Appendix 1 (as supplied by the authors): Supporting information

Non-nutritive sweeteners and cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials and prospective cohort studies

Table S1. MEDLINE (OVID) Search Strategy.

1	non-nutritive sweeteners/ (18)
2	((non-nutriti$ or nonnutriti$ or artificial$ or low calori$) adj3 sweeten$).ti,ab. (966)
3	intens$ sweetener?.ti,ab. (128)
4	(artificial sugar? or sugar free or sugarfree or reduced sugar? or sugar replac$ or sugar? substitute or sugar? substitutes or (artificial$ adj3 sweeten$)).ti,ab. (1693)
5	aspartame/ (816)
6	(aspartam? or aspartamum or canderel or (dipeptide adj (sweetener? or sweet)) or trisweet or tri-sweet or (equal adj brand?)).ti,ab. (1045)
7	(neotame or advantame).ti,ab. (62)
8	(asp-phe-ome or aspartylphenyl$ or (aspartyl$ adj3 (ester or phenylalanin$))).ti,ab. [http://chem.sis.nlm.nih.gov/chemidplus/rn/22839-47-0] (149)
9	Saccharin/ (2544)
10	(sac?hari$ or sac?harol or saxin or "sucre edulcor" or sucrette or sweeta or skose or zaharina or garantose or glucid or gluside or hermesetas or kandiset or natreen).ti,ab. (11689)
11	((benzo$ adj2 sulfimide) or benzosulfimide?).ti,ab. (5)
12	(sucralose or splenda).ti,ab. (321)
13	(trichlorogalacto-sucrose or trichlorosucrose or (trichloro$ adj3 sucrose)).ti,ab. [http://chem.sis.nlm.nih.gov/chemidplus/rn/56038-13-2] (5)
14	(aspartame or saccharin or sucralose or acetosulfam$ or Acesulfam$ or acesulpham$ or "Ace-K").ti. [most commonly used in foods] (1671)
15	Cyclamates/ (495)
16	(cyclamate? or Sugar twin or sucaryl).ti,ab. (623)
17	(cyclamic acid or cyclamsaeure or cyclohexanesulfamic acid or cyclohexylaminesulf$ acid).ti,ab. [http://chem.sis.nlm.nih.gov/chemidplus/rn/100-88-9] (15)
18	(goldswite or hermesetas or milisucre or nozucar or nutrasweet).ti,ab. (20)
19	(necta sweet or sucaryl or sugar twin or "sweet and low" or "sweet n low" or "sweet'n low" or sweet twin or (equal adj2 sweetener?)).ti,ab. (27)
20	(Palatinit$ or Isomalt$).ti,ab. (1672)
21	(Acesul??am$ or acetosul??am? or "Ace-K" or sunetta or "sweet one" or "swiss sweet").ti,ab. (273)
22	xylitol/ (2024)
23	xylitol.ti,ab. (2517)
24	(kannit or lkinit or newtol or xylite or xyliton or eutrit).ti,ab. (38)
25	stevia/ (168)
26	Steviol glycoside?.ti,ab. (110)
27	(stevia or truvia or purevia or enliten).ti,ab. (334)
28	(thaumatin? or tagatose or D-tagatose).ti,ab. (804)
29	(Luo Han Guo fruit extract? or Siraitia grosvenorii or Swingle fruit extract? or monk fruit extract? or nectresse or purelo or "monk fruit in the raw").ti,ab. (44)
30	Sweetening agents/ or Nutritive sweeteners/ [studies on sugar sweetened foods frequently report data on artificially sweetened foods] (4470)
31	(sweetening adj2 (agent? or substance or additiv$)).ti,ab. (189)
32	(sweetener? or sweetened or sweetner?).ti,ab. (4754)
33	or/1-32 [Sweeteners] (25534)
34	Carbonated Beverages/ (1924)
35	((calori$ free or (calori$ adj1 reduced) or diet or low calori$ or low cal or low sugar or non-calori$) adj2 (beverage? or carbonated or cocktail? or coffee or coffees or cola or colas or "dr pepper" or drink? or gingerale or ginger ale or iced tea? or lemonade? or limeade? or juice or juices or pop or pops or punch or punches or refreshment? or root beer or smoothy or smoothies or soda or sodas or sodapop? or soft drink? or softdrink? or sprite or "7-up" or tea or teas or water?)).ti,ab. (1196)
36	((diet or calori$ free or (calori$ adj1 reduced) or low calori$ or low cal or low sugar or non-calori$) adj2 (candies or candy or chocolate? or frozen dinner? or food or foods or snack$)).ti,ab. (1696)

37	or/34-36 [carbonated beverages frequently analysed for sugar content/nutritive; so consider this an independent set to OR with Sweetener set] (4670)
38	(letter or editorial or interview or news).pt. (1415344)
39	((letter or editorial or interview or news) and (randomized controlled trial or controlled clinical trial)).pt. (6015)
40	38 not 39 [for exclusion] (1409329)
41	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (928209)
42	exp animals/ not humans.sh. (3972666)
43	41 not 42 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing] (855824)
44	Pragmatic Clinical Trial/ or Clinical Trial/ or Multicenter study.pt. (616092)
45	(randomi?ed or placebo? or randomly or RCT$1).ti,ab. (643090)
46	random assignment?.ti,ab. (1765)
47	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).ti,ab. (132024)
48	trial.ti. (131316)
49	(controlled adj2 (study or studies)).ti,ab. or (controlled adj2 (trial or trials)).ab. (181503)
50	(multicentre or multicenter or multi-centre or multi-center).ti. or ((multicentre or multicenter or multi-centre or multi-center) adj1 (study or studies or trial or trials)).ab. (51865)
51	random assignment?.ti,ab. (1765)
52	exp "Clinical trials as topic"/ (282845)
53	(or/44-52) not (or/40,42) [Trial terms to supplement Cochrane filter] (1137053)
54	epidemiologic studies/ (6028)
55	Observational Study/ or Cohort studies/ or Longitudinal studies/ or Follow-up studies/ or "national longitudinal study of adolescent health"/ or prospective studies/ or comparative study/ or Intervention studies/ (2492591)
56	"controlled before-after studies"/ (17)
57	Interrupted Time Series Analysis/ (7)
58	((observational or cohort or longitudinal$ or followup or follow-up or prospectiv$ or comparative or intervention) adj3 (study or trial or trials or studies)).ti,ab. (584854)
59	(control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ti,ab. (502217)
60	("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw. (105165)
61	("time series" adj2 interrupt$).ti,ab,hw. (1127)
62	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ti,ab. (9697)
63	(or/54-62) not (or/40,42) [Observational Designs] (2581192)
64	(or/33,37) and (or/43,53,63) [set 1] (4674)
65	remove duplicates from 64 (4641)

Table S2. Study selection criteria.

Inclusion Criteria	1. Prospective, randomized, controlled trial of non-nutritive sweetener intervention, or Prospective observational cohort study reporting non-nutritive sweetener exposure 2. Non-nutritive sweetener exposure reported in adolescents (over 12 years of age) or adults 3. Minimum study duration of 6 months
Exclusion Criteria	1. Not original research (reviews, commentaries) 2. Non-human studies 3. Trials: a. Quasi-randomized, cross-over, or cluster randomized design b. Non-nutritive sweetener effects cannot be examined independently of other intervention components 4. Observational Studies: a. Cross sectional or retrospective design b. Analysis of non-nutritive sweetener effects was not fully prospective (associations presented for *change* in non-nutritive sweetener intake but not for baseline intakes) c. Non-nutritive sweetener associations with outcomes of interest were not adjusted for confounders/covariates. 5. No outcomes of importance to the review were reported or available via contact with study authors.

Table S3. Risk of bias assessments for randomized controlled trials evaluating non-nutritive sweetener and cardio-metabolic health, using the Cochrane Risk of Bias Tool.

Study	OVERALL	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Industry Funding
Blackburn et al. 1997 [1]	**HIGH**	Low	High	High	High	Low	High	Yes (Nutrasweet)
Hsieh et al. 2003 [2]	**LOW**	Low	Low	Low	Low	Low	Low	Not reported
Ferri et al. 2006 [3]	**UNCLEAR**	Low	Low	Low	Unclear	Unclear	Low	No
Tate et al. 2012 [4]	**HIGH**	Low	Low	High	Low	Low	Low	Yes (Nestle)
Maersk et al. 2012 [5]	**HIGH**	Unclear	High	High	Low	Unclear	High	No
Peters et al. 2016 [6]	**HIGH**	Low	Unclear	High	Unclear	Unclear	Unclear	Yes (American Beverage Association)
Madjd et al. 2015 [7]	**HIGH**	Low	Low	High	Low	Low	Low	No

Table S4. Key confounders considered in prospective cohort studies evaluating non-nutritive sweetener intake and long-term cardio-metabolic health.

Study	Cohort*	Key Confounders Considered										
		Age	Sex	BMI	Body Composition	Energy	Sugar or SSB	Diet Quality	Physical Activity	Race	SES	Smoking
Lutsey et al. 2008 [8]	ARIC	●	●			●		●	●	●	●	●
Bomback et al. 2010 [9]	ARIC	●	●	●		●				●	●	●
Palmer et al. 2008 [10]	BWHS	●	n				●	●	●	n	●	●
Duffey et al. 2012 [11]	CARDIA	●	●	●		●		●	●	●	●	●
Haines et al. 2007 [12]	EAT	●	●		●	●				●	●	
Lana et al. 2015 [13]	ENRICA	●	●	●		●		●	●		●	●
Fagherazzi et al. 2013 [14]	EPIC-E3N		n	●		●		●	●		●	●
O'Connor et al. 2015 [15]	EPIC-Norfolk	●	●	●	●	●	●		●		●	●
Dhingra et al. 2007 [16]	FOS	●	●			●		●	●			●
Field et al. 2014 [17]	GUTS II	●	●	●			●		●			
de Koning et al. 2012 [18]	HPFS	●	n	●		●		●	●			●
Bernstein et al. 2012 [19]	HPFS, NHS I	●	●	●		●	●	●	●			●
Bhupathiraju et al. 2013 [20]	HPFS, NHS I	●	●	●		●	●	●	●			●
Cohen et al. 2012 [21]	HPFS, NHS I, NHS II	●	●	●		●	●	●	●	●		●
Smith et al. 2015 [22]	HPFS, NHS I, NHS II	●	n	●			●		●			●
Gearon et al. 2014 [23]	MCCS	●	●	●			●	●	●		●	●
Nettleton et al. 2009 [24]	MESA	●	●	●	●	●			●	●	●	●
Fung et al. 2009 [25]	NHS I	●	n	●		●		●	●			●
Chen et al. 2009 [26]	NHS II	●	n	●			●	●	●	●		●
Pan et al. 2012 [27]	NHS II	●	n	●				●	●	●		●
Gardener et al. 2012 [28]	NOMAS	●	●	●	●		●	●	●	●	●	●
Parker et al. 1997 [29]	PHHP	●		●		●			●			●
Fowler et al. 2008 [30]	SAHS	●	●	●					●	●	●	●
Fowler et al. 2015 [31]	SAHS/SALSA	●	●	●	●				●	●	●	●
Sakurai et al. 2013 [32]	-	●	n	●		●	●		●			●
Barrio-Lopez et al. 2013 [33]	SUN	●	●	●		●		●	●			●
Bes-Rastrollo et al. 2006 [34]	SUN	●	●		●	●	●	●	●			●
Renault et al. 2015 [35]	TOP	●	n	●		●						●
Stinson et al. 2013 [36]	WHI	●	n	●		●	●		●	●	●	●
Vyas et al. 2015 [37]	WHI	●	n	●		●	●	●	●	●	●	●

BMI, body mass index; Body Comp., body composition (other than BMI); SES, socioeconomic status (education, income or occupation); SSB, sugar sweetened beverage. Sorted by cohort name. In some cases different outcomes from a single cohort are reported in separate studies, or multiple cohorts are reported in a single study.

*Cohort names: ARIC, Atherosclerosis Risk in Communities; BWHS, Black Women's Health Study; CARDIA, Coronary Artery Risk Development in Young Adults; E3N, Etude Epidemiologique aupres des femmes de la mutuelle generale de l'Education Nationale; EAT, Eating Among Teens; ENRICA, Study on Nutrition and Cardiovascular Risk in Spain; EPIC, European Prospective Investigation into Cancer and Nutrition; FOS, Framingham Offspring Study; GUTS II, Growing Up Today Study II; HPFS, Health Professionals Follow-Up Study; MCCS, Melbourne Collaborative Cohort Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHS, Nurses' Health Study; NOMAS, Northern Manhattan Study; PHHP, Pawtucket Heart Health Program; SAHS, San Antonio Heart Study; SALSA, San Antonio Longitudinal Study of Aging; SUN, Seguimiento Universidad de Navarra; TOP, Treatment of Obese Pregnant Women; WHI, Women's Health Initiative.

Table S5. Quality assessments for observational prospective cohort studies evaluating non-nutritive sweetener (NNS) intake using the Newcastle-Ottawa Scale.

Study	Cohort*	Quality Score (Max. 9)	Selection of Study Groups (Maximum 4) Representative cohort, Reliable NNS intake measure, Outcome not present at baseline	Comparability (Maximum 2) Controlled for baseline body composition and diet quality	Assessment (Maximum 3) Objective outcome measures, Follow up ≥1 year, Drop out <30%	Industry Funding
Lutsey et al. 2008 [8]	ARIC	8	****	*	***	No
Bomback et al. 2010 [9]	ARIC	9	****	**	***	No
Palmer et al. 2008 [10]	BWHS	6	***	**	*	No
Duffey et al. 2012 [11]	CARDIA	8	***	**	***	No
Haines et al. 2007 [12]	EAT	7	***	**	**	No
Lana et al. 2015 [13]	ENRICA	9	****	**	***	No
Fagherazzi et al. 2013 [14]	EPIC-E3N	8	***	**	***	No
O'Connor et al. 2015 [15]	EPIC-Norfolk	8	****	**	**	No
Dhingra et al. 2007 [16]	FOS	9	****	**	***	No
Field et al. 2014 [17]	GUTS II	6	***	*	**	No
de Koning et al. 2012 [18]	HPFS	8	***	**	***	No
Bernstein et al. 2012 [19]	HPFS, NHS I	8	***	**	***	No
Bhupathiraju et al. 2013 [20]	HPFS, NHS I	7	***	**	**	No
Cohen et al. 2012 [21]	HPFS, NHS I & II	8	***	**	***	No
Smith et al. 2015 [22]	HPFS, NHS I & II	6	***	**	*	No
Gearon et al. 2014 [23]	MCCS	8	***	**	***	Not reported
Nettleton et al. 2009 [24]	MESA	6	**	**	**	No
Fung et al. 2009 [25]	NHS I	8	***	**	***	No
Chen et al. 2009 [26]	NHS II	8	***	**	***	No
Pan et al. 2012 [27]	NHS II	7	***	**	**	No
Gardener et al. 2012 [28]	NOMAS	7	***	**	**	No
Parker et al. 1997 [29]	PHHP	9	****	**	***	No
Fowler et al. 2008 [30]	SAHS	7	***	*	***	No
Fowler et al. 2015 [31]	SAHS/SALSA	5	*	*	***	No
Sakurai et al. 2013 [32]	-	8	***	**	***	No
Barrio-Lopez et al. 2013 [33]	SUN	7	***	**	**	No
Bes-Rastrollo et al. 2006 [34]	SUN	8	****	**	**	No
Renault et al. 2015 [35]	TOP	7	***	**	**	No
Stinson et al. 2013 [36]	WHI	6	**	**	**	Not reported
Vyas et al. 2015 [37]	WHI	6	**	**	**	No

Sorted by cohort name. Red = low quality (0-6), Yellow = moderate quality (7-8), Green = high quality (9).
The Newcastle-Ottawa Scale requires certain evaluation criteria to be customized by the investigators. For the purpose of this review, we defined "adequate follow up duration" as ≥1 year and "adequate retention" as >70%. We also designated two "critical confounders": body composition at baseline (BMI or other measure of body composition), and diet (total energy or sugar intake, or a diet pattern or quality score). *Cohort names: ARIC, Atherosclerosis Risk in Communities; BWHS, Black Women's Health Study; CARDIA, Coronary Artery Risk Development in Young Adults; E3N, Etude Epidemiologique aupres des femmes de la mutuelle generale de l'Education Nationale; EAT, Eating Among Teens; ENRICA, Study on Nutrition and Cardiovascular Risk in Spain; EPIC, European Prospective Investigation into Cancer and Nutrition; FOS, Framingham Offspring Study; GUTS II, Growing Up Today Study II; HPFS, Health Professionals Follow-Up Study; MCCS, Melbourne Collaborative Cohort Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHS, Nurses' Health Study; NOMAS, Northern Manhattan Study; PHHP, Pawtucket Heart Health Program; SAHS, San Antonio Heart Study; SALSA, San Antonio Longitudinal Study of Aging; SUN, Seguimiento Universidad de Navarra; TOP, Treatment of Obese Pregnant Women; WHI, Women's Health Initiative.

Table S6. Subgroup analysis for non-nutritive sweetener (NNS) intake and weight change in randomized controlled trials.

Subgroup	N trials	Pooled SMD[95%CI] for NNS vs. control	I^2	p for subgroup differences	Citations
Overall	5	-0.17[-0.54, 0.21]	81%		1,4-7
Sex					
Females Only	2	0.04[-1.04, 1.11]	90%	0.58	1,7
Both Sexes	3	-0.29[-0.68, 0.10]	76%		4-6
On Weight Loss Program					
No	1	-0.12[-0.91, 0.66]	N/A	0.91	5
Yes	4	-0.17[-0.59, 0.25]			1,4,6,7
Industry Funding*					
No	2	0.30[-0.38, 0.99]	55%	0.09	5,7
Yes	3	-0.37[-0.71, -0.03]	77%		1,4,6
Intervention duration*					
6 months	3	0.13[-0.34, 0.59]	65%	0.0009	4,5,7
> 6 months	2	-0.55[-0.75, -0.34]	0%		1,6
Risk of Bias					
High	5	-0.17[-0.54, 0.21]	81%		1,4-7
Low or Unclear	0	N/A	N/A	N/A	

CI, confidence interval; NNS, non-nutritive sweetener; SMD, standardized mean difference.

*Both studies with >6 months duration were also industry-funded, making it difficult to isolate these factors.

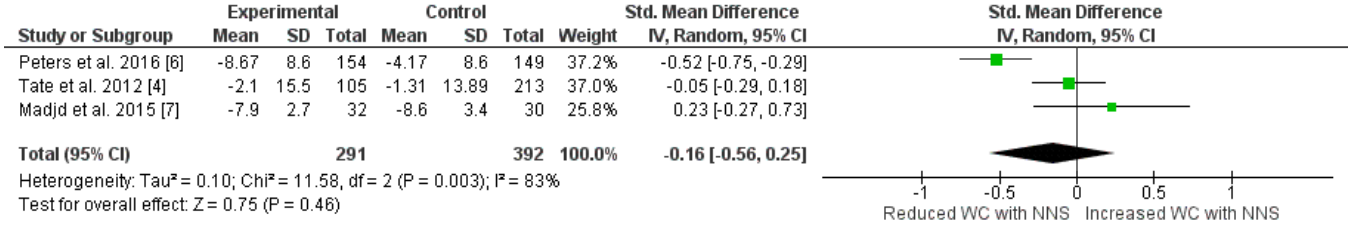
Table S7. Subgroup analysis for non-nutritive sweetener (NNS) intake and incident type 2 diabetes in cohort studies.

Subgroup	N* Cohorts	Pooled RR[95%CI] for highest vs. lowest NNS intake quantile	I^2	p for subgroup differences	Citations*
Overall	9	1.14[1.05, 1.25]	52%		10,14,15,20,24,27,32,36,38
Sex					
Male	2	1.31[0.86, 1.99]	74%	0.54	20,32
Female	6	1.14[1.02, 1.28]	57%		10,14,20,24,27,36
Baseline weight status					
Normal	3	1.99[1.21, 3.27]	0%	0.53	14,24,36
Overweight	3	1.61[1.08, 2.41]	37%		14,24,36
Obese	2	1.32[0.79, 2.21]	27%		14,36
Study quality					
Medium	6	1.13[1.02, 1.24]	60%	0.68	14,15,20,27,32,38
Low	3	1.19[0.94, 1.50]	57%		10,24,36
Mean age at baseline					
< 50 years	3	1.14[0.91, 1.43]	60%	0.86	10,27,32
≥ 50 years	6	1.17[1.05, 1.30]	56%		14,15,20,24,36,38
Mean follow up duration					
< 15 years	5	1.25[1.08, 1.45]	13%	0.11	10,15,24,32,36,38
≥ 15 years	4	1.09[1.00, 1.19]	60%		14,20,27
Minimum NNS dose in highest intake quantile					
< 1 serving/day	3	1.44[1.10, 1.89]	50%	0.14	14,15,32
1 serving/day	4	1.09[1.01, 1.16]	25%		10,20,24,38
> 1 serving/day	2	1.09[0.87, 1.36]	26%		27,36

CI, confidence interval; RR, risk ratio; NNS, non-nutritive sweetener.

*Some studies contribute data from multiple cohorts; some studies contribute stratified data to more than one sub-group; some studies do not contribute data for all sub-groups if stratified data were not available.

A) Waist circumference change in randomized controlled trials (NNS vs. comparator)



B) Incident overweight in cohort studies (comparing extreme NNS intake quantiles)

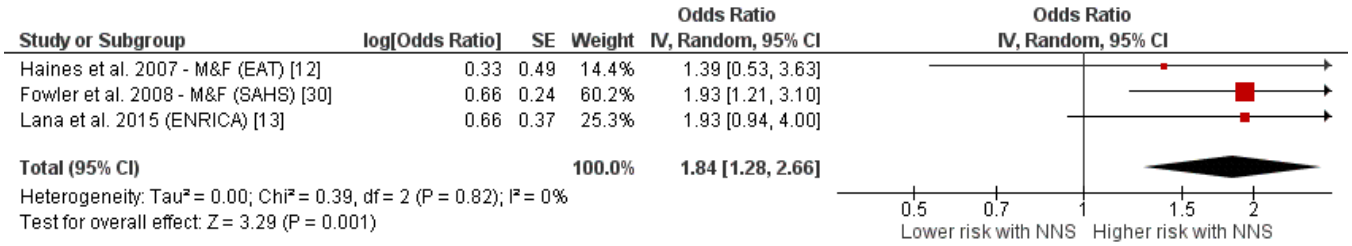
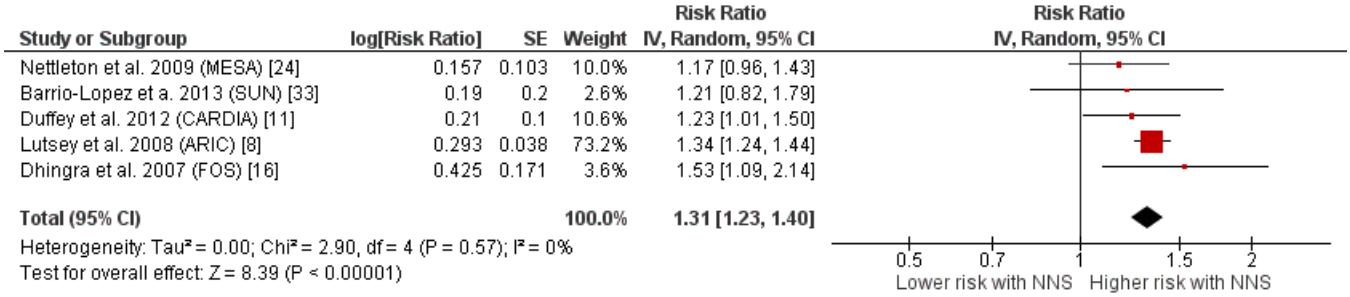


Figure S1. Non-nutritive sweeteners (NNS) and adiposity or overweight in randomized controlled trials and cohort studies. A) Waist circumference (WC) change in randomized controlled trials; B) incident overweight in cohort studies, comparing highest vs. lowest non-nutritive sweetener intake quantiles. Data from males and females (M&F) were pooled within studies that reported sex-stratified results. Cohort acronyms are defined in **Table S4**.

A) Metabolic syndrome in cohorts (highest vs. lowest NNS intake quantiles)



B) Type 2 diabetes in cohorts (per unit NNS intake)

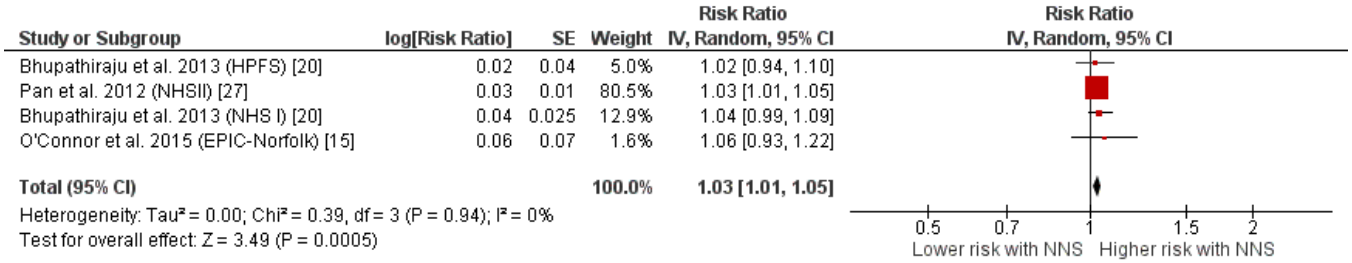


Figure S2. Non-nutritive sweeteners (NNS) and incident metabolic outcomes in cohort studies. (A) Metabolic syndrome for highest vs. lowest non-nutritive sweetener intake quantiles; (B) Type 2 diabetes per unit non-nutritive sweetener intake. Cohort acronyms are defined in **Table S4**.

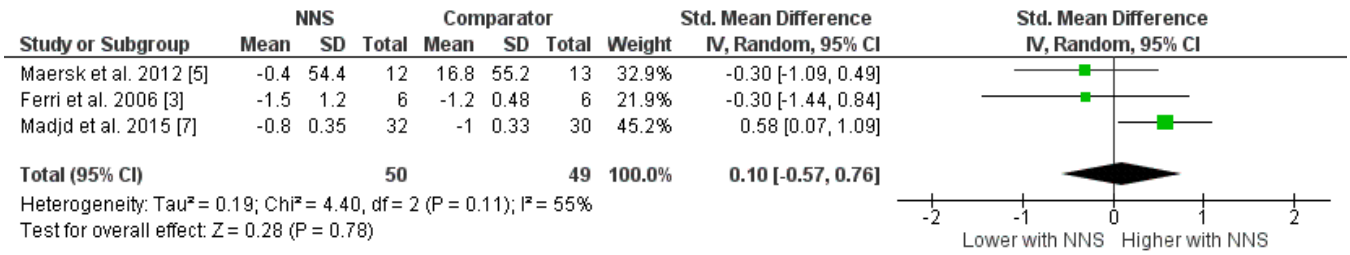
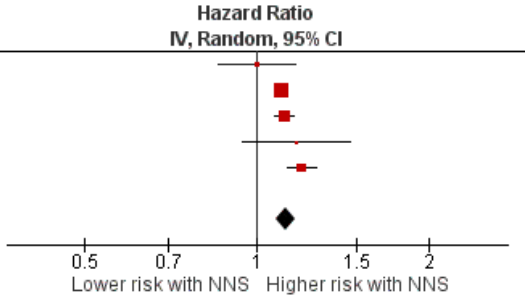


Figure S3. Non-nutritive sweeteners (NNS) and insulin resistance in randomized controlled trials; measured by homeostatic model of insulin resistance (HOMA-IR) score. NNS, non-nutritive sweetener; RCT, randomized controlled trial.

A) Hypertension

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Duffey et al. 2012 (CARDIA) [11]	0	0.08	4.8%	1.00 [0.85, 1.17]
Cohen et al. 2012 (NHS I) [21]	0.1	0.01	41.2%	1.11 [1.08, 1.13]
Cohen et al. 2007 (NHS II) [21]	0.11	0.02	30.3%	1.12 [1.07, 1.16]
Nettleton et al. 2009 (MESA) [24]	0.16	0.11	2.7%	1.17 [0.95, 1.46]
Cohen et al. 2012 (HPFS) [21]	0.18	0.03	21.0%	1.20 [1.13, 1.27]
Total (95% CI)			**100.0%**	**1.12 [1.08, 1.17]**

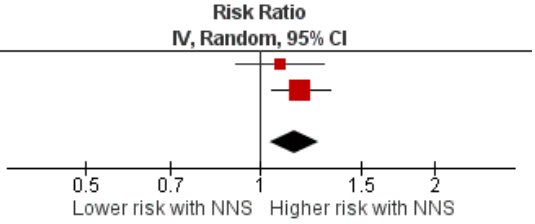
Heterogeneity: Tau² = 0.00; Chi² = 8.45, df = 4 (P = 0.08); I² = 53%
Test for overall effect: Z = 6.30 (P < 0.00001)



B) Stroke

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Bernstein et al. 2012 (HPFS) [19]	0.08	0.09	30.8%	1.08 [0.91, 1.29]
Bernsten et al. 2012 (NHS I) [19]	0.16	0.06	69.2%	1.17 [1.04, 1.32]
Total (95% CI)			**100.0%**	**1.14 [1.04, 1.26]**

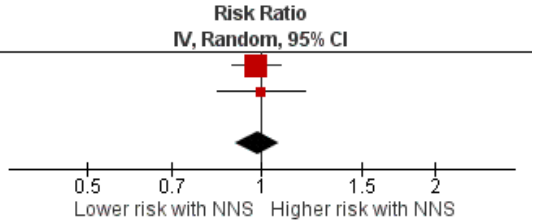
Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.71 (P = 0.007)



C) Coronary Heart Disease

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
de Koning et al. 2012 (HPFS) [18]	-0.02	0.05	76.4%	0.98 [0.89, 1.08]
Fung et al. 2009 (NHS I) [25]	0	0.09	23.6%	1.00 [0.84, 1.19]
Total (95% CI)			**100.0%**	**0.98 [0.90, 1.07]**

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)



D) CVD Events

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Vyas et al. 2015 (WHI) [37]	0.26	0.08	81.9%	1.30 [1.11, 1.52]
Gardener et al. 2012 (NOMAS) [28]	0.36	0.17	18.1%	1.43 [1.03, 2.00]
Total (95% CI)			**100.0%**	**1.32 [1.15, 1.52]**

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 3.84 (P = 0.0001)

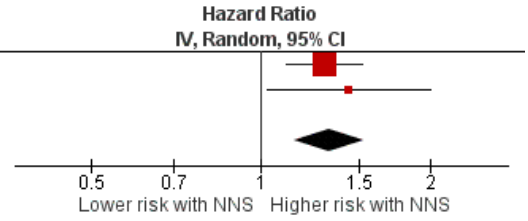


Figure S4. Non-nutritive sweeteners (NNS) and incident cardiovascular outcomes in cohort studies. (A) Hypertension; (B) Stroke; (C) Coronary heart disease; (D) Cardiovascular disease events, defined by original study authors as: coronary heart disease, heart failure, myocardial infarction, coronary re-vascularization procedure, ischemic stroke, peripheral arterial disease and CVD death (Vyas et al. 2014)[37] or stroke, myocardial infarction, and vascular death (Gardener et al. 2012)[28]. Highest vs. lowest non-nutritive sweetener intake quantiles. Cohort acronyms are defined in **Table S4**.

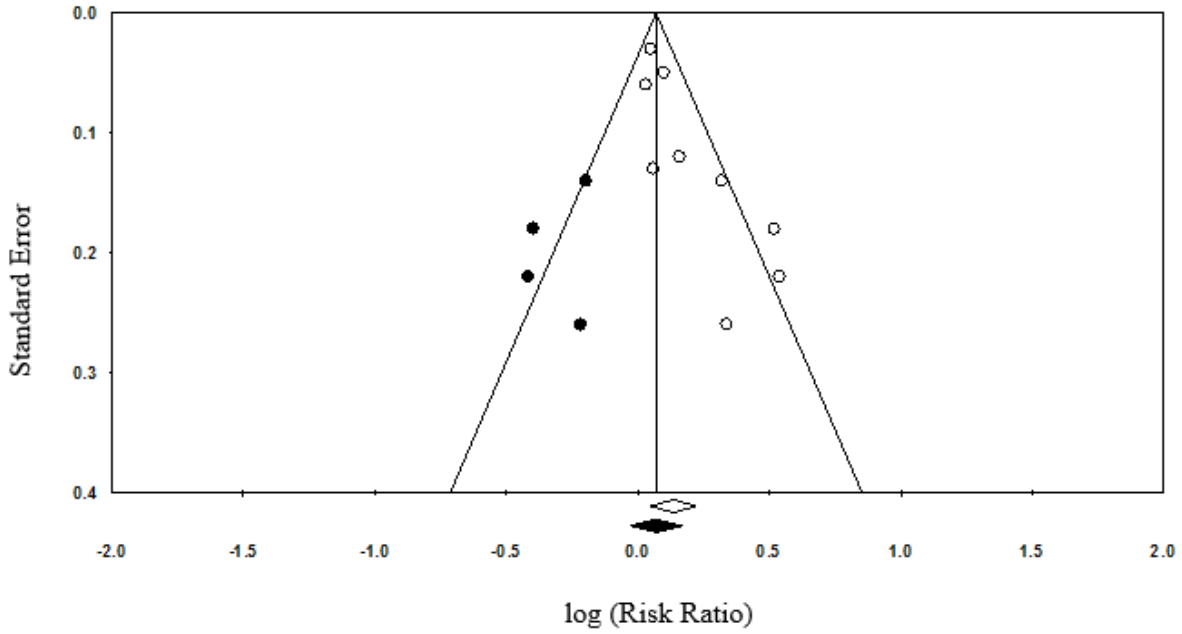


Figure S5. Funnel plot to evaluate potential publication bias among cohort studies reporting non-nutritive sweetener intake and incident type 2 diabetes. The pooled risk ratio from 9 published studies[10,14,15,20,24,27,32,36,38] (open circles) is 1.14 (95%CI 1.05 to 1.25). Using the trim and fill method to impute missing studies (closed circles), the adjusted risk ratio is 1.07 (95%CI 0.97 to 1.18).

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