RESEARCH

Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies

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ABSTRACT

BACKGROUND: Nonnutritive sweeteners, such as aspartame, sucralose and stevioside, are widely consumed, yet their long-term health impact is uncertain. We synthesized evidence from prospective studies to determine whether routine consumption of nonnutritive sweeteners was associated with long-term adverse cardiometabolic effects.

METHODS: We searched MEDLINE, Embase and Cochrane Library (inception to January 2016) for randomized controlled trials (RCTs) that evaluated interventions for nonnutritive sweeteners and prospective cohort studies that reported on consumption of nonnutritive sweeteners among adults and adolescents. The primary outcome was body mass index (BMI). Secondary outcomes included weight, obesity and other cardiometabolic end points.

RESULTS: From 11 774 citations, we included 7 trials (1003 participants; median follow-up 6 mo) and 30 cohort studies (405 907 participants; median follow-up 10 yr). In the included RCTs, nonnutritive sweeteners had no significant effect on BMI (mean difference –0.37 kg/m^2; 95% confidence interval [CI] –1.10 to 0.36; I^2 9%; 242 participants). In the included cohort studies, consumption of nonnutritive sweeteners was associated with a modest increase in BMI (mean correlation 0.05, 95% CI 0.03 to 0.06; I^2 0%; 21 256 participants). Data from RCTs showed no consistent effects of nonnutritive sweeteners on other measures of body composition and reported no further secondary outcomes. In the cohort studies, consumption of nonnutritive sweeteners was associated with increases in weight and waist circumference, and higher incidence of obesity, hypertension, metabolic syndrome, type 2 diabetes and cardiovascular events. Publication bias was indicated for studies with diabetes as an outcome.

INTERPRETATION: Evidence from RCTs does not clearly support the intended benefits of nonnutritive sweeteners for weight management, and observational data suggest that routine intake of nonnutritive sweeteners may be associated with increased BMI and cardiometabolic risk. Further research is needed to fully characterize the long-term risks and benefits of nonnutritive sweeteners. **Protocol registration:** PROSPERO-CRD42015019749

Obesity is a major public health challenge that contributes to type 2 diabetes and cardiovascular disease.[1] Evidence that sugar consumption is fuelling this epidemic[2–4] has stimulated the increasing popularity of nonnutritive sweeteners,[5] including aspartame, sucralose and stevioside. In 2008, more than 30% of Americans reported daily intake of nonnutritive sweeteners, and this proportion is increasing.[6] Researchers have suggested that nonnutritive sweeteners may have adverse effects on glucose metabolism, gut microbiota and appetite control.[7,8] Moreover, studies involving animals have reported that chronic exposure to nonnutritive sweeteners leads to increased food consumption, weight gain and adiposity.[9]

The position of the Academy of Nutrition and Dietetics is that nonnutritive sweeteners can help limit energy intake as a strategy to manage weight or blood glucose.[10] However, consumption of nonnutritive sweeteners has been paradoxically associated

with weight gain and incident obesity.[7,11] A previous meta-analysis[12] reported conflicting evidence: randomized controlled trials (RCTs) showed potential benefits (modest weight loss), whereas observational studies showed a small but significant association with increased body mass index (BMI). However, the review did not evaluate outcomes beyond body composition.[13] Several studies involving more than 100 000 new participants and representing several new geographic settings have since been published.[14–24]

Our objective was to synthesize evidence addressing this question: Is routine consumption of nonnutritive sweeteners by adults and adolescents associated with adverse long-term cardiometabolic effects in RCTs and prospective cohort studies?

Methods

This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[25] following a registered protocol.[26]

Search strategy and selection criteria

The search strategy was developed by an information specialist (M.F.) to overcome the limitations[13] of previous reviews. Our MEDLINE strategy (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.161390/-/DC1, Table S1) was peer reviewed and also translated for searches in Embase and The Cochrane Central Register of Controlled Trials. We included the following terms, among others: nonnutritive sweeteners, aspartame, saccharin, sucralose, xylitol, stevia, carbonated beverages, calories and food frequency. We did not limit the search by using terms related to outcomes of interest.

We conducted the searches from the time of database inception to January 2016 with no language restrictions; translation services were accessed to evaluate non-English citations. We also searched conference proceedings from the American Society for Nutrition, American Diabetes Association and Obesity Society. We manually searched reference lists of pertinent reviews and included studies for relevant citations, and we conducted grey literature searches of OpenSIGLE and Google Scholar. We used EndNote (version X6, Thompson Reuters, New York) to perform reference management.

We screened search results in duplicate using a team of 5 reviewers (A.M., A.R., J.L., L.C., M.J.). We included RCTs and observational studies that evaluated consumption of nonnutritive sweeteners in individuals who were more than 12 years of age (Appendix 1, Table S2). Studies evaluating children were reviewed separately.[27] We required a minimum study duration of 6 months to reflect routine consumption of nonnutritive sweeteners, to focus on long-term effects and to allow time for metabolic outcomes to develop. For observational studies, we required that associations with baseline intake of nonnutritive sweeteners (not only changes in intake during the course of the study) were reported to confirm temporality and limit confounding by reverse causation. Our primary outcome was change in BMI.

Secondary outcomes included changes in body weight; adiposity; glucose metabolism; and incidence of overweight/obesity, metabolic syndrome, type 2 diabetes, hypertension and other cardiorenal outcomes. If a study reported outcomes at multiple time points, we included the longest available follow-up.

Data extraction

We developed, piloted and deployed a standardized form for data extraction in DistillerSR (version 2, Evidence Partners Inc., Ottawa). A team of 5 reviewers (A.A., B.C., R.R., L.C., M.A.) independently extracted study data in duplicate that included baseline characteristics; interventions for nonnutritive sweeteners and comparators (for trials) or consumption of nonnutritive sweeteners and confounders or covariates (for cohorts); type, dose and duration of exposure to nonnutritive sweeteners; duration of follow-up; and cardiometabolic outcomes. For RCTs, we preferentially extracted data from intention-to-treat analyses or requested the data from authors. For cohorts, we extracted adjusted effect estimates in 2 formats: ratios comparing the highest versus lowest category of nonnutritive sweetener intake, and beta estimates quantifying linear associations per unit of nonnutritive sweetener intake. If multiple adjusted estimates were reported, we extracted the estimate from the statistical model that included the largest number of covariates. Data that were presented in nonextractable formats were requested from authors.

Assessment of study quality

Four reviewers (M.A., J.L., L.C., B.C.) assessed potential bias in RCTs using the Cochrane Collaboration Risk of Bias tool[29,30] and evaluated the quality of cohort studies using the 9-point Newcastle–Ottawa Scale.[31] Based on previous research[32,33] we designated 2 critical confounders for cohort studies: baseline body composition (BMI or other measure of body composition) and diet quality (total energy or sugar intake, or a diet pattern or quality score).

Statistical analysis

For the meta-analysis of continuous outcomes, we calculated mean differences (MD) or standardized MDs. For binary outcomes, we calculated pooled odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), and 95% confidence intervals (CIs). When nonnutritive sweetener intake units differed between cohort studies, we converted β estimates to *t* values (β/standard error) to generate a unitless metric[28] and calculated the pooled mean correlation. Subgroup analyses were planned a priori to explore heterogeneity and determine associations in prespecified strata. We conducted the analyses with random-effects models using Comprehensive Meta-Analysis Software (version 2.2.064) or RevMan (version 5.3.5). Statistical heterogeneity was quantified using the I^2 statistic. We assessed publication bias using funnel plots, and the trim and fill method.

Results

From 11 774 citations, we assessed 938 full-text articles for eligibility, and 37 studies involving a total of 406 910 individuals met our inclusion criteria: 7 RCTs[19,20,34–38] and 30 cohort studies[14–18,21–24,39–60] (Figure 1).

The 7 RCTs enrolled a total of 1003 participants who were obese,[38] overweight[19,20,34,35] or hypertensive[36,37] (Table 1). The interventions for nonnutritive sweeteners included beverages sweetened with aspartame or unspecified nonnutritive sweeteners,[19,20,34,35] stevioside capsules[36,37] or consumption of aspartame at the discretion of the participant.[38] The duration of interventions ranged from 6 to 24 months (median 6 mo, interquartile range [IQR] 6–14). Most RCTs were at unclear or high risk of bias (Table 1 and Appendix 1, Table S3).

The 30 observational studies reported outcomes from 22 distinct cohorts involving a total of 405 907 individuals (Table 2). Most of the studies used food frequency questionnaires to evaluate beverages containing nonnutritive sweeteners. More than 85% controlled for baseline body composition, diet quality, age, sex, smoking and physical activity, whereas less than 50% controlled for ethnicity and socioeconomic status (Appendix 1, Table S4). The duration of follow-up ranged from 1 to 38 years (median 10 yr, IQR 6–22). Most cohort studies were of moderate quality (Table 2 and Appendix 1, Table S5).

Primary outcome: body mass index

Two RCTs involving hypertensive participants who were taking stevioside capsules[36,37] and 1 RCT involving participants who were overweight and consuming artificially sweetened beverages[20] showed no significant effect on BMI over 6 to 24 months (MD –0.37 kg/m^2, 95% CI –1.10 to 0.36; I^2 9%; 3 trials; 242 participants; Table 3, Figure 2A). Two cohort studies that reported continuous nonnutritive sweetener intake in healthy participants[14,15] showed a positive correlation with BMI over 3 to 13 years (mean correlation 0.05, 95% CI 0.03 to 0.06; I^2 0%; 2 cohorts; 21 256 participants; Table 3, Figure 2B). A third cohort study that reported quantiles of nonnutritive sweetener intake[50] found that participants who consumed nonnutrive sweeteners daily had a greater increase in BMI during 8 years of follow-up than those who did not consume them (MD 0.77 kg/m^2, 95% CI 0.47 to 1.07 for daily v. no intake; 3371 participants). Overall, there was limited evidence for the effect of nonnutritive sweeteners on BMI, with 3 long-term cohort studies suggesting a modest increase in BMI that was not confirmed in 2 RCTs. The limited number of eligible studies precluded subgroup analyses.

Secondary outcomes

Weight

Among 5 RCTs evaluating interventions using nonnutritive sweeteners in participants who were obese,[19,20,34,35,38] there was no consistent effect on change in weight (standardized MD –0.17; 95% CI –0.54 to 0.21; I^2 81%; 5 trials; 791 participants) (Table 3, Figure 2C). Heterogeneity across the 5 trials was partially explained by differences in study duration: 2 longer trials[19,38] showed significant weight loss over 16 to 24 months of the intervention (standardized MD –0.55, 95% CI –0.75 to –0.34; I^2 0%; 2 trials), and 3 shorter (6 mo) trials[20,34,35] showed no effect for the use of nonnutritive sweeteners (standardized MD 0.13, 95% CI –0.34 to 0.59; I^2 65%; 3 trials) (p for subgroup differences = 0.009; Appendix 1, Table S6). Weight-loss effects also tended to be

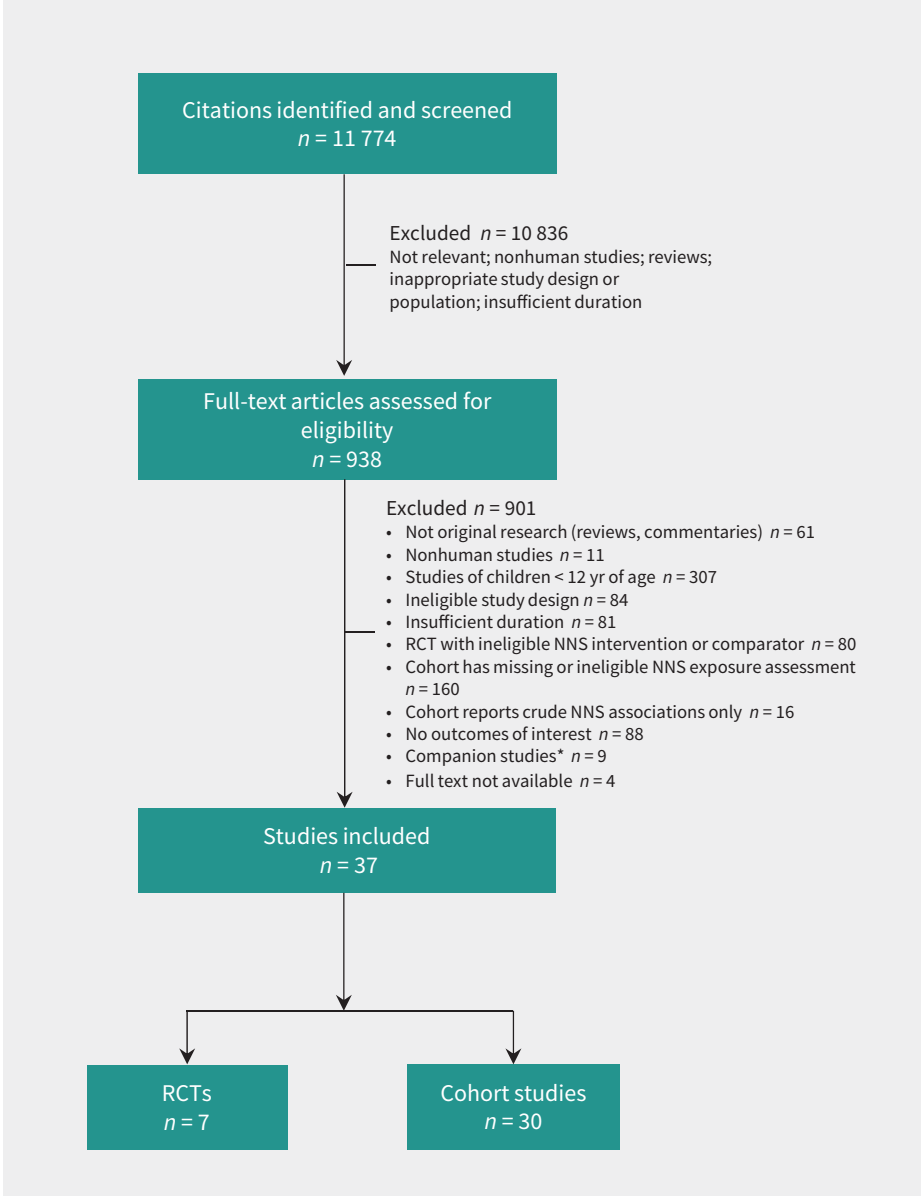

Figure 1: PRISMA flow diagram. NNS = nonnutritive sweetener, RCT = randomized controlled trial. *Companion studies included abstracts, trial registrations and earlier reports from included studies.

Table 1: Randomized controlled trials that evaluated nonnutritive sweetener interventions and long-term cardiometabolic health

Study,* country	No. of participants randomly assigned (% completed)	Sex	Population	Age, mean ± SD; yr	BMI, mean ± SD; kg/m²	Duration, mo	Type and source of NNS	Daily dose of NNS	Comparator(s)	Outcomes					Risk of bias†
										BMI	Weight	Waist	Body fat	HOMA-IR	
Blackburn et al. 1997,[38] USA	163 (53)	F	Obese, on weight-loss program	44 ± 10	37 ± 5	16	Aspartame ASB, packets, foodstuffs	Participants' discretion	Aspartame avoidance		•				High
Hsieh et al. 2003,[36] China	174 (97)	M, F	Mild hypertension	52 ± 7	23 ± 3	24	Stevioside capsules	1500 mg	Placebo	•					Low
Ferri et al. 2006,[37] Brazil	14 (86)	M, F	Mild hypertension	45 ± 7	27 ± 3	6	Stevioside capsules	3 phases: 3.8, 7.5, 15.0 mg/kg	Placebo	•				•	Unclear
Tate et al. 2012,[34] USA	213 (86)	M, F	Overweight, on weight-loss program	42 ± 11	36 ± 6	6	Unspecified ASB	Recommended ≥ 2 servings	Water, attention control‡		•	•			High
Maersk et al. 2012,[35] Denmark	33 (76)	M, F	Overweight	39 ± 8	33 ± 4	6	Aspartame ASB	1 L of diet cola	Water		•		•	•	High
Peters et al. 2016,[19] USA	308 (72)	M, F	Overweight, on weight-loss program	48 ± 11	34 ± 4	12	Unspecified ASB	At least 710 mL	Water with ASB avoidance		•	•			High
Madjd et al. 2015,[20] Iran	71 (87)	F	Overweight, on weight-loss program	32 ± 7	34 ± 3	6	Unspecified ASB	250 mL	Water	•	•	•		•	High

Note: ASB = artificially sweetened beverage, BMI = body mass index, F = female, HOMA-IR = homeostatic model assessment for insulin resistance, M = male, NNS = nonnutritive sweetener, SD = standard deviation.
*Sorted by year of publication.
†Risk of bias was assessed using the Cochrane Risk of Bias tool.[30] See Appendix 1, Table S3 for detailed risk of bias results for quality assessment.
‡Data from multiple comparator groups were combined.

stronger in RCTs with industry sponsorship[19,34,38] (standardized MD −0.37; 95% CI −0.71 to −0.03; I^2 77%; 3 trials) compared with RCTs that were not funded by industry[20,35] (standardized MD 0.30, 95% CI −0.38 to 0.99; I^2 55%; 2 trials) (p for subgroup differences = 0.09; Appendix 1, Table S6). Notably, both longer-term RCTs were funded by industry,[19,38] making it impossible to isolate the effect of trial duration and industry sponsorship in subgroup analyses. In addition, all 5 RCTs that evaluated weight change were at high risk of bias, prohibiting subgroup analyses according to this metric.

Two observational studies reported on intake of nonnutritive sweeteners and subsequent weight change in 4 cohorts over periods of 2 to 4 years[21,57] (Table 3, Figure 2D). There was a significant positive correlation between intake of nonnutritive sweeteners and weight gain (weighted mean correlation 0.06, 95% CI 0.05 to 0.07; I^2 46%; 4 cohorts; 32 405 participants) (Table 3).

Adiposity and overweight

Three RCTs involving participants who were obese and consuming diet soda as part of a weight-loss program reported inconsistent effects on waist circumference (standardized MD −0.16; 95% CI −0.56 to 0.25; I^2 83%; 3 trials; 683 participants) (Table 3, Appendix 1, Figure S1A). Heterogeneity across studies was related to the duration of intervention, with one 12-month trial showing a significant reduction in waist circumference[19] and two 6-month interventions finding no effect[20,34] (p for subgroup differences 0.001). One 6-month trial reported no effect on percentage of body fat.[35]

In contrast to RCTs, cohort studies with 4 to 9 years of follow-up showed that higher intake of nonnutritive sweeteners was associated with increasing waist circumference (MD 2.27 cm, 95% CI 0.96 to 3.58; 1 cohort; 384 participants)[18] (Table 3), higher incidence of abdominal obesity (OR 1.59, 95% CI 1.23 to 2.07; 1 cohort; 5011 participants)[60] (Table 3) and higher incidence of overweight (OR 1.84, 95% CI 1.28 to 2.66 for highest v. lowest intake quantiles; I^2 0%; 3 cohorts; 7917 participants)[22,50,59] (Table 3 and Appendix 1, Figure S1B).

Metabolic outcomes

Incidence for metabolic syndrome and type 2 diabetes was not reported in the RCTs. Pooled data from cohort studies with 4 to 24 years of follow-up showed higher risk of metabolic syndrome (RR 1.31, 95% CI 1.23 to 1.40; I^2 0%; 5 cohorts; 27 914 participants)[39,47,48,54,60] (Table 3 and Appendix 1, Figure S2A) and type 2 diabetes (RR 1.14, 95% CI 1.05 to 1.25; I^2 52%; 9 cohorts; 400 571 participants)[16,24,42,49,55,56,58,60] for the highest versus lowest quan-

Table 2 (part 1 of 2): Prospective cohort studies evaluating intake of nonnutritive sweetener and long-term cardiometabolic health

Study*	Cohort	Country, year of baseline NNS intake	No. of participants	Sex	Age at baseline, mean ± SD, or range; yr	BMI at baseline, mean ± SD, or % OW; kg/m²	Follow-up, yr	Type or source of NNS	Extreme NNS intake categories, servings†	Measure of continuous NNS intake	Outcome							Quality score‡
											BMI	Weight	Overweight/obesity	Metabolic syndrome	Type 2 diabetes	Hypertension	Other	
Lutsey et al. 2008[54]	ARIC	USA, 1987	9154	M, F	54 ± 6	–	9	AS soda	Extreme tertiles	–				•				8
Bomback et al. 2010[43]	ARIC	USA, 1987	14 002	M, F	54 ± 6	28 ± 5	9	AS soda	> 1/d v. < 1/d	–							CKD	9
Palmer et al. 2008[55]	BWHS	USA, 2001	43 960	F	38 ± 10	28 ± 7	4	AS soda	≥ 1/d v. < 1/mo	–					•			6
Duffey et al. 2012[48]	CARDIA	USA, 1986	3728	M, F	25 ± 26	25 ± 5	20	ASB	None v. any	–				•		•	IGT	8
Haines et al. 2007[59]	EAT	USA, 1998	2516	M, F	15 ± 2	11% OW	5	AS soda	–	serving/d			•					7
Lana et al. 2015§[22]	ENRICA	Spain, 2008	2030	M, F	18–60	26 ± 5	4	AS soda	≥ 1/d v. < 1/wk	–			•					9
Fagherazzi et al. 2013¶[49]	EPIC-E3N	France, 1993	66 118	F	53 ± 7	19% OW	17	ASB	> 603 mL/wk v. never	–					•			8
O'Connor et al. 2015¶[24]	EPIC-Norfolk	UK, 1993	24 653	M, F	58 ± 9	26 ± 4	11	ASB	≥ 169 mL/d v. none	serving/d					•			8
Dhingra et al. 2007[47]	FOS	USA, 1992	1864	M, F	55 ± 10	27 ± 5	4	AS soda	1/d v. < 1/wk	–				•				9
Field et al. 2014[14]	GUTS II	USA, 2004	7559	M, F	13 ± 2	20 ± 3	3	AS soda	–	serving/d	•							6
Bernstein et al. 2012[40]	HPFS	USA, 1986	43 371	M	62 ± 11	26 ± 3	22	AS soda	≥ 1/d v. none	serving /d							Stroke	8
Bhupathiraju et al. 2013**[42]	HPFS	USA, 1986	39 059	M	53 ± 10	25 ± 5	22	AS soda	≥ 1/d v. < 1/mo	serving/d					•			7
Cohen et al. 2012[45]	HPFS	USA, 1986	37 360	M	40–75	25 ± 3	22	ASB	≥ 1/d v. < 1/mo	–						•		8
de Koning et al. 2012[46]	HPFS	USA, 1986	42 883	M	40–75	26 ± 3	22	ASB	> 4/wk v. none	serving/d							CHD	8
Smith et al. 2015[21]	HPFS	USA, 1986	21 472	M	47 ± 6	25 ± 1	24	AS soda	–	serving/d		•						6
Gearon et al. 2014§[15]	MCCS	Australia, 1990	13 697	M, F	55 ± 9	26 ± 4	13	AS soda	–	serving/wk	•							8
Nettleton et al. 2009[60]	MESA	USA, 2000	5011	M, F	62 ± 11	28 ± 6	5	AS soda	≥ 1/d v. rare or never	–				•	•	•	Waist	6
Fung et al. 2009[51]	NHS I	USA, 1980	88 520	F	34–59	24 ± 2	24	AS soda	≥ 2/d v. < 1/mo	–							CHD	8
Bernstein et al. 2012[40]	NHS I	USA, 1980	84 085	F	58 ± 10	26 ± 5	28	AS soda	≥ 1/d v. none	serving /d							Stroke	8
Bhupathiraju et al. 2013[42]	NHS I	USA, 1984	74 749	F	50 ± 7	25 ± 5	24	AS soda	≥ 1/d v. < 1/mo	serving/d					•			7
Cohen et al. 2012††[45]	NHS I	USA, 1980	88 540	F	34–59	23 ± 3	38	ASB	≥ 1/d v. < 1/mo	–						•		8
Smith et al. 2015‡‡[21]	NHS I	USA, 1986	48 449	F	49 ± 6	24 ± 1	24	AS soda	–	serving/d		•						6
Pan et al. 2012§§[56]	NHS II	USA, 1991	82 902	F	36 ± 5	24 ± 5	18	ASB	≥ 4/d v. ≤ 1/wk	serving/d					•			7
Chen et al. 2009[44]	NHS II	USA, 1991	13 475	F	32 ± 3	23 ± 4	10	ASB	≥ 5/wk v. ≤ 3/mo	serving/d							GDM	8
Cohen et al. 2012††[45]	NHS II	USA, 1991	97 991	F	27–42	23 ± 4	16	ASB	≥ 1/d v. < 1/mo	–						•		8
Smith et al. 2015[21]	NHS II	USA, 1991	48 071	F	38 ± 4	23 ± 2	16	AS soda	–	serving/d		•						6

Table 2 (part 2 of 2): Prospective cohort studies evaluating intake of nonnutritive sweetener and long-term cardiometabolic health

Study*	Cohort	Country, year of baseline NNS intake	No. of participants	Sex	Age at baseline, mean ± SD, or range; yr	BMI at baseline, mean ± SD, or % OW; kg/m²	Follow-up, yr	Type or source of NNS	Extreme NNS intake categories, servings†	Measure of continuous NNS intake	Outcome							Quality score‡
											BMI	Weight	Overweight/obesity	Metabolic syndrome	Type 2 diabetes	Hypertension	Other	
Gardener et al. 2012[52]	NOMAS	USA, 1993	2564	M, F	69 ± 10	28 ± 6	10	AS soda	≥ 1/d v. < 1/mo	serving/wk							CVD	7
Parker et al. 1997[57]	PHHP	USA, 1986	465	M, F	47 ± 14	27 ± 5	4	Saccharin	–	log g/d		•						9
Fowler et al. 2008[50]	SAHS	USA, 1979	3371	M, F	44 ± 11	27 ± 6	8	ASB	≥ 22/wk v. none	–	•		•					7
Fowler et al. 2015¶¶[18]	SALSA	USA, 1992	384	M, F	70 ± 3	28 ± 5	9	AS soda	≥ 1/d v. none	–							Waist	5
Sakurai et al. 2013[16]	–	Japan, 2003	2037	M	46 ± 6	23 ± 3	7	AS soda	≥ 1/wk v. none	–					•			8
Barrio-Lopez et al. 2013§[39]	SUN	Spain, 1999	8157	M, F	36 ± 11	23 ± 3	6	AS soda	Extreme quintiles	–				•				7
Bes-Rastrollo et al. 2006§[41]	SUN	Spain, 1999	7194	M, F	37 ± 12	–	2	AS soda	Extreme quintiles	–							Gain > 1 kg	8
Renault et al. 2015[23]	TOP	Denmark, 2009	347	F	31 ± 4	34 ± 4	0.8	AS soda	≥ 1/d v. none	–							GWG	7
Vyas et al. 2015[17]	WHI	USA, 1993	59 614	F	63 ± 7	59% OW	9	ASB	≥ 2/d v. ≤ 3/mo	–							CVD	6
Stinson et al. 2013[58]	WHI	USA, 1996	62 082	F	50–9	–	9–14	ASB	> 3/d v. < 3/mo	–					•			6

Note: ARIC = Atherosclerosis Risk in Communities, AS soda = artificially sweetened soda (soft drinks), ASB = artificially sweetened beverages (including sodas and other beverages such as coffee or tea), BMI = body mass index, BWHS = Black Women's Health Study, CARDIA = Coronary Artery Risk Development in Young Adults, CHD = coronary heart disease, CKD = chronic kidney disease, CVD = cardiovascular disease, 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, F = female, GDM = gestational diabetes mellitus, GWG = gestational weight gain, GUTS II = Growing Up Today Study II, HPFS = Health Professionals Follow-Up Study, HOMA-IR = homeostatic model assessment for insulin resistance, IGT = impaired glucose tolerance, IQR = interquartile range, M = male, MCCS = Melbourne Collaborative Cohort Study, MESA = Multi-Ethnic Study of Atherosclerosis, NHS = Nurses' Health Study, NOMAS = Northern Manhattan Study, NNS = nonnutritive sweetener, OW = overweight, PHHP = Pawtucket Heart Health Program, SAHS = San Antonio Heart Study, SALSA = San Antonio Longitudinal Study of Aging, SD = standard deviation, SUN = Seguimiento Universidad de Navarra, TOP = Treatment of Obese Pregnant Women, WHI = Women's Health Initiative.
*Sorted by cohort name. In some cases, different outcomes from a single cohort are reported in separate studies. Where multiple cohorts are reported in a single study, characteristics are reported per cohort rather than per study.
†Unless otherwise specified.
‡Study quality was assessed using the Newcastle–Ottawa Scale;[31] maximum score = 9. See Appendix 1, Table S5 for detailed quality assessment results.
§Unpublished data provided by study authors.
¶Excluded study InterAct 2013[53] reports overlapping data from the international EPIC study.
**Excluded study de Koning et al. 2011[61] reports earlier type 2 diabetes data from this cohort.
††Excluded study Winkelmayer et al. 2005[62] reports earlier hypertension data from this cohort.
‡‡Excluded study Colditz et al. 1990[63] reports earlier weight data from this cohort.
§§Excluded study Schulze et al. 2004[64] reports earlier type 2 diabetes data from this cohort.
¶¶Body mass index data from this study were not reviewed because the SALSA cohort was recruited from the SAHS cohort, reported in Fowler et al. 2008.[50]

tiles of nonnutritive sweetener intake (Table 3, Figure 2E). In subgroup analyses, heterogeneity was not explained by baseline weight status, study quality, duration of follow-up or dose of nonnutritive sweeteners (Appendix 1, Table S7). Among 4 cohorts that reported continuous effect estimates, we found a 3% higher relative risk of type 2 diabetes per additional daily serving of nonnutritive sweetener (RR 1.03, 95% CI 1.01 to 1.05; I^2 0%; 4 cohorts; 221 363 participants)[24,42,53,56] (Table 3 and Appendix 1, Figure S2B). We found no statistically significant associations for insulin resistance (3 trials; Appendix 1, Figure S3), glycosylated hemoglobin (1 trial), glucose tolerance (1 cohort) or gestational diabetes (1 cohort) (Table 3).

Cardiorenal outcomes

Cardiorenal outcomes were not reported in the RCTs. Among cohort studies, we found that high nonnutritive sweetener intake was associated with a higher risk of hypertension over 5 to 38 years of follow-up (HR 1.13, 95% CI 1.06 to 1.20; I^2 64%; 5 cohorts; 232 630 participants)[45,48,60] (Table 3 and Appendix 1, Figure S4A). In addition, high intake of nonnutritive sweetener was associated with a higher risk of stroke (RR 1.14, 95% CI 1.04 to 1.26; I^2 0%; 2 cohorts; 128 176 participants)[40] and cardiovascular events (RR 1.32; 95% CI 1.15 to 1.52; I^2 0%; 2 cohorts; 62 178 participants),[17,52] whereas there was no significant association with coronary heart disease (RR 0.98; 95% CI 0.90 to 1.07; I^2 0%;

Table 3: Results from meta-analyses (where possible) or individual studies for intake of nonnutritive sweeteners and long-term cardiometabolic health outcomes in randomized controlled trials and cohort studies

Outcome: change or incidence	No. of studies* (participants)	Comparison	Estimate of NNS effect (95% CI) from meta-analysis or individual studies	Assoc.	Citation(s)*	Figure
Randomized controlled trials						
BMI	3 (242)	NNS v. control	MD –0.37 kg/m^2 (–1.10 to 0.36), I^2 9%	NS	20, 36, 37	2
Weight	5 (791)	NNS v. control	SMD –0.17 (–0.54 to 0.21), I^2 81%	NS	19, 20, 34, 35, 38	2
Percentage of fat mass	1 (25)	NNS v. control	MD –1.01% (–3.01 to 0.99)	NS	35	–
Waist circumference	3 (683)	NNS v. control	SMD –0.16 (–0.56 to 0.25), I^2 83%	NS	19, 20, 34	S1‡
Insulin resistance: HOMA-IR	3 (99)	NNS v. control	SMD +0.10 (–0.57 to 0.76), I^2 55%	NS	20, 35, 37	S3‡
HbA_{1c}	1 (62)	NNS v. control	MD +0.07% (–0.00 to 0.14)	NS	20	–
Cohort studies						
BMI	2 (21 256)	Continuous correlation	WMC +0.05 (0.03 to 0.06), I^2 0%	↑ Gain	14, 15	2
	1 (3371)	Highest NNS intake quantile v. none	MD +0.77 kg/m^2 (0.47 to 1.07)	↑ Gain	50	–
Weight	4 (32 405)	Continuous correlation	WMC +0.06 (0.05 to 0.07), I^2 46%	↑ Gain	21, 57	2
Gestational weight gain	1 (347)	Highest v. lowest NNS intake quantile	MD +2.5 kg (0.5 to 4.5)	↑ Gain	23	–
Weight gain > 1 kg	1 (7,194)	Highest v. lowest NNS intake quantile	OR 1.05 (0.93 to 1.19)	NS	41	–
Waist circumference	1 (384)	Daily v. no NNS consumption	MD +2.27 cm (0.96 to 3.58)	↑ Gain	18	–
Incident abdominal obesity	1 (5011)	Highest v. lowest NNS intake quantile	HR 1.59 (1.23 to 2.07)	↑ Gain	60	
Incident overweight/obesity	3 (7917)	Highest v. lowest NNS intake quantile	OR 1.84 (1.28 to 2.66), I^2 0%	↑ Risk	22, 50, 59	S1‡
Metabolic syndrome	5 (27 914)	Highest v. lowest NNS intake quantile	RR 1.31 (1.23 to 1.40), I^2 0%	↑ Risk	39, 47, 48, 54, 60	S2‡
Type 2 diabetes	4 (221 363)	Per daily serving of NNS	RR 1.03 (1.01 to 1.05), I^2 0%	↑ Risk	24, 42, 56	S2‡
	9 (400 571)	Highest v. lowest NNS intake quantile	RR 1.14 (1.05 to 1.25), I^2 52%	↑ Risk	16, 24, 42, 49, 55, 56, 58, 60	2
Gestational diabetes	1 (13 475)	Highest v. lowest NNS intake quantile	RR 0.87 (0.71 to 1.02)	NS	44	–
Impaired glucose tolerance	1 (3728)	No v. any NNS consumption	HR 1.07 (0.91 to 1.26)	NS	48	–
Hypertension	5 (232 630)	Highest v. lowest NNS intake quantile	HR 1.12 (1.08 to 1.13), I^2 53%	↑ Risk	45, 48, 60	S4‡
Stroke	2 (128 176)	Highest v. lowest NNS intake quantile	RR 1.14 (1.04 to 1.26), I^2 0%	↑ Risk	40	S4‡
Cardiovascular events†	2 (62 178)	Highest v. lowest NNS intake quantile	RR 1.32 (1.15 to 1.52), I^2 0%	↑ Risk	17, 52	S4‡
Coronary heart disease	2 (131 403)	Highest v. lowest NNS intake quantile	RR 0.98 (0.90 to 1.07), I^2 0%	NS	46, 51	S4‡
Chronic kidney disease	1 (14 002)	Highest v. lowest NNS intake quantile	OR 0.80 (0.64 to 1.00)	NS	43	–

Note: BMI = body mass index, CI = confidence interval, HbA_{1c} = glycosylated hemoglobin, HOMA-IR = homeostatic model assessment for insulin resistance, HR = hazard ratio, MD = mean difference, NNS = nonnutrititve sweetener, NS = not significant, OR = odds ratio, RR = risk ratio, SMD = standardized mean difference, WMC = weighted mean group correlation (unitless).
*Number of studies does not always equal the number of citations, because some citations report results from multiple studies.
†Defined by the study authors as coronary heart disease, heart failure, myocardial infarction, coronary revascularization procedure, ischemic stroke, peripheral arterial disease and cardiovascular death;[17] or stroke, myocardial infarction and vascular death.[52]
‡Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.161390/-/DC1.

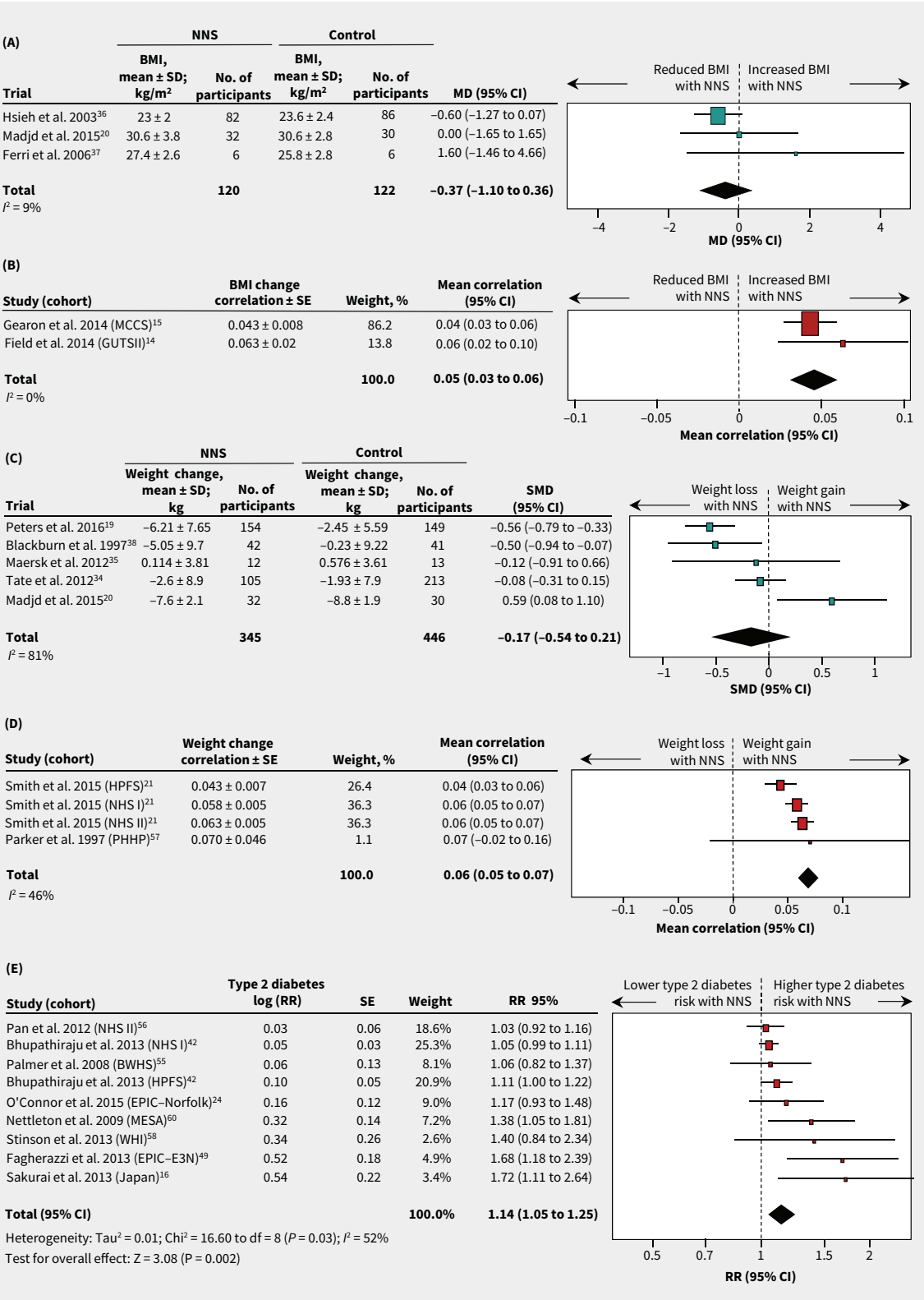

Figure 2: Forest plots of consumption of NNS and selected cardiometabolic health outcomes. (A) Differences in mean BMI between NNS consumption and control groups for RCTs. A value less than 0 represents reduced BMI with NNS consumption. (B) Correlaton of BMI change per unit of NNS intake for cohort studies. A value less than 0 represents a reduced BMI. (C) Standard mean differences in weight between NNS consumption and control groups for RCTs. A value less than 0.0 represents weight loss. (D) Correlation of weight change per unit NNS intake for cohort studies. A value less than 0 favours weight loss. (E) Incidence of type 2 diabetes for highest versus lowest quantiles of NNS intake in cohort studies. A value less than 1.0 represents a lower risk of type 2 diabetes. Additional outcomes are shown in Table 3, and Appendix 1, Figures S1–4. Squares represent effect estimates within each study, with 95% CIs represented by horizontal lines. Square size is proportional to the weight of each study. Diamonds represent the weighted mean effect estimates. Cohort acronyms are defined in Table 2. Note: BMI = body mass index, CI = confidence interval, MD = mean difference, NNS = nonnutritive sweetener, RCT = randomized controlled trial, RR = risk ratio, SD = standard deviation, SE = standard error, SMD = standardized mean difference.

2 cohorts; 131 403 participants)[46,51] (Table 3 and Appendix 1, Figures S4B–4D).

Publication bias

Because of the limited number of studies, we could not assess publication bias for most outcomes, with the exception of type 2 diabetes. Although the pooled RR from 9 published studies that reported incident type 2 diabetes in high versus low consumers of nonnutritive sweeteners was significant (RR 1.14, 95% CI 1.05 to 1.23), it was attenuated to 1.07 (95% CI 0.97 to 1.18) after imputing missing studies (Appendix 1, Figure S5). This suggests potential publication bias that favours studies reporting a positive association between nonnutritive sweetener consumption and type 2 diabetes.

Interpretation

Evidence from small RCTs with short follow-up (median 6 mo) suggests that consumption of nonnutritive sweeteners is not consistently associated with decreases in body weight, BMI or waist circumference. However, in larger prospective cohort studies with longer follow-up periods (median 10 yr), intake of nonnutritive sweeteners is significantly associated with modest long-term increases in each of these measures. Cohort studies further suggest that consumption of nonnutritive sweeteners is associated with higher risks of obesity, hypertension, metabolic syndrome, type 2 diabetes, stroke and cardiovascular disease events; however, publication bias was indicated for type 2 diabetes, and there are no data available from RCTs to confirm these observations.

Previous reviews[12,65] concluded that, although data from RCTs support weight-loss effects from sustained nonnutritive sweetener interventions, observational studies provide inconsistent results. Building on these findings, we included new studies[14–24] and found that consumption of nonnutritive sweeteners was not generally associated with weight loss among participants in RCTs, except in long-term (≥ 12 mo) trials with industry sponsorship. In addition, we found that consumption of nonnutritive sweeteners was associated with modest long-term weight gain in observational studies. Our results also extend previous meta-analyses that showed higher risks of type 2 diabetes[32,33] and hypertension[66] with regular consumption of nonnutritive sweeteners.

Our results highlight both the value and challenge of incorporating observational studies when examining the effect of real-world exposures on health outcomes that develop slowly over time. Although RCTs provide the highest quality of scientific evidence, they often fail to recapitulate chronic dietary exposures that are captured in decades-long cohort studies. However, it is not uncommon for hypotheses based on observational evidence to fail when tested in RCTs,[67] and these data should therefore be interpreted with caution.

Strengths of our systematic review include use of a registered protocol and sensitive, peer-reviewed search strategy. We synthesized evidence from both RCTs and observational studies, assessed multiple cardiometabolic outcomes and focused on long-term effects.

Limitations

The main limitation of our review is the unavoidable grouping of exposure and outcome variables. We could not evaluate different types or formulations of nonnutritive sweeteners because most studies did not report this information, and we could not assess dose effects owing to the limited number of RCTs and the semi-quantitative nature of the reporting of nonnutritive sweetener intake in cohort studies. In addition, some cardiometabolic outcomes could not be evaluated individually becuse of the way they were combined and reported in the original studies (e.g., "overweight and obesity," "cardiovascular events"). Finally, meta-analysis was not always possible because of reporting differences and the paucity of eligible studies.

The individual studies included in our review also have limitations. Most RCTs were at high risk of bias, and most cohort studies achieved only moderate quality scores. In the cohort studies, the ascertainment of exposure to nonnutritive sweeteners by self-report was likely incomplete,[6] and the comparison of extreme intake quantiles may have yielded biased results. Furthermore, these studies evaluated consumption of artificially sweetened beverages before 2004; however, nonnutritive sweeteners are increasingly found in other foods, and consumption has increased considerably in recent years.[6]

Observational studies are also subject to confounding bias, particularly when the exposure (e.g., nonnutritive sweeteners) is a potential "treatment" for the outcomes under investigation. However, critical confounders (baseline body composition and diet quality) were largely accounted for in the included studies, and we limited confounding by reverse causation by including only prospective studies that documented intake of nonnutritive sweeteners before weight change and disease incidence.

Randomized controlled trials of nonnutritive sweetener interventions also have known limitations.[68] All were relatively short in duration, and the majority were conducted as part of multifaceted weight loss programs in obese individuals, which does not address routine consumption of nonnutritive sweeteners by healthy individuals. In addition, some trials evaluated nonnutritive sweeteners in capsule form, which may alter their physiologic effects, while others were subject to potential bias from lack of blinding and industry sponsorship. Finally, several studies focused on BMI and waist circumference, which are imperfect indices of body composition, despite being established predictors of cardiovascular disease.[69,70]

Conclusion

Evidence from RCTs does not clearly support the intended benefits of nonnutritive sweeteners for weight management. In contrast, observational data suggest that routine consumption of nonnutritive sweeteners may be associated with a long-term increase in BMI and elevated risk of cardiometabolic disease; however, these associations have not been confirmed in experimental studies and may be influenced by publication bias. New studies are needed to compare different types and formulations of nonnutritive sweeteners, and to evaluate the net effect of substituting nonnutritive sweeteners for sugar. Improved assessment tools and biomarker approaches[71] should be used to accu-

rately capture consumption of nonnutritive sweeteners, and confounding bias must be carefully addressed. Given the widespread and increasing use of nonnutritive sweeteners, caution is warranted until the long-term risks and benefits of these products are fully characterized.

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