 15; StataCorp LP, College Station, TX). Each food source of fructose-containing sugar was considered as an exposure with incident hypertension as the outcome. We used the RR results from multivariable models with the most complete adjustment for potential confounders. Reported odds ratios and hazard ratios were considered an approximation of the RR.[20] We used natural log-transformed RRs and 95% CIs for all the analysis and reported results back in the original scale as RRs and 95% CIs. We used 3 separate meta-analysis methods to assess the association of each food source with hypertension.

We performed: (1) a pair-wise meta-analysis comparing highest- versus the lowest-dose categories separately for each food source of fructose-containing sugars using the DerSimonian–Laird random-effects model.[21] We used a fixed-effects model if the number of studies was $\leq$5.[22]

We performed (2) a fixed-effects dose-response meta-analysis to estimate linear and (3) nonlinear dose-relationships using the method of Greenland and Longnecker[23,24] as described by Orsini[25,26] and Crippa et al.[27] In this method, the RRs across all the dose categories of food sources and their 95% CIs are used to estimate the study-specific slope lines and combined to obtain an overall average slope, taking into account the correlation between summary estimates. The reason for using fixed effects was to minimize the undue influence of exaggerated results from extreme categories on the resulting study-specific slopes,[27] to calculate an estimate of heterogeneity using the equivalent 2-stage method, and to provide robust overall average estimates for the dose-response association without additional assumptions.[28]

For this analysis, dose was standardized to the same unit for each food source. If consumption was reported by servings per period of time, we converted it into grams or milliliters per day. We defined the assigned dose as the mean consumption in each category of food source. If the assigned doses were not reported, we approximated the mean dose for each category by using the midpoint of its lower and upper bounds. If the lowest-dose category of a study was open ended, we defined the lowest dose as 0. For open-ended upper categories, we took half of the adjacent category range to estimate the assigned dose. When cohort size or person-year per category was not available, categories were regarded equal in size, and follow-up and the case number per category was obtained by Bekkering's method.[29] For the nonlinear dose-response analysis, we fitted the model using restricted cubic splines with 3 knots at the 15th, 50th, and 85th distribution percentiles. If restricted cubic splines could not be calculated because of a limited number of observations, we fitted a second-order fractional polynomial curve to the data[26] and tested for goodness of fit of the model using the Akaike information criteria, deviance test (D), and the coefficient of determination (R^2) to select the best-fitting model.[30] We reported nonlinear associations as the main result for a study if the Wald test for departure from linearity was significant at $P<0.10$. RRs below 1 were considered as protective and above 1 as harmful associations.

For all 3 methods, interstudy heterogeneity was assessed using the Cochran Q (χ^2) statistic and quantified by the I^2 statistic, where $I^2 \geq 50\%$ and $P_Q<0.1$ represented evidence of substantial heterogeneity.[31,32] For dose-response meta-analyses, the I^2 and Cochrane Q statistics were estimated using the 2-stage method,[33] and, given that the P_Q had excessive power because of too many comparisons,[32] we multiplied it by the number of comparisons to equalize it with the P_Q from a pair-wise meta-analysis.

For the pair-wise meta-analysis, we explored sources of heterogeneity by sensitivity and subgroup analyses. Sensitivity analysis, in which each study was systematically removed, was carried out to explore the impact of individual studies on the pooled association estimates for each food source. If $\geq$10 cohort comparisons were available,[14] then a priori subgroup analyses were performed by meta-regression for follow-up (<10 years versus $\geq$10 years), sex (males versus females versus mixed), study quality (NOS<6 versus $\geq$6), age (<median versus $\geq$median), and funding source (agency versus industry versus mixed). As part of the sensitivity analysis, we also performed a pooled analysis of primary studies using extreme comparisons. If $\geq$10 cohort comparisons were available, then publication bias was assessed by visual inspection of funnel plot and statistical evaluation using the the Begg[34] and Egger[35] tests, with significance set at $P<0.10$. In the presence of publication bias, we used the Duval and Tweedie trim-and-

fill method to adjust for funnel-plot asymmetry by imputing missing study data.[36]

The STATA code for SSBs dose-response analysis is provided in Data S1, and dose-response raw data are provided in Data S2.

Grading of the Evidence

Overall quality and strength of the evidence at was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[37] Our certainty in the evidence was graded as "high," "moderate," "low," or "very low." Observational studies receive an initial grade of "low" and then can be down- or upgraded based on prespecified criteria. Criteria to downgrade included risk of bias (weight of studies show risk of bias as assessed by NOS<6), inconsistency (substantial unexplained interstudy heterogeneity, I^2>50%; P<0.10), indirectness (presence of factors that limit the generalizability of the results), imprecision in the pooled-risk estimate (the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for protection or harm [RR, 0.9–1.1]), and publication bias (evidence of small-study effects).[37] In contrast, criteria to upgrade included a large magnitude of effect (RR>2 or RR<0.5 in the absence of plausible confounders), dose-response gradient, and attenuation of the pooled-effect estimate by plausible confounders.[37]

Results

Search Results

Figure 1 shows the flow of the literature search. Of 3669 reports, 26 reports[38–63] with data from 15 unique prospective cohort studies met our inclusion criteria involving a total of 930 667 participants with 363 459 incident cases of hypertension. There were 13 cohort comparisons (427 630 participants [n]; 120 553 cases) for SSBs; 13 cohort comparisons (n=281 120; 148 928 cases) for fruit, 1 of which was from a case-cohort report; 9 cohort comparisons (n=235 705; 97 783 cases) for yogurt; 3 cohort comparisons (n=41 398; 12 106 cases) for dairy desserts; 2 cohort comparisons for 100% fruit juice (n=83 178; 46 811 cases); and 1 cohort comparison each for fruit drinks (n=424; 47 cases) and sweet snacks (n=439; 45 cases). Definitions of the food categories, as defined by the cohort studies, can be found in Table S2. We assumed that yogurt was a source of fructose, given that consumers prefer yogurt products with a moderate (≈7–10%) concentration of added sucrose.[64–66] We did not identify prospective cohort studies assessing the relation of grain and grain-based products or other fruit- or dairy-based products with incident hypertension. Two studies sent additional data that we could use.[56,57]

Study Characteristics

Table shows the characteristics of the included prospective cohort studies. Participants were from 7 countries, the majority from the United States, with a median age of 44 (range, 14–65) years. One cohort was conducted in children and teens (age range, 6–18 years),[43,53] 1 in young adults (age range, 18–30 years),[42,47] and the remaining 13 cohorts studies in general samples of adults. Median follow-up periods were 10 years (range, 3.6–28.0) for SSBs; 9 years (range, 4–26) for fruit; 14.6 years (range, 5–30) for yogurt; 10 years (range, 9–15) for dairy desserts; and 13.9 years (range, 7.8–20.0) for 100% fruit juice; and the follow-up period was 3.6 years for both fruit drinks and sweet snacks. Dietary intake assessments were performed with validated food frequency questionnaires in all studies. Intakes (rounded to the nearest 5) for SSBs, fruit, yogurt, dairy desserts, 100% fruit juice, fruit drinks, and sweet snacks ranged from 0 to 1420 mL/d, 0 to 640 g/d, 0 to 320 g/d, 5 to 530 mL/d, 0 to 230 mL/d, 0 to 70 mL/d, and 5 to 75 g/d, respectively. Ascertainment of incident cases of hypertension was done by independent blind assessment in 7 cohort studies[38–40,42,44,46–50,52,54,55] and by self-report in the other 8 cohort studies.[41,43,45,48,51,53,56–62] All cohort studies defined individuals with hypertension to have elevated systolic and/or diastolic blood pressure (BP) or take antihypertensive medication. The systolic BP cutoff ranged from 130 to 140 mm Hg, whereas the diastolic BP cutoff ranged from 80 to 90 mm Hg. All reports were funded by agency alone, except 3 reports[50,51,55] which were funded by both agency and industry.

Table S3 shows the confounding variables included in the most adjusted models for each of the included prospective cohort studies. The median number of variables in the most adjusted models was 12 (range, 7–22). All cohort studies adjusted for the prespecified primary confounding variable (age). Whereas Psaltopoulou et al[45] only adjusted for 3 of the 8 prespecified secondary confounding variables (smoking, markers of overweight/obesity, energy intake, physical activity, sex, diabetes mellitus, alcohol consumption, and sodium intake), the remaining cohort studies controlled for ≥4.

Table S4 shows the cohort study-quality assessments by the NOS. Only 2 of the 26 articles included scored <6 on the NOS scale, which denotes lower quality.[50,55]

Food Sources of Fructose-Containing Sugars on Incident Hypertension

Figure 2 shows the superplot of the summary estimates for pair-wise, linear, and nonlinear meta-analyses of the relation of each important food sources of fructose-containing sugars with incident hypertension.

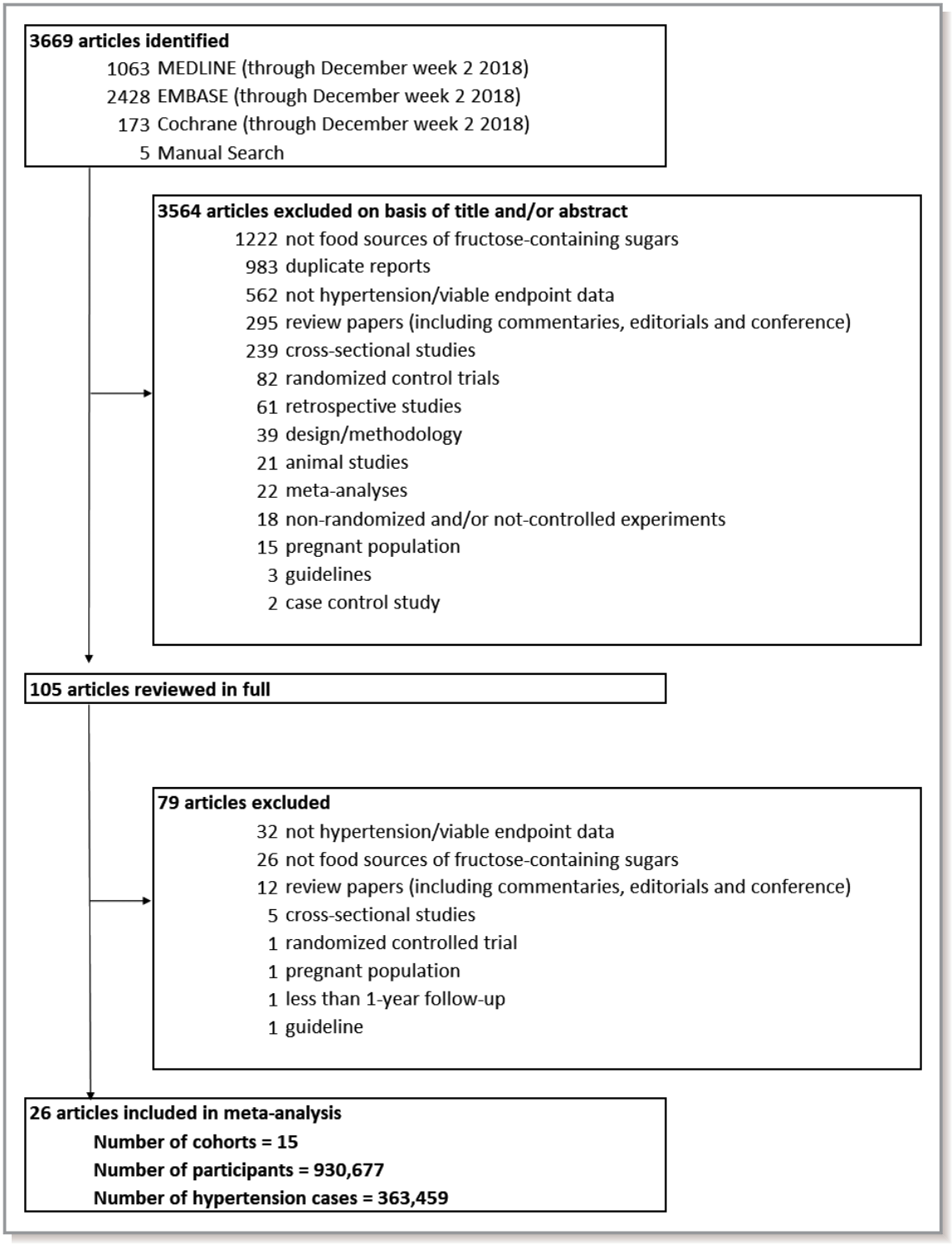

Figure 1. Flow of the literature search.

Figures S1 through S7 show the individual forest plots for the pair-wise meta-analysis of highest versus lowest category of intake for the individual food sources of fructose-containing sugars. Comparing highest versus lowest categories of intake, a harmful association with incident hypertension was shown for SSBs (RR=1.17 [95% CI, 1.11, 1.23]; Figure S1), whereas protective associations were shown for fruit (RR=0.81 [95% CI, 0.73, 0.89]; Figure S2), yogurt (RR=0.91 [95% CI, 0.86, 0.96]; Figure S3), and dairy desserts (RR=0.85 [95% CI, 0.76, 0.95]; Figure S4). Comparing highest versus lowest categories of intake, 100% fruit juice (RR=0.95 [95% CI, 0.85, 1.07]; Figure S5), fruit drinks (RR=1.27 [95% CI, 0.43, 3.75];

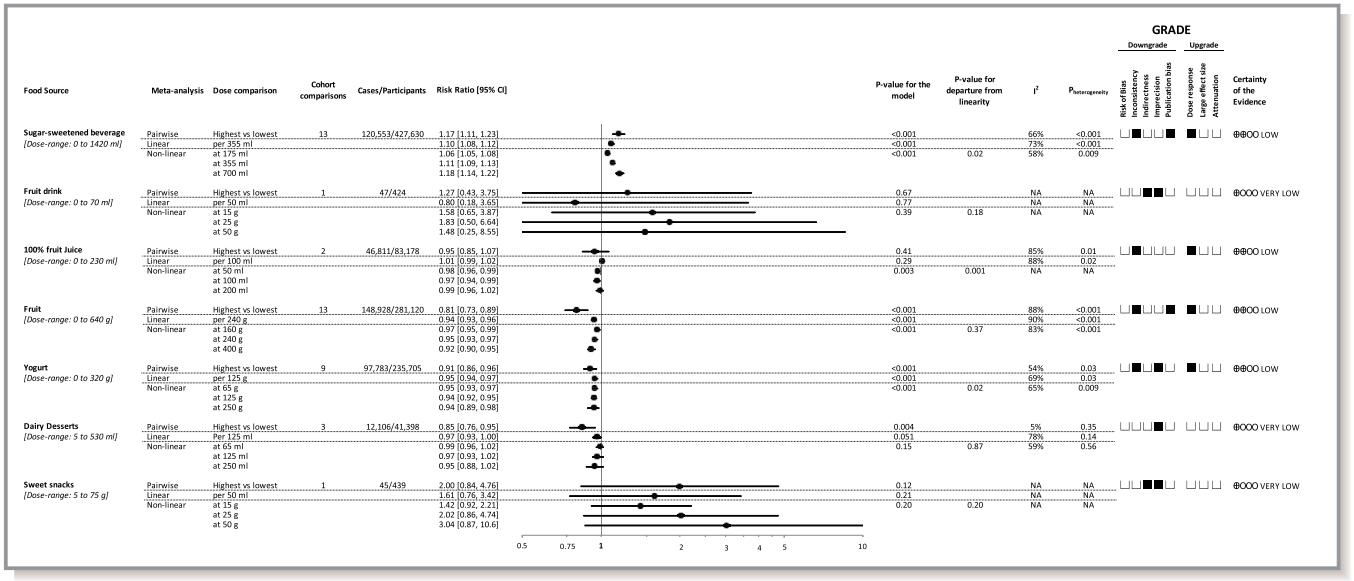

Figure 2. Relation of sources of fructose-containing sugars and incident hypertension. Pair-wise summary estimates were derived from pooled risk ratios for highest vs lowest intake of the food sources. Estimates of linear and nonlinear dose-response relationships are presented per intake level indicated in the column, "dose comparison." Dose-ranges are rounded to the nearest five. Data are expressed as risk ratios (RRs) with 95% CIs. Values of $I^2 \geq 50\%$ indicate substantial heterogeneity. RRs >1.0 indicate a harmful association. The Grading of Recommendations, Assessment, Development and Evaluation of prospective cohort studies are rated as "low" certainty of evidence and can be downgraded by 5 domains and upgraded by 3 domains. Filled black squares indicate downgrade or upgrades for each outcome. NA indicates not applicable.

Figure S6), or sweet snacks (RR=2.00 [95% CI, 0.84, 4.76]; Figure S7) did not show any association with incident hypertension.

Figure 2 shows the summary estimates and Figure 3 shows the dose-response relationships between the individual food source of fructose-containing sugars and risk of hypertension. Figure S8 has additional study-specific data points superimposed on the graphs seen in Figure 3.

Using data from 13 cohorts with a dose range of 0 to 1420 mL/d, there was a harmful dose-response relationship between SSBs intake and hypertension with evidence of nonlinearity (*P* value for departure from linearity=0.02). The nonlinear curve was similar to the linear association with a suggestion of plateauing of risk after 400-mL/d consumption. The estimated RR at 355 mL (1 serving) of SSBs was 1.11 [95% CI, 1.09, 1.13].

Using data from 2 cohorts with a dose range of 0 to 230 mL/d, there was a nonlinear U-shaped dose-response relationship between 100% fruit juice intake and hypertension (*P* value for nonlinearity=0.001). The curve suggested a maximum protective association between 50 and 150 mL/d and appearance of harmful association over intake of 200 mL/day. The estimated RR for 100 mL/d (one-half serving of small glass) of 100% fruit juice was 0.97 [95% CI, 0.94, 0.99].

Using data from 13 cohorts with a dose range of 0 to 640 g/d, there was a protective linear dose-response relationship between fruit intake and hypertension (*P* value for departure from linearity=0.46). The estimated RR per 240 g (3 servings) of fruit intake was 0.94 (95% CI, 0.93, 0.96).

Using data from 9 cohorts with a dose range of 0 to 319 g/d, there was a nonlinear protective dose-response relationship between yogurt intake and hypertension (*P* value for nonlinearity=0.02). The curve suggested a continuous reduction of RR until 100 g/d of intake, followed by a plateau. The estimated RR at 125 g (1 serving) of yogurt was 0.94 (95% CI, 0.92, 0.95).

Using data from 9 cohorts with a dose range of 0 to 530 mL/d, there was no dose-response relationship between dairy desserts intake and hypertension and no evidence of nonlinearity (*P*=0.87). The estimated RR at 125 mL (1 serving) of dairy dessert was 0.97 (95% CI, 0.93, 1.00), which contrasts against the result from the pair-wise analysis of highest versus lowest intake.

The associations for SSBs, fruit, yogurt, and 100% fruit juice were all complicated by evidence of substantial heterogeneity (I^2>50% and P_Q<0.10) in pair-wise, linear, and nonlinear analyses, except for 100% fruit juice for which the measure of heterogeneity could not be calculated for nonlinear analysis because of lack of relevant data points.

Table. Cohort Characteristics

Study, Year (reference)	Cohort	Population at Baseline	Country	Participants	Incident Cases	Age (y)	Years Range	Duration (mean or median)	Dietary Intake Assessment	Frequency of Administration	Quantile Division	Exposure (median or range)*	Serving Size	Outcome Assessment	Funding Sources
Sugar-sweetened beverages (SSBs)															
Barrio-Lopez et al, 2013[38]	SUN	Nonhypertensive; does not meet any of the criteria for MetS; not abnormal energy intake†	Spain	8157	1464	36 (mean)	2004 to 2012	6 y	Validated FFQ	Every 2 y	Quintile	(change in consumption) −1.35 to 2.4 servings/wk	330 mL	Validated self-report	Agency
Cohen et al, 2012[40]	NHS	Nonhypertensive	US	88 540 (F)	42 022	38 to 53	1980 to 2008	28 y	Validated FFQ	Every 4 y	Quartile	<1/mo to ≥1/d	Bottle, glass, or can	Self-reported Physician diagnosed	Agency
	NHSII			97 991 (F)	21 873	31 to 40	1991 to 2007	16 y							
	HPFS			37 360 (M)	13 439	42 to 63	1986 to 2008	22 y							
Dhingra et al, 2007[41]	FOC	Nonhypertensive; no baseline MetS, no prevalent CVD	US	2803	1377	53 (mean)	1987 to 2001	4 y	Validated FFQ	Years 0,4	Quartile	0 to ≥2 servings/d	12 oz	Independent blind assessment	Agency
Duffey et al, 2010[42]	CARDIA	Nonhypertensive; no baseline MetS	US	2639	609	18 to 30	1986 to 2006	20 y	Validated SFFQ	Years 0,7	Quartile	n/a	n/a	Self-reported Physician diagnosed	Agency
Kang et al, 2017[58]	KoGES	Nonhypertensive; no baseline MetS	Korea	4591	1309	40 to −69	(2001–2002) to (2009–2010)	10 y	Validated SFFQ	Every 2 y	Quartile	0 to ≥4 servings/wk	250 mL	Independent blind assessment	Agency
Kwak et al, 2018[59]	KoGES	Nonhypertensive; no CVD; no diabetes mellitus; no cancer	Korea	5775	1175	40 to 69	(2001–2002) to (2009–2010)	10 y	Validated SFFQ	Every 2 y	Quartile	0 to 3.5 servings/wk	n/a	Independent blind assessment	Agency
Mirmiran et al, 2015[43]	TLGS	Nonhypertensive; within ±3 SD of energy intake	Iran	424	47‡	14 (mean)	(2006–2008) to (2009–2011)	3.6 y	Validated SFFQ	Every 3 y	Quartile	1.12 to 100 mL/d	250 mL	Independent blind assessment	Agency
Sayon-Orea et al, 2015[46]	SUN	Nonhypertensive; not abnormal energy intake†; no chronic disease (cancer, diabetes mellitus, or CVD)	Spain	13 843	1308	36 (mean)	1999 to 2010	8.1 y	Validated SFFQ	Years 0,6	Tertile	0 to ≥7 servings/wk	6.7 oz	Validated self-report	Agency
Weng et al, 2013[60]	ARIC	Nonhypertensive; no abnormal energy intake§	US	9913	2853	45 to 64	(1987–1989) to (1996–1998)	9 y	Validated FFQ	Years 0,3	Tertile	0 to ≥1 serving/d	n/a	Independent blind assessment	Agency
Winkelmayer et al, 2005[52]	NHS	Nonhypertensive	US	61 091 (F)	19 541	30 to 55	1990 to 2002	12 y	Validated FFQ	Every 4 y	Quartile	<1 serving/d to ≥4/d	Serving size as indicated on FFQ	Self-reported Physician diagnosed	Agency
	NHSII			94 503 (F)	13 536	25 to 42	1991 to 2003					<1 serving/d to (4–5)/d			
Fruit															
Auerbach et al, 2017[54]	WHI	Nonhypertensive; not abnormal energy intake‖	US	80 539 (F)	46 202	50 to 79	(1993–1998) to (2004 to 2005)	7.8 y	Validated SFFQ	Every 6 to 12 mo	Quintile	0.3 to 2.4 servings/d	n/a	Self-reported Physician diagnosed	Agency
Borgi et al, 2016[39]	NHS	Nonhypertensive	US	39 164 (F)	35 375	30 to 55	1984 to 010	26 y	Validated FFQ	1984, 1986, every 4 y after	Quintile	≤4 servings/wk to ≥4 servings/d	Dependent on type of fruit¶	Self-reported Physician diagnosed	Agency
	NHSII			63 885 (F)	25 246	25 to 42	1991 to 2011	20 y							
	HPFS			20 010 (M)	16 752	40 to 75	1986 to 2010	24 y							
Kim et al, J Acad Nutr Diet, 2017[63]	KoGES	Nonhypertensive; no CVD; no cancer; no abnormal energy intake#	Korea	2005 (M)	606	40 to 69	(2001–2002) to (2009–2010)	8 y	Validated SFFQ	Every 2 y	Quartile	0 to ≥4 servings/d	100 g	Independent blind assessment	Agency
				2174 (F)	552										
Koochakpoor et al, 2018[62]	TLGS (case-cohort analysis)	Nonhypertensive; no MetS at baseline; no CVD	Iran	640 cases 644 controls		42	2002 to 2014	12 y	Validated SFFQ	Every 3 y	Quartile	n/a	n/a	Independent blind assessment	Agency

Continued

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Table. Continued

Study, Year (reference)	Cohort	Population at Baseline	Country	Participants	Incident Cases	Age (y)	Years Range	Duration (mean or median)	Dietary Intake Assessment	Frequency of Administration	Quantile Division	Exposure (median or range)*	Serving Size	Outcome Assessment	Funding Sources
Nunez-Cordoba et al, 2009[44]	SUN	Nonhypertensive; no CVD; not abnormal energy intake**	Spain	8594	426	20 to 95	1999 to 2006	4.1 y	Validated SFFQ	Every 2 y	Quintile	≤1 to >4 servings/d	Serving size as indicated on FFQ	Validated self-report	Agency
Psaltopoulou et al, 2004[45]	EPIC	Nonhypertensive	Greece	20 343	5424	20 to 86	1994 to 1999	5 y	Validated SFFQ	Every 3 to 5 y	Per SD increment	<1 to >3 servings/d	n/a	Independent blind assessment	Agency
Steffen et al, 2005[47]	CARDIA	Nonhypertensive; not abnormal energy intake††; no diabetes mellitus	US	4304	997	18 to 30	1986 to 2001	15 y	Validated SFFQ	Years 0,7	Quintile	<0.2 to >1.5 times/d	Frequency not servings	Independent blind assessment	Agency
Tsubota-Utsugi et al, 2011[48]	Ohasama	Nonhypertensive; within ±3 SD of energy intake	Japan	745	222	≥35	1998 to 2002	4 y	Validated FFQ	1 (baseline)	Quartile	≤38.40 to ≥100.03 g/d	n/a	Self-reported	Agency
Wang et al, 2012[50]	WHS	Nonhypertensive; no cancer; no CVD	US	28 082 (F)	13 633	39 to 89	(1992–1995) to 2007	12.9 y	Validated FFQ	1 (baseline)	Quintile	<0.5 to ≥3 servings/d	n/a	Self-reported Physician diagnosed	Agency and Industry
Weng et al, 2013[60]	ARIC	Nonhypertensive; no abnormal energy intake§	US	9913	2853	45 to 64	(1987–1989) to (1996–1998)	9 y	Validated FFQ	Years 0,3	Quintile	n/a	n/a	Independent blind assessment	Agency
Yogurt															
Alonso et al, 2009[56]	ARIC	Nonhypertensive; no CVD; no diabetes mellitus; no abnormal energy intake§	US	8208	2399	45 to 64	(1987–1989) to (1996–1998)	9 y	Validated FFQ	Every 3 y	Tertile	0.01 to 1.3 servings/d	n/a	Independent blind assessment	Agency
Buendia et al, 2018[55]	NHS	Nonhypertensive; no CVD; no diabetes mellitus; no cancer; not abnormal energy intake‡‡; no abnormal dairy intake§§	US	69 298	41 934	45 (mean)	1980 to 2010	30 y	Validated SFFQ	Every 4 y	Quintile	<1 serving/mo to ≥5 servings/wk	1 cup	Self-reported Physician diagnosed	Agency and industry
	NHSII			84 368	26 282	36 (mean)	1989 to 2009	20 y							
	HPFS			30 512	14 166	51 (mean)	1986 to 2010	24 y							
Engberink et al, 2009[57]	MORGEN	Nonhypertensive	Netherlands	3454	713	20 to 65	(1993–1997) to (1998–2002)	5 y	Validated SFFQ	1 (baselines)	Quartile	12 to 122 g/d	n/a	Independent blind assessment	Agency
Kim et al, Brit J Nutr, 2017[61]	KoGES	Nonhypertensive; no MetS at baseline; no CVD; no cancer	Korea	4335	1556	40 to 69	(2001–2002) to (2009–2010)	10 y	Validated SFFQ	Years 0,4	Quartile	0 to ≥4 servings/wk	140 mL	Independent blind assessment	Agency
Steffen et al, 2005[47]	CARDIA	Nonhypertensive; not abnormal energy intake††; no diabetes mellitus	US	4304	997	18 to 30	1986 to 2001	15 y	Validated SFFQ	Years 0,7	Tertile	<0.1 to >0.5 times/wk	Frequency not servings	Independent blind assessment	Agency
Wang et al, 2008[49]	WHS	Nonhypertensive, no cancer, no CVD, not "implausible" energy intake	US	28 886 (F)	8710	54 (mean)	(1992–1995) to 2005	10 y	Validated SFFQ	1 (baseline)	Quintile	<1 serving/mo to ≥1 servings/d	Serving size as indicated on SFFQ	Self-reported Physician diagnosed	Agency
Wang et al, 2015[51]	FHS	Nonhypertensive	US	2340	1026	52 (mean)	1991 to 2008	14.6 y	Validated FFQ	At each exam‖‖	Per 1 serving/wk increment	0 to 4.000 servings/wk	227 g	Independent blind assessment	Agency and industry
Dairy desserts															
Alonso et al, 2009[56]	ARIC	Nonhypertensive; no CVD; no diabetes mellitus; no abnormal energy intake§	US	8208	2399	45 to 64	(1987–1989) to (1996–1998)	9 y	Validated FFQ	Every 3 y	Tertile	0.04 to 1.5 servings/d	n/a	Independent blind assessment	Agency
Steffen et al, 2005[47]	CARDIA	Nonhypertensive; not abnormal energy intake ††; no diabetes mellitus	US	4304	997	18 to 30	1986 to 2001	15 y	Validated SFFQ	Years 0,7	Quintile	<0.1 to >2.2 times/wk	Frequency not servings	Independent blind assessment	Agency

Continued

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Table. Continued

Study, Year (reference)	Cohort	Population at Baseline	Country	Participants	Incident Cases	Age (y)	Years Range	Duration (mean or median)	Dietary Intake Assessment	Frequency of Administration	Quantile Division	Exposure (median or range)*	Serving Size	Outcome Assessment	Funding Sources
Wang et al, 2008[49]	WHS	Nonhypertensive, no cancer, no CVD, not "implausible" energy intake	US	28 886 (F)	8710	54 (mean)	(1992–1995) to 2005	10 y	Validated SFFQ	1 (baseline)	Quintile	<1 serving/mo to ≥1 servings/d	Serving size as indicated on SFFQ	Self-reported Physician Diagnosed	Agency
100% fruit juice															
Auerbach et al, 2017[54]	WHI	Nonhypertensive; not abnormal energy intake‖	US	80 539 (F)	46 202	50 to 79	(1993–1998) to (2004–2005)	7.8 y	Validated SFFQ	Every 6 to 12 mo	Quintile	0 to 7.8 oz/d	100 oz	Self-reported Physician diagnosed	Agency
Duffey et al, 2010[42]	CARDIA	Nonhypertensive; no baseline MetS	US	2639	609	18 to 30	1986 to 2006	20 y	Validated SFFQ	Years 0,7	Quartile	n/a	8 oz	Self-reported Physician diagnosed	Agency
Fruit drinks															
Mirmiran et al, 2015[43]	TLGS	Nonhypertensive; not ±3 SD of energy intake	Iran	424	47‡	14 (mean)	(2006–2008) to (2009–2011)	3.6 y	Validated SFFQ	Every 3 y	Quartile	1.12 to 100 mL/d	250 mL	Independent blind assessment	Agency
Sweet snacks															
Asghari et al, 2016[53]	TLGS	Nonhypertensive; not ±3 SD of energy intake	Iran	439	45‡	14 (mean)	(2006–2008) to (2009–2011)	3.6 y	Validated SFFQ	Every 3 y	Quartile	7 to 72.8 g/d	n/a	Independent blind assessment	Agency

CVD indicates cardiovascular disease; FFQ, food frequency questionnaire; HDL, high-density lipoprotein; MetS, metabolic syndrome; n/a, not applicable; SFFQ, semiquantitative food frequency questionnaire; SSBs, sugar-sweetened beverages.

*There was some variability in how the cohorts chose to represent their exposure levels, such as quantiles used and the frequency of intake vs servings/d intake. We compared the highest to lowest exposure quantile for each cohort study, regardless of the number of qunatiles (tertile, quartile, or quintile). For dose-response analysis, SSBs and fruit exposure levels were converted to servings. For SSBs, we performed the conversion based on serving sizes indicated in the articles. For fruit, we assumed that 1 serving=1/2 cup=87.5 g=1 instance of intake (frequency).

†Defined as <800 kcal/d in men and <500 kcal/d in women, or >4000 kcal/d in men and >3500 kcal/d in women.

‡Study only reported cases of metabolic syndrome, defined as having ≥3 of the following: abdominal obesity, high fasting glucose, low HDL cholesterol, hypertension, or high triglycerides.

§Defined as <700 kcal/d in men and <500 kcal/d in women, or >4500 kcal/d in men and >3500 kcal/d in women.

‖Defined as ≤600 kcal/d or ≥5000 kcal/d.

¶Serving sizes: raisins (1 oz)/grapes (half cup); apples/pears (1), bananas (1), strawberries (half cup), blueberries (half cup), prunes (half cup), avocado (half), cantaloupe (1/4 melon), oranges (1), peaches/apricots/plums (1 or half cup canned).

#Defined as <500 kcal/d or >6000 kcal/d.

**Defined as <800 kcal/d in men and <500 kcal/d in women, or >4200 kcal/d in men and >3800 kcal/d in women.

††Defined as <800 kcal/d in men and <600 kcal/d in women, or >8000 kcal/d in men and >6000 kcal/d in women.

‡‡Defined as <800 kcal/d for men and <500 kcal/d in women, or >4200 kcal/d in men and >3500 kcal/d in women.

§§Defined as ≥6 servings/d of total dairy, >4 servings/d of cheese, or ≥6 servings/d of milk.

‖‖Exams were (1991–1995), (1995–1998), (1998–2001), and (2005–2008).

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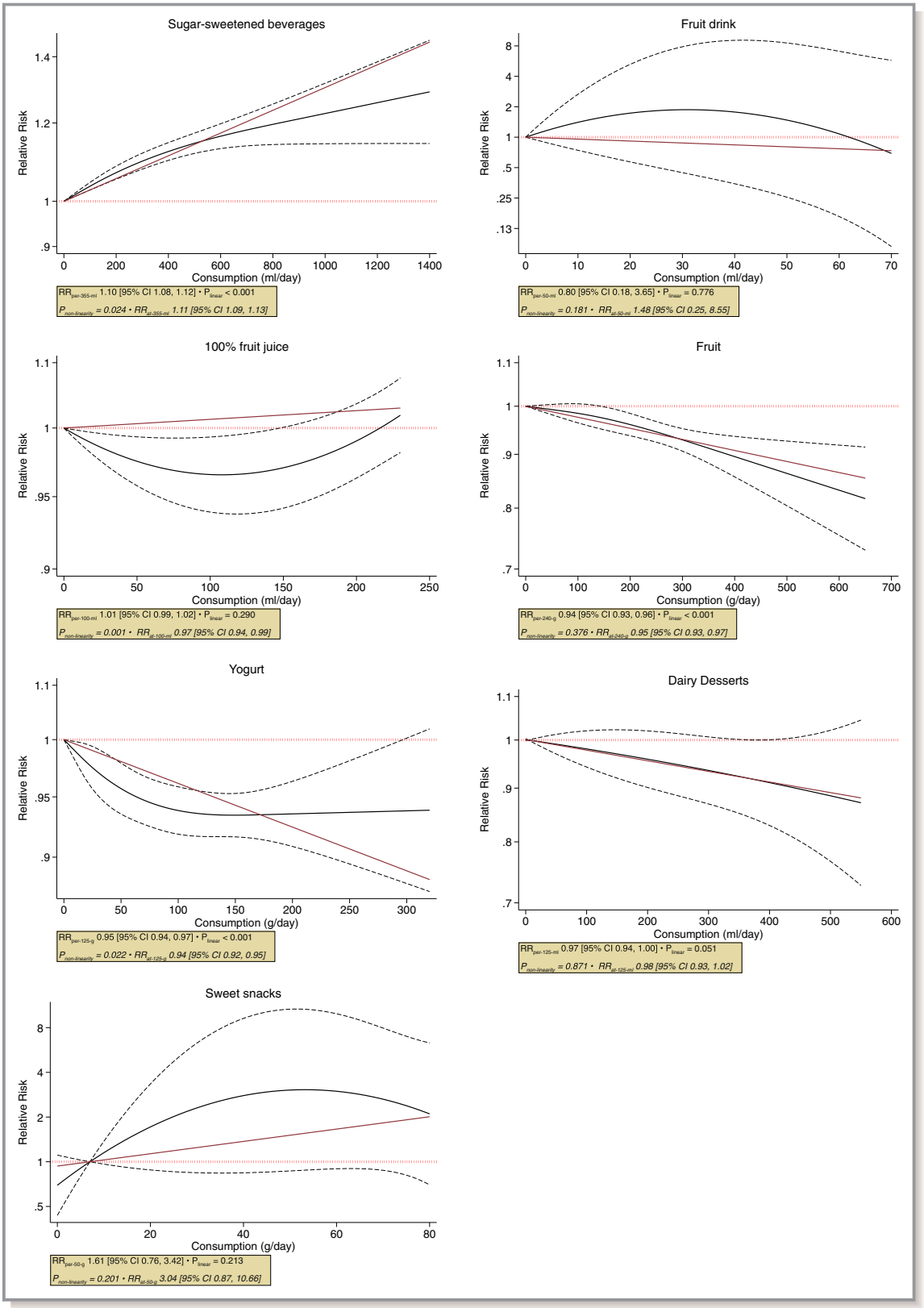

Figure 3. Dose-response relation between sources of fructose-containing sugars and incident hypertension. Dose-response relationship between intake of SSBs, fruit, 100% fruit juice, yogurt, fruit drink, dairy desserts, and sweet snacks with risk of hypertension. Red line represents the linear, and black lines represent the nonlinear models, respectively. Dotted lines represent 95% CIs of the nonlinear model. RR indicates risk ratio; SSBs, sugar-sweetened beverages.

There were no significant linear or nonlinear dose-response relationships between fruit drinks or sweet snacks and incident hypertension (Figures 2 and 3 and Figure S8).

Sensitivity Analyses and Subgroup Analyses

Table S5 shows the recalculation of the association estimates after systematic removal of each cohort study (not available for food groups of ≤2 studies) from the pair-wise meta-analysis. Systematic removal of each cohort study for SSBs or fruit did not alter the direction or significance of the association or the evidence of heterogeneity. Systematic removal of each cohort study for yogurt did not alter the direction or significance of the association. However, inter-study heterogeneity of the yogurt food group was altered when Kim et al[61] was removed from the pooled analysis, where it became nonsignificant (I^2=30%; P=0.19).

Figure S9 shows the subgroup analyses for SSBs, and Figure S10 shows the subgroup analyses for fruit. No subgroup analyses were able to explain the heterogeneity between study estimates in the association of SSBs with hypertension or the association of fruit with hypertension.

Publication Bias

Figure S11 shows the funnel plot assessing publication bias for SSBs. Visual inspection of the funnel plot showed evidence of asymmetry. Both the Begg (P=0.04) and Egger (P=0.02) tests indicated evidence of small-study effects. Adjustment for funnel-plot asymmetry by the recalculation of the pooled estimate by inputting missing cohort studies using the Duvall and Tweedie trim-and-fill method did not alter the significance of the relationship with only limited attenuation of the summary estimate (RR=1.12 [95% CI, 1.05, 1.19] versus original [RR=1.17; 95% CI, 1.11, 1.23]; Figure S12). Figure S13 shows the funnel plot assessing publication bias for fruit. Visual inspection of the funnel plot showed evidence of asymmetry, and the Begg (P=0.09) test was significant whereas the Egger (P=0.70) test was nonsignificant. The Duvall and Tweedie trim-and-fill method did not perform any trimming.

GRADE Assessment

Table S6 shows a summary of the GRADE assessment. Our certainty in our pooled estimates was "low" for a harmful association for SSBs, protective association at moderate doses for 100% fruit juice, protective association for fruit, and protective association for yogurt; and "very low" for no association for fruit drinks, sweet snacks, and dairy desserts. This was attributable to downgrades for inconsistency (SSBs, 100% fruit juice, fruit, and yogurt), indirectness (fruit drink, sweet snacks), imprecision (fruit drinks, yogurt, dairy desserts, and sweet snacks) and publication bias (SSBs, fruit), and upgrades for dose-response gradients (SSBs, fruit, yogurt, and 100% fruit juice).

Discussion

In our systematic review and meta-analysis, pooled analyses of 26 reports of 15 prospective cohort studies involving 930 677 participants with 363 459 incident cases of hypertension found that SSBs had a harmful association with incident hypertension whereas fruit and yogurt had protective associations with incident hypertension. One hundred percent fruit juice showed a U-shaped dose-response association with hypertension, showing protection at moderate doses (100–250 mL). There was no association of fruit drinks, dairy desserts, or sweet snacks with hypertension.

Findings in the Context of the Literature

Our results are consistent with established research on the harmful association between SSBs and incident hypertension. Our previous systematic review and meta-analysis found a significant 12% increase in incident hypertension when comparing highest to lowest SSBs intake.[8] This present study included more studies covering a wider range of cohorts and found a comparable 10% increase in incident hypertension with 1-serving (355-mL)/d intake using the linear dose response and 11% increase at 1 serving using the nonlinear dose response. We observed evidence for nonlinearity for SSBs, but the 2 curves (linear and nonlinear) visually suggested high similarity; the difference, though statistically significant, is clinically irrelevant. The dose-response relationship suggested an increase in risk of hypertension with SSBs intake at all higher doses when compared with no consumption. Other, more-recent systematic reviews and meta-analyses have identified a similar association between SSBs intake and incident hypertension.[67,68] Consistent harmful associations have also been shown with other related cardiometabolic diseases, such as diabetes mellitus, metabolic syndrome, and cardiovascular disease.[69,70] A possible explanation is that SSBs provide a form of liquid calories that produce less satiety than consumption of solid calories, resulting in overall increased energy intake, weight gain, and downstream hypertension.[71] Another is that the association between SSBs intake and incident hypertension is confounded by an unhealthy lifestyle.[72] Though the cohort studies included in our analyses consistently controlled for variables such as energy intake, physical activity, smoking, and alcohol intake, residual confounding could have contributed to the harmful association between SSBs intake and incident hypertension.

We also identified a U-shaped dose-dependent relationship between incident hypertension and 100% fruit juice intake, where intake below 200 mL showed protective associations with hypertension. The maximum protective association appeared to be between doses of 50 and 150 mL (≈0.5–1.0 servings), after which the dose-response curve suggested increasing RR with increasing dose, and even suggested harmful associations over intakes of 200 mL. This is in line with some national health guidelines, in which a 150-mL glass of fruit juice contributes toward daily fruit consumption.[73] Other cohort studies have shown that 100% fruit juice, compared with fruit drinks, has neutral[74] or even protective[75] associations with incident cardiometabolic disease. The protective association of 100% fruit juice noted at moderate doses may be the result of the range of nutrients and bioactive compounds within the juice.[76] However, the potential for harmful associations at higher doses may be attributable to the consumption of excess calories outweighing any potentially protective nutrients contained within 100% fruit juice.[77]

We did not find any association of 100% fruit juice intake in the pair-wise meta-analysis. This underscores the point that, without consideration of dose-response relationship, an analysis of extreme intakes ignores the dose entirely, assumes a false-linear relationship between the lowest and highest intake, and fails to detect important dose ranges for protective or harmful associations. While we argue that highest versus lowest analysis is possibly misleading, we reported it in our article because of our preregistered a priori analysis plan.

Recent systematic reviews and meta-analyses concur with our results of an inverse dose-response association between fruit and incident hypertension.[78,79] We also saw evidence for nonlinearity for fruit. However, similar to the SSBs curve discussed above, the small statistical difference may be clinically irrelevant. The dose-response relationship suggested a reduction in risk of hypertension with intake of fruit at all increased doses, albeit in the assessed dose-range when compared with no consumption. Consistent protective associations have been shown for fruit with other related cardiometabolic diseases, such as diabetes mellitus, cardiovascular disease, and all-cause mortality.[80–83] One popular hypothesis of the protective effects of fruit consumption pertains to their high phytochemical, especially flavonoid, content.[84] These flavonoids have been shown to decrease important factors in the development of hypertension and have been shown to reduce BP.[85–90] Various fruits are also rich in potassium with small amounts of magnesium and calcium, the combination of which has been shown to decrease BP.[91]

We identified a dose-dependent relationship between incident hypertension and yogurt intake, where intakes between 100 and 250 g/d showed maximum protective associations with hypertension. Our spline analysis of yogurt shows that the risk plateaus after intakes above 100 g/d, and that there is not a sufficient amount of precise data to suggest any more protection associated with increasing intake beyond 250 g/d. Yogurt has shown protective associations with various other cardiometabolic disease outcomes; a large systematic review identified that the consumption of different dairy products (sweetened or not) shows favorable or neutral associations with cardiometabolic outcomes of stroke, cardiovascular disease, coronary artery disease, hypertension, metabolic syndrome, and type 2 diabetes mellitus.[92] Specific to dairy products that contain fructose, yogurt has shown a protective association with body weight, and both yogurt and ice cream have shown protective associations with diabetes mellitus.[93,94] The link between dairy and hypertension is unclear. Dairy foods are rich in micronutrients, such as calcium, potassium, and magnesium, which may lower BP by several mechanisms.[95–97] Yogurt contains more calcium, potassium, and magnesium and more protein per serving compared with milk,[98] and these nutrients may be more bioavailable than in other dairy products.[99] The probiotics abundant in yogurt have also been found to reduce BP by inhibiting angiotensin-converting enzyme.[95] Despite these potential mechanistic explanations, a Mendelian randomization analysis did not find a casual link between dairy intake and reduced incident hypertension in prospective cohorts.[100]

Last, we did not find any associations of dairy desserts, fruit drinks, or sweet snacks with incident hypertension. Although we found a small protective association for dairy desserts when comparing highest versus lowest intake categories, this was not supported by the dose-response analysis. Dose-response analysis considers the full dose range and thus is more credible. The contrasting result for dairy desserts again underscores the importance of assessing the dose-response relationship using all categories rather than just using highest versus lowest analysis, which ignores the differing dose ranges used in different studies. Indeed, the highest category doses in our included studies were 93, 250, and 532 mL/d, a difference of more than twice in each study leading to inaccurate results in the highest versus lowest analysis. An additional limitation of the dairy desserts analysis was that although 2 studies defined dairy desserts as a mix of cakes, ice cream, sherbet, etc,[49,56] the other study was nonspecific with what the "dairy desserts" category encompassed.[47]

The lack of association for sweet snacks is not surprising, given that the result is only based on one cohort[53] that examined children and adolescents only and included a broad spectrum of sweet snack foods that may individually affect hypertension differently (eg, chocolate versus cakes). The fruit

drinks result is similarly limited in its examination of only a young population in Iran.[43]

Our differing results across the different food groups suggest that the fructose-containing sugars they contain may not be the primary basis of harm as noted in SSBs. This view is supported by systematic reviews and meta-analyses of prospective cohort studies which do not show an association of fructose-containing sugars with hypertension[10] or related cardiometabolic diseases, such as diabetes mellitus,[101] independent of food form. A harmful association, however, has been shown between total fructose intake and gout, independent of food form.[102] Even so, a recent comprehensive review by Caliceti et al found conflicting evidence with regard to the pathogenesis of cardiometabolic diseases from fructose-derived uric acid.[103] Moreover, systematic reviews and meta-analyses of controlled trials have failed to show a harmful effect of fructose in isocaloric substitution with other carbohydrates on hypertension[9] or related cardiometabolic outcomes.[104–108] Harmful effects have only been consistently observed in hypercaloric comparisons in which fructose supplements diets with excess calories at very high doses (>25% energy) in predominantly liquid form compared with the same diets without the excess calories,[9,104–109] a condition which may be more analogous to the intake of SSBs.

Strengths and Limitations

The strengths of our systematic review and meta-analysis are that we identified all available prospective cohorts through a systematic search strategy, performed quantitative syntheses using 3 different types of analysis (pair-wise highest versus lowest analysis, linear and nonlinear dose-response analysis) and assessed the quality and strength of the evidence by using the GRADE assessment. We had a large sample size, long duration of follow-up, and adjustment for many dietary and lifestyle factors in the included studies. Another strength is that ours is the first study that comprehensively compares all the major available food sources of fructose-containing sugars and their association with hypertension in prospective cohort studies. Additionally, our dose-response analyses show that the risk of incident hypertension associated with SSBs crosses the clinically important harm threshold of RR>1.10 above an intake of 1 serving/day.

Our systematic review and meta-analysis has several limitations. First, given that the studies are observational in nature, there is the possibility for residual measured and unmeasured confounding, a reason that GRADE starts observational studies at "low" quality. Second, there was evidence of indirectness in some of the relationships with limited generalizability of our findings to other populations and geographical locations. Third, sensitivity and subgroup analyses were unable to explain the heterogeneity found for SSBs and fruit. Fourth, fruit drinks, sweet snacks, yogurt, and dairy desserts were limited by serious imprecision in the pooled risk estimates given that the 95% CIs were wide and could not rule out clinically important harm or protection. Fifth, we observed evidence of publication bias for our findings for SSBs and fruit by visual inspection of funnel plot and by formal testing. Finally, there were a limited number of cohort comparisons for several food sources of sugars with unbalanced representation of different food sources. Although SSBs are the most important source of fructose-containing sugars by contributing 13% of total sugar intake in the Canadian diet—doubled for Americans—grains and grain products as well as sweets and desserts, 2 of the other top 10 most important food source of sugars,[17,18] were not represented. Other fruit and fruit products, such as jams, purees, and dried fruit, and dairy products, such as flavored milks, were also not represented.

Weighing these strengths and limitations using GRADE, the evidence was generally weak. We assessed our certainly in the evidence for the food sources to be "very low" for fruit drinks, sweet snacks, and dairy desserts to "low" for SSBs, 100% fruit juice, fruit, and yogurt owing to combinations of downgrades for inconsistency, indirectness, imprecision, and publication bias and upgrades for dose-response gradient for SSBs, fruit, yogurt, and 100% fruit juice.

Implications

Dietary guidelines have shifted from a focus on nutrient-based recommendations to a focus on food- and dietary pattern–based recommendations.[110,111] The main rationale for this paradigm shift has been the recognition that a focus on nutrients misses important interactions with other nutrients and the food matrix in which the nutrients are contained and subsequently consumed.[110] Our findings on food sources of, rather than solely, sugars support this view. The harmful association between SSBs and incident hypertension supports recommendations to limit SSBs, the most important source of sugars in the United States and Canada.[17,18] The evidence for this relationship, however, cannot necessarily be applied to other important food sources of sugars. Our findings on fruit, yogurt, dairy desserts, 100% fruit juice, fruit drinks, and sweet snacks suggest that in the context of a balanced, weight-maintaining diet, there may not be any reason to limit these foods for the prevention of hypertension, simply owing to their sugar content. On the contrary, the recommendation to increase the intake of fruit and yogurt may contribute to better diet quality and protect against the development of hypertension, especially when included as part of a DASH (Dietary Approaches to Stop Hypertension) dietary pattern,[112,113] in which fruit (which includes 100% fruit juice) and low-fat yogurt are important components.[114] Our results

suggest that 100% fruit juice, in moderation, might provide some of the protective nutrients from fruit which underscores the importance of examining the whole dose-response relationship for ranges and thresholds for harmful and protective associations. On the other hand, findings for dairy desserts, with the limited research available, may not directly translate to diet recommendations. Given that people are currently not meeting their recommended intakes of fruit and vegetables[115,116] or dairy,[111,116] there is an opportunity for people in North America to increase their intake of fruit and yogurt, especially at the expense of SSBs.

An issue identified in our analysis is that a highest versus lowest analysis used routinely by prospective cohort studies and other meta-analyses may lead to misleading results. This is because of the lack of consideration for the dose-response association between food sources of fructose-containing sugars and cardiometabolic disease. We showed differing results between highest versus lowest and dose-response relationship for 100% fruit juice and dairy desserts in our analysis. The highest versus lowest analysis ignored dose-range differences between different study populations whereas the dose-response analysis revealed the authentic relationship with incident hypertension seen with increasing intake. Investigators of prospective cohort studies studying important food sources should consider modeling dose-response associations with disease with a nonlinearity assessment. This will allow the identification of specific dose ranges or cutoffs for protection and harm that would have important implications for dietary guidelines and public policy. Failing to do so will only perpetuate the misinterpretation of the results and, consequently, inaccurate conclusions regarding relationships between sugar-containing foods and important health outcomes such as hypertension.

Conclusions

Our systematic review and meta-analysis of the available prospective cohort studies of the relation of important food sources of fructose-containing sugars and incident hypertension showed that the harmful association of SSBs with incident hypertension does not hold for other important food sources of fructose-containing sugars with protective associations even noted for yogurt, fruit, and 100% fruit juice in moderate doses. These findings suggest that caution is warranted in using the evidence from SSBs as a proxy for other food sources of sugars and support the ongoing transition from nutrient-focused recommendations to specific food- and dietary pattern–based recommendations insofar as they relate to sugars and hypertension. Our confidence in the estimates is weak, and additional prospective studies are needed to improve our estimates and better understand the dose-response relationship between important food sources of fructose-containing sugars and hypertension. There is a need for "high" quality, randomized controlled trials that give the best protection against bias and more research on other important food sources of fructose-containing sugars, such as grain and grain products and sweets and desserts, other fruit and fruit products, and dairy and dairy products. To better understand the interactions with the whole diet, useful avenues of investigation would include research on dietary patterns and the extent to which food sources of fructose-containing sugars in those dietary patterns contribute to the associations with hypertension.

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He is a member of the International Carbohydrate Quality Consortium (ICQC), executive board member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD, and is a director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. J.L. 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He is a member of the European Fruit Juice Association Scientific Expert Panel and Soy Nutrition Institute Scientific Advisory Committee. He is on the clinical practice guidelines expert committees of Diabetes Canada, EASD, Canadian Cardiovascular Society (CCS), and Obesity Canada. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), executive board member of the DNSG of the EASD, and director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Sobeys Inc. The remaining authors have no disclosures to report. There are no patents, products in development, or marketed products to declare.

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SUPPLEMENTAL MATERIAL

Data S1. Sample STATA dose-response code - SSBs intake and incident hypertension.

```
clear

version 15

import excel "[usedataset]", sheet("forStata") firstrow case(lower)
sort id quintile
list rr lci uci case id doseinml quintile
tab id

capture drop lnrr
capture drop lnse

gen type=2
gen lnrr=log(rr)
gen lnuci=log(uci)
gen lnlci=log(lci)
gen lnse =((lnuci-lnlci)/(2*invnorm(0.975)))
gen dose=doseinml

* scale check
sum dose, d

* linear DR
drmeta lnrr dose, data(py case) id(id) type(type) se(lnse) eform reml
lincom dose*355, eform //per 355 ml score
return list
global b0=r(estimate)
global b1: display %4.2f r(estimate)
global lci1: display %04.2f r(lb)
global uci1: display %04.2f r(ub)
global p1: display %04.3f r(p)
if $p1<0.0001 {
global p1="<0.0001"
else {
global p1="= $p1"
}
}
global captionlinear= "RR{sub:per 355 ml/per-serving} $b1 [95% CI $lci1, $uci1] {&bull} P{sub:linear} =
$p1"
drmeta_gof //goodness of fit for linear - Deviance=59.5 [lower better],  R2=0.66 [higher better]
drmeta lnrr dose, data(py case) id(id) type(type) se(lnse) eform reml
lincom dose*1, //per 1 score
global eb1=r(estimate)
display $eb1

* non-linear using splines
capture drop doses1
capture drop doses2
sum dose, d
mkspline doses = dose, nk(3) cubic displayknots
mat knots = r(knots)

*departure from linearity
drmeta lnrr doses1 doses2 , data(py case) id(id) type(type) se(lnse) reml
testparm doses2 //wald test test
global pdep0 r(p)
global pdep1: display %5.3f $pdep0
display $pdep1 //
global pnl ="P-value{sub:non-linearity}s = $pdep1"

* dose estimate non-linearity
```

```
global dl=355 //dose to show RR for 355 ml
drmeta lnrr doses1 doses2 , data(py case) id(id) type(type) se(lnse) reml
drmeta_graph, dose($dl) ref(0) matk(knots) eform list nodraw
matrix r=r(E)
global b$dl: display %4.2f r["r1","_xb"]
global lci$dl: display %04.2f r["r1","_lb"]
global uci$dl: display %04.2f r["r1","_ub"]
global rr$dl= "RR{sub:$dl g} ${b$dl} [${lci$dl}, ${uci$dl}]"
display "${rr$dl}"

global captionnl="$pnl {&bull} {it:${rr$dl}}"

tabstat  rr  dose, stat(min max)

global xtitle="xtitle(Consumption (g/day))"
global doserange= "dose(0(5)1400)"
global ytitle="ytitle(Relative Risk)"
global yscale="yscale(range(0.9 1.4)) ylabel(0.9 1 1.2 1.4, format(%5.2g))"
global yline="yline(1, lcol(red) lw(thick) lp(.))"
global title="t1title(Sugar-sweetened beverages)"

* non-linear with linear line with bubbles
drmeta lnrr doses1 doses2 , data(py case) id(id) type(type) se(lnse)  eform  reml
drmeta_graph, ref(0) matk(knots) eform addplot($eb1*d) $xtitle $doserange $ytitle $yscale $yline $title
graph addplot scatter rr dose if quintile==1,  mfcolor(gs13) mlcolor(gs10) below jitter(2) $yscale
graph addplot scatter rr dose[w=1/lnse^2] if quintile!=1, mcolor(gs15) ms(circle) below $yscale
note("$captionlinear" " " "$captionnl", size(vsmall) color(gs1) box)
graph export "ssb-spline-1a.pdf", replace

* non-linear with linear line without bubbles
drmeta lnrr doses1 doses2 , data(py case) id(id) type(type) se(lnse) reml
drmeta_graph , ref(0) matk(knots) eform addplot($eb1*d)  note("$captionlinear" " " "$captionnl",
size(vsmall) color(gs1) box)  $xtitle $doserange $ytitle $yscale $yline $title
graph export "ssb-spline-1b.pdf", replace
```

Data S2. Dose-response raw data.

Study - Cohort	Dietary Assessment	Exposure (median)	Relative Risk (95% CI)
SSBs			
Barrio-Lopez et al., 2013 – SUN [1]	Validated FFQ	0 ml/d 165 ml/d 330 ml/d	1.00 (Reference) 1.30 (1.10, 1.80) 1.60 (1.30, 2.10)
Cohen et al., 2012 – NHS [2]	Validated FFQ	12 ml/d 29 ml/d 203 ml/d 355 ml/d	1.00 (Reference) 1.02 (0.99, 1.04) 1.04 (1.01, 1.07) 1.12 (1.08, 1.17)
Cohen et al., 2012 – NHSII [2]		12 ml/d 29 ml/d 203 ml/d 355 ml/d	1.00 (Reference) 1.00 (0.96, 1.04) 1.07 (1.03, 1.11) 1.17 (1.11, 1.23)
Cohen et al., 2012 – HPFS [2]		12 ml/d 29 ml/d 203 ml/d 355 ml/d	1.00 (Reference) 0.97 (0.93, 1.02) 1.04 (1.00, 1.10) 1.06 (0.99, 1.14)
Dhingra et al., 2007 – FOC [3]	Validated FFQ	0 ml/d 355 ml/d 533 ml/d 710 ml/d	1.00 (Reference) 1.12 (0.94, 1.34) 1.14 (0.97, 1.32) 1.15 (0.92, 1.42)
Duffey et al., 2010 – CARDIA [4]	Validated SFFQ	0 ml/d 337 ml/d	1.00 (Reference) 1.06 (0.97, 1.16)
Kang et al., 2017 – KoGES [5]	Validated SFFQ	0 ml/d 36 ml/d 71 ml/d 143 ml/d	1.00 (Reference) 0.93 (0.83, 1.04) 1.28 (1.12, 1.48) 1.55 (1.18, 2.03)
Kwak et al., 2018 – KoGES [6]	Validated SFFQ	0 ml/d 58 ml/d 208 ml/d 875 ml/d	1.00 (Reference) 1.04 (0.87, 1.24) 1.12 (0.95, 1.33) 1.21 (1.02, 1.45)
Mirmiran et al. 2015 – TLGS [7]	Validated SFFQ	1 ml/d 9 ml/d 33 ml/d 100 ml/d	1.00 (Reference) 0.80 (0.27, 2.33) 1.35 (0.50, 3.51) 2.59 (1.05, 5.97)
Sayon-Orea et al., 2015 – SUN [8]	Validated SFFQ	0 ml/d 99 ml/d 198 ml/d	1.00 (Reference) 1.07 (0.94, 1.22) 1.34 (1.09, 1.65)
Weng et al., 2013 – ARIC [9]	Validated FFQ	0 ml/d 178 ml/d 355 ml/d	1.00 (Reference) 1.11 (1.01, 1.23) 1.02 (0.90, 1.16)
Winkelmayer et al., 2005 – NHS [10]	Validated FFQ	0 ml/d 355 ml/d 888 ml/d 1420 ml/d	1.00 (Reference) 1.09 (0.98, 1.22) 1.11 (0.95, 1.30) 1.44 (0.98, 2.11)
Winkelmayer et al., 2005 – NHSII [10]		0 ml/d 355 ml/d 888 ml/d 1420 ml/d	1.00 (Reference) 1.13 (1.03, 1.24) 1.24 (1.11, 1.38) 1.28 (1.01, 1.62)
Fruit			
Auerbach et al., 2017 – WHI [11]	Validated SFFQ	26 g/d 61 g/d	1.00 (Reference) 1.00 (0.99, 1.04)

		79 g/d	1.01 (0.98, 1.04)
		140 g/d	1.00 (0.97, 1.03)
		210 g/d	1.02 (0.98, 1.04)
Borgi et al., 2016 – NHS [12]	Validated FFQ	50 g/d	1.00 (Reference)
		69 g/d	0.97 (0.93, 1.01)
		88 g/d	0.95 (0.92, 0.99)
		219 g/d	0.94 (0.91, 0.98)
		350 g/d	0.96 (0.88, 1.03)
Borgi et al., 2016 – NHSII [12]		50 g/d	1.00 (Reference)
		69 g/d	1.03 (0.99, 1.07)
		88 g/d	0.97 (0.94, 1.07)
		219 g/d	0.91 (0.87, 0.95)
		350 g/d	0.91 (0.81, 1.02)
Borgi et al., 2016 – HPFS [12]		50 g/d	1.00 (Reference)
		69 g/d	0.95 (0.89, 1.00)
		88 g/d	0.92 (0.88, 0.97)
		219 g/d	0.92 (0.87, 0.97)
		350 g/d	0.88 (0.81, 0.97)
Kim et al. J Acad Nutr, 2017 – KoGES [13] (men)	Validated SFFQ	0 g/d	1.00 (Reference)
		150 g/d	0.58 (0.45, 0.75)
		300 g/d	0.44 (0.34, 0.57)
		400 g/d	0.44 (0.32, 0.60)
Kim et al. J Acad Nutr, 2017 – KoGES [13] (women)		0 g/d	1.00 (Reference)
		150 g/d	0.71 (0.54, 0.95)
		300 g/d	0.44 (0.33, 0.58)
		400 g/d	0.33 (0.24, 0.45)
Koochakpoor et al., 2018 – TLGS [14]	Validated SFFQ	0 g/d	1.00 (Reference)
		80 g/d	0.83 (0.68, 1.40)
		200 g/d	0.97 (0.58, 1.77)
		320 g/d	0.89 (0.63, 1.30)
Nunez-Cordoba et al., 2009 – SUN [15]	Validated SFFQ	160 g/d	1.00 (Reference)
		248 g/d	0.86 (0.66, 1.13)
		408 g/d	0.94 (0.70, 1.27)
		568 g/d	1.02 (0.72, 1.27)
		640 g/d	0.85 (0.59, 1.22)
Psaltopoulou et al., 2004 – EPIC [16]	Validated SFFQ	106 g/d	1.00 (Reference)
		318 g/d	0.61 (0.45, 0.83)
Steffen et al., 2005 – CARDIA [17]	Validated SFFQ	2 g/d	1.00 (Reference)
		31 g/d	0.88 (0.72, 1.06)
		61 g/d	0.83 (0.68, 1.01)
		105 g/d	0.85 (0.69, 1.04)
		131 g/d	0.75 (0.60, 0.94)
Tsubota-Utsugi et al., 2011 – Ohasama [18]	Validated FFQ	38 g/d	1.00 (Reference)
		51 g/d	0.73 (0.46, 1.09)
		82 g/d	0.78 (0.50, 1.16)
		100 g/d	0.51 (0.29, 0.81)
Wang et al., 2012 – WHS [19]	Validated FFQ	44 g/d	1.00 (Reference)
		88 g/d	0.99 (0.92, 1.06)
		153 g/d	0.98 (0.90, 1.06)
		219 g/d	0.98 (0.91, 1.06)
		263 g/d	0.95 (0.88, 1.04)
Weng et al., 2013 – ARIC [9]	Validated FFQ	89 g/d	1.00 (Reference)
		123 g/d	1.06 (0.94, 1.19)
		153 g/d	0.98 (0.87, 1.10)
		181 g/d	1.08 (0.96, 1.22)

		225 g/d	1.06 (0.93, 1.20)
Yogurt			
Alonso et al., 2009 – ARIC [20]	Validated FFQ	2 g/d 74 g/d 319 g/d	1.00 (Reference) 1.01 (0.89, 1.14) 1.11 (0.86, 1.41)
Buendia et al., 2018 – NHS [21]	Validated SFFQ	7 g/d 22 g/d 53 g/d 123 g/d 175 g/d	1.00 (Reference) 1.00 (0.97, 1.02) 0.99 (0.96, 1.01) 0.95 (0.92, 0.98) 0.87 (0.81, 0.94)
Buendia et al., 2018 – NHSII [21]		7 g/d 22 g/d 53 g/d 123 g/d 175 g/d	1.00 (Reference) 0.96 (0.93, 1.00) 0.95 (0.92, 0.98) 0.93 (0.90, 0.97) 0.89 (0.82, 0.96)
Buendia et al., 2018 – HPFS [21]		7 g/d 22 g/d 53 g/d 123 g/d 175 g/d	1.00 (Reference) 0.98 (0.93, 1.02) 0.94 (0.89, 0.99) 0.95 (0.89, 1.01) 1.01 (0.89, 1.15)
Engberink et al., 2009 – MORGEN [22]	Validated SFFQ	12 g/d 29 g/d 70 g/d 122 g/d	1.00 (Reference) 0.91 (0.74, 1.09) 0.86 (0.71, 1.05) 0.91 (0.74, 1.09)
Kim et al., Brit J Nutr, 2017 – KoGES [23]	Validated SFFQ	0 g/d 20 g/d 49 g/d 78 g/d	1.00 (Reference) 0.67 (0.58, 0.76) 0.71 (0.62, 0.81) 0.71 (0.59, 0.85)
Steffen et al., 2005 – CARDIA [24]	Validated SFFQ	4 g/d 11 g/d 18 g/d	1.00 (Reference) 1.00 (0.83, 1.20) 0.88 (0.75, 1.04)
Wang et al., 2008 – WHS [17]	Validated SFFQ	8 g/d 16 g/d 88 g/d 193 g/d	1.00 (Reference) 0.95 (0.90, 1.01) 0.95 (0.89, 1.01) 0.93 (0.81, 1.07)
Wang et al., 2015 – FHS [25]	Validated FFQ	0 g/d 227 g/d	1.00 (Reference) 0.95 (0.90, 0.99)
Dairy Desserts			
Alonso et al., 2009 – ARIC [17]	Validated FFQ	14 ml/d 273 ml/d 533 ml/d	1.00 (Reference) 0.91 (0.83, 0.99) 0.88 (0.74, 1.04)
Steffen et al., 2005 – CARDIA [20]	Validated SFFQ	4 ml/d 21 ml/d 40 ml/d 72 ml/d 93 ml/d	1.00 (Reference) 0.81 (0.67, 0.98) 0.87 (0.71, 1.05) 0.79 (0.65, 0.97) 0.74 (0.60, 0.92)
Wang et al., 2008 – WHS [22]	Validated SFFQ	8 ml/d 17 ml/d 89 ml/d 196 ml/d 250 ml/d	1.00 (Reference) 1.08 (1.02, 1.14) 1.04 (0.97, 1.10) 1.13 (0.98, 1.31) 0.90 (0.76, 1.07)
100% Fruit Juice			
Auerbach et al., 2017 – WHI [4]	Validated SFFQ	0 ml/d 30 ml/d 77 ml/d	1.00 (Reference) 0.98 (0.94, 1.01) 0.97 (0.94, 1.01)

		145 ml/d 231 ml/d	0.98 (0.94, 1.01) 1.01 (0.97, 1.04)
Duffey et al., 2010 – CARDIA [13]	Validated SFFQ	0 ml/d 114 ml/d	1.00 (Reference) 0.89 (0.82, 0.97)
Fruit Drinks			
Mirmiran et al. 2015 – TLGS [7]	Validated SFFQ	1 ml/d 8 ml/d 20 ml/d 67 ml/d	1.00 (Reference) 2.00 (0.71, 5.66) 1.91 (0.65, 5.60) 1.28 (0.04, 3.94)
Sweet Snacks			
Asghari et al., 2016 – TLGS [26]	Validated SFFQ	7 g/d 19 g/d 35 g/d 73 g/d	1.00 (Reference) 1.17 (0.45, 3.93) 2.49 (0.82, 7.59) 2.18 (0.70, 6.81)

Table S1. Search terms.

	MEDLINE		EMBASE		Cochrane
1	sugar*.mp.	1	sugar*.mp.	1	sugar*.mp.
2	exp fructose/	2	exp sugar/	2	exp fructose/
3	fructose.mp.	3	exp fructose/	3	fructose.mp.
4	HFCS.mp.	4	fructose.mp.	4	HFCS.mp.
5	exp High Fructose Corn Syrup/	5	HFCS.mp.	5	exp Nutritive Sweeteners/
6	sucrose.mp.	6	exp high fructose corn syrup/	6	sucrose.mp.
7	exp Dietary Sucrose/	7	sucrose.mp.	7	exp dietary sucrose/
8	sugar sweetened beverage*.mp.	8	exp dietary sucrose/	8	sugar sweetened beverage*.mp.
9	SSB.mp.	9	sugar sweetened beverage*.mp.	9	ssb.mp.
10	soda.mp.	10	SSB.mp.	10	soda.mp.
11	soft drink*.mp.	11	soda.mp.	11	soft drink*.mp.
12	exp Carbonated Beverages/	12	soft drink*.mp.	12	exp carbonated beverages/
13	carbonated beverages.mp.	13	exp soft drink/	13	non alcoholic beverage*.mp.
14	non alcoholic beverage*.mp.	14	exp Carbonated Beverages/	14	nonalcoholic beverage*.mp.
15	nonalcoholic beverage*.mp.	15	carbonated beverages.mp.	15	exp energy drinks/
16	exp Energy Drinks/	16	non alcoholic beverage*.mp.	16	energy drink*.mp.
17	energy drink*.mp.	17	nonalcoholic beverage*.mp.	17	smoothie*.mp.
18	smoothie*.mp.	18	exp energy drink/	18	((fruit or vegetable) and juice*).mp.
19	exp "Fruit and Vegetable Juices"/	19	energy drink*.mp.	19	fruit.mp.
20	fruit.mp.	20	smoothie*.mp.	20	exp fruit/
21	exp Fruit/	21	exp "fruit and vegetable juice"/	21	exp honey/
22	exp Honey/	22	fruit.mp.	22	y*g*rt.mp.
23	y*g*rt.mp.	23	exp fruit/	23	exp yogurt/
24	exp Yogurt/	24	exp honey/	24	ice cream*.mp.
25	ice cream*.mp.	25	y*g*rt.mp.	25	icecream*.mp.
26	icecream*.mp.	26	exp yoghurt/	26	exp ice cream/
27	exp Ice Cream/	27	exp ice cream/	27	cereal*.mp.
28	cereal*.mp.	28	ice cream*.mp.	28	dessert*.mp.
29	exp edible grain/	29	icecream*.mp.	29	sweets.mp.
30	dessert*.mp.	30	cereal*.mp.	30	confection*.mp.
31	sweets.mp.	31	dessert*.mp.	31	pastries.mp.
32	confection*.mp.	32	sweets.mp.	32	biscuit*.mp.
33	pastries.mp.	33	confection*.mp.	33	cookie*.mp.
34	biscuit*.mp.	34	exp bakery product/	34	cake*.mp.
35	cookie*.mp.	35	pastries.mp.	35	candy.mp.
36	cake*.mp.	36	biscuit*.mp.	36	candies.mp.
37	candy.mp.	37	cookie*.mp.	37	exp candy/

Table S1. Search terms (Continued)

MEDLINE		EMBASE		Cochrane	
38	candies.mp.	38	cake*.mp.	38	(chocolate adj2 milk).mp.
39	exp Candy/	39	candy.mp.	39	chocolate.mp
40	(chocolate adj2 milk).mp.	40	candies.mp.	40	exp cacao/
41	exp chocolate/	41	(chocolate adj2 milk).mp.	41	cacao.mp
42	chocolate.mp	42	exp chocolate/	42	or/1-41
43	exp cacao/	43	chocolate.mp	43	cohort.mp.
44	cacao.mp	44	exp cacao/	44	exp Prospective Studies/
45	or/1-44	45	cacao.mp	45	(prospective adj2 (cohort or study)).mp.
46	cohort.mp.	46	or/1-45	46	exp follow-up studies/
47	exp prospective study/	47	cohort.mp.	47	exp multivariate analysis/
48	(prospective adj2 (cohort or study)).mp.	48	exp prospective study/	48	exp proportional hazards models/
49	exp Follow-Up Studies/	49	(prospective adj2 (cohort or study)).mp.	49	follow up study.mp.
50	exp Multivariate Analysis/	50	exp multivariate analysis/	50	(longitudinal adj2 study).mp.
51	exp Proportional Hazards Models/	51	exp proportional hazards model/	51	or/43-50
52	follow up study.mp.	52	follow up study.mp.	52	hypertensive*.mp.
53	(longitudinal adj2 study).mp.	53	(longitudinal adj2 study).mp.	53	exp Hypertension/
54	or/46-53	54	or/47-53	54	hypertension*.mp.
55	hypertensive*.mp.	55	hypertensive*.mp.	55	HTN.mp.
56	exp Hypertension/	56	exp Hypertension/	56	blood pressure.mp.
57	hypertension*.mp.	57	hypertension*.mp.	57	exp Blood Pressure/
58	HTN.mp.	58	HTN.mp.	58	systolic blood pressure.mp.
59	blood pressure.mp.	59	blood pressure.mp.	59	SBP.mp.
60	exp Blood Pressure/	60	exp Blood Pressure/	60	diastolic blood pressure.mp.
61	systolic blood pressure.mp.	61	systolic blood pressure.mp.	61	DBP.mp.
62	SBP.mp.	62	SBP.mp.	62	or/52-61
63	diastolic blood pressure.mp.	63	diastolic blood pressure.mp.	63	and/42,51,62
64	DBP.mp.	64	DBP.mp.		
65	or/55-64	65	or/55-64		
66	and/45,54,65	66	and/46,54,65		

Database	Total
MEDLINE: December week 2 2018	1,063
EMBASE: December week 2 2018	2,428
Cochrane: December week 2 2018	173
Manual search	5
Total	**3,669**

The original search was conducted November week 1 2016. The search was updated twice, to December week 2 2018.

Table S2. Definitions of food categories.

Sugar-sweetened beverages (SSBs)	
Barrio-Lopez et al., 2013 – SUN [1]	Sugar-sweetened carbonated colas; fruit-flavoured carbonated sugar soft drinks
Cohen et al., 2012 – NHS, NHSII, HPFS [2]	Sugar-sweetened cola; sugar-sweetened caffeine-free cola; sugar-sweetened non-cola; and fruit punch or other sugar-sweetened fruit drink
Dhingra et al., 2007 – FOC [3]	Soft drinks (Coke, Pepsi, Sprite, or other carbonated soft drinks) – caffeinated or non-caffeinated
Duffey et al., 2010 – CARDIA [4]	Sugar-sweetened soda; fruit drinks
Kang et al., 2017 – KoGES [5]	Soft drinks (carbonated beverages, e.g., Cola and Sprite)
Kwak et al., 2018 – KoGES [6]	Soft drinks (coke or sprite) and other sweetened drinks (sweetened rice drink and sweetened citrus tea)
Mirmiran et al., 2015 – TLGS [7]	Sugar-sweetened carbonated soft drinks
Sayon-Orea et al., 2015 – SUN [8]	Sugar-sweetened carbonated colas; fruit-flavored carbonated sugar soft drinks
Weng et al., 2013 – ARIC [9]	Not specified
Winkelmayer et al., 2005 – NHS, NHSII [10]	Regular cola (Coke, Pepsi, or other cola beverages with sugar)
Fruit	
Borgi et al., 2016 – NHS, NHSII, HPFS [11]	Whole fruits: raisins/grapes; fresh apples/pears; bananas; strawberries; blueberries; prunes; avocado; cantaloupe; oranges; peaches/apricots/plums
Kim et al., J Acad Nutr Diet, 2017 – KoGES [12]	Tangerines, oranges, persimmon or dried persimmon, watermelon, strawberry, grape, pear, oriental melon/melon, peach or prune, apple, banana, and tomato
Auerbach et al., 2017 – WHI [13]	Not specified
Koochakpoor et al., 2018 – TLGS [14]	
Nunez-Cordoba et al., 2009 – SUN [15]	
Psaltopoulou et al., 2004 – EPIC [16]	
Steffen et al., 2005 – CARDIA [17]	
Tsubota-Utsugi et al., 2011 – Ohasama [18]	
Wang et al., 2012 – WHS [19]	
Weng et al., 2013 – ARIC [9]	
Yogurt	
Wang et al., 2008 – WHS [20]	Low-fat yogurt
Buendia et al., 2018 – NHS, NHSII, HPFS [21]	Yogurt (all types)
Alonso et al., 2009 – ARIC [22]	Not specified
Engberink et al., 2009 – MORGEN [23]	
Kim et al., Brit J Nutr, 2017 – KoGES [24]	
Steffen et al., 2005 – CARDIA [17]	
Wang et al., 2015 – FHS [25]	
Dairy desserts	
Steffen et al., 2005 – CARDIA [17]	Dairy desserts (not specified)
Wang et al., 2008 – WHS [20]	Low-fat sherbet
Alonso et al., 2009 – ARIC [22]	Ice cream
100% Fruit juice	
Duffey et al., 2010 – CARDIA [4]	Fruit juice (non-sweetened)
Auerbach et al., 2017 – WHI [13]	100% fruit juice
Fruit drinks	
Mirmiran et al., 2015 – TLGS [7]	Fruit juice – sugar-sweetened drinks and non-sweetened
Sweet snacks	
Asghari et al., 2016 – TLGS [26]	Candies, chocolates, cookies, cakes, biscuits, confectionery, caramels, and traditional Iranian confectioneries, such as gaz, sohan, noghl, halva, Yazdi cakes

Table S3. Confounding variables among the 26 articles on food sources of fructose-containing sugars and incident hypertension.

Cohort Study	Alonso et al., 2009 – ARIC [22]	Asghari et al., 2016 – TLGS [26]	Auerbach et al., 2017 – WHI [13]	Buendia et al., 2018 – HPFS, NHS, NHSII [21]	Barrio-Lopez et al., 2013 – SUN [1]	Borgi et al., 2016 – HPFS [11]	Borgi et al., 2016 – NHSII [11]	Borgi et al., 2016 - NHS [11]	Cohen et al., 2012 – HPFS [2]	Cohen et al., 2012 – NHSII [2]	Cohen et al., 2012 – NHS [2]	Dhingra et al., 2007 - FOC [3]	Duffey et al., 2010 – CARDIA [4]	Engberink et al., 2009 – MORGEN [23]	Kang et al., 2017 – KoGES [5]	Kim et al., Brit J Nutr, 2017 – KoGES [24]	Kim et al., J Acad Nutr Diet, 2017 – KoGES [12]	Koochakpoor et al., 2018 – TLGS [14]	Kwak et al., 2018 – KoGES [6]	Mirmiran et. al., 2015 – TLGS [7]	Nunez-Cordoba et al., 2009 – SUN [15]	Psaltopoulou et al., 2004 – EPIC [16]	Sayon-Orea et al., 2015 – SUN [8]	Steffen et al., 2005 – CARDIA [17]	Tsubota-Utsugi et al., 2011 - Ohasama [18]	Wang et al., 2008 – WHS [20]	Wang et al., 2012 – WHS [19]	Wang et al., 2015 – FHS [25]	Wang e al., 2013 – ARIC [9]	Winkelmayer et al., 2005 – NHS [10]	Winkelmayer et al., 2005 – NHSII [10]
Number of variables in fully adjusted model	14	7	14	11	12	15	17	16	21	22	22	11	12	13	13	12	16	8	15	11	12	10	22	10	12	16	17	10	9	8	9
Number of multivariable models presented	1	2	1	2	1	1	1	1	2	2	2	1	1	3	2	2	3	1	3	3	1	1	2	1	2	2	4	3	3	1	1
Timing of measurement of confounding variables	BL	BL	BL	Every 2y	BL	BL*	BL*	BL*	BL*	BL*	BL*	BL	BL	BL	BL†	BL†	BL†	BL	Every 2y	BL	BL	BL	BL	BL	BL	BL	BL	BL	Every exam ‡	BL	Every 2y	Every 2y
Pre-specified primary confounding variable																															
Age	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pre-specified secondary confounding variables																															
Smoking	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Markers of overweight/obesity (body mass index, weight, waist circumference, waist to hip ratio)	✓§	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓		✓	✓	✓§	✓		✓	✓	✓	✓		✓	✓
Energy intake	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		
Physical activity	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Sex	✓	✓	F‖	F‖/ M#	✓	M#	F‖	F‖	M#	F‖	F‖	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	F‖	F‖	✓	✓	F‖	F‖
Diabetes			✓												✓				✓							✓	✓	✓				
Alcohol consumption	✓				✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓		✓		✓	✓	✓	✓	✓			✓	✓
Sodium intake	✓		✓																✓		✓		✓		✓				✓		
Other confounding variables																															
Family history of HTN				✓		✓	✓	✓	✓	✓	✓										✓		✓							✓	✓
Attempting to lose weight									✓	✓	✓																				
Baseline blood pressure												✓														✓					
Baseline soft drink intake																															
Change in weight						✓	✓	✓	✓	✓	✓																				
Diet:																															
DASH style diet									✓	✓	✓																				

Cohort Study	Alonso et al., 2009 – ARIC [22]	Asghari et al., 2016 – TLGS [26]	Auerbach et al., 2017 – WHI [13]	Buendia et al., 2018 – HPFS, NHS, NHSII [21]	Barrio-Lopez et al., 2013 – SUN [1]	Borgi et al., 2016 – HPFS [11]	Borgi et al., 2016 – NHSII [11]	Borgi et al., 2016 - NHS [11]	Cohen et al., 2012 – HPFS [2]	Cohen et al., 2012 – NHSII [2]	Cohen et al., 2012 – NHS [2]	Dhingra et al., 2007 - FOC [3]	Duffey et al., 2010 – CARDIA [4]	Engberink et al., 2009 – MORGEN [23]	Kang et al., 2017 – KoGES [5]	Kim et al., Brit J Nutr, 2017 – KoGES [24]	Kim et al., J Acad Nutr Diet, 2017 – KoGES [12]	Kooc hakpoor et al., 2018 – TLGS [14]	Kwak et al., 2018 – KoGES [6]	Mirmiran et. al., 2015 – TLGS [7]	Nunez-Cordoba et al., 2009 – SUN [15]	Psaltopoulou et al., 2004 – EPIC [16]	Sayon-Orea et al., 2015 – SUN [8]	Steffen et al., 2005 – CARDIA [17]	Tsubota-Utsugi et al., 2011 - Ohasama [18]	Wang et al., 2008 – WHS [20]	Wang et al., 2012 – WHS [19]	Wang et al., 2015 – FHS [25]	Wenge al., 2013 – ARIC [9]	Winkelmayer et al., 2005 – NHS [10]	Winkelmayer et al., 2005 – NHSII [10]
Modified Dietary Guidelines Adherence Index (DGAI) score																												✓			
Mediterranean diet adherence					✓																										
Healthy Eating Index (HEI) score			✓																												
Energy from other beverages:																															
ASBs						✓	✓	✓	✓	✓	✓																		✓	✓	
Caffeinated tea, coffee														✓						✓									✓	✓	
Caffeinated coffee																												✓			
Fruit juice													✓**																		
Low fat milk													✓																		
SSBs						✓	✓	✓					✓**																		
Whole fat milk													✓																		
Bread														✓																	
Calcium									✓	✓	✓					✓															
Carbohydrates									✓	✓	✓																				
Glycemic index												✓																			
Total fructose									✓	✓	✓																				
Cereals																							✓								
Fast food					✓																										
Fat															✓											✓						
Saturated fat												✓																			
Trans fat									✓	✓	✓	✓																			
Fiber		✓							✓	✓	✓	✓			✓	✓				✓											
French fries					✓																										
Fruit	✓			✓										✓						✓			✓				✓				
Legumes																	✓						✓								
Low fat dairy																					✓		✓					✓			
Whole fat dairy																			✓				✓								
Total Dairy																	✓		✓												

Cohort Study	Alonso et al., 2009 – ARIC [22]	Asghari et al., 2016 – TLGS [26]	Auerbach et al., 2017 – WHI [13]	Buendia et al., 2018 – HPFS, NHS, NHSII [21]	Barrio-Lopez et al., 2013 – SUN [1]	Borgi et al., 2016 – HPFS [11]	Borgi et al., 2016 – NHSII [11]	Borgi et al., 2016 - NHS [11]	Cohen et al., 2012 – HPFS [2]	Cohen et al., 2012 – NHSII [2]	Cohen et al., 2012 – NHS [2]	Dhingra et al., 2007 - FOC [3]	Duffey et al., 2010 – CARDIA [4]	Engberink et al., 2009 – MORGEN [23]	Kang et al., 2017 – KoGES [5]	Kim et al., Brit J Nutr, 2017 – KoGES [24]	Kim et al., J Acad Nutr Diet, 2017 – KoGES [12]	Koochakpoor et al., 2018 – TLGS [14]	Kwak et al., 2018 – KoGES [6]	Mirmiran et. al., 2015 – TLGS [7]	Nunez-Cordoba et al., 2009 – SUN [15]	Psaltopoulou et al., 2004 – EPIC [16]	Sayon-Orea et al., 2015 – SUN [8]	Steffen et al., 2005 – CARDIA [17]	Tsubota-Utsugi et al., 2011 - Ohasama [18]	Wang et al., 2008 – WHS [20]	Wang et al., 2012 – WHS [19]	Wang et al., 2015 – FHS [25]	Wenge al., 2013 – ARIC [9]	Winkelmayer et al., 2005 – NHS [10]	Winkelmayer et al., 2005 – NHSII [10]
Magnesium									✓	✓	✓	✓																			
Meat/meat products/animal flesh					✓	✓	✓	✓						✓			✓														
Fish														✓							✓		✓								
Red meat					✓															✓			✓			✓	✓				
Nuts																											✓				
Olive oil																							✓								
Potassium	✓																✓		✓				✓								
Protein intake				✓																											
Vegetables	✓			✓		✓	✓	✓						✓						✓			✓			✓	✓				
Vitamin D									✓	✓	✓																				
Whole grains						✓	✓	✓									✓		✓		✓					✓	✓				
Vitamin use																									✓		✓	✓				
Medical history																															
CVD															✓	✓	✓		✓							✓						
Family History of Diabetes		✓																		✓											
Hypercholesterolemia																										✓	✓	✓				
Menopausal status			✓				✓	✓																			✓	✓				
Non-narcotic analgesics use						✓	✓	✓	✓	✓	✓																				
Oral contraceptive use							✓			✓	✓																				✓
Post-menopausal hormone use			✓																									✓			
Socio-economic status														✓		✓		✓													
Education			✓												✓		✓		✓			✓	✓	✓					✓		
Income															✓		✓		✓												
Ethno-cultural/geographical factors																															
Ethnicity			✓	✓		✓	✓	✓	✓	✓	✓		✓												✓		✓	✓		✓		
Exam center	✓												✓												✓					✓		
Study visit	✓																														
Residence (urban vs. rural)																✓	✓					✓									
Others																															
(Alcohol)[2]																							✓								

Cohort Study	Alonso et al., 2009 – ARIC [22]	Asghari et al., 2016 – TLGS [26]	Auerbach et al., 2017 – WHI [13]	Buendia et al., 2018 – HPFS, NHS, NHSII [21]	Barrio-Lopez et al., 2013 – SUN [1]	Borgi et al., 2016 – HPFS [11]	Borgi et al., 2016 – NHSII [11]	Borgi et al., 2016 - NHS [11]	Cohen et al., 2012 – HPFS [2]	Cohen et al., 2012 – NHSII [2]	Cohen et al., 2012 – NHS [2]	Dhingra et al., 2007 - FOC [3]	Duffey et al., 2010 – CARDIA [4]	Engberink et al., 2009 – MORGEN [23]	Kang et al., 2017 – KoGES [5]	Kim et al., Brit J Nutr, 2017 – KoGES [24]	Kim et al., J Acad Nutr Diet, 2017 – KoGES [12]	Koochakpoor et al., 2018 – TLGS [14]	Kwak et al., 2018 – KoGES [6]	Mirmiran et. al., 2015 – TLGS [7]	Nunez-Cordoba et al., 2009 – SUN [15]	Psaltopoulou et al., 2004 – EPIC [16]	Sayon-Orea et al., 2015 – SUN [8]	Steffen et al., 2005 – CARDIA [17]	Tsubota-Utsugi et al., 2011 - Ohasama [18]	Wang et al., 2008 – WHS [20]	Wang et al., 2012 – WHS [19]	Wang et al., 2015 – FHS [25]	Weng e al., 2013 – ARIC [9]	Winkelmayer et al., 2005 – NHS [10]	Winkelmayer et al., 2005 – NHSII [10]
(BMI)[2]									✓	✓	✓																				
Interactions btwn: (age and residence), (age and sex), (sex and residence)																						✓									
Interactions between: (follow-up time and physical activity), (follow-up time and age)																												✓			
Randomized treatment			✓																								✓	✓			
SNP for cyclin D2 polymorphism																		✓													

BL = Confounders measured only at baseline year
* Baseline for all confounders except for [change in weight], which was per food frequency questionnaire cycle
† Baseline for all confounders except for dietary confounders, which was assessed at baseline and follow-up
‡ Exams were (1991-1995), (1995-1998), (1998-2001), (2005-2008)
§ Both BMI and waist-to-hip ratio were controlled for
|| Indicates the study includes only female subjects
# Indicates the study includes only male subjects
** Fruit juice analysis controlled for SSB intake, whereas SSB analysis controlled for fruit juice intake
✓ Means variable adjusted for in the most adjusted model.

Table S4. Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Cohort Studies.

Study	Selection*	Outcome †	Comparability ‡	Total §
Alonso et al., 2009 [22]	4	3	2	9
Asghari et al., 2016 [26]	4	3	1	8
Auberbach et al., 2017 [13]	3	1	2	6
Barrio-Lopez et al., 2013 [1]	3	3	2	7
Borgi et al., 2016 [11]	3	2	2	6
Buenda et al., 2018 [21]	2	2	1	5
Cohen et al., 2012 [2]	3	2	2	6
Dhingra et al., 2007 [3]	4	2	1	6
Duffey et al., 2010 [4]	4	1	2	7
Engberink et al., 2009 [23]	3	2	1	6
Kang et al., 2017 [5]	4	2	2	8
Kim et al., Br J Nutr, 2017 [24]	4	2	2	8
Kim et al., J Acad Nutr Diet, 2017 [12]	4	2	2	8
Koochakpoor et al., 2018 [14]	4	3	1	8
Kwak et al., 2018 [6]	4	2	2	8
Mirmiran et al., 2015 [7]	4	3	1	8
Nun˜ez-Cordoba et al., 2009 [15]	3	3	2	7
Psaltopoulou et al., 2004 [16]	3	2	1	6
Sayon-Orea et al., 2015 [8]	3	2	2	6
Steffen et al., 2005 [17]	4	2	1	7
Tsubota-Utsugi et al., 2011 [18]	4	2	2	7
Wang et al., 2008 [20]	3	2	2	6
Wang et al., 2012 [19]	3	1	2	5
Wang et al., 2015 [9]	3	2	1	6
Weng et al., 2013 [9]	4	3	1	8
Winkelmayer et al., 2005 [10]	3	3	1	6

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

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

‡ Maximum 2 points awarding for controlling for the pre-specified primary confounding variable (age) and ≥ 6 of the secondary confounding variables (sex, any marker of adiposity, smoking, energy intake, physical activity, diabetes/dysglycemia, alcohol intake, sodium intake).

§ A maximum of 9 points could be awarded.

Table S5. Sensitivity analysis with systematic removal of each study.

Removal of:	Participants N	Cases N	Risk Ratio for Incident Hypertension			Heterogeneity	
			RR	95% CI	p-value	I^2	p-value
SSBs							
All included:	427,630	120,553	1.17	[1.11, 1.23]	<0.00001	66%	0.0004
Barrio-Lopez, Brit J Nutr, 2013 - SUN	8157	1464	1.14	[1.09, 1.20]	<0.00001	58%	0.006
Cohen, J Gen Intern Med, 2012 - HPFS	37360	13439	1.19	[1.12, 1.26]	<0.00001	66%	0.0006
Cohen, J Gen Intern Med, 2012 - NHS	88540	42022	1.19	[1.11, 1.28]	<0.00001	66%	0.0002
Cohen, J Gen Intern Med, 2012 - NHSII	97991	21873	1.18	[1.10, 1.25]	<0.00001	67%	0.0005
Dhingra, Circulation, 2007 - FOC	2803	1377	1.17	[1.11, 1.24]	<0.00001	69%	0.0002
Duffrey, Am J Clin Nutr, 2010 - CARDIA	2639	609	1.19	[1.12, 1.27]	<0.00001	63%	0.002
Kang, Brit J Nutr, 2017 - KoGES	4591	1309	1.15	[1.09, 1.21]	<0.00001	64%	0.001
Kwak, Eur J Nutr, 2018 - KoGES	5775	1175	1.17	[1.10, 1.24]	<0.00001	69%	0.0003
Mirmiran, Nutr Metab, 2015 - TLGS	424	47	1.16	[1.10, 1.22]	<0.00001	65%	0.0008
Sayon-Orea, Clin Nutr, 2015 - SUN	13843	1308	1.16	[1.10, 1.22]	<0.00001	67%	0.0005
Weng, Nutrients, 2013 - ARIC	9913	2853	1.18	[1.12, 1.25]	<0.00001	67%	0.0004
Winkelmayer, JAMA, 2005 - NHS	61091	19541	1.16	[1.10, 1.23]	<0.00001	68%	0.0003
Winkelmayer, JAMA, 2005 - NHSII	94503	13536	1.16	[1.10, 1.23]	<0.00001	68%	0.0003
Fruit							
All included:	281,120	148,928	0.81	[0.73, 0.89]	<0.0001	88%	<0.00001
Auerbach, Prev med, 2017 - WHI	80539	46202	0.77	[0.68, 0.87]	<0.0001	87%	<0.00001
Borgi, Hypertension, 2016 - HPFS	20010	16752	0.79	[0.70, 0.89]	<0.0001	89%	<0.00001
Borgi, Hypertension, 2016 - NHS	39164	35375	0.78	[0.69, 0.88]	<0.0001	89%	<0.00001
Borgi, Hypertension, 2016 - NHS II	63885	25246	0.79	[0.71, 0.88]	<0.0001	89%	<0.00001
Kim, J Acad Nutr Diet, 2017 - KoGES (men)	2085	606	0.84	[0.77, 0.93]	0.0005	86%	<0.00001
Kim, J Acad Nutr Diet, 2017 - KoGES (women)	2172	552	0.87	[0.80, 0.94]	0.0009	80%	<0.00001
Koochakpoor, Nutr Res, 2018 - TLGS	1284	640	0.80	[0.72, 0.89]	<0.0001	89%	<0.00001
Nun˜ez-Cordoba, Eur J Clin Nutr, 2009 - SUN	8594	426	0.80	[0.72, 0.89]	<0.0001	89%	<0.00001
Psaltopoulou, Am J Clin Nutr, 2004 - EPIC	20343	5424	0.82	[0.74, 0.91]	0.0002	88%	<0.00001
Steffen, Am J Clin Nutr, 2005 - CARDIA	4304	997	0.81	[0.73, 0.90]	0.0001	88%	<0.00001
Tsubota-Utsugi, J Hum Hypertens, 2011 - Ohasama	745	222	0.82	[0.74, 0.91]	0.0001	88%	<0.00001
Wang, Am J Hypertens, 2012 - WHS	28082	13633	0.78	[0.69, 0.88]	<0.0001	89%	<0.00001
Weng, Nutrients, 2013 - ARIC	9913	2853	0.78	[0.70, 0.87]	<0.00001	89%	<0.00001
Yogurt							
All included:	235705	97783	0.96	[0.86, 0.96]	0.0007	54%	0.03
Alonso, Eur J Clin Nutr, 2009 - ARIC	8208	2399	0.90	[0.85, 0.95]	0.0002	54%	0.03
Buendia, J Hypertens, 2018 - HPFS	30512	14166	0.90	[0.85, 0.95]	0.0002	53%	0.04
Buendia, J Hypertens, 2018 - NHS	69298	41934	0.92	[0.86, 0.98]	0.007	53%	0.04
Buendia, J Hypertens, 2018 - NHSII	84368	26282	0.91	[0.85, 0.97]	0.006	59%	0.02
Engberink, J Nutr, 2009 - MORGEN	3454	713	0.91	[0.86, 0.97]	0.002	58%	0.02
Kim, Brit J Nutr, 2017 - KoGES	4335	1556	0.92	[0.88, 0.96]	0.0003	**30%**	**0.19**
Steffen, Am J Clin Nutr, 2005 - CARDIA	4304	997	0.91	[0.86, 0.97]	0.002	60%	0.02
Wang, Brit J Nutr, 2015 - FHS	28886	8710	0.90	[0.84, 0.96]	0.002	53%	0.04
Wang, Hypertension, 2008 - WHS	2340	1026	0.90	[0.85, 0.96]	0.0008	58%	0.02

Each study was removed independently and the pooled estimate recalculated. The red and blue lines represent the original pooled risk estimate with all studies included. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant 50\%$ is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals.

Table S6. GRADE assessment.

Quality assessment								Study event rates (%)	Effect	Quality
No. of comparisons	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Other considerations		Relative Risk [95% CI]	Importance
SSBs intake on incident hypertension (follow-up median 10.0 years)										
13 [24, 26-29, 32, 38, 44-46]	Observational studies	No serious	Serious*	No serious	No serious	Detected†	Dose-response gradient‡	28%	RR 1.17 [1.11, 1.23]	⊕⊕⊖⊖ Low *,†, ‡
Fruit intake on incident hypertension (follow-up median 9.0 years)										
13 [25, 30, 31, 33, 34, 36, 40, 46, 48, 49]	Observational studies	No serious	Serious§	No serious	No serious	Detected ‖	Dose-response gradient#	53%	RR 0.81 [0.73, 0.89]	⊕⊕⊖⊖ Low §, ‖, #
Yogurt intake on incident hypertension (follow-up median 14.6 years)										
9 [33, 35, 37, 41-43, 47]	Observational studies	No serious	Serious**	No serious	Serious††	Not detected‡‡	Dose-response gradient§§	41%	RR 0.91 [0.86, 0.96]	⊕⊕⊖⊖ Low **,††,‡‡,§§
Dairy desserts intake on incident hypertension (follow-up median 10.0 years)										
3 [33, 35, 42]	Observational studies	No serious	No serious	No serious	Serious††	Not detected‡‡	None	29%	RR 0.85 [0.76, 0.95]	⊕⊖⊖⊖ Very low ††,‡‡
100% Fruit juice intake on incident hypertension (follow-up median 13.9 years)										
2 [28, 40]	Observational studies	No serious	Serious‖‖	No serious	No serious##	Not detected‡‡	Dose-response gradient***	56%	RR 0.95 [0.85, 1.07]	⊕⊕⊖⊖ Low ‡‡,‖‖,##,***
Fruit drinks intake on incident hypertension (follow-up 3.6 years)										
1 [29]	Observational study	No serious	No serious	Serious†††,‡‡‡	Serious§§§	Not detected‡‡	None	11%	RR 1.27 [0.43, 3.75]	⊕⊖⊖⊖ Very low ‡‡,†††,‡‡‡,§§§
Sweet snacks intake on incident hypertension (follow-up 3.6 years)										
1 [39]	Observational study	No serious	No serious	Serious†††,‡‡‡	Serious‖‖‖	Not detected‡‡	None	11%	RR 2.00 [0.84, 4.76]	⊕⊖⊖⊖ Very low ‡‡,***,†††,‖‖‖

* Downgrade for serious inconsistency, as there was evidence of substantial inter-study heterogeneity (I^2=66%, p=0.0004)

† There was evidence of funnel plot asymmetry via visual inspection and both the Egger (p=0.02) and Begg test were significant (p=0.04). Adjustment for funnel plot asymmetry by the recalculation of the pooled estimate by inputting missing studies using the Duvall and Tweedie trim and fill method did not alter the significance of the relationship, with only limited attenuation of the summary estimate (RR=1.12 [95% CI, 1.05-1.19]).

‡ Upgrade for dose-response gradient, as there was a significant harmful dose-response relationship between SSBs intake and hypertension with evidence for non-linearity (p=0.02).

§ Downgrade for serious inconsistency, as there was evidence of substantial inter-study heterogeneity (I^2=88%, p<0.00001).

‖ There was evidence of funnel plot asymmetry as the Begg test was significant (p=0.09), although the Egger test was not significant (p=0.70). The Duvall and Tweedie trim and fill method did not perform any trimming and the pooled estimate did not change.

Upgrade for dose-response gradient, as there was a significant protective and linear dose-response relationship between fruit intake and hypertension.

** Downgrade for serious inconsistency, as there was evidence of substantial inter-study heterogeneity (I^2=54%, p=0.03)

†† Downgrade for serious imprecision, as the upper CI bound crosses the clinically important protection threshold of RR=0.9.

‡‡ Bias cannot be excluded since we were unable to test for funnel plot asymmetry due to lack of power (<10 cohorts included in the analysis).

§§ Upgrade for dose-response gradient, as there was a significant protective dose-response relationship between yogurt intake and hypertension with evidence for non-linearity (p=0.02).

‖‖ Downgrade for serious inconsistency, as there was evidence of substantial inter-study heterogeneity (I^2=85%, p=0.01).

Although pairwise meta-analysis showed serious imprecision, this imprecision was explained by non-linear dose-response analysis.

*** Upgrade for dose-response gradient, as there was a significant U-shaped dose-response relationship between 100% fruit juice intake and hypertension (P-value for non-linearity=0.001).

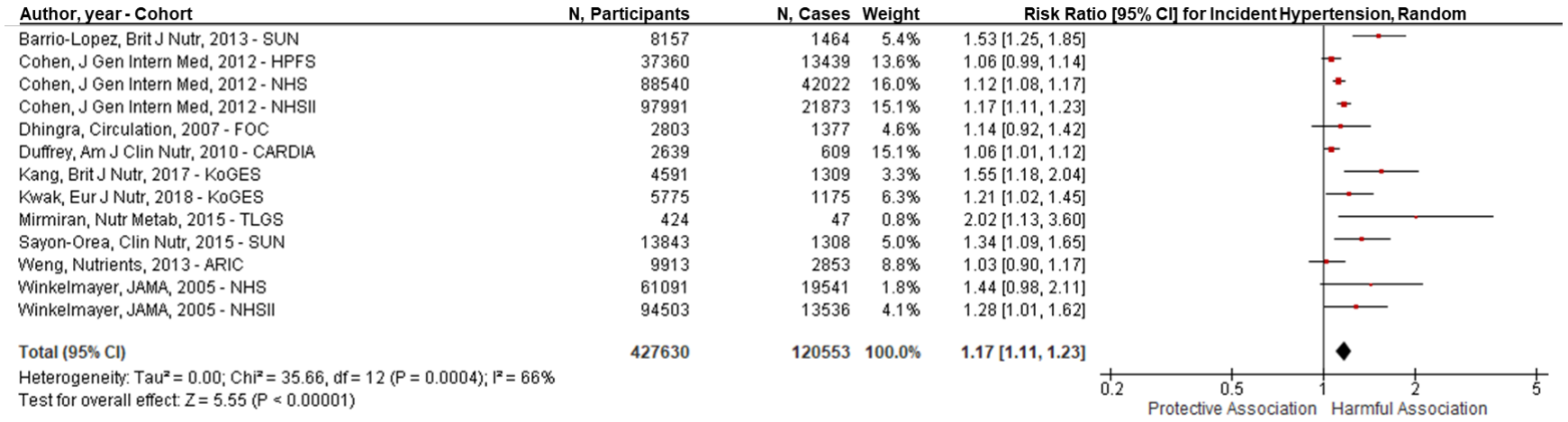
††† Downgrade for serious indirectness due to limited number of cohort comparisons in specific groups which may not be generalizable to the general population.

‡‡‡ Downgrade for serious indirectness, as only number of cases of metabolic syndrome was reported.

§§§ Downgrade as the sample sizes were very small (n=424) and the 95% CI were very large (0.43, 3.75) containing evidence of both clinically important protection (RR<0.9) and harm (RR>1.1).

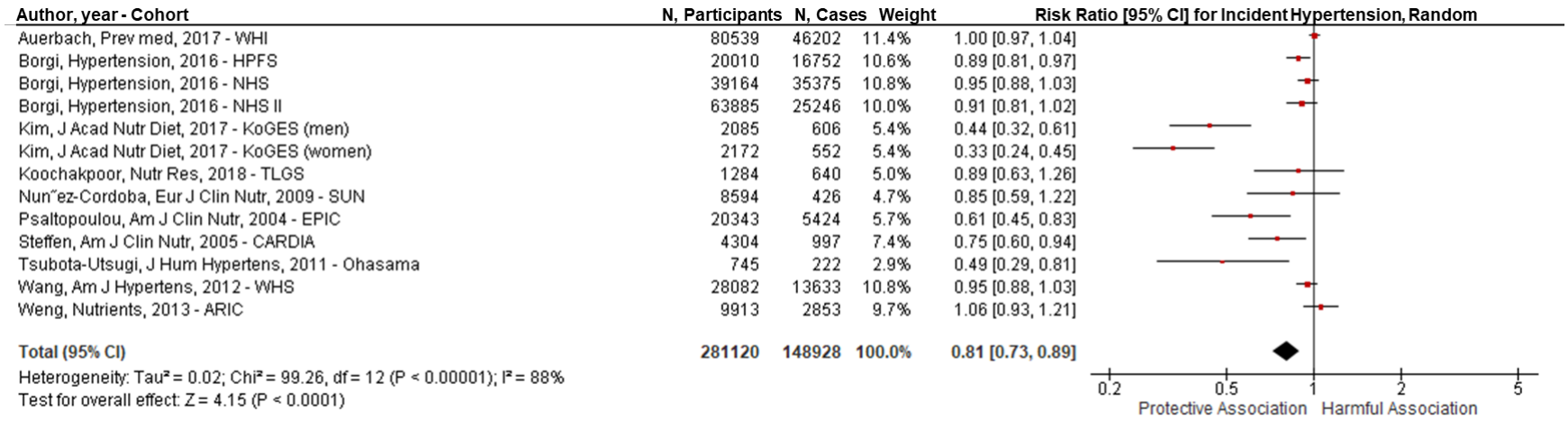
‖‖‖ Downgrade as the sample size was very small (n=439) and the 95% CI were very large (0.84, 4.76) containing evidence of both clinically important protection (RR<0.9) and harm (RR>1.1)

Figure S1. Forest plot – Pairwise meta-analysis of SSBs intake and incident hypertension.



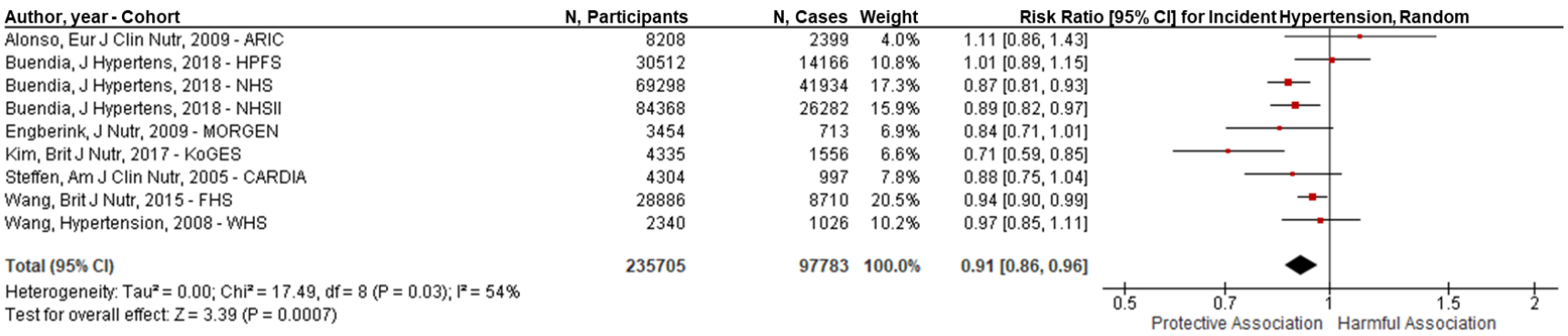
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant$ 50% is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals

Figure S2. Forest plot – Pairwise meta-analysis of fruit intake and incident hypertension.



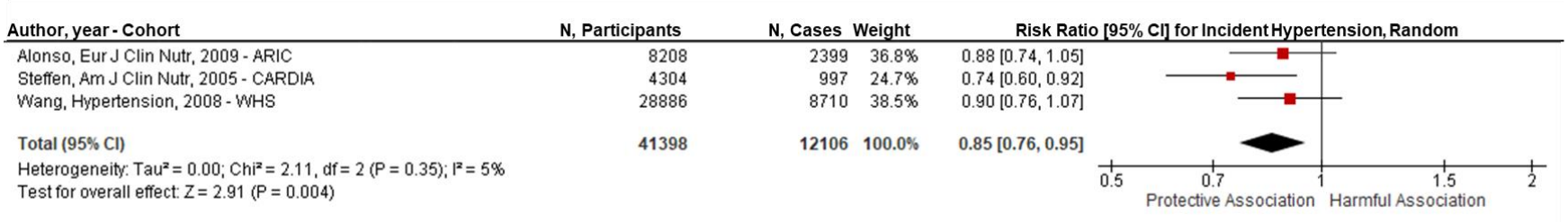
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant 50\%$ is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals. Mirmiran et al. only reported cases of metabolic syndrome.

Figure S3. Forest plot – Pairwise meta-analysis of yogurt intake and incident hypertension.



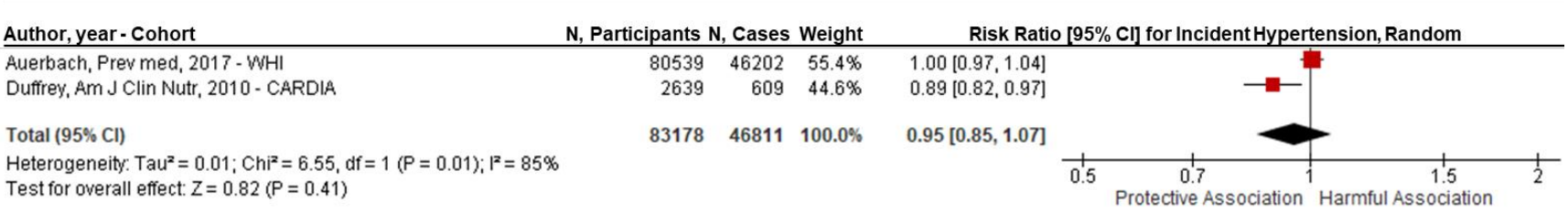
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant$ 50% is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals.

Figure S4. Forest plot – Pairwise meta-analysis of dairy desserts intake and incident hypertension.



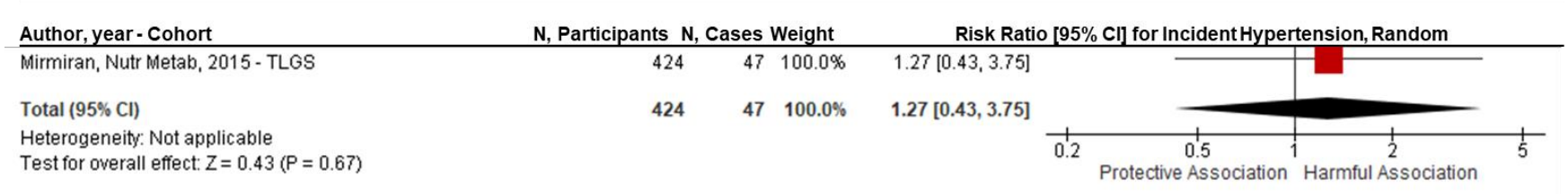
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant$ 50% is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals.

Figure S5. Forest plot – Pairwise meta-analysis of 100% fruit juice intake and incident hypertension.



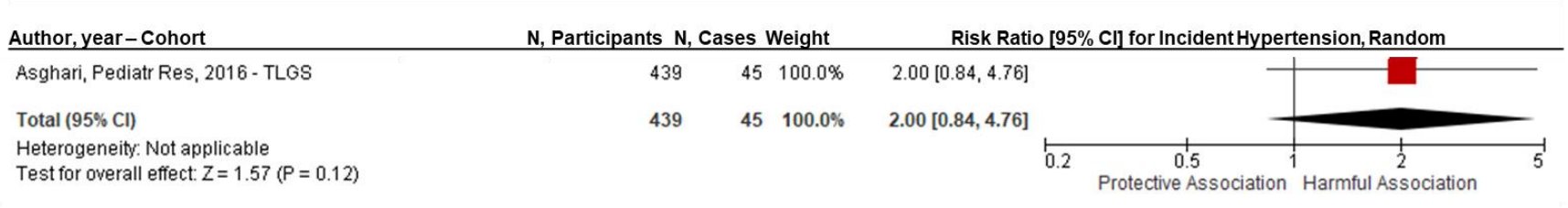
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant$ 50% is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals.

Figure S6. Forest plot – Pairwise meta-analysis of fruit drinks intake and incident hypertension.



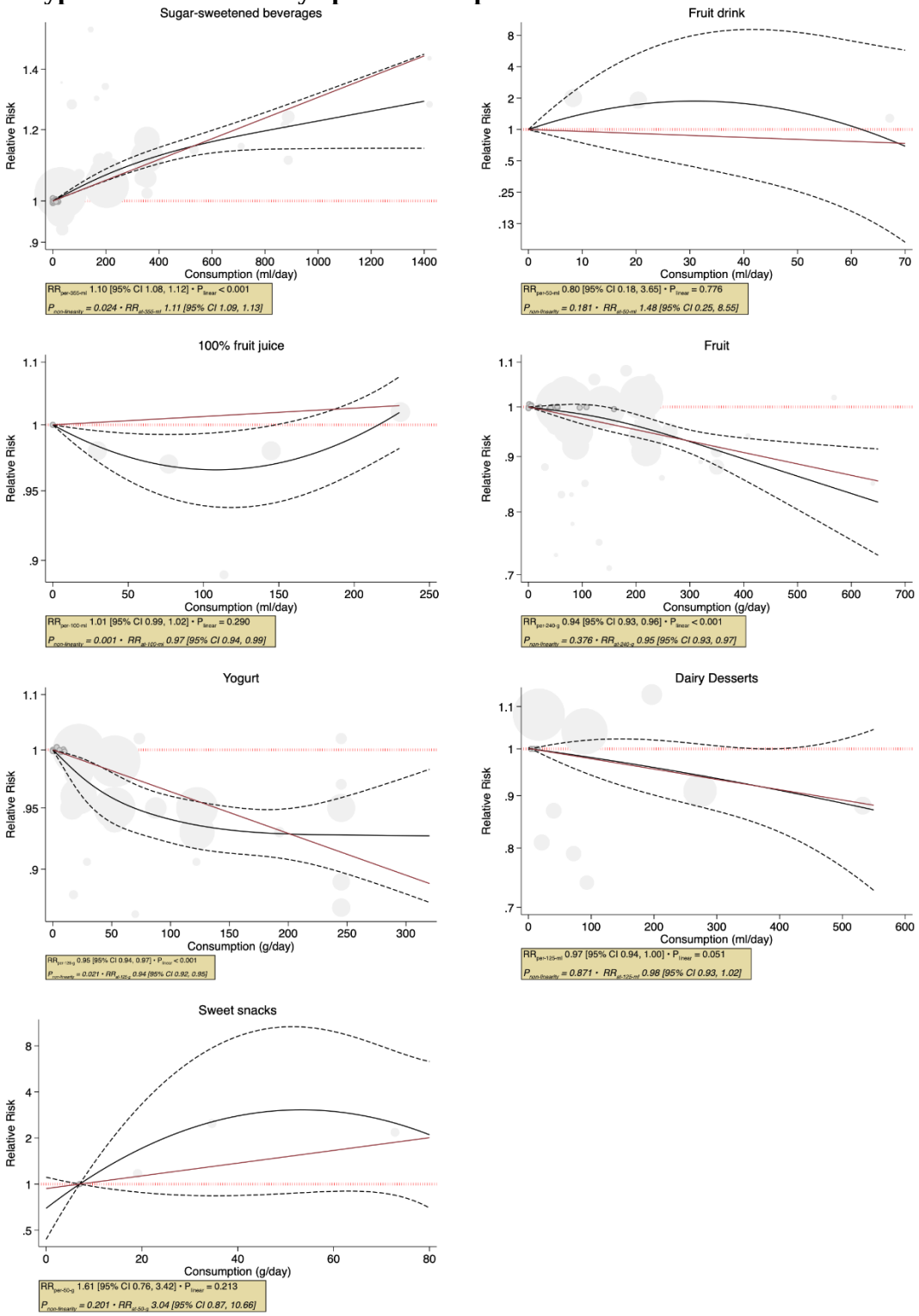
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant$ 50% is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals. *Study only reported cases of metabolic syndrome.

Figure S7. Forest plot – Pairwise meta-analysis of sweet Snacks intake and incident hypertension.



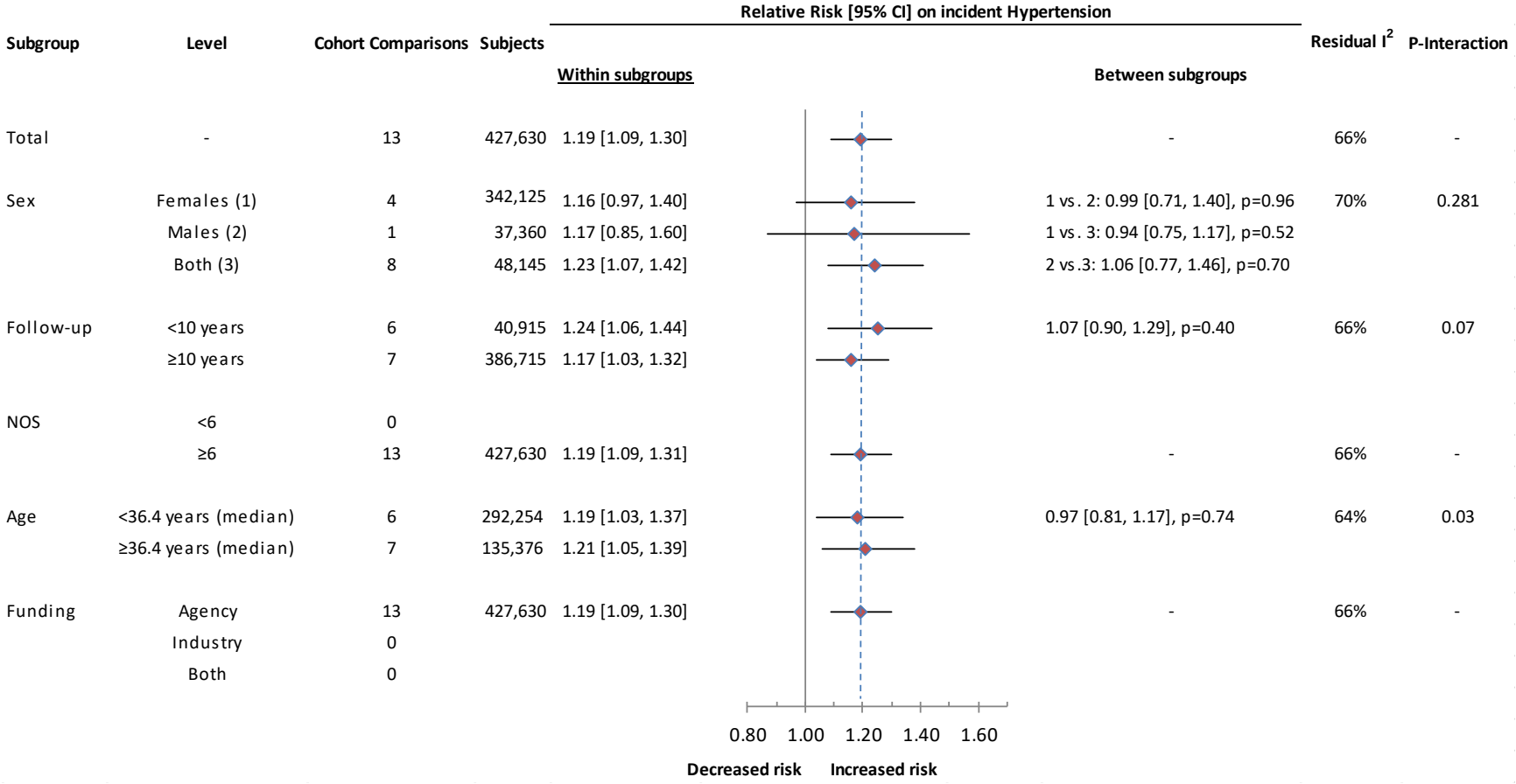
The black diamond represents the pooled risk estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (Chi^2) at a significance level of $p<0.10$, and quantified by the I^2 statistic. An I^2 value $\geqslant$ 50% is considered to indicate substantial heterogeneity. All results are presented as Relative Risks (RR) with 95% Confidence Intervals. *Study only reported cases of metabolic syndrome.

Figure S8. Dose-response relation between sources of fructose-containing sugars and incident hypertension with study-specific data points.



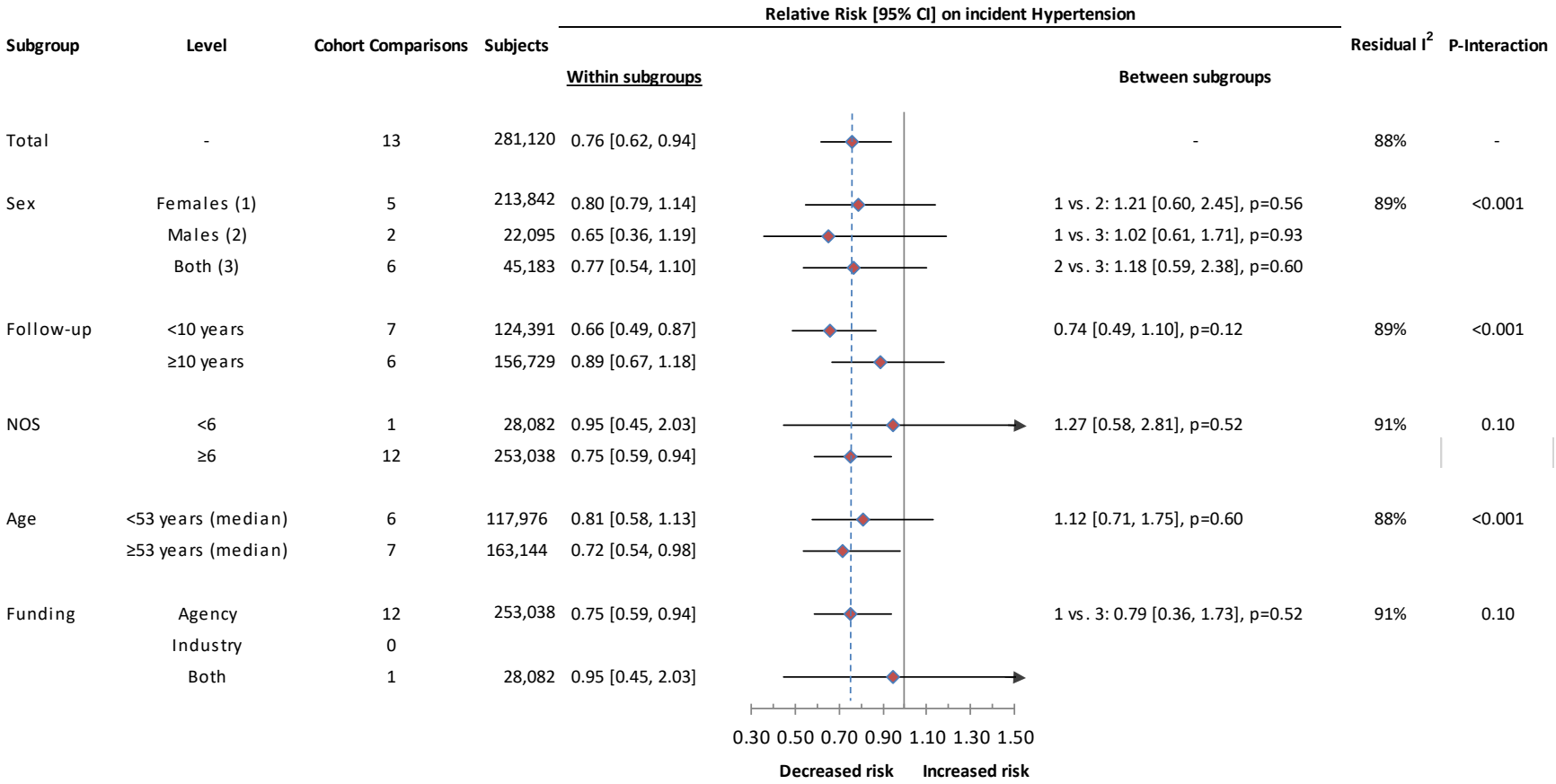
Dose-response relationship between intake of SSBs, fruit, 100% fruit juice, yogurt, fruit drink, dairy desserts, and sweet snacks with risk of hypertension. Red line represents the linear and black lines represent the non-linear models, respectively. Dotted lines represent 95% confidence intervals of the non-linear model. The light gray circles represent the relative risk-point estimates for the different doses from each study; the size of the circle is related to inverse of the variance. The smaller gray circles with dark gray outline represent the baseline dose category for each separate study; random-noise has been added in the graphic display for these baseline circles to show them separately.

Figure S9. Subgroup analyses of SSBs intake and incident hypertension.



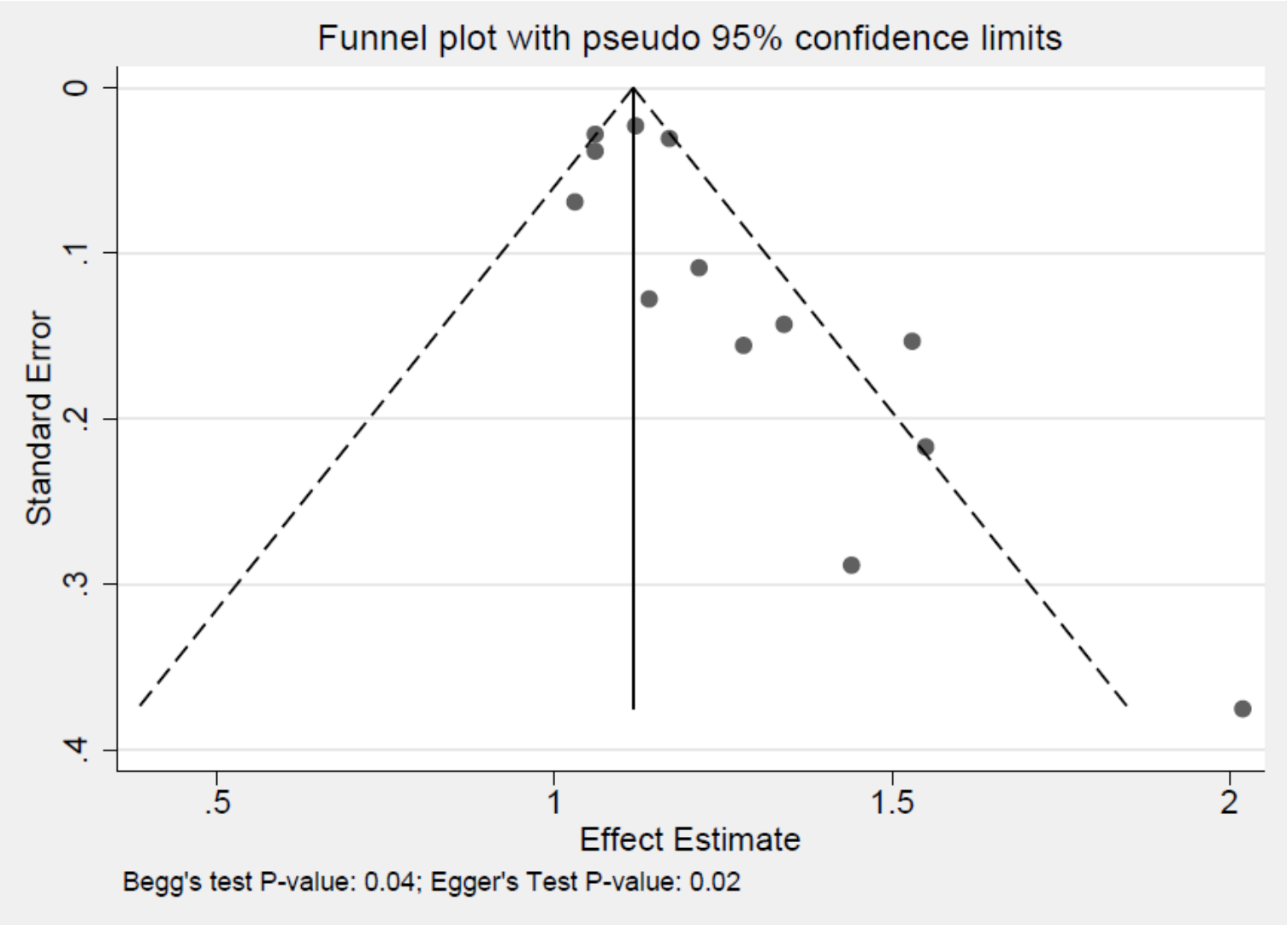
RR, relative risk; NOS, Newcastle-Ottawa Scale. Point estimates for each subgroup level (diamonds) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup.

Figure S10. Subgroup analyses of fruit intake and incident hypertension.



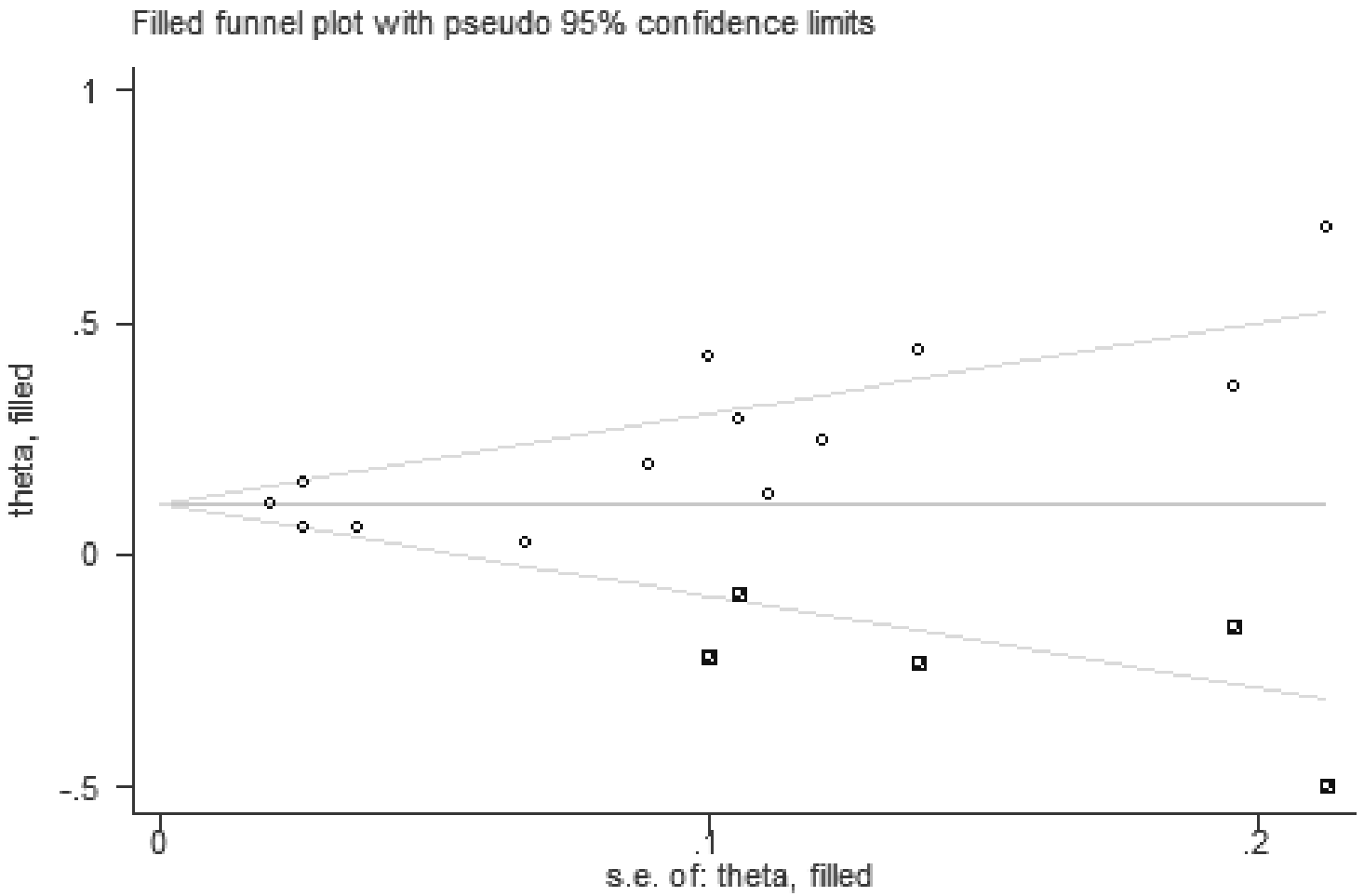
RR, relative risk; NOS, Newcastle-Ottawa Scale. Point estimates for each subgroup level (diamonds) are the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup.

Figure S11. Funnel plot of natural logarithm relative risk (RR) for incident hypertension comparing the highest and lowest quantiles of SSBs intake.



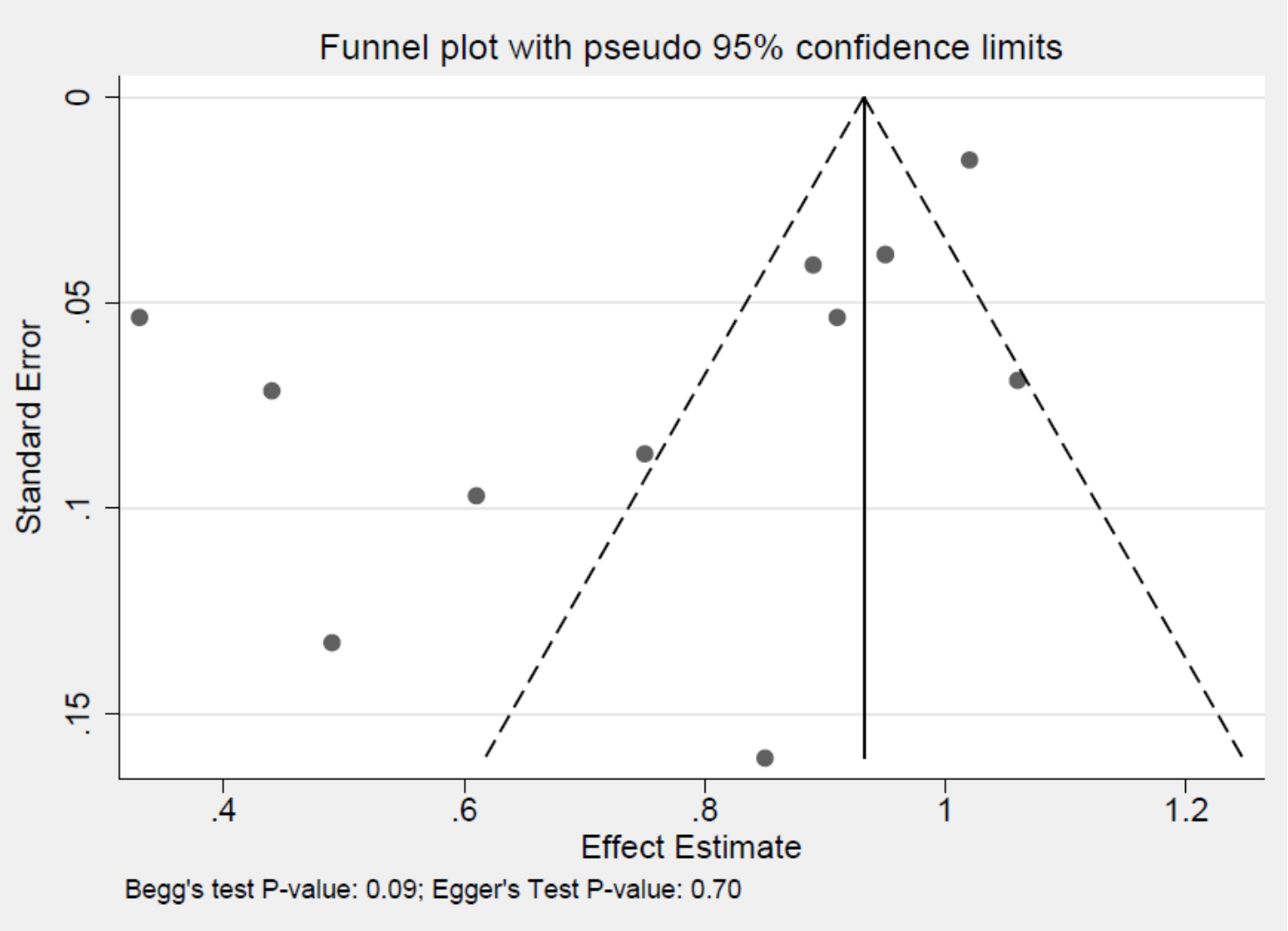
The vertical line represents the pooled effect estimate expressed as natural logarithm RR. Dashed lines represent pseudo-95% confidence intervals (CI). The circles represent risk effects for each cohort, and the horizontal lines represent standard errors of the effect estimate.

Figure S12. Trim and fill funnel plot of natural logarithm relative risk (RR) for incident hypertension comparing the highest and lowest quantiles of SSBs intake.



The horizontal line represents the pooled effect estimate expressed as natural logarithm RR. Diagonal lines represent pseudo-95% confidence intervals (CI). The circles represent risk effects for each cohort, and the squares represent filled data points. The horizontal axis represents standard errors of the effect estimate. Adjustment for funnel plot asymmetry by the recalculation of the pooled estimate by inputting missing cohort studies using the Duvall and Tweedie trim and fill method did not alter the significance of the relationship with only limited attenuation of the summary estimate (RR=1.12 [95% CI, 1.05, 1.19] versus original RR=1.17 [95% CI, 1.11, 1.23]).

Figure S13. Funnel plot of natural logarithm relative risk (RR) for incident hypertension comparing the highest and lowest quantiles of fruit intake.



The vertical line represents the pooled effect estimate expressed as natural logarithm RR. Dashed lines represent pseudo-95% confidence intervals (CI). The circles represent risk effects for each cohort, and the horizontal lines represent standard errors of the effect estimate.

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