Health effects of the use of non-sugar sweeteners

A systematic review and meta-analysis

Magali Rios-Leyvraz and Jason Montez

World Health Organization

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Contents

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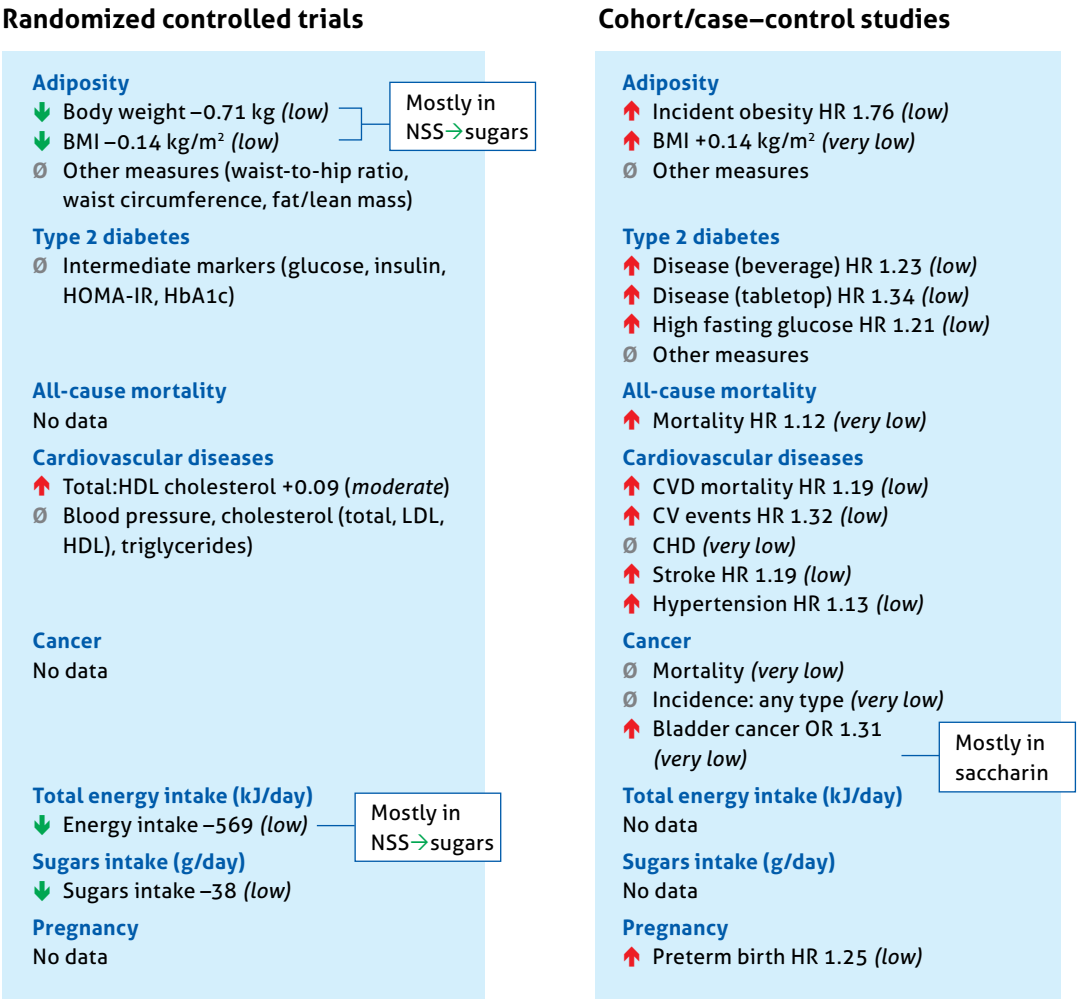
Abbreviations

ADI	acceptable daily intake
BMI	body mass index
CI	confidence interval
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	glycated haemoglobin
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment of insulin resistance
HR	hazard ratio
LDL	low-density lipoprotein
MD	mean difference
NCD	noncommunicable disease
NHANES	National Health and Nutrition Examination Survey
NSS	non-sugar sweeteners
NUGAG	Nutrition Guidance Expert Advisory Group
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SE	standard error
SMD	standardized mean difference
SSB	sugar-sweetened beverage
WHO	World Health Organization

Executive summary

A 2019 systematic review on intake of non-sugar sweeteners (NSS) in adults and children was updated and expanded to include studies in which NSS were not specified by name and studies of effects of NSS on pregnant women published through July 2021. A total of 283 studies were included in the review. Meta-analyses focused on randomized controlled trials, prospective cohort studies and case–control studies assessing cancer, and certainty in results was assessed via GRADE (Grading of Recommendations Assessment, Development and Evaluation). Results for key outcomes in adults (including pregnant women) are summarized in the figure below. In addition, a single randomized controlled trial conducted in children reported decreases in several measures of adiposity, but no significant effects or associations were observed in meta-analyses.



BMI: body mass index; CHD: coronary heart disease; CV: cardiovascular; CVD; cardiovascular disease; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HR: hazard ratio; LDL: low-density lipoprotein; OR: odds ratio; tabletop = NSS added to foods or beverages by the consumer.

Note: Text in parentheses refers to certainty in the evidence as assessed by GRADE. "Mostly in" refers to results of subgroup analysis; "NSS→sugars" refers to studies in which NSS were compared with sugars. ↑ = increased effect, ↓ = decreased effect, Ø = no effect.

1. Background

Consumption of free sugars has been linked to escalating rates of overweight and obesity *(2, 3)*, as well as development of diet-related noncommunicable diseases (NCDs), including dental caries, type 2 diabetes, cardiovascular diseases and cancer *(4–7)*.

As part of global efforts to stem the tide of obesity and diet-related NCDs, the World Health Organization (WHO) has issued guidance on intake of sugars, recommending that intake be significantly reduced *(8)*. With the current focus on reducing intake of free sugars, interest in non-sugar sweeteners (NSS) as a possible alternative has intensified.

NSS are no-calorie or low-calorie artificial and natural sweeteners that have been developed as an alternative to sugars. They are widely used as ingredients in pre-packaged foods and beverages, and are added to foods and beverages by consumers *(9–11)*. NSS include synthetically derived chemicals and natural extracts that may or may not be chemically modified. Because of their ability to impart sweet taste without calories, some argue that they can help to prevent overweight and obesity. However, others suggest that they may increase risk. From an oral health standpoint, NSS might reduce the risk of dental caries if used as a replacement for sugar. Although commercially available NSS are tested for toxicity before being introduced into the market, potential long-term effects on health of consuming NSS at levels below the acceptable daily intake (ADI) established by authoritative bodies are not as well characterized.

To inform the development of WHO guidance on NSS intake, a systematic review was commissioned and published in 2019 *(1)*. The current review is an update and expansion of that review: it updates the review with new studies published since the search was conducted in the original review, and also includes studies excluded from the original review in which NSS were not specified by name, as well studies assessing the effects of NSS intake in pregnant women. This review attempts to address both any inherent health effects of NSS (i.e. health effects attributable to NSS regardless of comparator), as well as health effects of NSS when compared with sugars or water, when consumed at safe levels as established by authoritative bodies.

2. Methods

The protocol for the current review was modified slightly from that used in the original review *(1)*. It was developed in accordance with the WHO guideline development process *(12)*, the PRISMA statement for preferred reporting items for systematic review and meta-analysis protocols *(13–15)*, and the *Cochrane handbook for systematic reviews of interventions (16)*.

2.1 Eligibility criteria

2.1.1 Participants

We included studies conducted in generally healthy populations of adults (≥18 years of age), children (<18 years of age) or pregnant women. Studies conducted in overweight, obese or mixed-weight populations were included, but studies conducted exclusively in pre-diabetic or diabetic populations were excluded. We also excluded studies conducted exclusively in populations with other diseases (except for case–control studies with hospital patient controls), as well as in vitro and animal studies.

2.1.2 Interventions and exposures

The interventions and exposures of interest were any type of NSS (excluding sugar alcohols and natural caloric sweeteners), whether specified by name or not, and whether used alone or in combination with other NSS.[1]

We included studies that reported use of NSS within the ADI as established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) *(17)* (**Table 1**) and excluded studies in which NSS intake explicitly exceeded the ADI. Studies were included if it was unclear whether an ADI had been exceeded (e.g. in prospective cohort studies, where exposures to NSS are generally not reported quantitatively in terms of amount of NSS, but rather in terms of servings of food or beverage containing NSS per day or week).

Table 1. ADI of NSS as established by JECFA

Sweetener	ADI (mg/kg of body weight)
Acesulfame K	15
Advantame	5
Aspartame	40
Cyclamate	11
Neotame	0.3
Saccharin	15
Steviol glycosides	4
Sucralose	5

ADI: acceptable daily intake; JECFA: Joint FAO/WHO Expert Committee on Food Additives; NSS: non-sugar sweeteners.

[1] This review uses the same definition for non-sugar sweeteners as in the original review *(1)* – that is, NSS include all artificial sweeteners and natural non-caloric sweeteners. They do not include sugar alcohols or modified sugars. For simplicity, "NSS" is used throughout the main body of this document to refer to non-sugar sweeteners regardless of what they were called in the individual studies (e.g. non-nutritive sweeteners, artificial sweeteners, low/no-calorie sweeteners).

2.1.3 Comparators

We included studies that compared NSS consumption with no or lower doses of NSS consumption. We included trials that compared the intervention with any type of sugar, placebo, plain water or no intervention. Trials with concomitant interventions were included, provided that the concomitant interventions were similar and equally balanced between the comparison arms. We did not include studies that only compared one or more NSS to one another, without also comparing with a sugar, placebo, plain water or no intervention.

2.1.4 Outcomes

The health outcomes of interest for adults and children were identified by the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health as:

- measures of adiposity (e.g. body weight, body mass index [BMI], overweight/obesity, fat and lean mass);
- type 2 diabetes and pre-diabetes (incidence and intermediate markers of glycaemic control);
- cardiovascular diseases (incidence and intermediate markers, such as blood pressure and lipids);
- cancer;
- dental caries;
- chronic kidney disease;
- eating behaviour (e.g. appetite, satiety, energy intake);
- sweet preference (e.g. subjective measures, sugars intake);
- neurocognition;
- mood and behaviour; and
- asthma and allergies (for children only).

In addition, we included all-cause mortality; cause-specific mortality related to cardiovascular diseases and cancer; and pregnancy and birth outcomes for pregnant women, based on outcomes specified in this review for children, as well as those previously identified for previous pregnancy reviews (including gestational diabetes, birthweight and gestation-related outcomes). We also included any outcomes assessed to be adverse outcomes or events that were not included in the list of outcomes of interest.

2.1.5 Study design

Randomized controlled trials (RCTs) (including parallel, cluster and crossover trials), nonrandomized controlled trials, prospective cohort studies, case–control studies and cross-sectional studies were included in the review. Because there was ample evidence from RCTs and prospective cohort studies for most major outcomes of interest, results from these study designs and case–control studies reporting on cancer outcomes[1] were included in the main meta-analyses and assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[2] Results from other study types were pooled in secondary analyses and/or summarized narratively as supplementary data (when data from RCTs and/or prospective cohort studies were not available) and were not assessed using GRADE. All other study designs, including nonrandomized

[1] A majority of studies reporting on cancer outcomes are of case–control design, and therefore were included in meta-analyses and GRADE assessment to avoid excluding this significant body of evidence. Case–control studies reporting on other outcomes were not included in meta-analysis and GRADE assessment.

[2] https://www.gradeworkinggroup.org/

controlled trials, ecological studies, case series and case reports, reviews, and meta-analyses were excluded.

2.1.6 Duration

Studies with a minimum intervention duration or follow-up of 13 days for blood lipid outcomes, 1 year for disease incidence outcomes (i.e. incident cancer, cardiovascular diseases, type 2 diabetes), and 7 days for all other outcomes in adults and children were included. Outcomes for pregnant women required assessment of NSS exposure during pregnancy without restrictions on follow-up time.

2.1.7 Other

There were no restrictions by type of setting, language or date of publication.

2.2 Search strategy

We conducted a multipronged search, building on the search conducted in the original systematic review *(1)*. This included:

- screening the excluded studies list from the original review for studies that were excluded because the NSS was unspecified;
- systematically searching MEDLINE,[1] Embase and the Cochrane Central Register of Controlled Trials (CENTRAL), from 1 January 2017 to 26 July 2021 to update the original review; and
- because we slightly modified the search strategy used in the original review to increase the sensitivity, searching the same databases with the added or modified terms and without date restrictions to pick up any relevant studies not included in the original search.

The search strategies are shown in **Annex 1**.

2.3 Selection process

After collection of all potential records and removal of duplicates, all the titles, abstracts and full texts were screened for eligibility in duplicate by two researchers. The data management software Covidence[2] was used for the selection process. Any disagreement on the exclusion or inclusion of a record between the two reviewers was resolved by discussion.

2.4 Data extraction

Data extraction was done in two steps. In the first step, the basic study information, such as study design, population, country, funding, intervention, comparator, outcome, sample size and summary of effect, were extracted for all studies. In the second step, the full information was extracted for a subset of studies, depending on the study designs available for each outcome. The order of priority for full data extraction was RCTs, prospective cohort studies, nonrandomized controlled trials, case–control studies and cross-sectional studies.

If multiple interventions were conducted in a study, the comparisons allowing the best estimate of the effect of NSS were selected. Data were not extracted for arms of trials with multifactorial interventions that were not matched for everything except NSS across arms of the trial. If outcomes were measured at multiple time points, the time points nearest to the beginning and the end of the intervention were selected for experimental studies, or the longest follow-up for observational studies. If a single study was published in multiple articles, the most complete and recent estimates were extracted.

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[1] Including MEDLINE In-Process & Other Non-Indexed Citations

[2] https://www.covidence.org/

Because of slight baseline imbalance in most of the RCTs included in the review (concomitant with relatively small effect sizes), we extracted change from baseline values for each arm in a trial.

For prospective cohort studies reporting adjusted results from multiple models, the effect sizes corresponding to the most adjusted models were extracted. In prospective cohort studies where the upper quantile was clearly above the ADI for a particular NSS, data were extracted from the next lower quantile to be used for comparison with the lowest, referent quantile. In prospective cohort studies, when effect sizes were reported continuously, the effect size reporting per serving size was used. If the only effect sizes available were not per serving size (e.g. per fluid ounce, per *N* mL), they were scaled to a serving size of 300 mL.

If data were ambiguous, not reported in a usable format, missing or not yet published (in the case of ongoing studies identified from trial registries), we contacted the responsible researcher via email. If data were only available from figures, they were extracted using the validated software Plot Digitizer.[1]

2.5 Assessment of risk of bias

Risk of bias in RCTs was assessed using the Cochrane risk of bias (ROB) tool *(16)*. In assessing risk of bias in RCTs, emphasis was placed on adequate randomization, and limited loss to follow-up (incomplete outcome data) and selective reporting. Blinding of participants would have been difficult in many studies, given different behavioural advice, and the obvious taste differences between sugars, water and NSS. Risk of bias related to blinding of participants was assessed as:

- high in studies comparing clear differences in advice, or comparing water with NSS;
- low in studies delivering NSS via capsule; and
- unclear where NSS were compared with sugars, as it is not clear whether participants would have been able to taste the difference in foods or beverages.

Risk of bias in prospective cohort studies and case–control studies was assessed by the risk of bias in nonrandomized studies of interventions (ROBINS-I) method *(18)* and confirmed with the Newcastle–Ottawa Scale.[2] Risk of bias assessments using each method were largely in agreement, and Newcastle–Ottawa Scale results were used in assessing the quality of the evidence for observational studies via the GRADE framework.[3]

Publication bias was assessed with enhanced funnel plots and Egger's test when data from at least 10 studies could be meta-analysed *(16, 19)*.

2.6 Data analysis

Data transformations and imputations were done according to the *Cochrane handbook for systematic reviews of interventions (16)* and following the recommendations of Borenstein et al. *(20)*. Whenever possible, the different effect sizes reported were transformed to a common effect size to allow meta-analysis. If standard deviations were missing, they were calculated from standard errors, confidence intervals, *P* values or *t* values; approximated using the Taylor series expansion; or imputed from the standard errors reported in the same study. Where the standard deviation or equivalent was not reported for the change from baseline, we derived a correlation coefficient from well-conducted trials reporting the same outcome for the same or very similar intervention *(16)*. When multiple trials provided data and the calculated correlation coefficients were very similar within an arm of the trial, we averaged them. When the correlation coefficients across arms (i.e. across intervention and control arms) were similar, we averaged these into an outcome-specific single correlation coefficient to be used on any arm in a trial for that outcome.

[1] http://plotdigitizer.sourceforge.net
[2] http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
[3] https://www.gradeworkinggroup.org/

When we were unable to identify relevant studies from which to derive a correlation coefficient, a value of 0.5 was selected, and sensitivity analyses using values of 0.25 and 0.75 were conducted to assess the impact on the results.

If comparable outcome data from two or more studies were available, we conducted random effects meta-analyses using the DerSimonian–Laird method *(21)*. Meta-analyses were conducted separately for adults, children and pregnant women, and, within each population, separately for RCTs, prospective cohort studies and case–control studies. In multi-arm trials, arms were combined for the main meta-analyses when they included:

- two or more relevant comparators to NSS (i.e. sugar-sweetened beverages [SSBs] and water controls); or
- two or more NSS interventions (e.g. multiple doses of the same NSS or multiple, different NSS).

Trial arms were combined using the formula for combining groups recommended in the *Cochrane handbook for systematic reviews of interventions (16)*. Heterogeneity was assessed with the I^2 statistic. Sources of heterogeneity and confounding were explored using pre-specified subgroup, sensitivity and meta-regression analyses. A priori analyses included differences in effects between:

- normal-weight and overweight populations;
- comparators of NSS (i.e. water, sugar, nothing/placebo);
- study designs (including weight loss vs non–weight loss studies);
- publication types (e.g. poster/abstract, journal article);
- participant consumption patterns of foods and beverages containing free sugars and foods and beverages containing NSS;
- durations of the intervention/exposure; and
- risks of bias in the studies.

Studies that could not be meta-analysed were reported narratively.

For the 1997 study by Blackburn et al. *(22)*, the data reported for the longest follow-up (week 151) were used in all analyses except for subgroup analyses by study design (weight loss vs non–weight loss studies); for these analyses, the data reported at the end of the weight maintenance phase were used (week 71). In the original study by Engel et al. (2018) *(23)*, standard deviations were erroneously reported as standard errors. A correction was issued in 2020 fixing this error *(24)*, and values used in this review are the corrected values.

Statistical analyses were conducted with RAnalyticFlow (version 3.1.8) with the package meta.

2.7 Assessment of quality of evidence

The quality of (certainty in) the evidence was assessed using the GRADE framework.[1] Certainty in the evidence was assessed as very low, low, moderate or high, based on risk of bias, inconsistency, indirectness and imprecision, as well as other considerations including possibility of publication bias and evidence of a dose–response relationship (in the case of observational studies).

[1] https://www.gradeworkinggroup.org/

3. Results

From more than 8000 records identified, a total of 370 records, representing 283 unique studies conducted in adults, children, pregnant women or mixed populations, were included in this review:

- 50 RCTs
- 97 prospective cohort studies
- 47 case–control studies assessing cancer outcomes
- 5 nonrandomized controlled trials
- 69 cross-sectional studies
- 15 ongoing/registered trials (for which published results were not identified).

The flowchart of the study selection process is shown in **Fig. 1**. Studies were identified that assessed virtually all priority health outcomes for each population of interest, and the coverage of outcomes across study types is shown in **Fig. 2** and in tabular form in **Annex 2**. Characteristics of included studies are shown in **Annex 3** and of ongoing trials in **Annex 4**. Reasons for exclusion of studies can be found in **Annex 10**, and differences between this review and the original review can be found in **Annex 11**.

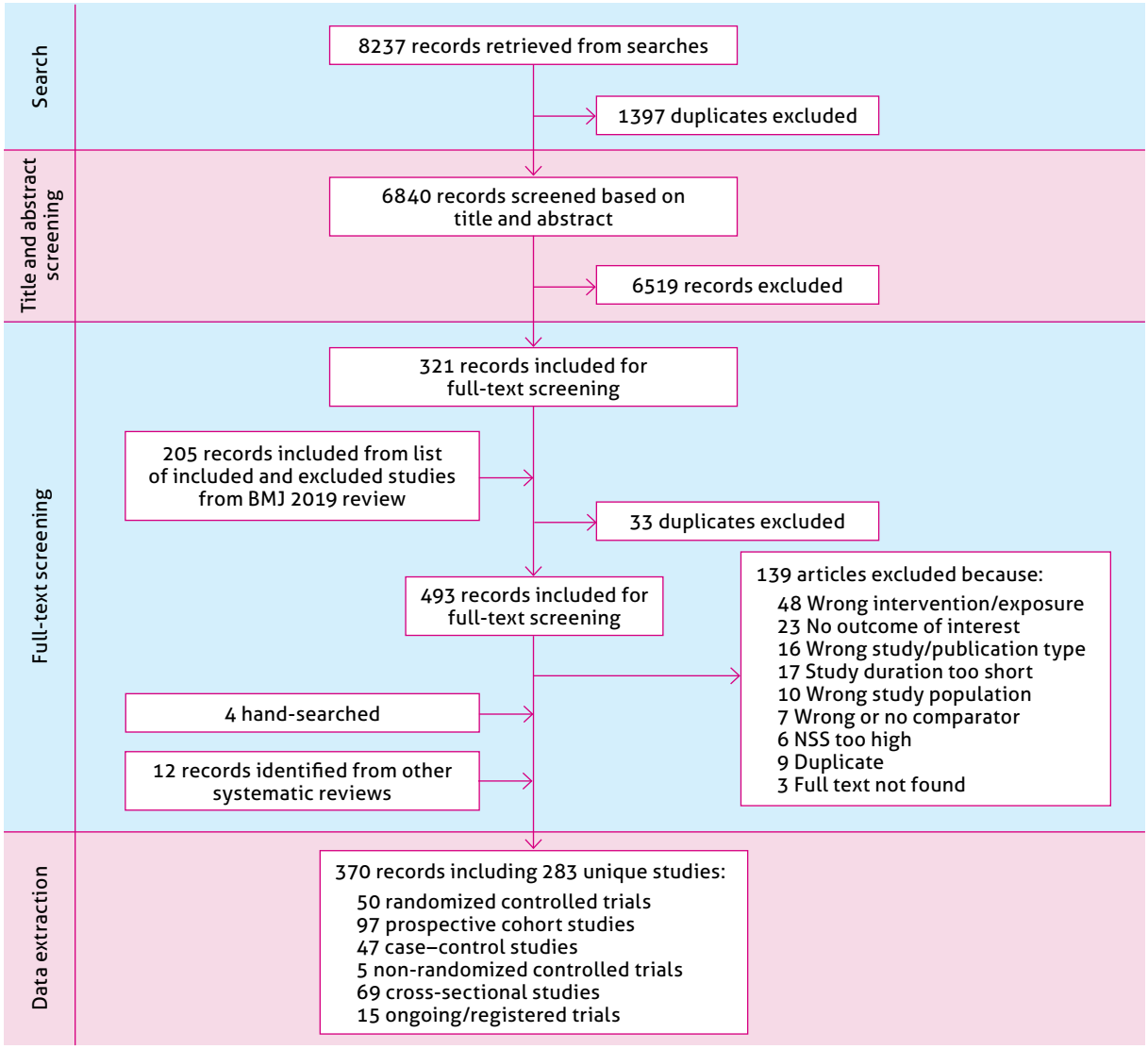
This review includes 45 RCTs conducted in adults, four in children, and one including both adults and children. No relevant trials in pregnant women were identified. Trial duration in adults (including follow-up post-intervention) ranged from 7 days to more than 3 years. Trials in adults were conducted in lean populations (n = 10), mixed-weight populations (n = 20) or exclusively overweight populations (n = 15). They were generally of mixed sex (n = 38), but one trial included males only, and five trials included females only (one trial did not specify). Eight of the trials conducted in adults were crossover trials; the remainder had a parallel design. Thirteen of the trials used an unspecified NSS in their intervention, 12 used aspartame, six used sucralose, three used stevia, one used saccharin, five used a mix of more than one NSS, one used advantame, and four tested multiple NSS separately (saccharin, aspartame, rebaudioside A/stevia, sucralose; sucralose, stevia; aspartame, acesulfame K). Trials in adults were conducted in Australia (n = 2), Denmark (n = 2), France (n = 2), Greece (n = 1), the Republic of Korea (n = 4), the Islamic Republic of Iran (n = 1), Latvia (n = 1), Mexico (n = 6), New Zealand (n = 2), Switzerland (n = 1), Thailand (n = 1), the United Kingdom (n = 7), the United States (n = 14) and multiple countries (n = 1).

The four RCTs in children were all of parallel design, conducted in mixed-sex populations (except for one conducted in females only), and lasted from 6 weeks to 18 months. Two trials used stevia in the intervention arm, one used a mix of sucralose and acesulfame K, and one used sucralose. One trial in children was conducted in each of India, Italy, the Netherlands and South Africa.

The single parallel trial conducted in adults and children included a mixed-sex population, used aspartame in the intervention, and was conducted in the United States.

Seventeen of the trials conducted in adults, two of the trials conducted in children, and the trial with both adults and children were either fully or partially funded by industry. Interventions included providing dietary advice (with or without the provision of food) to effect behaviour change (e.g. replacing sugar-sweetened foods and/or beverages with those that contained NSS or were unsweetened), using supplemental foods and beverages containing sugars or NSS, asking habitual users of NSS to discontinue use, and providing NSS in capsule form compared with a placebo. The focus of the trials was not always on assessing the effects of NSS; several trials had

Fig. 1. Flow chart of study identification and selection



the primary goal of testing the effects of sugars and used NSS as a control. To reflect this, we refer to the results of trials as having achieved a higher intake of NSS in one or more arms, rather than explicitly increasing NSS intake or replacing sugars, for example. Additional detail about the RCTs can be found in **Table A3.1** of **Annex 3**.

Significant concerns were noted regarding one RCT included in this review with respect to how data were reported, possible numerical errors, and unusual results for some outcomes *(25)*. Sensitivity analyses, in which this trial was removed, did not significantly alter the results for any outcome, including body weight, waist circumference, body fat percentage, fasting glucose, fasting insulin, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), energy intake or sugars intake. Excluding this trial also did not significantly affect heterogeneity (i.e. did not push the value for I^2 across the threshold for serious inconsistency of 50%), although results for BMI became statistically significant (see **section 3.1.1**). The study was therefore retained in the main analyses.

This review includes 64 prospective cohort studies conducted in adults (representing approximately 35 unique cohorts), 15 cohort studies in children (representing 13 unique cohorts), one cohort study in children and adults (representing one unique cohort) and 17 cohort studies in

pregnant women (representing 12 unique cohorts). Of the studies in adults, 47 were of mixed sex, 15 were exclusively female, and two were exclusively male. All studies of children were of mixed sex, except one that was exclusively girls. Follow-up in cohort studies in adults ranged from 2 years to more than 30 years, in children from 8 months to 10 years, and in pregnant women from 8 months to 16 years. Cohort studies in adults were conducted in Australia (*n* = 3), France (*n* = 4), Japan (*n* = 1), Mexico (*n* = 1), the Russian Federation (*n* = 1), Spain (*n* = 4), the United Kingdom (*n* = 1), the United States (*n* = 44) and multiple countries (*n* = 5). Cohort studies in children were conducted in Australia (*n* = 1), Denmark (*n* = 1), the United Kingdom (*n* = 1) and the United States (*n* = 12). The cohort study conducted in children and adults was conducted in Australia. Cohort studies in pregnant women were conducted in Canada (*n* = 1), Denmark (*n* = 6), Germany (*n* = 1), Iceland (*n* = 1), the Netherlands (*n* = 1), Norway (*n* = 2), Slovenia (*n* = 1), the United Kingdom (*n* = 1) and the United States (*n* = 3). Additional detail about the prospective cohort studies can be found in **Table A3.2** in **Annex 3**. The prospective cohort studies included in this review adjusted extensively for potential confounders, which are summarized in **Annex 5**.

This review includes 41 case–control studies assessing cancer outcomes in adults (one study reports results from two populations separately, and one reports on multiple, unspecified populations together, for a total of 42 data sets). All case–control studies were conducted in populations of mixed weight. Two were conducted exclusively in males, three exclusively in females and the rest in mixed-sex populations. Twenty-two studies assessed effects of unspecified sweeteners, 11 of multiple sweeteners, seven of saccharin and two of aspartame. Studies were conducted in Argentina (*n* = 2), Canada (*n* = 4), China (*n* = 2), Denmark (*n* = 3), Egypt (*n* = 1), France (*n* = 2), Italy (*n* = 2), Japan (*n* = 2), Lebanon (*n* = 1), Serbia (*n* = 1), Spain (*n* = 1), Sweden (*n* = 2), the United Kingdom (*n* = 2), the United States (*n* = 15) and multiple countries (*n* = 1). Two studies conducted in the United States assessing cancer in children were also included.[1] Additional detail about the case–control studies can be found in **Annex 3**.

Results from nonrandomized controlled trials and cross-sectional studies are provided in sections 3.1, 3.2 and 3.3 as supplementary evidence when little to no evidence is available from trials, prospective cohort studies or case–control studies (in the case of cancer).

Risk of bias and GRADE assessments can be found in **Annex 6** and **Annex 7**, respectively. Results of funnel plot analysis can be found in **Annex 8**.

3.1 Adults

3.1.1 Adiposity

A total of 32 RCTs *(22, 23, 25–54)* and 13 prospective cohort studies *(55–69)* reporting on measures of adiposity were included in meta-analyses. Results for measures of adiposity are summarized in **Table 2**.

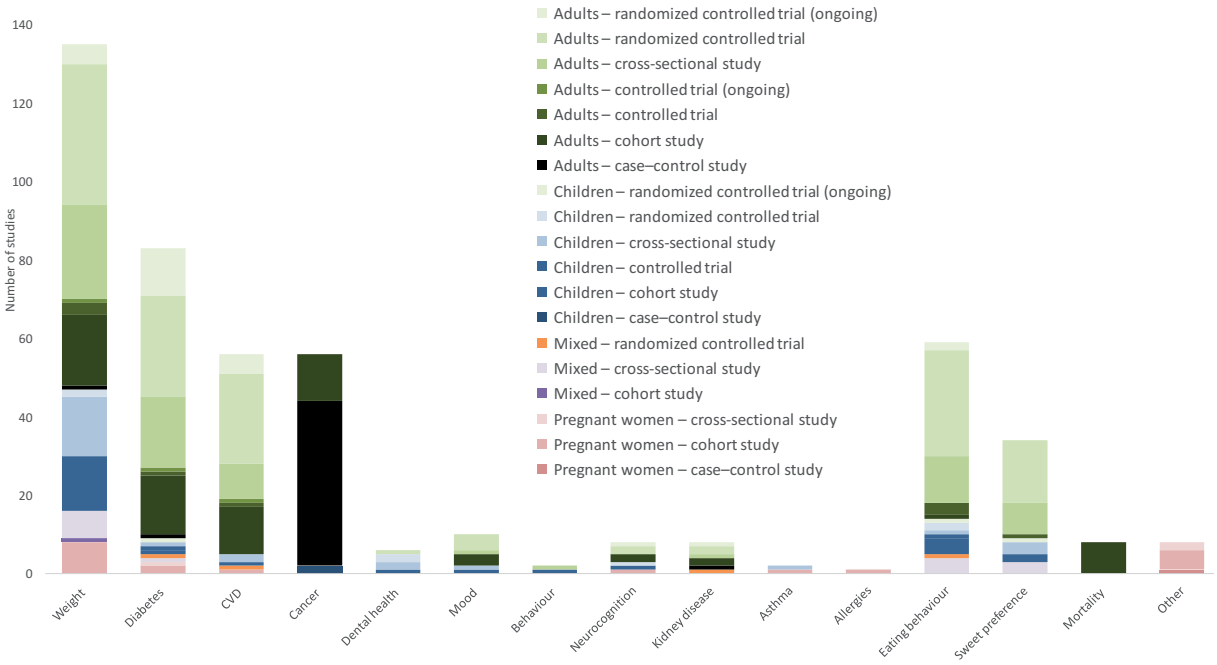
As assessed in RCTs, higher intakes of NSS resulted in a reduction in body weight of 0.71 kg (**Fig. 3**) and BMI of 0.14 kg/m^2, although the latter was not quite statistically significant (**Fig. 4**). No significant effects were observed for other measures of adiposity as assessed in RCTs (**Table 2**; **Annex 9: Fig. A9.1–A9.5**). Higher intakes of NSS were associated with a 0.14 kg/m^2 increase in BMI and a 76% increase in risk of incident obesity as assessed in prospective cohort studies (**Fig. 5** and **6**). No other significant associations were observed in prospective cohort studies (**Table 2; Annex 9: Fig. A9.6–A9.9**).

Data from studies that could not be included in meta-analyses

Six RCTs reported no significant effect on weight or intermediate markers of adiposity in adults, but could not be included in the meta-analyses because of missing data *(33, 70–75)*. In an RCT of

[1] In addition, three case-control studies assessing outcomes other than cancer in adults were included in the review but were not assessed as part of the evidence base as data was available from higher quality RCTs and/or prospective observational studies.

Fig. 2. Outcomes reported by study design and population



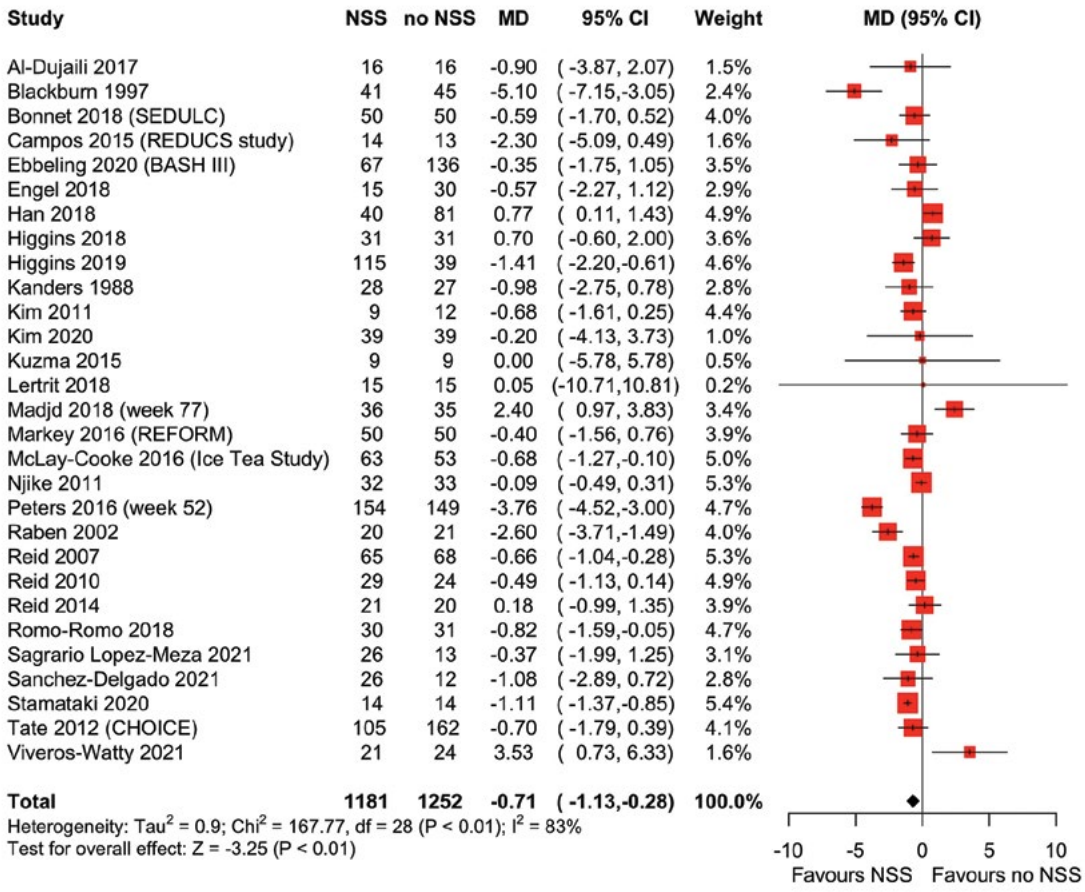
CVD: cardiovascular disease.
Note: Disease outcomes include both disease incidence and risk factors.

Table 2. Summary of results for NSS intake and measures of adiposity in adults

Measure of adiposity (unit)	No. of studies/cohorts	Effect estimate (95% CI)	I^2 (%)	Figure
Weight (kg)	29 RCTs	**MD –0.71 (–1.13, –0.28)**	83	3
	4 cohorts (cont)	MD –0.12 (–0.40, 0.15)	76	A9.6
	5 cohorts (hvl)	MD –0.01 (–0.67, 0.64)	49	A9.7
BMI (kg/m^2)	23 RCTs	MD –0.14 (–0.30, 0.02)	71	4
	5 cohorts (hvl)	**MD 0.14 (0.03, 0.25)**	79	5
Incident obesity	2 cohorts (hvl)	**HR 1.76 (1.25, 2.49)**	0	6
Waist circumference (cm)	10 RCTs	MD –0.24 (–1.06, 0.58)	74	A9.1
	3 cohorts (hvl)	MD 0.92 (–1.73, 3.56)	85	A9.8
Abdominal obesity	4 cohorts (hvl)	HR 1.33 (0.91, 1.96)	91	A9.9
Waist-to-hip ratio	3 RCTs	MD 0.00 (–0.01, 0.01)	0	A9.2
Body fat mass (kg)	6 RCTs	MD –0.54 (–1.56, 0.49)	87	A9.3
Body fat mass (%)	10 RCTs	MD –0.11 (–0.78, 0.56)	74	A9.4
Body lean mass (kg)	6 RCTs	MD –0.29 (–0.70, 0.11)	48	A9.5

cont: continuous, per serving; hvl: highest versus lowest category of intake.
Note: Bold font indicates a statistically significant effect.

Fig. 3. Effect of NSS intake on body weight (kg) in randomized controlled trials



both adults and children *(76)*, overweight participants (*n* = 57) between 10 and 21 years of age (mean age: 19 years) were given capsules totalling 2.7 g aspartame daily or a lactose placebo. At the end of the intervention, when compared to the placebo arm, the aspartame arm had lost 1.09 kg (standard error [SE]: 0.87).

In a prospective cohort study conducted in both adults and children (14–22 years of age), substituting 100 g/day of SSBs with diet drink was association with a 0.20 kg (SE 0.05) higher BMI and a 0.18 cm (SE 0.05) higher waist circumference *(77)*. In other prospective cohort studies, authors reported that intake of NSS-sweetened beverages is likely to represent an important driver of the relationship between lower education and greater weight gain over time in Australian women *(78)*. No associations were observed between consumption of NSS-sweetened beverages and risk of weight gain *(79)*, or the amount of fat in the liver or incidence of non-alcoholic fatty liver disease *(80)*.

Subgroup and sensitivity analyses

Subgroup analyses suggest that the effect of NSS on body weight may be greatest in those who are overweight (**Fig. 7**), and those intentionally trying to lose weight by restricting energy intake (**Fig. 8**), though neither test for subgroup differences were statistically significant, and pooled effects for some of the subgroups may have been skewed by outliers. Differences were observed for individual subgroups in subgroup analysis of body weight and BMI by comparator: adding NSS to the diet compared with nothing (or placebo), and adding NSS to the diet compared with sugars (either NSS replacing sugars, or both NSS and sugars being added to the diet, in separate arms of a trial) both resulted in decreases in body weight and BMI, whereas NSS compared with water showed no effect on body weight and a nonsignificant increase in BMI (test for subgroup

Fig. 4. Effect of NSS intake on body mass index (kg/m²) in randomized controlled trials

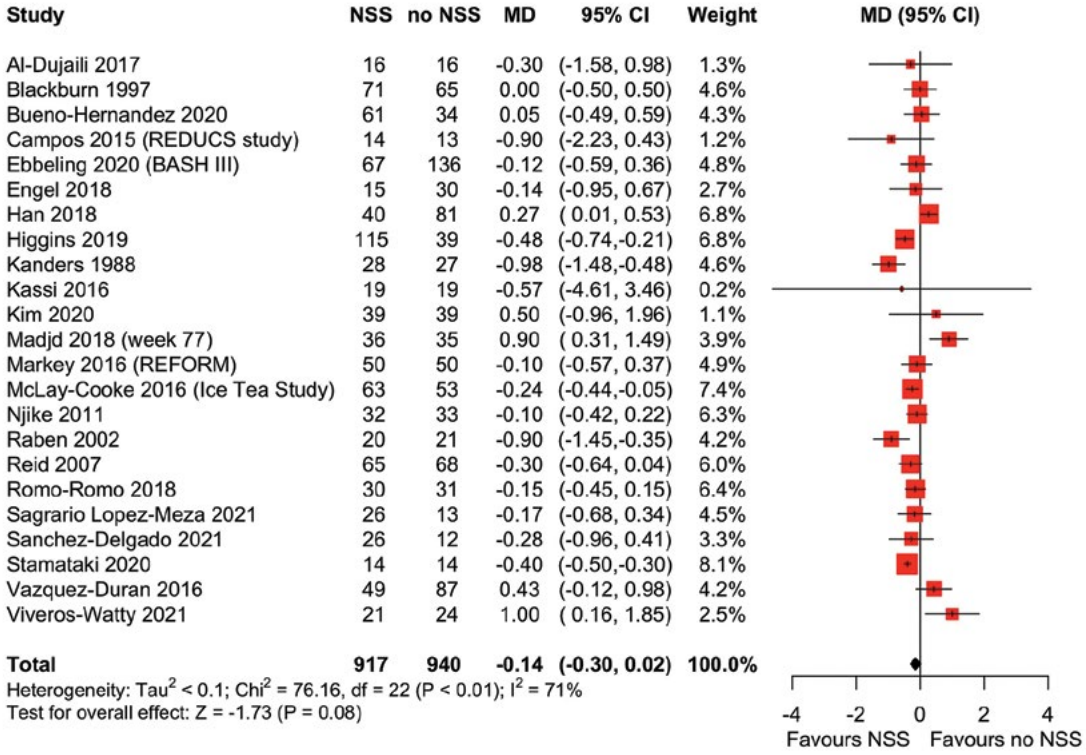


Fig. 5. Association between NSS intake and body mass index (kg/m²) in prospective cohort studies

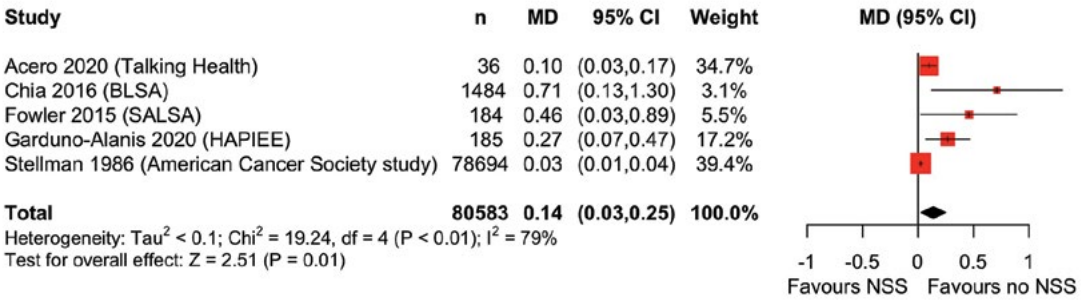


Fig. 6. Association between NSS intake and incident obesity in prospective cohort studies

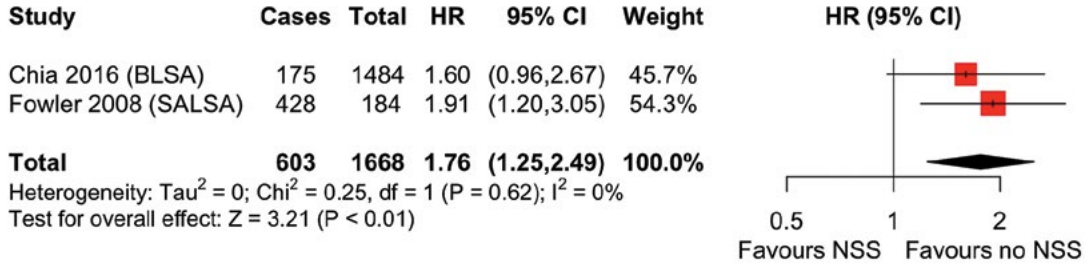
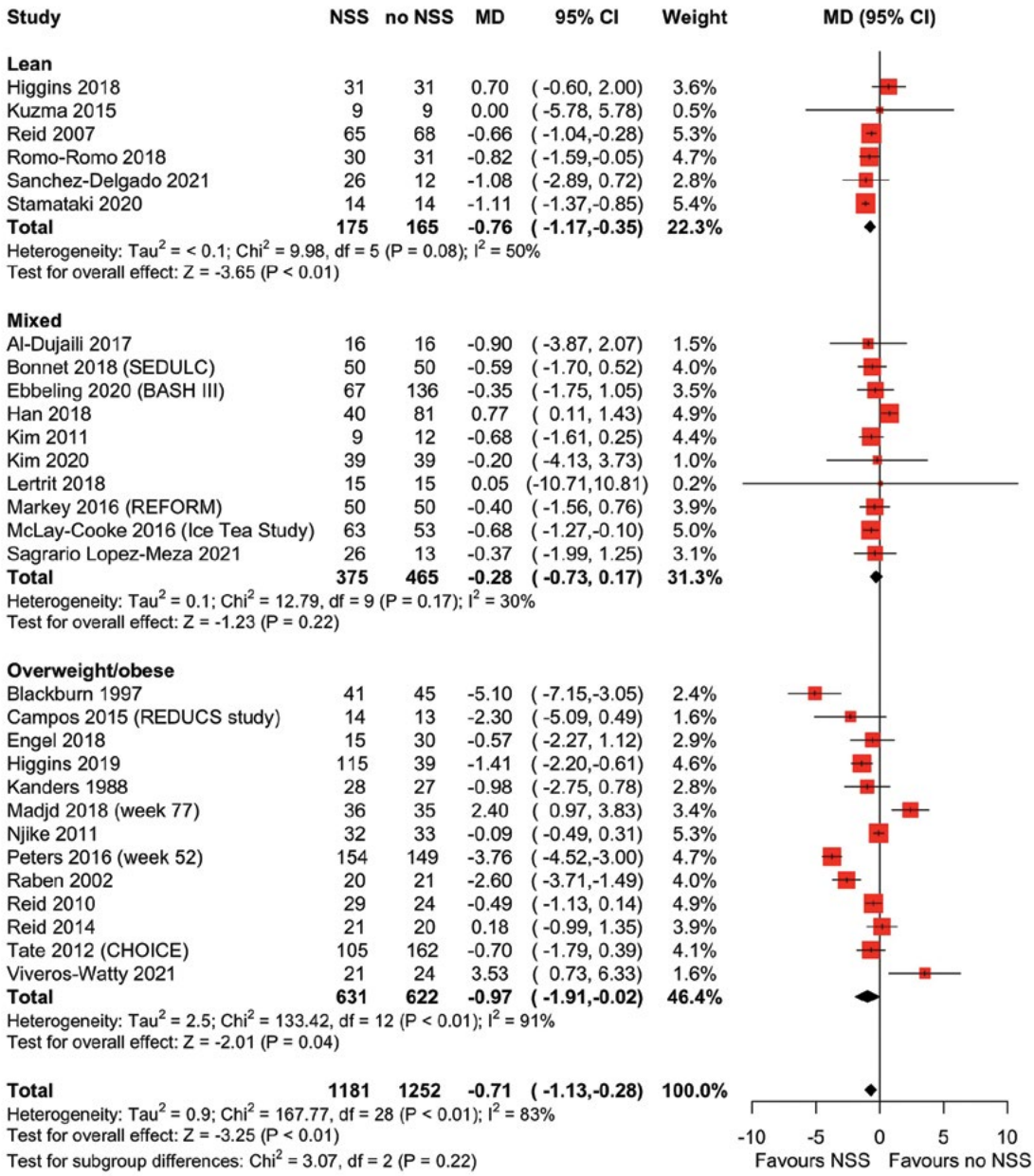


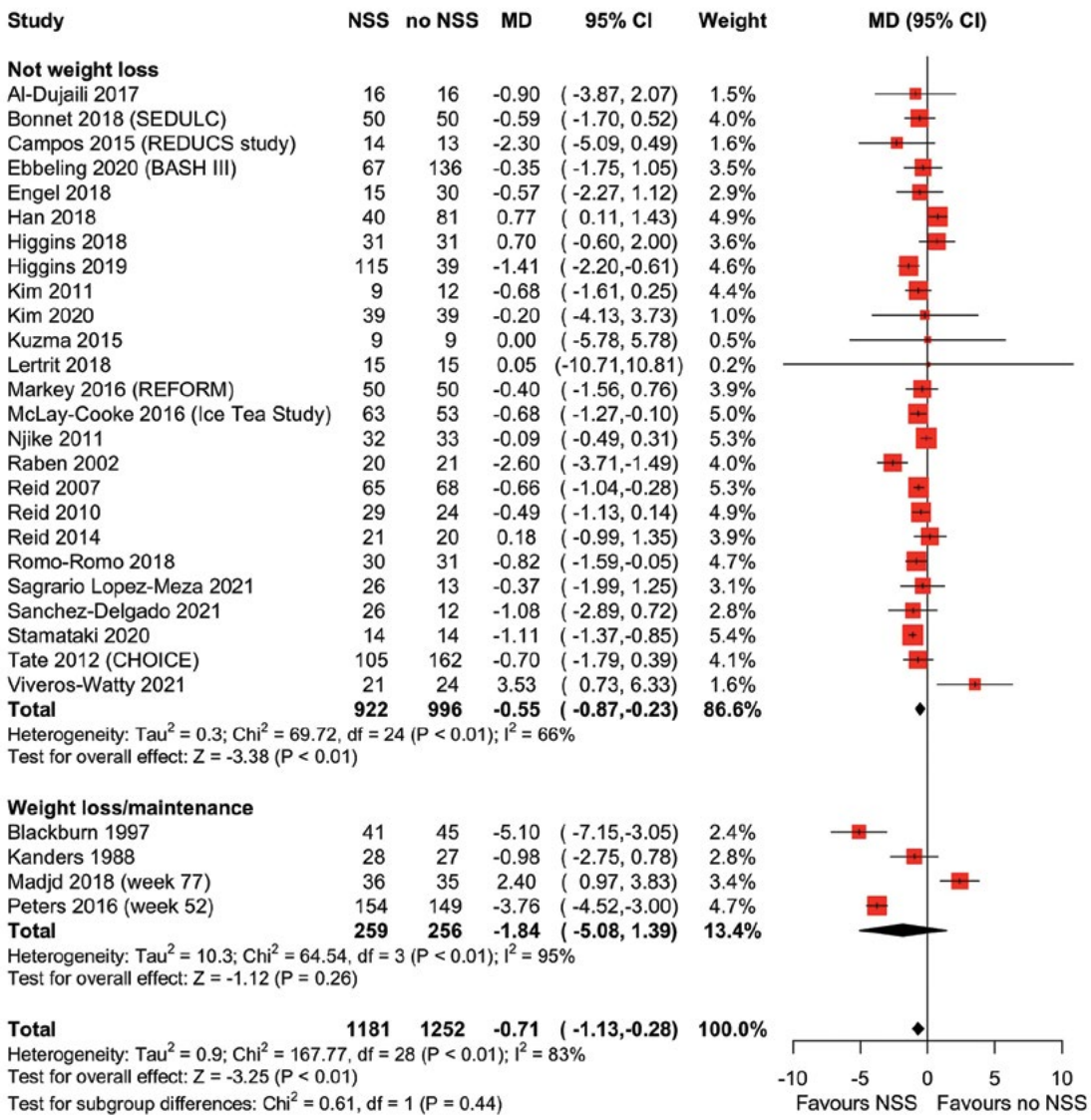
Fig. 7. Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by baseline weight status



differences was only statistically significant for BMI) (**Fig. 9 and 10**). The observed changes in body weight and BMI were likely mediated by a reduction in energy intake as all studies that compared NSS to sugars and reported both body weight or BMI, and energy intake collectively, showed reductions in body weight, BMI and energy intake (data not shown), whereas studies not comparing NSS to sugars did not collectively show a reduction in energy intake (**section 3.1.7.1: Fig. 29**). When studies were limited to those that gave explicit instructions to habitual consumers of SSBs or sugar-containing foods to replace these foods and beverages with alternatives sweetened with NSS, the effect on body weight remained but was slightly attenuated and became statistically nonsignificant (**Fig. 11**), and an effect on BMI was no longer observed (**Fig. 12**).

Sensitivity analyses in which one study that appeared to contain numerical errors and/or unusual results for some outcomes *(25)* was excluded did not significantly change the results for body

Fig. 8. Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by study design (weight loss studies vs non–weight loss studies)

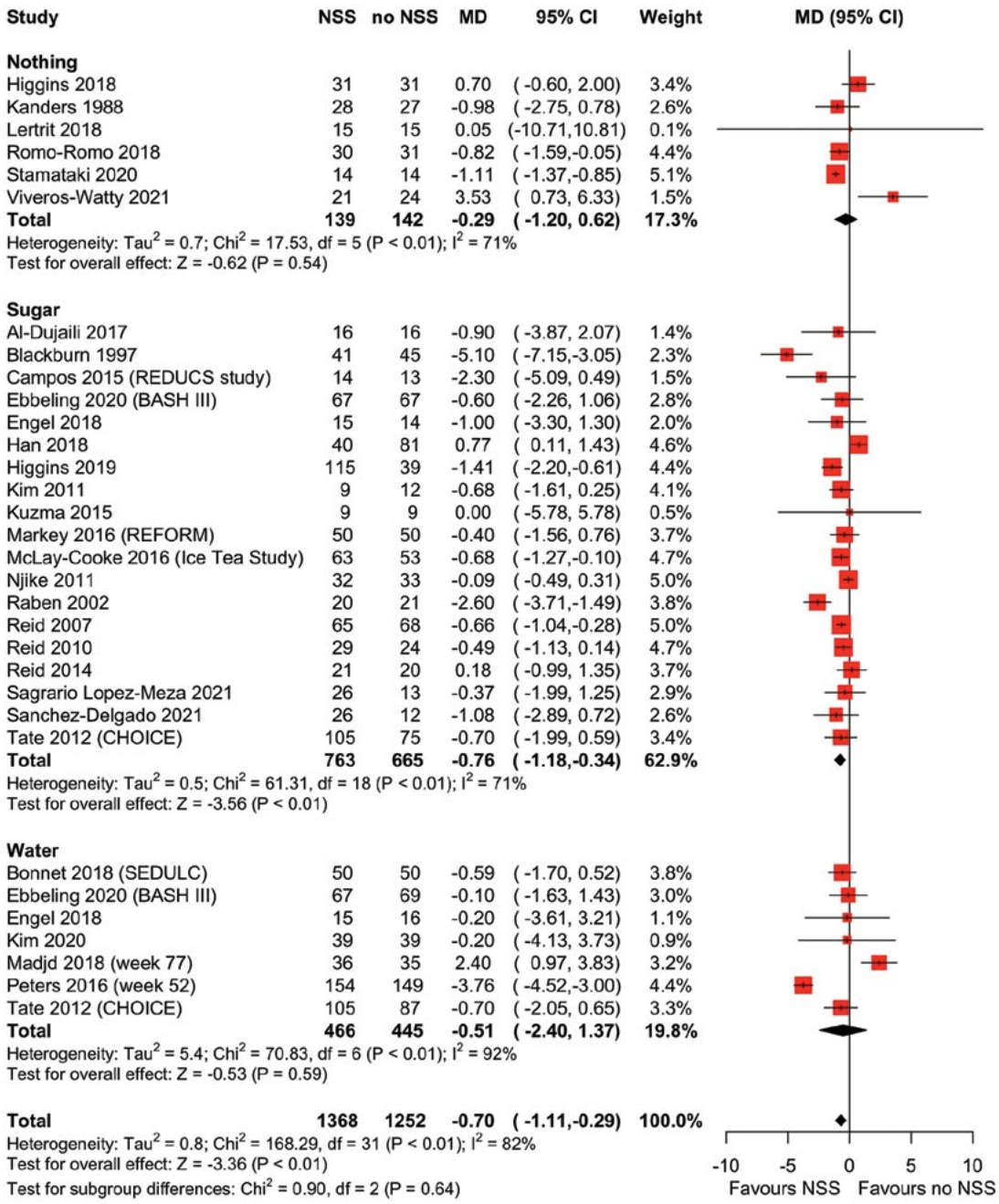


Note: Weight loss studies were those in which participants were instructed to restrict energy intake AND consume NSS or control. Weight maintenance studies were those that followed up participants after active weight loss, with instructions on energy intake designed to prevent weight gain. Non–weight loss studies were those that had no intentional weight loss component.

weight (mean difference [MD] –0.78; 95% confidence interval [CI] –1.20, –0.35; I^2 83%) or BMI (MD –0.17; 95% CI –0.33, –0.02; I^2 69%), although the result for BMI became statistically significant.

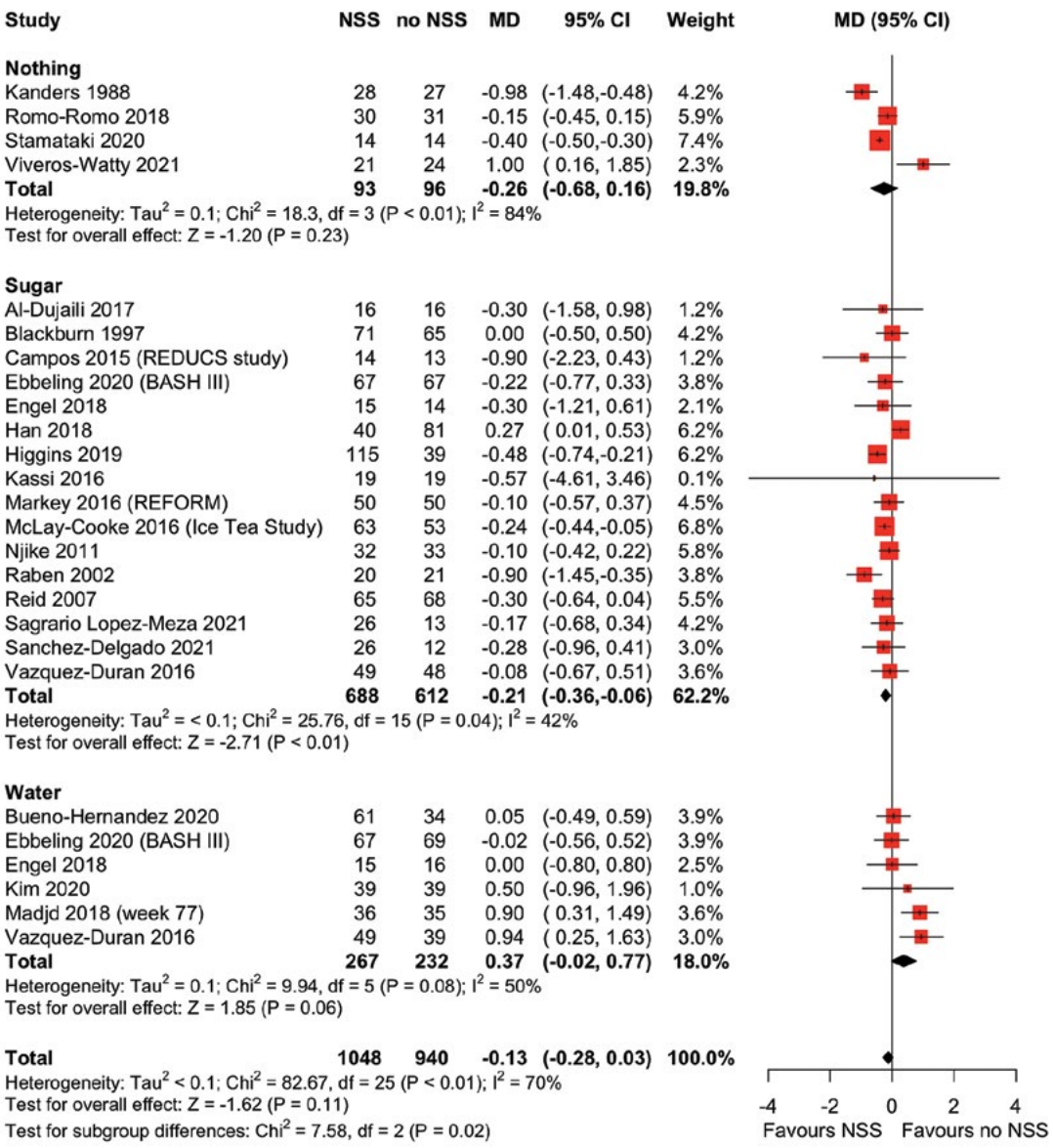
Greater weight reduction in trials of longer duration was suggested by subgroup analysis and meta-regression; however, results were not statistically significant for either (**Annex 9: Fig. A9.10** and **A9.11**). Significant differences were also observed for subgroup analysis of BMI by consumption pattern; however, the differences between consumption pattern subgroups did not allow a coherent interpretation (**Annex 9: Fig. A9.12**). Results of meta-regression found a dose–response relationship between changes in body weight or BMI and changes in energy intake – that is, greater decreases in energy intake were associated with greater decreases in body weight and BMI (**Annex 9: Fig. A9.13** and **A9.14**). Results of other subgroup analyses did not suggest meaningful differences (**Annex 9: Fig. A9.15–A9.21**).

Fig. 9. Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by comparator



Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

Fig. 10. Effect of NSS on body mass index (kg/m²) in randomized controlled trials, subgrouped by comparator



Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

Fig. 11. Effect of NSS intake on body weight (kg) for trials with explicit replacement of sugars with NSS

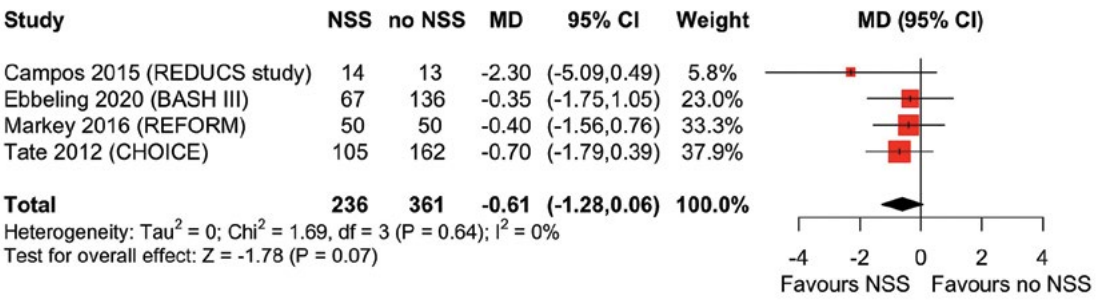
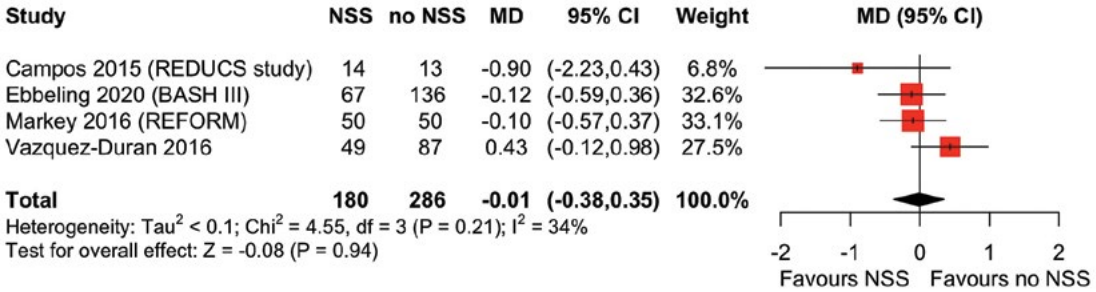


Fig. 12. Effect of NSS intake on body mass index (kg/m²) for trials with explicit replacement of sugars with NSS



Sensitivity analyses using a fixed effects model, removing abstract-only publications, and removing crossover studies and studies of shorter duration (<8 weeks) did not significantly change the effect observed for body weight (data not shown). Sensitivity analysis in which studies that were at least partially funded by industry were removed attenuated the reduction in body weight, which was no longer statistically significant (MD –0.33 kg; 95% CI –0.80, 0.13; 18 studies with 1277 participants; I^2 74%).

Supplementary results from nonrandomized controlled trials

In addition to the results observed for RCTs and prospective cohort studies, a reduction in body weight of 0.48 kg was observed in pooling of nonrandomized controlled trials (MD –0.48 kg; 95% CI –0.64, –0.32; 3 studies with 233 participants; I^2 44%) (81-83) (**Fig. A9.22**).

3.1.2 Type 2 diabetes

Results for type 2 diabetes are summarized in **Table 3**.

3.1.2.1 Incident type 2 diabetes

Twelve prospective cohort studies (comprising 14 cohorts) reporting on the risk of developing type 2 diabetes were included in meta-analyses *(66, 84–94)*. As assessed in prospective cohort studies, higher intakes of NSS were associated with increased risk of developing type 2 diabetes, regardless of whether the NSS were consumed in beverage form (a 23% increase in risk; **Fig. 13**) or added to foods or beverages by the consumer, i.e. tabletop (a 34% increase in risk; **Fig. 14**).[1]

[1] Fagherazzi et al. (2013) *(86)* and Fagherazzi et al. (2017) *(85)* reported results for the entire French E3N cohort, which is part of the EPIC Interact European cohort. Interact Consortium et al. (2013) *(94)* includes a small number of the E3N cohort in its analysis (less than 1% of the full cohort). Therefore, both studies were included in the analysis of type 2 diabetes risk, with beverages as the exposure.

To address reverse causation, all 12 prospective cohort studies adjusted for relevant confounders, including BMI (**Annex 5**), and most performed a number of relevant sensitivity analyses, including the exclusion of diabetes cases in the first 3–7 years of follow-up from baseline. Most studies reported quantitively or narratively that the effect was not significantly affected (**Table 4**).

Table 3. Summary of results for NSS intake and type 2 diabetes

Measure of type 2 diabetes (unit)	No. of studies/ cohorts	Effect estimate (95% CI)	I^2 (%)	Figure
Incident type 2 diabetes (beverages)	13 cohorts	**HR 1.23 (1.14, 1.32)**	6	13
Incident type 2 diabetes (tabletop)	2 cohorts	**HR 1.34 (1.21, 1.48)**	0	14
Fasting glucose (mmol/L)	16 RCTs	MD –0.01 (–0.05, 0.04)	0	A9.23
Fasting insulin (pmol/L)	10 RCTs	MD –0.49 (–4.99, 4.02)	74	A9.24
HbA1c (%)	6 RCTs	MD 0.02 (–0.03, 0.07)	0	A9.25
HOMA-IR	11 RCTs	MD 0.03 (–0.32, 0.38)	89	A9.26
High fasting glucose	3 cohorts	HR 1.21 (1.01, 1.45)	47	A9.27

HbA1c: glycated haemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.
Note: Bold font indicates a statistically significant effect.

Fig. 13. Association between NSS-containing beverage intake and risk of type 2 diabetes in prospective cohort studies

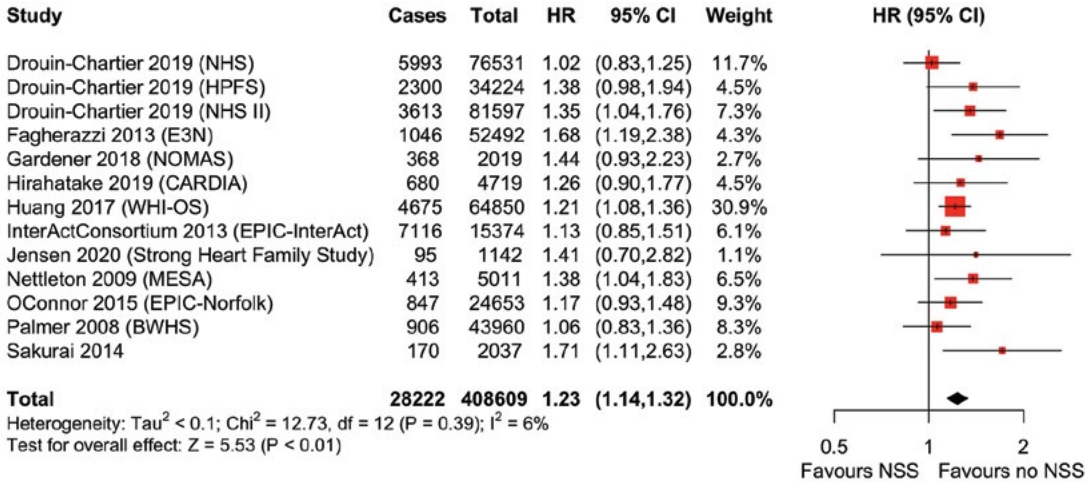
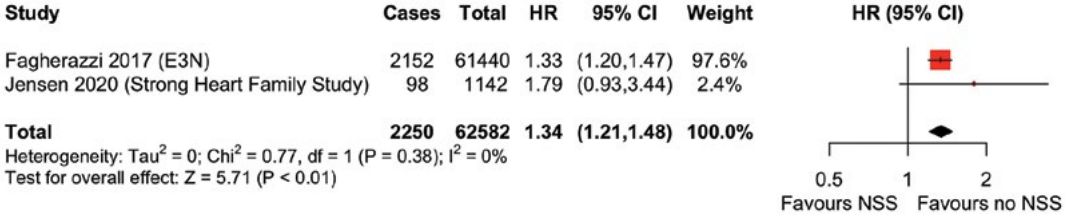


Fig. 14. Association between tabletop NSS use and risk of type 2 diabetes in prospective cohort studies



3.1.2.2 *Intermediate markers of disease*

Twenty-one RCTs *(23, 25–30, 35–37, 39, 40, 45-47, 49, 51, 53, 95–97)* and three prospective cohort studies *(61, 62, 66)* reporting on intermediate markers of type 2 diabetes were included in meta-analyses. No significant effects were observed for any measure of glycaemic control as assessed in RCTs (**Table 3**; **Annex 9: Fig. A9.23–A9.26**). Higher intakes of NSS were associated with a 21% increase in risk of high fasting glucose[1] as assessed in prospective cohort studies (hazard ratio [HR] 1.21; 95% CI 1.01, 1.45; 3 studies with 11 213 participants; I^2 47%) (**Table 3**; **Annex 9: Fig. A9.27**).

Because there was generally very little heterogeneity or very few studies for each outcome, subgroup analyses were not performed.

Table 4. Summary of sensitivity analyses within cohort studies

Study	Key sensitivity analysis	Original effect (95% CI)	Post-sensitivity analysis (95% CI)
Drouin-Chartier 2019 (NHS)	4-year lag in analysis (after change in beverage consumption)	1.02 (0.83, 1.25)	1.20 (1.12, 1.28) (all 3 cohorts pooled)
Drouin-Chartier 2019 (NHS II)	4-year lag in analysis (after change in beverage consumption)	1.35 (1.04, 1.76)	
Drouin-Chartier 2019 (HPFS)	4-year lag in analysis (after change in beverage consumption)	1.38 (0.98, 1.93)	
Fagherazzi 2013	Excluding first 5 years	1.68 (1.19, 2.39)	1.81 (1.19, 2.73)
Fagherazzi 2017	Excluding first 5 years	1.33 (1.20, 1.47)	1.76 (1.59, 1.96)
Gardener 2018	Excluding first 3 years	1.44 (0.93, 2.24)	1.63 (1.04, 2.56)
Hirahatake 2019	Excluding first 7 years	1.37 (0.98, 1.92)	No significant change
Huang 2017	Excluding first 4 years	1.21 (1.08, 1.36)	1.18 (1.02. 1.37)
InterAct Consortium 2013	Excluding first 2 and 5 years	1.13 (0.85, 1.52)	Results not reported for NSS-sweetened beverages
Jensen 2020	None reported	1.41 (0.70, 2.80)	NA
Nettleton 2009	Adjusted for change in body weight	1.38 (1.04, 1.82)	No significant change
O'Connor 2015	Excluding first 5 years	1.17 (0.93, 1.48)	1.03 (0.88,1.22)
Palmer 2008	None reported	1.06 (0.83, 1.36)	NA
Sakurai 2014	Excluded those receiving dietary intervention for NCDs	1.71 (1.11, 2.63)	No significant change

HPFS: Health Professionals Follow-up Study; NA: not applicable; NCDs: noncommunicable diseases; NHS: Nurses' Health Study.

Results from studies that could not be included in meta-analyses

Eight trials that could not be included in the meta-analyses reported no significant effect of NSS on intermediate markers of diabetes *(27, 31, 33, 52, 70, 72–74, 98)*. One study reported that NSS augmented glucose absorption (15%; $P \leq 0.05$) and glycaemic responses to enteral glucose (26%; $P \leq 0.01$) *(99)*. Studies reporting on glucose and insulin area under the curve (AUC) and

[1] High fasting glucose (as part of the criteria for assessing metabolic syndrome, as indicated in the relevant included studies) was defined as ≥100 mg/dL.

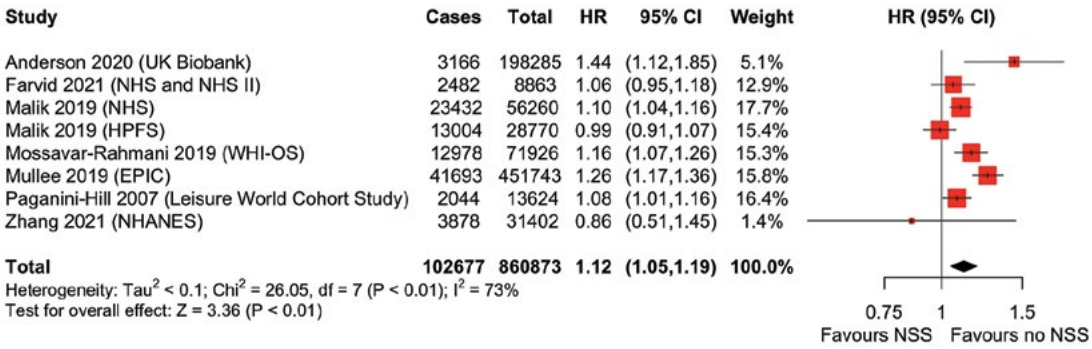
incremental AUC (iAUC) were not amenable to meta-analysis; however, most did not report significant differences *(23, 26, 31, 35, 53, 100, 101)*. One trial found a significant increase in glucose iAUC in the NSS arm compared with the sucrose arm ($P < 0.05$) *(96)*.

In an RCT conducted in overweight participants, adults and children ($n = 57$) between 10 and 21 years of age (mean age 19 years) were given capsules or a lactose placebo. At the end of the intervention, fasting glucose was 0.32 mmol/L (SE 0.16) higher in the aspartame arm compared with the placebo arm *(76)*.

3.1.3 All-cause mortality

Seven prospective cohort studies (comprising eight cohorts) reporting on the risk of all-cause mortality were included in meta-analyses *(69, 102–107)*. As assessed in prospective cohort studies, higher intakes of NSS-containing beverages were associated with a 12% increase in risk of all-cause mortality (Fig. 15). Three of the six cohorts with P_{trend} data had P_{trend} values <0.5. In addition, three of the studies with positive associations that conducted sensitivity analyses, in which cases were excluded from the first 3–8 years of follow-up, reported little to no impact on results. In the 2019 study by Malik et al. *(102)*, the effect in the Nurses' Health Study (NHS) cohort was attenuated when the data were adjusted for incident hypertension, hypercholesterolaemia, type 2 diabetes, coronary heart disease and stroke, but was still significant in those consuming four or more NSS-sweetened beverages per day. The association observed in the 2020 study by Anderson et al. *(69)* was no longer statistically significant when participants with recent weight loss or who died in the first 2 years of follow-up were excluded. The association was stronger when participants with prevalent disease associated with unintentional weight loss at baseline were excluded from the analysis or when BMI was not adjusted for in the multivariate model.

Fig. 15. Association between NSS-containing beverage intake and risk of all-cause mortality in prospective cohort studies



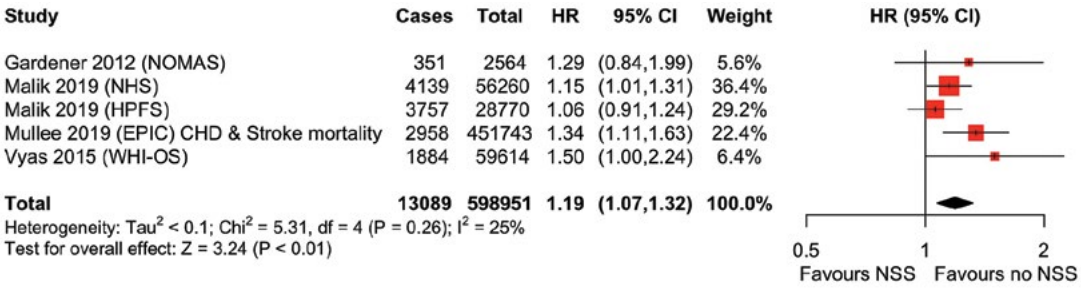
3.1.4 Cardiovascular diseases

Results for cardiovascular diseases are summarized in Table 5.

3.1.4.1 Cardiovascular disease mortality

Four prospective cohort studies (comprising five cohorts) reporting on the risk of cardiovascular disease mortality were included in meta-analyses *(102, 104, 108, 109)*. As assessed in prospective cohort studies, higher intakes of NSS-containing beverages were associated with a 19% increase in risk of cardiovascular disease mortality (Fig. 16).

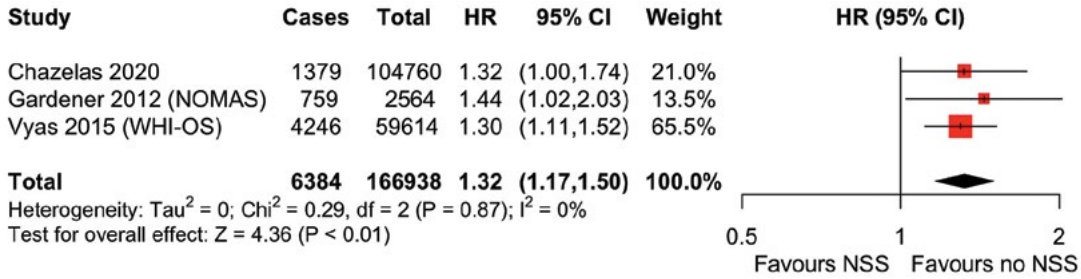
Fig. 16. Association between NSS-containing beverage intake and risk of cardiovascular disease mortality in prospective cohort studies



3.1.4.2 *Cardiovascular events*

Three prospective cohort studies reporting on the risk of cardiovascular events were included in meta-analyses *(108–110)*. As assessed in prospective cohort studies, higher intakes of NSS-containing beverages were associated with a 32% increase in risk of cardiovascular events[1] (**Fig. 17**).

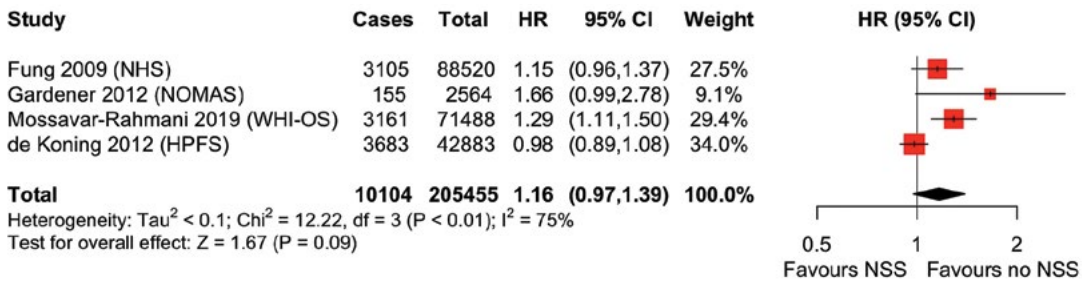
Fig. 17. Association between NSS-containing beverage intake and risk of cardiovascular events in prospective cohort studies



3.1.4.3 *Coronary heart disease*

Four prospective cohort studies reporting on the risk of coronary heart disease were included in this review *(103, 108, 111, 112)*. As assessed in prospective cohort studies, higher intakes of NSS-containing beverages were associated with a nonsignificant increase in risk of coronary heart disease (**Fig. 18**). A fifth prospective cohort study found no association between NSS-containing beverage intake and coronary heart disease mortality (HR 1.11; 95% CI 0.72, 1.70) *(107)*.

Fig. 18. Association between NSS-containing beverage intake and risk of coronary heart disease in prospective cohort studies

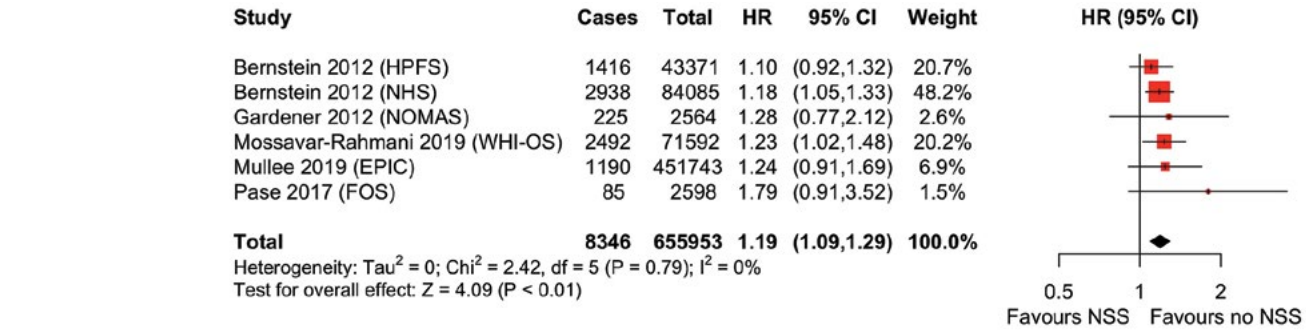


[1] Cardiovascular events in Gardener et al. (2012) *(108)* included stroke, myocardial infarction and vascular death. In Vyas et al. (2015) *(109)*, they included coronary heart disease, myocardial infarction, heart failure, coronary revascularization procedure, ischaemic stroke, peripheral artery disease and cardiovascular disease mortality.

3.1.4.4 *Stroke*

Five prospective cohort studies (comprising six cohorts) reporting on the risk of stroke were included in this review *(103, 104, 108, 113, 114)*. As assessed in prospective cohort studies, higher intakes of NSS-containing beverages were associated with a 19% increase in risk of any type of stroke (**Fig. 19**), with significant increases in risk of both haemorrhagic stroke (HR 1.33; 95% CI 1.03, 1.72; two studies and three comparisons with 196 884 participants; I^2 22%) and ischaemic stroke (HR 1.22; 95% CI 1.04, 1.44; three studies and four comparisons with 200 827 participants; I^2 44%) when assessed individually (**Annex 9: Fig. A9.28** and **A9.29**). Sensitivity analyses conducted within the individual studies, in which those with significant weight change within 4–5 years of baseline *(113)*, or type 2 diabetes or cardiovascular disease within 3 years of baseline were removed *(103)*, did not significantly affect the results. However, removing those with prevalent hypertension, cardiovascular disease or type 2 diabetes abrogated the effect in the 2017 study by Pase et al. *(114)*.

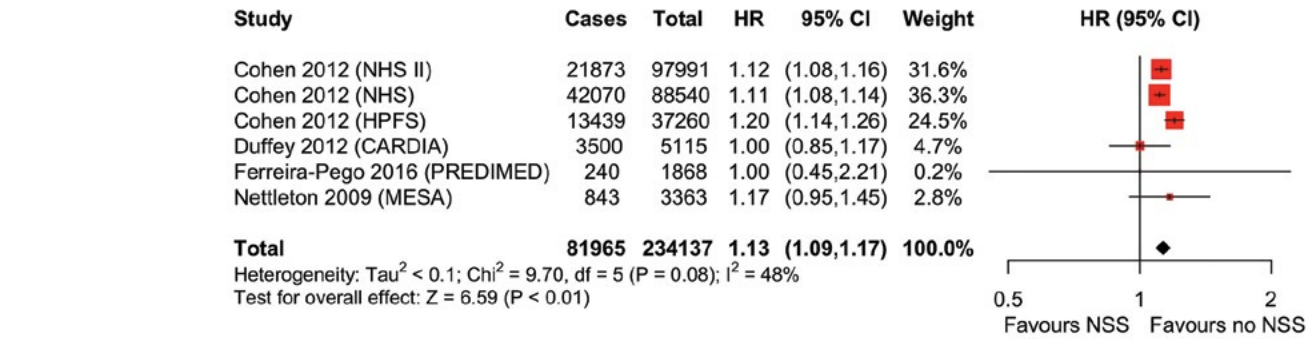
Fig. 19. Association between NSS-containing beverage intake and risk of stroke in prospective cohort studies



3.1.4.5 *Hypertension*

Four prospective cohort studies (comprising six cohorts) reporting on the risk of hypertension[1] were included in this review *(61, 62, 66, 115)*. As assessed in prospective cohort studies, higher intakes of NSS-containing beverages were associated with a 13% increase in risk of hypertension (**Fig. 20**).

Fig. 20. Association between NSS-containing beverage intake and risk of hypertension in prospective cohort studies



[1] Defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or taking antihypertensive medication.

3.1.4.6 *Intermediate markers of disease*

Nineteen RCTs *(23, 25, 27–30, 36-40, 46–50, 52, 96, 97)* and four prospective cohort studies *(61, 62, 66, 116)* reporting on intermediate markers of cardiovascular diseases were included in meta-analyses. As assessed in RCTs, higher intakes of NSS did not have a significant effect on systolic or diastolic blood pressure (**Fig. 21** and **22**), though a trend to lower systolic blood pressure was observed with NSS intake. With the exception of a small, but significant, increase in total cholesterol:HDL cholesterol (MD 0.09; 95% CI 0.02, 0.16; four trials with 326 participants; I^2 0%) (**Annex 9: Fig. A9.30**), no significant effects were observed for any blood lipid measure in RCTs or prospective cohort studies (**Table 5**; **Annex 9: Fig. A9.31–A9.34**), including LDL cholesterol or triglycerides (**Fig. 23** and **24**).

Fig. 21. Effect of NSS intake on systolic blood pressure (mmHg) in randomized controlled trials

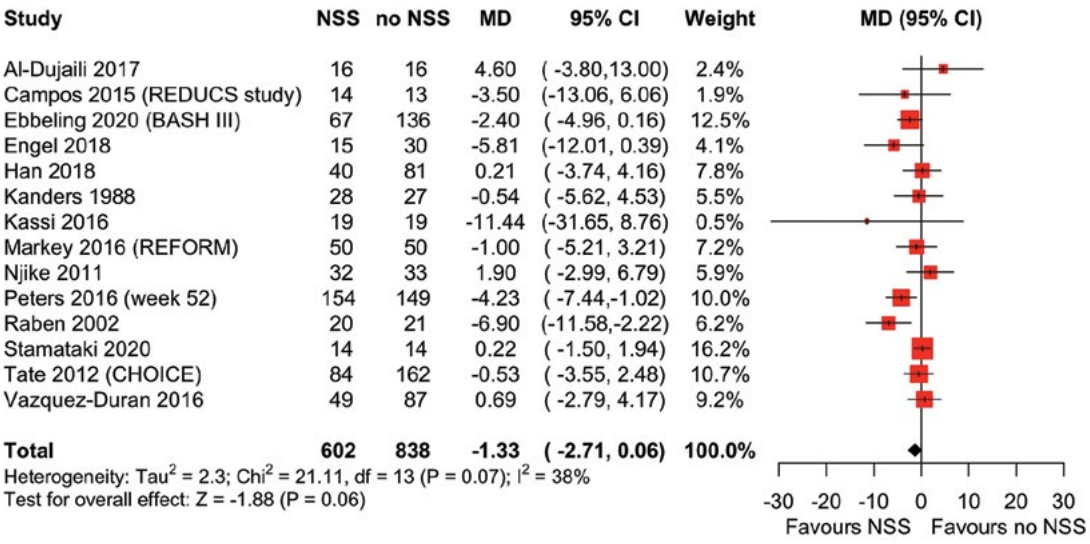


Fig. 22. Effect of NSS intake on diastolic blood pressure (mmHg) in randomized controlled trials

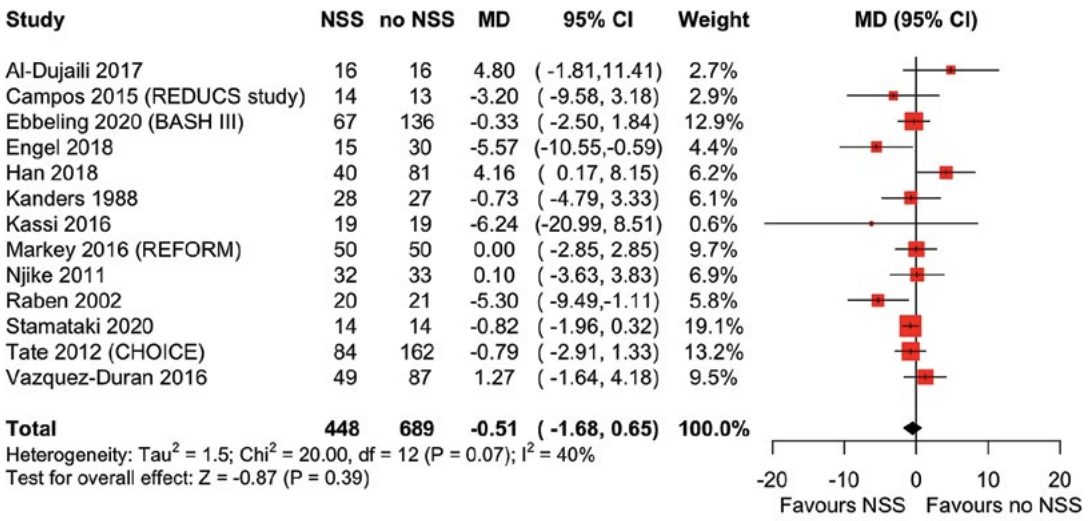


Fig. 23. Effect of NSS intake on LDL cholesterol (mmol/L) in randomized controlled trials

Study	NSS	no NSS	MD	95% CI	Weight
Ebbeling 2020 (BASH III)	67	136	0.05	(-0.09,0.18)	13.3%
Engel 2018	15	30	-0.50	(-1.23,0.23)	0.7%
Han 2018	40	81	0.00	(-0.05,0.06)	26.1%
Higgins 2018	31	31	0.16	(-0.10,0.42)	4.8%
Kassi 2016	19	19	0.24	(-1.00,1.49)	0.2%
Madjd 2018 (week 77)	36	35	0.00	(-0.17,0.17)	9.3%
Markey 2016 (REFORM)	50	50	0.07	(-0.13,0.27)	7.3%
McLay-Cooke 2016 (Ice Tea Study)	63	53	0.24	(-0.20,0.69)	1.8%
Njike 2011	32	33	0.02	(-0.06,0.10)	21.5%
Peters 2016 (week 52)	154	149	-0.11	(-0.26,0.05)	10.9%
Viveros-Watty 2021	21	24	0.56	(0.06,1.05)	1.5%
Warrington 2011	12	12	0.39	(0.03,0.75)	2.7%
Total	**540**	**653**	**0.03**	**(-0.03,0.09)**	**100.0%**

Heterogeneity: $Tau^2 < 0.1$; $Chi^2 = 16.12$, df = 11 (P = 0.14); $I^2 = 32\%$
Test for overall effect: Z = 1.06 (P = 0.29)

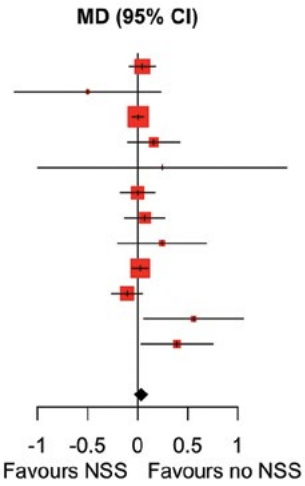


Fig. 24. Effect of NSS intake on triglycerides (mmol/L) in randomized controlled trials

Study	NSS	no NSS	MD	95% CI	Weight
Campos 2015 (REDUCS study)	14	13	0.30	(-0.32, 0.92)	1.4%
Ebbeling 2020 (BASH III)	67	136	0.01	(-0.09, 0.10)	14.5%
Engel 2018	15	30	-0.31	(-1.06, 0.43)	1.0%
Han 2018	40	81	0.19	(-0.11, 0.49)	4.7%
Higgins 2018	31	31	-0.05	(-0.25, 0.15)	8.1%
Madjd 2018 (week 77)	36	35	0.10	(0.01, 0.19)	15.1%
Markey 2016 (REFORM)	50	50	-0.03	(-0.18, 0.12)	10.7%
McLay-Cooke 2016 (Ice Tea Study)	63	53	-0.17	(-0.48, 0.13)	4.5%
Njike 2011	32	33	-0.05	(-0.10, 0.01)	17.1%
Peters 2016 (week 52)	154	149	-0.27	(-0.43,-0.12)	10.4%
Raben 2011	11	12	-0.32	(-0.73, 0.09)	2.9%
Sanchez-Delgado 2021	13	25	-0.31	(-0.68, 0.06)	3.4%
Viveros-Watty 2021	21	24	0.25	(-0.20, 0.70)	2.4%
Warrington 2011	12	12	-0.02	(-0.35, 0.31)	4.0%
Total	**559**	**684**	**-0.04**	**(-0.11, 0.04)**	**100.0%**

Heterogeneity: $Tau^2 < 0.1$; $Chi^2 = 29.00$, df = 13 (P < 0.01); $I^2 = 55\%$
Test for overall effect: Z = -1.03 (P = 0.30)

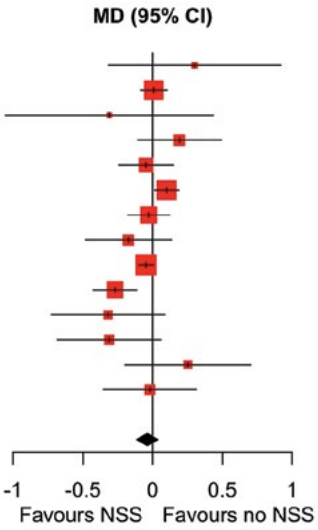


Table 5. Summary of results for NSS intake and cardiovascular diseases

Measure of CVD (unit)	Number of studies/cohorts	Effect estimate (95% CI)	I^2 (%)	Figure
CVD mortality	5 cohorts	**HR 1.19 (1.07, 1.32)**	25	16
Cardiovascular events	3 cohorts	**HR 1.32 (1.17, 1.50)**	0	17
Coronary heart disease	4 cohorts	HR 1.16 (0.97, 1.39)	75	18
Stroke	6 cohorts	**HR 1.19 (1.09, 1.29)**	0	19
Hypertension	6 cohorts	**HR 1.13 (1.09, 1.17)**	48	20
Systolic blood pressure (mmHg)	14 RCTs	MD –1.33 (–2.71, 0.06)	38	21
Diastolic blood pressure (mmHg)	13 RCTs	MD –0.51 (–1.68, 0.65)	40	22
Total cholesterol (mmol/L)	14 RCTs	MD 0.01 (–0.09, 0.11)	32	A9.31
LDL cholesterol (mmol/L)	12 RCTs	MD 0.03 (–0.03, 0.09)	32	23
HDL cholesterol (mmol/L)	13 RCTs	MD 0.00 (–0.03, 0.03)	45	A9.32
Total cholesterol:HDL cholesterol	4 RCTs	**MD 0.09 (0.02, 0.16)**	0	A9.30
Low HDL cholesterol	4 cohorts	HR 1.03 (0.92, 1.16)	0	A9.33
Triglycerides (mmol/L)	14 RCTs	MD –0.04 (–0.11, 0.04)	55	24
High triglycerides	4 cohorts	HR 1.03 (0.88, 1.21)	37	A9.34

CVD: cardiovascular diseases; HDL: high-density lipoprotein; LDL: low-density lipoprotein.
Note: Bold font indicates a statistically significant effect.

Data from studies that could not be included in meta-analyses

Five RCTs that could not be included in meta-analyses reported no effect of NSS on intermediate cardiovascular disease markers *(31, 33, 70, 72–74)*. One prospective cohort study found no association between NSS-sweetened beverage intake and common carotid artery intima-media thickness (CCA-IMT) ($P = 0.96$), common carotid artery adventitial diameter (CCA-AD) ($P = 0.34$) or carotid plaque ($P = 0.39$) *(117)*.

In a replacement analysis from the Harvard Pooling Project of Diet and Coronary Disease[1] that could not be included in the meta-analysis, replacing SSBs with beverages containing NSS was associated with a 12% reduction in risk of coronary events (HR 0.88; 95% CI 0.81, 0.95; 305 480 participants); however, this study did not allow independent assessment of NSS-sweetened beverages *(118)*.

In an RCT conducted in overweight adults and children (n = 57) between 10 and 21 years of age (mean age: 19 years), participants were given capsules or a lactose placebo. At the end of the intervention, the aspartame arm compared with the placebo arm had an increase of 1 mmHg (SE 3.5) in systolic blood pressure, 1 mmHg (SE 2.6) in diastolic blood pressure, 0.18 mmol/L (SE 0.23) in total cholesterol, and 0.12 mmol/L (SE 0.10) in triglycerides *(76)*.

3.1.5 Cancer

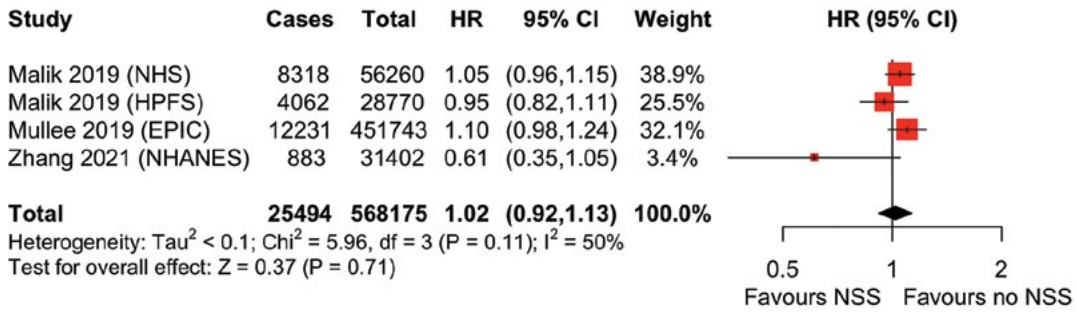
Results for cancer are summarized in **Table 6**.

[1] Data were pooled from the following cohorts and studies: Atherosclerosis Risk in Communities Study, Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study, Health Professionals Follow-up Study, Iowa Women's Health Study, Women's Health Study and Nurses' Health Study.

3.1.5.1 *Cancer mortality*

Three prospective cohort studies (comprising four cohorts) reporting on the risk of cancer mortality were included in meta-analyses *(102, 104, 107)*. As assessed in prospective cohort studies, no significant association was observed between higher intakes of NSS-containing beverages and cancer mortality (**Fig. 25**).

Fig. 25. Association between NSS-containing beverage intake and risk of cancer mortality in prospective cohort studies

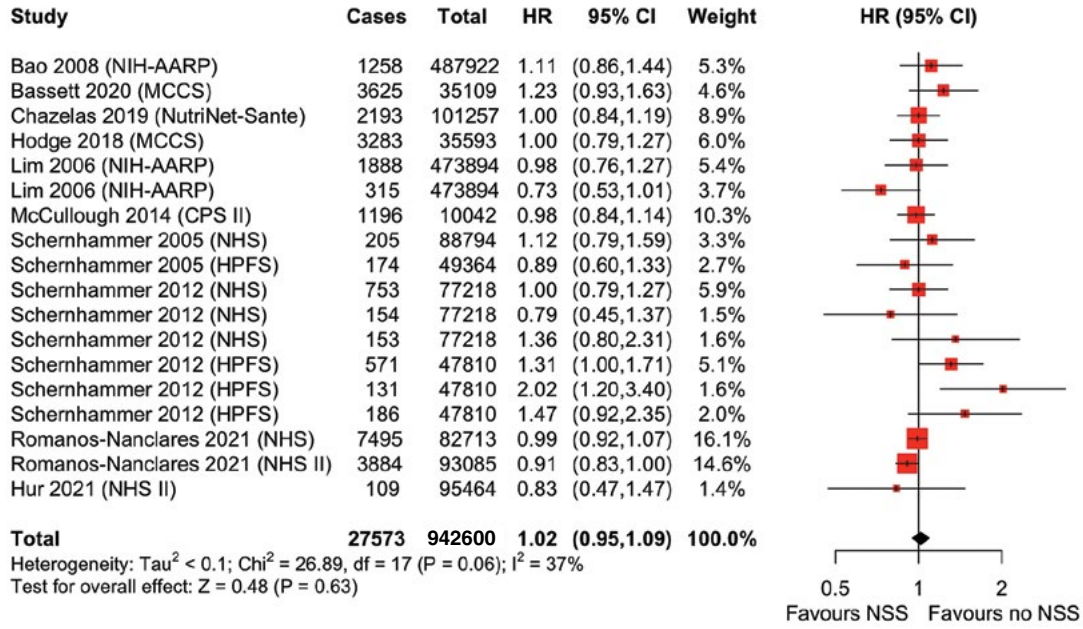


3.1.5.2 *Cancer incidence*

A total of 48 studies investigating the association between NSS and cancer were included in meta-analyses: 39 case–control studies *(119–162)* and nine cohort studies *(163–171)*.

As assessed in prospective cohort studies, no significant association was observed between higher intakes of primarily NSS-containing beverages and any type of cancer (**Fig. 26**).

Fig. 26. Association between primarily NSS-containing beverage intake and risk of any type of cancer in prospective cohort studies



Note: In calculating the total number of participants across all studies, the values displayed for NIH-AARP, MCCS, NHS and HPFS in separate studies were averaged, to avoid double-counting participants.

Table 6. Summary of results for NSS intake and cancer

Cancer site	No. of studies/cohorts	Effect estimate (95% CI)	I^2 (%)	Figure
Cancer mortality	4 cohorts	HR 1.02 (0.92, 1.13)	50	25
Any type	7 cohorts	HR 1.02 (0.95, 1.09)	37	26
Bladder	26 case–controls	**OR 1.31 (1.06, 1.62)**	92	27
Brain	2 case–controls 1 cohort	OR 1.13 (0.76, 1.69) RR 0.73 (0.46, 1.15)	0 NA	A9.37 NA
Breast	3 case–controls 4 cohorts	OR 0.83 (0.64, 1.08) HR 0.98 (0.89, 1.09)	47 55	A9.38 A9.39
Colorectum	3 case–controls 3 cohorts	OR 0.85 (0.68, 1.07) HR 0.80 (0.63, 1.01)	0 0	A9.40 A9.41
Endometrium	1 case–control 1 cohort	OR 0.96 (0.66, 1.39) HR 0.81 (0.42, 1.56)	NA NA	NA NA
Kidney	4 case–controls 1 cohort	OR 1.25 (0.94, 1.65) HR 0.92 (0.46, 1.84)	61 NA	A9.42 NA
Larynx	1 case–control	**OR 2.34 (1.20, 4.56)**	NA	NA
Lung	2 case–controls	**OR 0.40 (0.26, 0.61)**	0	A9.43
Oesophagus	1 case–control	OR 1.24 (0.54, 2.83)	NA	NA
Oral cavity and pharynx	1 case–control	OR 0.77 (0.36, 1.64)	NA	NA
Ovary	1 case–control 1 cohort	**OR 0.56 (0.38, 0.82)** HR 1.37 (0.72, 2.61)	NA NA	NA NA
Pancreas	4 case–controls 3 cohort	OR 0.88 (0.51, 1.50) RR 1.06 (0.88, 1.28)	83 0	A9.44 A9.45
Prostate	2 case–controls 2 cohorts	OR 0.88 (0.30, 2.62) HR 1.09 (0.67, 1.75)	40 66	A9.46 A9.47
Stomach	2 case–controls 1 cohort	OR 0.79 (0.50, 1.26) HR 1.03 (0.53, 1.99)	0 NA	A9.48 NA
Leukaemia	3 cohorts	RR 1.24 (0.92, 1.69)	0	A9.49
Multiple myeloma	4 cohorts	RR 1.05 (0.70, 1.59)	70	A9.50
Hodgkin lymphoma	1 cohort	RR 0.77 (0.44, 1.33)	NA	NA
Non-Hodgkin lymphoma	4 cohorts	RR 1.08 (0.87, 1.34)	64	A9.51
All cancers	1 case–control 1 cohort	RR: 0.90 (0.67, 1.23) HR : 1.00 (0.84, 1.19)	NA NA	NA NA
Cancers not related to obesity	1 cohort	**HR: 1.23 (1.02, 1.48)**	NA	NA
Cancers related to obesity[a]	1 cohort	HR: 1.00 (0.79, 1,27)	NA	NA

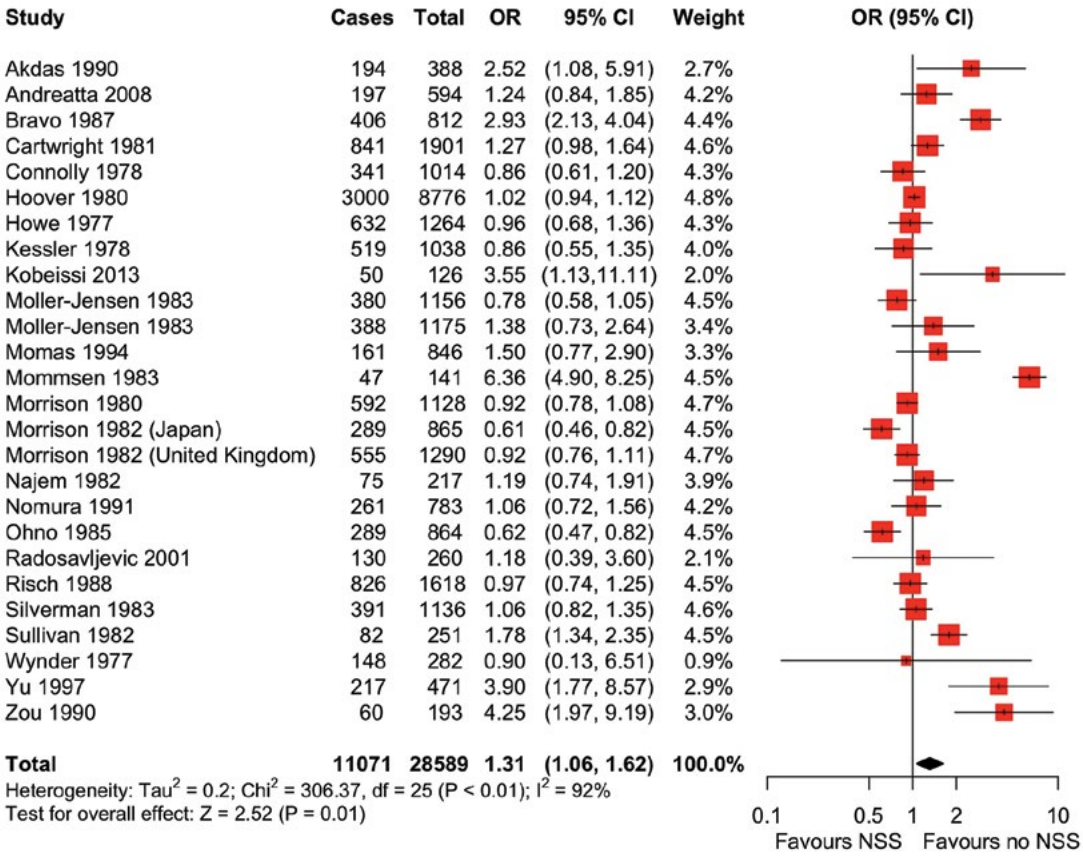
NA: not applicable.

[a] Defined as liver cancer, aggressive prostate cancer, ovarian cancer, gallbladder cancer, kidney cancer, colorectal cancer, oesophageal cancer, postmenopausal breast cancer, pancreatic cancer, endometrial cancer and gastric cardia cancer *(165)*.

Note: Bold font indicates a statistically significant effect.

Meta-analysis results of the association between NSS intake and individual types of cancers are summarized in **Table 6**. As assessed in case–control studies, a 31% increase in risk of bladder cancer was observed with NSS intake (**Fig. 27**). Subgroup analysis suggests that tabletop use of NSS, particularly saccharin, may be associated with bladder cancer (**Annex 9: Fig. A9.35** and **A9.36**), although the differences between subgroups were not statistically significant for saccharin. Other significant associations were observed for NSS intake and increased risk of cancer of the larynx and cancers not related to obesity,[1] and decreased risk of cancer of the lung and ovary; however, only one or two studies contributed data to each of these results, so they must be interpreted with caution. All other results were nonsignificant, including a study of the effects of consumption of NSS-sweetened beverages on survival in women already diagnosed with breast cancer (not shown in **Table 6**) *(106)*, though a trend towards decreased risk of colorectal cancer with NSS use was observed.

Fig. 27. Association between NSS intake and risk of bladder cancer



3.1.6 Chronic kidney disease

Results for chronic kidney disease are summarized in **Table 7**.

Two RCTs (29, 97) and two prospective cohort studies *(173, 174)* reporting on the risk of chronic kidney disease were included in meta-analyses.

As assessed in prospective cohort studies, no association was observed between NSS intake and chronic kidney disease[2] (**Annex 9: Fig. A9.52**). One prospective study reported an association

[1] Defined as prostate cancer, diffuse large B-cell lymphoma, noncardia gastric cancer, lung cancer, melanoma, premenopausal breast cancer, bladder cancer, brain cancer, cancer of unknown primary, lymphoid leukaemia and other cancers *(172)*

[2] Lin 2011 reported the association between NSS use and decline in estimated glomerular filtration rate (eGFR) of ≥30% *(173)*, and Rebholz 2017 the association between NSS use and chronic kidney disease with one defining characteristic being a ≥25% decline in eGFR *(174)*.

Table 7. Summary of results for NSS intake and chronic kidney disease

Measure of chronic kidney disease	No. of trials/cohorts	Estimate (95% CI)	I^2 (%)	Figure
Chronic kidney disease	2 cohort	HR 1.41 (0.89, 2.24)	86	A9.52
Incident end-stage renal disease	1 cohort	OR 1.64 (1.18, 2.28)	NA	NA
Microalbuminuria	1 cohort	OR 0.92 (0.52, 1.64)	NA	NA
Creatinine (mmol/L)	2 RCTs	MD 8.80 (–14.65, 32.25)	92	A9.53
Albumin (g/L)	2 RCTs	MD 0.00 (–0.56, 0.56)	0	A9.54

NA: not applicable.

between NSS intake and a 64% increase in risk of end-stage renal disease (95% CI 1.18, 2.28; one study with 15 368 participants). No other significant effects or associations were observed.

3.1.7 Eating behaviour

Twenty-six RCTs *(22, 23, 25–31, 34–37, 39, 41–45, 47, 50, 52–54, 175, 176)* were included in meta-analyses.

3.1.7.1 Energy intake

As assessed in RCTs, higher intakes of NSS resulted in a reduction in total energy intake of more than 560 kJ per day (Fig. 28). Subgroup analysis indicates that energy intake is reduced when NSS are used to replace sugars (Fig. 29), but also in mixed-weight or overweight/obese individuals (Fig. 30), although the difference between subgroups in the latter is not statistically significant and there is considerable residual heterogeneity within most individual subgroups. Results of additional subgroup analyses can be found in Annex 9: Fig. A9.55–A9.58.

Fig. 28. Effect of NSS intake on total energy intake (kJ/day) in randomized controlled trials

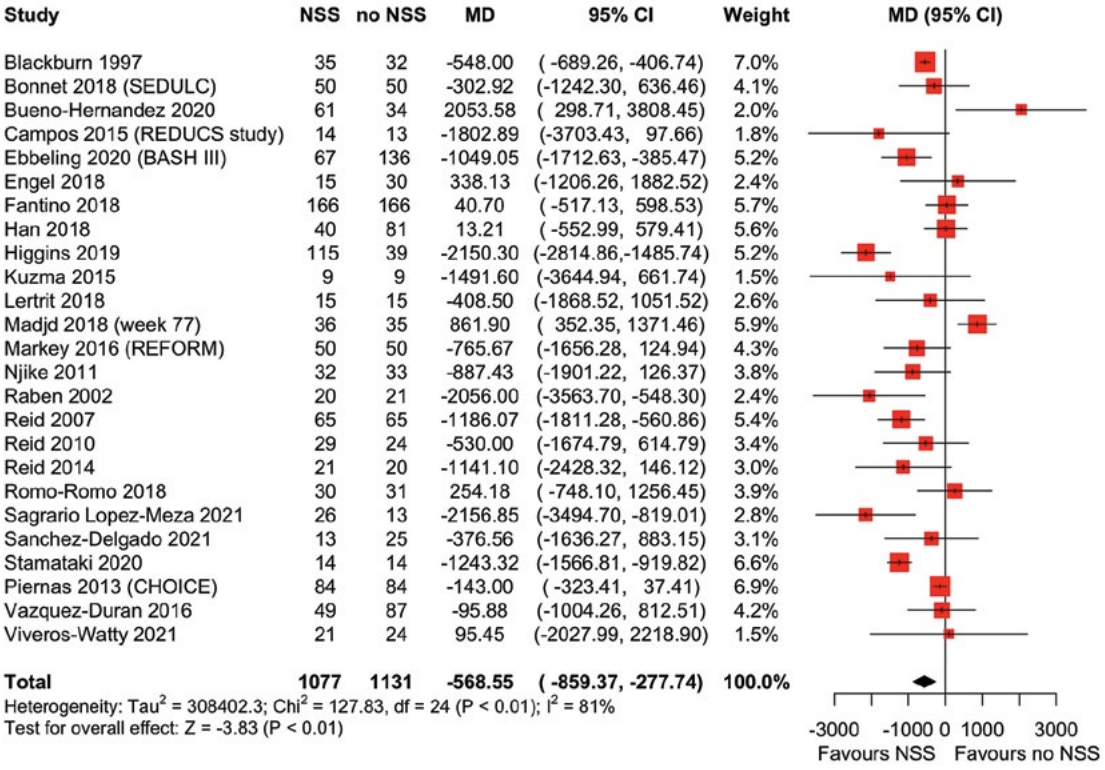
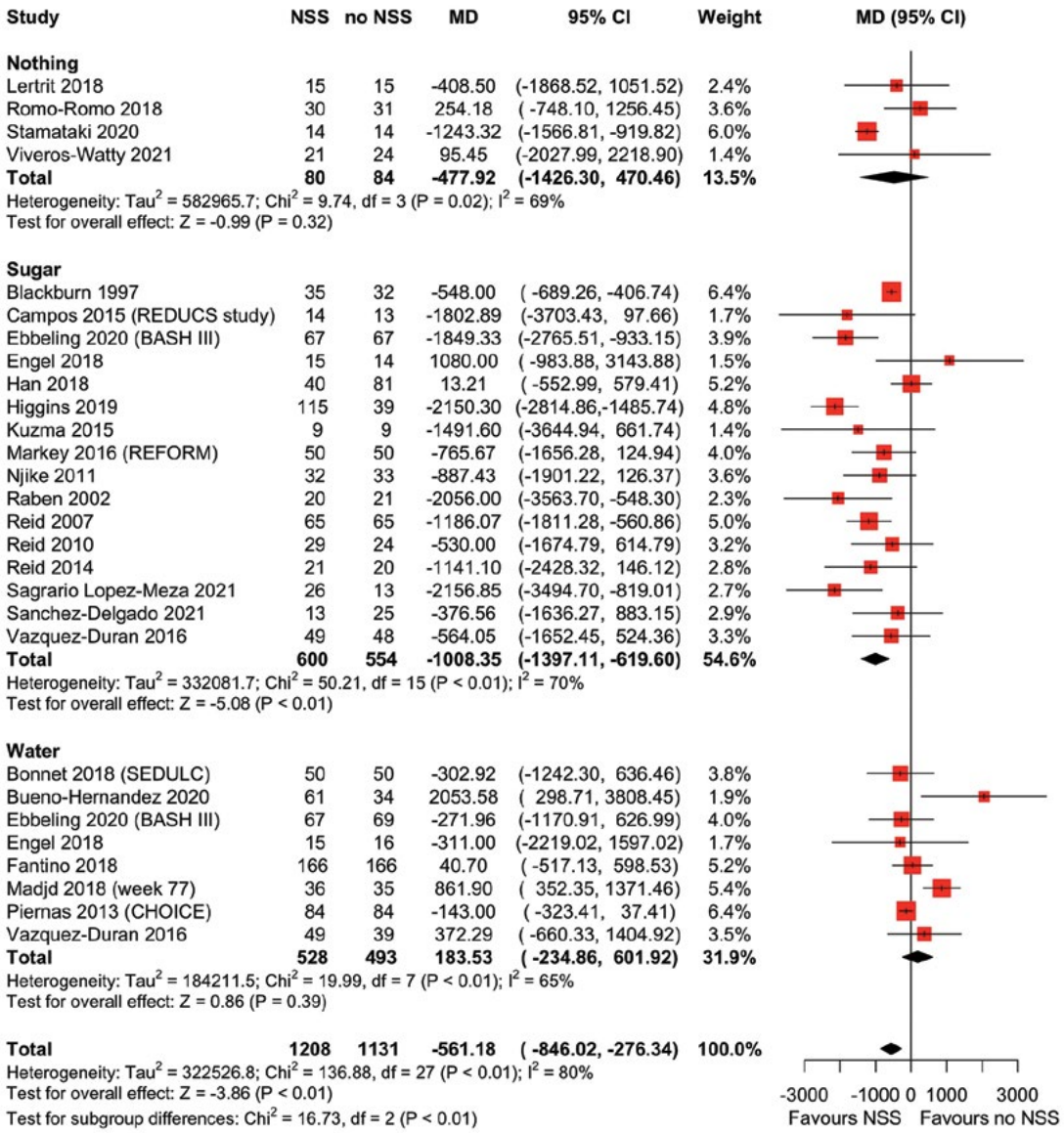


Fig. 29. Effect of NSS intake on total energy intake (kJ/day) in randomized controlled trials, subgrouped by comparator



Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS to a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

In a nonrandomized controlled trial that compared responses to NSS-sweetened beverages, SSBs and water in habitually high and low consumers of NSS-sweetened beverages, high consumers had a greater energy intake than low consumers *(177)*.

3.1.7.2 Hunger

As assessed in RCTs, no significant effect of NSS intake on subjective measures of hunger was observed (standardized mean difference [SMD] 0.24; 95% CI –0.86, 0.38; five trials with 817 participants; I^2 100%) (**Annex 9: Fig. A9.59**). In addition, in one trial, the participants in the control arm reported overall higher hunger scores compared with an arm receiving stevia *(52)*. Three other RCTs *(41–43)* and one nonrandomized controlled trial *(177)* reported no effects narratively.

3.1.7.3 *Satiety*

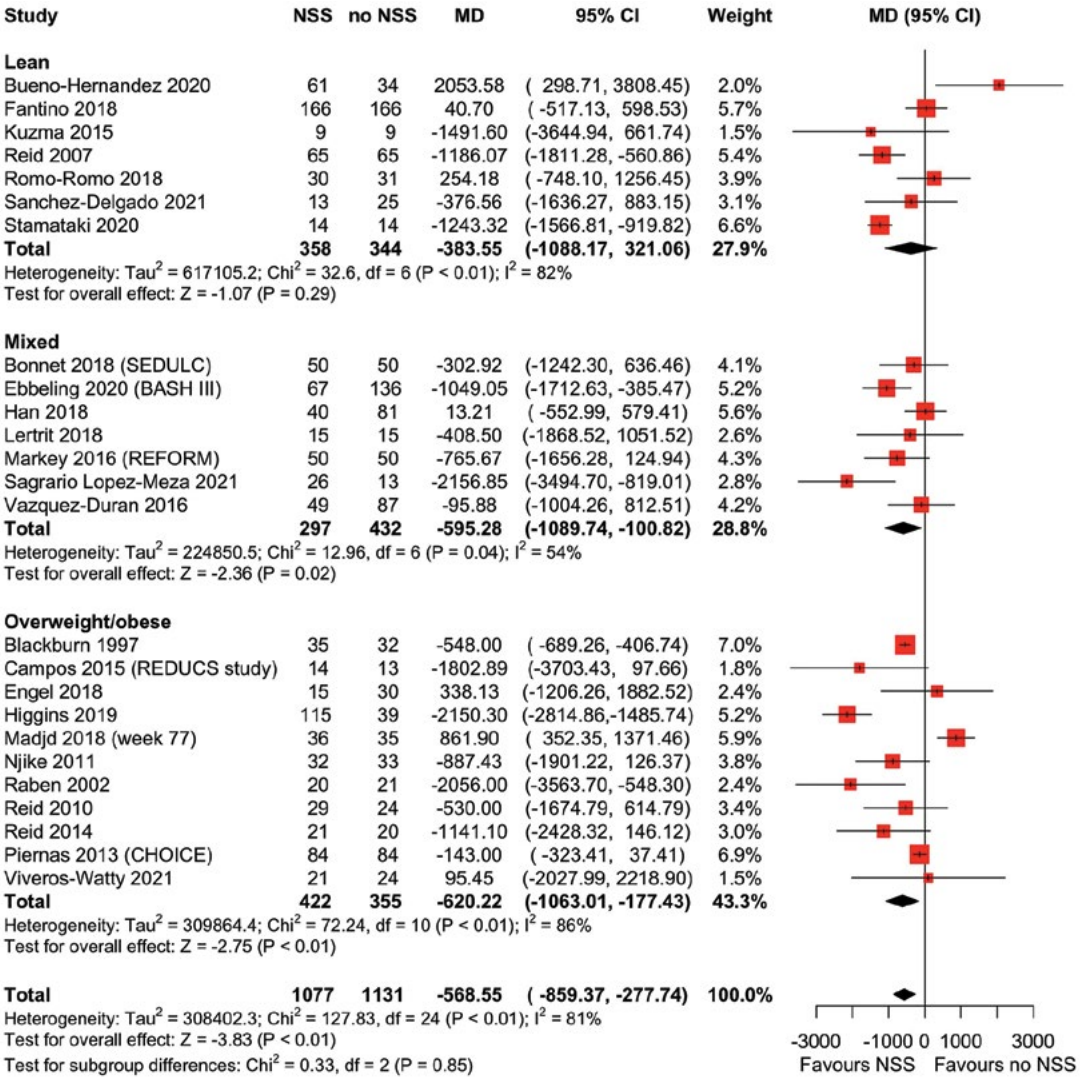
As assessed in RCTs, a small but significant decrease in subjective measures of satiety or fullness was observed with NSS intake (SMD –0.15; 95% CI –0.30,–0.01; three trials with 518 participants; I^2 98%) (**Annex 9: Fig. A9.60**). In addition, one RCT *(41)* and one nonrandomized controlled trial *(177)* reported no effects narratively.

3.1.7.4 *Appetite and desire to eat*

As assessed in RCTs, a small but significant effect of NSS intake on subjective measures of appetite or desire to eat was observed (SMD 0.23; 95% CI 0.04, 0.42; three trials with 518 participants; I^2 99%) (**Annex 9: Fig. A9.61**). Two additional RCTs reported no effects narratively *(32, 41)*.

In a nonrandomized controlled trial that compared responses to NSS-sweetened beverages, SSBs and water in habitually high and low consumers of NSS-sweetened beverages, high consumers had a greater desire to eat than low consumers, independent of beverage *(177)*.

Fig. 30. Effect of NSS intake on total energy intake (kJ/day) in randomized controlled trials subgrouped by body weight status



3.1.7.5 *Other outcomes related to eating behaviour*

One RCT found no effect of NSS, compared with no NSS, on eating control *(22)*. Another found lower ingestive frequency and smaller portions in the NSS arm, but no difference in preoccupation with food *(31)*. In a third trial comparing NSS and sugars, no differences in a three-factor eating questionnaire (rating attitudes about foods and body weight) were found between the two arms *(41)*.

In an analysis of the cross-sectional National Health and Nutrition Examination Survey (NHANES) data, individuals who consumed NSS had more eating episodes per day, which started earlier in the morning and lasted longer across the day, than those who did not *(178)*. Another cross-sectional study comparing heavy users and non-users of NSS-sweetened beverages found that heavy users scored higher on body weight concerns and guilt related to overeating *(179)*.

3.1.8 Sweet preference

3.1.8.1 *Sugars intake*

Twelve RCTs were included in meta-analyses *(22, 25–27, 37, 41–43, 45, 46, 175, 176, 180)*. As assessed in RCTs, higher intakes of NSS resulted in a reduction in sugars intake of approximately 39 g per day (**Fig. 31**). Not unexpectedly, subgroup analysis indicates that sugars intake is reduced significantly when NSS are used to replace sugars (**Fig. 32**), but also in overweight/obese individuals (**Fig. 33**), although there is considerable residual heterogeneity within the sugars and overweight/obese subgroups themselves. Results of additional subgroup analyses can be found in **Annex 9: Fig. A9.62–A9.65**.

Fig. 31. Effect of NSS intake on sugars intake (g/day) in randomized controlled trials

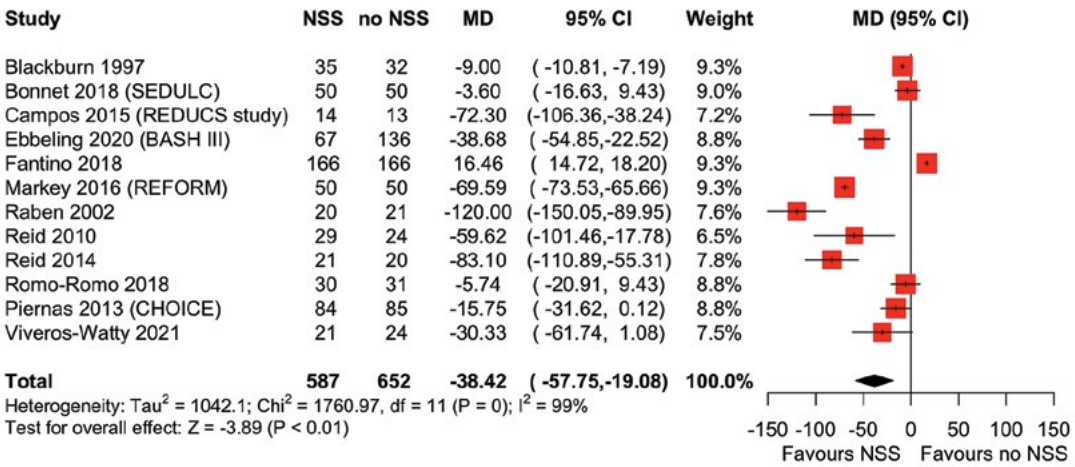


Fig. 32. Effect of NSS intake on sugars intake (g/day) in randomized controlled trials, subgrouped by comparator

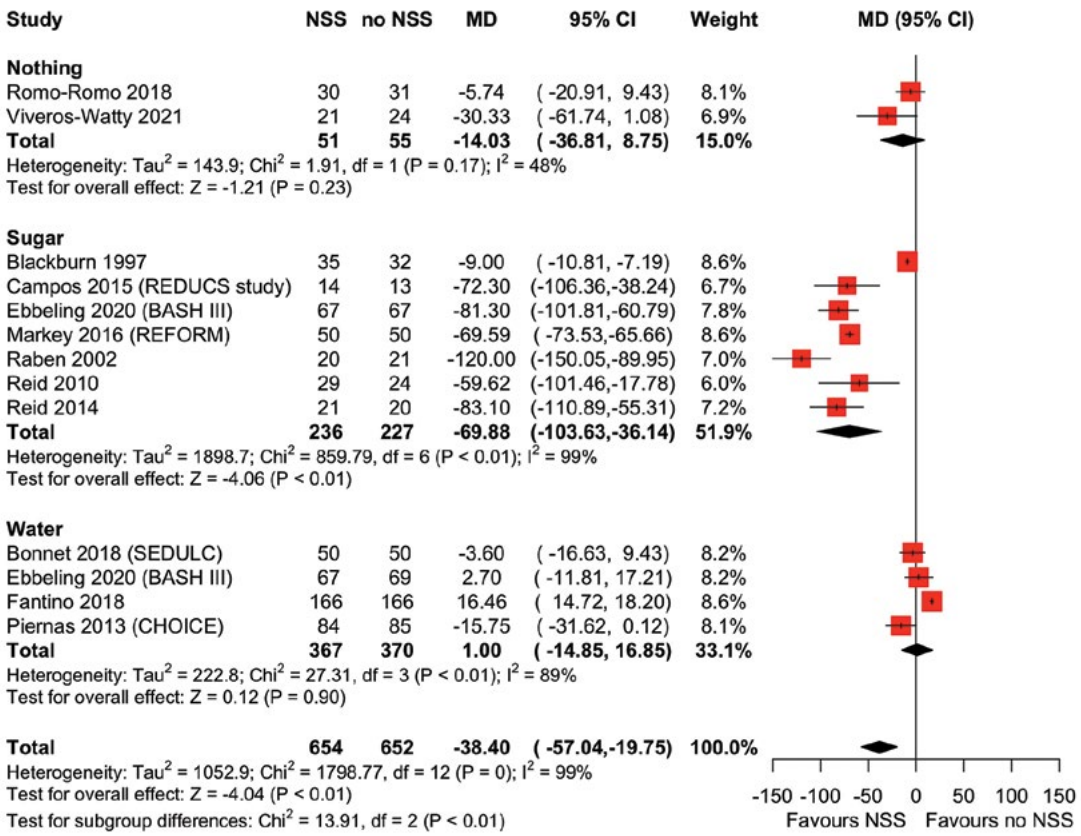
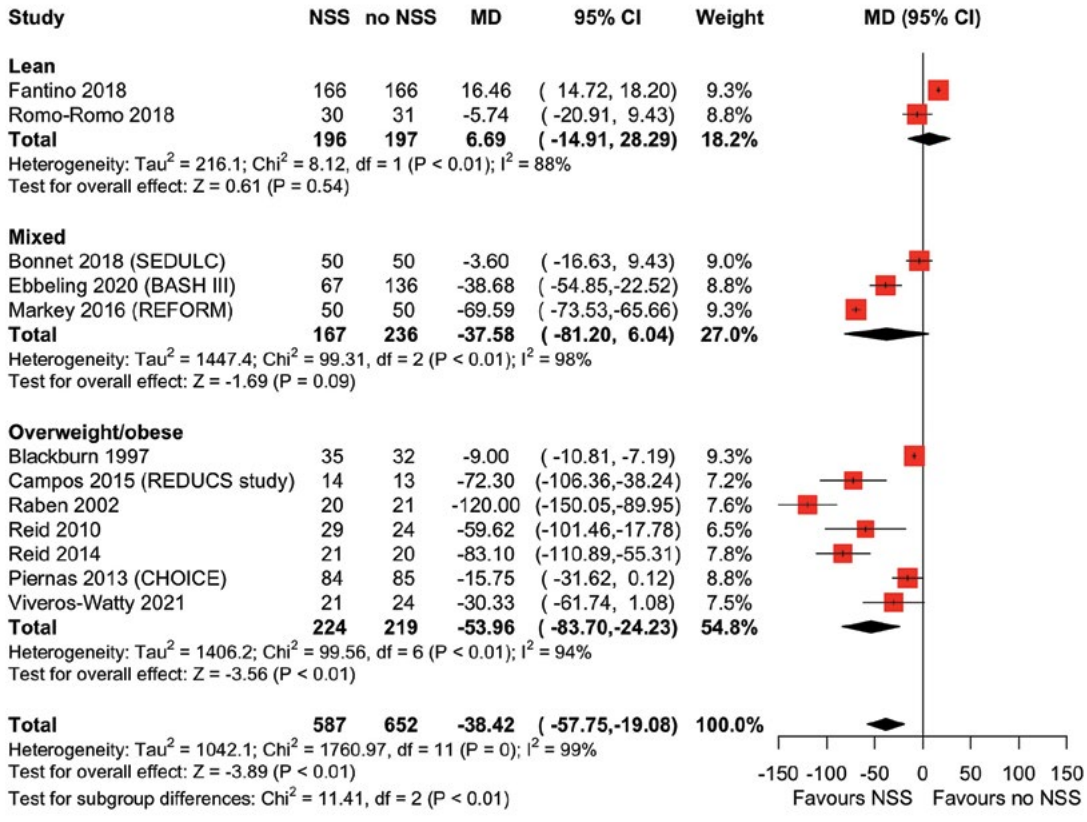


Fig. 33. Effect of NSS intake on sugars intake (g/day) in randomized controlled trials, subgrouped by body weight status



Data from studies that could not be included in meta-analyses

Several studies reported on the effects of NSS intake on measures related to sweet taste perception, including sweet preference and liking, and sweet taste threshold. In two RCTs comparing sugars with NSS, desire for sweets changed over the course of the intervention but did not differ between arms *(22, 41)*. In another trial comparing NSS-sweetened beverages with water, individuals who were given the NSS-sweetened beverage did not significantly choose more sweet foods during the test meal than those who were given water *(175)*. A fourth trial, comparing NSS-sweetened, sugar-sweetened and unsweetened beverages, found that sweetness threshold was reduced in the unsweetened beverage arm, but not in the NSS-sweetened or sugar-sweetened beverage arms *(28)*. A fifth trial reported that those who replaced SSBs with either NSS-sweetened beverages or water showed no differences in liking between beverages and that both were equally effective in reducing consumption of SSBs *(181)*. A sixth trial reported a significant positive correlation between sweet cravings and sugars intake but not between sweet cravings and stevia intake *(52)*.

In a nonrandomized controlled trial that compared responses to NSS-sweetened beverages, SSBs and water in habitually high and low consumers of NSS-sweetened beverages, low consumers demonstrated an increase in appetite in response to sweet taste that high consumers did not, suggesting a decoupling of expectation of energy with sweet taste in the high consumers *(177)*.

In a cross-sectional analysis comparing high and low users of NSS-sweetened beverages and SSBs, high users preferred sweeter orange juice than low users *(182)*.

3.1.9 Dental caries

In a 6-month RCT, participants were assigned to consume sugar-sweetened or NSS-sweetened soft drinks, and neither group developed caries nor experienced acid erosion of the enamel at any point during the intervention *(183)*.

3.1.10 Mood

In two similar RCTs conducted in normal-weight *(44)* and overweight women *(42)*, who were provided with aspartame-sweetened or sucrose-sweetened soft drinks for 4 weeks, no effect was found on mood. Similarly, in an RCT in which participants were provided aspartame-sweetened, sucrose-sweetened or unsweetened beverages and capsules for 20 days, no effect was found on mood *(184)*.

A prospective cohort study found an association between consuming NSS-sweetened beverages and increased risk of depression over 7 years of follow-up in adults (adjusted odds ratio [OR] for soft drinks 1.25; 95% CI 1.15, 1.35; and adjusted OR for coffee or tea 1.11; 95% CI 0.99, 1.24) *(185)*. However, two additional prospective cohort studies did not find a significant association between NSS intake and depression over 1–4 years of follow-up *(186, 187)*, or with anxiety or general mood.

3.1.11 Neurocognition

In an RCT in which adults were given aspartame-sweetened, sucrose-sweetened or unsweetened beverages and supplements over 20 days, there were no significant effects on cognitive or neuropsychological measures (verbal learning, attention span, memory, motor response, cognitive efficiency, long-term memory) *(184)*. In a second RCT, those receiving stevia for 6 weeks did not display any changes in cognitive function, whereas those receiving sucralose showed a significant decrease in overall memory, encoding memory and executive functions *(54)*.

In a prospective cohort study, after 6 years of follow-up, adults drinking NSS-sweetened beverages more than once per month had nonsignificantly lower cognitive function (STICS-m[1] score difference: b –0.19; 95% CI –0.78, 0.40; $P = 0.53$) *(188)*. In another cohort study, the 10-year

[1] Spanish version of the modified Telephone Interview for Cognitive Status (TICS-m)

risk of developing dementia or Alzheimer's disease was increased among adults consuming NSS-sweetened beverages daily compared with those consuming none (HR 2.47; 95% CI 1.15, 5.30, for dementia; and HR 2.89; 95% CI 1.18, 7.07, for Alzheimer's disease), adjusted for prevalent hypertension, cardiovascular diseases, type 2 diabetes and risk factors for these diseases *(114)*.

3.1.12 *Behaviour*

No studies in adults were identified.

3.2 Children

3.2.1 Adiposity

Results are summarized in **Table 8**.

Two RCTs *(189, 190)* and 14 cohort studies *(191–204)* reported on NSS intake and measures of adiposity in children.

Meta-analyses of the small number of studies reporting data in a manner amenable to meta-analysis yielded no significant results for any measure of adiposity. One fairly large, well-conducted RCT, however, reported significant reductions in body weight, BMI z-score (i.e. BMI adjusted for child age and sex), waist circumference and body fat mass when SSBs were replaced with NSS-sweetened beverages *(189)*.

Table 8. Summary of results for NSS intake and measures of adiposity in children

Adiposity outcomes (unit)	No. of studies	Effect estimate (95% CI)	I^2 (%)	Figure
Body weight	1 RCT 2 cohorts	**MD –1.01 (–1.54, –0.48)** MD 0.03 (–0.14, 0.21)	NA 0	NA A9.66
BMI (kg/m²)	5 cohorts (cont) 2 cohorts (hvl)	MD 0.08 (–0.01, 0.17) MD 0.04 (–0.32, 0.40)	89 44	A9.67 A9.68
BMI z-score	2 RCTs 3 cohorts (cont) 1 cohort (hvl)	MD –0.07 (–0.26, 0.11) MD –0.23 (–0.70, 0.25) MD 0.0 (–0.3, 0.3)	48 86 NA	A9.69 A9.70 NA
Waist circumference (cm)	1 RCT	**MD –0.66 (–1.23, –0.09)**	NA	NA
Body fat mass (kg)	1 RCT 1 cohort	**MD –0.57 (–1.02, –0.12)** MD –1.00 (–2.52, 0.52)	NA NA	NA NA
Body fat mass (%)	1 RCT 2 cohorts	**MD –1.07 (–1.99, –0.15)** MD –1.53 (–5.73, 2.66)	NA 77	NA A9.71
Overweight	2 cohorts	OR 1.25 (0.43, 3.66)	36	A9.72

cont: continuous, per serving; hvl: highest versus lowest category of intake; NA: not applicable.
Note: Bold font indicates a statistically significant effect.

3.2.2 Type 2 diabetes

No studies reported on development of type 2 diabetes in children, but one nonrandomized crossover trial *(205)* and one prospective cohort study *(193)* reported on intermediate markers. In a trial comparing sucrose, aspartame or saccharin given for 3 weeks to 3–10-year-old children, NSS collectively did not significantly affect postprandial glucose (MD 0.22 mmol/L; SE 0.29) when compared with sucrose. In a cohort of 12–18-year-old overweight children followed up for 1 year, chronic consumers of NSS-sweetened beverages had no difference in intermediate markers of diabetes when compared with NSS-sweetened beverage initiators and non-consumers, except for glycated haemoglobin (HbA1c), which increased more in chronic consumers of NSS-sweetened beverages (P = 0.01).

3.2.3 Cardiovascular diseases

No studies reported on development of cardiovascular diseases in children, but one prospective cohort study *(193)* reported on intermediate markers. In a cohort of 12–18-year-old overweight children followed up for 1 year, chronic consumers of NSS-sweetened beverages had no difference in total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides when compared with NSS-sweetened beverage initiators and non-consumers.

3.2.4 Cancer

Two case–control studies reported on NSS intake and brain cancer in children *(206, 207)*. One study looked at mothers' intake of NSS-sweetened beverages during pregnancy and cancer in offspring, and the other at intake of aspartame from drinks and tabletop sweeteners by both mothers during pregnancy and offspring in childhood. Intake of NSS was not significantly associated with brain cancer in offspring (OR 1.14; 95% CI 0.80, 1.63; two studies with 1151 participants; I^2 5%) (**Annex 9: Fig. A9.73**).

3.2.5 Eating behaviour

3.2.5.1 Energy intake

Four studies of mixed design reported on NSS intake and daily energy intake *(190, 193, 200, 205)*. Results varied considerably and are summarized in **Table 9**.

Table 9. Summary of results for energy intake in children

Study	Design	Comparison	*n*	MD in kJ/day (SE)
Taljaard 2013	RCT	NSS vs sugar	386	–419 *(204)*
Wolraich 1994	Non-RCT	NSS vs sugar	48	–1066 (not reported)
Davis 2018	Cohort	Chronic NSSB users vs never users Initiators of NSSB vs never users	84 89	2462 *(572)* 432 *(661)*
Striegel-Moore 2006	Cohort	Per 100 g/day increase in diet soda	2371	122 *(17)*

kJ: kilojoules; MD: mean difference; *n*: number of study participants; NSSB: NSS-sweetened beverages; SE: standard error.

3.2.5.2 Hunger

One RCT conducted in children reported no effect of NSS on hunger in a narrative manner *(205)*.

3.2.5.3 Satiety

In one RCT conducted in children comparing NSS-sweetened beverages and SSBs, subjective assessment of satiety was not significantly different *(208)*. The same trial found that children liked and wanted the NSS-sweetened beverages slightly less than the SSBs after 18 months.

3.2.6 Sweet preference

3.2.6.1 Sugar intake

Three studies reported on NSS intake and sugars intake *(193, 200, 205)*. In a nonrandomized controlled trial, the sugars intake of children given foods and drinks with NSS was 88 g/day less than for those given foods and drinks with sucrose. In a 1-year-long prospective cohort study, chronic users of NSS-sweetened beverages had a sugars intake that was 40.2 g/day (SE 11.6) higher than never users, whereas initiators of NSS-sweetened beverage use had a sugars intake that was 23.9 g/day (SE 17.9) lower than never users. In a 10-year-long prospective cohort study, for every 100 g/day increase in NSS-sweetened beverage intake, sugars intake tended to decrease, but not significantly. Results are summarized in **Table 10**.

Table 10. Summary of results for sugars intake in children

Study	Design	Comparison	*n*	MD (SE)
Wolraich 1994	Non-RCT	NSS vs sugar	48	−88.3 (not reported)
Davis 2018 (SOLAR)	Cohort	Chronic NSSB users vs never users Initiators of NSSB vs never users	84 89	40.2 (11.6) −23.9 (17.9)
Striegel-Moore 2006	Cohort	Per 100 g/day increase in diet soda	2371	−0.3 (0.2)

MD: mean difference; *n*: number of study participants; NSSB: NSS-sweetened beverages; SE: standard error.

3.2.7 Dental caries

In one RCT, snacks containing stevia or sugars were given twice daily to children for 6 weeks. At the end of the trial, the concentrations of cariogenic *Streptococcus mutans* bacteria and lactobacilli ($\chi 2$ 8.01; $P < 0.01$), and the probability of developing caries (measured by a cariogram) in the stevia arm had decreased compared with baseline, whereas there were no statistically significant changes in the sugars arm *(209)*.

In another RCT, mouth rinse containing stevia or placebo was used daily by children for 6 months. At the end of the trial, there was a significant improvement in the stevia arm compared with the placebo arm in plaque scores ($P = 0.03$) and gingival scores ($P = 0.01$). There were no changes in the number of cavitated lesions in the stevia arm, but there was an increase in cavitated lesions in the placebo arm (from 5.6% to 5.8%) *(210)*.

A prospective cohort study found that low intakes of NSS-sweetened beverages were associated with fewer teeth surfaces having caries compared with no intake ($P < 0.025$). However, the association with high intakes of NSS-sweetened beverages was not reported *(211)*.

A cross-sectional study found that consumption of NSS-sweetened beverages (≥1 cup/day) was associated with higher OR of toothache (adjusted for age, sex, socioeconomic status, language background, place of residence and brushing teeth) *(212)*. Another cross-sectional study found that NSS intake was higher in those with caries than in those without ($P = 0.036$), but did not find any significant difference in caries prevalence according to NSS-sweetened beverage intake *(213)*.

3.2.8 Mood

A nonrandomized controlled trial in which children were given sucrose, aspartame or saccharin for 3 weeks in a crossover manner found no differences in mood *(205)*. However, a cross-sectional study among children found that children who consumed NSS-sweetened foods or drinks had higher theta/beta ratios (an electroencephalographic measure used to assess attention, emotional regulation, or resilience to stress), which may indicate a negative impact on mood *(214)*.

3.2.9 Behaviour

In a nonrandomized controlled trial, children who were described by their parents as sensitive to sugars were given sucrose, aspartame or saccharin for 3 weeks in a crossover manner. As rated by their parents and teachers, there were no significant differences between the diets in the ratings of different measures of the children's behaviour, including conduct, attention deficit, deviation, attention, hyperactivity, social skills or oppositional behaviour *(205)*.

3.2.10 Neurocognition

In an RCT, children were given drinks with sucralose or sucrose for 8.5 months. There were no significant differences between the two groups in cognition measures (tested using the Kaufman Assessment Battery for Children version II [KABC-II] subtests and the Hopkins Verbal Learning Test [HVLT]) *(190)*.

In a prospective cohort study following children in utero up to 7 years of age, early and mid-childhood cognition scores were inversely associated with maternal intake of NSS-sweetened beverages during pregnancy (PPVT-III,[1] early childhood: –1.2; 95% CI –2.9, 0.5; total WRAVMA, early childhood: –1.5; 95% CI –2.9,–0.1; KBIT-II verbal, mid-childhood: –3.2; 95% CI –5.0, –1.5; KBIT-II nonverbal, mid-childhood: –2.0; 95% CI –4.3, 0.2; WRAVMA drawing, mid-childhood: –1.7; 95% CI –4.1, 0.6; WRAML visual memory, mid-childhood: –0.1; 95% CI –0.7, 0.5); however, there was no association between early and mid-childhood cognition scores and childhood intake of NSS-sweetened beverages at 3 years *(215)*.

In a nonrandomized controlled trial in which children were given sucrose, aspartame or saccharin for 3 weeks in a crossover manner, no significant differences were found in cognition *(205)*.

3.2.11 Asthma

A cross-sectional analysis within the PIAMA birth cohort found that intake of NSS-sweetened beverages in 11-year-old children (≥2 glasses/week) was associated with higher but nonsignificant odds of asthma (adjusted OR 1.08; 95% CI 0.74, 1.59) *(216)*.

3.2.12 Allergies

No studies were identified that directly assessed allergies in children consuming NSS. See **Section 3.3.3.4**.

3.3 Pregnant women

3.3.1 Maternal outcomes

3.3.1.1 Gestational diabetes

In a cohort study among pregnant women, intake of NSS-sweetened beverages was not associated with the risk of developing gestational diabetes (adjusted relative risk [RR] 0.92; 95% CI 0.81, 1.04) *(217)*; a cross-sectional study also found no association *(218)*. A separate cross-sectional study did identify an association between NSS-sweetened beverages and gestational diabetes in 376 pregnant women attending a diabetes clinic for routine screening for gestational diabetes (adjusted OR 1.77; 95% CI 1.09, 2.86) *(219)*.

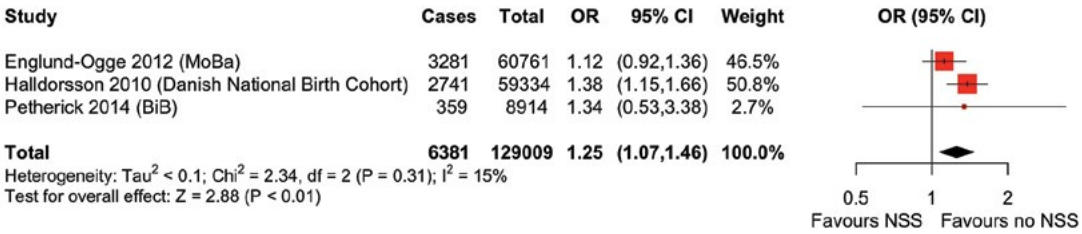
3.3.2 Birth outcomes

3.3.2.1 Preterm birth

Three prospective cohort studies reported on use of NSS-sweetened beverages during pregnancy and preterm delivery *(220–222)*. Results of meta-analysis suggest that NSS intake during pregnancy is associated with a 25% increase in risk of preterm birth (*Fig. 34*). A dose–response relationship was observed in the two studies that reported a significant association. Additional analyses suggested that the association was primarily for late preterm delivery (between weeks 34 and 37), not early preterm delivery (<32 weeks), and that the association was similar for lean and overweight women *(220, 221)*. Analyses in one of the studies further suggested that the preterm delivery associated with intake of NSS-sweetened beverages was primarily medically induced delivery rather than spontaneous preterm delivery, although adjustment for hypertension and removal of women with diagnosed pre-eclampsia did not alter the effect significantly *(221)*. A cross-sectional study reported no difference in gestational age at delivery between highest and lowest consumers of NSS-sweetened beverages *(218)*.

[1] PPVT-III: Peabody Picture Vocabulary Test-III; WRAVMA: Wide Range Assessment of Visual Motor Ability; KBIT-II: Kaufman Brief Intelligence Test 2nd edition; WRAML: Wide Range Assessment of Memory and Learning.

Fig. 34. Association between NSS intake and risk of preterm birth



3.3.2.2 *Birthweight*

A secondary analysis of the cluster-randomized GeliS trial, which assessed the effects of a healthy lifestyle during pregnancy, found that intake of NSS-sweetened beverages during pregnancy was not associated with birthweight or BMI, or categorical assessments of low or high birthweight, or small or large for gestational age *(223)*.

In a Dutch cohort of pregnant women, intake of NSS-sweetened products before conception was associated with increased birthweight (adjusted z-score coefficient per 10 g per 1000 kcal/day: 0.001; 95% CI 0.000, 0.001; *P* = 0.002) *(224)*.

3.3.2.3 *Large for gestational age*

In a cohort study with women with gestational diabetes in Slovenia, intake of low-calorie beverages[1] was not associated with large for gestational age (Spearman correlation 0.118; *P* nonsignificant) *(225)*.

3.3.3 Health effects in offspring

3.3.3.1 *Adiposity*

In a prospective cohort study of pregnant women conducted in Canada, daily intake of NSS-sweetened beverages during pregnancy (compared with less than one serving per month) was associated with a 0.2 increase in infant BMI z-score (95% CI 0.02, 0.38) and a more than twofold increase in risk of overweight at 1 year of age (adjusted OR 2.19; 95% CI 1.23, 3.88). Adjustment for maternal BMI, diet quality, total energy intake or other obesity risk factors did not change the results *(226)*.

In a prospective cohort study conducted in the United States, consumption of NSS-sweetened beverages during pregnancy was not associated with BMI z-score or waist circumference in offspring at mid-childhood (median age: 7.7 years) *(227)*.

In a prospective cohort study conducted in Denmark, the children of women with gestational diabetes who consumed more than one NSS-sweetened beverage per day (compared with never) had a higher BMI z-score (b 0.59; 95% CI 0.23, 0.96) and risk of overweight or obesity (RR 1.93; 95% CI 1.24, 3.01) at 7 years of age *(228)*.

3.3.3.2 *Neurocognition*

In a prospective cohort study following children in utero up to 7 years of age, early and mid-childhood cognition scores were inversely associated with maternal intake of NSS-sweetened beverages during pregnancy (PPVT-III,[2] early childhood: –1.2; 95% CI –2.9, 0.5; total WRAVMA,

[1] Based on the reporting of other beverage types in this study, it was determined that "low-calorie beverages" consisted primarily, if not entirely, of NSS-sweetened beverages.

[2] PPVT-III: Peabody Picture Vocabulary Test-III; WRAVMA: Wide Range Assessment of Visual Motor Ability; KBIT-II: Kaufman Brief Intelligence Test 2nd edition; WRAML: Wide Range Assessment of Memory and Learning.

early childhood: –1.5; 95% CI –2.9, –0.1; KBIT-II verbal, mid-childhood: –3.2; 95% CI –5.0, –1.5; KBIT-II nonverbal, mid-childhood: –2.0; 95% CI –4.3, 0.2; WRAVMA drawing, mid-childhood: –1.7; 95% CI –4.1, 0.6; WRAML visual memory, mid-childhood: –0.1; 95% CI –0.7, 0.5); however, there was no association between early and mid-childhood cognition scores and childhood NSS-sweetened beverage intake at 3 years *(215)*.

3.3.3.3 *Asthma*

In a Danish birth cohort, the association between intake of NSS-sweetened beverages during pregnancy and child asthma at 1.5 years and 7 years was assessed. Consumption of more than 1 serving/day of NSS-sweetened beverages during pregnancy was associated with higher odds of the child having asthma at 18 months of age (adjusted OR 1.14; 95% CI 1.00, 1.28) and at 7 years of age (adjusted OR 1.20; 95% CI 1.07, 1.35) *(229)*.

3.3.3.4 *Allergies*

In a Danish birth cohort, intake of more than 1 serving/day of NSS-sweetened beverages during pregnancy was associated with statistically nonsignificant higher odds of the child ever having allergic rhinitis by 7 years of age (OR 1.11; 95% CI 0.86, 1.43) *(229)*.

3.3.3.5 *Adverse effects*

In a Norwegian birth cohort study, intake of artificially sweetened beverages during pregnancy was not significantly associated with higher risks of congenital heart disease in the offspring (adjusted OR 0.95–0.96, nonsignificant) *(230)*, nor was consumption of NSS-sweetened beverages in a Danish cohort (≥4 servings/day versus no use; for carbonated beverages, adjusted OR 1.01; 95% CI 0.32, 3.21; P_{trend} 0.06; for noncarbonated beverages, adjusted OR 1.08; 95% CI 0.65, 1.80; P_{trend} 0.72) *(231)*.

A case–control study found no significant association of spontaneous abortion with intake of saccharin during pregnancy *(232)*.

3.3.4 Additional outcomes[1]

3.3.4.1 *Gestational weight gain*

In the TOP study (RCT) in Denmark, gestational weight gain and risk for excessive gestational weight were higher in pregnant women consuming NSS ≥1/day compared with 0/day (MD 2.0 kg; 95% CI –0.2, 4.2; and RR 1.50; 95% CI 1.17, 1.92, respectively) *(233)*.

In a cohort study with women with gestational diabetes in Slovenia, gestational weight gain was not significantly associated with intake of low-calorie beverages[2] (Spearman correlation 0.118; *P* nonsignificant) *(225)*.

In a prospective cohort study in Iceland (the PREWICE cohort), pregnant women with excessive gestational weight gain consumed more NSS-sweetened beverages (median: 0.5 times per week; interquartile range [IQR] 0.1 to 2.0; $P < 0.01$) than those with optimal and suboptimal gestational weight gain (median 0.1; IQR 0.1 to 1.0) *(234)*.

[1] Not specified a priori.

[2] Based on the reporting of other beverage types in this study, it was determined that "low-calorie beverages" consisted primarily, if not entirely, of NSS-sweetened beverages.

3.3.4.2 Cardiometabolic health (maternal)

In a cohort study of women with gestational diabetes in Denmark, intake of two or more NSS-sweetened beverages per week during and after pregnancy (when compared with four or fewer per month) was associated with significantly higher HbA1c (6.0%; 95% CI 2.8, 9.1), fasting glucose (7.1 mmol/L; 95% CI 2.2, 12.4) and obesity (RR 1.37; 95% CI 1.04, 1.81), but no significant difference in fasting insulin, HOMA-IR, triglycerides, HDL cholesterol, LDL cholesterol, BMI, waist circumference or type 2 diabetes *(235)*.

4. Discussion

Summary of results

This systematic review of a large number of RCTs, prospective cohort studies and case–control studies found that NSS use results in a small reduction in body weight and BMI in adults, as assessed in RCTs (*low* certainty evidence) without significant effects on other measures of adiposity or cardiometabolic health, including fasting glucose, insulin, blood lipids and blood pressure (*very low* to *high* certainty evidence). The effects appear more pronounced when NSS are compared with sugars, and it is likely that they are mediated by a reduction in energy intake, which is only observed in studies in which NSS are compared to sugars. When NSS are used specifically as replacements for sugars (mostly in the form of replacing SSBs with NSS-sweetened beverages), the effects on body weight and BMI are smaller, and neither are statistically significant (*moderate* certainty evidence).

Results from prospective cohort studies suggest that higher NSS intake is associated with increased body weight, and increased risk of type 2 diabetes, cardiovascular diseases and all-cause mortality (*very low* to *low* certainty evidence). Results from case–control studies suggest an association between saccharin intake and bladder cancer (*very low* certainty evidence), but significant associations for other types of cancer were not observed in case–control studies or meta-analysis of prospective cohort studies (*very low* to *low* certainty evidence).

Relatively fewer studies were found for children, and results were largely inconclusive. One fairly large, well-conducted RCT in which SSBs were replaced with NSS-sweetened beverages reported a small reduction in measures of adiposity (*moderate* certainty evidence). However, the effect was not observed when this study was meta-analysed with another study, and was not corroborated by results from prospective cohort studies.

Results for pregnant women suggest that higher NSS intake is associated with increased risk of preterm birth (*low* certainty evidence) and possibly adiposity in offspring (*very low* certainty evidence).

Interpretation

The results suggest that, in the short term, NSS use may lead to small reductions in adiposity without any significant impact on cardiometabolic risk. There is suggestion of negative health effects with long-term use, but the evidence is ultimately inconclusive.

That a difference in body weight with NSS intake was observed in shorter term RCTs, primarily when NSS were compared with sugars, is not unexpected given current knowledge regarding the role of sugars in unhealthy weight gain, particularly when they are consumed in beverage form. Evidence suggests that the body does not sense calories from SSBs in the same manner as those in solid foods, in terms of satiety *(236)* – as a result, they are not compensated for by a reduction in energy intake in the rest of the diet, thus leading to positive energy balance. Because most of the studies included in this review that compared NSS with sugars did so by providing NSS-sweetened beverages or SSBs as a supplement to the existing diet, it is likely that those receiving the SSBs did not fully compensate for the extra calories from the added sugars, whereas those receiving NSS-sweetened beverages were not consuming these extra calories. This is supported by the observation that energy intake was significantly higher in those not receiving NSS, exclusively in studies that compared NSS with sugars. Because the effects of NSS on adiposity were smaller for studies in which NSS were used specifically as a replacement for

sugars, it may be that the effects observed for NSS compared with sugars in the main analyses are being driven in part by the inability to compensate for added sugars rather than the ability of NSS to limit energy intake per se, and consequently weight gain.

In contrast to the shorter-term effects on adiposity observed in RCTs, longer-term cohort data with follow-up to 10 years, while more limited, suggest increased risk of adiposity with higher NSS intake. Although long-term data from RCTs are limited, two trials were identified that lasted 1 year or more (the duration of most of the RCTs was less than 6 months) *(22, 180)*. Both trials reported a modest reduction in body weight, although one trial, which consisted of active weight loss with or without NSS for 16 weeks followed by 12 months of active maintenance and another 18 months of post-trial follow-up, reported significant differences only at the two latter time points: weight loss was similar between NSS and no NSS at the end of the 16-week active weight loss phase *(22)*. Two additional trials lasting 12–18 months were included; however, they both tested the effects of asking habitual NSS users to switch to water (and reported vastly different results), and therefore do not directly provide insight on how longer-term use of NSS affects adiposity.

Differences were also seen between RCTs and prospective cohort studies in the effect of NSS use on intermediate markers of diabetes and cardiovascular diseases and incident disease. RCTs found no such effects, whereas positive associations were observed in the prospective cohort studies between NSS use and mortality and disease.

The reason for the discrepancy between the results of the RCTs and prospective cohort studies is unclear, although reverse causation has been noted as a possible explanatory factor for the observed associations in cohort studies *(237, 238)*. In the context of NSS, reverse causation implies that individuals assessed as higher consumers of NSS at baseline have recently experienced changes in body weight, are already in a "predisease" state or are otherwise at high risk for disease (e.g. overweight, elevated risk factors) and, in response, have initiated or increased NSS intake, thus leading to a spurious association between NSS intake and increased body weight, mortality or disease. Indeed, in some studies, those with the highest intakes of NSS had higher body weight or BMI, had poorer overall diet quality, or were at higher risk for disease at baseline than those with lower intakes, and associations between NSS and disease outcomes only remained significant in those with higher BMIs when results were stratified by BMI, suggesting that reverse causation may be contributing to the observed association. However, other studies reported no significant baseline imbalances between highest and lowest consumers of NSS, and/or lower risk for disease among highest consumers of NSS at baseline (e.g. better diet quality, more exercise, less smoking). The greater association of NSS use in people with higher BMI can be interpreted either as an indication of reverse causation or as NSS contributing to weight gain as an intermediate step along the pathway to disease.

Recognizing that reverse causation might be particularly relevant for NSS, many of the authors of the cohort studies took great lengths to address it. They undertook extensive adjustments for potential confounders and robust sensitivity analyses to test the impact of removing data that might contribute to reverse causation – for example, excluding data from the first several years after baseline assessment, or from participants with identified risk factors for disease, or who had experienced unplanned weight change prior to baseline assessment. In the case of type 2 diabetes and stroke, the positive association remained in the majority of studies that performed such analyses, and in some cases strengthened. In addition, more than half the cohort studies assessing the effects of NSS on incident type 2 diabetes that reported a P_{trend} value reported a statistically significant P_{trend}, suggesting the possibility of a dose–response relationship. The results of these additional analyses are difficult to reconcile with reverse causation being the sole cause of the positive association between NSS use and type 2 diabetes as it would suggest a long latency period before manifestation of disease, and that those at increasingly greater risk of disease at baseline would have consumed proportionately more NSS, which is possible but not necessarily self-evident or logically explained. The results of similar sensitivity analyses for

mortality and cardiovascular diseases are not as consistent, but also do not rule out a bona fide association between NSS intake and increased risk.

Although the discordant results between shorter-term RCTs and longer-term cohort studies may be partially or largely a result of reverse causation and/or residual confounding, an alternative explanation may be found in likely differences in how NSS were consumed between the experimental settings of RCTs and in free-living populations as assessed in prospective cohort studies. In most of the RCTs included in this review, NSS were consumed as an alternative to sugars, and, in many, NSS were provided directly as a stand-alone item (mostly beverages) to consume. Although it is not known how the NSS in every trial were actually consumed, given the design of many of the trials, it is reasonable to assume that the NSS were generally treated as an experimental food or beverage to be consumed, likely on its own, and in many cases specifically as a replacement for sugars. In contrast, real-world consumption of NSS as assessed in cohort studies is more complex and could follow a variety of patterns including as a conscious, specific replacement of sugars, but also as a general part of the diet without concern for whether or not they are replacing sugars, or have low or no calories. NSS could also be used as a justification for consuming other sugary or unhealthy foods – that is, people who have consumed a food or beverage with NSS might feel that it is acceptable to then consume sugar-containing (or otherwise unhealthy) foods or drinks *(239)*. Evidence does suggest that many people consume products with NSS not in replacement of, but in addition to, foods containing sugars, as well as other unhealthy foods *(240–242)*, and results of a cross-sectional study of children completing the NHANES survey in the United States suggest that consuming both NSS and sugars is associated with greater total energy intake than consuming either alone *(242)*. The effects of consuming NSS and sugars together have also been explored in a recent RCT (included in this review) that reported that the intake of sucralose alone does not impair insulin sensitivity, but, when consumed together with another carbohydrate (maltodextrin), it both impairs insulin sensitivity and decreases the neural response to sugars intake, suggesting that sucralose, when consumed with carbohydrates, disrupts gut–brain regulation of glucose metabolism *(100)*. Evidence for effects of regularly consuming NSS and sugars together is very limited, and further research is clearly needed. However, these results do suggest a possible explanation for some of the differences observed between the RCTs and prospective cohort studies.

Mechanisms by which NSS as a class of molecules might exert effects that increase risk for obesity and certain NCDs have been reviewed extensively and include interaction with extra-oral taste receptors *(243)*, possibly with alteration of the gut microbiome *(244)*. Because sugars and all known NSS presumably elicit sweet taste through the TAS1R heterodimeric sweet-taste receptor *(245)*, which has been identified not just in the oral cavity but in other glucose-sensing tissues *(243)*, it is not surprising that such a group of vastly different chemical entities could be responsible for similar effects on health. However, as NSS are a diverse group of molecules, the magnitude or precise effects on disease risk might differ slightly, and off-target interactions (i.e. interactions other than with the sweet-taste receptor) could differ significantly between individual NSS *(246)*. Several of the RCTs included in this review used individual sweeteners, but the limited meta-analyses did not suggest any striking differences, although a small number of studies included in the review concluded that there appeared to be NSS-specific differences in effects on body weight, for example. Virtually none of the cohort studies reported on individual NSS as exposures.

The results of the review suggest an association between NSS intake and risk of bladder cancer, with the effect being almost entirely driven by use of saccharin, primarily via tabletop use (i.e. added by the consumer). The results were unexpected given that, despite early concerns regarding a possible link between saccharin and bladder cancer based on results of studies in rodents *(247)*, subsequent studies in humans failed to replicate the findings *(248)*. A 2015 systematic review on NSS intake and cancer did not find an association between NSS intake and bladder cancer; however, the review included only five studies in total *(249)*. A number of the

studies included in the current review are decades old; many lack important details, including information on doses being consumed in the studies; and nearly half have serious risk of bias. As a result, confidence (certainty) in the results for bladder cancer is very low, and therefore the results must be interpreted cautiously.

The results for pregnant women require further scrutiny, but are in line with a recent study that provided supporting mechanistic data from animal and in vitro studies regarding a possible association between NSS intake during pregnancy and childhood adiposity *(250)*. Although there are questions about the nature of the association observed between NSS intake during pregnancy and preterm birth, including potential mechanisms, the recent finding from a systematic review of an association between preterm birth and childhood obesity *(251)* draws a link between the two main observations in this review for NSS intake during pregnancy. Given that NSS use may be increasing among pregnant women *(10)*, further research is needed to confirm the findings for pregnant women.

Agreement with other recent systematic reviews

Result of this review largely agree with those of other recent systematic reviews, in that replacing sugars with NSS in the short term results in reductions in body weight, with little impact on other cardiometabolic risk factors, but is associated with increased risk of type 2 diabetes, cardiovascular diseases and mortality in the longer term.

As in the current review, a 2021 systematic review and meta-analysis of NSS consumption and body weight and energy intake in intervention studies found that body weight, BMI and energy intake were lower among those receiving NSS when compared with sugars, but not water *(252)*. Similarly, a 2020 systematic review of the effects of NSS intake on body weight as assessed in RCTs found a small reduction in body weight with NSS intake, which was strongest in overweight and obese individuals, and when NSS replaced sugars *(253)*. Similarly, the review did not find a significant pooled effect on body weight in children. Strong similarity in results between previous reviews and the current review are observed despite less restrictive inclusion and exclusion criteria in the earlier reviews (e.g. inclusion of trials that were not randomized *(254)*, employed doses that exceeded the ADI *(255)*, included exclusively pre-diabetic or diabetic participants *(256)*, or used interventions where the effects of NSS could not be isolated, such as replacement of SSBs with "noncaloric beverages" *(257, 258)*, which resulted in slightly different, but largely the same, sets of studies for each outcome between the earlier reviews and the current one). A 2018 systematic review of observational studies found a significant association between NSS use and increased BMI in children *(259)*; however, the review included three cross-sectional studies in the meta-analysis that showed fairly large associations between NSS intake and BMI, which is likely to have skewed the results (the three studies accounted for 32% of the weight in the meta-analysis). Because it is very likely, especially in children, that consumption of NSS is initiated as a result of weight gain, cross-sectional studies are not an informative study design for assessing causation; we therefore did not include them in assessing body weight outcomes.

Three systematic reviews with dose–response meta-analyses published in 2021 found significant associations between consumption of NSS-sweetened beverages and all-cause and cardiovascular disease mortality. However, there was some inconsistency between the studies in the nature of the identified dose–response relationships, with some reporting linear relationships and others reporting J-shaped or nonlinear relationships *(260–262)*. Two of these reviews that also assessed the effects of consumption of NSS-sweetened beverages on cancer mortality found no evidence of an association. Similarly, a 2021 systematic review and meta-analysis of NSS consumption and gastrointestinal cancer as assessed in cohort and case–control studies found no association *(263)*.

A 2017 systematic review assessing body weight and disease outcomes in studies with a minimum duration of 6 months found significant associations between higher NSS intake and increased risk of incident obesity, type 2 diabetes, hypertension, cardiovascular events and stroke *(264)*. A

nonsignificant reduction in body weight as assessed in RCTs was reported; however, the review included only five RCTs reporting on body weight, far fewer than the number included in the current review. A 2017 systematic review of the effects of NSS on measures of glycaemic control found that NSS intake did not appreciably effect blood glucose levels *(265)*. Similarly, a 2021 systematic review and meta-analysis of NSS consumption and chronic kidney disease in cohort and case–control studies found no association between NSS consumption and risk of chronic kidney disease; however, dose–response analysis suggested increased risk above seven servings of NSS per week *(266)*.

A 2021 systematic review on the effects of NSS use during pregnancy and birth outcomes found significant associations between NSS use and increased risk of preterm birth, decrease in gestational age and increased birthweight *(267)*. A 2016 systematic review on the effects of early exposure to NSS (including use during pregnancy) on longer-term metabolic outcomes did not identify any studies that reported on NSS use during pregnancy and metabolic outcomes in offspring *(268)*. The current review also found an association between NSS use and preterm birth, as well as a suggestion of slightly increased adiposity later in childhood, although the data for the latter and other birth outcomes were not amenable to meta-analyses.

Strengths and limitations

The strengths of this review are breadth and depth of the data identified from different study types, and rigorous assessment of the certainty in the evidence via the GRADE framework. Limitations include our inability to meta-analyse a significant portion of the data, particularly outcomes measured predominantly in subjective terms. In addition, because a head-to-head comparison of NSS vs water as replacement for SSB was not prioritized by the NUGAG Subgroup, we were unable to fully account for the effects of water compared with NSS-sweetened beverages as a replacement for SSBs – that is, our literature search strategy was not designed to identify studies that exclusively assessed water as a replacement, without NSS as a comparator.[1] We were also limited in our ability to assess potentially differential health effects of individual sweeteners, and while very few of the cohort studies provided detail on specific sweeteners as exposures, it is likely that in most studies, especially those with many years of follow-up, NSS consumed were primarily those that have been on the market for many years, and that newer sweeteners were less well represented.

Because so many different interventions and experimental designs were employed to assess the effects of NSS intake in the included RCTs, it was difficult to relate the pooled effects to the primary interest of NSS as a replacement for sugars in the context of body weight. Although a small number of studies specifically assessed the effects on habitual users of sugar-sweetened foods and beverages of replacing these foods and beverages with NSS-sweetened alternatives, most trials provided NSS or sugars as an addition to the diet, others provided nothing or water as the comparator, still others provided NSS in capsule form, and a small number assessed the inclusion of NSS in the context of a calorie restricted diet. In addition, two trials assessed the effects of asking habitual users of NSS-sweetened beverages to switch to water. As a result, the majority of the available evidence for effects of NSS used as a replacement for sugars on measures of adiposity is indirect.

Concluding remarks

The results of this review suggest that, in shorter-term RCTs, those consuming NSS had lower body weight and BMI at the end of the trials than those not consuming NSS, particularly when compared with sugars (including when NSS were explicitly used as replacements for sugars), but not when compared with water. Those consuming NSS also exhibited a significant reduction in energy intake, primarily when NSS were compared to sugars. Therefore, NSS may be effective at

[1] The search strategy employed in the original systematic review *(1)* was also not designed to identify studies that exclusively assessed water as a replacement, without NSS as a comparator.

assisting with short-term weight loss when their use leads to a reduction in total energy intake. Results from prospective cohort studies suggest the possibility of long-term harm in the form of increased risk of obesity, type 2 diabetes, cardiovascular diseases and mortality. Further research is needed to determine whether the observed associations are genuine or a result of reverse causation and/or residual confounding. Further research is also needed in children and pregnant women, the latter for which prospective cohort studies currently suggest possible unfavourable effects of NSS consumption on birthweight and adiposity in offspring later in life.

ANNEX 1.

Search strategies

The following search terms were used to search the respective databases as indicated.

MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations (Ovid), and Embase (Ovid)

1 artificial sweetener*.mp.
2 exp Aspartame/
3 aspartame.mp.
4 acesulfame.mp.
5 Ace K.mp.
6 Saccharin/
7 saccharin*.mp.
8 neotame.mp.
9 sucralose.mp.
10 advantame.mp.
11 Cyclamates/
12 cyclamate.mp.
13 alitame.mp.
14 neohesperidin.mp.
15 stevia.mp.
16 Stevia/
17 steviol*.mp.
18 stevioside*.mp.
19 rebaudioside*.mp.
20 rebiana*.mp.
21 thaumatin*.mp.
22 brazzein*.mp.
23 mogroside*.mp.
24 sweetening agent/ or non-nutritive sweetener/ or nutritive sweetener/
25 ((non-calori* or noncalori*) adj (sweetener* or sweetner*)).mp.
26 ((non-sugar or nonsugar) adj (sweetener* or sweetner*)).mp.
27 ((non-nutritive or nonnutritive) adj (sweetener* or sweetner*)).mp.
28 ((low-calori* or lowcalori*) adj (sweetener* or sweetner*)).mp.
29 ((intense or high intensity or high potency) adj3 (sweetener* or sweetner*)).mp.
30 natural sweetener*.mp.
31 nonnutritive sweetener/

32 natural sweetening agent*.mp.

33 ((non-caloric or noncaloric) adj (beverage* or drink* or soft drink*)).mp.

34 sugar substitute*.mp.

35 (diet soda*).mp

36 (diet beverage*).mp

37 (diet drink*).mp

38 (diet cola*).mp

39 (sugar-free).mp

40 (calorie-free).mp

41 (artificially sweetened).mp

42 (non-nutritively sweetened).mp

43 (non-calorically sweetened).mp

44 (Low calorie beverage).mp

45 (Low calorie drink).mp

46 (Low calorie soda).mp

47 or/1-46

48 exp animals/ not humans.mp.

49 47 not 48

50 limit 49 to yr="2017 -Current"

51 or/1-40

52 51 not 48

53 49 not 52

Cochrane CENTRAL

#1 "artificial sweetener*"

#2 MeSH descriptor: [Aspartame] explode all trees

#3 aspartame

#4 acesulfame

#5 "Ace K"

#6 MeSH descriptor: [Saccharin] this term only

#7 saccharin

#8 neotame

#9 sucralose

#10 advantame

#11 MeSH descriptor: [Cyclamates] explode all trees

#12 cyclamate

#13 alitame

#14 neohesperidin

#15 MeSH descriptor: [Sweetening Agents] this term only

#16 MeSH descriptor: [Non-Nutritive Sweeteners] this term only

#17 MeSH descriptor: [Nutritive Sweeteners] this term only

#18 stevia

#19 MeSH descriptor: [Stevia] this term only

#20 steviol*

#21 stevioside*

#22 rebaudioside*

#23 rebiana*

#24 thaumatin*

#25 brazzein*

#26 mogroside*

#27 (non-calori* or noncalori*) near (sweetener* or sweetner*)

#28 (non-sugar or nonsugar) near (sweetener* or sweetner*)

#29 (non-nutritive or nonnutritive) near (sweetener* or sweetner*)

#30 (low-calori* or lowcalori*) near (sweetener* or sweetner*)

#31 (intense or high intensity or high potency) near/3 (sweetener* or sweetner*)

#32 "natural sweetener*"

#33 "natural sweetening agent*"

#34 (non-caloric or noncaloric) near (beverage* or drink* or soft drink*)

#35 "sugar substitute*"

#36 "diet soda*"

#37 "diet beverage*"

#38 "diet drink*"

#39 "diet cola*"

#40 "sugar-free"

#41 "calorie-free"

#42 "artificially sweetened"

#43 "non-nutritively sweetened"

#44 "non-calorically sweetened"

#45 "Low calorie beverage"

#46 "Low calorie drink"

#47 "Low calorie soda"

#48 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 [limited to Jan 2017 – present]

#49 #48 NOT the original search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35) [no time limits]

#50 #48 OR #4

ANNEX 2. Outcomes reported by study design and population

Population and study design	Weight (+ markers)	Diabetes (+ markers)	CVD (+ markers)	CHD	Stroke	Cancer	Dental health	Mood	Behaviour	Cognition	CKD (+ markers)	Asthma	Allergy	Eating behaviour	Sweet preference	Mortality	Other
Adults	**88**	**74**	**51**	**4**	**2**	**54**	**1**	**8**	**1**	**5**	**7**	**0**	**0**	**45**	**25**	**8**	**0**
Case–control study	1	1	0	0	0	42	0	0	0	0	1	0	0	0	0	0	0
Cohort study	18	15	12	4	2	12	0	3	0	2	2	0	0	1	0	8	0
Controlled trial	3	1	1	0	0	0	0	0	0	0	0	0	0	3	1	0	0
Cross-sectional study	24	18	9	0	0	0	0	1	1	0	1	0	0	12	8	0	0
Randomized controlled trial	36	26	23	0	0	0	1	4	0	2	2	0	0	27	16	0	0
Randomized controlled trial (ongoing)	5	12	5	0	0	0	0	0	0	1	1	0	0	2	0	0	0
Controlled trial (ongoing)	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Children	**31**	**4**	**3**	**0**	**0**	**2**	**5**	**2**	**1**	**2**	**0**	**1**	**0**	**9**	**6**	**0**	**0**
Case–control study	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0
Cohort study	14	1	1	0	0	0	1	0	0	0	0	0	0	4	2	0	0
Controlled trial	0	1	0	0	0	0	0	1	1	1	0	0	0	1	0	0	0
Cross-sectional study	15	1	2	0	0	0	2	1	0	0	0	1	0	1	3	0	0
Randomized controlled trial	2	0	0	0	0	0	2	0	0	1	0	0	0	2	0	0	0
Randomized controlled trial (ongoing)	0	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0
Mixed	**8**	**2**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**5**	**3**	**0**	**0**
Cohort study	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cross-sectional study	7	1	0	0	0	0	0	0	0	0	0	0	0	4	3	0	0
Randomized controlled trial	0	1	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0
Pregnant women	**8**	**3**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**1**	**1**	**0**	**0**	**0**	**8**
Case–control study	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Cohort study	8	2	1	0	0	0	0	0	0	1	0	1	1	0	0	0	5
Cross-sectional study	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Total	**135**	**83**	**56**	**4**	**2**	**56**	**6**	**10**	**2**	**8**	**8**	**2**	**1**	**59**	**34**	**8**	**8**

CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular diseases.

ANNEX 3. Characteristics of included studies

Table A3.1 Randomized controlled trials

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
ADULTS											
Al-Dujaili 2017 *(48)*	United Kingdom	–	Crossover	Mixed	16 (mixed)	19–60	Stevia	Tabletop	Sugars	7 days (3 days washout)	Provision of stevia (600 mg/day) or sugars (15 g/day) to be used preferably in a hot drink. Avoidance of other forms of sweeteners or sugars during the study.
Angelopoulos 2015, 2016a, 2016b *(73, 74, 269)*	United States	–	Parallel (abstract only)	Mixed	71 (mixed)	–	Unspecified	Soft drink	Sugars, water	6 months	Provision of two 12-ounce servings of artificially-sweetened, sugar- sweetened or unsweetened beverages per day with American Dietetic Association (ADA) exchange diet.
Baird 2000 *(70)*	United States	–	Parallel	Mixed	118 (mixed)	–	Sucralose	Water	Fructose	3 weeks	Provision of water solution with sucralose (125, 250 and 500 mg/day during weeks 1–3, 4–7 and 8–12, respectively) or fructose. Highest dose (500 mg) is likely above ADI (5 mg/day/kg), and mean weight of participants is 70 kg; therefore data not extracted for this dose.
Ballantyne 2011 *(71)*	United Kingdom	–	Parallel (abstract only)	Overweight	40 (male)	30–55	Aspartame	Drink	Sucrose	8 weeks	Provision of aspartame- or sucrose-sweetened drinks (250 mL) 4× per day. All participants were informed that they were receiving sugars drinks (i.e. half the participants were misinformed).
Blackburn 1997 *(22)*	United States	1988	Parallel	Overweight	163 (female)	43–55	Aspartame	Drink, food, tabletop	Avoiding aspartame	3.5 years (3 weeks washout + 16 weeks intervention + 1 year maintenance program + 2 years additional follow-up)	All participants followed a weight loss program. Participants in the aspartame arm were given aspartame-sweetened pudding, milkshakes and noncarbonated beverage mix; and packets of tabletop sweetener. The no-aspartame arm was told to avoid products sweetened with any low-energy sweetener and to use sugars or honey instead, and were given a non-energy-containing flavoured seltzer water to drink instead of diet soda. Data from the 2-year follow-up were included in the main analysis.

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
Bonnet 2018 (SEDULC) *(26)*	France	2012	Crossover	Mixed	50 (mixed)	31 (mean)	Aspartame, acesulfame K	Soft drink	Water	12 weeks	Provision of aspartame-sweetened (258 mg/day) and acesulfame K-sweetened (26 mg/day) soda or water, 330 mL each, 2× per day.
Bueno-Hernández 2020 *(53)*	Mexico	2016	Parallel	Lean	137 (mixed)	18–35	Sucralose	Drink	Placebo	10 weeks	Provision of bottles (60 mL) containing sucralose-sweetened water (62 or 123 mg/day) or unsweetened water 9× per week.
Campos 2015 (REDUCS study) *(27)*[1]	Switzer-land	2011	Parallel	Overweight	31 (mixed)	20–43	Unspecified	Soft drink	Sugars	12 weeks	Habitual consumers of SSBs were instructed to replace SSBs with artificially sweetened beverages, or not replace them. Provision of artificially and sugar-sweetened carbonated soft drinks and iced tea.
Crutchley 2013 *(72)*	Unclear	–	Parallel (abstract only)	Mixed	–	–	Unspecified	Soft drink	Sugars	8 weeks	Replacement of SSBs with diet soft drinks.
Dalenberg 2020 *(100)*[2]	United States	2015	Parallel	Mixed	39 (mixed)	20–45	Sucralose	Soft drink	Sucrose	2 weeks	Provision of sucralose-sweetened (60 mg/day) or sucrose-sweetened (30 g/day) beverages 7× over 2 weeks. The separate trial in adolescents was halted based on preliminary results of the trial in adults.
Ebbeling 2020 (BASH III) *(180)*[3]	United States	2011	Parallel	Mixed	203 (mixed)	18–40	Unspecified	Soft drink	SSB, water	1 year	Habitual consumers of SSBs were instructed to replace SSBs with artificially sweetened beverages or unsweetened beverages (i.e. water: still or sparkling, with or without flavour). Provision of beverages.
Engel 2018 *(23)*[4]	Denmark	2008	Parallel	Overweight	73 (mixed)	20–50	Aspartame	Soft drink	SSB, water, milk	6 months	Provision of sucrose-sweetened regular cola, aspartame-sweetened diet cola, water or semi-skimmed milk (1 L/day). Participants were allowed to drink water, coffee, tea and their regular amount of alcohol.
Fantino 2018 *(175)*[5]	France	2014	Crossover	Lean	166 (mixed)	18–45	Acesulfame K + aspartame + sucralose	Soft drink	Water	5 weeks	Provision of acesulfame K-, aspartame- and sucralose-sweetened lemonade or water (330 mL) 3× per day.
Han 2018 *(29)*	Republic of Korea	2016	Parallel	Mixed	121 (mixed)	20–40	Sucralose	Soft drink	D-allulose	12 weeks	Provision of grapefruit-flavoured, noncarbonated bottled drink (2 × 30 mL), sweetened with either sucralose (24 mg/day) or the rare low-energy sugar D-allulose (8 g/day or 14 g/day).

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
Higgins 2018 *(30)*	United States	2016	Parallel	Lean	100 (mixed)	18–60	Aspartame	Drink, capsule	Placebo	12 weeks	Provision of 1) 0 mg aspartame/day (2 capsules collectively containing 680 mg dextrose and 80 mg PABA, and 2 empty capsules); 2) 350 mg aspartame/day (sachets of flavoured dry powder beverage mixture reconstituted by participants to yield 500 mL, containing 350 mg aspartame and 80 mg PABA, 2 capsules collectively containing 680 mg dextrose and 2 empty capsules); or 3) 1050 mg aspartame/day (sachets of flavoured dry powder beverage mixture reconstituted by participants to yield 500 mL, containing 350 mg aspartame and 80 mg PABA, 4 capsules collectively containing 700 mg aspartame and 680 mg dextrose).
Higgins 2019 *(31)*	United States	2016	Parallel	Overweight	154 (mixed)	18–60	Saccharin, aspartame, rebaudioside A, sucralose	Soft drink	Sucrose	12 weeks	Provision of 1.25–1.75 L/day of an equally sweet fruit-flavoured beverage with sucrose (100–140 g/day), saccharin (0.73 g/day), aspartame (0.58 g/day), rebaudioside A (0.66 g/day) or sucralose (0.16 g/day).
Judah 2020 *(181)*	United Kingdom, United States	–	Parallel	Mixed	158 (mixed)	≥18	Unspecified	Drink	Sugars	2 months	Participants were recruited online, and the intervention was delivered online. Regular consumers of SSBs were advised to substitute their SSBs with either water or diet drinks.
Kanders 1988 *(32)*	United States	1986	Parallel	Overweight	59 (mixed)	20–60	Aspartame	Drink, food, tabletop	Avoiding aspartame	12 weeks	Provision of intervention arm's milk exchanges as aspartame-sweetened pudding or milkshake. Participants were instructed to consume 2 per day and were encouraged to use low-calorie table sweetener, aspartame, diet sodas and gelatin as desired. Control arm avoided the use of all aspartame- or saccharin-sweetened products. Both arms followed a balanced deficit diet consisting of 1000 kcal for females and 1200 kcal for males.
Kassi 2016 *(49)*	Greece	–	Parallel (abstract only)	Metabolic syndrome	38 (mixed)	47 (mean)	Stevia	Food	Sugar-sweetened snack	4 months	Provision of a stevia-sweetened snack 4× per week or a sugar-sweetened snack 1× per week.

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARATOR(S)	DURATION	DESCRIPTION
Kim 2011 *(33)*	Republic of Korea	–	Parallel (abstract only)	Mixed	51 (mixed)	College students	Aspartame	Drink	Sugars, fructo-oligosaccharide	4 weeks	Provision of 2 drinks (700 mL) per day sweetened with aspartame, sugar, low-fructo-oligosaccharides or high-fructo-oligosaccharides. The comparison aspartame versus sugars was extracted.
Kim 2020 *(51)*	Republic of Korea	2018	Crossover	Mixed	39	18–75	Acesulfame K + aspartame	Soft drink	Water	2 weeks	Participants were assigned to 0.6 L/day of artificially sweetened soft drink with acesulfame K (126.6 mg/day) and aspartame (86.4 mg/day), or mineral water for 2 weeks, in a crossover study, with a 4-week washout period.
Kreuch 2020 *(99)*	Australia	2015	Parallel (abstract only)	Mixed	36	18–75	Acesulfame K + sucralose	Capsule	Placebo	2 weeks	Participants were assigned to capsules containing NSS (92 mg sucralose and 52 mg acesulfame K) or placebo, 3× per day for 2 weeks.
Kuzma 2015 *(34)*	United States	2009	Crossover	Lean	10 (mixed)	18–25	Aspartame	Drink	Glucose, fructose	8 days	Provision of 4 servings per day of an equally sweet beverage sweetened with fructose, glucose or a low-calorie sweetener (Equal, primarily aspartame). Provision of food. Crossover trial separated by 20 days washout. We compared aspartame vs fructose and glucose.
Lee 2012 *(95)*	Republic of Korea	–	Parallel (abstract only)	Mixed	51 (mixed)	College students	Aspartame	Drink	Sugars, fructo-oligosaccharide	2 weeks	Provision of aspartame, sugar, low-fructo-oligosaccharides, high-fructo-oligosaccharides, or low fructo-oligosaccharides with milk. Mode of delivery was unclear.
Lertrit 2018 *(35)*	Thailand	2016	Crossover	Mixed	15 (mixed)	≥18	Sucralose	Capsule	Placebo	4 weeks	Provision of hard gelatin capsules (1× per day) with sucralose (200 mg) or empty capsules.
López-Meza 2021 *(270)*	Mexico	–	Parallel	Lean	39 (mixed)	18–35	Sucralose, stevia	Tabletop	Sucrose	6 weeks	Participants underwent a 1-week washout period, then were divided into three arms receiving packets of sucrose, sucralose or steviol glycosides each day for 6 weeks.

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
Madjd 2018 *(36)*[6]	Iran (Islamic Republic of)	2014	Parallel	Overweight	89 (female)	18–50	Unspecified	Drink	Water	18 months (6 months weight loss + 12 months weight maintenance)	Habitual NSS users consumed either 250 mL diet beverage after main meal 5× per week (and the rest of beverages was water) or consumed only water (no other drinks). Both arms avoided consuming beverages during the meal and adding low-calorie sweeteners to tea/coffee, and were instructed to follow a hypoenergetic diet and increase activity levels.
Markey 2016 (REFORM) *(37)*	United Kingdom	2012	Crossover	Mixed	50 (mixed)	20–49	Unspecified	Drink, food, capsule	Sugars	8 weeks (4 weeks washout)	Provision of regular diet (with sugar-sweetened foods and drinks) or a reformulated diet (with sugar-reduced foods and drinks).
McLay-Cooke 2016 (Ice Tea Study) *(38)*	New Zealand	2010	Parallel (PhD thesis)	Mixed	118 (mixed)	20–55	Acesulfame K + aspartame	Soft drink	Sugar, maltodex-trin	8 weeks	Provision of diet (acesulfame K and aspartame) or regular (sugar and maltodextrin) soft drinks, 500 mL per day.
Njike 2011 *(39)*	United States	2005	Crossover	Overweight	44 (mixed)	40–64	Unspecified	Hot drink	Sugars	6 weeks (4 weeks washout)	Provision of hot cocoa beverages (2× per day): 1) sugar-free cocoa (cocoa powder + unspecified NSS), 2) sugar-sweetened cocoa (cocoa powder + 45.5 g sugar), 3) placebo (0 cocoa powder + 55 g sugar). Participants were instructed to maintain their usual physical activity and dietary habits, and refrain from consuming flavonoid-rich foods for 24 hours before each test day.
Peters 2016 *(40)*[7]	United States	2012	Parallel	Overweight	303 (mixed)	21–65	Unspecified	Soft drink	Water	1 year (12 weeks weight loss + 40 weeks weight maintenance)	Habitual NSS users were asked to consume at least 710 mL per day of water (control) or NSS beverage per day. Part of a behavioural weight management program that included 12 weeks of weight loss followed by 40 weeks of weight maintenance.

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
Piernas 2013 (CHOICE) *(176)* Tate 2012 (CHOICE) *(46)*	United States	2008	Parallel	Overweight	Piernas: 210 (mixed) Tate: 318 (mixed)	18–65	Unspecified	Soft drink	Water	6 months	Habitual consumers of SSBs were instructed to replace ≥2 servings per day (≥200 kcal) of caloric-sweetened beverages with water or NSS-sweetened beverages. Provision of 4 servings of 340–454 mL/day. NSS-sweetened beverages included still and carbonated beverages (e.g. diet versions of Coke and Sprite [Coca-Cola Company]; Pepsi, Mountain Dew, Aquafina Splash Water [PepsiCo]; Dr Pepper [Dr Pepper Snapple Group]; Diet Lipton Tea [Unilever], Nestea [Nestlé] and low-calorie fruit drinks that contain low-calorie sweeteners (e.g. Tropicana Lemonade [PepsiCo]).
Raben 2002 *(41)*[8] Raben 2011 *(96)*	Denmark	–	Parallel	Overweight	2002: 41 (mixed) 2011: 23 (mixed)	20–50	Unspecified	Drink, food	Sucrose	10 weeks	Provision of 1) supplemental drinks and foods containing sucrose (~2 g/kg per day, 125–175 g/day), or 2) similar drinks and foods containing artificial sweeteners (~7 mg/kg per day, 0.48–0.67 g/day). The percentage contributions of the different artificial sweeteners were 54% from aspartame, 22% from acesulfame K, 23% from cyclamate, and 1% from saccharin. Beverages included soft drinks and flavoured fruit juices. Foods included yoghurt, marmalade, ice-cream and stewed fruits. Subjects were not informed about the true purpose of the study, but were all told that they would receive supplements containing artificial sweeteners, some of which would be newly developed.
Reid 2007 *(44)*	United Kingdom	–	Parallel	Lean	133 (female)	20–55	Aspartame	Soft drink	Sucrose	4 weeks	Provision of sucrose- or aspartame-sweetened drinks (4 × 250 mL/day). Participants were informed that they were receiving either sugary drinks or "diet" drinks, meaning that half were correctly informed about the drink content and half were misinformed. Participants were recruited according to whether they were or were not currently watching their weight.

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
Reid 2010 *(42)*	United Kingdom	–	Parallel	Overweight	53 (female)	20–55	Aspartame	Soft drink	Sucrose	4 weeks	Provision of sucrose- or aspartame-sweetened drinks (4 × 250 mL/day).
Reid 2014 *(43)*	United Kingdom	–	Parallel	Obese	41 (female)	20–55	Aspartame	Soft drink	Sucrose	4 weeks	Provision of sucrose- or aspartame-sweetened drinks (4 × 250 mL/day). All participants believed they received sucrose-sweetened beverages.
Romo-Romo 2018 *(45)*9	Mexico	2015	Parallel	Lean	66 (mixed)	18–55	Sucralose	Tabletop	No inter-vention	14 days	Intervention arm received 3× sachets (Splenda, each containing 12 mg sucralose, 958 mg dextrose and 30 mg maltodextrin) added to beverages at meals. Control did not receive sachets. Both arms were instructed to maintain their habitual food intake and physical activity.
Sánchez-Delgado 2021 *(271)*	Mexico	–	Parallel	Lean	42 (mixed)	18–30	Sucralose, steviol glycosides	Drink, food	Sucrose	6 weeks (1 week washout before start)	Provision of 1) sucrose (40 g/day,) 2) sucralose (48 mg/day), or 3) steviol glycoside (100 mg/day). Participants were directed to add the corresponding sweeteners to unsweetened beverages or food of their choice, every day, maintaining a supplementation diary and using a nutrition guide. They also received a permanent recommendation to restrict consumption of added sugars and non-caloric sweetener.
Serrano 2021 *(272)*	United States	2017	Parallel	Lean	54 (mixed)	18–45	Saccharin	Capsule	Placebo, lactisole, or saccharin with lactisole	2 weeks	Participants were randomized to placebo, saccharin, lactisole (an inhibitor of the sweet-taste receptor), or saccharin with lactisole, administered in capsules twice daily to achieve the maximum ADI for 2 weeks.
Spiers 1998 *(184)*	United States	–	Crossover	Mixed	48 (mixed)	18–35	Aspartame	Soft drink, capsule	Sucrose, placebo	20 days	Provision of sodas and capsules with 1) aspartame (15 mg/kg per day), 2) sucrose (90 g/day), or 3) placebo (unsweetened sodas and capsules with microcrystalline cellulose and silicon dioxide).
Stamataki 2020 *(52)*[10]	United Kingdom	2019	Parallel	Lean	28 (mixed)	18–40	Stevia	Tabletop	No inter-vention	12 weeks	The intervention arm consumed 5 stevia drops (2× per day) in habitually consumed drinks. The control arm did not change their diet.

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARATOR(S)	DURATION	DESCRIPTION
Vázquez-Durán11 2016 *(50)*	Mexico	2012	Parallel	Lean	148 (mixed)	18–30	Unspecified	Drink	Unsweetened beverages, SSBs and non-caloric sweetened beverages (no change)	3 and 6 months	3 arms: 1) no sweetened beverages were permitted; only plain water, lemon and hibiscus-flavoured water, coffee and tea without sugars were permitted; 2) only beverages with non-caloric sweeteners, plain water, lemon and hibiscus-flavoured water, coffee and tea without sugars were permitted; 3) no modification in consumption of beverages, and only general recommendations given about beverages. All arms were given individualized isocaloric diets monitored via a 24-hour record of consumption and frequency of meals.
Viveros-Watty 2021 *(25)*	Mexico	2017	Parallel	Overweight	45 (mixed)	19–27	Unspecified	Drink	Water	12 weeks	Habitual consumers of NSS-sweetened beverages were split into 2 arms: one continued consuming NSS-sweetened beverages, and the other was instructed to stop consuming.
Warrington 2011 *(97)*	Latvia	–	Parallel	Mixed	24 (mixed)	18–55	Advantame	Capsule	Placebo (cellulose)	4 weeks	Provision of capsules (3× per day) containing 10 mg advantame or cellulose.
Young 2017 *(273)*	Australia	–	Parallel	Mixed	27 (mixed)	18–75	Sucralose + acesulfame K	Capsule	Placebo (hydroxypropyl methylcellulose)	2 weeks	Provision of capsules (3× per day) with sucralose (92 mg/day total) and acesulfame K (52 mg/day total) or placebo.
CHILDREN											
Cocco 2019 *(209)*	Italy	–	Parallel	Mixed	264 (mixed)	6–9	Stevia	Food	Sugar	6 weeks	Provision of snacks (2× per day) containing stevia, maltitol or sugar. Instructions to make no changes in dietary and oral hygiene habits, and to use a fluoridated toothpaste during the experimental period.
de Ruyter 2012 (DRINK) *(274)* de Ruyter 2013 (DRINK) *(275)*	Netherlands	2009	Parallel	Mixed	2012: 641 (mixed) 2013: 203 (mixed)	5–11	Sucralose + acesulfame K	Soft drink	Sucrose	18 months	Replacement of SSBs with artificially sweetened beverages. Provision of sucralose-sweetened (34 mg per day) plus acesulfame K–sweetened (12 mg/day) or sucrose-sweetened (26 g/day) noncarbonated beverage (250 mL/day).

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARA-TOR(S)	DURATION	DESCRIPTION
Taljaard 2013 (BeForMi study) *(190)*	South Africa	2010	Parallel	Mixed	398 (mixed)	6–11	Sucralose	Drink	Sucrose	8.5 months	Provision of drinks (200 mL/day, 5× per week) with 1) micronutrients and sucrose (20.6 g/day total), 2) sucrose (20.6 g/day total), 3) micronutrients and sucralose (25 mg/day total), or 4) sucralose (25 mg/day total). We compared the sugars and sucralose arms.
Vandana 2017 *(210)*	India	2014	Parallel	Mixed	108 (female)	12–15	Stevia	Mouth rinse	Placebo	6 months	Daily mouth rinse with 10% stevia or placebo.
MIXED (ADULTS AND CHILDREN)											
Knopp 1976 *(76)*	United States	–	Parallel	Overweight	59 (mixed)	10–21	Aspartame	Capsule	Lactose	13 weeks	Provision of 3× 300 mg gelatin capsules 3× per day with aspartame (equivalent to 2.7 g per day) or a lactose placebo. Instructions were given for an individualized calorie-restricted diet.

–: study did not provide data; ADI: Acceptable daily intake; NSS: non-sugar sweeteners; PABA: para-aminobenzoic acid; SSB: sugar-sweetened beverage.

[1] Campos et al. (2015) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Campos et al. (2015) *(276)*. Campos et al. (2017) *(277)* is a substudy of Campos et al. (2015).

[2] Dalenberg et al. (2020) consisted of two separate studies: one in adults and one in adolescents. The study in adolescents was halted prematurely based on results of the study in adults.

[3] Ebbeling et al. (2020) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Ebbeling et al. (2019) *(28)*.

[4] Engel et al. (2018) provides data for all participants of a trial originally reported in Maersk et al. (2012) *(183)*, which was missing data from some participants. Therefore, only data from Engel et al. (2018) are included in the meta-analyses in this review. In addition, a correction was issued in 2020 *(24)*, as standard deviations were reported in the original publication instead of standard errors, and the corrected values have been used in this review.

[5] Fantino et al. (2018) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Fantino et al. (2017) *(278)*.

[6] Madjd et al. (2018) reported data for 12 months of weight maintenance following 6 months of weight loss. Data for the 6-month weight loss period are reported in Madjd et al. (2015) *(279)*.

[7] Peters et al. (2016) reported data for 40 weeks of weight maintenance following 12 weeks of weight loss. Data for the 12-week weight loss period are reported in Peters et al. (2014) *(280)*.

[8] Raben et al. (2002) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Raben et al. (2001) *(281)*. Sorenson et al. (2014) is a substudy of Raben et al. (2002) assessing outcomes that are not outcomes of interest *(282)*.

[9] A subsequent publication in 2020 *(283)* reported the same data for a slightly smaller sample size and with less detail. Therefore, data from Romo-Romo et al. (2018) were retained in the systematic review.

[10] Stamataki et al. (2020) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Stamataki, Crooks & McLaughlin (2020) *(284)*.

[11] Vázquez-Durán et al. (2016) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Vázquez-Durán et al. (2013) *(285)*.

Note: Blue font indicates that the study received industry funding.

Table A3.2 Prospective cohort studies

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
ADULTS										
Acero 2020 (Talking Health) *(68)*	United States	2012	Mixed	101 (mixed)	≥18	Unspecified	Drink, food	Decreased SSB with increased NSS consumption	6 months	Effectiveness trial of 6 months to reduce SSB consumption. The data were analysed as for a cohort study, comparing participants who decreased or increased their SSB and NSS intake. 24-hour recalls at baseline and after 6 months were used to estimate NSS intake from food and drinks. A participant was considered a consumer if they consumed the equivalent of 1 oz diet soda from foods or beverages.
Anderson 2020 (UK Biobank) *(69)*	United Kingdom	2007	Mixed	198 285 (mixed)	40–69	Unspecified	Drink	>2/day vs 0/day	7	24-hour recall questionnaire to assess ASBs on 5 occasions.
Angeles Pérez-Ara 2020 (MooDFOOD) *(187)*	Germany, Netherlands, Spain, United Kingdom	2015	Over-weight/ obese	941 (mixed)	18–75	Unspecified	Soft drink	≥1/day vs <1/week	1	Trial comparing the effect of different supplements on depression. Data were analysed as for a cohort. FFQ at baseline and after 12 months to estimate intake of carbonated/soft drinks with NSS.
Bao 2008 (NIH-AARP Diet and Health Study) *(163)*	United States	1995	Mixed	487 922 (mixed)	50–71 (baseline)	Unspecified	Soft drink	Median 817 mL/day vs none	7	FFQ on diet soft drink intake over past 12 months at baseline.
Bassett 2020 (MCCS) *(169)*[1]	Australia	1990	Mixed	35 109 (mixed)	53–55 (mean)	Unspecified	Soft drink	>1/day vs <1/month	19	FFQ at baseline on consumption of diet (artificially sweetened) soft drinks.
Bernstein 2012 *(113)* NHS	United States	1980	Mixed	84 085 (female)	30–55 (baseline)	Unspecified	Soft drink	≥1/day vs none	28	FFQ with low-calorie (diet or artificially sweetened) sodas; included low-calorie cola with caffeine (e.g. Diet Coke, Tab with caffeine), low-calorie cola without caffeine (e.g. Pepsi Free) and other low-calorie carbonated beverages (e.g. Diet 7-Up, Fresca, Diet Mountain Dew, diet ginger ale).
HPFS		1986		43 371 (male)	40–75 (baseline)				22	
Bes-Rastrollo 2006 (SUN) *(79)*	Spain	1999	Mixed	7194 (mixed)	41 (mean)	Unspecified	Soft drink	Per serving	2–4	Semi-quantitative FFQ.
Chazelas 2019 (NutriNet-Santé) *(164)*	France	2009	Mixed	101 257 (mixed)	18–72	Unspecified	Drink	>7.9 mL/day vs 0–2.7 mL/day (male) >11.6 mL/day vs 0–4.6 mL/day (female)	5	ASBs included beverages containing non-nutritive sweeteners, such as diet soft drinks, sugar-free syrups, and diet milk-based beverages.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Chazelas 2020 (NutriNet-Santé) *(110)*	France	2009	Mixed	104 760 (mixed)	18–72	Unspecified	Drink	176.7 mL/day vs 0 mL/day	5	24-hour dietary records every 6 months. ASBs were defined as any beverages containing NSS.
Chia 2016 (BLSA) *(60)*	United States	1984	Mixed	1454 (mixed)	≥20	Unspecified	Drink, food	User vs non-user	10	7-day dietary record of food or drink containing low-calorie sweetener (aspartame, saccharin, acesulfame potassium or sucralose).
Chia 2018 (BLSA) *(98)*	United States	1984	Mixed	232 (mixed)	≥20	Unspecified	Drink, food	User vs non-user	10	7-day dietary record of food or drink containing low-calorie sweetener (aspartame, saccharin, acesulfame potassium or sucralose).
Cohen 2012 *(115)*[2] NHS	United States	1980	Mixed	88 540 (female)	30–55 (baseline)	Unspecified	Soft drink, fruit drink	≥1/day vs <1/month	38	FFQ every 4 years. ASBs included on the questionnaire were artificially sweetened cola, caffeine-free cola, non-cola, fruit punch or other fruit drink.
NHS II		1991		97 991 (male)	25–42 (baseline)				16	
HPFS		1986		37 360 (male)	40–76 (baseline)				22	
de Koning 2012 (HPFS) *(111)*	United States	1986	Mixed	42 833 (male)	40–75 (baseline)	Unspecified	Drink	4.5/week–18/day vs none	20–22	FFQ every 4 years. ASBs were defined as caffeinated, caffeine-free and noncarbonated low-calorie beverages.
Drouin-Chartier 2019 *(84)*[3] NHS	United States	1986	Mixed	76 531 (female)	30–55 (baseline)	Unspecified	Drink	Increase >0.5 serving/day vs no change (and decrease >0.5 serving/day vs no change)	2 783 210 person years	FFQ every 4 years with low-calorie beverages with or without caffeine.
NHS II		1991		81 597 (female)	25–42 (baseline)					
HPFS		1986		34 224 (male)	40–75 (baseline)					
Duffey 2012 (CARDIA) *(61)*	United States	1985	Mixed	4161 (mixed)	18–30 (baseline)	Unspecified	Drink	User vs non-user	20	Validated questionnaire on general dietary practices and typical intake of foods during past month, assessed at baseline and years 7 and 20. Diet beverages.
Fagherazzi 2013 (E3N) *(86)*	France	1993	Mixed	66 118 (female)	43–86	Unspecified	Soft drink, fruit drink	>603 mL/week vs 0 mL/week	14	Validated diet history questionnaire. Quantities were estimated by using a photo booklet. Artificially sweetened fruit drinks or soda.
Fagherazzi 2017 (E3N) *(85)*	France	1993	Mixed	61 440 (female)	43–86	Unspecified	Tabletop	Always or almost always vs never or rarely	18	Diet history questionnaire at baseline. Question: "Do you usually use artificial sweeteners, either in packets or tablets (for coffee, tea, etc.)?"

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Farvid 2021 *(106)* NHS	United States	1986	Mixed	8863 (female)	30–55 (baseline)	Unspecified	Drink	>3/week vs non-user	11.5 (median)	Women completed a validated FFQ every 4 years after diagnosis of breast cancer and were followed until death or the end of follow-up (2014 for the NHS and 2015 for the NHS II).
NHS II		1991			25–42 (baseline)					
Ferreira-Pego 2016 (PREDIMED) *(62)*	Spain	2003	Mixed	1868 (mixed)	55–80	Unspecified	Soft drink	>5/week vs <1/week	3	Semi-quantitative FFQ at baseline and yearly after. Artificially sweetened soft drinks.
Fowler 2008 (SALSA) *(63)*	United States	1979	Mixed	5158 (mixed)	25–64 (baseline)	Unspecified	Drink, tabletop	User vs non-user and >21/week vs none	7–8	Participants reporting soft drink use were asked whether they usually drank sugar-free sodas, regular sodas or similar amounts of each; their artificially sweetened soda dose was calculated accordingly. For abstainers, artificially sweetened soda dose was set equal to zero. "Usual" sweeteners for coffee and tea were ascertained, and artificial sweetener dosage was calculated accordingly (or set equal to zero for abstainers). Participants were also asked whether they "usually" used sugars or sugar substitutes. Artificially sweetened soda, coffee and tea intakes were summed to estimate ASB consumption. In cohort 1 only, baseline 24-hour dietary recalls were performed. In cohort 2 only, follow-up use of artificial sweetener (present or absent) was ascertained.
Fowler 2015 (SALSA) *(64)*	United States	1992	Mixed	5158 (mixed)	≥65 (baseline)	Unspecified	Soft drink	≥1/day vs none and any vs none	9	Question: "How many bottles or cans of sugar-free soft drinks do you drink per week?"
Fung 2009 (NHS) *(112)*	United States	1980	Mixed	88 520 (female)	34–59 (baseline)	Unspecified	Soft drink	≥2/day vs <1/month	24	Semi-quantitative FFQ on diet over the past year, at baseline and at follow-up every 4 years. ASBs consisted of all types of low-calorie, sweet, carbonated beverages, such as diet colas and other diet carbonated beverages.
Gardener 2012 (NOMAS) *(108)*[4]	United States	1993	Mixed	2564 (mixed)	≥40 (baseline)	Unspecified	Soft drink	≥1/day vs <1/month	10	Semi-quantitative FFQ on diet over past year at baseline. Diet soda.
Gardener 2018 (NOMAS) *(87)*	United States	1993	Mixed	2019 (mixed)	≥40 (baseline)	Unspecified	Soft drink	>6/week vs <1/ month	11	Semi-quantitative FFQ on diet over past year at baseline. Diet soda.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Garduno-Alanis 2020 (HAPIEE) *(65)*	Russia5	2002	Mixed	5205 (mixed)	45–69 (baseline)	Unspecified	Soft drink	≥1/day vs none	4	FFQ on diet over past 3 months with artificially sweetened soft drinks. One portion was 200 mL. Categories of intake: never drinkers, occasional drinkers (<1 drink per day) and daily drinkers (≥1 drinks per day).
Gearon 2014 (MCCS) *(78)*	Australia	1990	Mixed	13 697 (mixed)	53 (mean baseline)	Unspecified	Soft drink	Dose–response	13	Diet soft drinks.
Guo 2014 (NIH-AARP Diet and Health Study) *(185)*	United States	1995	Mixed	263 923 (mixed)	50–71 (baseline)	Aspartame, saccharin, unspecified	Soft drink, drink, tab-letop	Drinkers vs non-drinkers ≥4/day vs none	10	FFQ on diet over past 12 months at baseline. Diet soft drink, diet fruit drinks, diet iced tea, aspartame or Equal, saccharin or Sweet'N Low.
Haslam 2020 (FOS) *(116)*	United States	1991	Mixed	6730 (mixed)	Varied	Unspecified	Soft drink	>1/day vs <1/month	12.5	FFQ. Low-calorie sweetened beverages included low-calorie cola, low-calorie caffeine-free cola, and other low-calorie carbonated beverages.
Hirahatake 2019 (CARDIA) *(88)*	United States	1985	Mixed	4719 (mixed)	18–30 (baseline)	Unspecified	Soft drink, fruit drink	≥2/day vs none	30	Validated diet history questionnaire at baseline and years 7 and 20 on general dietary practices and typical intake of foods over previous month. ASBs were soft drinks and fruit drinks sweetened with non-nutritive (non-caloric) sweeteners.
Hodge 2018 (MCCS) *(165)*	Australia	1990	Mixed	35 593 (mixed)	40–69	Unspecified	Soft drink	≥1/day vs <1/month	13	FFQ on diet over past year, with diet (artificially sweetened) soft drinks.
Huang 2017 (WHI-OS) *(89)*	United States	1996	Mixed	64 850 (female)	50–79 (baseline)	Unspecified	Drink	≥2/day vs <3/month	8	FFQ at baseline, about intake of ASBs over past 3 months. "During the past 3 months, how often did you drink these beverages?" (Beverages refer to diet drinks such as Diet Coke or diet fruit drinks, with a 355 mL can as a reference size.)
Hur 2021 (NHS II) *(170)*	United States	1991	Mixed	95 464 (female)	25–42 (baseline)	Unspecified	Drink	≥2/day vs <1/week		Assessed SSB consumption via validated FFQs every 4 years. Modelled effect on colorectal cancer risk of replacing each serving per day of adulthood SSB intake with that of ASBs, coffee, reduced-fat milk or total milk.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
InterAct-Consortium 2013 (EPIC-InterAct) *(94)*	Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom	1991	Mixed	27 058 (mixed)	35–79 (baseline)	Unspecified	Soft drink	≥1/day vs <1/month	16	Dietary questionnaire of intake over past 12 months at baseline with artificially sweetened soft drinks, including carbonated/soft/isotonic drinks and diluted syrups. A serving of soft drink was defined as 330 mL.
Jensen 2020 (SHFS) *(90)*	United States	2007	Mixed	1359 (mixed)	42 (mean)	Unspecified, saccharin, sucralose, aspartame	Soft drink, tabletop	≥7/week vs none (beverages) Always vs none (tabletop)	8	Questions: (1) How often do you drink diet drinks, like diet Coke, in the past week (never, once a week, twice a week, 3–4 times a week, 5–6 times a week, every day, more than once a day)? (2) How often do you use artificial sweeteners to sweeten your drinks (never, occasionally, often, always)? (3) If you ever use artificial sweeteners, what type do you use (saccharin, sucralose, aspartame, other – identified by brand name and colour of packet: Sweet N' Low [pink packet], Splenda [yellow packet], Equal [blue packet], NutraSweet [white packet], or Sunett [purple packet])?
Keller 2020 (HPP) *(118)*[6]	United States	Varied	Mixed	284 345 (mixed)	≥35	Unspecified	Drink	Per daily serving	8	FFQ at baseline. ASBs included any diet drinks sweetened with artificial sweeteners.
Lana 2015 (ENRICA) *(186)*	Spain	2008	Mixed	2132 (mixed)	18–60 (baseline)	Unspecified	Soft drink	≥1/day vs <1/week	4	Diet history at baseline. ASBs included diet or light soft drinks.
Lim 2006 (NIH-AARP Diet and Health Study) *(166)*	United States	1995	Mixed	473 984 (mixed)	50–71 (baseline)	Aspartame	Drink	≥100, 400 or 600 mg/day vs none	5	FFQ on diet over past 12 months at baseline. Diet soft drink, diet fruit drinks, diet iced tea, aspartame added to coffee or tea.
Lin 2011 (NHS) *(173)*	United States	1989	Mixed	3318 (female)	≥42	Unspecified	Soft drink	≥2/day vs <1/month	11	Biennial FFQ. Participants were asked to report the number of servings ("one glass, bottle or can") consumed on average over the past year for low-calorie sugar-free carbonated beverages with or without caffeine.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Ma 2016 (FHS 3rd Generation) *(55)*	United States	2002	Mixed	1003 (mixed)	35–72 (baseline)	Unspecified	Soft drink	≥1/day vs <1/month	6	Semi-quantitative FFQ at baseline. Diet soda intake was assessed using the following 3 items: (1) low-calorie cola; (2) low-calorie, caffeine-free cola; and (3) other low-calorie carbonated beverage.
Malik 2019 *(102)* NHS	United States	1980	Mixed	80 647 (female)	30–55 (baseline)	Unspecified	Drink	≥2/day vs <1/month	34	Semi-quantitative FFQ at baseline. ASBs were defined as caffeinated, caffeine-free and noncarbonated low-calorie or diet beverages.
HPFS		1986		37 716 (male)	40–75 (baseline)				28	
McCullough 2014 (CPS-II) *(167)*	United States	1999	Mixed	100 442 (mixed)	47–95	Unspecified, aspartame	Soft drink, tabletop	≥1 can/day vs none (beverage) 145 mg/day vs 0 mg/day (tabletop)	10	FFQ at baseline and after 4 years of consumption over past year. Mean consumption of artificially and sugar-sweetened carbonated beverages ("1 glass, bottle, or can [355 mL]") during the past year was queried with use of frequency categories ranging from "never" to "≥4 per day". Beverages types were divided into cola with caffeine, and other carbonated beverages with or without caffeine. Participants were asked about "use of NutraSweet or Equal (1 packet) (not Sweet N Low)" (manufactured by the NutraSweet Corporation, formerly Searle and Co.). Frequency responses ranged from "never" to "≥6 per day". Total aspartame intake was calculated with use of the following values: 180 mg aspartame/355 mL (1 serving) of low-calorie cola with caffeine, 90 mg/355 mL of other low-calorie soda with caffeine, 70 mg/355 mL of other low-calorie soda without caffeine, and 20 mg aspartame per packet of NutraSweet or Equal reported, as used previously.
Mossavar-Rahmani 2019 (WHI-OS) *(103)*	United States	1996	Mixed	81 714 (female)	50–79 (baseline)	Unspecified	Drink	≥2/day vs <1/week	12	FFQ at baseline, about intake of ASBs over past 3 months. "During the past 3 months, how often did you drink these beverages?" (Beverages refer to diet drinks such as Diet Coke or diet fruit drinks, with a 355 mL can as a reference size.)

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Mullee 2019 (EPIC) *(104)*	Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom	1992	Mixed	477 206 (mixed)	50.8 (mean)	Unspecified	Soft drink	≥2/day vs <1/month	16	Dietary questionnaire of intake over past 12 months at baseline. The group of soft drinks included carbonated/soft/isotonic drinks and diluted syrups, and were classified into sugar-sweetened and artificially sweetened in all centres except 3 (Italy, Spain and Sweden). A serving of soft drink was defined as 330 mL.
Muñoz-Garcia 2019 (SUN) *(188)*	Spain	1999	Mixed	806 (mixed)	55+	Unspecified	Soft drink	Per daily serving	6	Semi-quantitative FFQ for year before recruitment. SSBs included carbonated colas and fruit-flavoured, carbonated, sugary soft drinks. ASBs were considered the low-calorie or artificially sweetened versions of the SSBs.
Nettleton 2009 (MESA) *(66)*	United States	2000	Mixed	6814 (mixed)	45–84 (baseline)	Unspecified	Soft drink	≥1/day vs rare/none	5	FFQ at baseline. Diet soda intake was quantified from an item listing "Diet soft drinks, unsweetened mineral water".
O'Connor 2015 (EPIC-Norfolk) *(91)*	United Kingdom	1993	Mixed	25 639 (mixed)	40–79 (baseline)	Unspecified	Drink	169–5848 mL/day vs non-user	11	7-day food diary at baseline. Intakes (g/day) were estimated for (1) soft drinks (soft drinks, squashes and juice-based drinks sweetened with sugar), (2) sweetened tea or coffee, (3) sweetened-milk beverages (e.g. milkshakes, flavoured milks, hot chocolate), (4) ASB and (5) fruit juice.
Paganini-Hill 2007 (Leisure World Cohort Study) *(105)*	United States	1981	Mixed	13 624 (mixed)	44–101 (baseline)	Unspecified	Soft drink	>1 can/week vs none	23	Baseline questionnaire with "How many cans or glasses per WEEK do you drink of the following – cola beverages with sugar, other soft drinks with sugar, cola beverages artificially sweetened, other soft drinks artificially sweetened?"
Palmer 2008 (BWHS) *(92)*	United States	1995	Mixed	43 960 (female)	21–69 (baseline)	Unspecified	Soft drink	≥1/day vs <1/month	4	FFQ with diet soft drinks.
Park 2020 (FHS, FOS) *(80)*[7]	United States	2002	Mixed	1636	Mean 59.5 (women) Mean 45.3 (men)	Unspecified	Soft drink	<1/month vs ≥1/ week	6	Semi-quantitative FFQ on diet soda consumption.
Parker 1997 (PHHP) *(56)*	United States	1986	Mixed	465 (mixed)	18–64	Saccharin	Unclear	0.1–28.2 g/day vs 0 g/day	4	Semi-quantitative FFQ.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Pase 2017 (FOS) *(114)*	United States	1971	Mixed	2888 (mixed)	45+	Unspecified	Soft drink	≥1/day vs 0/week	10	FFQ at baseline and every 4 years. Diet beverages included low-calorie cola with caffeine, low-calorie caffeine-free cola and other low-calorie beverages.
Rebholz 2017 (ARIC) *(174)*[8]	United States	1987	Mixed	15 368 (mixed)	45–64 (baseline)	Unspecified	Soft drink	>7/week vs <1/week	23	FFQ at baseline and visit 3. Diet soda was described on the FFQ as one 237 mL glass of low-calorie soft drinks such as Diet Coke, Diet Pepsi or Diet 7-Up.
Romanos-Nanclares 2021 *(171)* NHS	United States	1980	Mixed	82 713 (female)	30–55 (baseline)	Unspecified	Drink	≥1/day vs <1/month	4 655 153 person years	FFQ at baseline and every 4 years. Cumulatively averaged intakes of SSBs and NSS-sweetened beverages from FFQs were tested for associations with incident breast cancer cases and subtypes.
NHS II		1991		93 085 (female)	25–42 (baseline)					
Sakurai 2014 *(93)*	Japan	2003	Mixed	2037 (male)	35–55 (baseline)	Unspecified	Soft drink	≥1/week vs rare/none	5.5	Diet history questionnaire. Diet soda consisted of non-calorie carbonated soft drinks.
Schernhammer 2005 *(286)* NHS	United States	1984	Mixed	77 218 (female)	30–55 (baseline)	Unspecified	Soft drink	>3/week vs <1/month	20	FFQ at baseline and every 4 years. Diet soft drinks included low-calorie cola, low-calorie caffeine-free cola, and other low-calorie carbonated beverages.
HPFS		1986		47 810 (male)	40–75 (baseline)					
Schernhammer 2012 *(168)* NHS	United States	1984	Mixed	77 218 (female)	30–55 (baseline)	Unspecified, aspartame	Soft drink, tabletop	Soft drink: ≥1/day vs none Tabletop: ≥129 vs 0 mg/day (male) ≥143 vs 0 mg/day (female)	22	Semi-quantitative FFQ on consumption over past year, every 4 years. The frequency of diet soda consumption was assessed per 12 fl oz (355 mL, equivalent to one bottle, glass or can) serving for the following 3 items: diet cola with caffeine, diet cola without caffeine and other diet soda. Use of aspartame sweeteners added at the table (i.e. NutraSweet and Equal [manufactured by the NutraSweet Company, formerly Searle and Co]) was initially included on the FFQ in 1994 and was assessed as individual serving packets. Total aspartame intake was calculated as the sum from diet soda and packets (20 mg). The aspartame content of each soda item on the FFQ was assigned as a weighted average of the representative sodas in that category (70–180 mg/serving).
HPFS		1986		47 810 (male)	40–75 (baseline)					

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Smith 2015 *(57)*[9] NHS	United States	1986	Mixed	121 701 (female)	30–55 (baseline)	Unspecified	Soft drink	Per daily serving	4	FFQ every 4 years. Diet soda intake over past year, converted into servings per day.
NHS II		1991		116 683 (female)	25–42 (baseline)					
HPFS		1986		51 530 (male)	40–76 (baseline)					
Stellman 1986 (American Cancer Society study) *(67)*[10]	United States	1982	Mixed	78 694 (female)	50–69 (baseline)	Unspecified	Soft drink, tabletop	User vs non-user	6	Question: "Do you now or have you ever added artificial sweeteners (saccharin or cyclamates) to coffee, tea, or other drinks or food?" Choices were: yes, currently, formerly, never. The next question was "If ever used artificial sweeteners, indicate amount per day and for how long", with separate space to record packets, drops and tablets. Also asked were quantity and duration of both current and former use of diet soda and diet iced tea. The study was restricted to those who either had never used artificial sweeteners or were long-term current users, defined as those who answered "yes, currently" to the usage question and who had used packets, tablets, drops and diet beverages for at least 10 years. Former users of artificial sweetener were excluded.
Stepien 2016 (EPIC) *(287)*	Denmark, France, Greece, Germany, Italy, Netherlands, Norway, Spain, Sweden, United Kingdom	1992	Mixed	477 206 (mixed)	50–60 (baseline)	Unspecified	Soft drink	Per daily serving	11	Dietary questionnaire of intake over past 12 months at baseline. The group of soft drinks included carbonated/soft/isotonic drinks and diluted syrups, and were classified into sugar-sweetened and artificially sweetened in all centres except 3 (Italy, Spain and Sweden). A serving of soft drink was defined as 330 mL.
Stern 2017 (Mexican Teachers' Cohort) *(58)*	Mexico	2006	Mixed	11 218 (female)	25–64 (baseline)	Unspecified	Soft drink	Per daily serving Increase of >1 week vs no change	2	Semi-quantitative FFQ. One question on sugar-free soda.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Tucker 2015 *(59)*	United States	–	Mixed	170 (female)	35–45	Unspecified	Soft drink	User vs non-user	4	Usual soft drink intake was assessed with a questionnaire that included 6 soft drink questions. Frequency and type of soft drinks consumed were measured using questions that focused on use of artificially sweetened soft drinks, sugar-sweetened soft drinks, beverage size, and number of soft drinks consumed per week.
Vyas 2015 (WHI-OS) *(109)*	United States	1993	Mixed	59 614 (female)	50–79 (baseline)	Unspecified	Drink	≥2/day vs 0–3/ month	6–10	FFQ at baseline, about intake of ASBs over past 3 months. "During the past 3 months, how often did you drink these beverages?" (Beverages refer to diet drinks such as Diet Coke or diet fruit drinks, with a 355 mL can as a reference size.)
Wang 2019 (SWAN) *(117)*	United States	1996	Mixed	1235 (female)	42–52 (baseline)	Unspecified	Soft drink	≥1/day vs none	Up to 20	FFQ at baseline, year 5 and year 9. Nineteen beverages were aggregated into 8 non-overlapping groups: coffee, tea, SSBs, ASBs, fruit juices, whole milk, milk with lower fat content (2% milk, 1% milk and skim milk), and alcoholic beverages. The intake of each group was calculated by summing the individual items in that group. To capture long-term intakes, the intake of each beverage group was calculated by averaging across up to 3 available dietary measurements (baseline, visit 5 and visit 9).
Zhang 2021 (NHANES) *(107)*	United States	1999	Mixed	31 402 (mixed)	³20 (baseline)	Unspecified	Soft drink	≥2/day vs 0/day	7.9	One or two 24-hour dietary recalls at baseline. ASBs were defined as sugar-free soft drinks and carbonated water. Linkage of NHANES with National Death Index using a probabilistic matching algorithm.
CHILDREN										
Berkey 2004 (GUTS) *(191)*	United States	1996	Mixed	16 771 (mixed)	9–16	Unspecified	Soft drink	Per daily serving	2	FFQ on diet soda.
Blum 2005 *(192)*	United States	1992	Mixed	164 (mixed)	8–12	Unspecified	Soft drink	Per daily serving	2	24-hour dietary recall with diet soda.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Davis 2018 (SOLAR) *(193)*	United States	2004	Overweight	98 (mixed)	12–18	Unspecified	Drink	Chronic user vs never	1	2 × 24-hour dietary recalls at baseline and endline. ASBs included sodas, coffees, energy drinks, teas, sports drinks, juices and flavoured waters. Chronic user was defined as consuming ASBs at baseline and follow-up. Never user (control) was defined as not consuming ASBs at baseline or follow-up.
Field 2014 (GUTS II) *(194)*	United States	2004	Mixed	7559 (mixed)	9–16 (baseline)	Unspecified	Soft drink	Per daily serving	7	Semi-quantitative FFQ every 2 years with diet soda.
Haines 2012 (EAT) *(195)*	United States	1998	Mixed	2516 (mixed)	12–16 (baseline)	Unspecified	Soft drink	≥1/day vs 0/week	5	Diet soda intake assessed by Project EAT-I survey, a 221-item self-report instrument.
Kral 2008 *(204)*	United States	–	Mixed	49 (mixed)	3–6	Unspecified	Soft drink	Dose–response	3	3-day weighted food record every year. Diet soda including carbonated non-caloric beverages.
Laska 2012 (IDEA, ECHO) *(196)*	United States	2006	Mixed	693 (mixed)	15 (mean baseline)	Unspecified	Soft drink	Per daily serving	2	FFQ diet over the past month. Question about "diet or sugar-free soda or pop".
Ludwig 2001 *(197)*	United States	1995	Mixed	548 (mixed)	11–13	Unspecified	Soft drink	Per daily serving	19	FFQ of intake over past 30 days. One question, concerning diet soda, was used to establish the intake of diet soda per day.
Macintyre 2018 (GUS) *(198)*	United Kingdom	2006	Mixed	2332 (mixed)	4–8	Unspecified	Soft drink	≥1/day vs <1/week	3	Exposure to ASBs was measured at age 4–5 with the question: "How often does X drink diet or low calorie soft drinks? INTERVIEWER: Include cans, bottles, mixers. Include diet or low-cal flavoured water here. Do not include fresh fruit juice or water".
Marshall 2003 (IFS) *(211)*	United States	1992	Mixed	642 (mixed)	4–7	Unspecified	Soft drink	Low vs no intake	7	3-day food and beverage diaries at 1, 2, 3, 4 and 5 years of age. Sugar-free soda pop.
Newby 2004 (North Dakota WIC Program for Children) *(199)*	United States	1995	Mixed	1345 (mixed)	2–5	Unspecified	Soft drink	Per daily serving	8 months	FFQ at baseline and follow-up. Diet soda included all no- or low-calorie soda.
Striegel-Moore 2006 (NGHS) *(200)*	United States	1987	Mixed	2371 (mixed)	9–10 (baseline)	Unspecified	Soft drink	Per daily serving	10	3 consecutive-day food records at years 1, 2, 3, 4, 5, 7, 8 and 10. Diet soda included all diet carbonated beverages, excluding water.
Vanselow 2009 (EAT) *(201)*	United States	1998	Mixed	2294 (mixed)	12–16 (baseline)	Unspecified	Soft drink	≥1/day vs 0/week	5	FFQ, included low-calorie soft drinks.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Zheng 2015a (CAPS) *(202)*	Australia	1997–1999	Mixed	237 (mixed)	7–12	Unspecified	Drink	Per daily serving	3	3× 24-hour recall at 9 years. Beverages were grouped into 6 categories: (1) water (tap, bottled and unflavoured mineral), (2) SSBs (regular soft drinks, fruit drinks, cordials and sugar-sweetened sport drinks), (3) milk (full fat, reduced fat, skim and flavoured), (4) coffee/tea (plain and sweetened), (5) 100% fruit juice (apple, blackcurrant, grape, orange and fruit blend), and (6) diet drink (low-energy drinks sweetened with artificial sweeteners).
Zheng 2015b (Healthy Start Study) *(203)*	Denmark	2009	Mixed	288 (mixed)	2–6	Unspecified	Drink	Per daily serving	1.5	4-day dietary record. Beverages were classified as (1) water (tap water, sparkling water and still water), (2) milk (skimmed milk, low-fat milk, whole milk, butter milk and flavoured milk), (3) sugary drinks (sugar-sweetened carbonated and fruit-flavoured drinks, and fruit juice) and (4) diet drinks (ASBs).
Zheng 2019 (Raine) *(77)*	Australia	2003	Mixed	667 (mixed)	14–22	Unspecified	Drink	Per 100 mL/day	8	Semi-quantitative FFQ at baseline (14 years). Six beverage types were evaluated in the present study: (1) SSBs (carbonated soft drinks including cola, cordials or fruit drink concentrate, and fruit juice drinks with the exclusion of 100% fruit juice), (2) plain water (spring and mineral water), (3) tea and coffee (plain and sweetened), (4) diet drinks (low-calorie, artificially sweetened drinks), (5) 100% fruit juice (100% fruit and vegetable juices), and (6) milk (whole, reduced fat, skim, dairy and soy milk).
PREGNANT WOMEN										
Azad 2016 (CHILD) *(226)*[11]	Canada	2009	Mixed	3033	32 (mean)	Unspecified	Soft drink, hot drink	≥1/day vs <1/month	1	FFQ in 2nd–3rd trimester. Intake of NSS-sweetened beverages was determined from reported consumption of diet soft drinks or pop (1 serving = 355 mL) and artificial sweetener added to tea or coffee (1 serving = 1 packet).

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Chen 2009 (NHS II) *(217)*	United States	1991	Mixed	1347	31–32 (mean)	Unspecified	Soft drink	1/day vs 0–3/month	10	Semi-quantitative FFQ about intake over past year. Pre-pregnancy diet beverage consumption. Diet beverages included low-calorie cola with caffeine, low-calorie caffeine-free cola, and other low-calorie beverages.
Cohen 2018 (Project Viva) *(215)*	United States	1999	Mixed	1234	32 (mean baseline)	Unspecified	Soft drink	Per daily serving	7	Self-administered semi-quantitative FFQ during 1st and 2nd trimester of pregnancy and mid-childhood.
Dale 2019 (MoBa) *(230)*	Norway	1999	Mixed	88 514	30 (mean)	Unspecified	Soft drink	≥70 mL/day vs ≤25 mL/day, ≥4/day vs none	9	Semi-quantitative FFQ (2×) in pregnancy with artificially sweetened soft drink.
Englund-Ögge 2012 (MoBa) *(220)*	Norway	1999	Mixed	60 761	30 (mean)	Unspecified	Soft drink	≥70 mL/day vs ≤25 mL/day, ≥4/day vs none	9	Semi-quantitative FFQ (2×) in pregnancy with artificially sweetened soft drink.
Gillman 2017 (Project Viva) *(227)*	United States	1999	Mixed	1078	32 (mean baseline)	Unspecified	Soft drink	Per daily serving	7	Self-administered, semi-quantitative FFQ during 1st and 2nd trimesters of pregnancy and mid-childhood.
Gunther 2019 (GeliS) *(223)*	Germany	2013[12]	Mixed	2286	18–43	Unspecified	Soft drink	Per daily serving	9	FFQ during early and late pregnancy. Light drinks included low- or non-caloric sweetened beverages.
Halldorsson 2010 (Danish National Birth Cohort) *(221)*	Denmark	1996	Mixed	59 334	29 (mean)	Unspecified	Soft drink	≥4/day vs never, ≥1/week vs <1/week	8 months (from pregnancy week 6–10 to delivery) Up to 7	FFQ at ~25 weeks of pregnancy for intake over past month. Artificially sweetened carbonated and non-carbonated soft drink.
Hinkle 2019 (DWH) *(235)*	Denmark	1996	Mixed	607	31–32 (mean)	Unspecified	Soft drink, hot drink	≥2/week in pregnancy and at follow-up vs ≤4/month in pregnancy and at follow-up	Up to 16	FFQ at ~25 weeks of pregnancy for intake over past month, and FFQ 9–16 years later. ASBs with or without coffee and tea with added artificial sweeteners.
Hrolfsdottir 2019 (PREWICE) *(234)*	Iceland	2015	Mixed	1326	30 (mean)	Unspecified	Drink	Excessive, optimal and suboptimal gestational weight gain	9 months	FFQ during first trimester, with ASBs.

STUDY	COUNTRY	STUDY START (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Maslova 2013 (Danish National Birth Cohort) *(229)*	Denmark	1996	Mixed	60 466	21–39	Unspecified	Soft drink	≥4/day vs never, ≥1/week vs <1/week	8 months (from pregnancy week 6–10 to delivery) Up to 7	FFQ at ~25 weeks of pregnancy for intake over past month. Artificially sweetened carbonated and non-carbonated soft drink.
Munda 2019 *(225)*	Slovenia	2017	Mixed	57	22–42	Unspecified	Drink	Linear	9 months	FFQ before and during pregnancy.
Petherick 2014 (BiB) *(222)*	United Kingdom	2007	Mixed	8914	26–27 (mean)	Unspecified	Soft drink	>4/day vs 0/day	9 months	Questionnaire on intake of artificially sweetened cola over past 4 weeks. Consumption was categorized as 0, 1, 2, 3 or ≥4 cups per day, with each cup measuring 200 mL.
Renault 2015 (TOP study) *(233)*	Denmark	2009	Mixed	342	31 (mean)	Unspecified	Soft drink	≥1/day vs 0/day	9 months	FFQ at beginning (weeks 11–14) and end (weeks 36–37) of pregnancy. Artificially sweetened carbonated soft drinks.
Salavati 2020 (Perined-Lifelines Cohort) *(224)*	Netherlands	2006[13]	Mixed	1698	29 (mean)	Unspecified	Drink, food	Per 10 g of ASBs standardized to 1000 kcal/day	13 months	FFQ with artificially sweetened products.
Schmidt 2020 (Danish National Birth Cohort) *(231)*	Denmark	1996	Mixed	66 387	–	Unspecified	Drink	≥4/day vs none	10	FFQ at 25 weeks of pregnancy. Intakes of artificially sweetened carbonated and uncarbonated drinks.
Zhu 2017 (DWH) *(228)*	Denmark	1996	Mixed	918	31 (mean)	Unspecified	Soft drink	≥1/day vs never	Up to 7	FFQ at ~25 weeks of pregnancy for intake over past month and for a subsample; also at 33–35 weeks of pregnancy

–: study did not provide data; ADI: acceptable daily intake; ASB: artificially sweetened beverage; FFQ: food frequency questionnaire; NSS: non-sugar sweeteners; SSB: sugar-sweetened beverage.

[1] Bassett et al. (2020) is the published version of Bassett et al. (2019) *(172)*, which is a preprint.

[2] Cohen et al. (2012) updates the results (i.e. reports on additional follow-up from baseline) of a previous report on hypertension in two of these cohorts: Winkelmayer et al. (2005) *(288)*.

[3] Drouin-Chartier et al. (2019) updates the results (i.e. reports on additional follow-up from baseline) of previous reports on type 2 diabetes in these cohorts: Schulze et al. (2004) *(289)*, de Koning et al. (2011) *(290)* and Bhupathiraju et al. (2013) *(291)*.

[4] Gardener et al. (2012) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Gardener et al. (2011) *(292)*.

[5] Study includes body mass index data from Russia, Poland and Czech Republic, but the data are only provided longitudinally for Russia.

[6] Pooling study not included in meta-analyses but reported narratively. Includes Atherosclerosis Risk in Communities Study (ARIC), Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study (ATBC), Health Professionals Follow-up Study (HPFS), Iowa Women's Health Study (IWHS), Women's Health Study (WHS) and Nurses' Health Study (NHS).

[7] Park et al. (2020) is a prospective cohort study assessing the same population assessed cross-sectionally in Ma et al. (2015) *(293)*.

[8] Rebholz et al. (2017) updates the results (i.e. reports on additional follow-up from baseline) of a previous report on chronic kidney disease in this cohort: Bomback et al. (2010) *(294)*.
[9] Smith et al. (2015) updates the results (i.e. reports on additional follow-up from baseline) of previous reports on body weight in these cohorts: Colditz et al. (1990) *(295)*, Schulze et al. (2004) *(289)*, Mozaffarian et al. (2011) *(296)* and Pan et al. (2013) *(297)*.
[10] A subsequent analysis of the dietary quality of the participants in this cohort was conducted but provided no new information on outcomes of interest: Stellman et al. (1988) *(298)*.
[11] A subsequent publication in 2020 *(250)* reported the same data but with less detail. Therefore, data from Azad et al. (2016) were retained in the systematic review.
[12] This study is a secondary cohort analysis of the GeliS ("healthy living in pregnancy") RCT, which was initiated in 2013 and completed in 2018.
[13] The Perined-Lifelines linked birth cohort was created by linking two existing databases: a large population-based cohort study (The Lifelines Cohort study, which enrolled participants beginning in 2006) and the Dutch national birth registry (Perined).

Table A3.3 Case–control studies reporting on cancer

STUDY	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON	DESCRIPTION
ADULTS									
Akdaş 1990 *(119)*	Turkey	1980	Mixed	388 (mixed)	24–80	Unspecified	Tabletop	User vs non-user	Interview asking about "use of artificial sweeteners".
Andreatta 2008 *(120)*	Argentina	1999	Mixed	594 (mixed)	–	Unspecified, saccharin/cyclamate, aspartame/ acesulfame K	Tabletop	Ever vs never	Dietary recall of habitual use of artificial sweeteners over past 5 years. Artificial sweeteners were classified into saccharin/cyclamate and aspartame/acesulfame K.
Asal 1988 *(121)*	United States	1981	Mixed	964 (mixed)	–	Unspecified	Tabletop	Ever vs never	Question on ever use of artificial sweeteners or sugar substitutes.
Bosetti 2009 *(122)*	Italy	1991	Mixed	3117 (mixed)	22–80	Unspecified, saccharin	Tabletop	User vs non-user	FFQ, usual diet 2 years before diagnosis, users vs non-users. FFQ included specific questions on weekly consumption of saccharin and other low-calorie sweeteners (mainly aspartame) expressed in sachets or tablets.
Bravo 1987 (123, 124)	Spain	1978	Mixed	812 (mixed)	<90	Unspecified, saccharin	Soft drink, tabletop, wine	User vs non-user	Users vs non-users of artificial sweetener (saccharin) and artificially sweetened beverages (wine and sodas)
Cabaniols 2011 *(125)*	France	2005	Mixed	244 (mixed)	20–86	Aspartame	Tabletop	≥1/week vs <1/week	FFQ over past 5 years, non-consumers (<1 per week) and regular consumers (≥1 per week) of aspartame sweetener.
Cartwright 1981 *(126)*	United Kingdom	–	Mixed	1901 (mixed)	–	Saccharin	Tabletop	User vs non-user	Questionnaire on saccharin use.
Chan 2009 *(127)*	United States	1995	Mixed	2233 (mixed)	21–85	Unspecified	Soft drink	≥1/day vs 0/ day	Sugar-free carbonated beverages included low-calorie colas, low-calorie caffeine-free colas, and other low-calorie carbonated beverages, such as Diet 7-Up, Fresca and diet ginger ale.
Connolly 1978 *(128)*	Canada	–	Mixed	1044 (mixed)	–	Unspecified	Tabletop	Ever vs never	Question: "Do or did you use artificial sweeteners?"

STUDY	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON	DESCRIPTION
Ewertz 1990 *(129)*	Denmark	1983	Mixed	2822 (female)	<70	Unspecified	Hot drink	User vs non-user	Semi-quantitative FFQ 1 year after diagnosis and 1 year before diagnosis. Artificial sweeteners in coffee or tea.
Gallus 2007 *(130)*	Italy	1991	Mixed	16 004 (mixed)	57–66 (median)	Undefined, saccharin	Tabletop	>2/day vs 0/day	FFQ about diet 2 years before diagnosis (cases) or before hospital admission (controls). FFQ included specific questions on weekly consumption of sugars (expressed in teaspoons/week), and saccharin and other sweeteners (expressed in sachets or tablets/week).
Gold 1985 *(131)*	United States	1977	Mixed	603 (mixed)	66–69 (mean)	Unspecified	Soft drink, tabletop	Ever vs never	FFQ on diet before onset of the illness with diet soda and artificial sweeteners.
Goodman 1986 *(132)*	United States	1977	Mixed	534 (mixed)	20–80	Unspecified, saccharin	Drink, tabletop	User vs non-user	User of saccharin or diet beverage was defined as consumer of 30 mg saccharin or 110 mL diet beverage per week for a period of 1 year of more.
Hardell 2001 *(133)*	Sweden	1994	Mixed	699 (mixed)	21–80	Aspartame	Drink	User vs non-user	Consumption of low-calorie drinks was asked about, including years of intake, times per day or week, and amount of drink each time, to assess the intake of aspartame.
Hoover 1980 *(134)*	United States	1977	Mixed	8793 (mixed)	21–84	Unspecified	Drink, food, tabletop	Ever vs never	Personal interview in home with detailed history of artificial sweetener use in 3 forms (tabletop sweetener, diet drinks and diet foods).
Howe 1977, 1980 (135, 136)	Canada	1974	Mixed	632 (mixed)	67–69 (mean)	Unspecified, saccharin	Drink, food, tabletop	Ever vs never	The following question was asked: "Do you now, or have you ever used sugar substitutes?" If yes, the number of tablets or drops usually used and the frequency and duration of using that brand were determined for each brand or type used. Other questions related to similar data for the use of diet drinks and for dietetic foods such as puddings, salad dressings and confectionery.
Iscovich 1978 *(299)*	Argentina	1983	Mixed	351 (mixed)	–	Saccharin	Unclear	User vs non-user	Interviewer-administered questionnaire, with saccharin.
Kessler 1976, 1978 (138, 139)	United States	1972	Mixed	1038 (mixed)	–	Unspecified, saccharin, cyclamate	Drink, food, tabletop	2/day vs 0/day	Intensive personal interview on use of NSS. Use of NSS was probed for table sweeteners, diet beverages, diet foods, and total intake in all forms. For each specific NSS-containing substance, information was obtained on the frequency, quantity and duration of use by type and brand. Excluded 1 year before cancer diagnosis.
Kobeissi 2013 *(140)*	Lebanon	2002	Mixed	159 (male)	≥50	Unspecified	Tabletop	Always vs never	Face-to-face interview on artificial sweetener consumption before diagnosis.

STUDY	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON	DESCRIPTION
Mahfouz 2014 *(141)*	Egypt	2010	Mixed	450 (mixed)	<20 to >60 (53% were 40–60)	Unspecified	Tabletop	User vs non-user	Questionnaire on dietary habits 2 years before cancer diagnosis. Artificial sweetener.
Mettlin 1989 *(142)*	United States	1982	Mixed	1138 (mixed)	35–90	Unspecified	Soft drink	≥2/day vs never	Questionnaire with diet cola intake: number of glasses, cups or drinks usually drunk each day.
Møller-Jensen 1983 *(143)*	Denmark	1979	Mixed	1175 (mixed)	–	Unspecified, saccharin, cyclamate	Drink, food, tabletop	≥15/day vs never, user vs never	Detailed history questionnaire on artificial sweeteners, which included information on regular use of artificial sweeteners in coffee, tea or foods for at least 3 months. If affirmative, further information was sought on the reasons for such use, age at starting and stopping regular use, commercial brand name, amount normally used, and regular use 1 year before interview.
Momas 1994 *(144)*	France	1987	Mixed	1085 (male)	≥50	Saccharin	Tabletop	≥365 in life vs <365 in life	Questionnaire. Intake of artificial sweeteners dealt with the use of saccharin as added to food/beverages only. Consumption of saccharin from other sources (food and drink) was not considered.
Mommsen 1983 *(145)*	Denmark	1977	Mixed	141 (female)	44–83	Saccharin	Unclear	User vs never	Questionnaire. Saccharin.
Morgan 1974 *(146)*	Canada	–	Mixed	464 (mixed)	–	Unspecified	Soft drink, food, tabletop	User vs non-user	Questionnaire with artificial sweetener intake. Users were defined by regular use for more than 1 year of diet desserts, sugar-free soft drinks or sugar substitutes.
Morrison 1979 *(147)*	Unclear (7 countries)	1969	Mixed	12 736 (mixed)	≥40	Unspecified	Drink, tabletop	User vs non-user	Exposure used was the one recorded at the first monitored hospital admission. Users used artificial sweeteners or diet drinks for more than 3 years.

STUDY	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON	DESCRIPTION
Morrison 1980 *(148)*	United States	1976	Mixed	1128 (mixed)	21–89	Unspecified	Drink, food, tabletop	Used vs never	Interview on exposure history. Subjects were asked "Have you ever consumed diet or low-calorie beverages – Tab Fresca, Diet Pepsi or artificially sweetened instant tea, lemonade, punch, or fruit juice, for instance?" Those who answered "yes" were asked the average frequency of consumption during the period of use, when use began, the time period of maximum frequency, what the maximum frequency had been, current frequency, and time of discontinuation of use, if applicable. Subjects were also asked whether they had "ever used substitutes for sugars or artificial sweeteners such as Sweet'N Low, Sucaryl, saccharin or cyclamates". Those who answered "yes" were asked when use began; the reason for use; whether they had ever used saccharin and when use of that substance began; current use; the usual brand used; the current amounts and frequencies used in coffee, tea and other beverages and foods; and, if no longer used, the time of discontinuation. All subjects were also asked current frequencies of use of "low-calorie, dietetic, or low-sugar brands of ice cream, cookies or candy, canned fruit, pudding or gelatin, jam or jelly, salad dressing or other diet or low-calorie foods". Subjects in Japan were only asked about sugar substitutes, not dietetic beverages and foods.
Morrison 1982 *(149)*	United Kingdom	1976	Mixed	1290 (mixed)	21–89	Unspecified	Drink, food, tabletop	Used vs never	Participants were asked if they consumed diet or low-calorie beverages (with examples), when use began, their average frequency of consumption during period of use, the period of maximum frequency, the current frequency and the time of discontinuation of use, if applicable. Participants were also asked if they consumed any sweetener other than sugar, when use began, whether used currently, usual brand, current amounts and frequencies of use, and time of discontinuation, if applicable. Participants were asked about the current frequency of use of low-calorie and low-sugar brands of various foods.
	Japan	1976	Mixed	882 (mixed)	21–89	Unspecified	Tabletop	User vs non-user	Participants were asked about their use of sugar substitutes added to beverages and foods.
Najem 1982 *(150)*	United States	1978	Mixed	217 (mixed)	67–71 (mean)	Unspecified, saccharin	Drink, tabletop	User vs non-user	Questionnaire on ingestion of coffee, cola beverages and saccharin.

STUDY	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON	DESCRIPTION
Nomura 1991 *(151)*	United States	1977	Mixed	783 (mixed)	30–93	Unspecified, saccharin	Soft drink, tabletop	6+ serving years, 3+ can years vs non-user	Diet history of usual week 1 year before diagnosis, included artificially sweetened beverages, such as diet or low-calorie sodas, and information on use and frequency of use of saccharin, cyclamates and other artificial sweeteners.
Norell 1986 *(152)*	Sweden	1982	Mixed	400 (mixed)	40–79	Unspecified	Tabletop	User vs non-user	Questionnaire on past exposures, including artificial sweeteners, before illness.
Ohno 1985 *(153)*	Japan	1976	Mixed	882 (mixed)	20–90	Unspecified	Tabletop	Ever vs never	Interview at home, including use of sugar substitute or artificial sweeteners.
Radosavljević 2001 *(154)*	Serbia	1997	Mixed	260 (mixed)	26–81	Unspecified	Tabletop	User vs non-user	Interview: asked when started, daily amount, kind, duration, and cessation of intake of tea and artificial sweeteners.
Risch 1988 *(155)*	Canada	1979	Mixed	1618 (mixed)	35–79	Unspecified, saccharin, cyclamate	Drink, food, tabletop	>4/day, >1/day, >3/day vs 0/day	History questionnaire, including regular consumption of tabletop artificial sweeteners, and low-calorie foods and drinks. Reported artificial sweeteners were classified by brand name and date of use as saccharin, cyclamate or both, to estimate average daily intake and cumulative lifetime consumption of these substances.
Silverman 1983 *(156)*	United States	1977	Mixed	1136 (mixed)	21–84	Unspecified	Drink, food, tabletop	Ever vs never	To elicit detailed information on consumption of artificial sweeteners, the questionnaire included items on use of tabletop sweeteners, diet drinks and diet foods.
Simon 1975 *(157)*	United States	1965	Mixed	525 (female)	63 (mean)	Saccharin, cyclamate	Hot drink	User vs non-user	Questionnaire, including questions on coffee additives, and type and strength of coffee and decaffeinated coffee. Use of cyclamate in coffee or tea.
Sullivan 1982 *(158)*	United States	1977	Mixed	251 (mixed)	21–85	Unspecified	Drink	Number of glasses/week	In-home interview, use of artificial sweeteners.
Wynder 1977 *(159)*	United States	1973	Mixed	315 (mixed)	40–80	Unspecified	Tabletop	≥15 years of use vs non-user	Interview. Considered only consumption of artificial sweeteners that had been on the market for several decades, not those, such as cyclamates, that were developed in the recent past.
Wynder 1980 *(160)*	United States	1977	Mixed	782 (mixed)	–	Saccharin	Drink, tabletop	Ever, ≥15 years of use vs never	Interview. Data on intake of coffee, tea and other beverages, including those containing artificial sweeteners.
Yu 1997 *(161)*	China	1987	Mixed	471 (mixed)	≥20	Saccharin	Tabletop	≥19/year vs 0/year	Questions on use of saccharin.
Zou 1990 *(162)*	China	1987	Mixed	240 (mixed)	22–78	Saccharin	Tabletop	≥20/year vs <1/year	Saccharin use in times/year and number of years.

STUDY	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON	DESCRIPTION
CHILDREN									
Bunin 2005 *(206)*	United States	1991	Mixed	630 (mixed)	<6	Unspecified	Soft drink	≥2/day vs <1/month	FFQ on diet during early pregnancy and mid-pregnancy, with diet soda.
PREGNANT WOMEN AND CHILDREN									
Gurney 1997 *(207)*	United States	1984	Mixed	150 (mixed)	0–19	Aspartame	Drink, tabletop	User vs non-user	Aspartame consumption during pregnancy and during childhood, before date of diagnosis, from biological mother. Questions were asked about the child's consumption of aspartame or NutraSweet, including age at first consumption, time period of consumption and frequency of consumption, for any food, chewing gum or diet drink. Questions were also asked about the mother's consumption of aspartame or NutraSweet, including trimesters of consumption, time period of consumption and frequency of consumption, for any food, chewing gum or diet drink during pregnancy or while breastfeeding. Subdivided into all sources and diet drinks.

–: study did not provide data; FFQ: food frequency questionnaire; NSS: non-sugar sweetener.

Table A3.4 Included nonrandomized controlled trials and cross-sectional studies

NONRANDOMIZED CONTROLLED TRIALS					
Appleton 2007 *(177)*	Hieronimus 2020 (83)[1]	Naismith 1995 (81)	Tordoff 1990 (82)	Wolraich 1994 (children) *(205)*	
CROSS-SECTIONAL STUDIES					
ADULTS					
Appleton 2001 *(179)*	Arrais 2019 (PNAUM) *(300)*	Barrett 2017 (Fenland Study) *(301)*	Bleich 2014 (NHANES) *(302)*	Bouchard 2010 (NHANES) *(303)*	Bragg 2013 *(304)*
Brunkwall 2019 (MDCS) *(305)*	Carroll 2016 (NDNS) *(306)*	Chen 1991 *(307)*	Crichton 2015 (MSLS and ORISCAV-LUX) *(308)*	de Castro 2009 *(309)*	den Biggelaar 2019 (Maastricht Study) *(310)*
Deshmukh-Taskar 2009 (Bogalusa Heart Study) *(311)*	Drewnowski 2016 (NHANES) *(312)*	Duran Aguero 2015 *(313)*	Fernandes 2013 *(314)*	Fitzgerald 2008 *(315)*	Geraldo 2013 *(316)*
Gomez Roig 2017 (pregnant women) *(317)*	Hartman 2017 (HHHF) *(318)*	Hedrick 2017 (Talking Health) *(319)*	Hess 2018 *(320)*	Hunt 2020 *(321)*	Kuk 2016 (NHANES) *(322)*
Leahy 2017 (NHANES) *(323)*	Mackenzie 2006 (NHANES) *(324)*	Mahar 2007 *(182)*	Malek 2018 (NHANES) *(325)*	Marques-Vidal 2017 (CoLaus study) *(326)*	Miller 2020 *(327)*
Mostad 2014 (HUNT) *(328)*	Nicolì 2021 (pregnant women) *(219)*	Perez 2021 (pregnant women) *(218)*	Pergrin Marriott 2016 (NHANES) *(178)*	Shoham 2008 (NHANES) *(329)*	Tamez 2018 (Mexican Teachers Cohort) *(330)*
Wensel 2019 (OPREVENT2) *(331)*	Winther 2017 *(332)*	Wulaningsih 2017 (NHANES) *(333)*	Yarmolinsky 2016 (ELSA-Brasil) *(334)*	Yoshida 2007 (FOS) *(335)*	Yu 2017 (Atlantic PATH) *(336)*
Yu 2018 (NHS) *(337)*					
CHILDREN					
Beck 2014 *(338)*	Berentzen 2015 (PIAMA) *(216)*	Duran Agüero 2014 *(339)*	Forshee 2003 (CSFII) *(340)*	Giammattei 2003 *(341)*	Hardy 2018 (NSW Schools Physical Activity and Nutrition Survey [SPANS]) *(212)*
Katzmarzyk 2016 (ISCOLE) *(342)*	Kim 2017 *(214)*	Laverty 2015 (MCS) *(343)*	Ledoux 2011 *(344)*	Mariscal-Arcas 2014 *(345)*	Milla Tobarra 2014 (Cuenca study) *(346)*
O'Connor 2006 (NHANES) *(347)*	Seferidi 2018 (NDNS) *(347)*	Serra Majem 1993 *(213)*	Skeie 2019 (Tromso Study) *(348)*	Souza 2016 *(349)*	Venegas Hargous 2020 (FEChiC) *(350)*
MIXED (ADULTS AND CHILDREN)					
Barraj 2019 (NHANES and WWEIA) *(351)*	French 2013 *(352)*	Grech 2018 (NNPAS) *(353)*	Jones 2019 (CCHS-Nut) *(354)*	Serra-Majem 1996 *(355)*	Silva Monteiro 2018 (Brazilian National Dietary Survey) *(356)*
Sylvetsky 2017 and 2019 (NHANES) (242, 357)					

[1] Hieronimus et al. (2020) is a more complete data set that was originally reported in Stanhope et al. (2015) *(254)* and Hieronimus et al. (2019) *(358)*.

ANNEX 4. Characteristics of ongoing/registered trials

STUDY	STATUS	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARATOR	DURATION	DESCRIPTION
ADULTS											
NCT02252952 *(359)*	Unknown	United States	2013	Mixed	99 (mixed)	20–50	Unspecified	Drink	Sugar, water	6 months	Provision of 2 × 355 mL/day beverages with sugars (any beverage from a range of caffeine-free, sugar-sweetened drinks), beverages with artificial sweetener (any beverage from a range of caffeine-free drinks sweetened with non-caloric sweetener) or water. Combined with a structured weight maintenance diet.
NCT02487537 (ILIAS-2) *(360)*	Completed	Germany	2015	Mixed	16 (male)	18–50	Unspecified	Soft drink	Unsweetened soft drink	4 weeks	Provision of 1 L/day custom-made sweetened soft drink (contains an amount of sweetener that is isosweet compared with 100 g of sucrose in 1 L of beverage) or unsweetened soft drink.
NCT02548767 *(361)*	Recruiting	United States	2016	Mixed	72 (mixed)	18–40	Aspartame	Drink	High-fructose corn syrup	8 weeks	Provision of 1) 0%, or 2) 25% of energy requirement as high-fructose corn syrup–sweetened beverages with an energy-balanced diet; or 3) 0%, or 4) 25% of energy requirement as high-fructose corn syrup–sweetened beverages with an ad libitum diet for 8 weeks. All diets, formulated to achieve a comparable macronutrient intake (55% energy as carbohydrate, 35% fat, 15% protein) among all 4 experimental arms, will be provided to the subjects throughout the entire study.
NCT02569762 *(362)*	Completed	Canada	2016	Normal	17 (mixed)	18–45	Sucralose, aspartame	Drink	–	1 week (4 weeks run-in and washout)	Provision of a mixed flavoured beverage sweetened with aspartame or sucralose.
NCT02580110 *(363)*	Completed	Sweden	2015	Mixed	39 (mixed)	40–70	Stevia, saccharin	Drink	Sucrose	2 weeks	Provision of a beverage (1000 mL/day) with 1) 66 g sucrose, 2) 0.220 g stevia glycosides, or 3) 0.216 g saccharin.
NCT02591134 (SWITCH) *(364)*	Suspended (in response to COVID-19)	United Kingdom	2016	Over-weight	432 (mixed)	18–65	Unspecified	Drink	Water	12 weeks	Participants will be provided with a list of permitted beverages (carbonated and still drinks) and are expected to consume at least 2 portions (2 × 330 mL/day), or will be instructed to consumed water.
NCT03032640 (ISTAR-micro) *(365)*	Active, not recruiting	United States	2017	Normal	90 (mixed)	18–45	Saccharin	Capsule	Placebo	2 weeks	Provision of capsules with 1) sodium saccharin (2 × 200 mg/day), 2) placebo (2 × 500 mg/day), 3) sodium saccharin and lactisole (2 × 200 mg/day and 2 × 335 mg/day), or 4) lactisole (2 × 335 mg/day).

STUDY	STATUS	COUNTRY	STUDY START (YEAR)	WEIGHT STATUS	NUMBER OF PARTICIPANTS	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARATOR	DURATION	DESCRIPTION
NCT03259685 *(366)*	Recruiting	Canada	2017	Over-weight	66 (mixed)	18–55	Aspartame + acesulfame K/stevia	Soft drink	Sugar	10 weeks	Provision of soft drinks (710 mL/day): 1) regular soft drinks (with sugar), 2) diet soft drinks (with aspartame and acesulfame K), 3) stevia-sweetened soft drinks (with steviol glycosides).
NCT03407079 (SweetMeds Study) *(367)*	Recruiting	United States	2018	Over-weight	150 (female)	18–60	Sucralose	Capsule	Placebo	4 weeks	Provision of capsules with 1) sucralose (approximately 4 mg/kg/day) or 2) placebo. Primary aim was to investigate the effect of sucralose on drug metabolism of digoxin and midazolam.
NCT03543644 (STOP Sugars NOW trial) *(368)*	Active, not recruiting	Canada	2018	Over-weight	81 (mixed)	18–75	Unspecified	Soft drink	Sugar, water	4 weeks	Participants will 1) keep their regular intake of sugar-sweetened beverages, 2) replace with non-nutritive sweetened beverage, or 3) replace with water.
NCT03708939 *(369)*	Recruiting	Israel	2017	Mixed	200 (mixed)	18–70	Aspartame, sucralose, saccharin, stevia	Table-top	Glucose	2 weeks	Consumption of glucose, sucralose, aspartame, stevia or saccharin (4 mg/day of artificial sweetener).
NCT04016337 (BEBESANO) *(370)*	Completed	Spain	2017	Over-weight	138 (mixed)	35–55	Sucralose, stevia	Drink	Saccharose	2 months	Provision of drink (330 mL/day) made with lemon and maqui, and sweetened with saccharose, sucralose or stevia.
NCT04182464 *(371)*	Recruiting	Mexico	2019	Normal	24 (mixed)	20–45	Sucralose	Capsule	Placebo (corn starch)	1 month	Provision of capsules with 1) sucralose (3 × 90 mg/day), or 2) placebo – corn starch (3 × 90 mg/day). Instruction to consume the capsule with each meal (3/day).
NCT04904133 *(372)*	Completed	Turkey	2017	Mixed	42 (female)	19–45	Aspartame + acesulfame K, saccharin, sucralose	Drink	Water	2 weeks	Provision of water (330 mL/day) sweetened with 1) saccharin (140 mg), 2) sucralose (66 mg), 3) aspartame + acesulfame K (88 mg), or 4) nothing (control).
CHILDREN											
NCT02499705 *(373)*	Terminated (prematurely unblinded based on outcome in other trial; adverse event was reported)	United States	2014	Mixed	15 (mixed)	13–17	Sucralose	Drink	Sucrose	2 weeks	Provision of equisweet flavoured beverages with sucralose (2 packets), sucrose, or Splenda and maltodextrin.

NSS: non-sugar sweeteners.
Note: In addition, two ongoing nonrandomized controlled trials were identified: Huber T et al. *(374)* and Steffen et al. *(375)*.

ANNEX 5. Adjustments for potential confounders in cohort studies

Table A5.1 Key adjustments in prospective cohort studies in adults

	Age	Sex	Alcohol	Smoking	BMI	Other fat	Disease risk	Total energy	Sugars/SSBs	Other diet
Anderson 2020	◆	◆	◆	◆	◆			◆	◆	◆
Angeles Perez-Ara 2020		◆	◆	◆	◆		◆			
Bao 2008		◆	◆	◆	◆			◆	◆	◆
Bassett 2019		◆	◆	◆					◆	◆
Bernstein 2012			◆	◆					◆	◆
Bes-Rastrollo 2006	◆	◆	◆	◆				◆	◆	◆
Chazelas 2019	◆	◆	◆	◆	◆		◆	◆		
Chazelas 2020	◆	◆	◆	◆	◆		◆	◆	◆	◆
Chia 2016	◆	◆		◆						◆
Chia 2018	◆	◆		◆	◆					
Cohen 2012	◆		◆	◆	◆	◆	◆	◆	◆	◆
de Koning 2012	◆		◆	◆	◆		◆	◆		◆
Drouin-Chartier 2019	◆		◆	◆	◆		◆	◆	◆	◆
Duffey 2012	◆	◆		◆	◆					◆
Fagherazzi 2013				◆	◆		◆	◆		◆
Fagherazzi 2017				◆	◆		◆		◆	◆
Farvid 2021	◆		◆	◆	◆			◆		
Ferreira-Pego 2016	◆	◆		◆	◆		◆	◆		◆
Fowler 2008	◆			◆	◆					
Fowler 2015	◆	◆		◆	◆		◆			
Fung 2009	◆		◆	◆			◆			◆
Gardener 2012	◆	◆	◆	◆	◆		◆	◆	◆	◆
Gardener 2018	◆	◆	◆	◆	◆		◆	◆		◆
Garduno-Alanis 2020	◆	◆	◆	◆	◆		◆	◆		◆
Guo 2014	◆	◆		◆	◆			◆		
Haslam 2020	◆	◆	◆	◆			◆	◆	◆	◆
Hirahatake 2019				◆		◆		◆		
Hodge 2018			◆	◆				◆	◆	◆
Huang 2017	◆		◆	◆	◆	◆		◆	◆	
Hur 2021	◆		◆	◆	◆		◆	◆		◆
InterAct Consortium 2013		◆	◆	◆					◆	
Jensen 2020	◆	◆		◆	◆			◆	◆	◆
Keller 2020			◆	◆	◆		◆	◆	◆	◆
Lana 2015	◆	◆	◆		◆		◆	◆		◆
Lim 2006	◆	◆			◆		◆			
Lin 2011	◆			◆	◆		◆	◆		
Ma 2016	◆	◆	◆	◆		◆		◆	◆	◆
Malik 2019	◆		◆	◆	◆		◆	◆	◆	◆
McCullough 2014	◆			◆	◆		◆	◆	◆	
Mossavar-Rahmani 2019	◆		◆	◆	◆		◆			◆
Mullee 2019		◆	◆	◆	◆			◆		◆
Munoz-Garcia 2019	◆	◆		◆	◆		◆	◆		◆
Nettleton 2009	◆	◆		◆	◆	◆		◆		
O'Connor 2015	◆	◆	◆	◆	◆	◆	◆			
Paganini-Hill 2007	◆	◆	◆	◆	◆		◆			
Palmer 2008	◆			◆	◆		◆		◆	◆
Parker 1997	◆			◆	◆			◆		
Pase 2017	◆	◆				◆	◆	◆		
Rebholz 2017	◆	◆		◆	◆		◆	◆	◆	◆
Romanos-Nanclares 2021	◆		◆		◆		◆	◆		
Sakurai 2014	◆		◆	◆	◆		◆	◆	◆	◆
Schernhammer 2005	◆			◆			◆	◆	◆	
Schernhammer 2012	◆		◆	◆	◆			◆	◆	◆
Schulze 2004	◆		◆	◆	◆					◆
Smith 2015	◆		◆	◆	◆					◆
Stellman 1986	◆	◆	◆	◆			◆			
Stepien 2016	◆	◆	◆	◆	◆		◆			
Stern 2017	◆		◆	◆				◆	◆	◆
Tucker 2015	◆					◆				
Vyas 2015	◆		◆	◆	◆		◆	◆	◆	◆
Wang 2019	◆		◆	◆	◆		◆			◆
Zhang 2021	◆	◆	◆	◆	◆		◆	◆	◆	◆

BMI: body mass index; Other fat: measures of adiposity other than BMI; Other diet: components of diet other than energy or sugars; SSBs: sugar-sweetened beverage
Note: Some studies included single sex cohorts, and therefore adjusting for sex was not possible.

Table A5.2 Complete list of adjustments in all prospective cohort studies

STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
ADULTS	
Anderson 2020	Sociodemographic factors (age, sex, ethnic group); economic and lifestyle factors (income, qualifications, total physical activity, sedentary behaviour, smoking status, alcohol); BMI and total energy intake; potential dietary confounders (red meat, processed meat, fruit, vegetables, total fat, total fibre, total sugars intake (total sugars was not used when total sugars intake was the exposure of interest).
Angeles Pérez-Ara 2020	Study site; gender; sex; marital status; educational level; BMI; MoodFood diet score; smoking; alcohol use; physical activity; high blood pressure; diabetes; stomach or intestinal ulcer.
Bao 2008	Sex; race; education; BMI; alcohol; smoking; physical activity; energy-adjusted red meat consumption; energy-adjusted folate consumption; total energy intake; SSB intake.
Bassett 2020	Alcohol intake; country of birth; Mediterranean diet score; physical activity (frequency and intensity); socioeconomic position; sex; smoking status; sugar-sweetened soft drink consumption.
Bernstein 2012	Intakes of red meat, poultry, fish, nuts, whole- and low-fat dairy products, and fruit and vegetables; cereal fibre; alcohol intake; trans fat intake; cigarette smoking; parental history of early myocardial infarction (before age 60 years); multivitamin use; aspirin use at least once per week; vitamin E supplement use; menopausal status in women; physical exercise; sugar-sweetened sodas.
Bes-Rastrollo 2006	Age; sex; total energy intake from non-sugar-sweetened soft drink sources; fibre intake; alcohol intake; milk consumption; leisure-time physical activity; smoking status; snacking; television watching; baseline weight.
Chazelas 2019	Age; sex; energy intake without alcohol; sugars intake from other dietary sources (all sources except sugary drinks); alcohol, sodium, lipid, and fruit and vegetable intakes; BMI; height; physical activity; smoking status; number of 24-hour dietary records; family history of cancer; educational level; the following prevalent conditions at baseline: type 2 diabetes, hypertension, major cardiovascular event (myocardial infarction or stroke), and dyslipidaemia (triglycerides or cholesterol, or both). For breast cancer: in addition to above, adjusted for the number of biological children, menopausal status at baseline, hormonal treatment for menopause at baseline and during follow-up, and oral contraception use at baseline and during follow-up.
Chazelas 2020	Age; sex; BMI; sugars intake from other dietary sources; number of 24-hour dietary records; smoking status; educational level; physical activity; family history of cardiovascular disease; intakes of alcohol, energy, fruit and vegetables, red and processed meat, nuts, whole grains, legumes, saturated fatty acids, and sodium; proportion of ultraprocessed food in the diet (NOVA classification); presence of type 2 diabetes, dyslipidaemia, hypertension, hypertriglyceridemia, and treatments for these conditions (ASB and sugary drink models were mutually adjusted).
Chia 2016	Year of visit; age; sex; age by sex interaction; race; current smoking status; dietary intake (caffeine, fructose, protein, carbohydrate, fat); physical activity; diabetes status; DASH score.
Chia 2018	Age; sex; race and lifestyle factors including physical activity (frequency and duration); smoking status; BMI; year of recruitment; year of study visit; number of years from dietary assessment to oral glucose tolerance test assessment.
Cohen 2012	Age; race; family history of hypertension; physical activity; calcium, magnesium and vitamin D intake; cereal fibre and trans fat intake; carbohydrate consumption; DASH-style diet; total fructose consumption; daily calories; alcohol; whether or not they were trying to lose weight; smoking status; oral contraceptive use (in female cohorts); non-narcotic analgesic use; BMI, BMI^2 and weight change between surveys; SSB intake.
de Koning 2012	Age; smoking; physical activity; alcohol intake; multivitamin use; family history of coronary heart disease; pre-enrolment weight change; low-calorie diet; diet quality (Alternative Healthy Eating Index); total energy intake; BMI; previous type 2 diabetes; high triglycerides; high cholesterol; high blood pressure.
Drouin-Chartier 2019	Age; race; family history of diabetes; physical examination during the 4-year cycle; menopausal status and postmenopausal hormone use; oral contraceptive use; smoking status; initial and change in physical activity level; initial and change in alcohol consumption; initial BMI; initial calorie intake; initial and change in Alternative Healthy Eating Index score (calculated without the alcohol and sugary beverage components); initial and change in intakes of water, coffee, tea and milk; initial intakes of sugary beverages, or SSBs and fruit juices, and ASBs; changes in intake of ASBs, fruit juices, SSBs or sugary beverages.

STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
Duffey 2012	Race; sex; study centre; baseline age; BMI; smoking status; family structure; total energy intake; physical activity; maximum education reported during the study; either diet beverage consumption (in dietary pattern model) or dietary pattern (in diet beverage consumption model).
Fagherazzi 2013	Years of education; smoking status; physical activity; hypertension; hypercholesterolaemia; use of hormone replacement therapy; family history of diabetes; self-reported use of antidiabetic drugs; alcohol intake; omega-3 fatty acid intake; carbohydrate intake; coffee intake; fruit and vegetables, and processed meat consumption; dietary pattern (Western or Mediterranean); total energy intake (excluding energy from alcohol and carbohydrates); BMI.
Fagherazzi 2017	Alcohol consumption; carbohydrate intake; energy intake from protein and lipids; level of education; smoking status; hypertension; hypercholesterolaemia; family history of diabetes; physical activity; BMI.
Farvid 2021	Age at diagnosis; calendar year of diagnosis; time between diagnosis and first food frequency questionnaire; calendar year at start of follow-up of each 2-year questionnaire cycle; prediagnostic BMI; BMI change after diagnosis; postdiagnostic smoking; postdiagnostic physical activity; oral contraceptive use; postdiagnostic alcohol consumption; postdiagnostic total energy intake; prediagnostic menopausal status, age at menopause and postmenopausal hormone use status; postdiagnostic aspirin use; race; stage of disease; estrogen receptor/progesterone receptor (ER/PR) status; radiotherapy; chemotherapy; hormonal treatment.
Ferreira-Pego 2016	Intervention group; age; sex; leisure time physical activity; BMI; smoking status; cumulative average consumption of dietary variables (vegetables, legumes, fruit, cereals, meat, fish, bakery, dairy products, olive oil, nuts); cumulative total energy intake; alcohol and alcohol squared; MetS components at baseline.
Fowler 2008	Gender; ethnicity; baseline age, education, socioeconomic index, BMI, exercise frequency and smoking status; interim change in exercise level; smoking cessation.
Fowler 2015	Sex; age; ethnicity; education; neighbourhood; beginning BMI; leisure physical activity level; diabetes; smoking status; length of interval.
Fung 2009	Age; smoking; alcohol intake; family history of disease; physical activity; aspirin use; menopausal status and postmenopausal hormone use; history of hypertension and high blood cholesterol; diet quality (Alternative Healthy Eating Index).
Gardener 2012	Demographics (age, sex, race/ethnicity, education); behavioural risk factors (smoking, moderate alcohol use, moderate to heavy physical activity); daily diet (total calories, grams of protein, grams of total fat, grams of saturated fat, grams of carbohydrates, mg of sodium); BMI; daily diet; vascular risk factors (previous cardiac disease, peripheral vascular disease, history of diabetes, history of hypercholesterolaemia, history of hypertension, metabolic syndrome); waist circumference; blood sugar; HDL cholesterol, LDL cholesterol and triglycerides; mutually adjusted for each type of soft drink.
Gardener 2018	Age; sex; race/ethnicity; Mediterranean diet; total calories; smoking; physical activity; moderate alcohol use; BMI; hypertension; hypercholesterolaemia.
Garduno-Alanis 2020	Age; sex; education; marital status; smoking, alcohol consumption; physical activity; energy consumption; fruit and vegetable consumption; cardiovascular disease, cancer or diabetes in medical history.
Guo 2014	Age at baseline; sex; race; education level; marital status; smoking status; consumption of beer, liquor and wine; physical activity (frequency); BMI; energy intake.
Haslam 2020	Age; sex; total energy; education; current smoking status; current diabetes mellitus status; physical activity index; alcohol; waist circumference; servings/day of vegetables, whole fruits, whole grains, nuts/seeds and seafood; percentage energy from saturated fat; mutual adjustment for SSBs, low-calorie sweetened beverages and fruit juices.
Hirahatake 2019	Study centre; education; smoking; dieting behaviour; cumulative average energy intake; cumulative average physical activity; cumulative average Mediterranean diet score; baseline BMI; weight changes from baseline to diabetes diagnosis; censoring or end of follow-up (whichever came first) as a potential mediator; SSB intake.
Hodge 2018	SEIFA (Socio-Economic Indexes for Area); country of birth; alcohol intake; smoking status; physical activity; Mediterranean diet score; sugar-sweetened soft drink consumption; waist circumference.
Huang 2017	Age; race; marital status; family income; education; family history of diabetes; BMI; change in BMI; waist-to-hip ratio; systolic blood pressure; health insurance status; antihypertensive use; antihyperlipidemic use; hormone replacement therapy use; calibrated energy intake; SSB consumption; glycaemic load based on available carbohydrates; glycaemic index based on available carbohydrates; Alternative Healthy Eating Index; cardiovascular history; hysterectomy history; smoking status; physical activity; sitting time; alcohol consumption.

STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
Hur 2021	Age; energy intake; race; height; BMI; menopausal status and menopausal hormone; family history of colorectal cancer; pack years of smoking; physical activity; regular use of aspirin; regular use of nonsteroidal anti-inflammatory drugs; current use of multivitamins; intake of alcohol, red and processed meat, dietary fibre, total folate (from foods and supplements) and total calcium; Alternative Healthy Eating Index 2010 score without SSBs and alcohol; lower endoscopy due to screening or for other indications within the past 10 years.
InterAct Consortium 2013	Sex; educational level; physical activity; smoking status; alcohol consumption; consumption of sugar-sweetened soft drinks; consumption of juice.
Jensen 2020	Age; sex; study site; BMI; education; steps per day; smoking; self-reported quality of life; total calories consumed per day; percentage of total calories from saturated fat; fruit and vegetable servings per day; processed meat servings per day; total fibre consumed per day; SSB consumption.
Keller 2020	SSB intake; smoking; physical activity; education; alcohol; diet (cereal fibres, trans fat, polyunsaturated fat/saturated fat ratio); total energy; BMI; baseline hypertension; high cholesterol.
Lana 2015	Age; sex; educational level; current smoker; sleep; living alone; energy intake; coffee consumption; Mediterranean diet score; alcohol consumption; current dieting; weight loss of 45 kg in the past 4 years; leisure physical activity; BMI; hypertension; diabetes; hypercholesterolaemia; self-reported disease (cardiovascular disease, cancer, asthma or chronic bronchitis, sleep apnoea, peptic ulcer, cholelithiasis, cirrhosis, osteoarthritis, hip fracture, eye cataract, periodontal disease).
Lim 2006	Age at study entry; sex; ethnicity; BMI; history of diabetes.
Lin 2011	Age; caloric intake; hypertension; BMI; diabetes; cigarette smoking; physical activity; cardiovascular disease.
Ma 2016	Baseline outcome values; sex; age; smoking status; physical activity score; energy intake; alcohol intake; saturated fat intake; SSB intake; multivitamin use; intake of whole grains, fruits, vegetables, coffee, nuts and fish; change in body weight.
Malik 2019	Age; smoking; alcohol intake; postmenopausal hormone use (for Nurses' Health Study cohort); physical activity; family history of diabetes; family history of myocardial infarction; family history of cancer; multivitamin use; ethnicity; aspirin use; baseline history of hypertension and hypercholesterolaemia; intake of whole grains, fruit, vegetables, and red and processed meat; total energy; BMI; SSB intake.
McCullough 2014	Age at baseline; gender; history of diabetes; BMI; smoking status; energy intake; SSB intake.
Mossavar-Rahmani 2019	Age; race; education; diabetes mellitus; cardiovascular diseases; high cholesterol requiring medication; hypertension (defined as blood pressure ≥140/90 mmHg); BMI; smoking; alcohol; Healthy Eating Index; MET.
Mullee 2019	BMI; physical activity index; educational status; alcohol consumption; smoking status and intensity; smoking duration; ever use of contraceptive pill; menopausal status; ever use of menopausal hormone therapy; intakes of total energy, red and processed meat, fruits and vegetables, coffee, and fruit and vegetable juice; stratified by age, EPIC center and sex.
Muñoz-Garcia 2019	Sex; age at baseline; STICS-m (Spanish version of the modified Telephone Interview of Cognitive Status); Apolipoprotein E 4; years of university education; follow-up time until baseline STICS-m score; hypertension; HDL and total cholesterol; BMI; smoking; cardiovascular diseases; prevalent diabetes; physical activity; Mediterranean diet adherence score; total energy intake.
Nettleton 2009	Study site; age; sex; race/ethnicity; energy intake; education; physical activity; smoking status; pack-years; weekly or more supplement use; waist circumference; BMI.
O'Connor 2015	Age; sex; social class; education level; family history of diabetes; physical activity level; smoking status; alcohol consumption; season; intake of other sweet beverages; total energy intake; BMI; waist circumference.
Paganini-Hill 2007	Age; sex; smoking; exercise; BMI; alcohol intake; history of hypertension, angina, heart attack, stroke, diabetes, rheumatoid arthritis and cancer.
Palmer 2008	Age; questionnaire cycle; education; physical activity; smoking status; family history of diabetes; intake of red meat, processed meat, cereal fibre and coffee; glycaemic index; intake of SSBs and juice.
Parker 1997	Age; smoking status; BMI; aerobic activity; total energy intake.

STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
Pase 2017	Age; sex; total caloric intake; systolic blood pressure; treatment of hypertension; prevalent cardiovascular disease; atrial fibrillation; left ventricular hypertrophy; total cholesterol; HDL cholesterol; prevalent diabetes mellitus; waist-to-hip ratio.
Rebholz 2017	Age; sex; race; education level; smoking status; physical activity; total caloric intake; baseline estimated glomerular filtration rate; BMI; diabetes; systolic blood pressure; serum uric acid; diet quality (modified Alternative Healthy Eating Index 2010); dietary sodium; dietary fructose; frequency of consumption of sugar-sweetened beverages.
Romanos-Nanclares 2021	Age; SSB or NSS-sweetened beverage intake; race; age at menarche; age at menopause; postmenopausal hormone use; history of oral contraceptive use; parity and age at first birth; breastfeeding history; family history of breast cancer; history of benign breast disease; height; cumulatively updated alcohol intake; cumulatively updated total caloric intake; physical activity; BMI at age 18 years; modified Alternative Healthy Eating Index score (with SSBs and alcohol removed); socioeconomic status; change in weight since age 18 years.
Sakurai 2014	Age; BMI; family history of diabetes; smoking; alcohol drinking; habitual exercise; presence of hypertension; presence of dyslipidaemia; receiving diet treatment for chronic disease; total energy intake; total fibre intake; consumption of SSB; fruit juice consumption; vegetable juice consumption; coffee consumption.
Schernhammer 2005	Age; gender; follow-up cycle; history of diabetes; smoking status; caloric intake; nonvigorous physical activity; SSB intake.
Schernhammer 2012	Age; questionnaire cycle; sugar-sweetened soda consumption; fruit and vegetable consumption; multivitamin use; intakes of alcohol, saturated fat, animal protein and total energy; race; BMI; height; discretionary physical activity; smoking history; menopausal status and use of hormone replacement therapy (women only).
Schulze 2004	Age; alcohol intake; physical activity; smoking, postmenopausal hormone use; oral contraceptive use; cereal fibre intake; total fat intake; BMI; baseline energy intake from non-soda sources and changes over time; baseline intake of red meat, French fries, processed meat, sweets, snacks, vegetables and fruits; and changes in confounders over time.
Smith 2015	Age; BMI at the beginning of each 4-year period; sleep duration; prevalent levels of and changes in (specific to the analysis) physical activity, alcohol use, amount of time spent watching television, smoking, and all dietary components simultaneously.
Stellman 1986	Not adjusted per se, but rather participants selected to have equivalent sex; age; socioeconomic status; cigarette smoking; and no history of diabetes, heart disease or cancer – conditions that may affect both weight and dietary behaviour (including artificial sweetener use).
Stepien 2016	Non-alcoholic energy intake; BMI; sex-specific physical activity; education level; alcohol intake at recruitment and alcohol intake pattern; smoking intensity, duration and history; diabetes status; stratified by age, sex and study centre
Stern 2017	Baseline sugar-sweetened soda consumption; age; state; 2006 and 2008 physical activity; baseline smoking status; alcohol consumption; oral contraceptive use; menopausal status; postmenopausal hormone therapy use; changes in smoking status, alcohol consumption and consumption of red meat, dairy, yoghurt, fruit, vegetables, nuts, white bread, flour tortillas, corn tortillas, orange or grapefruit juice, and homemade sweetened beverages.
Tucker 2015	Age; menopausal status; baseline body weight; physical activity.
Vyas 2015	Age; race; education and income; smoking status; BMI; history of diabetes, hypertension or hyperlipidaemia; alcohol intake; log calibrated energy intake; physical activity; SSB intake; salt intake; hormone therapy.
Wang 2019	Age at the carotid scan; race/ethnicity; education level; financial strain; self-rated overall health; BMI; smoking status; nonoccupational physical activity level; menopausal status; use of hormone therapy from baseline to the visit of the carotid scan; number of missing visits for dietary measurements; total energy intake; Alternative Healthy Eating Index; intake of tea; intake of alcoholic beverages; intake of beverage condiments; elevated blood pressure; elevated fasting glucose; elevated triglycerides; reduced HDL cholesterol.
Zhang 2021	Age; sex; family income-poverty ratio level; race; education level; marital status; alcohol consumption; smoking; leisure-time physical activity; BMI; prevalent high cholesterol level; hypertension; diabetes; history of cardiovascular disease and cancer; 2015 healthy eating index score; total energy intake; simultaneously included intakes of SSBs and ASBs.

STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
CHILDREN	
Berkey 2004 (GUTS)	Sex; age; Tanner stage of development; race; menarche (girls) ; prior BMI z-score; height growth; milk type; physical activity; inactivity; intake of SSB and other beverages.
Blum 2005	Unclear.
Davis 2018 (SOLAR)	Sex; Tanner stage of development at baseline and 1-year follow-up; energy intake; BMI z-score.
Field 2014 (GUTS II)	Age; time between assessments; BMI at start of the period; Tanner stage of development; hours per day of television viewing; hours per week of vigorous activity.
Haines 2012 (EAT)	Age cohort; socioeconomic status; race/ethnicity.
Kral 2008	Change in BMI z-score or waist circumference at ages 3–5 years; total energy intake from food at age 3 years.
Laska 2012 (IDEA, ECHO)	Physical activity; stage of puberty; race; parental education; eligibility for free/reduced-price lunch; age; study; total energy intake.
Ludwig 2001	Baseline anthropometrics (BMI and triceps-skinfold thickness); demographics (age, sex, ethnicity); indicator variables for schools (the largest as the omitted category); diet (percentage energy from fat at baseline, energy-adjusted fruit juice intake at baseline, change in these variables from baseline to follow-up); physical activity; time spent watching television and videos; change in time spent watching television and videos; total energy intake.
Macintyre 2018 (GUS)	Unclear.
Marshall 2003 (IFS)	Age at dental examination; sex; fluoride exposure; dietary variables significant at $P < 0.10$ in univariate analysis.
Newby 2004 (North Dakota WIC Program for Children)	Age; sex; energy; sociodemographic variables; ethnicity; residence; level of poverty; maternal education; birthweight.
Striegel-Moore 2006 (NGHS)	Consumption of other types of beverages; site; visit; race; total caloric intake (in all models except that with caloric intake as the dependent variable).
Vanselow 2009 (EAT)	Age; sex; race/ethnicity; socioeconomic status; baseline BMI; baseline of same beverage; all baseline beverages; baseline and time strenuous physical activity; time weekday television watching; coffee and tea consumption.
Zheng 2015a (CAPS)	Age; gender; BMI z-score at age 8 years; Socioeconomic Index for Area scores; maternal age at birth; parental education level; parental countries of birth; maternal age at birth; presence of gestational diabetes; breastfeeding characteristics; pubertal status; study randomization group; total energy intake.
Zheng 2015b (Healthy Start Study)	Age; BMI z-score; sex; intervention allocation; physical activity; whether parents were divorced; number of siblings living with the child; annual income; maternal education level; paternal education level; maternal pre-pregnancy overweight; beverage intake residuals with adjustment for total energy intake; energy intake from non-beverage sources.
Zheng 2019 (Raine)	Baseline BMI; waist circumference; overweight or obesity; intakes of water, tea/coffee, diet drink, 100% fruit juice and milk; age; gender; dietary misreporting; physical activity; maternal education; family income; healthy dietary pattern; western dietary pattern scores at age 4 years; total energy intake.
PREGNANT WOMEN	
Azad 2016 (CHILD)	Maternal total energy intake; Healthy Eating Index score; maternal postsecondary education; maternal smoking and diabetes during pregnancy; breastfeeding duration; infant sex; introduction of solid foods before 4 months; SSB intake.
Chen 2009 (NHS II)	Age; parity; race/ethnicity; cigarette smoking status; family history of diabetes in a first-degree relative; alcohol intake; physical activity; BMI; western dietary pattern score.
Cohen 2018 (Project Viva)	Maternal age; pre-pregnancy BMI; parity; college graduate; fish intake (average of first and second trimesters); smoking during pregnancy; household income at enrolment; corresponding intake during pregnancy (i.e. sucrose, fructose, SSBs, fruit juice, diet soda); child sex, race/ethnicity, and birthweight for gestational age z-score.
Dale 2019 (MoBa)	Year of birth; smoking before pregnancy; mother's age; education; parity; diabetes mellitus; pre-pregnancy BMI.
Englund-Ogge 2012 (MoBa)	Preterm delivery; maternal age; pre-pregnancy BMI; height; total energy intake; marital status; parity; smoking during pregnancy; education; SSB intake.
Gillman 2017 (Project Viva)	Maternal age; race/ethnicity; education; smoking; parity; prepregnancy BMI; household income; child age and sex; child beverage intake.
Gunther 2019 (GeliS)	Pre-pregnancy BMI; age; parity; group assignment.

STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
Halldorsson 2010 (Danish National Birth Cohort)	Maternal age; height; pre-pregnancy BMI; total energy intake; cohabitant status; parity; smoking during pregnancy; familial socio-occupational status.
Hinkle 2019 (DWH)	Current age; pre-pregnancy BMI at the index pregnancy; primiparous; smoking; moderate or vigorous physical activity; pre-pregnancy chronic diseases; Alternative Healthy Eating Index; coffee intake; tea intake.
Hrolfsdottir 2019 (PREWICE)	Maternal pre-pregnancy BMI; age; parity; smoking during pregnancy; educational level; total gestational length; offspring sex.
Maslova 2013 (Danish National Birth Cohort)	Maternal age; smoking; parity; prepregnancy BMI; physical activity; breastfeeding; socioeconomic position; child sex; maternal history of asthma; maternal history of allergies; paternal history of asthma; paternal history of allergies; energy intake.
Munda 2019	Paternal height; employment status; glycated haemoglobin (HbA1c).
Petherick 2014 (BiB)	Maternal age; booking BMI; height; marital status; parity; smoking; education; ethnicity; SSB intake.
Renault 2015 (TOP study)	Energy intake; maternal age; smoking during pregnancy; parity; pre-pregnancy BMI; intervention group.
Salavati 2020	Energy intake; maternal BMI; maternal age; smoking; alcohol; education level; urbanization level; parity; sex of newborn; ethnicity; intake of other 21 food groups.
Schmidt 2020	Maternal age; region of residence; maternal energy intake; calendar year of pregnancy onset; birth order; maternal pre-pregnancy diabetes; BMI; smoking; alcohol consumption; physical activity; socioeconomic position; gestational diabetes in previous pregnancy.
Zhu 2017 (DWH)	Maternal: pre-pregnancy BMI; age; socioeconomic status; smoking during pregnancy; intakes of total energy, desserts and sweets, oil/margarine/butter, potato, processed meat, refined grains, whole grains and SSBs during pregnancy; physical activity during pregnancy. Offspring: sex, breastfeeding duration, consumption of artificially and sugar-sweetened beverages at 7 years (only for outcomes at 7 years), physical activity at 7 years (only for outcomes at 7 years).

ASB: artificially-sweetened beverage; BMI: body mass index; DASH: Dietary Approaches to Stop Hypertension; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MET: metabolic equivalent of task (the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest); MetS: metabolic syndrome; SSB: sugar-sweetened beverage.

ANNEX 6.

Risk of bias assessment

Figure A6.1. Risk of bias in randomized controlled trials (Cochrane risk of bias tool)

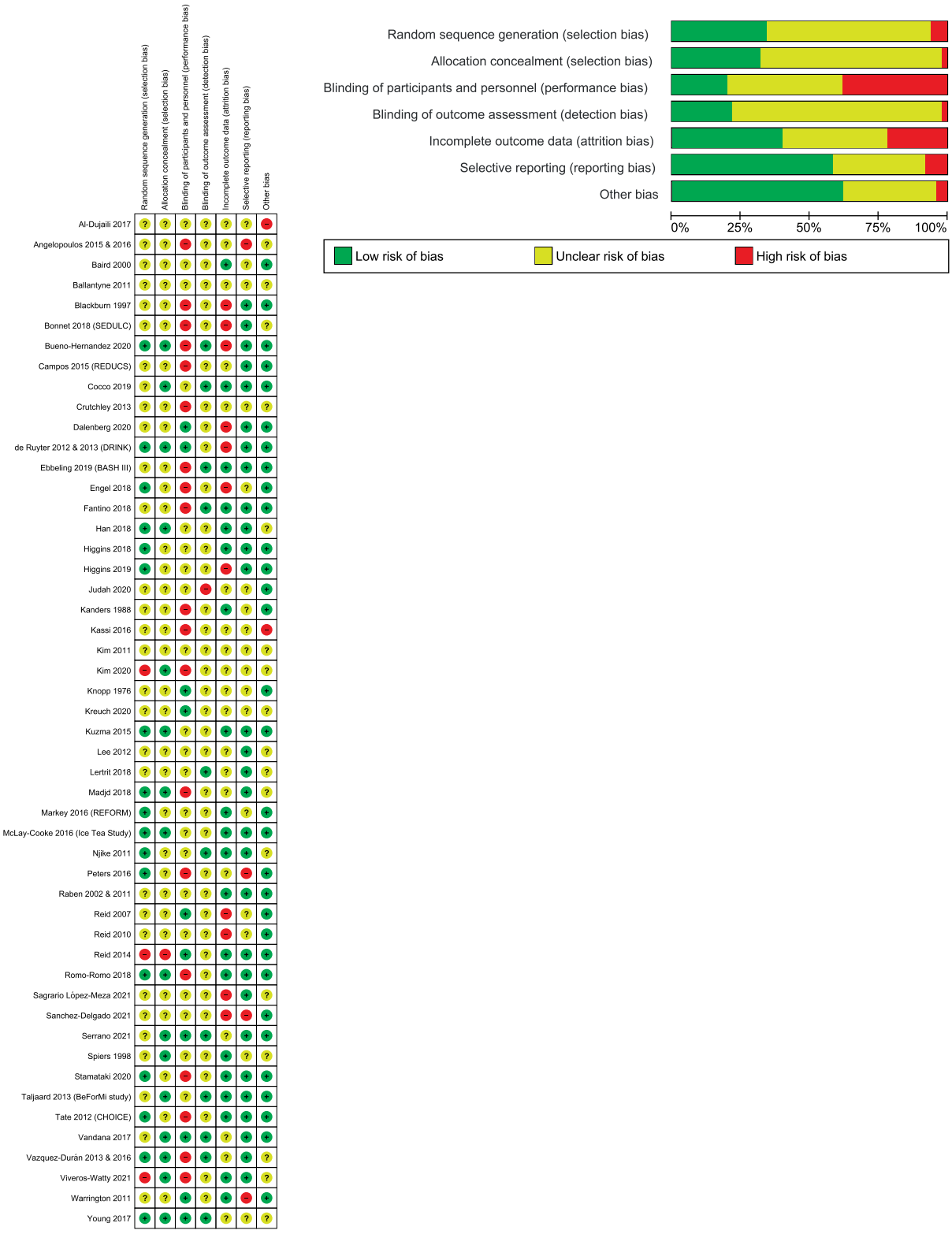


Table A6.1 Risk of bias in prospective cohort studies (Newcastle–Ottawa scale)

STUDY	REPRESENTATIVENESS OF EXPOSED COHORT	SELECTION OF NON-EXPOSED COHORT	ASCERTAINMENT OF EXPOSURE	OUTCOME OF INTEREST NOT PRESENT AT START OF STUDY	COMPARABILITY OF COHORTS	ASSESSMENT OF OUTCOME	ADEQUACY OF LENGTH OF FOLLOW-UP	ADEQUACY OF FOLLOW-UP OF COHORTS	TOTAL (MAX 9)
Acero 2020 (Talking Health)	–	✱	✱	–	–	✱	✱	–	4
Anderson 2020 (UK Biobank)	✱	✱	✱	✱	✱ ✱	✱	✱	–	8
Angeles Pérez-Ara 2020 (MooDFOOD)	–	✱	✱	✱	–	–	✱	–	4
Azad 2016 (CHILD)	✱	✱	✱	–	✱	✱	✱	✱	7
Bao 2008 (NIH-AARP Diet and Health Study)	✱	✱	–	✱	✱✱	✱	✱	–	7
Bassett 2020 (MCCS)	✱	✱	✱	✱	✱	✱	✱	–	7
Berkey 2004 (GUTS)	✱	✱	✱	✱	✱	–	✱	✱	7
Bernstein 2012 (NHS, HPFS)	–	✱	✱	✱	✱✱	✱	✱	✱	8
Bes-Rastrollo 2006 (SUN)	✱	✱	✱	–	–	–	✱	–	4
Blum 2005	–	✱	✱	–	–	✱	✱	–	4
Chazelas 2019 (NutriNet-Santé)	–	✱	✱	✱	✱✱	✱	✱	✱	8
Chazelas 2020 (NutriNet-Santé)	✱	✱	✱	✱	✱ ✱	✱	✱	–	8
Chen 2009 (NHS II)	–	✱	✱	✱	✱✱	–	✱	✱	7
Chia 2016 (BLSA)	–	✱	✱	✱	✱✱	✱	✱	✱	8
Chia 2018 (BLSA)	–	✱	✱	–	–	✱	✱	–	4
Cohen 2018 (Project Viva)	–	✱	✱	–	✱	✱	✱	✱	6
Cohen 2012 (NHS, NHS II, HPFS)	–	✱	✱	✱	✱✱	–	✱	–	6
Dale 2019 (MoBa)	✱	✱	✱	✱	✱	✱	✱	–	7
Davis 2018 (SOLAR)	–	✱	✱	–	–	✱	✱	–	4
de Koning 2012 (HPFS)	–	✱	✱	✱	✱	–	✱	✱	6
Drouin-Chartier 2019 (NHS, NHS II, HPFS)	–	✱	✱	✱	✱✱	–	✱	✱	7
Duffey 2012 (CARDIA)	✱	✱	✱	✱	✱	✱	✱	–	7
Englund-Ogge 2012 (MoBa)	✱	✱	✱	✱	✱	✱	✱	–	7
Fagherazzi 2013 & 2017 (E3N)	–	✱	✱	✱	✱	✱	✱	✱	7
Farvid 2021 (NHS and NHS II)	–	✱	✱	✱	✱	–	✱	–	5
Ferreira-Pego 2016 (PREDIMED)	–	✱	✱	✱	✱	✱	✱	–	6
Field 2014 (GUTS II)	–	✱	✱	–	✱	–	✱	–	4
Fowler 2008 (SALSA)	–	✱	✱	–	✱✱	✱	✱	–	6
Fowler 2015 (SALSA)	–	✱	✱	–	✱	✱	✱	–	5
Fung 2009 (NHS)	–	✱	✱	✱	✱	–	✱	✱	6

STUDY	REPRESENTATIVENESS OF EXPOSED COHORT	SELECTION OF NON-EXPOSED COHORT	ASCERTAINMENT OF EXPOSURE	OUTCOME OF INTEREST NOT PRESENT AT START OF STUDY	COMPARABILITY OF COHORTS	ASSESSMENT OF OUTCOME	ADEQUACY OF LENGTH OF FOLLOW-UP	ADEQUACY OF FOLLOW-UP OF COHORTS	TOTAL (MAX 9)
Gardener 2012 (NOMAS)	*	*	–	*	**	*	*	*	8
Gardener 2018 (NOMAS)	*	*	–	*	*	*	*	*	7
Garduno-Alanis 2020 (HAPIEE)	*	*	*	*	*	*	*	–	7
Gearon 2014 (MCCS)	*	*	–	–	*	–	*	–	4
Gillman 2017 (Project Viva)	–	*	*	–	*	*	*	*	6
Gunther 2019 (GeliS)	–	*	*	–	*	*	*	*	6
Guo 2014 (NIH-AARP Diet and Health Study)	*	*	–	*	*	–	*	–	5
Haines 2012 (EAT)	–	*	*	–	*	–	*	*	5
Halldorsson 2010 (Danish National Birth Cohort)	*	*	*	–	*	*	*	*	7
Haslam 2020 (FOS)	–	*	*	*	**	*	*	*	8
Hinkle 2019 (DWH)	–	*	*	–	*	*	*	–	5
Hirahatake 2019 (CARDIA)	*	*	*	*	**	*	*	–	8
Hodge 2018 (MCCS)	*	*	*	*	*	*	*	*	8
Hrolfsdottir 2019 (PREWICE)	–	*	*	–	–	–	*	*	4
Huang 2017 (WHI-OS)	*	*	*	*	**	–	*	–	7
Hur 2021 (NHS II)	–	*	*	*	*	–	*	*	6
InterActConsortium 2013 (EPIC-InterAct)	–	*	*	*	**	*	*	–	7
Jensen 2020 (Strong Heart Family Study)	–	*	*	*	**	–	*	–	6
Keller 2020 (HPP)	–	*	*	*	**	*	*	–	7
Kral 2008	–	*	*	–	–	*	*	–	4
Lana 2015 (ENRICA)	*	*	–	–	*	–	*	*	5
Laska 2012 (IDEA and ECHO)	–	*	*	–	*	*	*	*	6
Lim 2006 (NIH-AARP Diet and Health Study)	*	*	–	*	*	*	*	*	7
Lin 2011 (NHS)	–	*	*	–	*	*	*	*	6
Ludwig 2001	–	*	*	–	*	*	*	*	6
Ma 2016 (FHS 3rd Generation)	–	*	*	–	**	*	*	–	6
Macintyre 2018 (GUS)	*	*	*	*	**	*	*	*	9
Maslova 2013 (Danish National Birth Cohort)	*	*	*	–	*	*	*	*	7
Malik 2019 (NHS, HPFS)	–	*	*	*	**	*	*	*	8
Marshall 2003 (IFS)	–	*	*	–	–	*	*	–	4

STUDY	REPRESENTATIVENESS OF EXPOSED COHORT	SELECTION OF NON-EXPOSED COHORT	ASCERTAINMENT OF EXPOSURE	OUTCOME OF INTEREST NOT PRESENT AT START OF STUDY	COMPARABILITY OF COHORTS	ASSESSMENT OF OUTCOME	ADEQUACY OF LENGTH OF FOLLOW-UP	ADEQUACY OF FOLLOW-UP OF COHORTS	TOTAL (MAX 9)
McCullough 2014 (CPS-II)	–	✱	✱	✱	✱✱	–	✱	–	6
Mossavar-Rahmani 2019 (WHI-OS)	✱	✱	✱	✱	✱	✱	✱	–	7
Mullee 2019 (EPIC)	–	✱	✱	✱	✱✱	✱	✱	✱	8
Munda 2019	–	✱	✱	–	–	✱	✱	–	4
Muñoz-Garcia 2019 (SUN)	–	✱	✱	–	✱✱	–	✱	✱	6
Nettleton 2009 (MESA)	✱	✱	–	✱	✱	✱	✱	✱	7
Newby 2004 (North Dakota WIC Program for Children)	–	✱	✱	✱	✱	✱	✱	–	6
OConnor 2015 (EPIC-Norfolk)	–	✱	✱	✱	✱✱	✱	✱	–	7
Paganini-Hill 2007 (Leisure World Cohort Study)	–	✱	–	✱	✱	✱	✱	✱	6
Palmer 2008 (BWHS)	–	✱	✱	✱	–	–	✱	✱	5
Park 2020 (FHS, FOS)	–	✱	✱	✱	✱✱	✱	✱	–	7
Parker 1997 (PHHP)	–	✱	✱	–	✱	✱	✱	–	5
Pase 2017 (FOS)	–	✱	✱	✱	✱	✱	✱	–	6
Petherick 2014 (BiB)	–	✱	✱	–	✱✱	✱	✱	–	6
Rebholz 2017 (ARIC)	–	✱	–	✱	✱✱	✱	✱	–	6
Renault 2015 (TOP study)	–	✱	✱	✱	✱	–	✱	✱	6
Romanos-Nanclares 2021 (NHS and NHS II)	–	✱	✱	✱	✱	–	✱	–	5
Sakurai 2014	–	✱	✱	✱	✱✱	✱	✱	✱	8
Salavati 2020 (Perined-Lifelines Cohort)	✱	✱	–	✱	✱✱	✱	✱	–	7
Schernhammer 2005 (NHS, HPFS)	–	✱	✱	✱	✱✱	–	✱	✱	7
Schernhammer 2012 (NHS, HPFS)	–	✱	✱	✱	✱✱	✱	✱	✱	8
Schmidt 2020 (Danish National Birth Cohort)	✱	✱	–	✱	✱✱	✱	✱	–	7
Smith 2015 (NHS, NHS II, HPFS)	–	✱	✱	✱	✱✱	–	✱	–	6
Stellman 1986 (American Cancer Society study)	–	✱	✱	–	–	–	✱	–	3
Stepien 2016 (EPIC)	–	✱	✱	✱	✱	✱	✱	✱	7
Stern 2017 (Mexican Teachers Cohort)	–	✱	✱	–	✱✱	–	✱	–	5
Striegel-Moore 2006 (NGHS)	–	✱	✱	–	✱	✱	✱	✱	6
Tucker 2015	–	✱	✱	–	–	✱	✱	–	4

STUDY	REPRESENTATIVENESS OF EXPOSED COHORT	SELECTION OF NON-EXPOSED COHORT	ASCERTAINMENT OF EXPOSURE	OUTCOME OF INTEREST NOT PRESENT AT START OF STUDY	COMPARABILITY OF COHORTS	ASSESSMENT OF OUTCOME	ADEQUACY OF LENGTH OF FOLLOW-UP	ADEQUACY OF FOLLOW-UP OF COHORTS	TOTAL (MAX 9)
Vyas 2015 (WHI-OS)	✱	✱	✱	✱	✱✱	✱	✱	✱	9
Vanselow 2009 (EAT)	–	✱	✱	–	✱	–	✱	✱	5
Wang 2019 (SWAN)	–	✱	✱	–	✱	✱	✱	–	5
Zheng 2015a (CAPS)	–	✱	✱	–	✱	✱	✱	–	5
Zheng 2015b (Healthy Start Study)	✱	✱	✱	–	✱✱	✱	✱	–	7
Zheng 2019 (Raine)	–	✱	✱	–	✱	✱	✱	–	5
Zhu 2017 (DWH)	✱	✱	✱	–	✱✱	✱	✱	–	7
Zhang 2021 (NHANES)	✱✱	✱	✱	✱	✱	✱	–	–	7

Table A6.2 Risk of bias in case–control studies (Newcastle–Ottawa scale)

STUDY	DEFINITION OF CASES	REPRESENTATIVE-NESS OF CASES	SELECTION OF CONTROLS	DEFINITION OF CONTROLS	COMPARABILITY OF CASES AND CONTROLS	ASSESSMENT OF EXPOSURE	SAME METHOD OF ASCERTAINMENT FOR CASES AND CONTROLS	NONRESPONSE RATE	TOTAL SCORE (MAX 9)
Akdas 1990	✱	–	–	✱	✱✱	–	✱	–	5
Andreatta 2008	✱	–	–	✱	✱✱	–	✱	–	5
Asal 1988	✱	–	✱	–	–	–	–	–	2
Bosetti 2009	✱	–	–	✱	✱✱	–	✱	✱	6
Bravo 1987	✱	–	–	✱	✱	–	✱	–	4
Bunin 2005	✱	✱	✱	–	✱✱	–	✱	–	6
Cabaniols 2011	–	✱	–	–	✱	–	✱	–	3
Cartwright 1981	–	✱	–	–	✱	–	✱	–	3
Chan 2009	–	–	✱	–	✱✱	–	✱	✱	5
Connolly 1978	–	–	–	–	✱	–	–	–	1
Ewertz 1990	–	✱	✱	✱	✱	✱	✱	–	6
Gallus 2007	✱	–	–	–	✱✱	–	✱	✱	5
Gold 1985	–	–	✱	✱	✱✱	–	✱	–	5
Goodman 1986	✱	✱	–	✱	✱	–	✱	✱	6
Gurney 1997	–	–	✱	–	✱✱	–	–	–	3
Hardell 2001	✱	–	✱	–	✱	✱	✱	✱	6
Hoover 1980	✱	✱	✱	–	✱✱	–	✱	✱	7
Howe 1977 and 1980	–	✱	✱	–	✱	–	✱	–	4

STUDY	DEFINITION OF CASES	REPRESENTATIVE-NESS OF CASES	SELECTION OF CONTROLS	DEFINITION OF CONTROLS	COMPARABILITY OF CASES AND CONTROLS	ASSESSMENT OF EXPOSURE	SAME METHOD OF ASCERTAINMENT FOR CASES AND CONTROLS	NONRESPONSE RATE	TOTAL SCORE (MAX 9)
Iscovich 1978	*	–	*	–	*	–	–	*	4
Kessler 1976 and 1978	*	*	–	*	**	*	*	–	7
Kobeissi 2013	*	–	–	*	–	–	*	–	3
Mahfouz 2014	*	–	*	*	*	–	*	–	5
Mettlin 1989	–	*	–	*	**	*	*	–	6
Moller-Jensen 1983	*	*	*	–	*	–	*	–	5
Momas 1994	*	*	*	–	**	–	–	–	5
Mommsen 1983	–	–	*	–	**	–	*	–	4
Morgan 1974	*	–	–	–	*	*	*	–	4
Morrison 1979	–	*	–	–	*	–	*	–	3
Morrison 1980	*	*	*	–	*	–	*	*	6
Morrison 1982 (Japan)	*	*	*	–	*	–	*	*	6
Morrison 1982 (United Kingdom)	*	*	*	–	*	–	*	*	6
Najem 1982	*	–	–	–	*	–	*	–	3
Nomura 1991	*	*	*	–	**	–	*	*	7
Norell 1986	*	*	*	–	*	*	*	–	6
Ohno 1985	*	*	*	–	**	–	*	*	7
Radosavljevic 2001	*	*	–	*	*	–	*	–	5
Risch 1988	–	–	*	–	**	–	*	–	4
Silverman 1983	*	*	*	–	*	–	*	*	6
Simon 1975	–	–	–	*	*	*	*	*	5
Sullivan 1982	–	–	*	–	–	–	–	–	1
Wynder 1977	*	–	–	*	*	*	*	–	5
Wynder 1980	*	–	*	*	–	–	–	–	3
Yu 1997	*	–	–	–	**	–	*	–	4
Zou 1990	*	*	–	*	*	–	*	–	5

ANNEX 7. GRADE evidence profiles

GRADE evidence profile 1
Question: What is the effect of higher vs lower intake of non-sugar sweeteners in adults?
Population: General adult population

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[6]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE[4] (95% CI)	ABSOLUTE – PER 1000[5] (95% CI)	
Adiposity: body weight (kg)											
29	RCT	Serious[7]	Serious[8]	Not serious	Not serious	None	1252	1181	**MD –0.71** (–1.13 to –0.28)	–	⨁⨁◯◯ LOW
4	Observational (continuous)	Not serious[9]	Serious[8]	Not serious	Not serious[10]	None	118457		**MD –0.12** (–0.40 to 0.15)	–	⨁◯◯◯ VERY LOW
5	Observational (high vs low)	Serious[11]	Not serious	Not serious	Not serious[10]	None	11874		**MD –0.01** (–0.67 to 0.64)	–	⨁◯◯◯ VERY LOW
Adiposity: BMI (kg/m^2)											
23	RCT	Serious[7]	Serious[8]	Not serious	Not serious[12]	None	940	917	**MD –0.14** (–0.30 to 0.02)	–	⨁⨁◯◯ LOW
5	Observational (high vs low)	Not serious[9]	Serious[8]	Not serious	Not serious	None	80583		**MD 0.14** (0.03 to 0.25)	–	⨁◯◯◯ VERY LOW
Adiposity: incident obesity											
2	Observational	Not serious[9]	Not serious	Not serious	Not serious[13]	None	603/1668 (36.2%)		**HR 1.76** (1.25, 2.49)	**275 more** (from 91 more to 539 more)	⨁⨁◯◯ LOW
Adiposity: abdominal obesity											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	5381/10895 (49.4%)		**HR 1.33** (0.91 to 1.96)	**163 more** (from 44 fewer to 474 more)	⨁◯◯◯ VERY LOW
Adiposity: waist-to-hip ratio											
3	RCT	Serious[15]	Not serious	Not serious	Serious[16]	None	121	79	**MD 0.00** (–0.01 to 0.01)	–	⨁⨁◯◯ LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[6]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE[4] (95% CI)	ABSOLUTE – PER 1000[5] (95% CI)	
Adiposity: waist circumference (cm)											
10	RCT	Not serious[17]	Serious[8]	Not serious	Not serious[10]	None	688	564	**MD –0.24** (–1.06 to 0.58)	–	⨁⨁⨁◯ MODERATE
3	Observational (high vs low)	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	12886		**MD 0.92** (–1.73 to 3.56)	–	⨁◯◯◯ VERY LOW
Adiposity: fat mass (kg)											
6	RCT	Not serious[18]	Serious[8]	Not serious	Serious[14]	None	332	286	**MD –0.54** (–1.56 to 0.49)	–	⨁⨁◯◯ LOW
Adiposity: fat mass (%)											
10	RCT	Not serious[18]	Serious[8]	Not serious	Serious[14]	None	343	414	**MD –0.11** (–0.78 to 0.56)	–	⨁⨁◯◯ LOW
Adiposity: lean mass (kg)											
6	RCT	Not serious[18]	Not serious	Not serious	Not serious[10]	None	255	284	**MD –0.29** (–0.70 to 0.11)	–	⨁⨁⨁⨁ HIGH
Diabetes: incident diabetes											
13	Observational (beverages)	Not serious[9]	Not serious	Not serious	Not serious	None[19]	28222/408609 (6.9%)		**HR 1.23** (1.14 to 1.32)	**16 more** (from 10 more to 22 more)	⨁⨁◯◯ LOW
2	Observational (tabletop)	Not serious[9]	Not serious	Not serious	Not serious	None	2250/62582 (3.6%)		**HR 1.34** (1.21 to 1.48)	**12 more** (from 8 more to 17 more)	⨁⨁◯◯ LOW
Diabetes: fasting glucose (mmol/L)											
16	RCT	Serious[20]	Not serious	Not serious	Not serious[10]	None	844	650	**MD –0.01** (–0.05 to 0.04)	–	⨁⨁⨁◯ MODERATE
Diabetes: fasting insulin (pmol/L)											
10	RCT	Not serious[21]	Serious[8]	Not serious	Serious[14]	None	444	315	**MD –0.49** (–4.99 to 4.02)	–	⨁⨁◯◯ LOW
Diabetes: HbA1c (%)											
6	RCT	Not serious[22]	Not serious	Not serious	Serious[16]	None	212	199	**MD 0.02** (–0.03 to 0.07)	–	⨁⨁⨁◯ MODERATE
Diabetes: HOMA-IR											
11	RCT	Serious[23]	Serious[8]	Not serious	Not serious[10]	None	457	329	**MD 0.03** (–0.32 to 0.38)	–	⨁⨁◯◯ LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[6]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE[4] (95% CI)	ABSOLUTE – PER 1000[5] (95% CI)	
Diabetes: high fasting glucose											
3	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	6086/11213 (54.3%)		**HR 1.21** (1.01 to 1.45)	**114 more** (from 5 more to 245 more)	⨁⨁◯◯ LOW
Dental caries											
1	RCT	Serious[24]	Unable to assess[25]	Not serious	Very serious[26]	None	14	15	In a 6-month RCT among adults *(26)*[27], the participants who were assigned to consume sugar-sweetened or NSS-sweetened soft drinks did not develop caries or acid erosion of the enamel during the intervention.		⨁◯◯◯ VERY LOW
All-cause mortality											
8	Observational	Not serious[9]	Serious[8]	Not serious	Not serious	None	102677/860873 (11.9%)		**HR 1.12** (1.05 to 1.19)	**14 more** (from 6 more to 23 more)	⨁◯◯◯ VERY LOW
Cardiovascular diseases: cardiovascular disease mortality											
5	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	13089/598951 (2.2%)		**HR 1.19** (1.07 to 1.32)	**4 more** (from 2 more to 7 more)	⨁⨁◯◯ LOW
Cardiovascular diseases: cardiovascular events											
3	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	6384/166938 (3.8%)		**HR 1.32** (1.17 to 1.50)	**12 more** (from 6 more to 19 more)	⨁⨁◯◯ LOW
Cardiovascular diseases: coronary heart disease											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	10104/205455 (4.9%)		**HR 1.16** (0.97 to 1.39)	**8 more** (from 1 fewer to 19 more)	⨁◯◯◯ VERY LOW
Cardiovascular diseases: stroke											
6	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	8346/655953 (1.3%)		**HR 1.19** (1.09 to 1.29)	**2 more** (from 1 more to 4 more)	⨁⨁◯◯ LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[6]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE[4] (95% CI)	ABSOLUTE – PER 1000[5] (95% CI)	
Cardiovascular diseases: hypertension											
6	Observational	Not serious[9]	Not serious	Not serious	Not serious	None	81965/234137 (35%)		**HR 1.13** (1.09 to 1.17)	**46 more** (from 32 more to 60 more)	⨁⨁◯◯ LOW
Cardiovascular diseases: systolic blood pressure (mmHg)											
14	RCT	Serious[28]	Not serious	Not serious	Not serious[10]	None	838	602	**MD –1.33** (–2.71 to 0.06)	–	⨁⨁⨁◯ MODERATE
Cardiovascular diseases: diastolic blood pressure (mmHg)											
13	RCT	Serious[28]	Not serious	Not serious	Not serious[10]	None	689	448	**MD –0.51** (–1.68 to 0.65)	–	⨁⨁⨁◯ MODERATE
Cardiovascular diseases: LDL-cholesterol (mmol/L)											
12	RCT	Serious[28]	Not serious	Not serious	Serious[14]	None	653	540	**MD 0.03** (–0.03 to 0.09)	–	⨁⨁◯◯ LOW
Cardiovascular diseases: total cholesterol (mmol/L)											
14	RCT	Serious[28]	Serious[8]	Not serious	Not serious[10]	None	567	511	**MD 0.01** (–0.09 to 0.11)	–	⨁⨁◯◯ LOW
Cardiovascular diseases: HDL cholesterol (mmol/L)											
13	RCT	Serious[28]	Not serious	Not serious	Not serious[10]	None	659	546	**MD 0.00** (–0.03 to 0.03)	–	⨁⨁⨁◯ MODERATE
Cardiovascular diseases: total cholesterol to HDL cholesterol ratio											
4	RCT	Not serious[29]	Not serious	Not serious	Serious[16]	None	166	160	**MD 0.09** (0.02 to 0.16)	–	⨁⨁⨁◯ MODERATE
Cardiovascular diseases: low HDL cholesterol											
4	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	5823/11916 (48.9%)		**HR 1.03** (0.92 to 1.16)	**15 more** (from 39 fewer to 78 more)	⨁◯◯◯ VERY LOW
Cardiovascular diseases: triglycerides (mmol/L)											
14	RCT	Serious[28]	Serious[8]	Not serious	Serious[14]	None	684	559	**MD –0.04** (–0.11 to 0.04)	–	⨁◯◯◯ VERY LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[6]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE[4] (95% CI)	ABSOLUTE – PER 1000[5] (95% CI)	
Cardiovascular diseases: high triglycerides											
4	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	6673/12728 (52.4%)		**HR 1.03** (0.88 to 1.21)	**16 more** (from 63 fewer to 110 more)	⨁◯◯◯ VERY LOW
Cancer: cancer mortality											
4	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	25494/568175 (4.5%)		**HR 1.02** (0.92 to 1.13)	**1 more** (from 4 fewer to 6 more)	⨁◯◯◯ VERY LOW
Cancer: incidence (any type)											
7	Observational	Not serious[9]	Not serious	Not serious	Serious[14]	None	27573/942600 (2.9%)		**HR 1.02** (0.95 to 1.09)	**1 more** (from 1 fewer to 3 more)	⨁◯◯◯ VERY LOW
Cancer: incidence (bladder)											
26	Observational (case-control)	Serious[11]	Serious[8]	Not serious	Not serious	None	11071 cases 28589 controls		**OR 1.31** (1.06 to 1.62)	–	⨁◯◯◯ VERY LOW
Chronic kidney disease: incident disease											
2	Observational	Not serious[9]	Serious[8]	Not serious	Serious[14]	None	3161/18372 (17.2%)		**HR 1.41** (0.89 to 2.24)	**71 more** (from 19 fewer to 213 more)	⨁◯◯◯ VERY LOW
Chronic kidney disease: creatinine (μmol/L)											
2	RCT	Serious[30]	Serious[8]	Not serious	Very serious[31]	None	93	52	**MD 8.80** (–14.65 to 32.25)	–	⨁◯◯◯ VERY LOW
Chronic kidney disease: albumin (g/L)											
2	RCT	Serious[30]	Not serious	Not serious	Serious[16]	None	93	52	**MD 0.00** (–0.56 to 0.56)	–	⨁⨁◯◯ LOW
Energy intake (kJ/day)											
25	RCT	Serious[32]	Serious[8]	Not serious	Not serious	None	1131	1077	**MD –569** (–859 to –278)	–	⨁⨁◯◯ LOW
Sugars intake (g/day)											
12	RCT	Serious[33]	Serious[8]	Not serious	Not serious	None	652	587	**MD –38.4** (–57.8 to –19.1)	–	⨁⨁◯◯ LOW

BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HR: hazard ratio; LDL: low-density lipoprotein; MD: mean difference; NSS: non-sugar sweeteners; OR: odds ratio; RCT: randomized controlled trial.

[1] Unless otherwise noted, observational studies are prospective cohort studies that assessed outcomes by comparing the highest quantile of intake to the lowest. Some cohort studies assessed outcomes continuously, as noted in the evidence profile.

[2] All studies were conducted in the population of interest (i.e. general adult population). Although most studies were conducted in North America and Europe, and very few were conducted in low- and middle-income countries (LMICs), physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless they are introduced to these populations. With the exception of LDL cholesterol, blood lipids, glycaemic markers and blood pressure are largely unvalidated intermediate markers of disease and, although informative, are not a surrogate for disease. However, the WHO NUGAG Subgroup on Diet and Health prioritized intermediate markers in the outcomes of interest and, therefore, none of these outcomes were downgraded for indirectness.

[3] Funnel plot analyses conducted for outcomes with 10 studies or more. Unless otherwise noted, funnel plot analysis did not suggest significant risk for publication bias.

[4] For observational studies, relative effects are most-adjusted multivariate estimates (i.e. the multivariate association measure with the highest number of covariates as reported in individual studies).

[5] Based on the event rate in the studies – that is, the number of people with events divided by the total number of people. The absolute effect (per 1000 people) is calculated using the following equation: absolute effect = 1000 × [event rate × (1 – RR)]. The magnitude of absolute effect in "real world" settings depends on baseline risk, which can vary across different populations.

[6] Critical outcomes in this evidence profile are shown in blue and important outcomes in black, as prioritized by the WHO NUGAG Subgroup on Diet and Health. Outcomes can be assessed as either not important, important or critical for decision-making in the WHO guideline development process *(12)*.

[7] Most RCTs included in the meta-analyses for measures of adiposity were assessed as having unclear risk of bias overall as a result of lack of necessary detail in reporting the methods that were used. Less than half of the trials for body weight and slightly more than half for BMI appeared to use appropriate methods of random sequence generation (one or two employed inadequate randomization methods). Less than a quarter of the trials reported adequate allocation concealment for body weight and a third for BMI (except for one trial with inadequate allocation concealment of body weight; details in remaining trials were not reported and thus assessed as unclear). Blinding of participants was only possible in one or two studies; it was not possible in half the remaining trials (studies comparing NSS with water or nothing) and unclear in the other half (NSS compared with sugars, because it is unknown to what extent the participants could taste the difference between foods and beverages sweetened with NSS and those sweetened with sugars). Only a very small number of trials provide sufficient information to enable an assessment regarding blinding of outcome assessment. A little fewer than half the trials did not report significant participant dropout or imbalance in dropout rates across arms, and about half of the remaining trials reported significant dropout rates (>15%), which represent a serious concern. However, most trials did not provide sufficient detail regarding reasons for participant dropout, so it is difficult to determine whether attrition might have affected results. Selective reporting of outcomes was clearly evident in only a very small number of trials; of the remaining trials, about half were assessed as low risk of bias and half as unclear risk of bias. No other significant sources of bias were identified. Although most trials appeared to be well conducted, the widespread lack of detail in the reporting of methods creates significant uncertainty regarding risk of bias. Downgraded once as a conservative measure.

[8] $I^2 \geq 50\%$, indicating a significant level of heterogeneity. Where the number of studies was sufficient to explore heterogeneity via subgroup and sensitivity analyses, results of the analysis did not significantly explain the observed heterogeneity. Downgraded once.

[9] Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

[10] A small mean effect, likely of little to no clinical significance, and neither bound of the 95% CI includes a potentially important benefit or harm. Therefore, considered a sufficiently precise estimate of no effect. Not downgraded.

[11] Mean Newcastle–Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

[12] One bound of the 95% CI includes potentially important benefit or harm and the other bound crosses the null in the opposite direction, but only very slightly and as a result of the outlying effect in one study *(25)*. In sensitivity analysis in which the study is removed, the upper bound no longer crosses the null. Not downgraded.

[13] The sample size is relatively small for prospective cohort studies, but sufficiently large and with a high event rate. Not downgraded.

[14] One bound of the 95% CI includes potentially important benefit or harm and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

[15] Only one trial was assessed as having adequately randomized and maintained allocation concealment (others unclear). One trial was an abstract only with overall high risk of bias. Remaining domains for the other two trials were assessed as half with low risk of bias and half with unclear risk. Downgraded once.

[16] A small mean effect, likely of little to no clinical significance, and neither bound of the 95% CI includes a potentially important benefit or harm. However, the sample size is small. Downgraded once.

[17] All but one trial had adequate randomization, and nearly half had adequate allocation concealment (the remainder were unclear). One trial had incomplete data, and another concerns about selective reporting. Six trials could not blind participants, and it was unclear if participants were blinded in the other two. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[18] The majority of trials had adequate randomization, but only one or two had adequate allocation concealment (the remainder were unclear). Two trials had incomplete data. Two trials could not blind participants, and it was unclear if participants were blinded in the remaining trials. For fat mass (%), there were concerns in one trial about selective reporting. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[19] Six out of the 10 comparisons that reported a P_{trend} reported a P_{trend} of <0.05, suggestive of a dose–response relationship within those individual studies. However, as a conservative measure, it was not upgraded. Funnel plot analysis suggested slight possibility of publication bias, but not of significant concern. Not downgraded.

[20] Slightly more than half the trials had adequate randomization, and one had inadequate randomization. Only four of the trials had adequate allocation concealment (the remainder were unclear). More than half the trials could not blind participants to treatment. Two trials had incomplete data, and there were concerns about selective reporting in two trials (one trial had both). One trial was an abstract only with overall high risk of bias. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[21] In these trials, the majority had adequate randomization, and one had inadequate randomization. Half had adequate allocation concealment (the remainder were unclear). Slightly more than half the trials could not blind participants to treatment. One trial had incomplete data. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[22] In these trials, the majority had adequate randomization, and half had adequate allocation concealment (the remainder were unclear). Half the trials could not blind participants to treatment. One trial had incomplete data, and one had concerns about selective reporting. One trial was an abstract only with overall high risk of bias. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[23] Fewer than half the trials had adequate randomization, and one had inadequate randomization. Only four of the trials had adequate allocation concealment (the remainder were unclear). More than half the trials could not blind participants to treatment. Two trials had incomplete data. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[24] This single study had adequate randomization but insufficient information to assess allocation concealment, blinding of outcome assessment or selective reporting. It was at high risk of bias for blinding of participants and incomplete data. Downgraded once.

[25] Unable to assess inconsistency in a single study. Downgraded once.

[26] Extremely small sample size. Downgraded twice.

[27] The data for dental caries were reported in the original publication of this trial, Maersk et al. (2012) *(183)*.

[28] The majority of trials had adequate randomization, but fewer than half had adequate allocation concealment (the remainder were unclear). A significant number of trials could not blind participants, and it was unclear if participants were blinded in the remaining trials. One or two trials trial had incomplete data, and there were concerns in 1–3 trials about selective reporting. One or two of the trials for most outcomes were abstract only and of high risk of bias overall. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[29] The majority of trials had adequate randomization, but only one had adequate allocation concealment (the remainder were unclear). Only one trial could not blind participants. The remaining domains were approximately half with low risk of bias and half unclear. Not downgraded.

[30] One trial was fairly well reported, and the other was mostly unclear, with concerns about selective reporting of outcomes. Downgraded once.

[31] The 95% CI crosses the null and includes both significant benefit and harm. Downgraded twice.

[32] A little fewer than half the trials had adequate randomization, and about a quarter had adequate allocation concealment (the remainder were unclear). One trial was at high risk of bias for both inadequate randomization and allocation concealment. Half the trials could not blind participants and it was unclear if participants were blinded in all but two of the remaining trials. Eight trials had incomplete data, and there were concerns in one trial about selective reporting. The remaining domains were approximately half with low risk of bias and half unclear. Downgraded once.

[33] A third of the trials had adequate randomization, and one had adequate allocation concealment (the remainder were unclear). One trial was at high risk of bias for both inadequate randomization and allocation concealment. More than half the trials could not blind participants, and it was unclear if participants were blinded in all but one of the remaining trials. Three trials trial had incomplete data. The remaining domains were more low risk of bias than unclear, but not by a significant margin. Downgraded once.

GRADE evidence profile 2

Question: What is the effect of replacing sugars with non-sugar sweeteners in adults?

Population: General adult population

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[3]
NO. OF STUDIES/ COHORTS	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[1]	IMPRECISION	OTHER[2]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Adiposity: body weight (kg)											
4	RCT	Not serious[4]	Not serious	Not serious	Serious[5]	None	361	236	**MD –0.61** (–1.28 to 0.06)	–	⨁⨁⨁◯ MODERATE
Adiposity: BMI (kg/m²)											
4	RCT	Not serious[4]	Not serious	Not serious	Serious[5]	None	286	180	**MD –0.01** (–0.38 to 0.35)	–	⨁⨁⨁◯ MODERATE

BMI: body mass index; CI: confidence interval; MD: mean difference; NSS: non-sugar sweeteners; RCT: randomized controlled trial.

[1] All studies were conducted in the population of interest (i.e. general adult population). Although most studies were conducted in North America and Europe, and very few were conducted in low- and middle-income countries (LMICs), physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless they are introduced to these populations. With the exception of LDL cholesterol, blood lipids, glycaemic markers and blood pressure are largely unvalidated intermediate markers of disease and, although informative, are not a surrogate for disease. However, the WHO NUGAG Subgroup on Diet and Health prioritized intermediate markers in the outcomes of interest and therefore, none of these outcomes were downgraded for indirectness.

[2] Too few studies to conduct funnel plot analyses.

[3] Both outcomes are critical outcomes as prioritized by the WHO NUGAG Subgroup on Diet and Health. Outcomes can be assessed as either not important, important or critical for decision-making in the WHO guideline development process *(12)*.

[4] Half the trials had adequate randomization, but most lacked sufficient detail to assess whether allocation concealment was adequate (unclear risk of bias). Three of the four trials could not blind participants to treatment. There were no other significant sources of bias. Not downgraded.

[5] One bound of the 95% CI includes potentially important benefit or harm and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

GRADE evidence profile 3

Question: What is the effect of higher vs lower intake of non-sugar sweeteners in children?

Population: General child population

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[4]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Adiposity: body weight (kg)											
1	RCT	Not serious[5]	Unable to assess[6]	Not serious	Not serious	None	319	322	**MD –1.01** (–1.54 to –0.48)	–	⨁⨁⨁◯ MODERATE
2	Observational (continuous)	Not serious[7]	Not serious	Not serious	Not serious[8]	None	1633		**MD 0.03** (–0.14 to 0.21)	–	⨁⨁◯◯ LOW
Adiposity: BMI (kg/m²)											
5	Observational (continuous)	Not serious[7]	Serious[9]	Not serious	Not serious[8]	None	11907		**MD 0.08** (–0.01 to 0.17)	–	⨁◯◯◯ VERY LOW
2	Observational (high vs low)	Not serious[7]	Not serious	Not serious	Serious[10]	None	2426		**MD 0.04** (–0.32 to 0.40)	–	⨁◯◯◯ VERY LOW
Adiposity: BMI z score											
2	RCT	Not serious[11]	Not serious	Not serious	Serious[10]	None	424	840	**MD –0.07** (–0.26 to 0.11)	–	⨁⨁⨁◯ MODERATE
3	Observational (continuous)	Not serious[7]	Serious[9]	Not serious	Serious[10]	None	610		**MD –0.23** (–0.70 to 0.25)	–	⨁◯◯◯ VERY LOW
1	Observational (high vs low)	Serious[12]	Unable to assess[6]	Serious[13]	Serious[10]	None	98		**MD 0.00** (–0.30 to 0.30)	–	⨁◯◯◯ VERY LOW
Adiposity: waist circumference (cm)											
1	RCT	Not serious[5]	Unable to assess[6]	Not serious	Not serious	None	319	322	**MD –0.66** (–1.23 to –0.09)	–	⨁⨁⨁◯ MODERATE
Adiposity: fat mass (kg)											
1	RCT	Not serious[5]	Unable to assess[6]	Not serious	Not serious	None	319	322	**MD –0.57** (–1.02 to –0.12)	–	⨁⨁⨁◯ MODERATE
1	Observational	Serious[12]	Unable to assess[6]	Serious[13]	Serious[10]	None	98		**MD –1.00** (–2.52 to 0.52)	–	⨁◯◯◯ VERY LOW
Adiposity: fat mass (%)											
1	RCT	Not serious[5]	Unable to assess[6]	Not serious	Not serious	None	319	322	**MD –1.07** (–1.99 to –0.15)	–	⨁⨁⨁◯ MODERATE
2	Observational	Not serious[7]	Serious[9]	Not serious	Serious[10]	None	720		**MD –1.53** (–5.73 to 2.66)	–	⨁◯◯◯ VERY LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[4]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Adiposity: incident overweight											
2	Observational	Not serious[7]	Not serious	Not serious	Very serious[14]	None	235/3064 (7.7%)		**OR 1.25** (0.43 to 3.66)	**19 more** (from 44 fewer to 205 more)	⨁◯◯◯ VERY LOW
Diabetes: intermediate markers											
1	Observational	Serious[12]	Unable to assess[6]	Serious[14]	Serious[10]	None	98		In this cohort of 12–18-year-old overweight children followed up for 1 year, chronic consumers of NSS-sweetened beverages had no difference in intermediate markers of diabetes when compared with NSS-sweetened beverage initiators and non-consumers, except for HbA1c, which increased more in chronic consumers of NSS-sweetened beverages ($P = 0.01$) *(193)*.		⨁◯◯◯ VERY LOW
Dental caries											
2	RCT	Not serious[15]	Unable to assess[16]	Not serious	Serious[10]	None	115	116	*Unable to meta-analyse* In one trial, snacks containing stevia or sugars were given twice daily to children for 6 weeks. At the end of the trial, in the stevia arm, the concentrations of cariogenic bacteria *Streptococcus mutans* and lactobacilli ($\chi^2 = 8.01$; $P < 0.01$) and the probability of developing caries (measured by a cariogram) decreased compared with baseline, whereas there were no statistically significant changes in the sugars arm *(209)*. In another trial, mouth rinse containing stevia or placebo was used daily by children for 6 months. At the end of the trial, there was a significant improvement in the stevia arm compared with the placebo group in plaque scores ($P = 0.03$) and gingival scores ($P = 0.01$). There were no changes in the number of cavitated lesions in the stevia arm, but there was an increase in cavitated lesions in the placebo arm (from 5.6% to 5.8%) *(210)*.		⨁⨁◯◯ LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[4]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Dental caries (continued)											
1	Observational	Serious[12]	Unable to assess[6]	Not serious	Unable to assess[17]	None	642		This prospective cohort study found that low intakes of NSS-sweetened beverages were associated with fewer teeth surfaces having caries compared with no intake ($P < 0.025$). However, the association with high intakes of NSS-sweetened beverages was not reported *(211)*.		⨁◯◯◯ VERY LOW
Cardiovascular diseases: blood lipids											
1	Observational	Serious[12]	Unable to assess[6]	Serious[14]	Serious[10]	None	98		In this cohort of 12–18-year-old overweight children followed up for 1 year, chronic consumers of NSS-sweetened beverages had no difference in total, HDL and LDL cholesterol, and triglycerides when compared with NSS-sweetened beverage initiators and non-consumers *(193)*.		⨁◯◯◯ VERY LOW
Cancer: brain cancer											
2	Observational (case-control)	Serious[12]	Not serious	Not serious	Serious[10]	None	371 cases 780 controls		**OR 1.14** (0.80 to 1.63)	**2 more** (from 2 fewer to 7 more)	⨁◯◯◯ VERY LOW
Energy intake (kJ/day)											
1	RCT	Not serious[18]	Unable to assess[6]	Not serious	Serious[10]	None	199	187	In this trial, the energy intake of children receiving drinks with sugars was 419 kJ/day higher than in those receiving drinks with NSS *(190)*.		⨁⨁⨁◯ MODERATE
2	Observational	Serious[12]	Unable to assess[17]	Not serious	Unable to assess[17]	None	173 (cohort 1) 2371 (cohort 2)		*Unable to meta-analyse* In one cohort study, energy intake in those who initiated consuming NSS-sweetened beverages was 432 kJ/day higher and in chronic/existing consumers of NSS-sweetened beverages was 2462 kJ/day higher than in those who did not consume NSS-sweetened beverages after 1 year of follow-up *(193)*. In the second cohort study, energy intake was 122 kJ/day higher per 100 g/day increase in NSS-sweetened beverage consumption *(200)*.		⨁◯◯◯ VERY LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[4]
NO. OF STUDIES/ COHORTS	STUDY DESIGN[1]	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[2]	IMPRECISION	OTHER[3]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Sugars intake (g/day)											
2	Observational	Serious[12]	Unable to assess[17]	Not serious	Unable to assess[17]	None	173 (cohort 1) 2371 (cohort 2)		*Unable to meta-analyse* In one cohort study, chronic users of NSS-sweetened beverages had a 40.2 g/day (SE 11.6) higher sugars intake than never users, whereas initiators of NSS-sweetened beverages had a 23.9 g/day (SE 17.9) lower sugars intake than never users *(193)*. In a second cohort study, sugars intake was not associated with NSS-sweetened beverage intake *(200)*.		⨁◯◯◯ VERY LOW
Neurocognition											
1	RCT	Not serious[18]	Unable to assess[6]	Not serious	Serious[10]	None	200	199	In an RCT, children were given drinks with sucralose or sucrose for 8.5 months. There were no significant differences between the two arms in cognition measures (tested using the Kaufman Assessment Battery for Children version II [KABC-II] subtests and the Hopkins Verbal Learning Test [HVLT]) *(190)*.		⨁⨁◯◯ LOW
1	Observational	Not serious[7]	Unable to assess[6]	Not serious	Unable to assess[17]	None	1234		In a cohort study following children in utero up to 7 years of age, early- and mid-childhood cognition scores were not associated with childhood intake of NSS-sweetened beverages at 3 years *(215)*.		⨁◯◯◯ VERY LOW

BMI: body mass index; CI: confidence interval; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MD: mean difference; OR: odds ratio; NSS: non-sugar sweeteners; RCT: randomized controlled trial; SE: standard error.

1 Unless otherwise noted, observational studies are prospective cohort studies that assessed outcomes by comparing the highest quantile of intake to the lowest. Some cohort studies assessed outcomes continuously, as noted in the evidence profile.

2 Unless otherwise noted, all studies were conducted in the population of interest (i.e. general child population). Although most studies were conducted in North America and Europe, and very few were conducted in low- and middle-income countries (LMICs), physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless they are introduced to these populations.

3 Too few studies to conduct funnel plot analyses.

4 Critical outcomes in this evidence profile are shown in blue and important outcomes in black, as prioritized by the WHO NUGAG Subgroup on Diet and Health. Outcomes can be assessed as either not important, important or critical for decision-making in the WHO guideline development process *(12)*.

[5] This single RCT was well conducted, with adequate randomization and allocation concealment. There was a high attrition rate, with more than 20% of participants dropping out; however, imputation of missing values suggested no imbalance in arms with or without missing participants. Not downgraded.

[6] Unable to assess inconsistency as there is only a single study. Downgraded once.

[7] Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

[8] A small mean effect, likely of little to no clinical significance, and neither bound of the 95% CI includes a potentially important benefit or harm. Therefore, considered a sufficiently precise estimate of no effect. Not downgraded

[9] $I^2 \geq 50\%$, indicating a significant level of heterogeneity. Downgraded once.

[10] One bound of the 95% CI includes potentially important benefit or harm and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

[11] These RCTs were well conducted, although for one it was unclear whether it was adequately randomized. Both had adequate allocation concealment. There was a high attrition rate, with more than 20% of participants dropping out of one trial; however, imputation of missing values suggested no imbalance in arms with or without missing participants. No other sources of significant bias noted. Not downgraded.

[12] Mean Newcastle–Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

[13] This single, very small cohort was conducted exclusively in overweight Hispanic adolescents. As evidence from this review suggests that people with overweight and/or obesity may respond differently to the use of NSS from people of normal weight, this cohort may not be an adequate representation of the general child population. Downgraded once, together with inconsistency.

[14] The 95% CI crosses the null and includes both significant benefit and harm. Downgraded twice.

[15] Neither trial included sufficient information to assess whether randomization was adequate, but both had adequate allocation concealment, and other domains were mostly assessed as low risk of bias. Not downgraded.

[16] Unable to assess inconsistency as there only two studies which could not be meta-analysed, although both report lower risk of caries with NSS. Downgraded once as a conservative measure.

[17] Unable to assess. Downgraded once.

[18] It was unclear whether this single, well-conducted trial was adequately randomized, but other domains – save for blinding of participants (unclear) – were assessed as low risk of bias. Not downgraded.

GRADE evidence profile 4

Question: What is the effect of higher vs lower intake of non-sugar sweeteners in pregnant women?

Population: Pregnant women

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[3]
NO. OF STUDIES/ COHORTS	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[1]	IMPRECISION	OTHER[2]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Gestational diabetes											
1	Observational	Not serious[4]	Unable to assess[5]	Not serious	Serious[6]	None	860/13475 (6.4%)		**RR 0.92** (0.81 to 1.04)	**5 fewer** (from 12 fewer to 0 more)	⨁◯◯◯ VERY LOW
Preterm birth											
3	Observational	Not serious[4]	Not serious	Not serious	Not serious	None	6381/129009 (4.9%)		**OR 1.25** (1.07 to 1.46)	**12 more** (from 3 more to 23 more)	⨁⨁◯◯ LOW
Birth weight											
3	Observational	Serious[7]	Unable to assess[5]	Not serious	Unable to assess[8]	None	3716		*Unable to meta-analyse* In a cohort analysis of the German GeliS trial, the daily intake of light drinks during pregnancy was associated nonsignificantly with growth measures in the child at birth (birthweight – adjusted regression coefficient –5; 95% CI -18, 6; BMI at birth – adjusted regression coefficient 0.005; 95% CI –0.020, 0.035; low birthweight – adjusted OR 0.99; 95% CI 0.91, 1.08; small for gestational age – adjusted OR 1.03; 95% CI 0.98, 1.09; and large for gestational age – adjusted OR 1.01; 95% CI 0.85, 1.07) *(223)*. In a Dutch cohort of pregnant women, intake of NSS-sweetened products before conception was associated with increased birthweight (adjusted z-score coefficient per 10 g per 1000 kcal/day: 0.001; 95% CI 0.000, 0.001; *P* = 0.002) (224). In a cohort study with women with gestational diabetes in Slovenia, intake of low-calorie beverages[9] was not associated with large for gestational age (Spearman correlation 0.118; *P* nonsignificant) *(225)*.		⨁◯◯◯ VERY LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[3]
NO. OF STUDIES/ COHORTS	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[1]	IMPRECISION	OTHER[2]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Offspring adiposity											
3	Observational	Not serious[4]	Unable to assess[5]	Not serious	Unable to assess[8]	None	5029		*Unable to meta-analyse* In a prospective cohort study of pregnant women conducted in Canada, the daily intake of NSS-sweetened beverages during pregnancy (compared with less than 1 serving per month) was associated with a 0.2 increase in infant BMI z-score (95% CI 0.02, 0.38) and a more than twofold increase in risk of overweight at 1 year of age (adjusted OR 2.19; 95% CI 1.23, 3.88). Adjustment was made for maternal BMI, diet quality, total energy intake and other obesity risk factors *(226)*. In a prospective cohort study conducted in the United States, consumption of NSS-sweetened beverages during pregnancy was not associated with BMI z-score or waist circumference in offspring at mid-childhood (median of 7.7 years of age) *(227)*. In a prospective cohort study conducted in Denmark, the children of women with gestational diabetes who consumed NSS-sweetened beverages at ≥1/day (compared with never) had a higher BMI z-score (β 0.59; 95% CI 0.23, 0.96) and risk of overweight or obesity (RR 1.93; 95% CI 1.24, 3.01) at 7 years of age *(228)*.		⨁◯◯◯ VERY LOW
Offspring asthma											
1	Observational	Not serious[4]	Unable to assess[5]	Not serious	Not serious	None	1536/31849 (4.8%)		**OR 1.20** (1.07 to 1.35)	**10 more** (from 3 more to 17 more)	⨁◯◯◯ VERY LOW
Offspring allergies											
1	Observational	Not serious[4]	Unable to assess[5]	Not serious	Serious[6]	None	1855/37971 (4.9%)		**OR 1.11** (0.86 to 1.43)	**5 more** (from 7 fewer to 21 more)	⨁◯◯◯ VERY LOW

ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY[3]
NO. OF STUDIES/ COHORTS	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS[1]	IMPRECISION	OTHER[2]	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
Offspring neurocognition											
1	Observational	Not serious[4]	Unable to assess[5]	Not serious	Unable to assess[8]	None	1234		In a prospective cohort study following children in utero up to 7 years of age, early- and mid-childhood cognition scores were inversely associated with maternal intake of NSS-sweetened beverages during pregnancy (PPVT-III, early childhood: –1.2; 95% CI –2.9, 0.5; total WRAVMA, early childhood: –1.5; 95% CI –2.9, –0.1; KBIT-II verbal, mid-childhood: –3.2; 95% CI –5.0, –1.5; KBIT-II nonverbal, mid-childhood: –2.0; 95% CI –4.3, 0.2; WRAVMA drawing, mid-childhood: –1.7; 95% CI –4.1, 0.6; WRAML visual memory, mid-childhood: –0.1; 95% CI –0.7, 0.5), but not with childhood intake of NSS-sweetened beverages at 3 years *(215)*.		⨁◯◯◯ VERY LOW

BMI: body mass index; CI: confidence interval; KBIT-II, Kaufman Brief Intelligence Test 2nd edition; OR: odds ratio; PPVT-III: Peabody Picture Vocabulary Test-III; NSS: non-sugar sweeteners; OR: odds ratio; RR: relative risk; WRAML: Wide Range Assessment of Memory and Learning; WRAVMA: Wide Range Assessment of Visual Motor Ability.

1 All studies were conducted in the population of interest (i.e. general population of pregnant women). Although most studies were conducted in North America and Europe, and very few were conducted in low- and middle-income countries (LMICs), physiological responses to NSS are not expected to differ significantly across different populations. Behavioural responses may differ between those who are habituated to sweet-tasting foods and beverages and those whose diets contain little to no sweet foods or beverages. However, in populations with limited exposure to NSS (which may be found more widely in LMICs), the effects observed on the consumption of NSS in this review may be largely irrelevant unless they are introduced to these populations.

2 Too few studies to conduct funnel plot analyses.

3 Outcomes specific to pregnancy were not prioritized by the WHO NUGAG Subgroup on Diet and Health, and therefore there is no designation as critical or important.

4 Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

5 Unable to assess inconsistency as there is only a single study, or a small number of studies that could not be meta-analysed. Downgraded once.

6 One bound of the 95% CI includes potentially important benefit or harm and the other bound crosses the null in the opposite direction, and/or the sample size is small. Downgraded once.

7 Mean Newcastle–Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

8 Unable to assess. Downgraded once.

9 Based on the reporting of other beverage types in this study, it was determined that "low-calorie beverages" consisted primarily, if not entirely, of NSS-sweetened beverages.

ANNEX 8.

Funnel plots

Fig. A8.1 Body weight (kg) among adults in randomized controlled trials

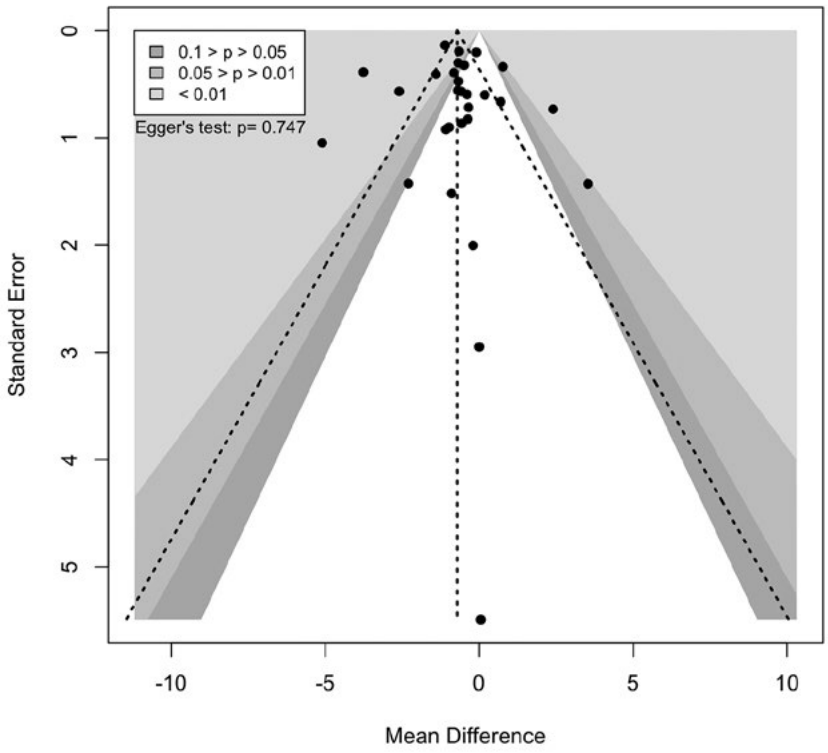


Fig. A8.2. Body mass index (kg/m²) among adults in randomized controlled trials

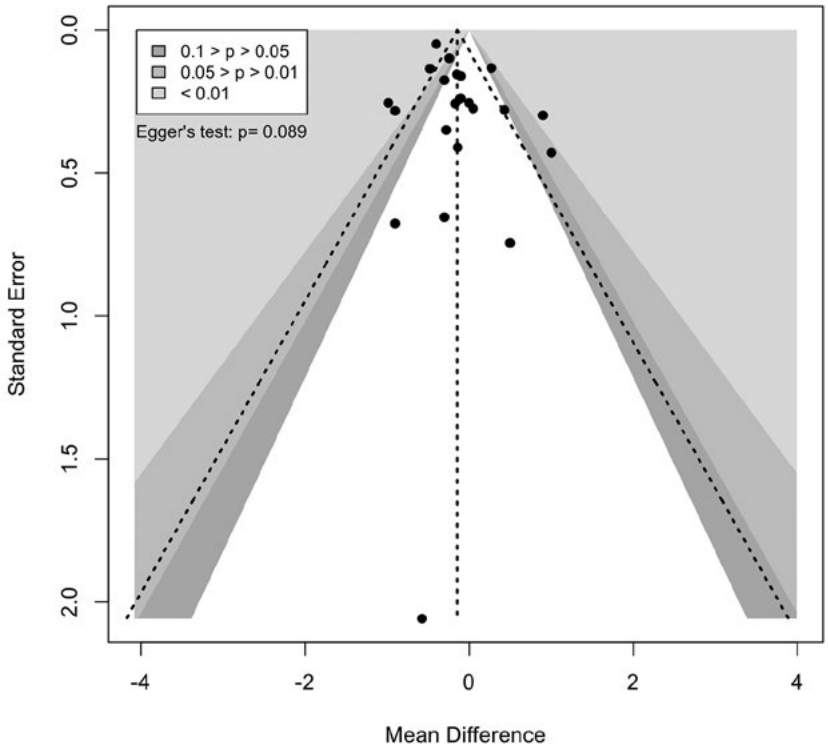


Fig. A8.3 Fasting glucose (mmol/L) among adults in randomized controlled trials

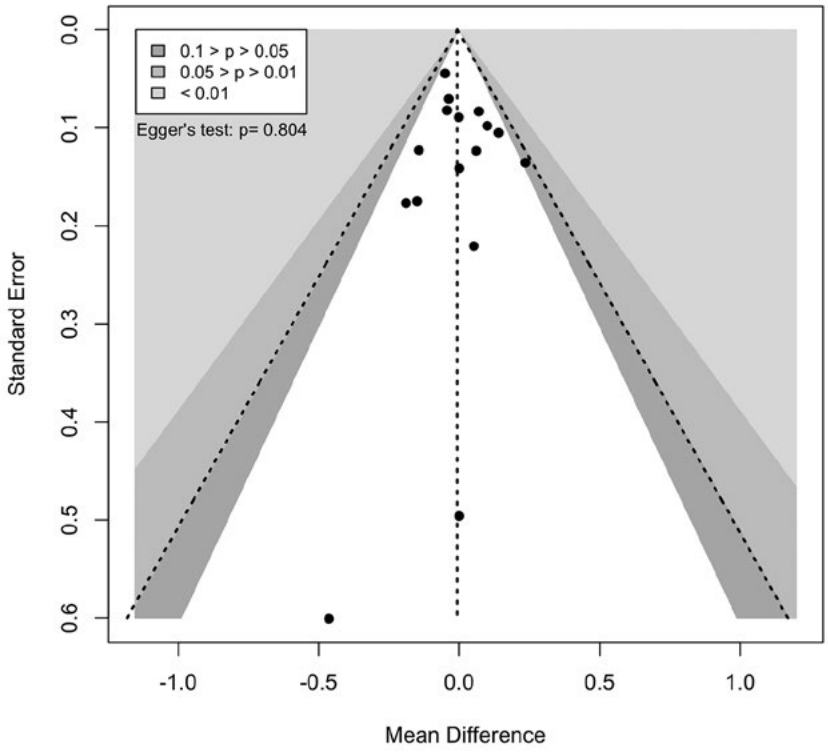


Fig. A8.4 Type 2 diabetes among adults in cohort studies

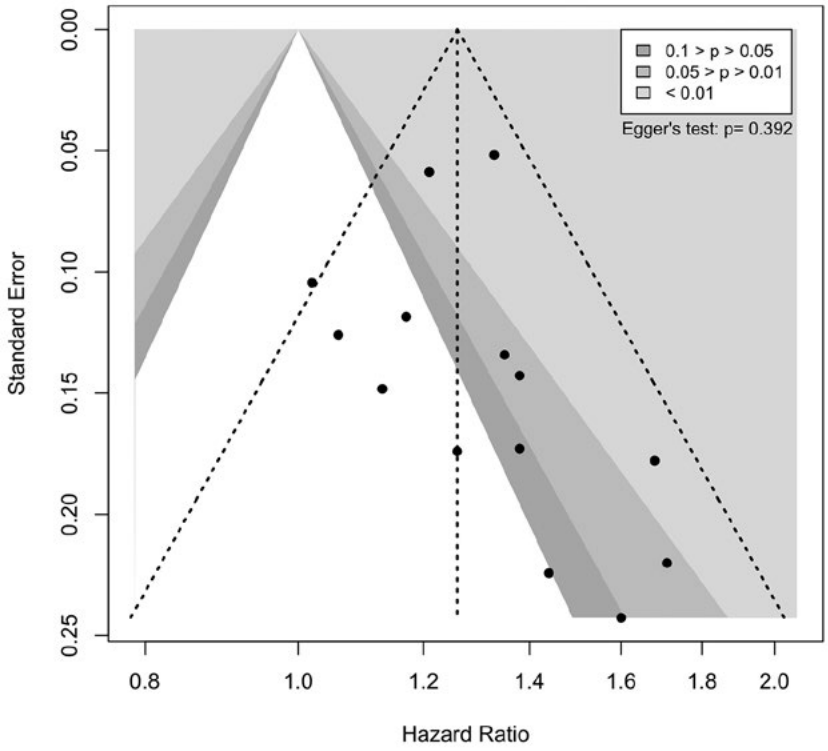


Fig. A8.5 Funnel plot of HOMA-IR among adults in randomized controlled trials

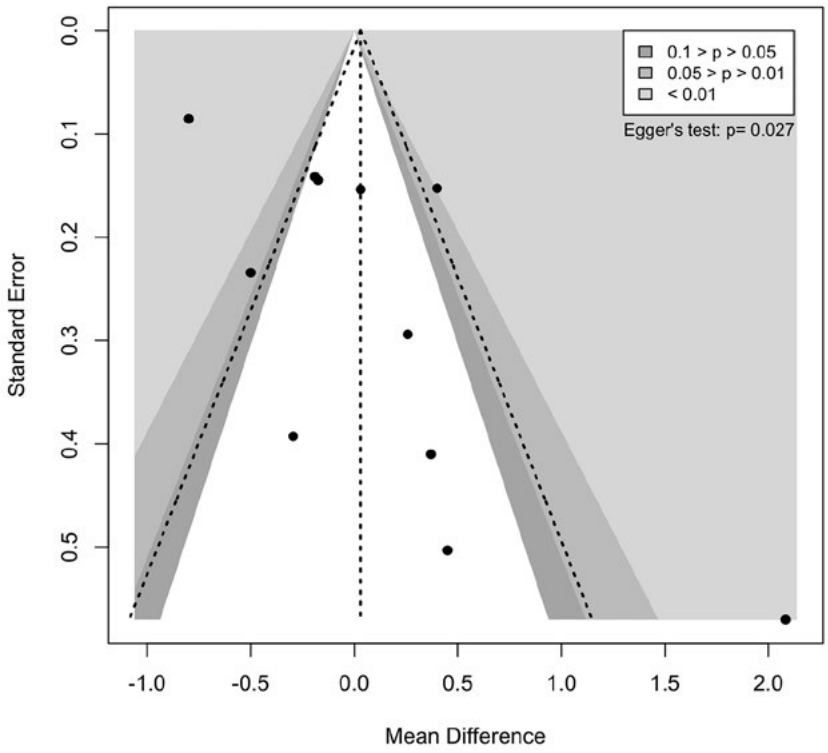


Fig. A8.6 Systolic blood pressure (mmHg) among adults in randomized controlled trials

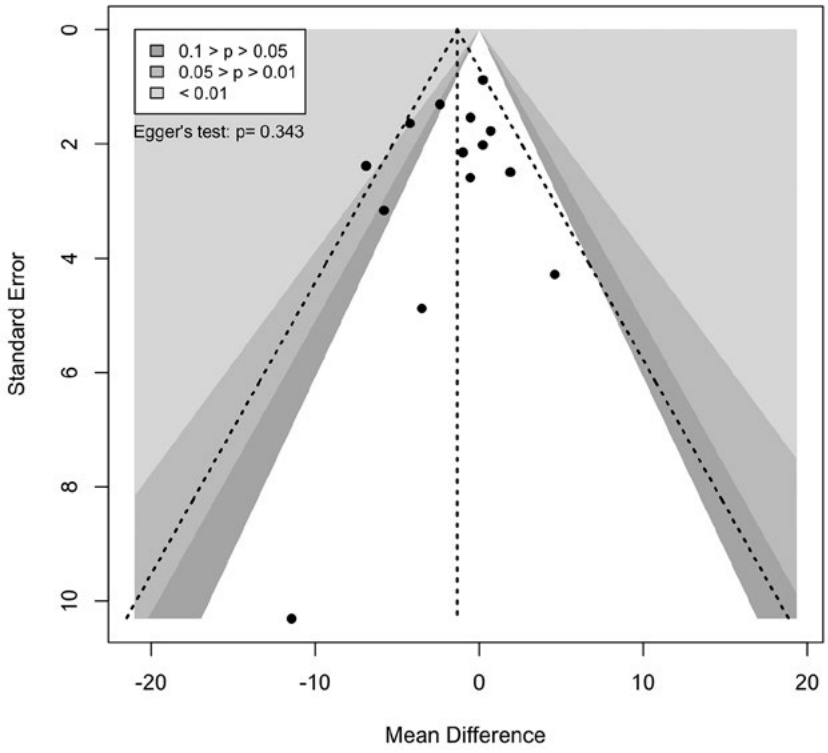


Fig. A8.7 Diastolic blood pressure (mmHg) among adults in randomized controlled trials

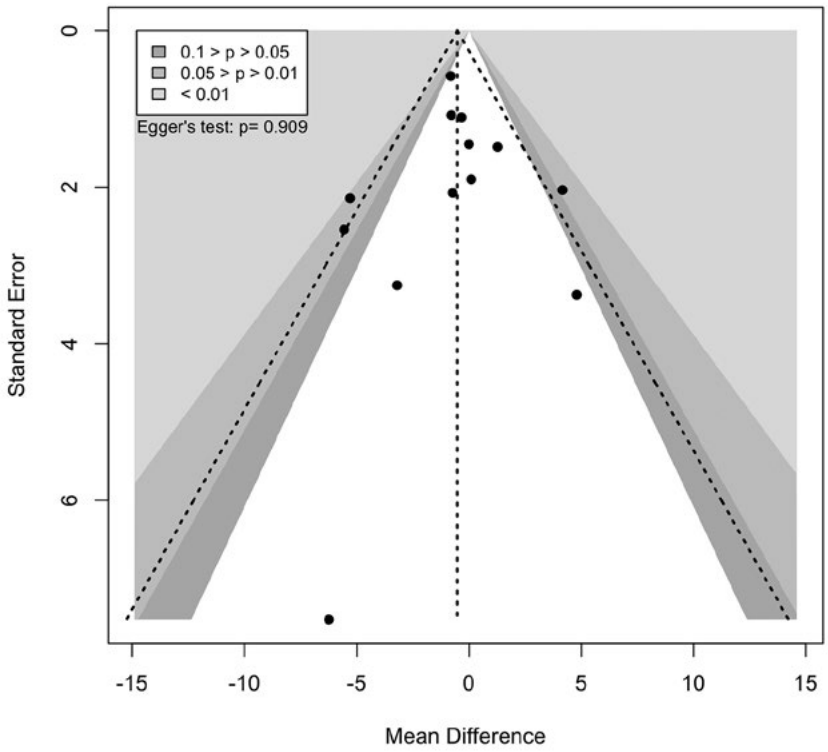


Fig. A8.8 LDL cholesterol (mmol/L) among adults in randomized controlled trials

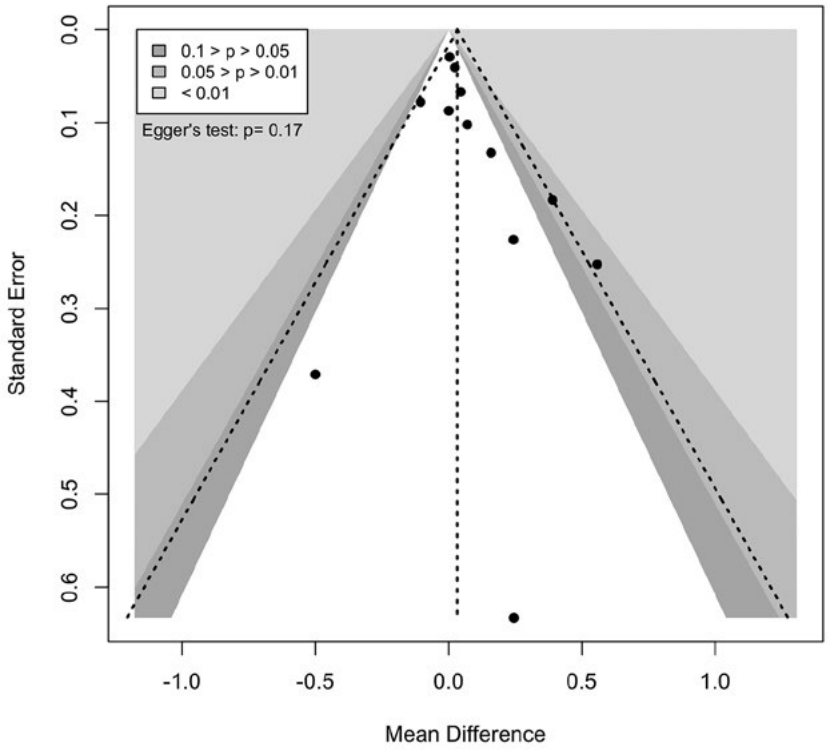


Fig. A8.9 HDL cholesterol (mmol/L) among adults in randomized controlled trials

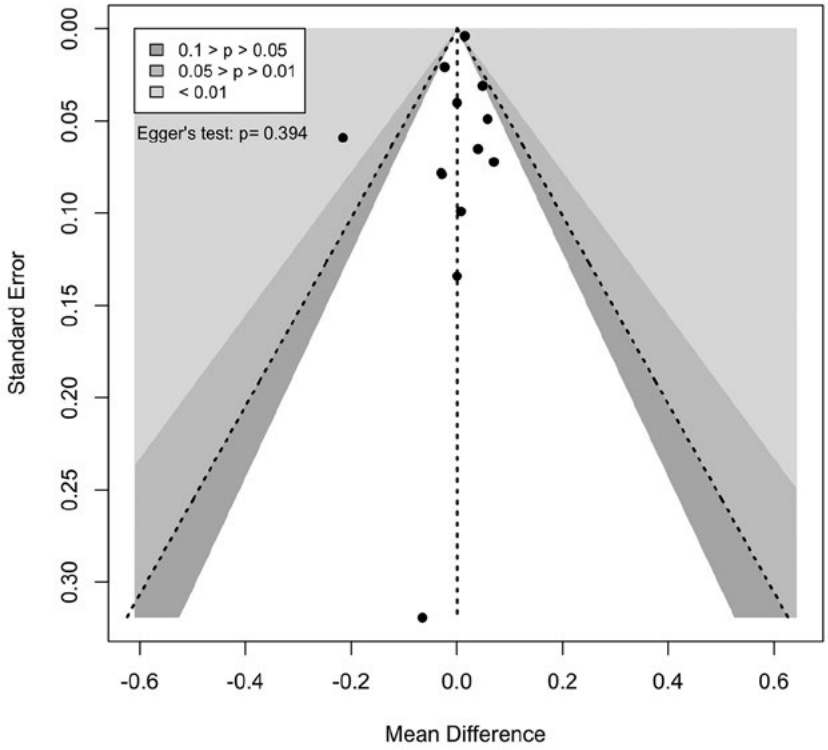


Fig. A8.10 Bladder cancer among adults in case–control studies

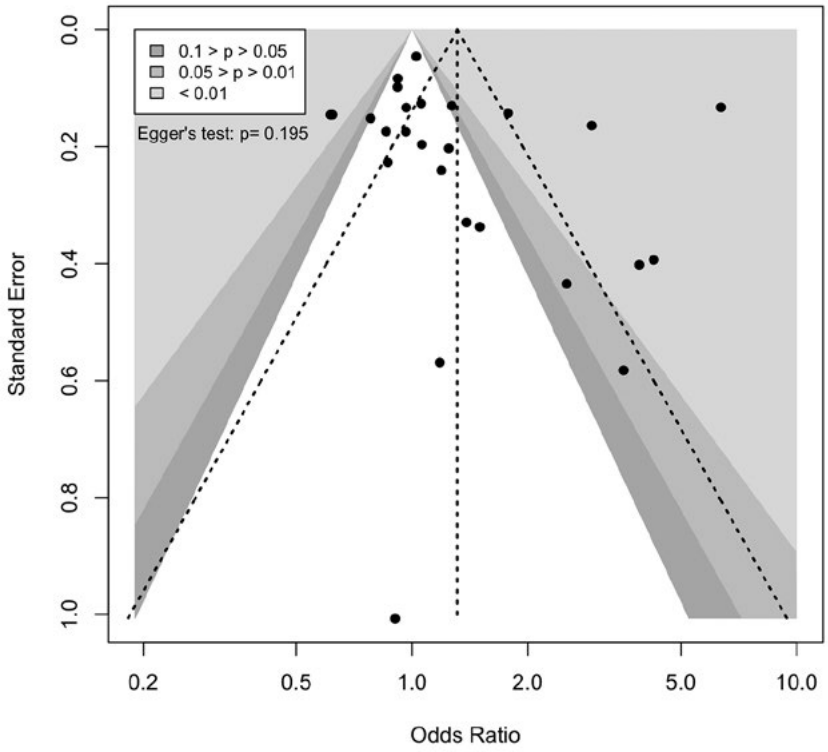


Fig. A8.11 Energy intake (kJ/day) among adults in randomized controlled trials

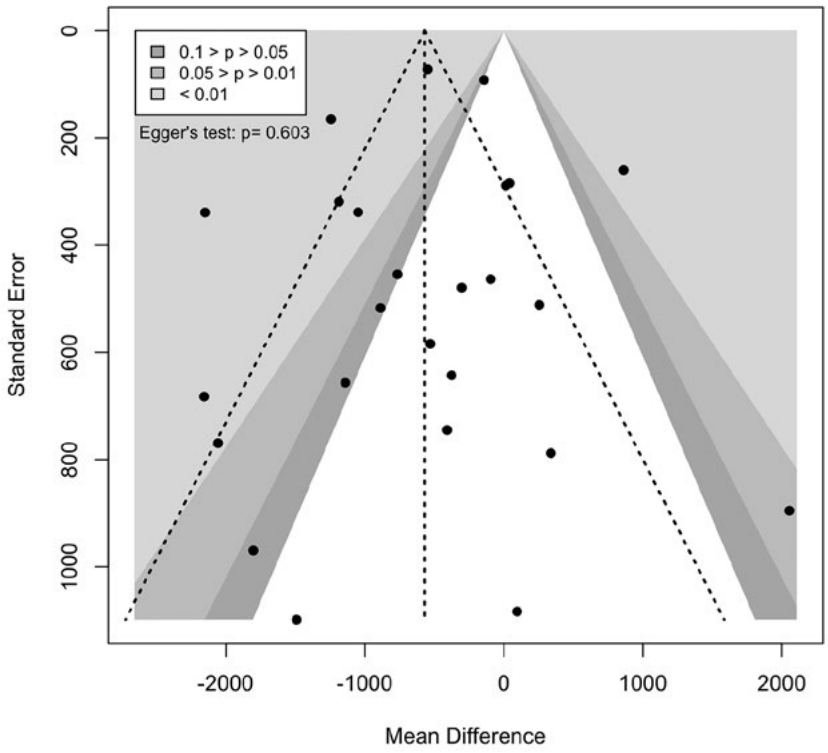
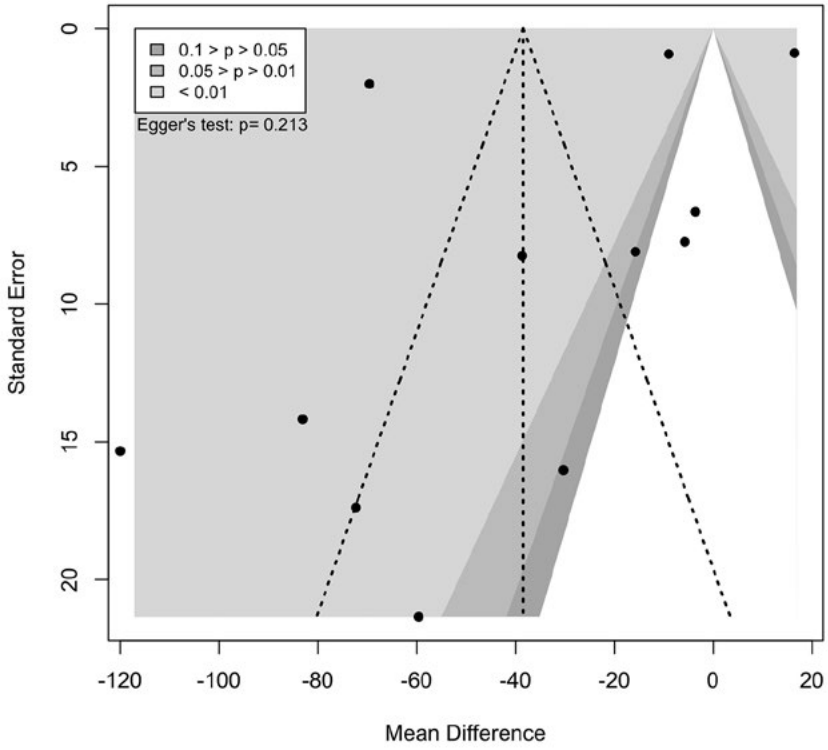


Fig. A8.12 Sugars intake (g/day) among adults in randomized controlled trials



ANNEX 9.

Supplementary figures

Fig. A9.1 Effect of NSS on waist circumference (cm) in randomized controlled trials in adults

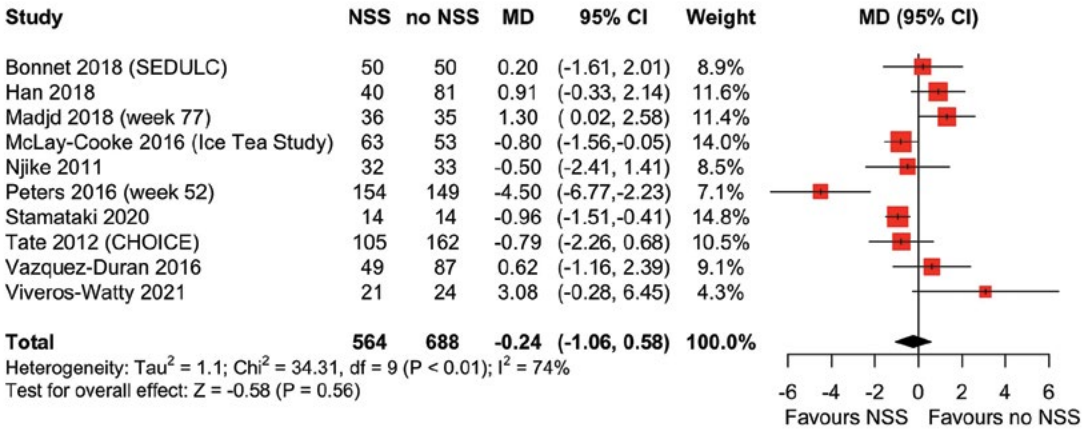


Fig. A9.2 Effect of NSS on waist-to-hip ratio in randomized controlled trials in adults

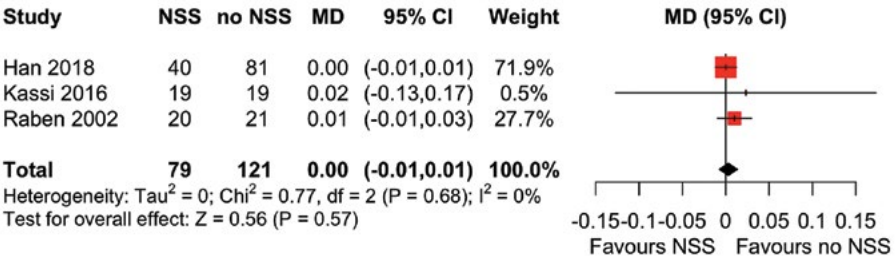


Fig. A9.3 Effect of NSS on fat mass (kg) in randomized controlled trials in adults

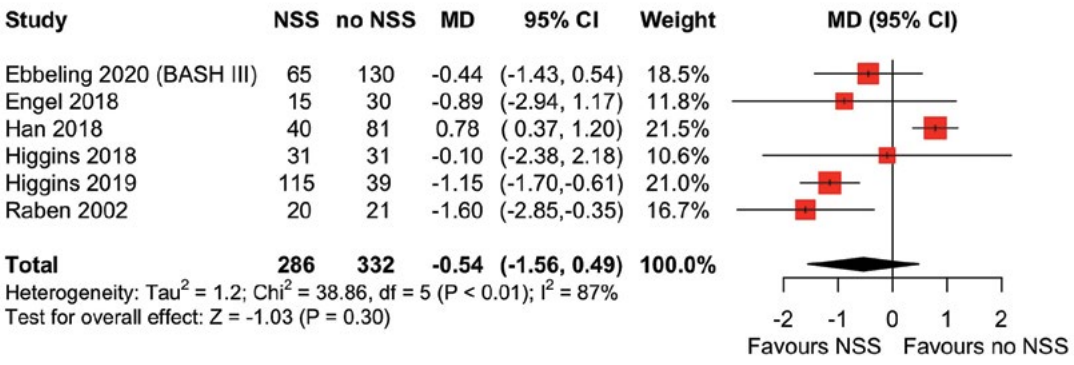


Fig. A9.4 Effect of NSS on fat mass (%) in randomized controlled trials in adults

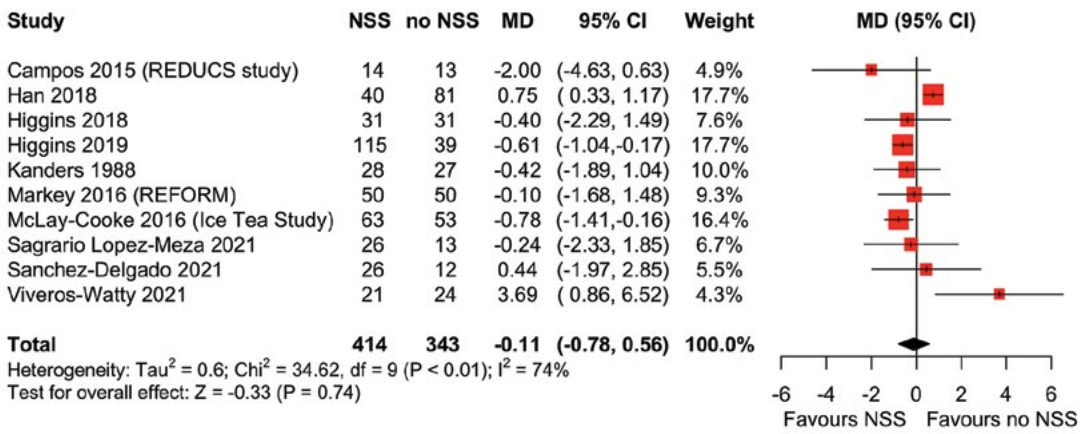


Fig. A9.5 Effect of NSS on lean mass (kg) in randomized controlled trials in adults

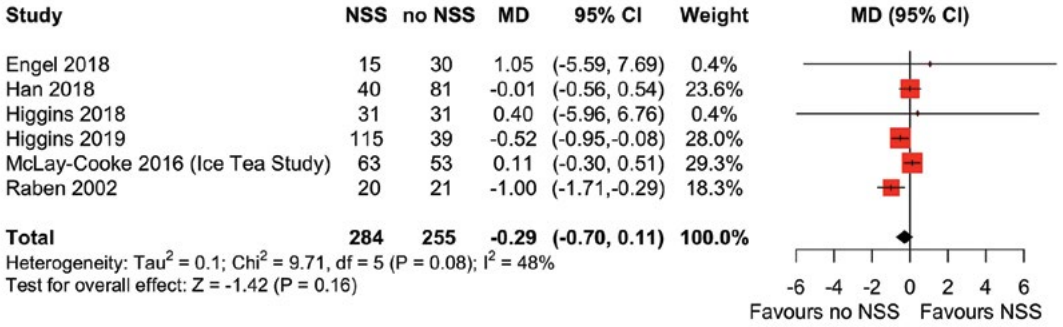


Fig. A9.6 Association between NSS and body weight (kg) in prospective cohort studies (continuous effect) in adults

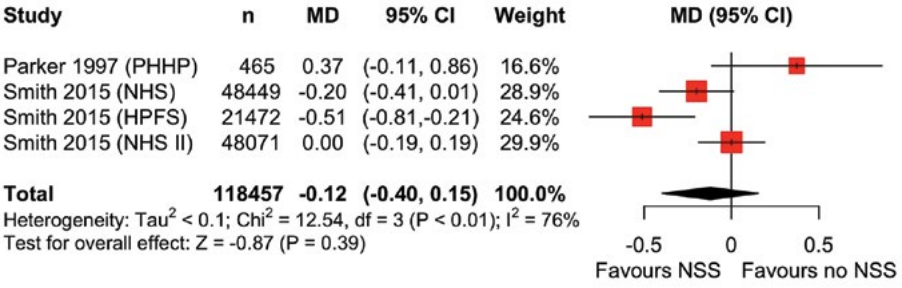


Fig. A9.7 Association between NSS and body weight (kg) in prospective cohort studies (highest versus lowest) in adults

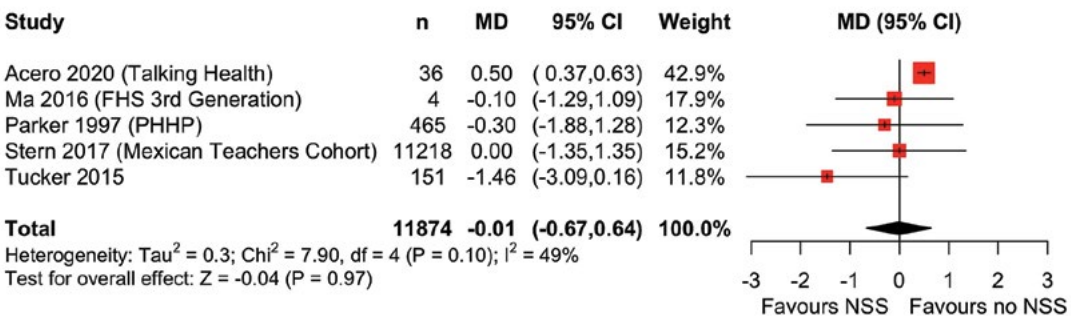


Fig. A9.8 Association between NSS and waist circumference (cm) in cohort studies (highest versus lowest) in adults

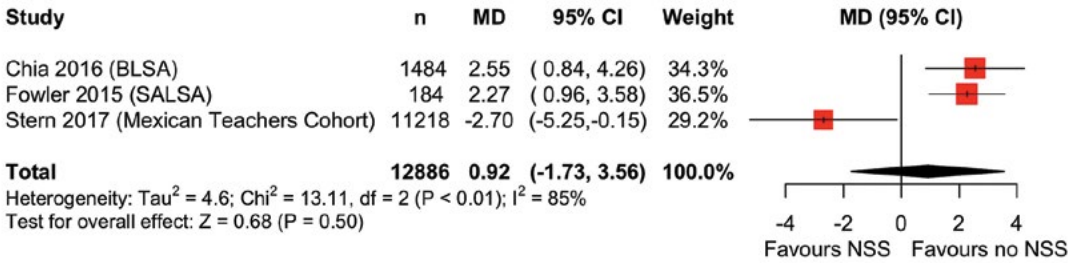


Fig. A9.9 Association between NSS and abdominal obesity in cohort studies (highest versus lowest) in adults

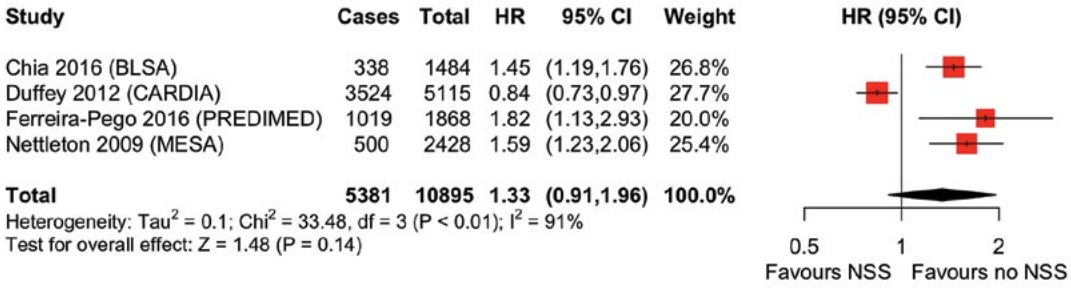
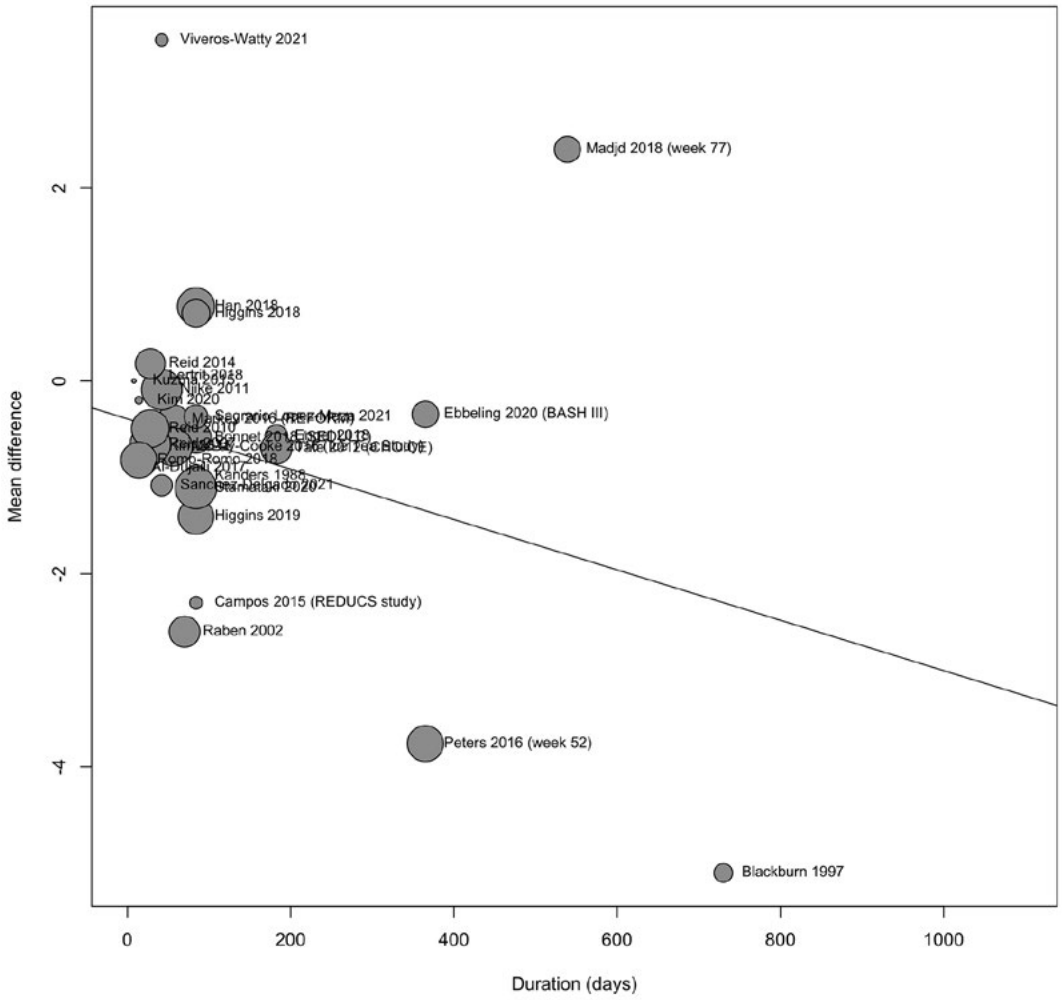


Fig. A9.10 Meta-regression: body weight results in randomized controlled trials by study duration



Note: B coefficient = –0.002; *P* = 0.052.

Fig. A9.11 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by study duration, in adults

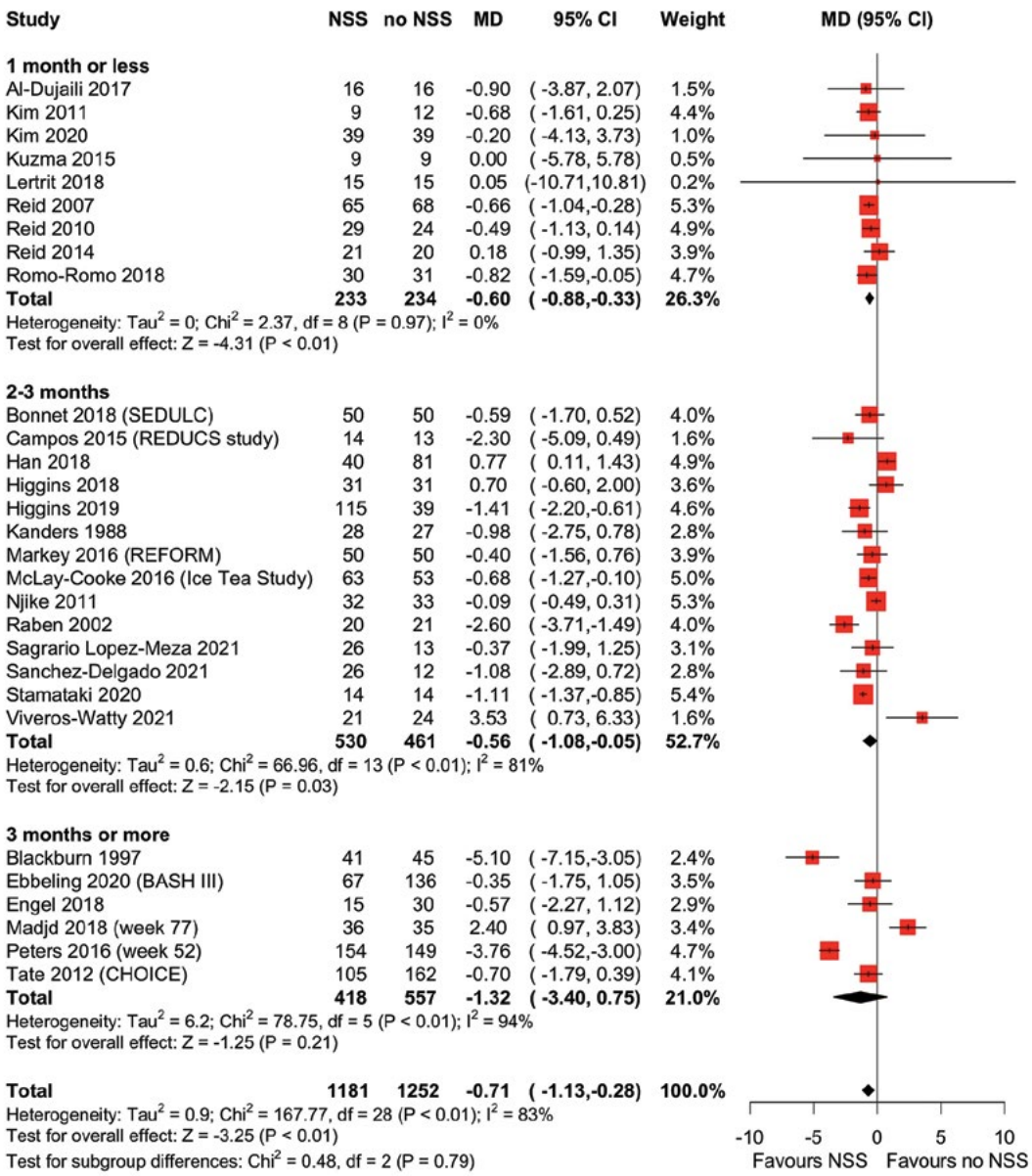


Fig. A9.12 Effect of NSS on body mass index (kg/m²) in randomized controlled trials, subgrouped by consumption pattern, in adults

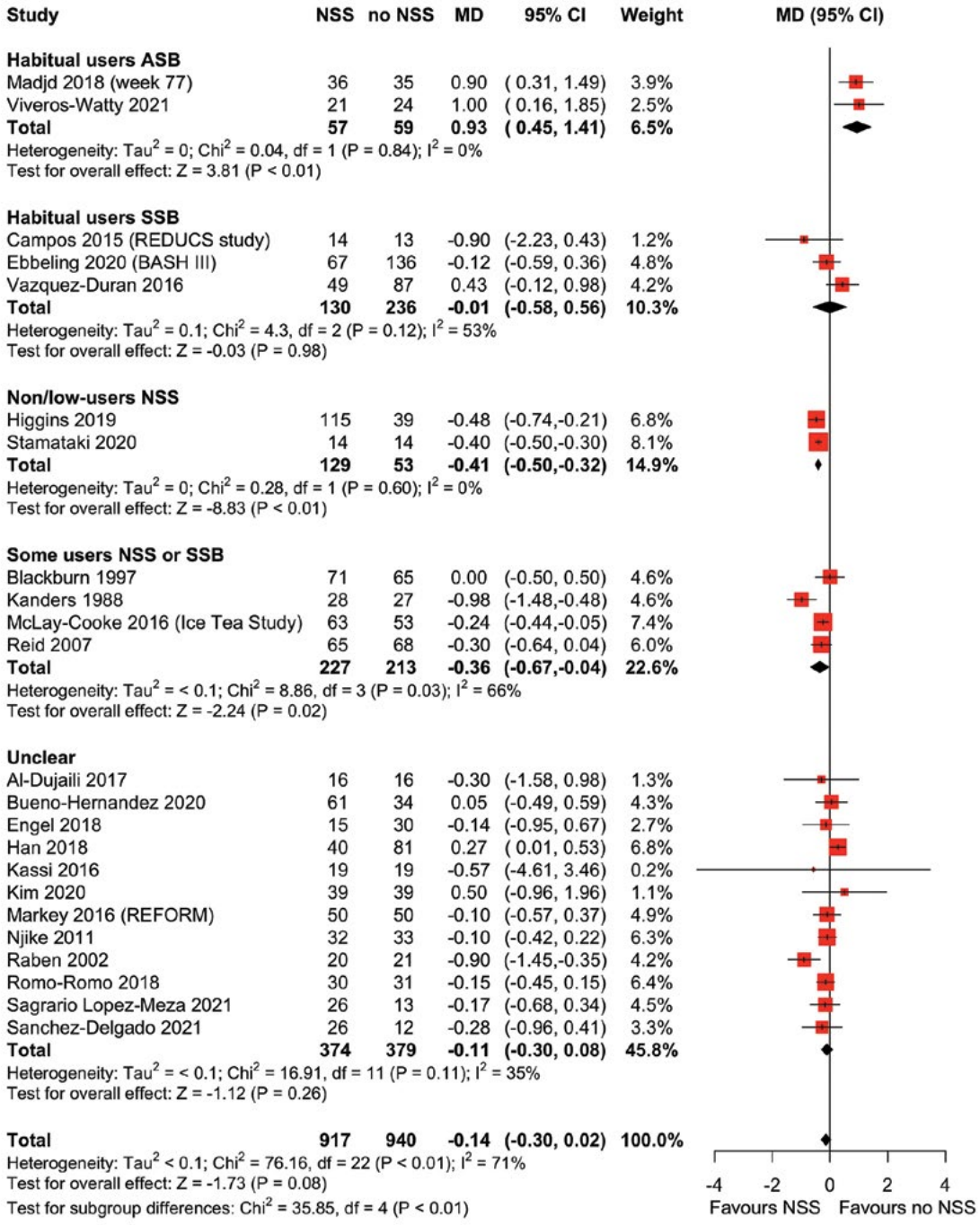
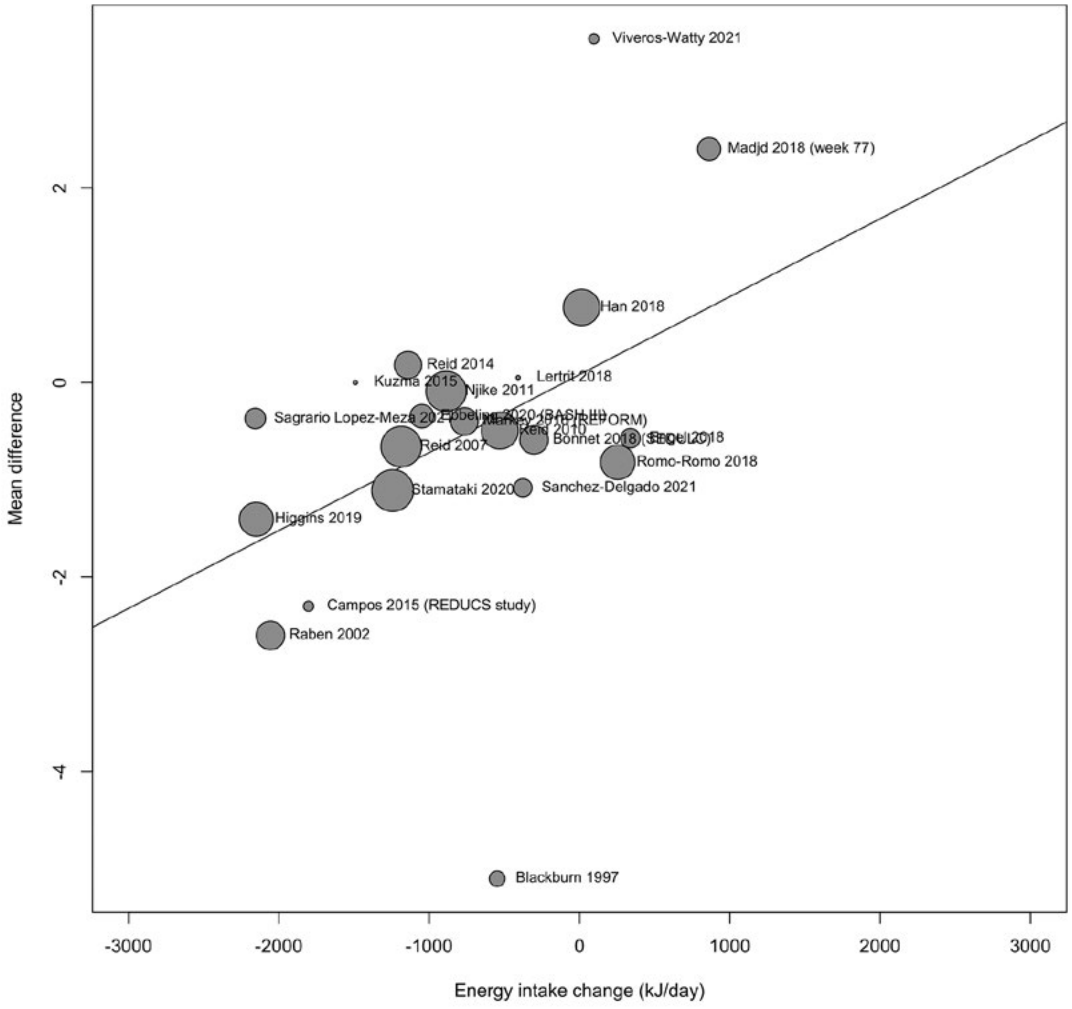
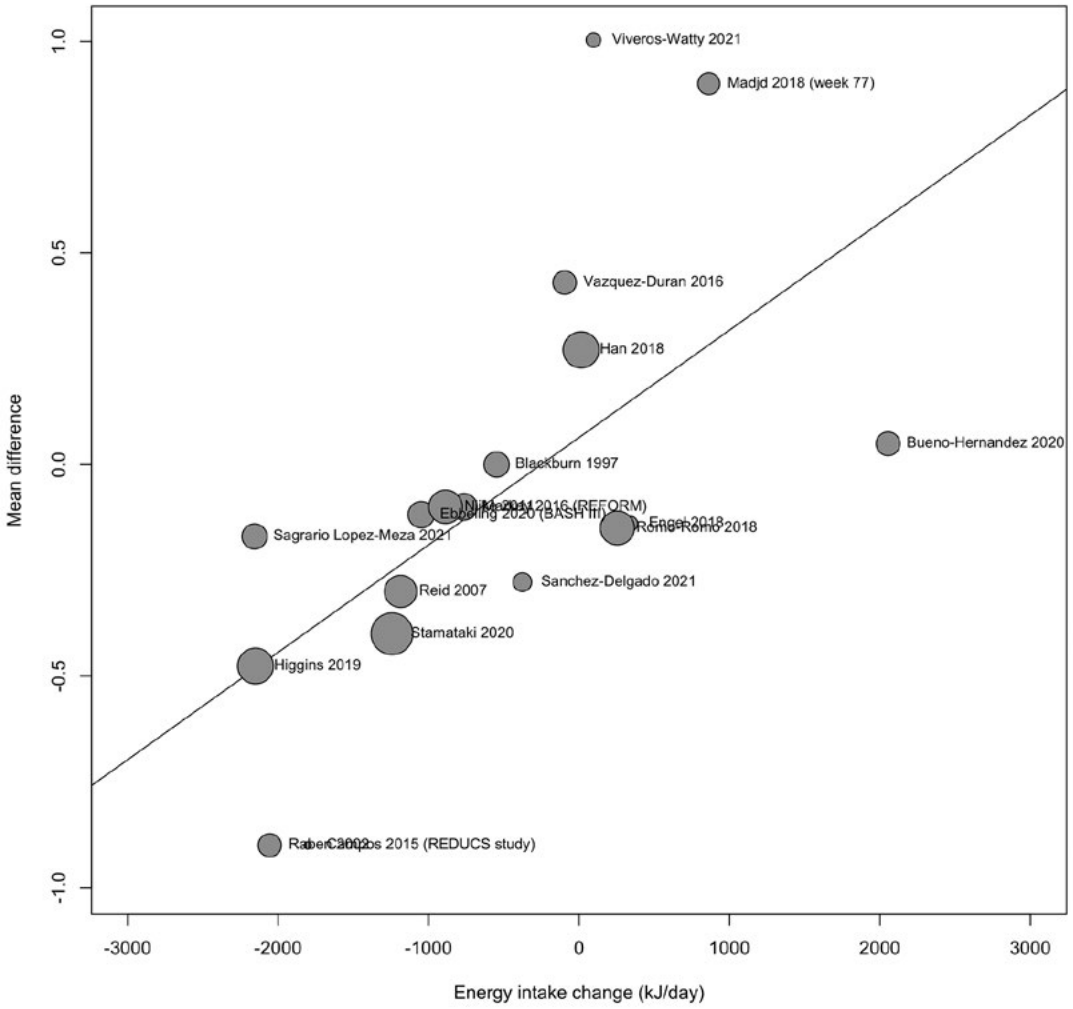


Fig. A9.13 Meta-regression: body weight by energy intake in randomized controlled trials



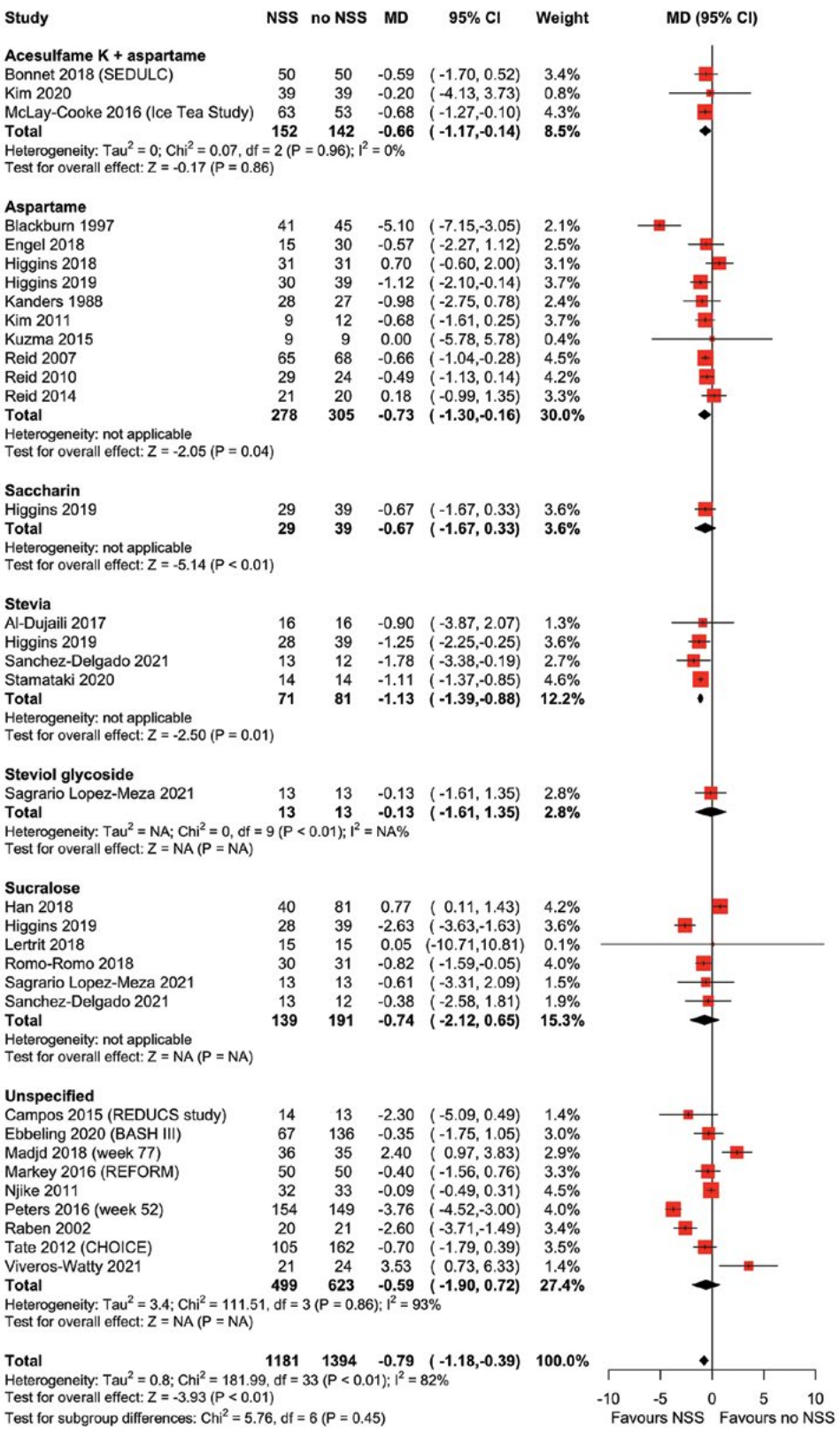
Note: B coefficient = 0.008; *P* = 0.009.

Fig. A9.14 Meta-regression: body mass index by energy intake in randomized controlled trials



Note: B coefficient = 0.0003; $P < 0.001$.

Fig. A9.15 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by type of NSS, in adults



Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

Fig. A9.16 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by delivery mode, in adults

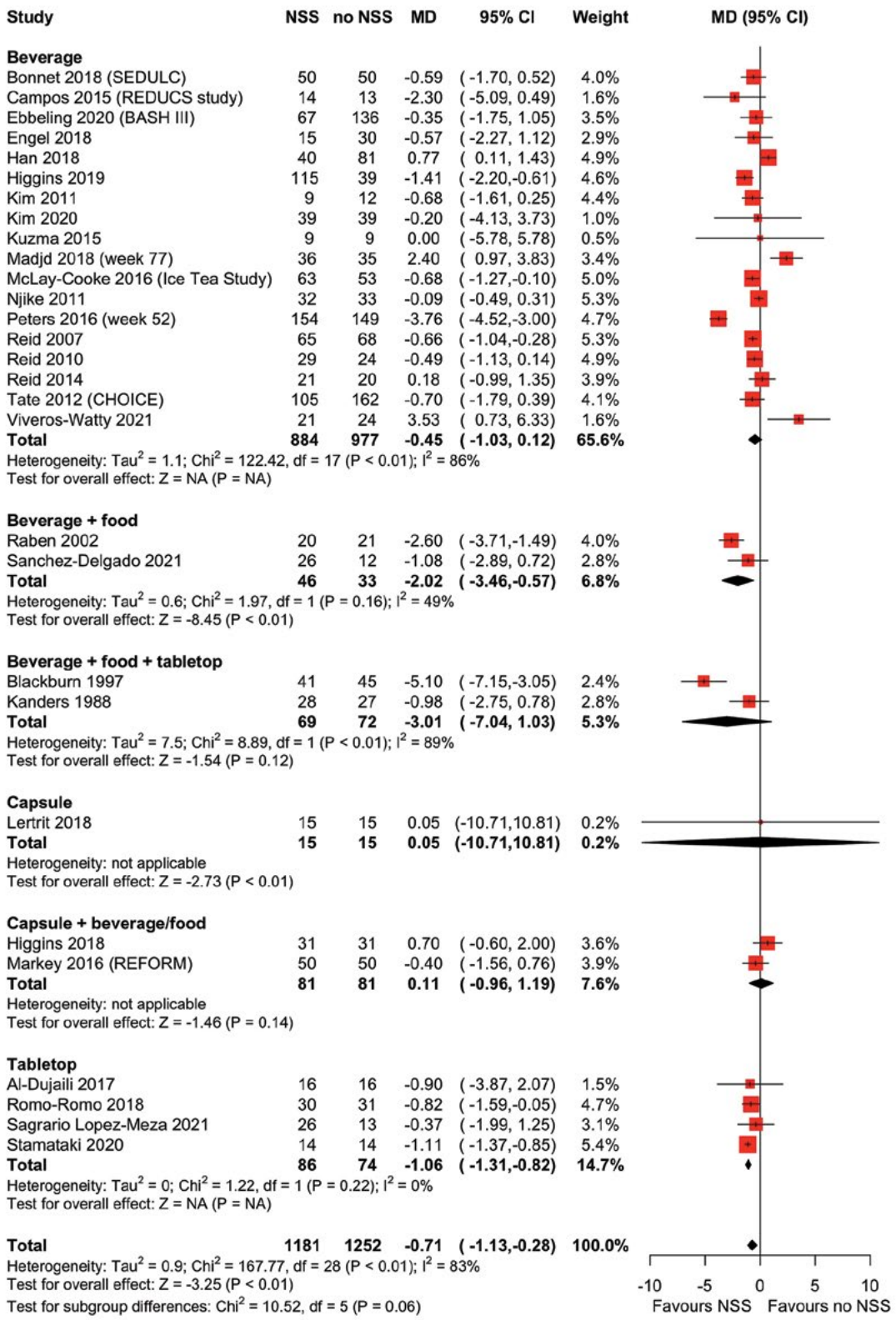


Fig. A9.17 Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by consumption pattern

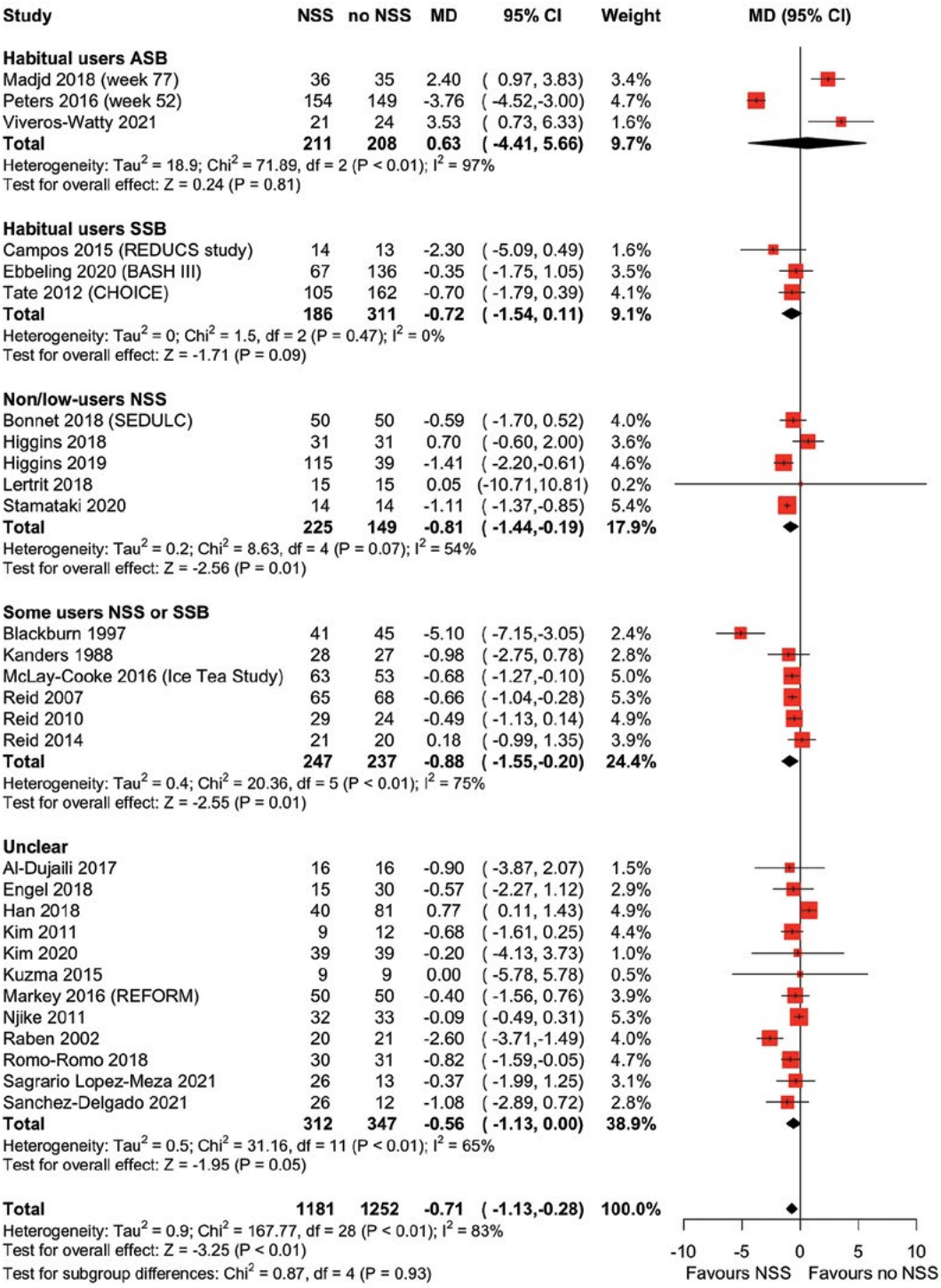


Fig. A9.18 Effect of NSS on body mass index (kg/m²) in randomized controlled trials, subgrouped by weight status, in adults

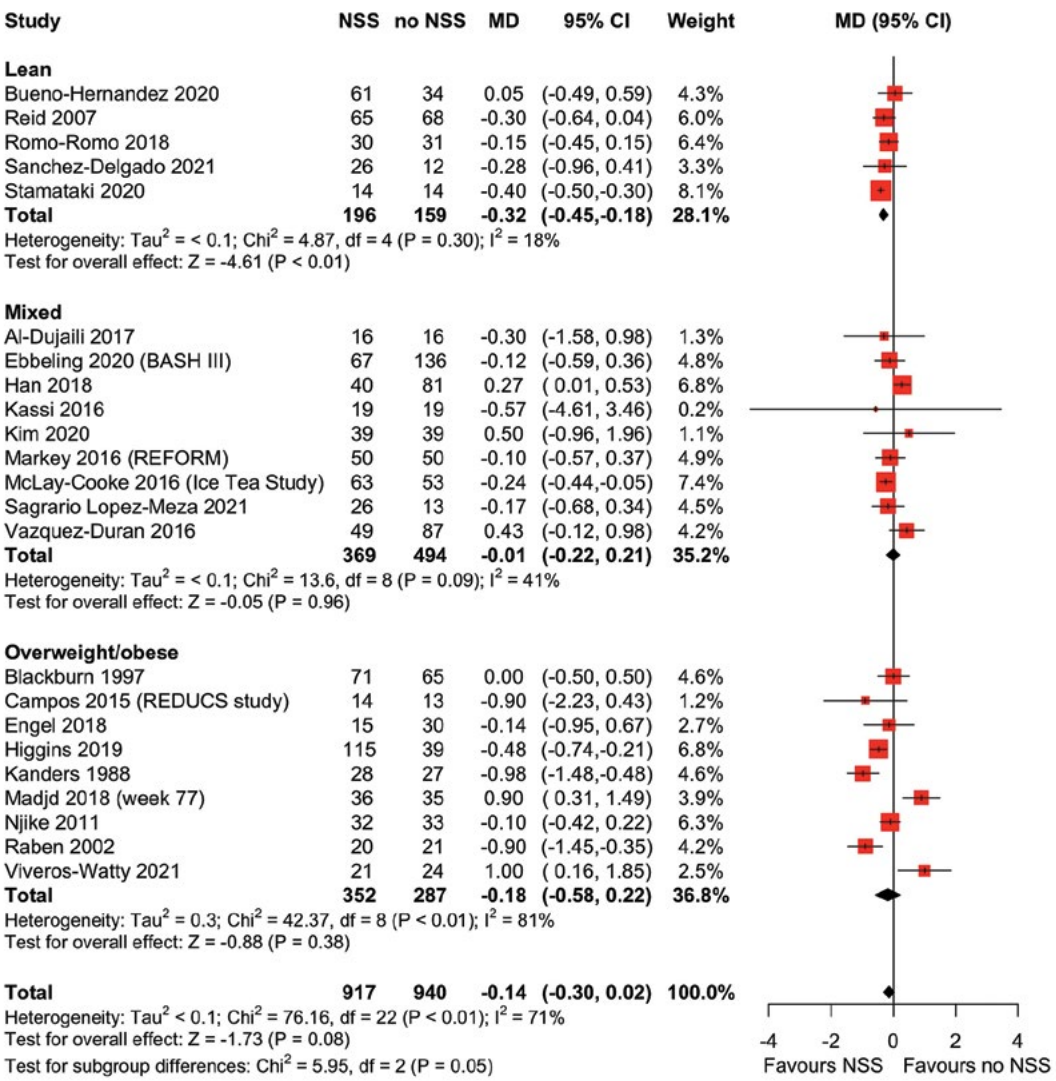


Fig. A9.19 Effect of NSS on body mass index (kg/m²) in randomized controlled trials, subgrouped by delivery mode, in adults

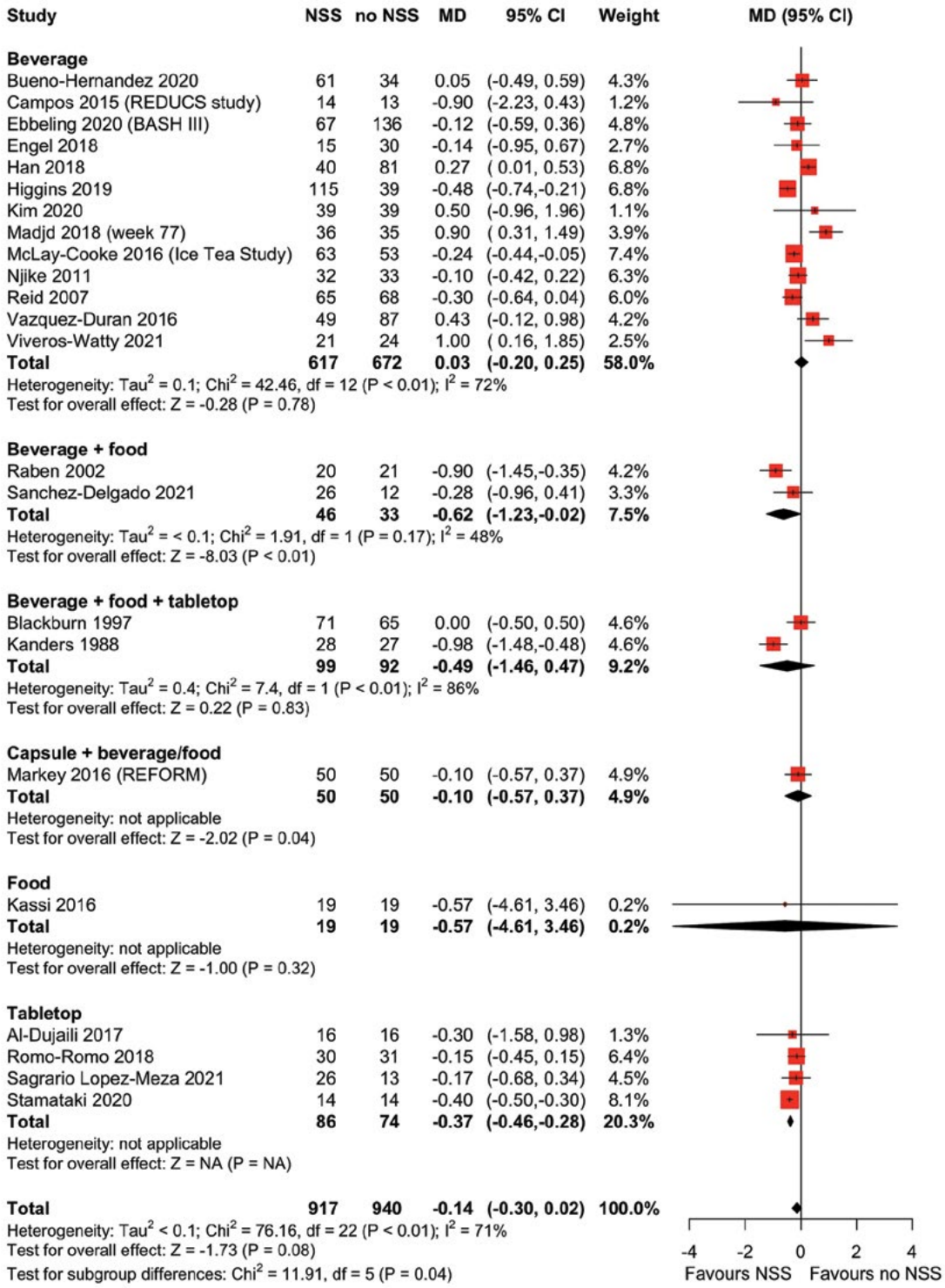
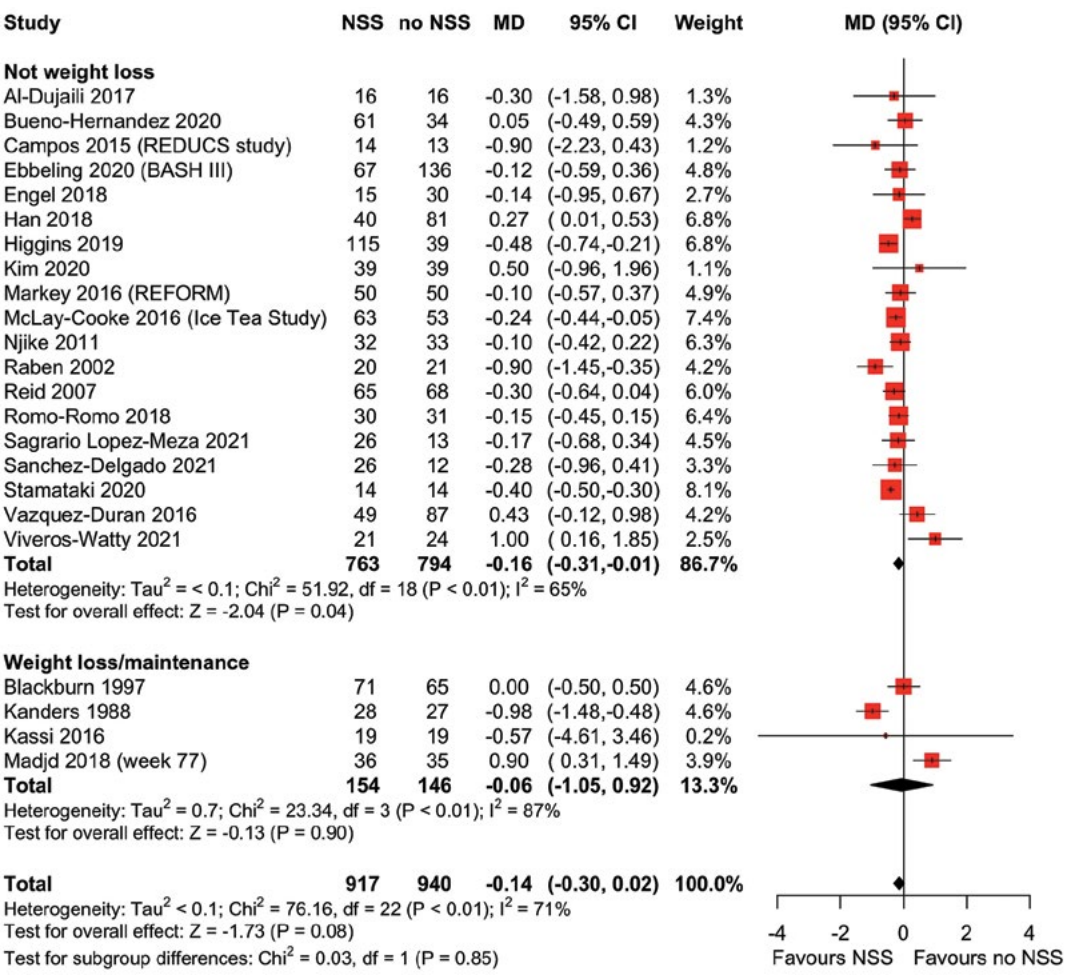
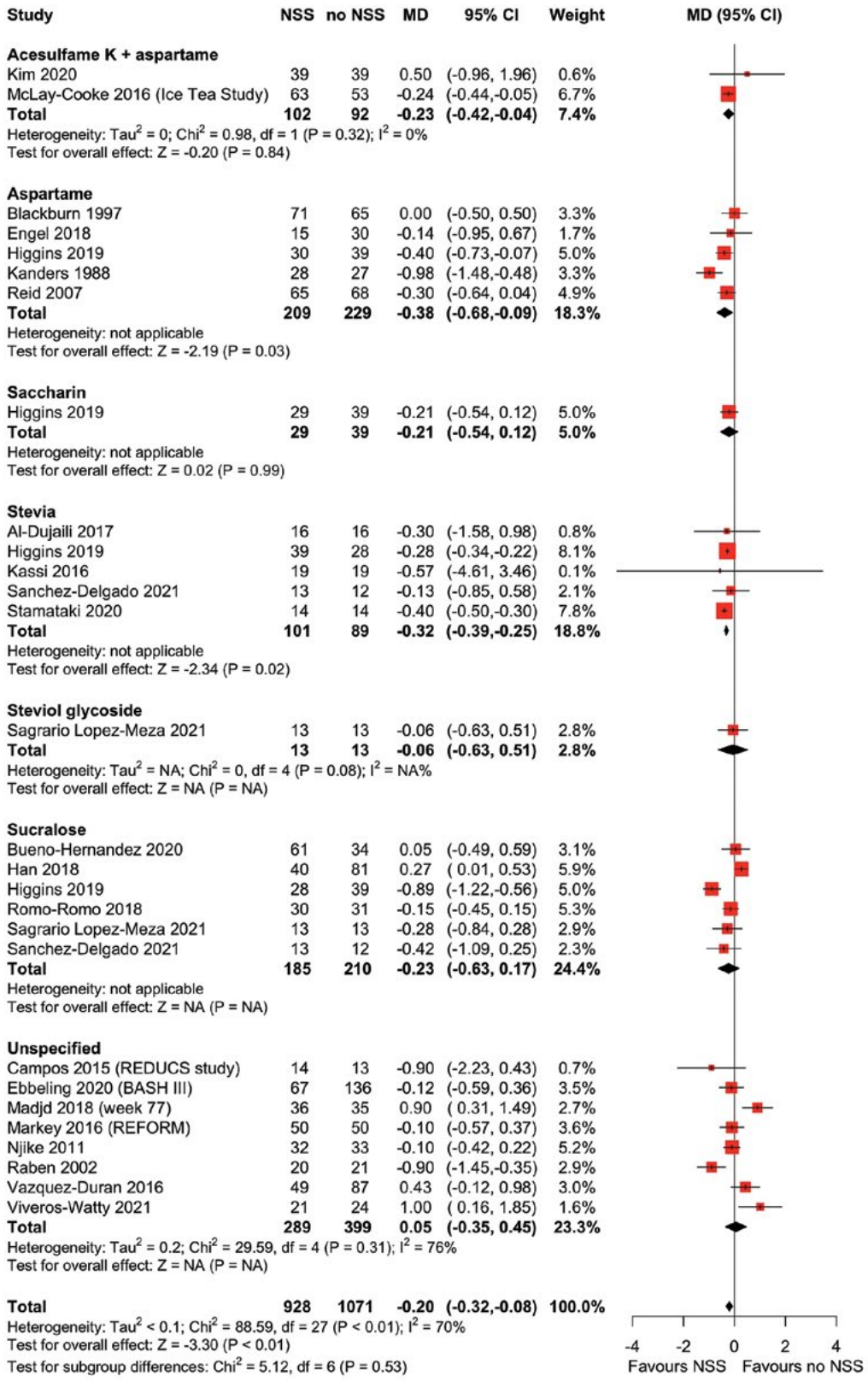


Fig. A9.20 Effect of NSS on body mass index (kg/m²), subgrouped by study design (weight loss studies versus non–weight loss studies), in adults



Note: Weight loss studies were those in which the participants were instructed to restrict energy intake AND consume NSS or control. Weight maintenance studies were those that followed up participants after active weight loss, with instructions on energy intake designed to prevent weight gain. Non–weight loss studies were those that had no intentional weight loss component.

Fig. A9.21 Effect of NSS intake on body mass index (kg/m²), subgrouped by NSS type



Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

Fig. A9.22 Effect of NSS on body weight (kg) in nonrandomized controlled trials in adults

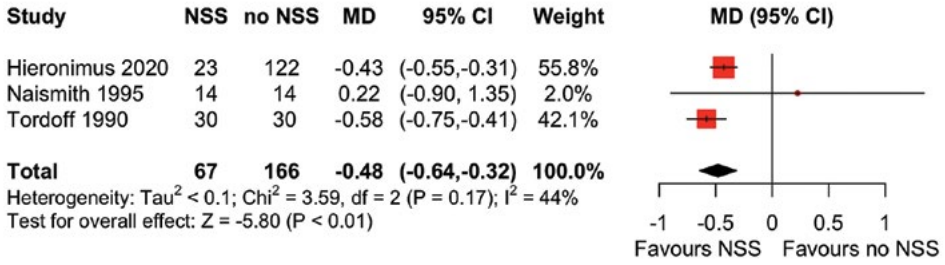


Fig. A9.23 Effect of NSS on fasting glucose (mmol/L) in randomized controlled trials in adults

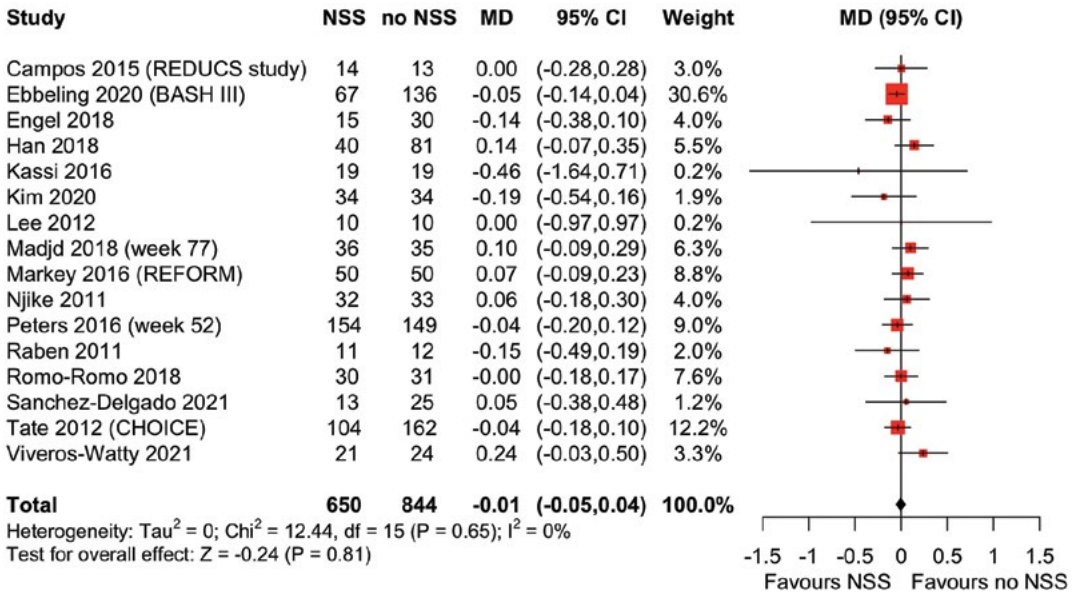


Fig. A9.24 Effect of NSS on fasting insulin (pmol/L) in randomized controlled trials in adults

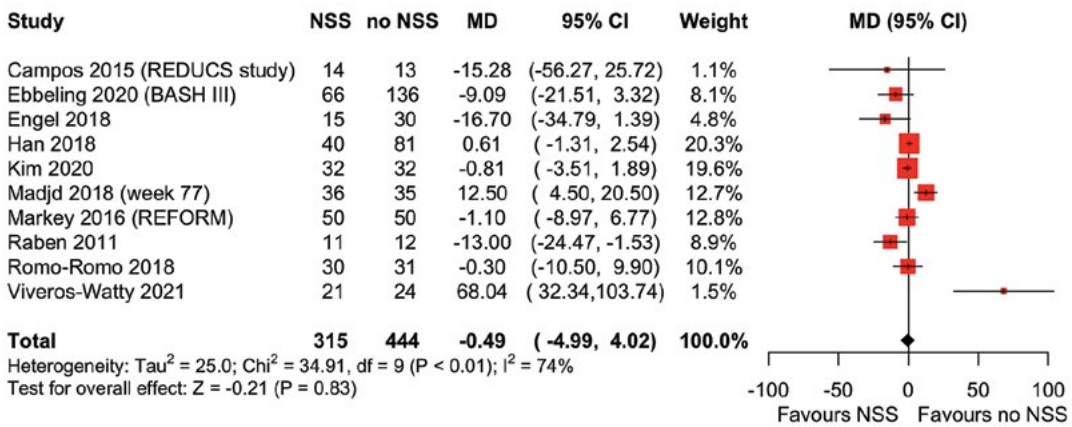


Fig. A9.25 Effect of NSS on HbA1c (%) in randomized controlled trials in adults

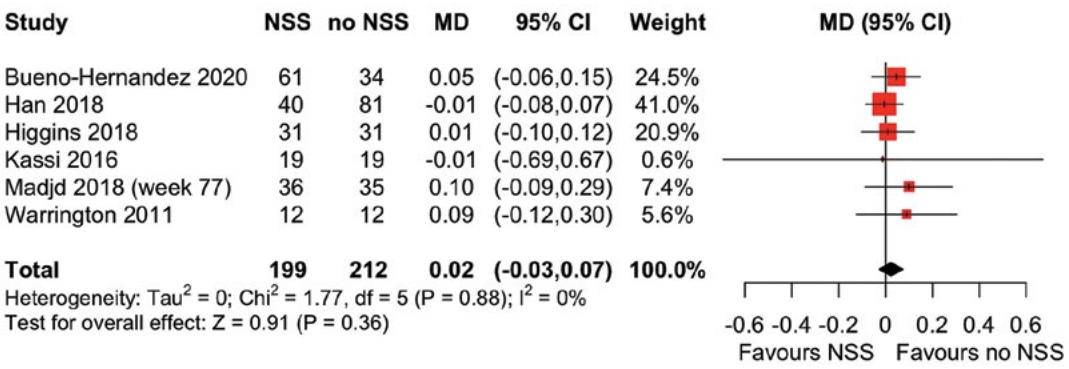


Fig. A9.26 Effect of NSS on HOMA-IR in randomized controlled trials in adults

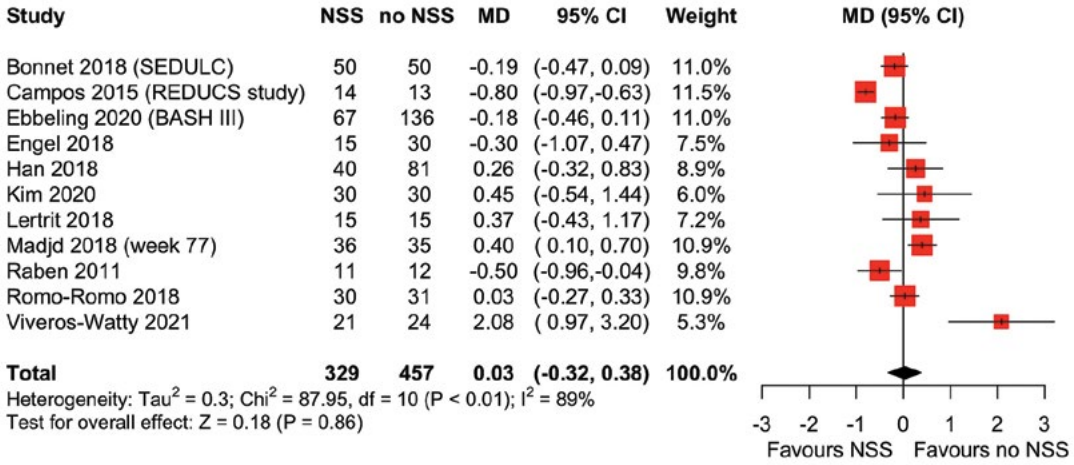
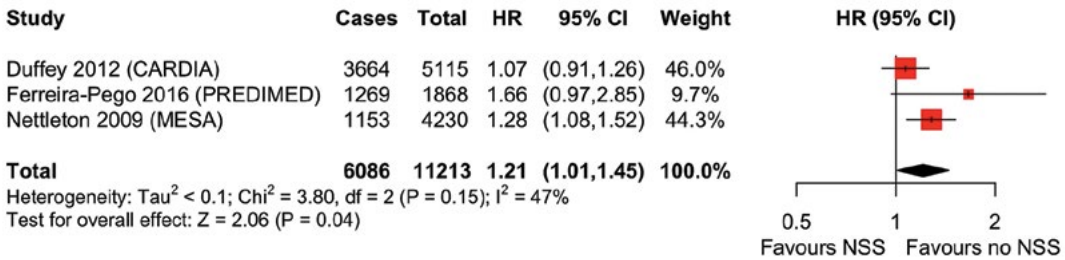


Fig. A9.27 Association between NSS and high fasting glucose in cohort studies (highest versus lowest) in adults



Note: High fasting glucose is defined as ≥5.5 mmol/L.

Fig. A9.28 Association between NSS and haemorrhagic stroke in cohort studies (highest versus lowest) in adults

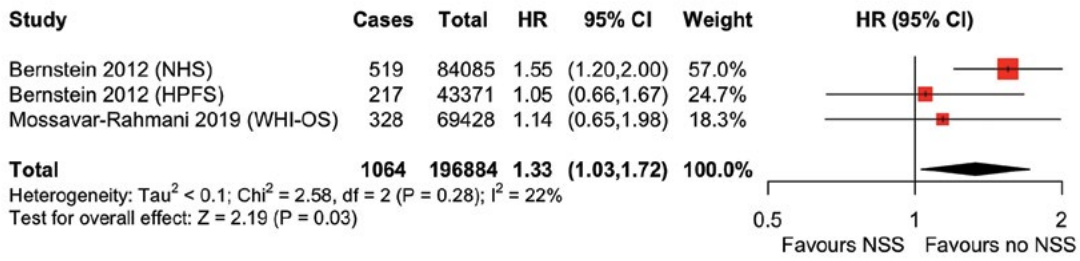


Fig. A9.29 Association between NSS and ischaemic stroke in cohort studies (highest versus lowest) in adults

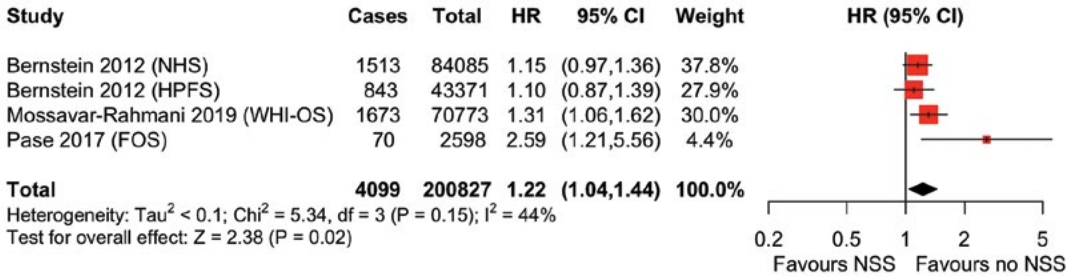


Fig. A9.30 Effect of NSS on total:HDL cholesterol in randomized controlled trials in adults

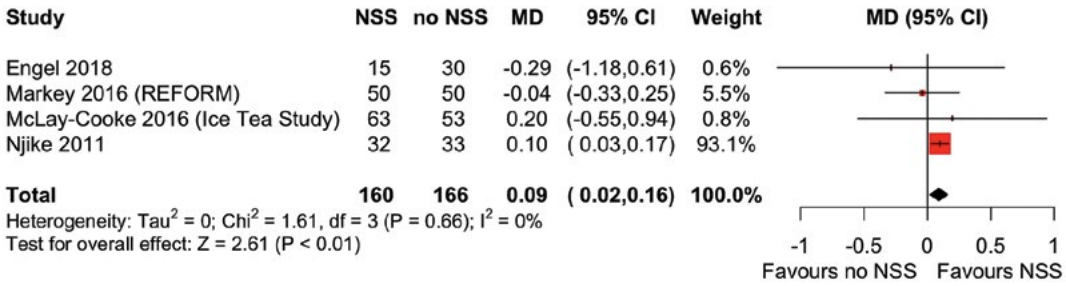


Fig. A9.31 Effect of NSS on total cholesterol (mmol/L) in randomized controlled trials in adults

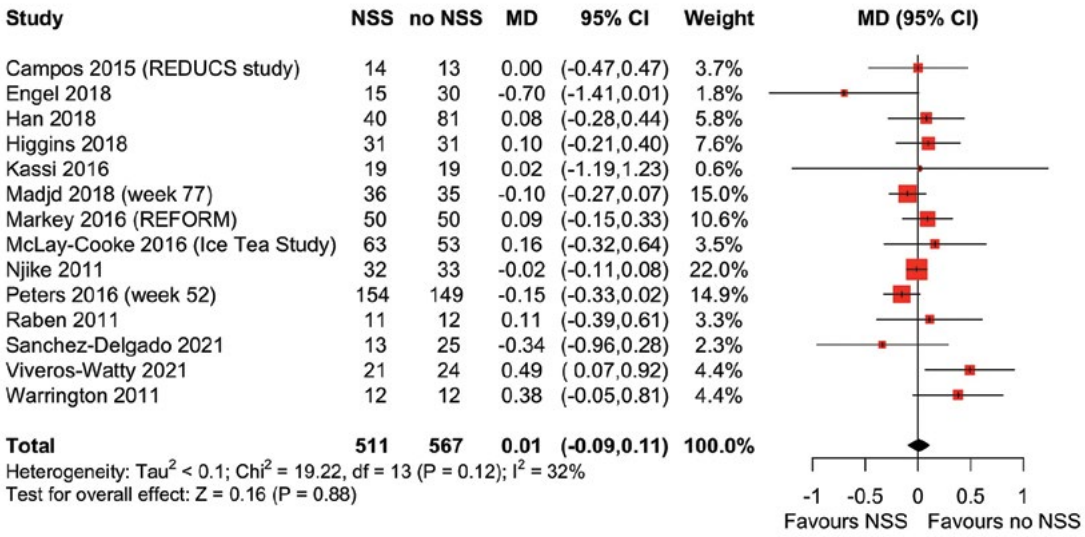


Fig. A9.32 Effect of NSS on HDL cholesterol (mmol/L) in randomized controlled trials in adults

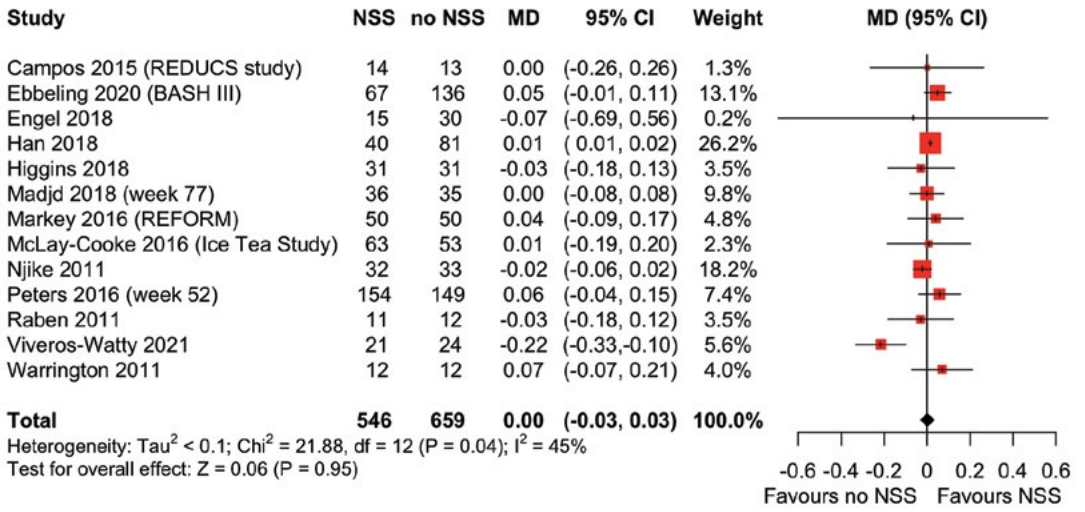
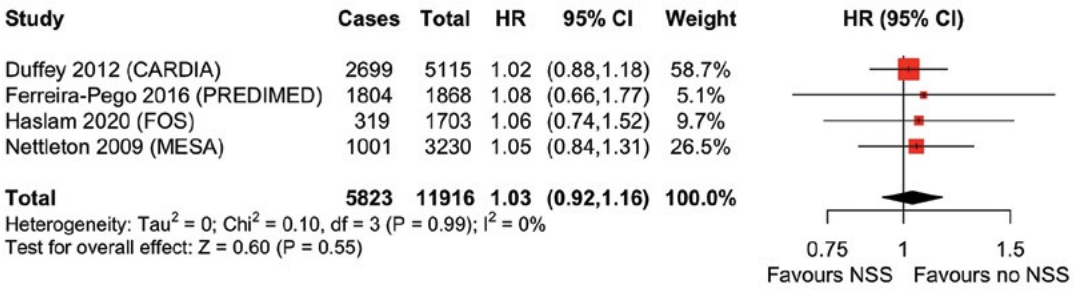
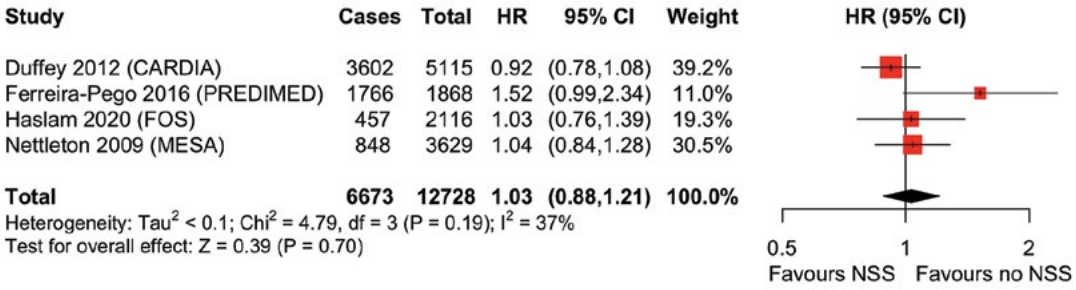


Fig. A9.33 Association between NSS and low HDL cholesterol in cohort studies (highest versus lowest) in adults



Note: Low HDL cholesterol is defined as ≥5.5 mmol/L.

Fig. A9.34 Association between NSS and high triglycerides in cohort studies (highest versus lowest) in adults



Note: High triglycerides are defined as ≥1.70 mmol/L.

Fig. A9.35 Association between NSS and bladder cancer in case–control studies, subgrouped by mode of delivery, in adults

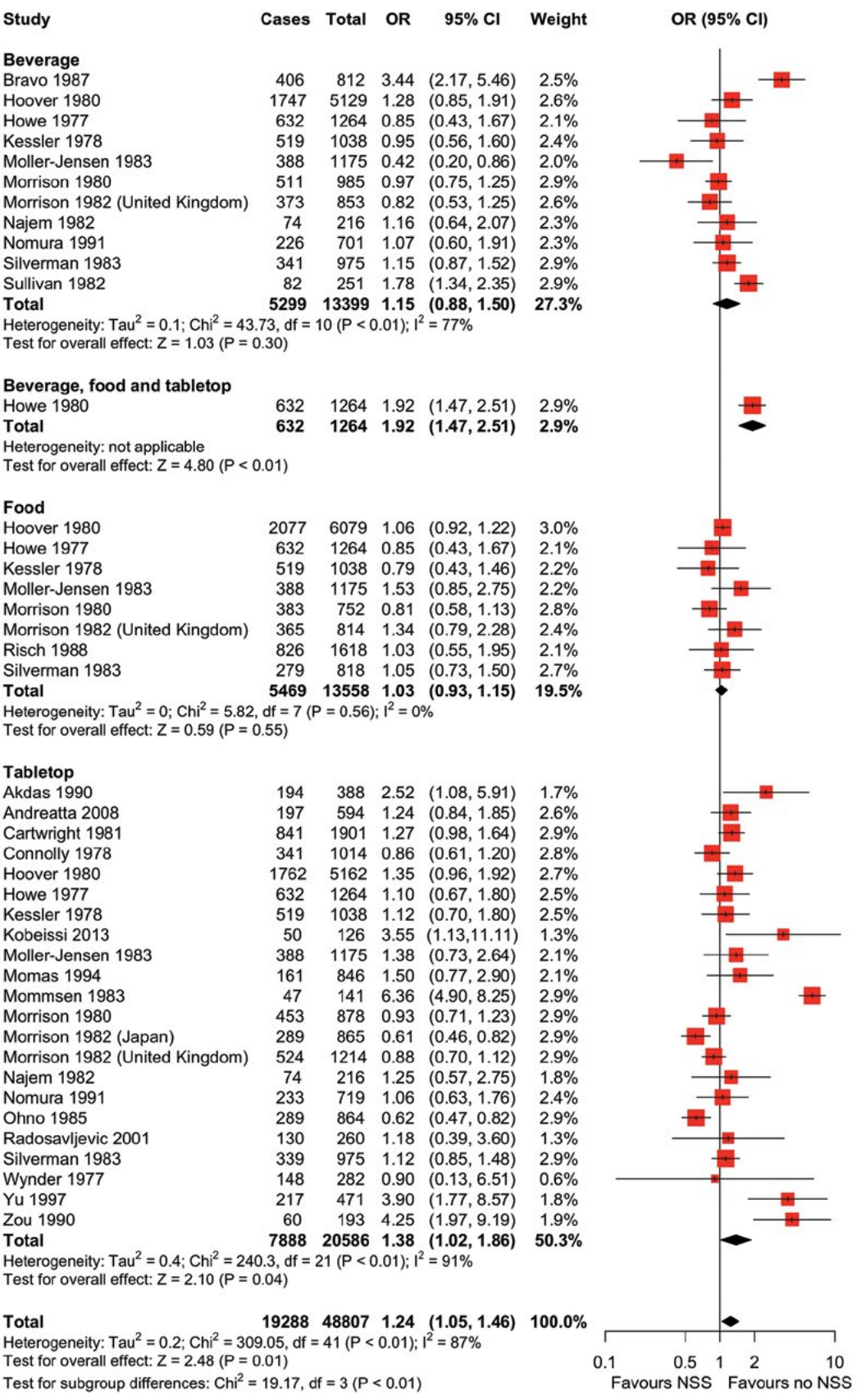
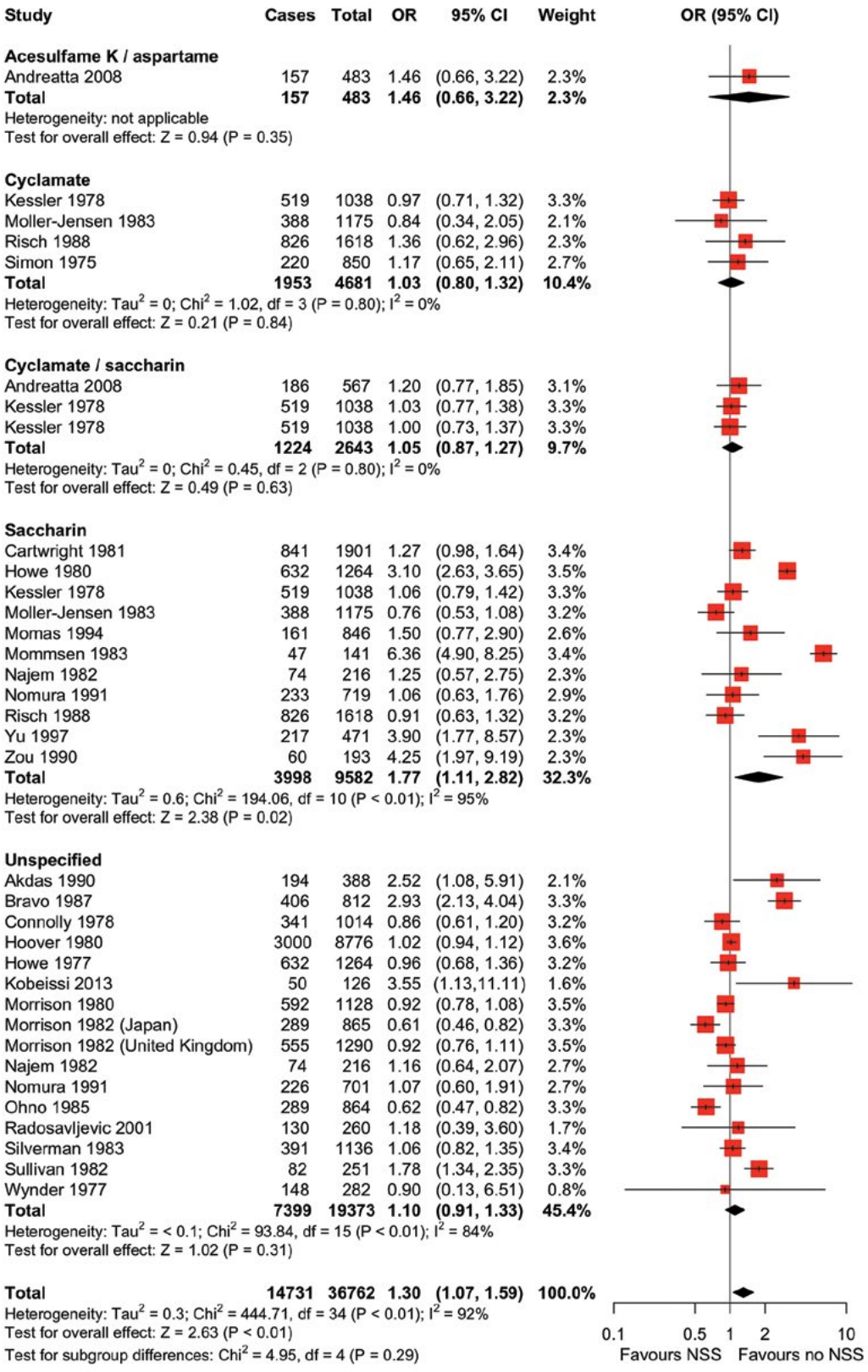


Fig. A9.36 Association between NSS and bladder cancer in case–control studies, subgrouped by NSS type, in adults



Note: Some studies appear more than once because they had multiple arms (comparing different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

Fig. A9.37 Association between NSS and brain cancer in case–control studies in adults

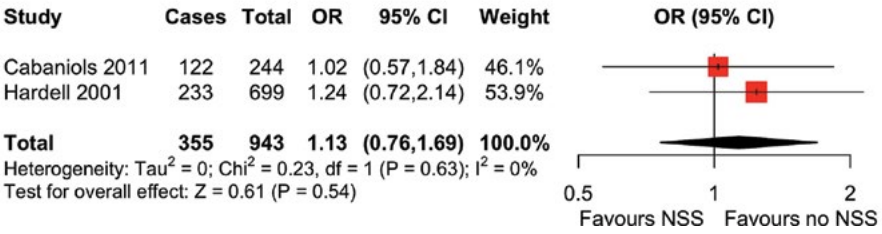


Fig. A9.38 Association between NSS and breast cancer in case–control studies in adults

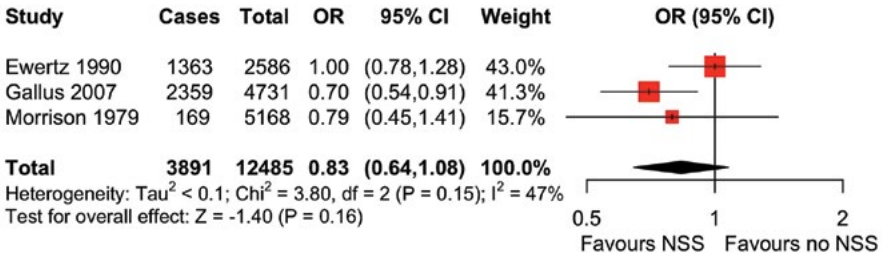


Fig. A9.39 Association between NSS and breast cancer in prospective cohort studies in adults

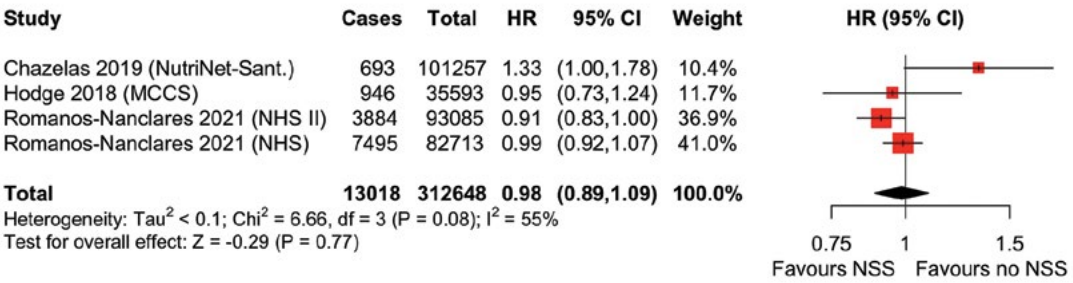


Fig. A9.40 Association between NSS and colorectal cancer in case–control studies in adults

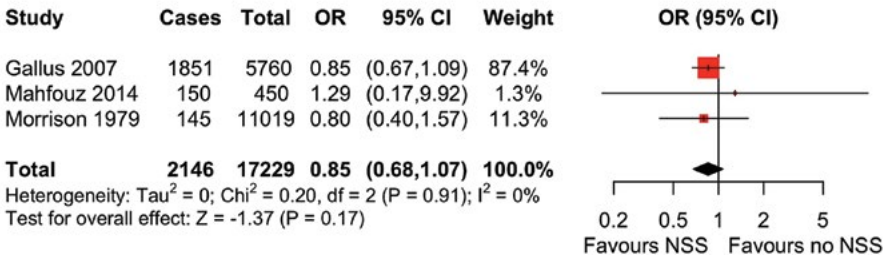


Fig. A9.41 Association between NSS and colorectal cancer in prospective cohort studies in adults

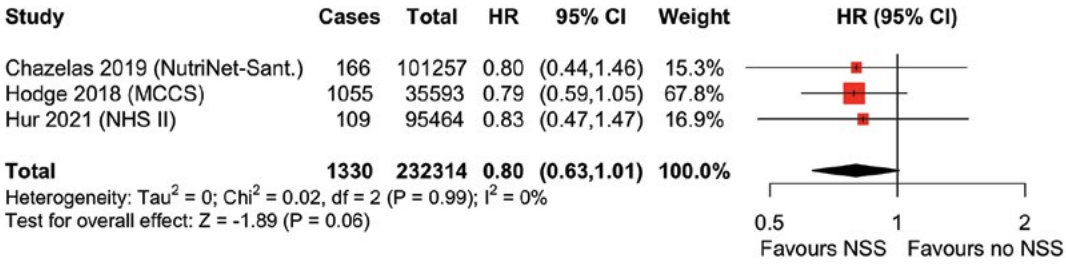


Fig. A9.42 Association between NSS and renal cancer in case–control studies in adults

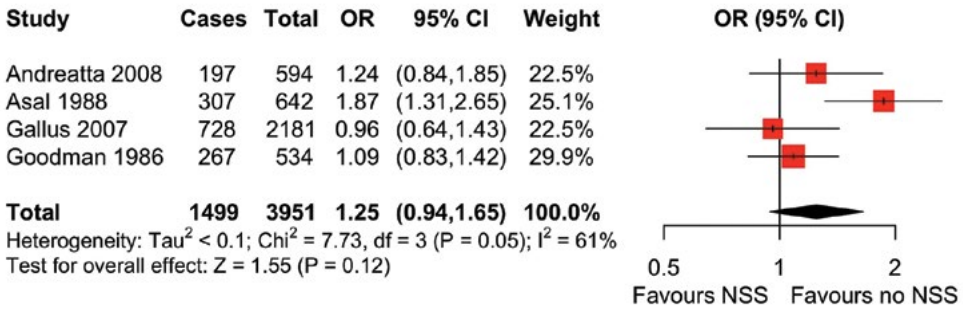


Fig. A9.43 Association between NSS and lung cancer in case–control studies in adults

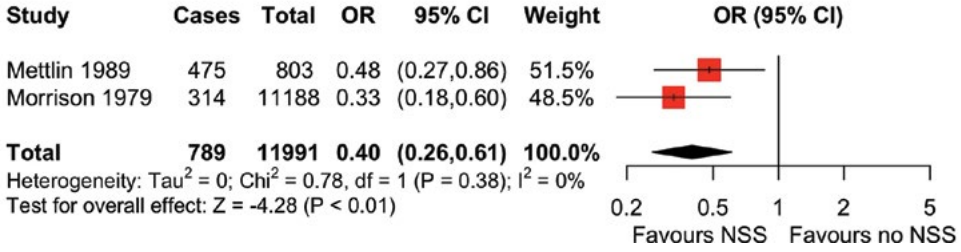


Fig. A9.44 Association between NSS and pancreatic cancer in case–control studies in adults

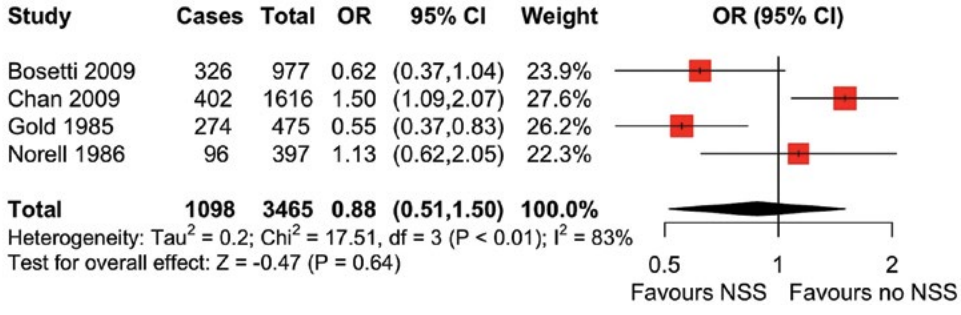


Fig. A9.45 Association between NSS and pancreatic cancer in prospective cohort studies in adults

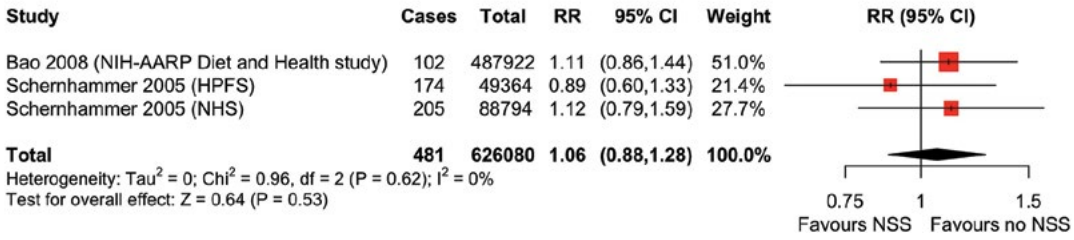


Fig. A9.46 Association between NSS and prostate cancer in case–control studies in adults

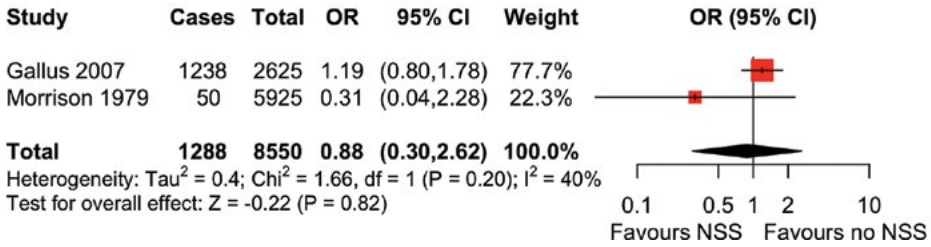


Fig. A9.47 Association between NSS and prostate cancer in prospective cohort studies in adults

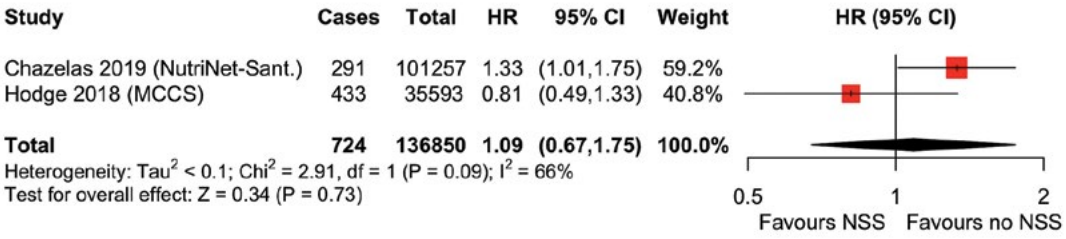


Fig. A9.48 Association between NSS and gastric cancer in case–control studies in adults

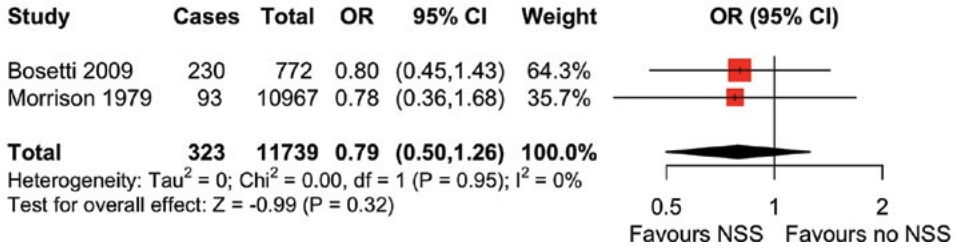


Fig. A9.49 Association between NSS and leukaemia in cohort studies in adults

Study	Cases	Total	RR	95% CI	Weight
Lim 2006 (NIH-AARP Diet and Health study)	279	473984	1.25	(0.82,1.91)	52.0%
Schernhammer 2012 (NHS)	153	77218	1.04	(0.58,1.86)	27.7%
Schernhammer 2012 (HPFS)	186	47810	1.56	(0.79,3.07)	20.3%
Total	**618**	**599012**	**1.24**	**(0.92,1.69)**	**100.0%**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.80$, df = 2 (P = 0.67); $I^2 = 0\%$
Test for overall effect: Z = 1.40 (P = 0.16)

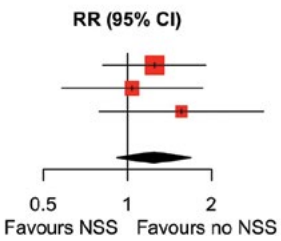


Fig. A9.50 Association between NSS and multiple myeloma in cohort studies in adults

Study	Cases	Total	RR	95% CI	Weight
Lim 2006 (NIH-AARP Diet and Health study)	273	473984	1.03	(0.64,1.66)	25.8%
McCullough 2014 (CPS-II)	198	100442	0.96	(0.92,1.01)	39.3%
Schernhammer 2012 (NHS)	154	77218	0.59	(0.32,1.09)	21.1%
Schernhammer 2012 (HPFS)	131	47810	3.36	(1.38,8.19)	13.9%
Total	**756**	**699454**	**1.05**	**(0.70,1.59)**	**100.0%**

Heterogeneity: $Tau^2 = 0.1$; $Chi^2 = 10.09$, df = 3 (P = 0.02); $I^2 = 70\%$
Test for overall effect: Z = 0.24 (P = 0.81)

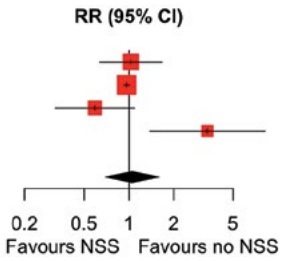


Fig. A9.51 Association between NSS and non-Hodgkin lymphoma in cohort studies in adults

Study	Cases	Total	RR	95% CI	Weight
Lim 2006 (NIH-AARP Diet and Health study)	1279	473984	0.95	(0.70,1.29)	22.5%
McCullough 2014 (CPS-II)	998	100442	1.03	(0.87,1.21)	32.5%
Schernhammer 2012 (NHS)	753	77218	0.91	(0.69,1.20)	24.4%
Schernhammer 2012 (HPFS)	571	47810	1.64	(1.17,2.29)	20.6%
Total	**3601**	**699454**	**1.08**	**(0.87,1.34)**	**100.0%**

Heterogeneity: $Tau^2 < 0.1$; $Chi^2 = 8.28$, df = 3 (P = 0.04); $I^2 = 64\%$
Test for overall effect: Z = 0.68 (P = 0.49)

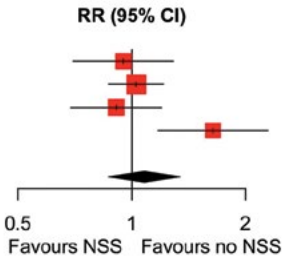
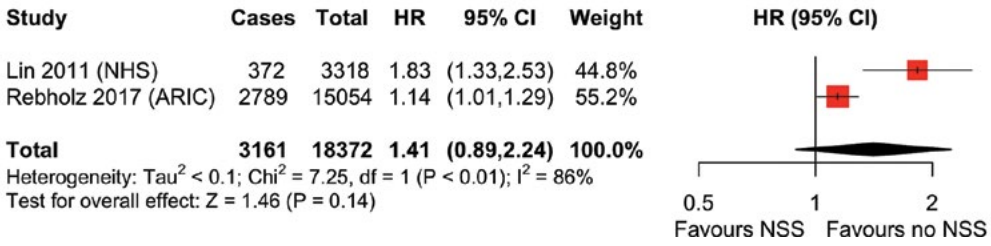


Fig. A9.52 Association between NSS and chronic kidney disease in cohort studies in adults



Note: Lin 2011 reported the association between NSS use and decline in estimated glomerular filtration rate (eGFR) of ≥30% *(173)*, and Rebholz 2017, the association between NSS use and chronic kidney disease with one defining characteristic being a ≥25% decline in eGFR *(174)*. Lin 2011 reported the association as an odds ratio which was converted to hazard ratio for this analysis using standard methods as described *(16)*.

Fig. A9.53 Effect of NSS on creatinine (mmol/L) in randomized controlled trials in adults

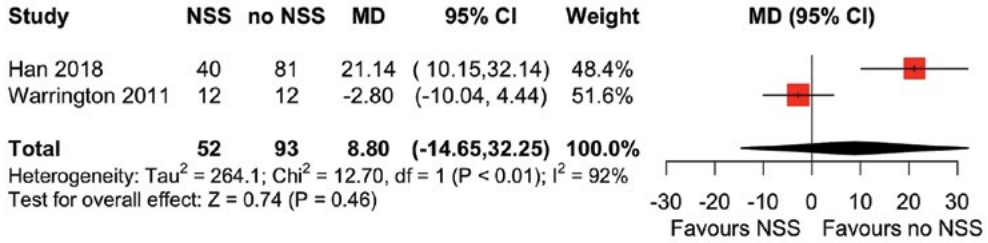


Fig. A9.54 Effect of NSS on albumin (g/L) in randomized controlled trials in adults

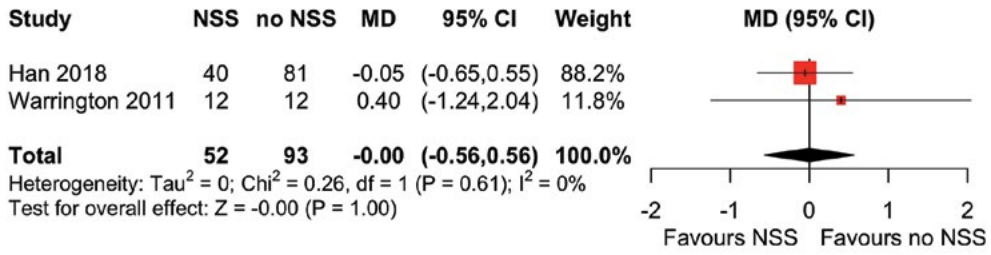


Fig. A9.55 Effect of NSS on energy intake (kJ/d) in randomized controlled trials, subgrouped by consumption pattern, in adults

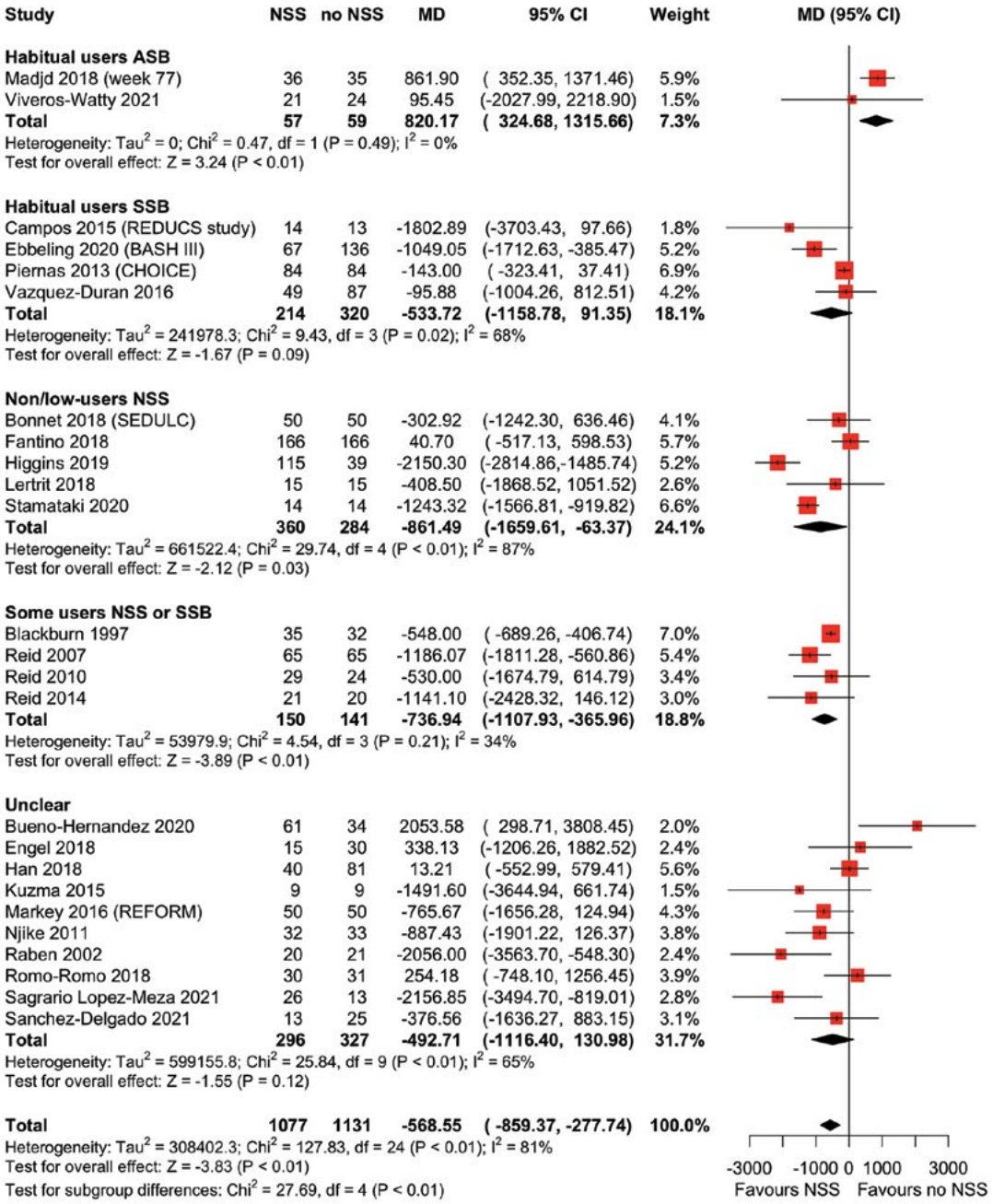


Fig. A9.56 Effect of NSS on energy intake (kJ/d) in randomized controlled trials, subgrouped by delivery mode, in adults

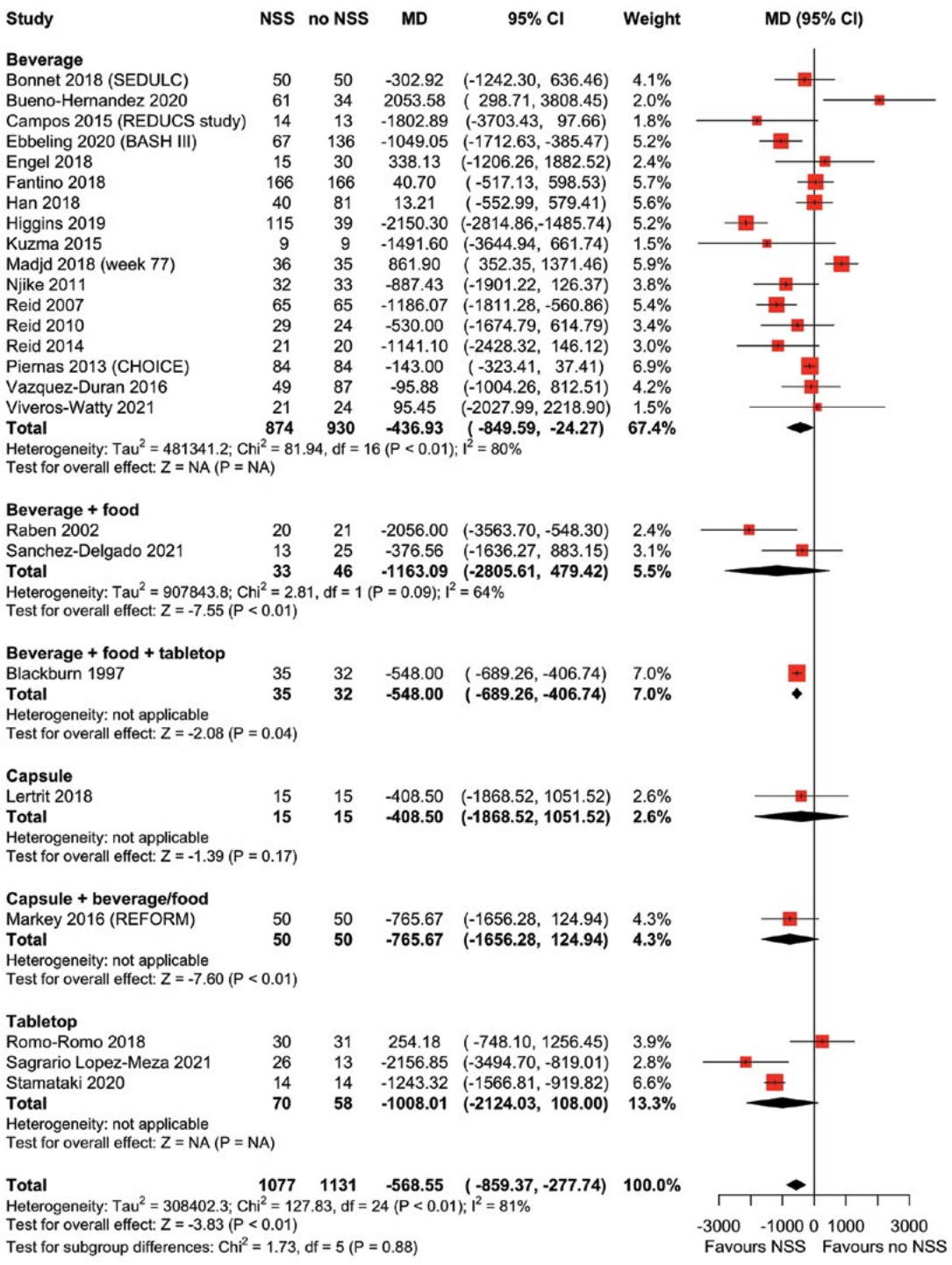
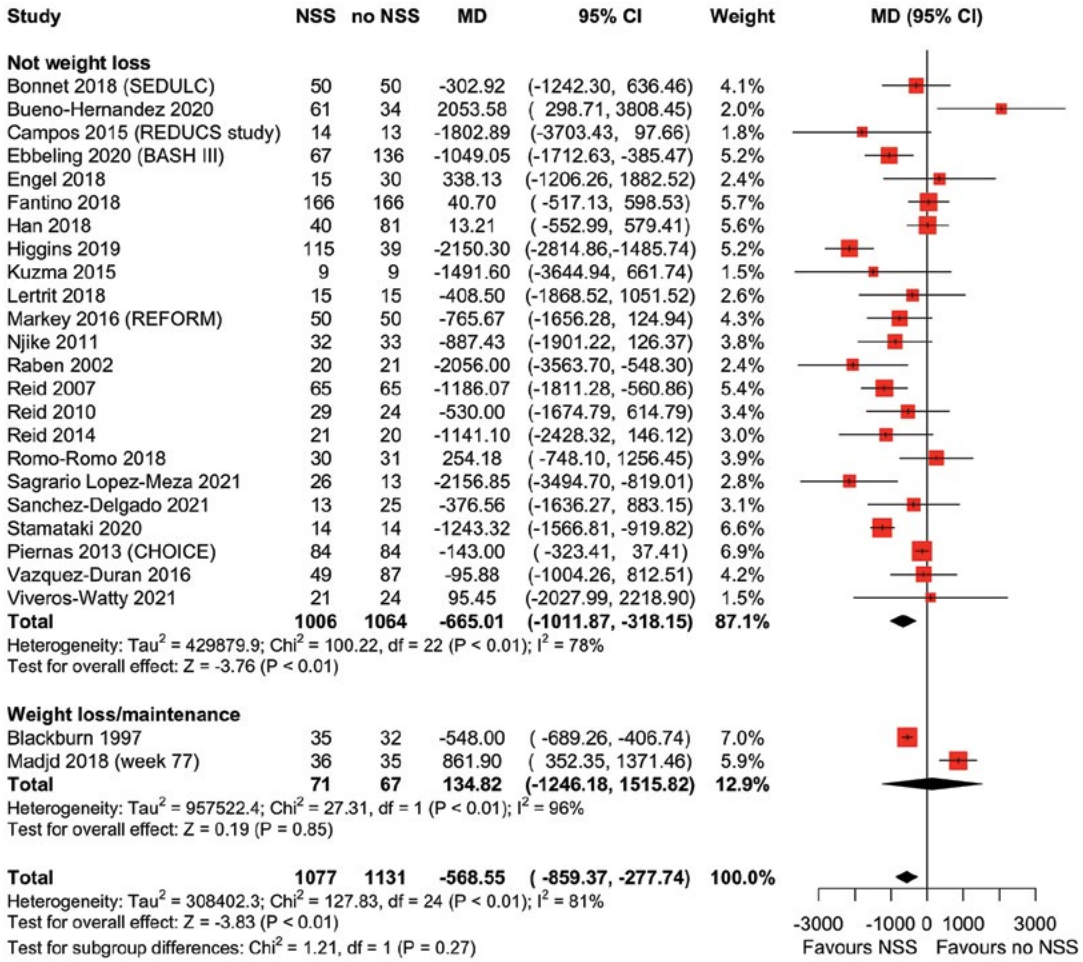
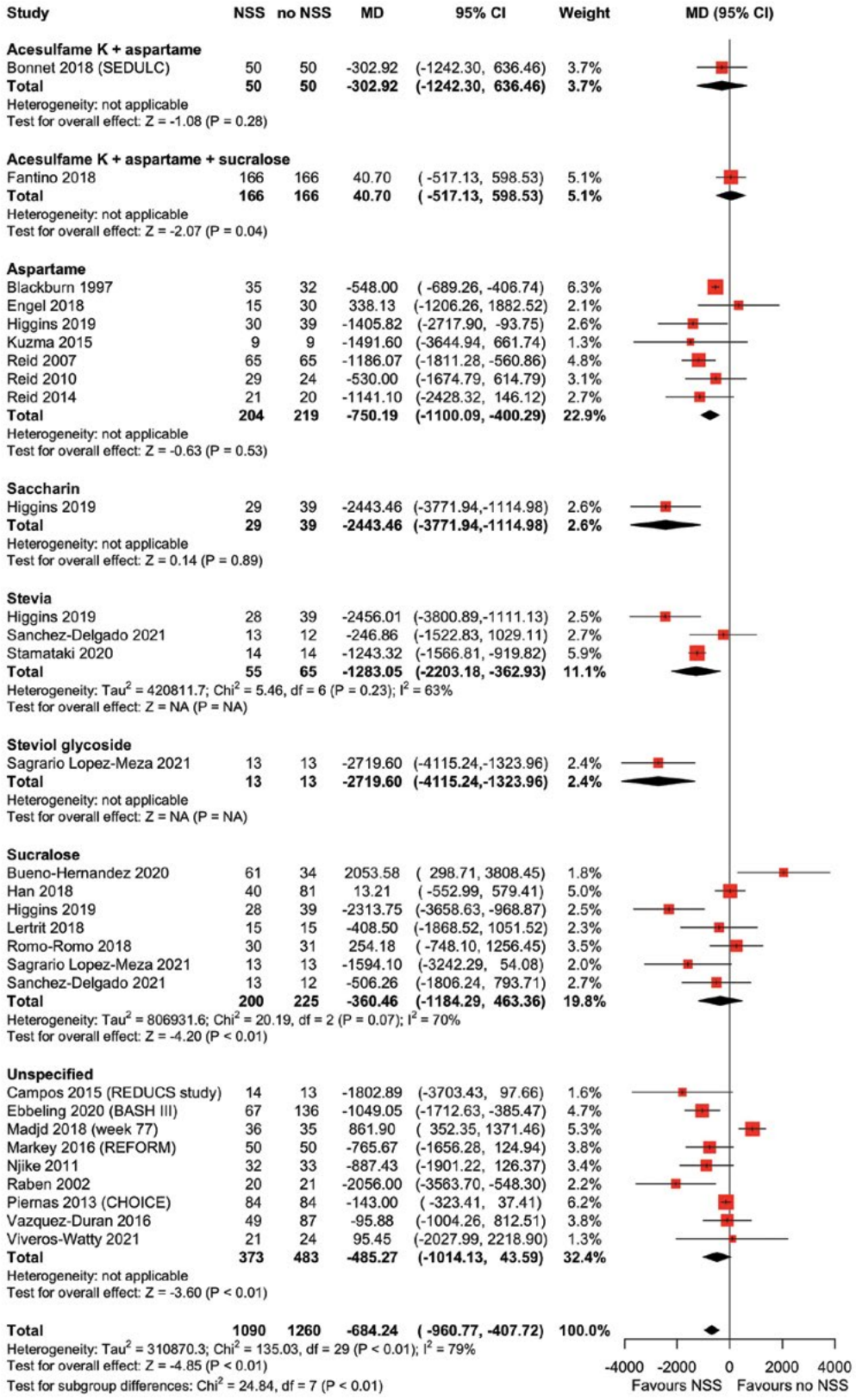


Fig. A9.57 Effect of NSS on energy intake (kJ/d) in randomized controlled trials, subgrouped by study design (weight loss studies versus non–weight loss studies), in adults



Note: Weight loss studies were those in which the participants were instructed to restrict energy intake AND consume NSS or control. Weight maintenance studies were those that followed up participants after active weight loss, with instructions on energy intake designed to prevent weight gain. Non–weight loss studies were those that had no intentional weight loss component.

Fig. A9.58 Effect of NSS on energy intake (kJ/d) in randomized controlled trials, subgrouped by NSS type, in adults



Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

Fig. A9.59 Effect of NSS on hunger in randomized controlled trials in adults

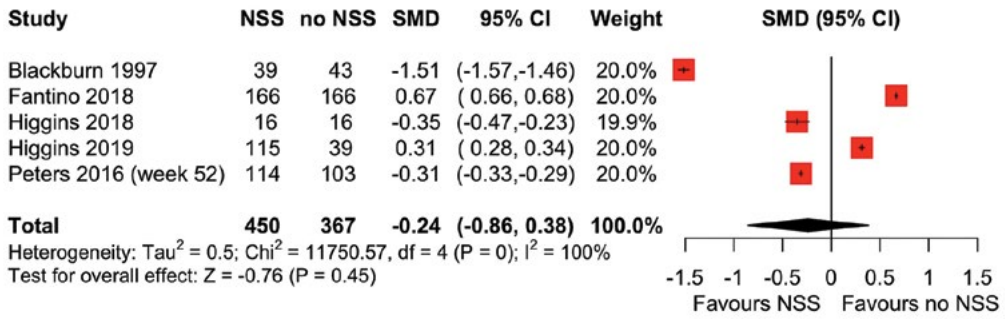


Fig. A9.60 Effect of NSS on satiety in randomized controlled trials in adults

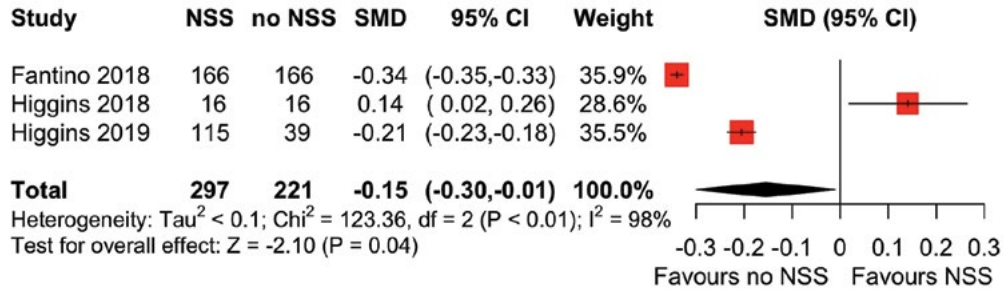


Fig. A9.61 Effect of NSS on appetite/desire to eat in randomized controlled trials in adults

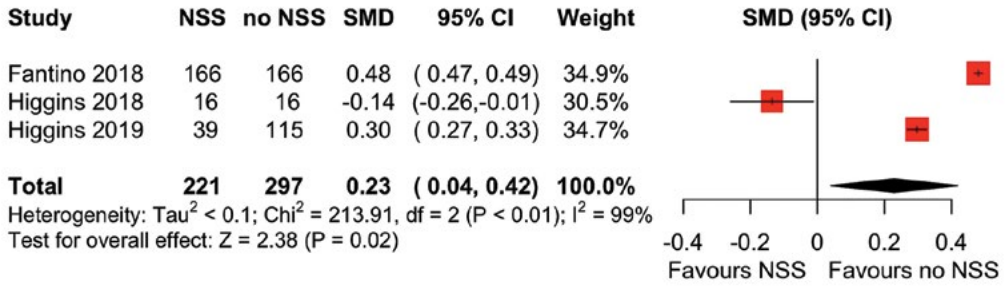


Fig. A9.62 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by consumption pattern, in adults

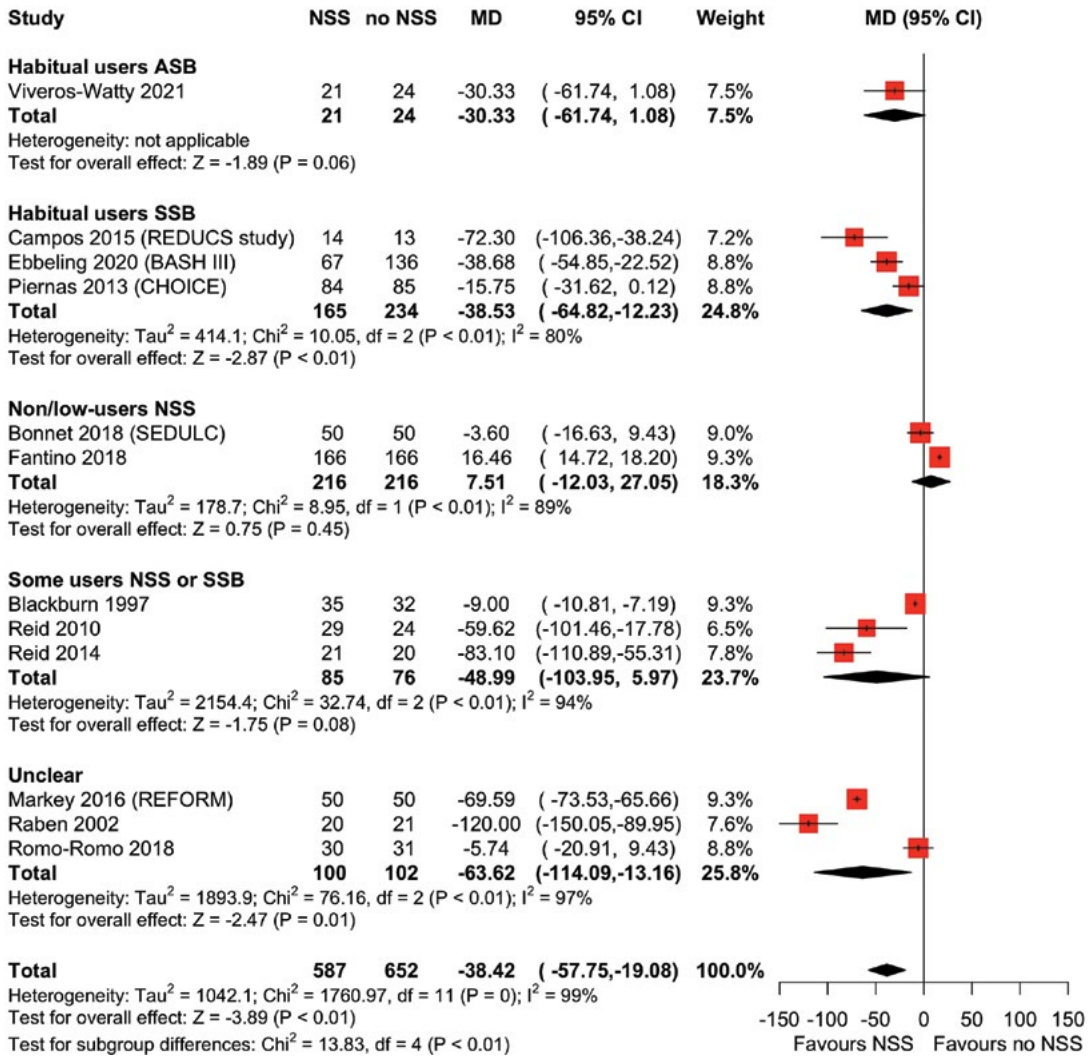


Fig. A9.63 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by delivery mode, in adults

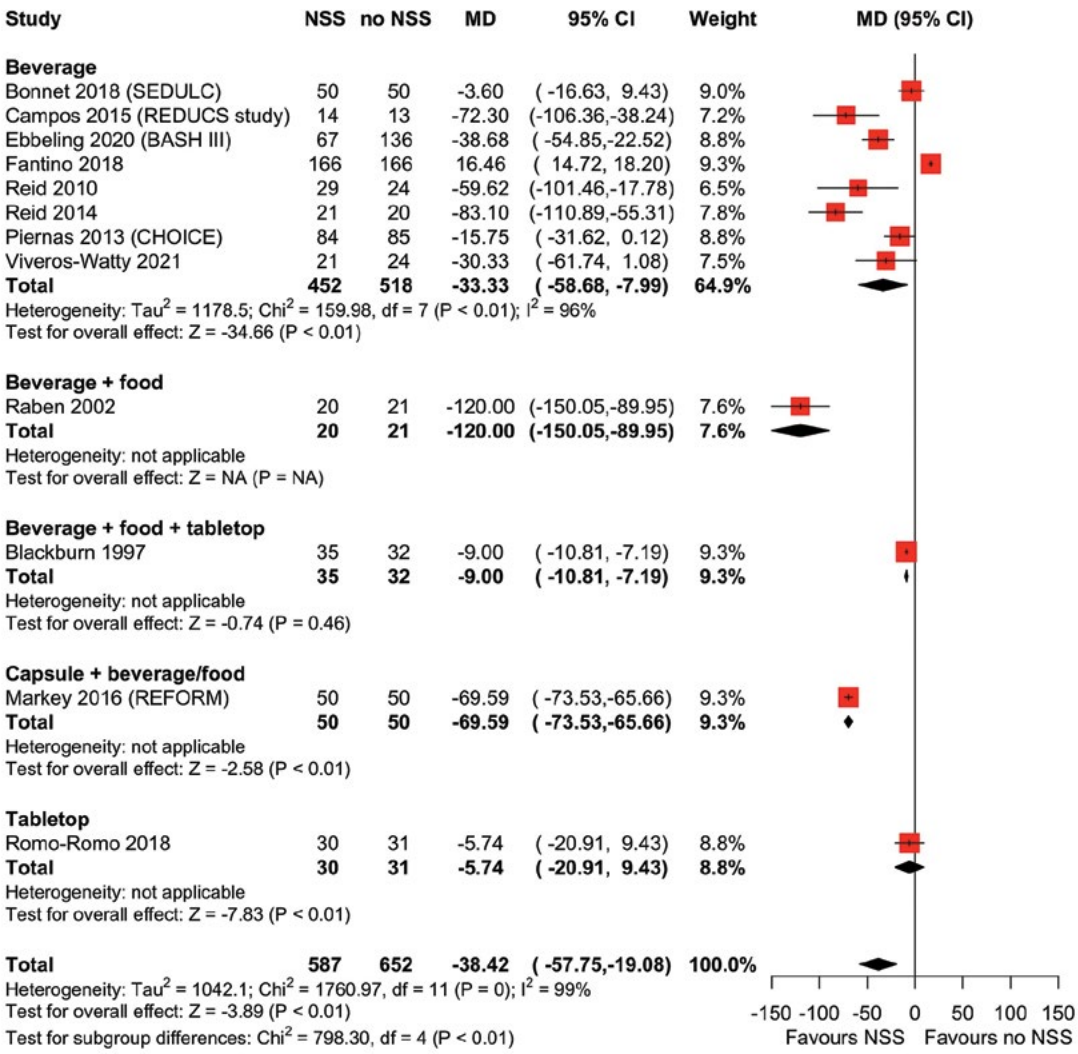


Fig. A9.64 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by NSS type, in adults

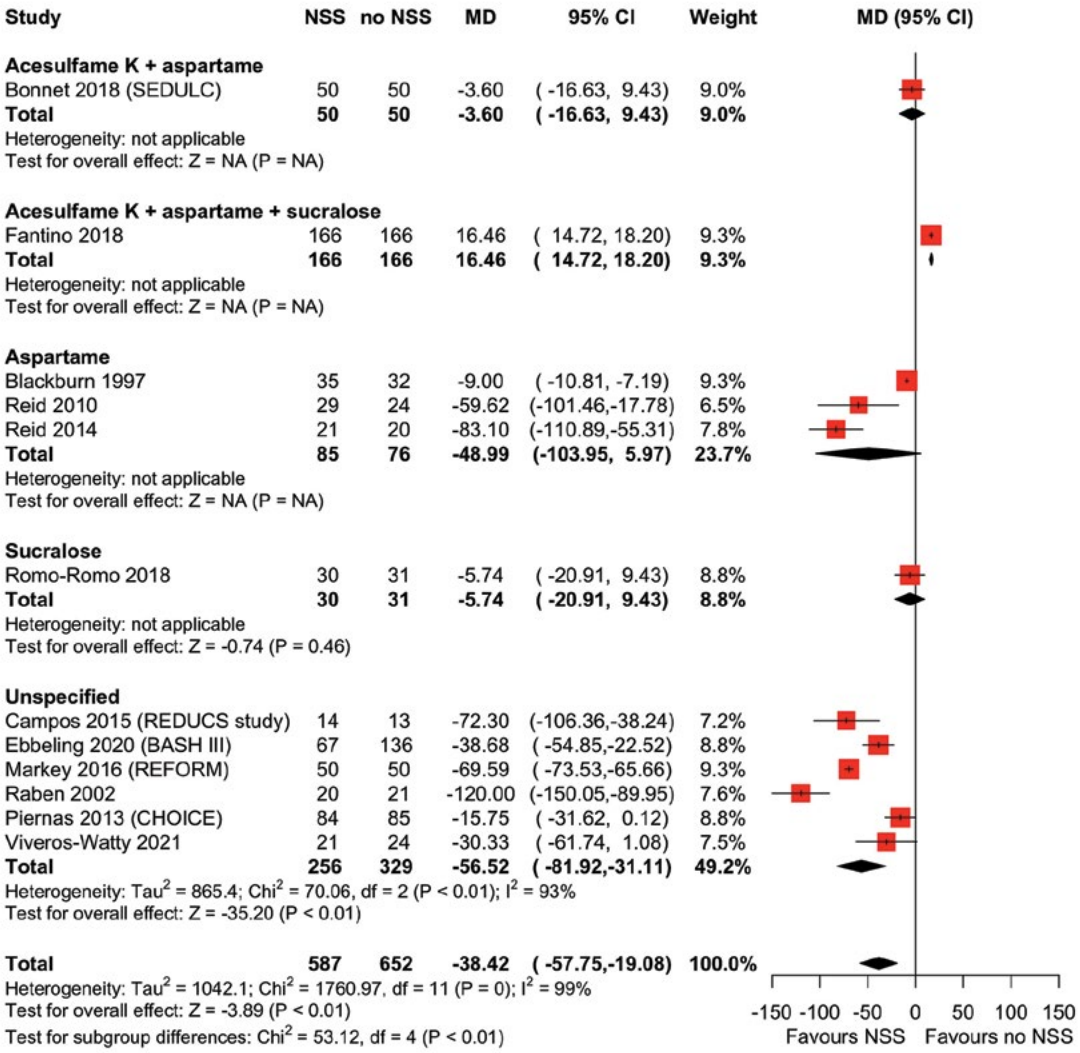


Fig. A9.65 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by study design (weight loss studies versus non–weight loss studies), in adults

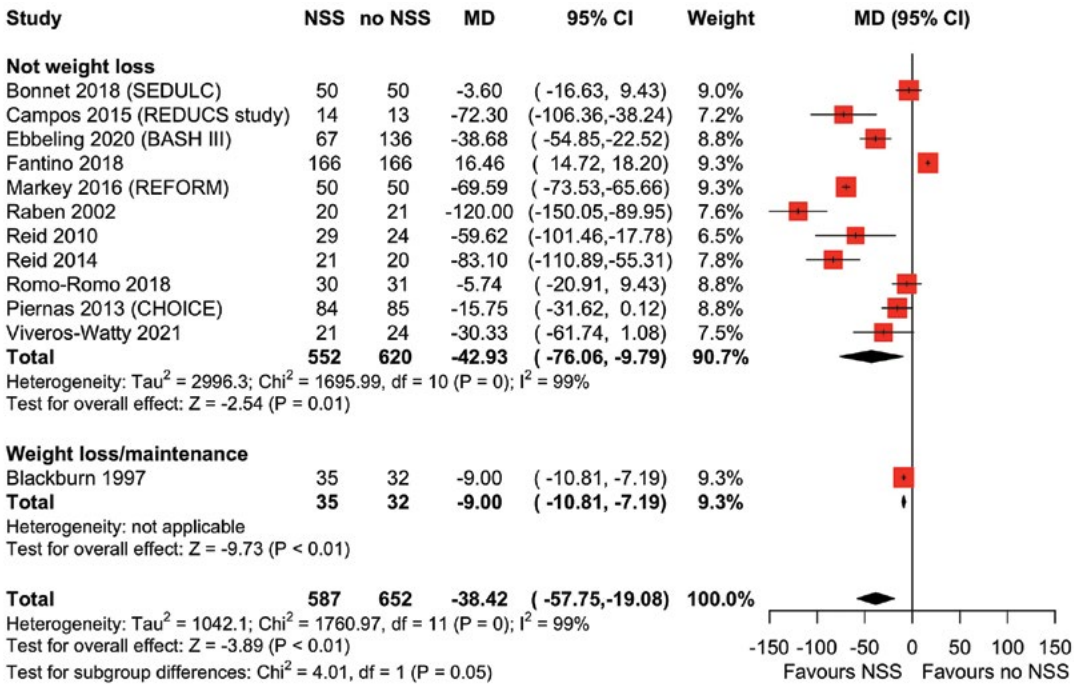


Fig. A9.66 Association between NSS and body weight (kg) in cohort studies (continuous) in children

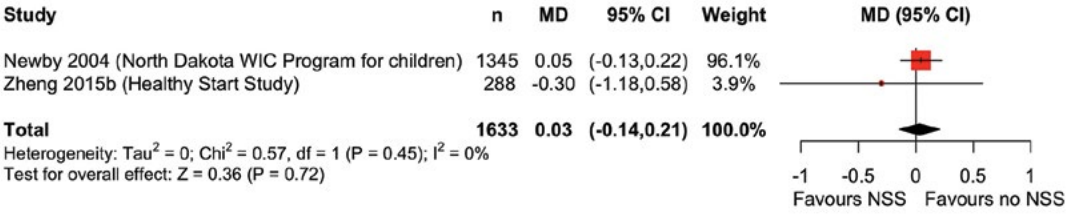


Fig. A9.67 Association between NSS and body mass index (kg/m²) in cohort studies (continuous) in children

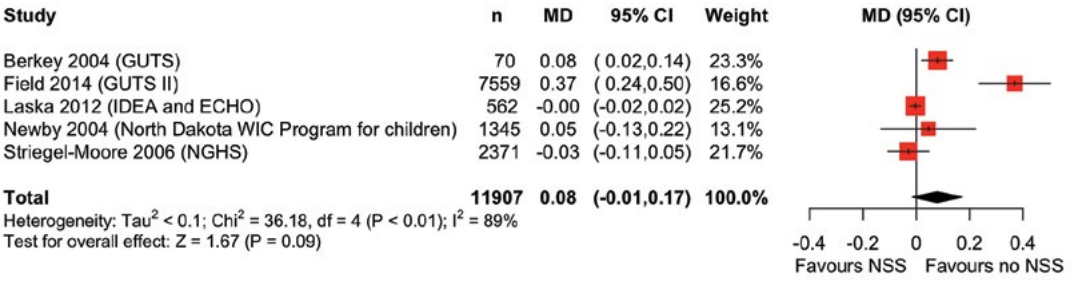


Fig. A9.68 Association between NSS and body mass index (kg/m²) in cohort studies (higher versus lower) in children

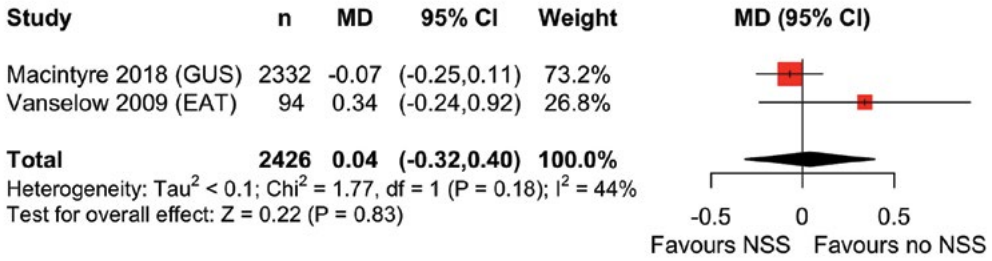


Fig. A9.69 Effect of NSS on BMI z-score in randomized controlled trials in children

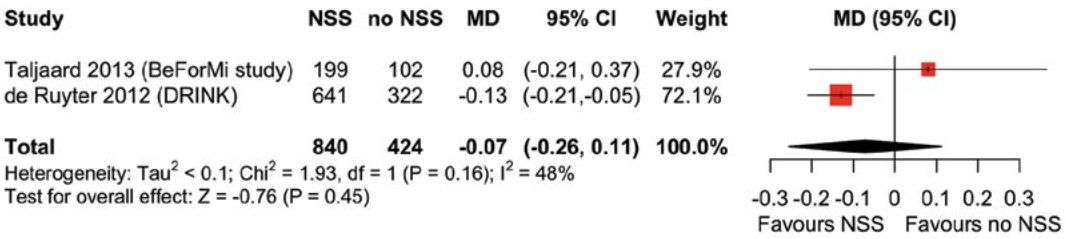


Fig. A9.70 Association between NSS and BMI z-score in cohort studies (continuous) in children

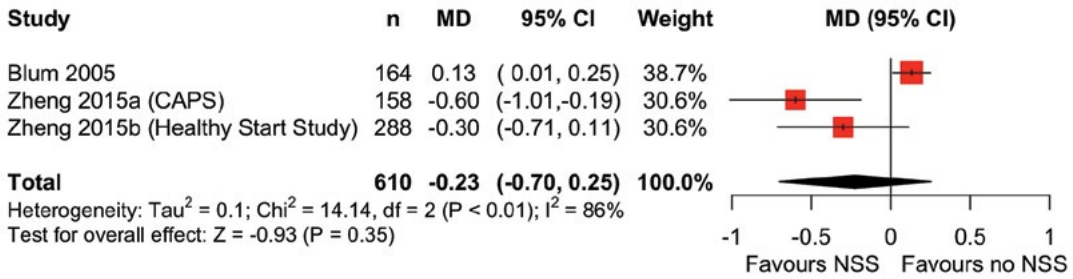


Fig. A9.71 Association between NSS and body fat mass (%) in cohort studies in children

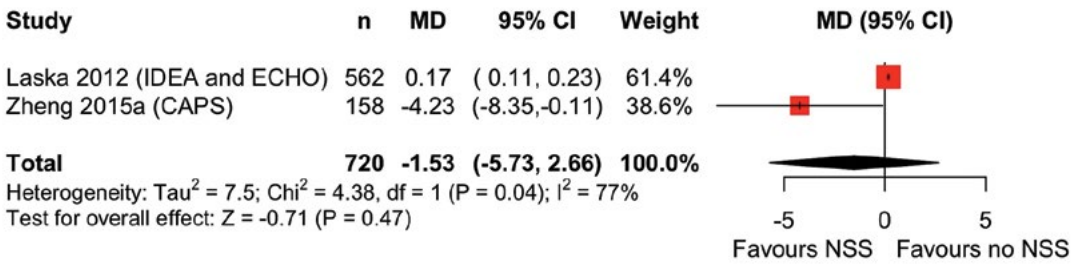


Fig. A9.72 Association between NSS and overweight in cohort studies in children

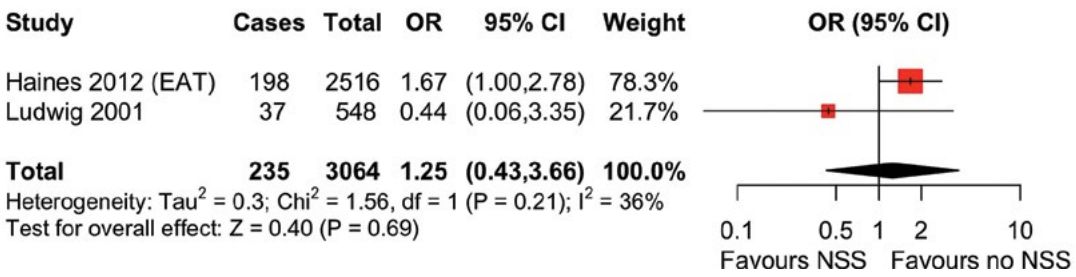
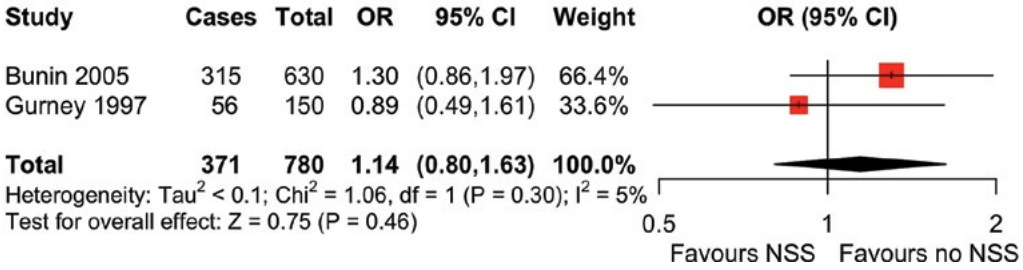


Fig. A9.73 Association between NSS and brain cancer in cohort studies in children



ANNEX 10.

Excluded studies

STUDY	REASON FOR EXCLUSION
Afonso 2013 *(376)*	Wrong study population
Aguero 2019 *(377)*	Wrong study/publication type
Ahmad 2020 *(378)*	Wrong intervention/exposure
Ahmad 2020b *(379)*	Wrong or no comparator
Akhavan 2011 *(380)*	Study duration too short
Ali 2017 *(381)*	Duplicate
Alsubaie 2017 *(382)*	Wrong intervention/exposure
Alviso-Orellana 2018 *(383)*	Wrong intervention/exposure
Anonymous 2015 *(384)*	Wrong study/publication type
Anonymous 2016 *(385)*	Wrong study/publication type
Anonymous 2019 *(386)*	Wrong study/publication type
Appelhans 2013 *(387)*	Wrong intervention/exposure
Appelhans 2017 *(388)*	Wrong intervention/exposure
Armstrong 1974 *(389)*	Wrong study/publication type
Barraj 2020 *(390)*	No outcome of interest
Barriocanal 2008 *(391)*	NSS too high
Bawa 2018 *(392)*	Wrong intervention/exposure
Bawadi 2019 *(393)*	Wrong intervention/exposure
Beck 2017 *(394)*	Wrong intervention/exposure
Bellisle 2001 *(395)*	Wrong intervention/exposure
Bolt-Evensen 2018 *(396)*	No outcome of interest
Cancer Prevention Study I 1992 *(397)*	Wrong study/publication type
Chen 2021 *(398)*	Wrong intervention/exposure
ChiCTR-IOR-17011657 2017 *(399)*	Wrong or no comparator
Cohen 1978 *(400)*	Wrong study/publication type
Conway 2017 *(401)*	No outcome of interest
Conway 2021 *(402)*	No outcome of interest
Creighton 2014 *(403)*	Wrong study/publication type
Creze 2018 *(404)*	Wrong or no comparator
Cros 2020 *(405)*	Study duration too short
Cullen 2004 *(406)*	Wrong study population
De Christopher 2018 *(407)*	No outcome of interest

STUDY	REASON FOR EXCLUSION
De Ruyter 2013 *(408)*	Duplicate
De SagrarioLopez-Meza 2018 *(409)*	NSS too high
Den Biggelaar 2020 *(410)*	Wrong study population
Deschamps 1971 *(411)*	Study duration too short
Ebbeling 2006 *(258)*	Wrong intervention/exposure
Ebbeling 2012 *(257)*	Wrong intervention/exposure
Fantino 2018 *(412)*	Duplicate
Farr 2021 *(413)*	Study duration too short
Forster 1993 *(414)*	Wrong study/publication type
Franchi 2021 *(415)*	No outcome of interest
Frey 1976 *(255)*	NSS too high
Friedhoff 1971 *(416)*	Wrong study population
Fritschka 2019 *(417)*	Wrong study/publication type
Fuentealba Arevalo 2019 *(418)*	No outcome of interest
Gehring 1990 *(419)*	Wrong study/publication type
Gerber 2020[a]	Full text not found
Gibson 2016 *(420)*	Wrong intervention/exposure
Ginieis 2018 *(421)*	Study duration too short
Gligore 1971 *(422)*	Full text not found
Goto 1990 *(423)*	Wrong intervention/exposure
Griffioen-Roose 2013 *(424)*	Study duration too short
Grotz 2017 *(425)*	NSS too high
Gui 2017 *(426)*	Wrong intervention/exposure
He 2018 *(427)*	Wrong intervention/exposure
Heckenmueller 2021 *(428)*	Wrong study/publication type
Hennon 1965 *(429)*	Full text not found
Hong 2018 *(430)*	Wrong intervention/exposure
Hu 2014 *(431)*	No outcome of interest
IRCT20140310016925N3 2018 *(432)*	No outcome of interest
Ismail 1984 *(433)*	Wrong intervention/exposure
Jensen 1982 *(434)*	Wrong study/publication type
Johnson 2007 *(435)*	Wrong intervention/exposure
Kant 2003 *(436)*	Wrong intervention/exposure
Kato 2020[b]	Wrong intervention/exposure
Kenney 2017 *(437)*	Wrong intervention/exposure
Kim 2019 *(438)*	Wrong intervention/exposure
Koebnick 2018 *(439)*	Wrong intervention/exposure
Kruesi 1987 *(440)*	Study duration too short
Laforest-Lapointe 2021 *(441)*	Duplicate
Larsson 2014 *(442)*	Wrong intervention/exposure
Larsson 2016 *(443)*	Wrong intervention/exposure
Lemeshow 2018 *(444)*	No outcome of interest
Lertrit 2017 *(445)*	Duplicate

STUDY	REASON FOR EXCLUSION
Lertrit 2018 *(446)*	Duplicate
Leung 2018 *(447)*	Wrong intervention/exposure
Lindseth 2014 *(448)*	Wrong study/publication type
Lodefalk 2006 *(449)*	Wrong study population
Lotto 2020 *(450)*	Wrong intervention/exposure
Lutsey 2008 *(451)*	No outcome of interest
Lutsey 2009 *(452)*	No outcome of interest
Maillot 2019 *(453)*	Wrong intervention/exposure
Maki 2008 *(454)*	NSS too high
Maloney 2019 *(455)*	Study duration too short
Markus 2020 *(456)*	Study duration too short
Marshall 2017 *(457)*	Wrong intervention/exposure
Marshall 2018 *(458)*	Wrong intervention/exposure
Marshall 2019 *(459)*	Wrong intervention/exposure
Marshall 2019 *(460)*	Wrong intervention/exposure
Marshall 2020 *(461)*	Wrong intervention/exposure
Mayasari 2018 *(462)*	Wrong or no comparator
McNaughton 2008 *(463)*	Wrong intervention/exposure
Meyer-Gerspach 2018 *(464)*	Study duration too short
Miguel-Berges 2020 *(465)*	No outcome of interest
Miranda Lora 2020 *(466)*	Study duration too short
Mirghani 2020[c]	No outcome of interest
Mirghani 2021 *(467)*	Duplicate
Morin 2018 *(468)*	Wrong intervention/exposure
Mullie 2017 *(469)*	Wrong study/publication type
Nazari 2018 *(470)*	Wrong intervention/exposure
NCT00381160 2006 *(471)*	Wrong intervention/exposure
NCT04230824 2020 *(472)*	Wrong or no comparator
NCT04857554 2021 *(473)*	Study duration too short
Nejadsadeghi 2018 *(474)*	Wrong intervention/exposure
Nicklas 2003 *(475)*	Wrong intervention/exposure
Nissensohn 2015 *(476)*	Wrong intervention/exposure
Patel 2018 *(477)*	Wrong intervention/exposure
Petersen 2015 *(478)*	No outcome of interest
Porikos 1977 *(479)*	Study duration too short
Porikos 1982 *(480)*	Wrong or no comparator
Qiu 2020 *(481)*	No outcome of interest
Rusmevichientong 2018 *(482)*	No outcome of interest
Samman 2020 *(483)*	Wrong intervention/exposure
Sanchez-Delgado 2019 *(47)*	Duplicate
Shaywitz 1994 *(484)*	Wrong study population
Shin 2018 *(485)*	Wrong intervention/exposure
Small 2020	Duplicate (abstract)
Soparkar 1978 *(486)*	No outcome of interest
Stamataki 2020c *(487)*	Study duration too short

STUDY	REASON FOR EXCLUSION
Stookey 2007 *(488)*	Wrong intervention/exposure
Storey 2009 *(489)*	No outcome of interest
Sushanthi 2020 *(490)*	Study duration too short
Sylvetsky 2020 *(491)*	Wrong study population
Sylvetsky 2020b *(492)*	Wrong or no comparator
Tey 2017 *(493)*	Study duration too short
Thomson 2019 *(494)*	NSS too high
Tucker 2006 *(495)*	No outcome of interest
Turner-McGrievy 2016 *(496)*	No outcome of interest
van den Eeden 1991 *(497)*	No outcome of interest
Walker 1982 *(498)*	Wrong study/publication type
Walton 1993 *(499)*	Wrong study population
Wang 2017 *(500)*	Wrong study population
Williams 2017 *(501)*	Wrong intervention/exposure
Wilson 2000 *(502)*	Study duration too short
Yao 2014 *(503)*	No outcome of interest
Young 2018 *(504)*	No outcome of interest
Zanela 2002 *(505)*	Wrong intervention/exposure
Zhang 2021 *(506)*	Wrong intervention/exposure
Zollner 1971 *(507)*	Wrong study population

[a] http://dx.doi.org/10.1016/j.clnesp.2020.09.651
[b] https://jglobal.jst.go.jp/en/detail?JGLOBAL_ID=202002239574388156
[c] https://amj.net.au/index.php/AMJ/article/viewFile/3712/1809

ANNEX 11.

Differences in study selection between original review and current update

Table A11.1 Eligibility criteria in original review and update

CHARACTERISTIC	ORIGINAL ELIGIBILITY CRITERIA	NEW CRITERIA
Population	Included general, healthy population of adults (≥18 years) or children (<18 years) Excluded diseased populations, in vitro studies and animal studies	Also included pregnant women
Intervention/exposure	Included any type of NSS, either as an individual intervention or in combination with other NSS Excluded studies that did not specify the type of sweetener Excluded studies where dose was above ADI	Also included NSS unspecified by name
Comparators	Any alternative intervention – for example, any other type of caloric or non-caloric sweetener, any type of sugar, no intervention, placebo, or plain water	Also included comparison of no/low vs high intakes of NSS
Outcomes	Body weight, oral health, incidence of diabetes, eating behaviour, preference for sweet taste, incidence of any type of cancer, incidence of cardiovascular disease, incidence of chronic kidney disease, incidence of asthma, incidence of allergies, mood, behaviour and neurocognition	Also included mortality and pregnancy-related outcomes
Study design	Included parallel grouped or crossover (quasi-) randomized controlled trials, cluster randomized trials, nonrandomized controlled trials, prospective and retrospective cohort studies, case–control studies and cross-sectional studies	Unchanged
Duration	Minimum of 7 days	Minimum of 13 days for blood lipid outcomes, 1 year for disease incidence outcomes (i.e. incident cancer, cardiovascular disease, type 2 diabetes) and 7 days for all other outcomes

ADI: acceptable daily intake; NSS: non-sugar sweeteners.

Table A11.2 Studies excluded from original because sweetener not specified, but included in update

Akdaş 1990	Howe 1980	Pfeiffer 2015
Andreatta 2008	Hunt 2015	Piernas 2011
Asal 1988	InterActConsortium 2013	Piernas 2013
Azad 2016	Kantor 1985	Radosavljević 2001
Berkey 2004	Kessler 1976	Risch 1988
Bleich 2014	Kobeissi 2013	Sakurai 2014
Blum 2005	Kral 2008	Saldana 2007
Bomback 2010	Laverty 2015	Schernhammer 2012
Bravo 1987a	Lin 2011	Schulze 2004
Campos 2015	Ma 2016	Silverman 1983
Chan 2009	Mahfouz 2014	Souza 2016
Chen 1991	Markey 2016	Stellman 1986
Chia 2016	Morgan 1974	Stellman 1988
Connolly 1978	Morrison 1979	Stepien 2016
de Koning 2011	Morrison 1980	Striegel-Moore 2006
de Koning 2012	Morrison 1982	Sullivan 1982
Drewnowski 2016	Mozaffarian 2011	Tate 2012
Duffey 2012	Nettleton 2009	Vanselow 2009
Ewertz 1990	Norell 1986	Vázquez-Durán 2016
Fagherazzi 2017	O'Connor 2006	Vyas 2015
Forshee 2003	Ohno 1985	Winkelmayer 2005
Fowler 2015	Pan 2013	Wynder 1980
Geraldo 2013	Pergrin Marriott 2016	Yarmolinsky 2016
Giammattei 2003	Peters 2016	Zou 1990
Hoover 1980	Petherick 2014	

Table A11.3 Studies excluded from original review but included in update

STUDY	REASON FOR EXCLUSION FROM ORIGINAL REVIEW	REASON FOR INCLUSION IN UPDATE/ EXPANSION
Appleton 2001	No direct/concurrent comparison arm	Comparison of habitual heavy users and non-users of ASB
Bhupathiraju 2013	No direct/concurrent comparison arm	Comparison of intakes of ASB
Bouchard 2010	Wrong study type	Cross-sectional study an eligible study type
Bravo 1987	Wrong study type	Case–control study an eligible study type
Crichton 2015	Wrong intervention	Comparison of intakes of diet soft drinks
DeCastro 1993	Wrong intervention	Comparison of intakes of diet sodas
Drewnowski 2013	Wrong study type	Cross-sectional study an eligible study type
Durán Agüero 2015	No direct/concurrent comparison arm	Comparison of intakes of stevia
Englund-Ögge 2012	Wrong study population	Pregnant women eligible
Fagherazzi 2013	No direct/concurrent comparison arm	Comparison of intakes of ASB
Fowler 2008	No direct/concurrent comparison arm	Comparison of intakes of ASB
Fung 2009	No direct/concurrent comparison arm	Comparison of intakes of ASB
Halldorsson 2010	Wrong study population	Pregnant women eligible
Kline 1978	Outcome irrelevant	Miscarriage eligible outcome for pregnant women
Ledoux 2011	Wrong study type	Cross-sectional study an eligible study type
Ludwig 2001	No direct/concurrent comparison arm	Comparison of intakes of diet soda
Mackenzie 2006	Wrong study type	Cross-sectional study an eligible study type
Mahar 2007	Wrong outcome (no health outcome)	Sweetness liking an eligible outcome
Masic 2017	Wrong outcome (no health outcome)	Protocol of trial. Outcomes were weight, body composition, appetite and cognition
Maslova 2013	Wrong study population	Intake of ASB during pregnancy and asthma and allergic rhinitis during childhood
Paganini-Hill 2007	Outcome irrelevant	Outcome was mortality
Peters 2014	Study duration too short	Study duration of 12 weeks
Shoham 2008	Wrong study type	Cross-sectional study an eligible study type
Sylvetsky 2012	Wrong study type	Cross-sectional study an eligible study type
Taljaard 2013	Wrong study type	Randomized controlled trial
Vázquez-Durán 2013	Missing	Eligible study type, population, comparison and outcome
Winther 2016	Sweetener not defined	Sweetener defined in full text (Winther 2017)

ASB: artificially sweetened beverage

Table A11.4 Studies included in original review but excluded from update

STUDY	REASON FOR EXCLUSION FROM NEW REVIEW
Frey 1976	NSS level above ADI
Lindseth 2014	Study design not eligible: before and after study (no parallel control arm)
Maki 2008	NSS level above ADI
Porikos 1982	Study design not eligible: before and after study (no parallel control arm)
van den Eeden 1991	No outcome of interest (sleep)
Zanela 2002	Impossible to isolate the effect of NSS (comparison of 1) mentholated deionized water, 2) chlorhexidine gluconate with sodium fluoride, 3) chlorhexidine digluconate, and 4) stevioside with sodium fluoride)

ADI: acceptable daily intake; NSS: non-sugar sweeteners.

Table A11.5 Outcome data included in update but not in original review

STUDY	OUTCOME	ORIGINAL REVIEW	UPDATE/EXPANSION
Bes-Rastrollo 2006	Weight gain	Not reported in publication	Obtained necessary data from other review
Blackburn 1997	Body weight	Standard error or standard deviation not reported	Imputed standard error
Kanders 1988	Body weight	Standard error or standard deviation not reported	Imputed standard error
Reid 2007	Body weight	Not reported in publication	Obtained necessary data from authors
Reid 2010	Body weight	Not reported in publication	Obtained necessary data from authors

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World Health Organization

For more information, please contact:

Department of Nutrition and Food Safety
World Health Organization
Avenue Appia 20, CH-1211 Geneva 27, Switzerland

Fax: +41 22 791 4156
Email: nutrition@who.int
https://www.who.int/teams/nutrition-and-food-safety