

# **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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# 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.

## Randomized controlled trials

**Adiposity**

- ↓ Body weight  $-0.71$  kg (*low*)
- ↓ BMI  $-0.14$  kg/m<sup>2</sup> (*low*)
- ∅ Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

**Type 2 diabetes**

- ∅ Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

**All-cause mortality**

No data

**Cardiovascular diseases**

- ↑ Total:HDL cholesterol  $+0.09$  (*moderate*)
- ∅ Blood pressure, cholesterol (total, LDL, HDL), triglycerides

**Cancer**

No data

**Total energy intake (kJ/day)**

- ↓ Energy intake  $-569$  (*low*)

**Sugars intake (g/day)**

- ↓ Sugars intake  $-38$  (*low*)

**Pregnancy**

No data

Mostly in NSS → sugars

## Cohort/case-control studies

**Adiposity**

- ↑ Incident obesity HR 1.76 (*low*)
- ↑ BMI  $+0.14$  kg/m<sup>2</sup> (*very low*)
- ∅ Other measures

**Type 2 diabetes**

- ↑ Disease (beverage) HR 1.23 (*low*)
- ↑ Disease (tabletop) HR 1.34 (*low*)
- ↑ High fasting glucose HR 1.21 (*low*)
- ∅ Other measures

**All-cause mortality**

- ↑ Mortality HR 1.12 (*very low*)

**Cardiovascular diseases**

- ↑ CVD mortality HR 1.19 (*low*)
- ↑ CV events HR 1.32 (*low*)
- ∅ CHD (*very low*)
- ↑ Stroke HR 1.19 (*low*)
- ↑ Hypertension HR 1.13 (*low*)

**Cancer**

- ∅ Mortality (*very low*)
- ∅ Incidence: any type (*very low*)
- ↑ Bladder cancer OR 1.31 (*very low*)

**Total energy intake (kJ/day)**

No data

**Sugars intake (g/day)**

No data

**Pregnancy**

- ↑ Preterm birth HR 1.25 (*low*)

Mostly in saccharin

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, ∅ = 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 ( $\geq 18$  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.<sup>1</sup>

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.

<sup>1</sup> 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<sup>1</sup> were included in the main meta-analyses and assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.<sup>2</sup> 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

<sup>1</sup> 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.

<sup>2</sup> <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,<sup>1</sup> 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<sup>2</sup> 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.

<sup>1</sup> Including MEDLINE In-Process & Other Non-Indexed Citations

<sup>2</sup> <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.<sup>1</sup>

## 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.<sup>2</sup> 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.<sup>3</sup>

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.

<sup>1</sup> <http://plotdigitizer.sourceforge.net>

<sup>2</sup> [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

<sup>3</sup> <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.<sup>1</sup> 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).

<sup>1</sup> <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 ( $n = 1$ ).

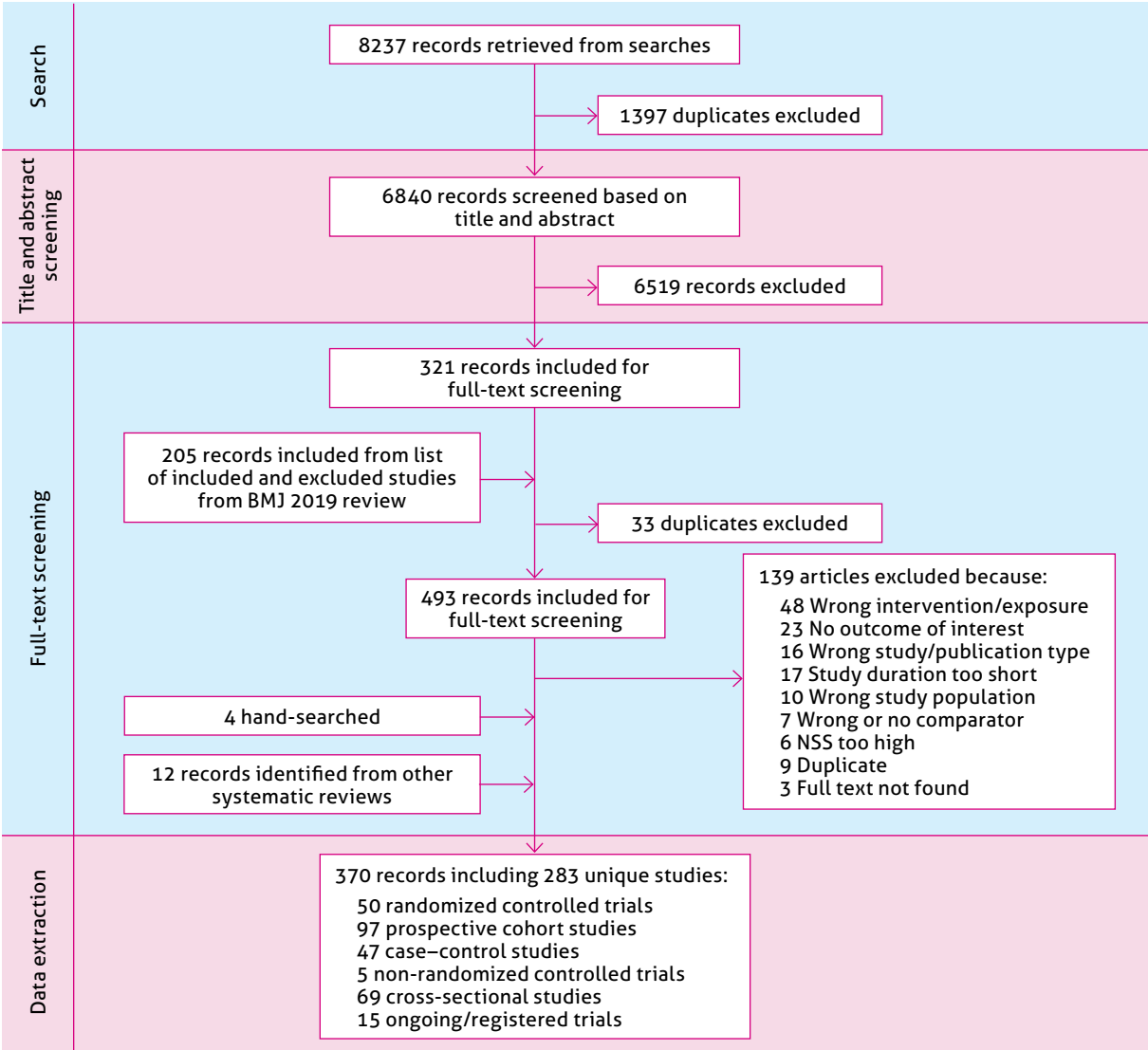
The four RCTs in children were all of parallel design, conducted in mixed-sex populations (except for one conducted in females only), and lasted from 6 weeks to 18 months. Two trials used stevia in the intervention arm, one used a mix of sucralose and acesulfame K, and one used sucralose. One trial in 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.<sup>1</sup> 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](#).

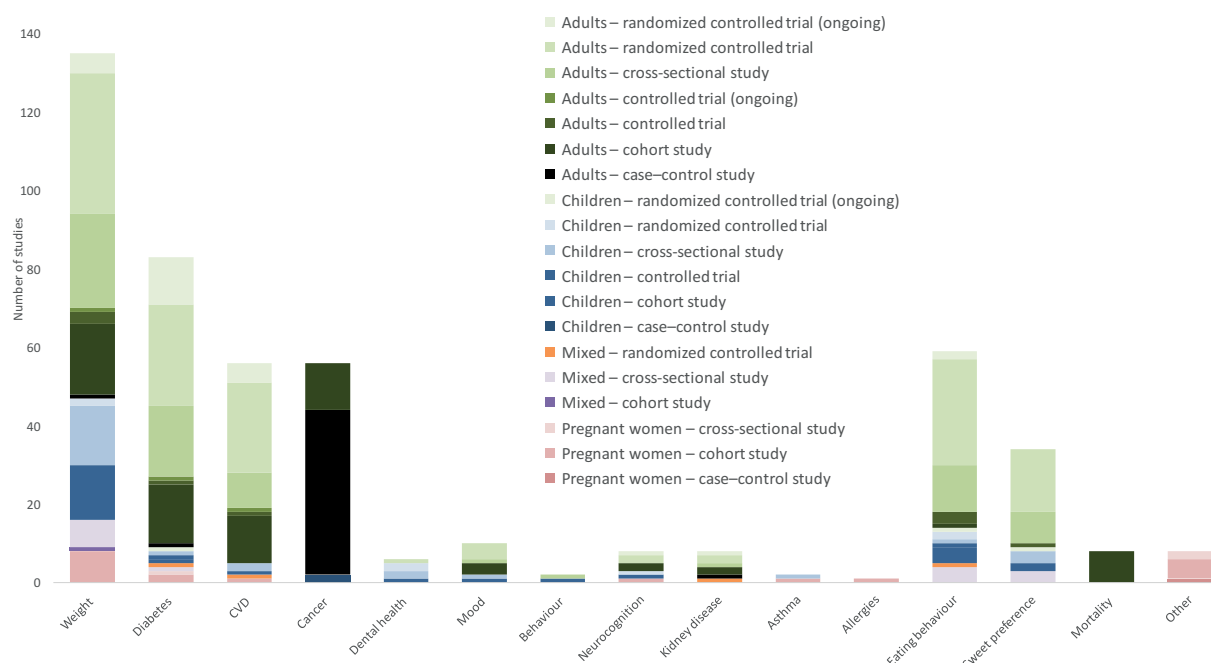
As assessed in RCTs, higher intakes of NSS resulted in a reduction in body weight of 0.71 kg ([Fig. 3](#)) and BMI of 0.14 kg/m<sup>2</sup>, although the latter was not quite statistically significant ([Fig. 4](#)). No significant effects were observed for other measures of adiposity as assessed in RCTs ([Table 2](#); [Annex 9: Fig. A9.1–A9.5](#)). Higher intakes of NSS were associated with a 0.14 kg/m<sup>2</sup> 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

<sup>1</sup> 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.

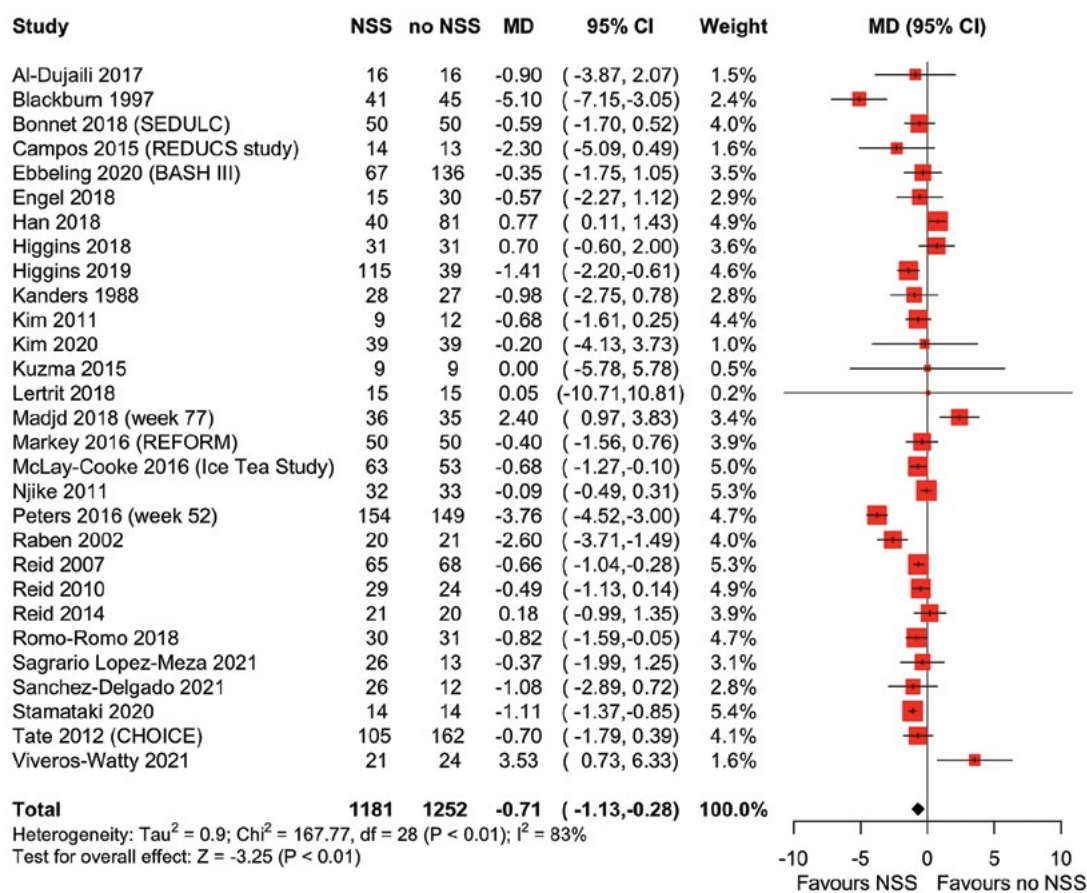
**Table 2. Summary of results for NSS intake and measures of adiposity in adults**

Measure of adiposity (unit)	No. of studies/cohorts	Effect estimate (95% CI)	I <sup>2</sup> (%)	Figure
Weight (kg)	29 RCTs	<b>MD -0.71 (-1.13, -0.28)</b>	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 <sup>2</sup> )	23 RCTs	MD -0.14 (-0.30, 0.02)	71	4
	5 cohorts (hvl)	<b>MD 0.14 (0.03, 0.25)</b>	79	5
Incident obesity	2 cohorts (hvl)	<b>HR 1.76 (1.25, 2.49)</b>	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**



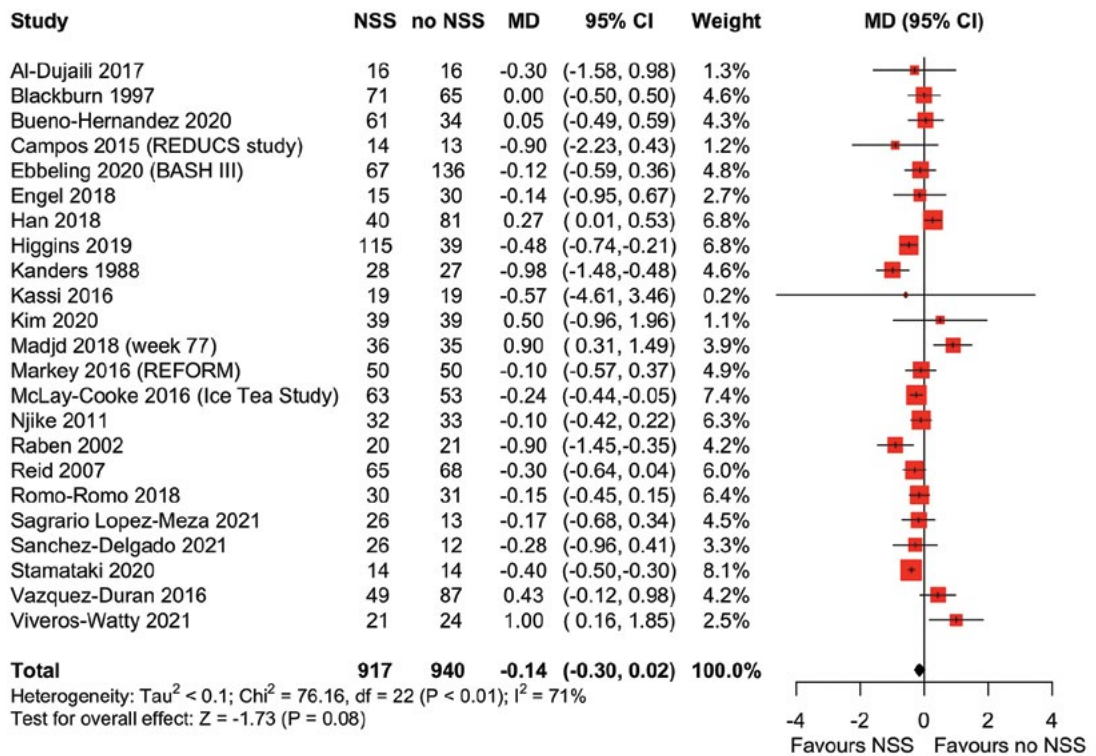
both adults and children (76), overweight participants ( $n = 57$ ) between 10 and 21 years of age (mean age: 19 years) were given capsules totalling 2.7 g aspartame daily or a lactose placebo. At the end of the intervention, when compared to the placebo arm, the aspartame arm had lost 1.09 kg (standard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

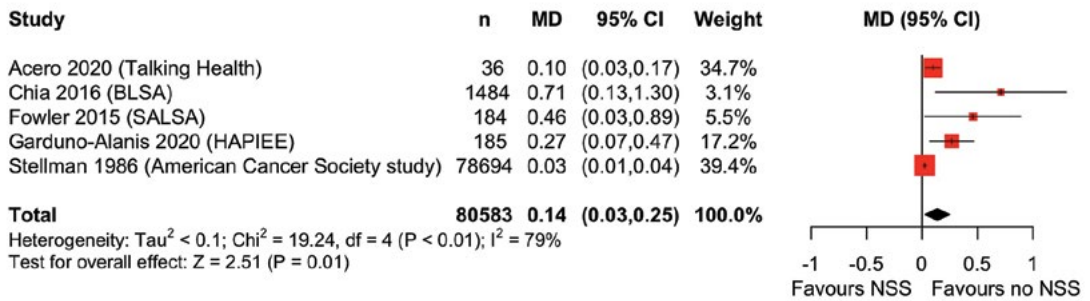
### Subgroup and sensitivity analyses

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

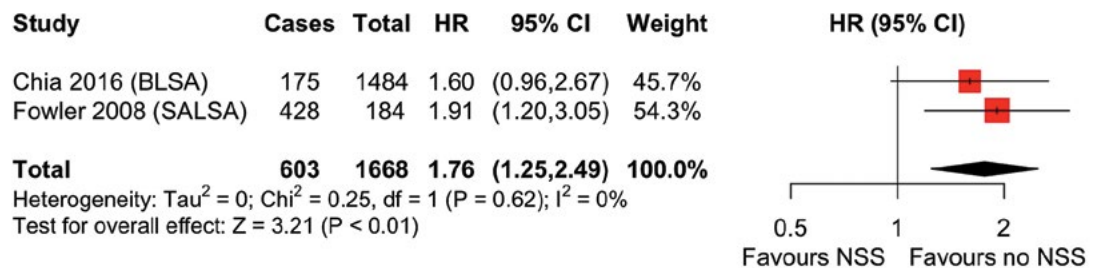
**Fig. 4. Effect of NSS intake on body mass index (kg/m<sup>2</sup>) in randomized controlled trials**



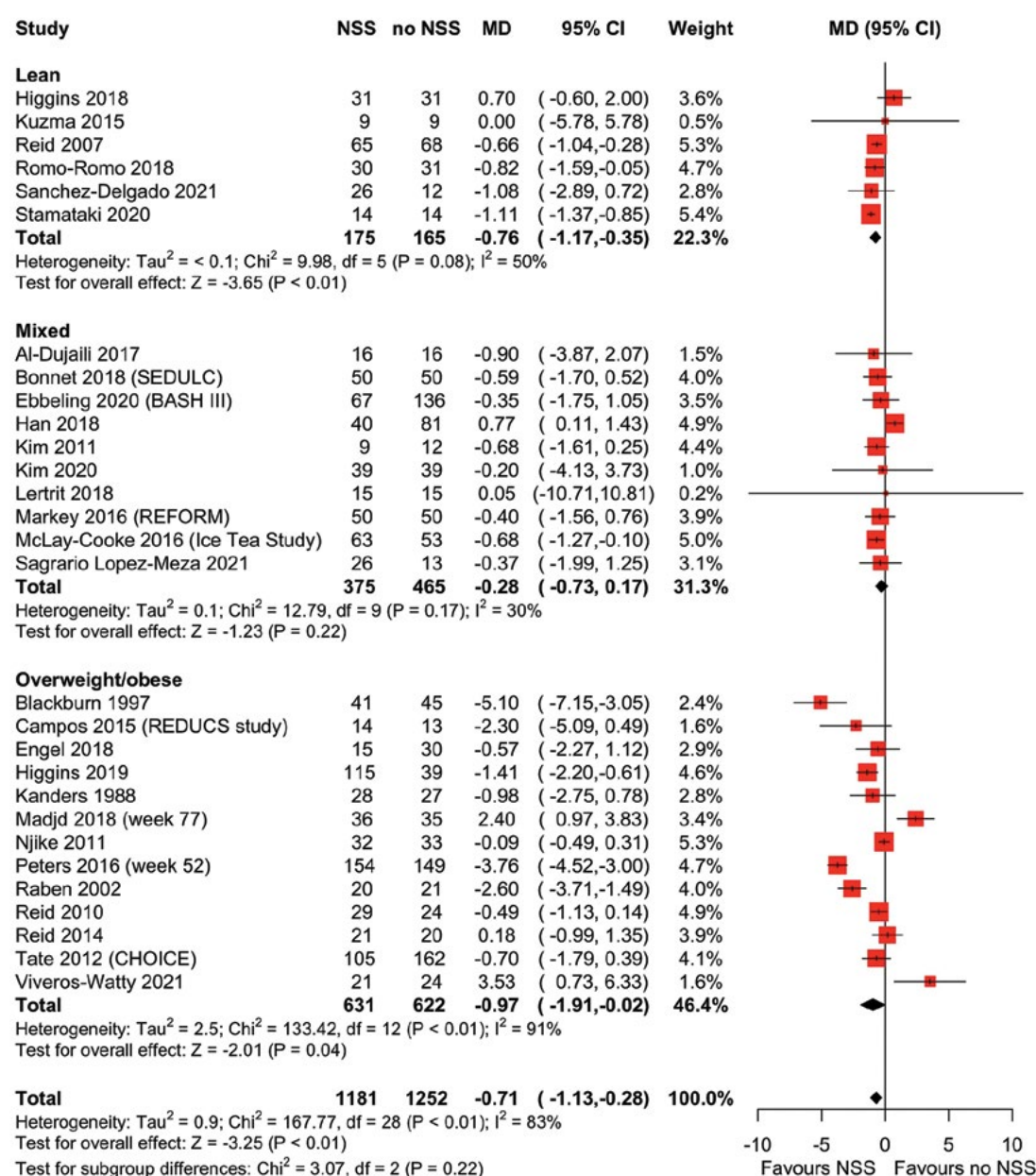
**Fig. 5. Association between NSS intake and body mass index (kg/m<sup>2</sup>) in prospective cohort studies**



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



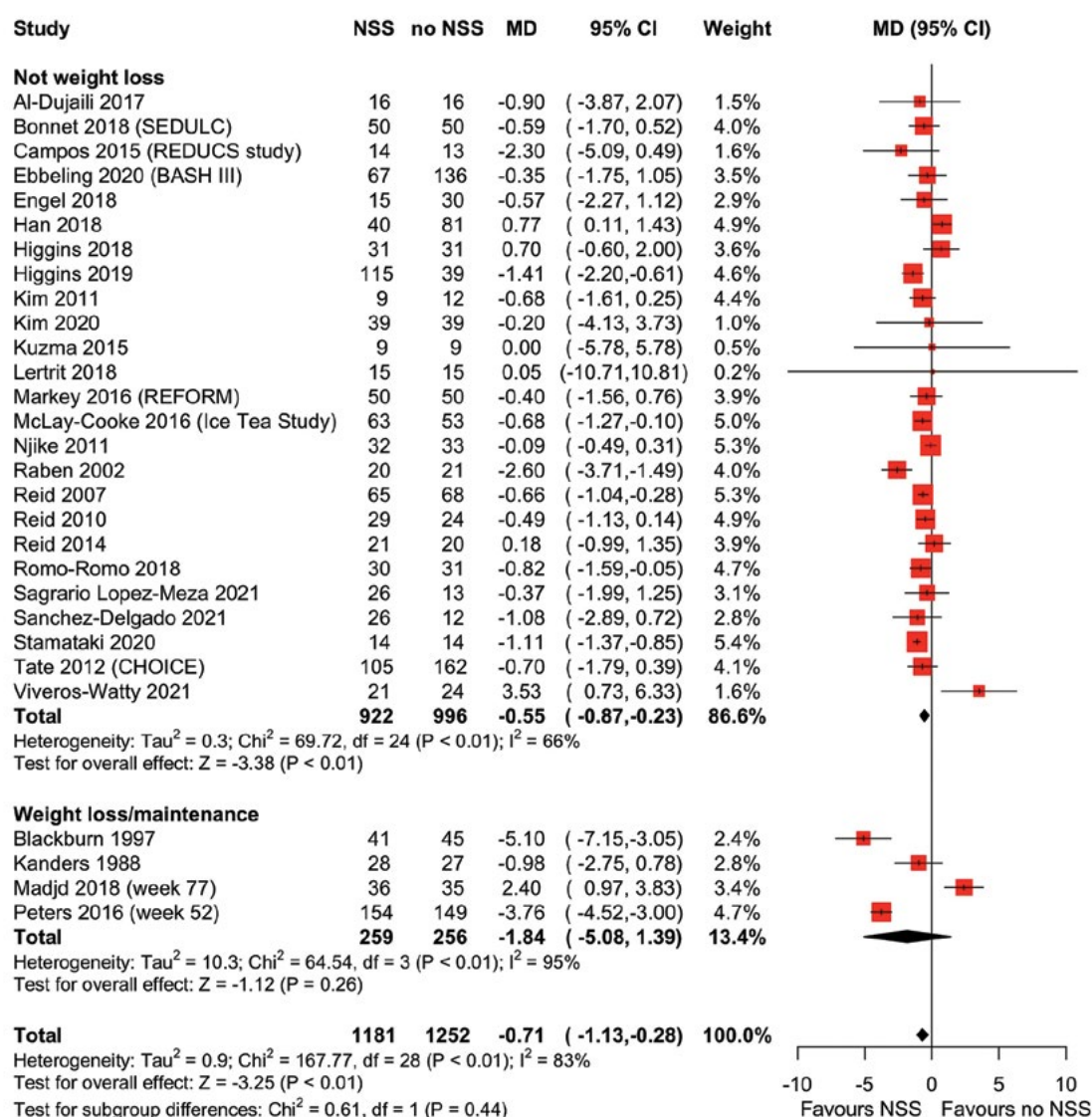
**Fig. 7. Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by baseline weight status**



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)**

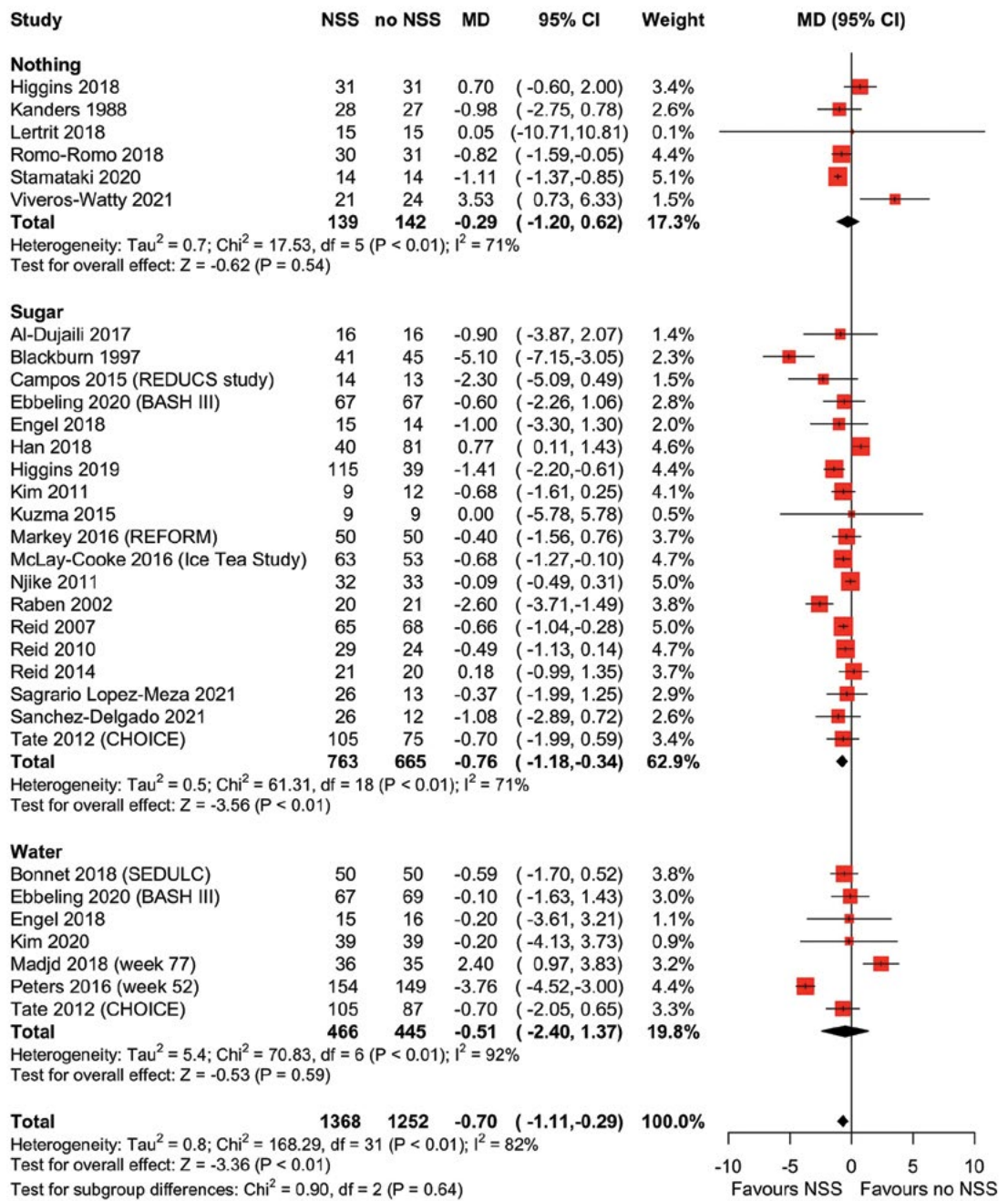


*Note:* Weight loss studies were those in which participants were instructed to restrict energy intake AND consume NSS or control. Weight maintenance studies were those that followed up participants after active weight loss, with instructions on energy intake designed to prevent weight gain. Non-weight 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<sup>2</sup> 83%) or BMI (MD -0.17; 95% CI -0.33, -0.02; I<sup>2</sup> 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](#)).

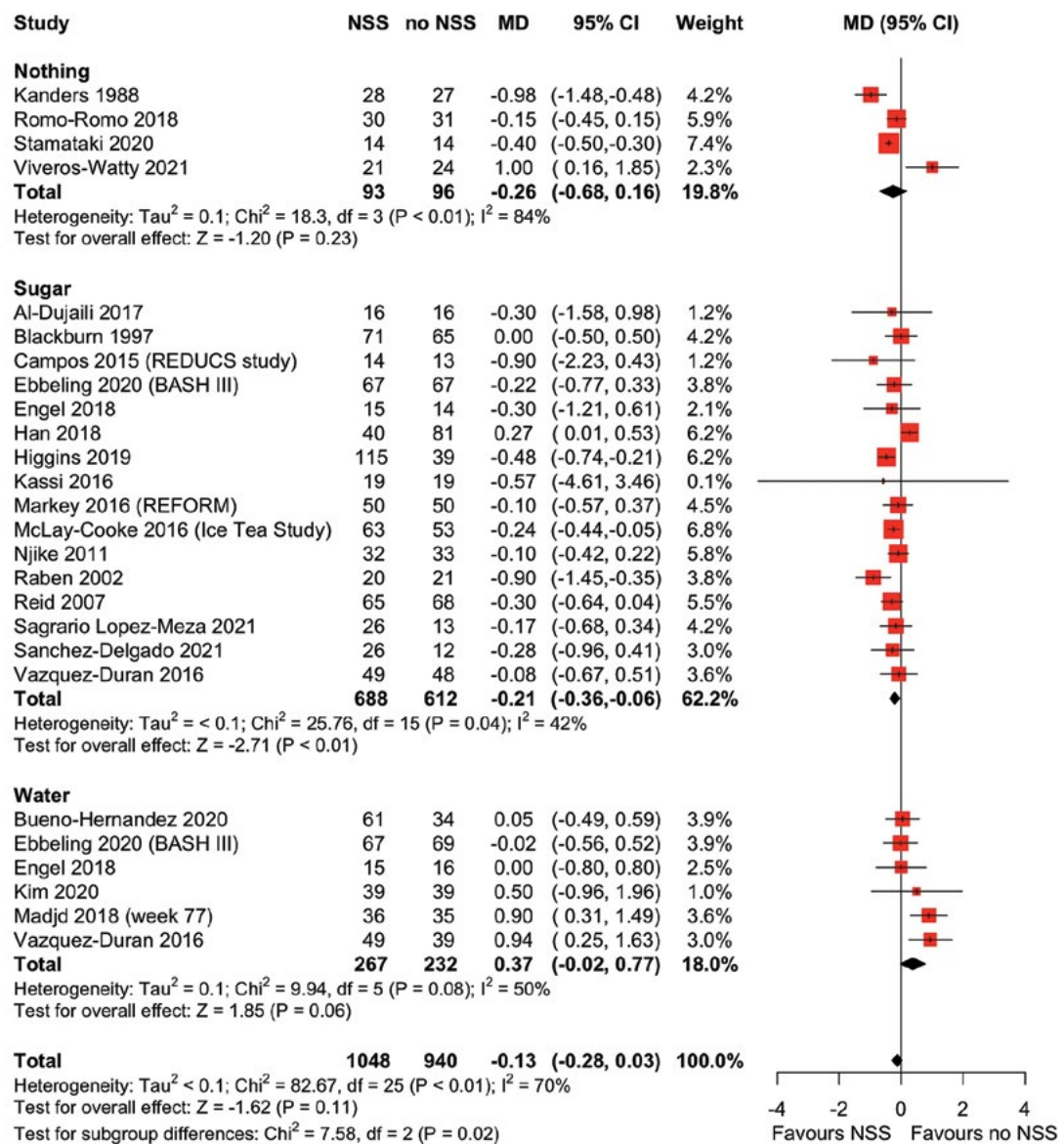
**Fig. 9. Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by comparator**



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.

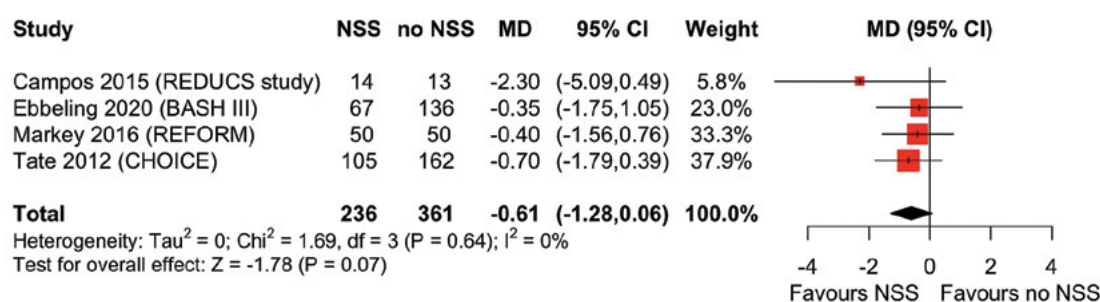


**Fig. 10. Effect of NSS on body mass index (kg/m<sup>2</sup>) in randomized controlled trials, subgrouped by comparator**

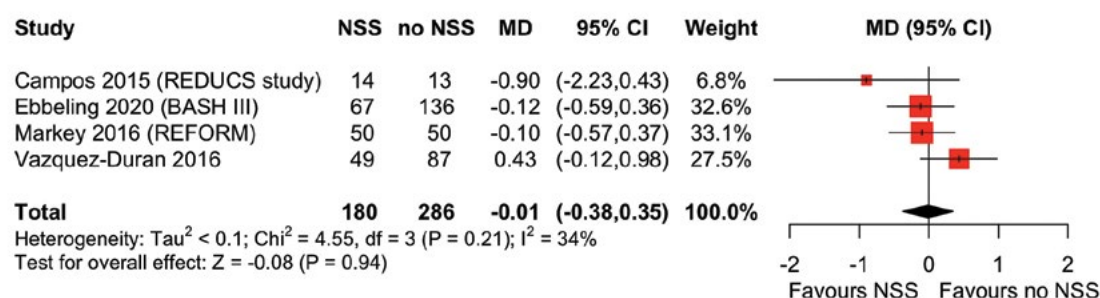


*Note:* Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from 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/m<sup>2</sup>) 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).<sup>1</sup>

<sup>1</sup> 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 quantitatively or narratively that the effect was not significantly affected (Table 4).

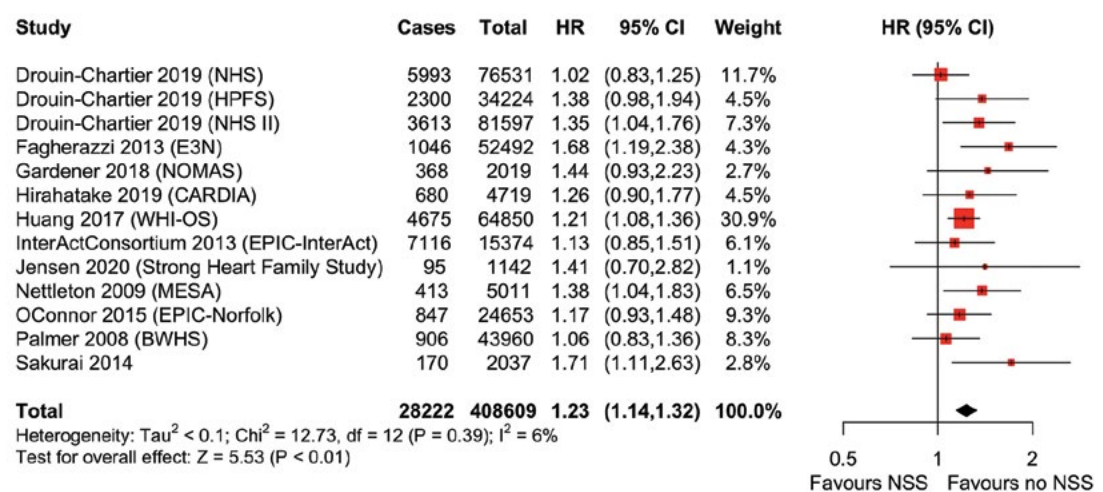
**Table 3. Summary of results for NSS intake and type 2 diabetes**

Measure of type 2 diabetes (unit)	No. of studies/cohorts	Effect estimate (95% CI)	I <sup>2</sup> (%)	Figure
Incident type 2 diabetes (beverages)	13 cohorts	<b>HR 1.23 (1.14, 1.32)</b>	6	13
Incident type 2 diabetes (tabletop)	2 cohorts	<b>HR 1.34 (1.21, 1.48)</b>	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

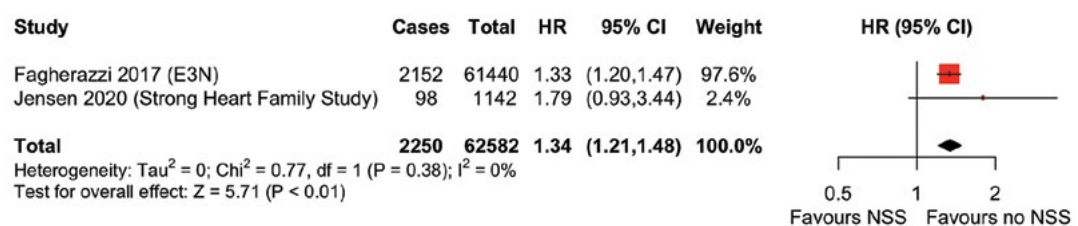
HbA1c: glycated haemoglobin; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance.

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<sup>1</sup> as assessed in prospective cohort studies (hazard ratio [HR] 1.21; 95% CI 1.01, 1.45; 3 studies with 11 213 participants; I<sup>2</sup> 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

<sup>1</sup> High fasting glucose (as part of the criteria for assessing metabolic syndrome, as indicated in the relevant included studies) was defined as  $\geq 100$  mg/dL.

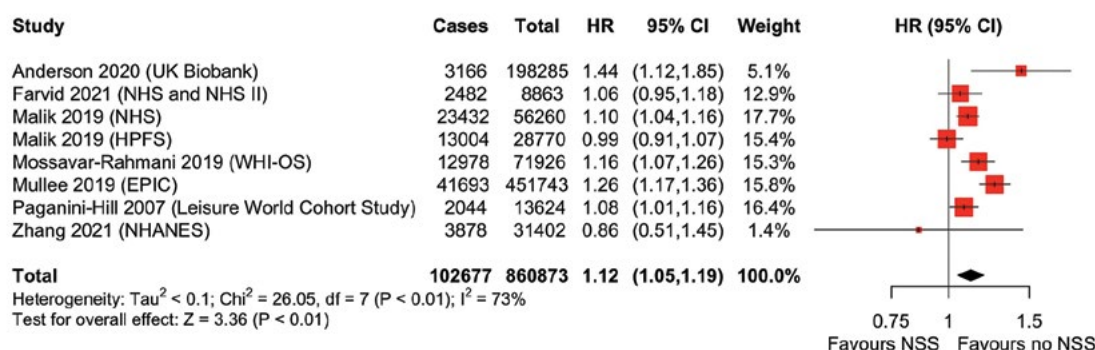
incremental AUC (iAUC) were not amenable to meta-analysis; however, most did not report significant differences (23, 26, 31, 35, 53, 100, 101). One trial found a significant increase in glucose iAUC in the NSS arm compared with the sucrose arm ( $P < 0.05$ ) (96).

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**



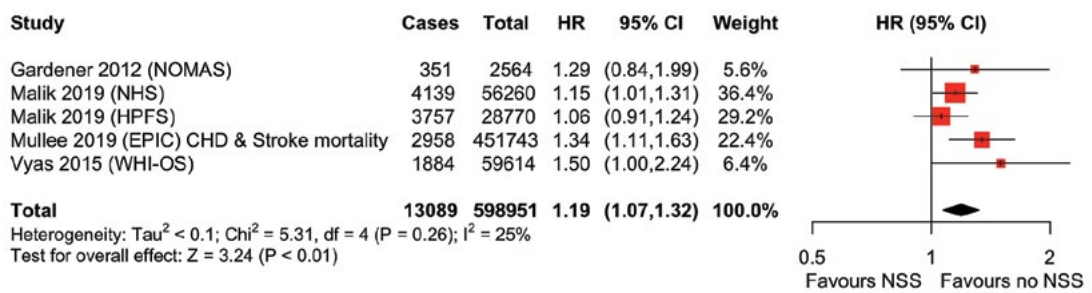
### 3.1.4 Cardiovascular diseases

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).

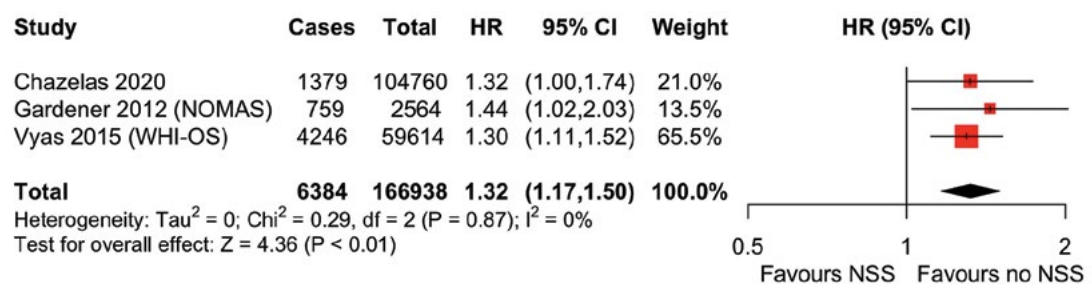
**Fig. 16. Association between NSS-containing beverage intake and risk of cardiovascular disease mortality in prospective cohort studies**



### 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<sup>1</sup> (Fig. 17).

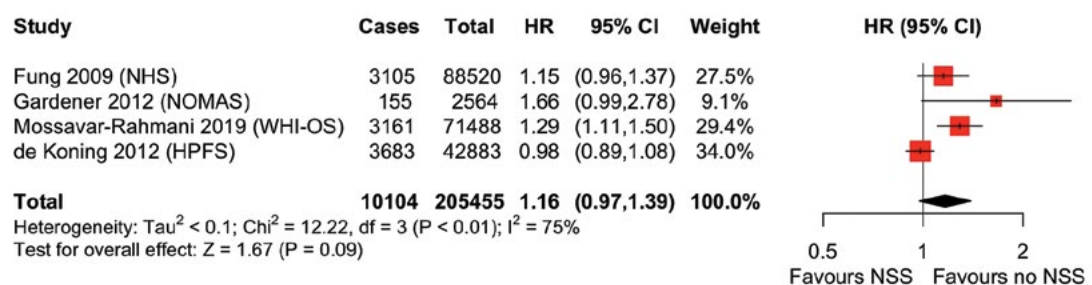
**Fig. 17. Association between NSS-containing beverage intake and risk of cardiovascular events in prospective cohort studies**



### 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**

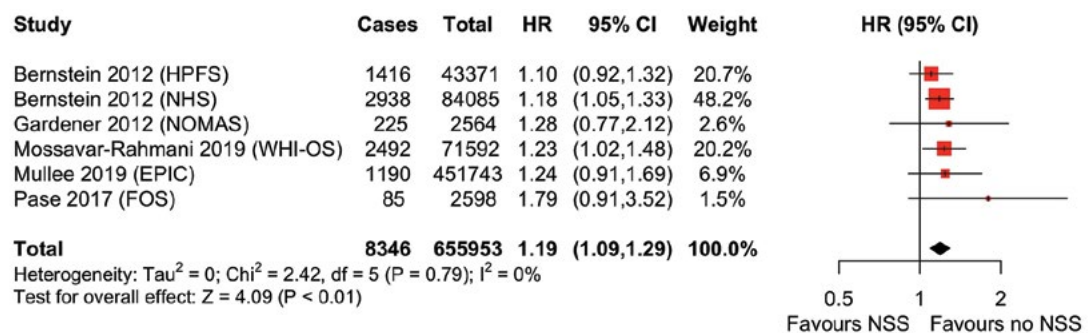


<sup>1</sup> Cardiovascular events in Gardener et al. (2012) (108) included stroke, myocardial infarction and vascular death. In Vyas et al. (2015) (109), they included coronary heart disease, myocardial infarction, heart failure, coronary revascularization procedure, ischaemic stroke, peripheral artery 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).

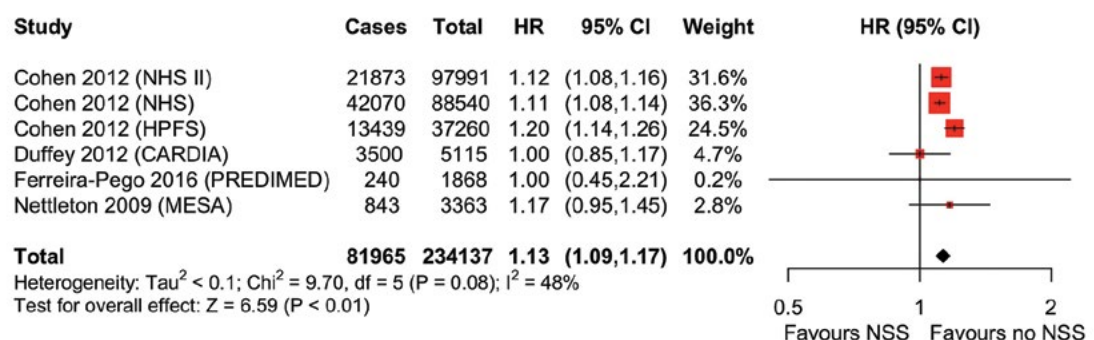
**Fig. 19. Association between NSS-containing beverage intake and risk of stroke in prospective cohort studies**



### 3.1.4.5 Hypertension

Four prospective cohort studies (comprising six cohorts) reporting on the risk of hypertension<sup>1</sup> 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**

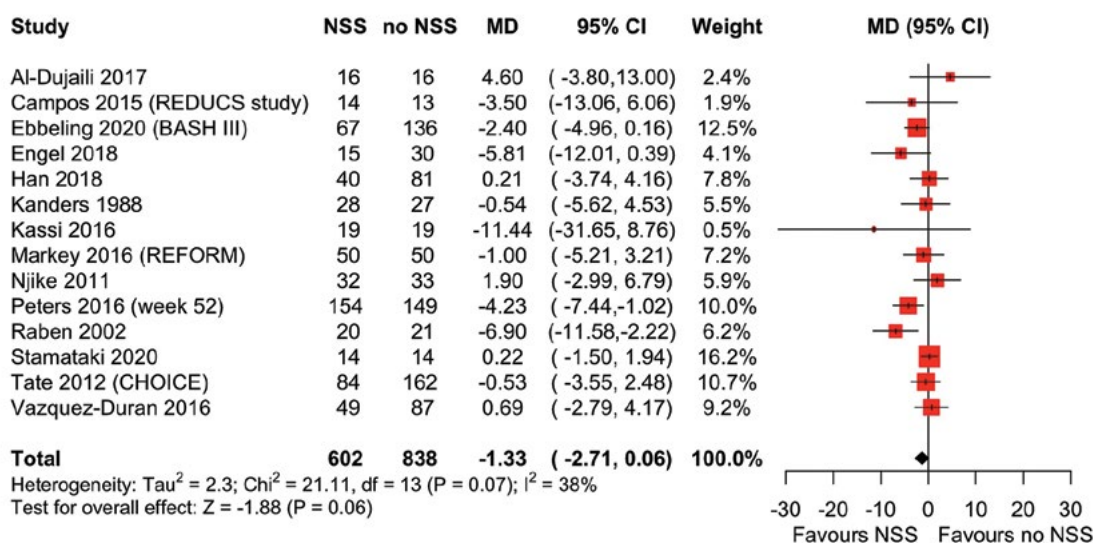


<sup>1</sup> Defined as systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure  $\geq 85$  mmHg, or taking antihypertensive medication.

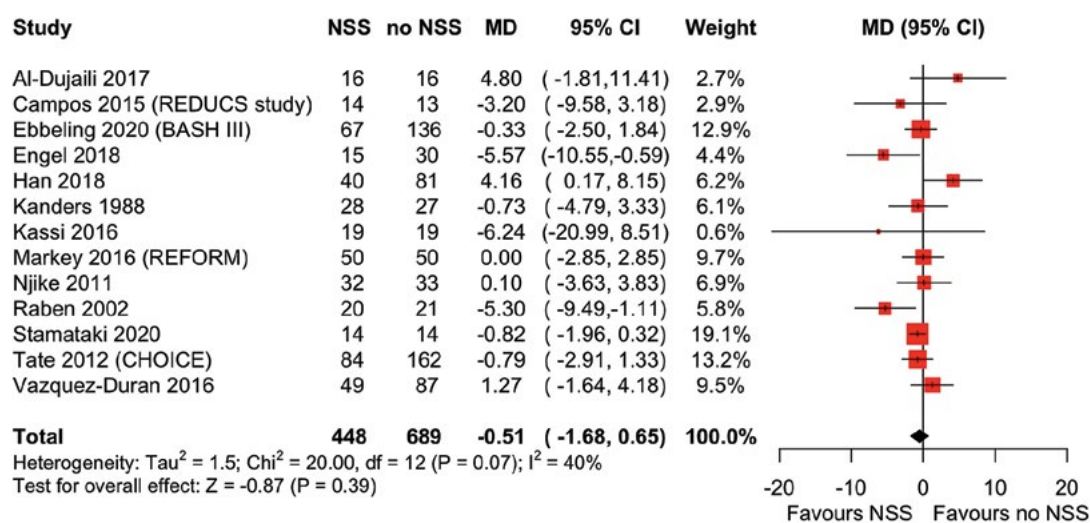
### 3.1.4.6 Intermediate markers of disease

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**

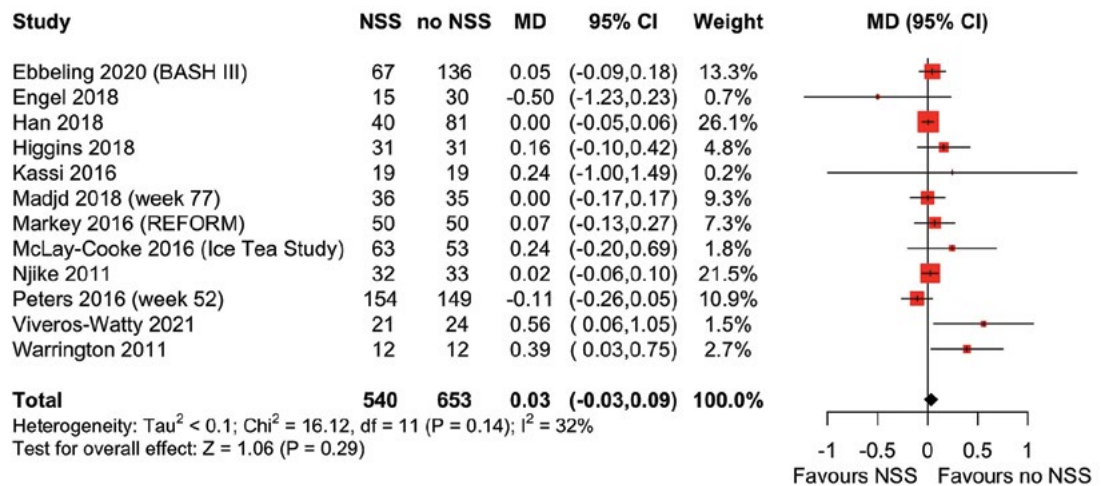


**Fig. 22. Effect of NSS intake on diastolic blood pressure (mmHg) in randomized controlled trials**

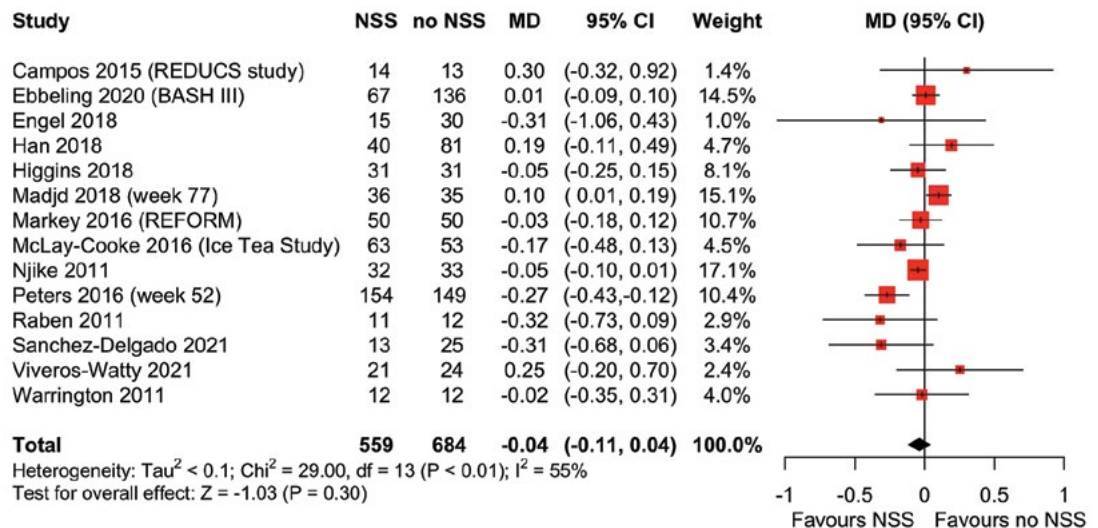




**Fig. 23. Effect of NSS intake on LDL cholesterol (mmol/L) in randomized controlled trials**



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



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

Measure of CVD (unit)	Number of studies/cohorts	Effect estimate (95% CI)	I <sup>2</sup> (%)	Figure
CVD mortality	5 cohorts	<b>HR 1.19 (1.07, 1.32)</b>	25	16
Cardiovascular events	3 cohorts	<b>HR 1.32 (1.17, 1.50)</b>	0	17
Coronary heart disease	4 cohorts	HR 1.16 (0.97, 1.39)	75	18
Stroke	6 cohorts	<b>HR 1.19 (1.09, 1.29)</b>	0	19
Hypertension	6 cohorts	<b>HR 1.13 (1.09, 1.17)</b>	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	<b>MD 0.09 (0.02, 0.16)</b>	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<sup>1</sup> 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

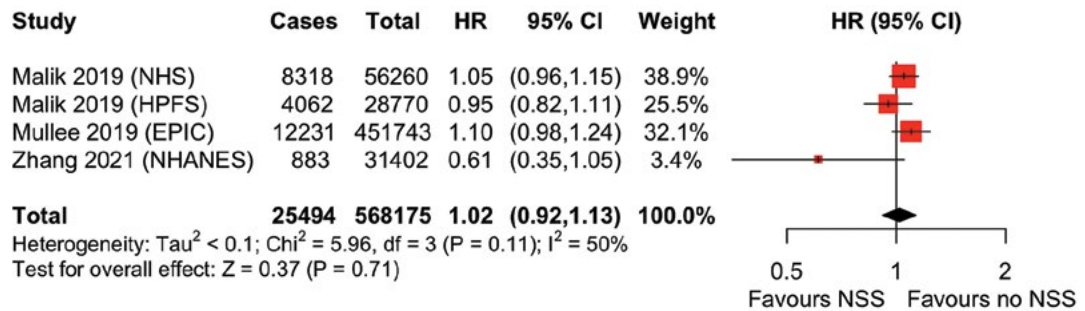
Results for cancer are summarized in [Table 6](#).

<sup>1</sup> 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**

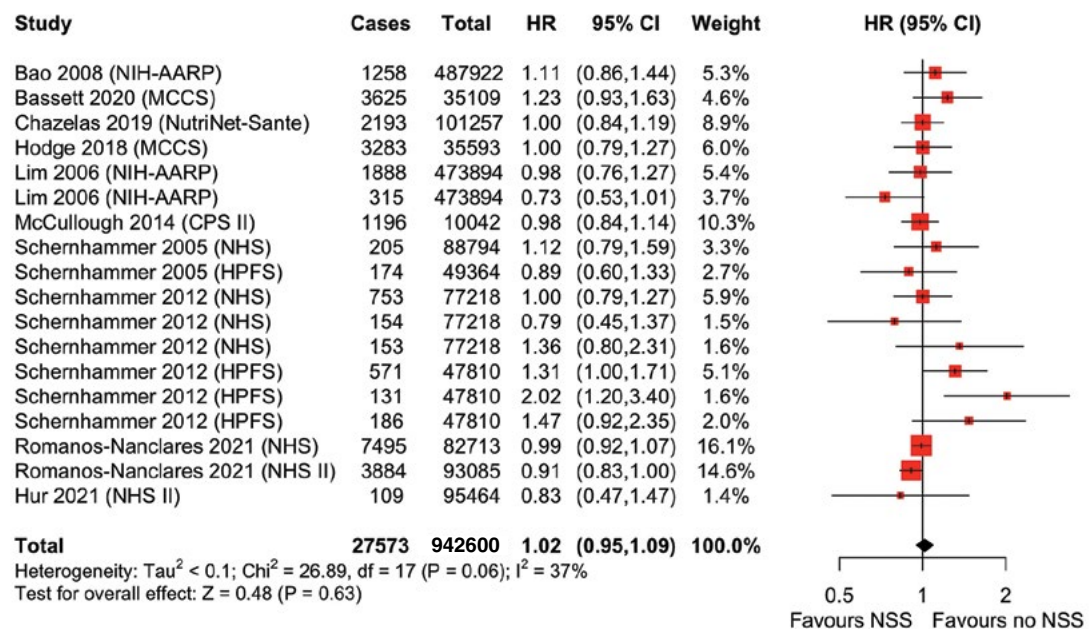


### 3.1.5.2 Cancer incidence

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 <sup>2</sup> (%)	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	<b>OR 1.31 (1.06, 1.62)</b>	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	<b>OR 2.34 (1.20, 4.56)</b>	NA	NA
Lung	2 case–controls	<b>OR 0.40 (0.26, 0.61)</b>	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	<b>OR 0.56 (0.38, 0.82)</b> 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	<b>HR: 1.23 (1.02, 1.48)</b>	NA	NA
Cancers related to obesity <sup>a</sup>	1 cohort	HR: 1.00 (0.79, 1.27)	NA	NA

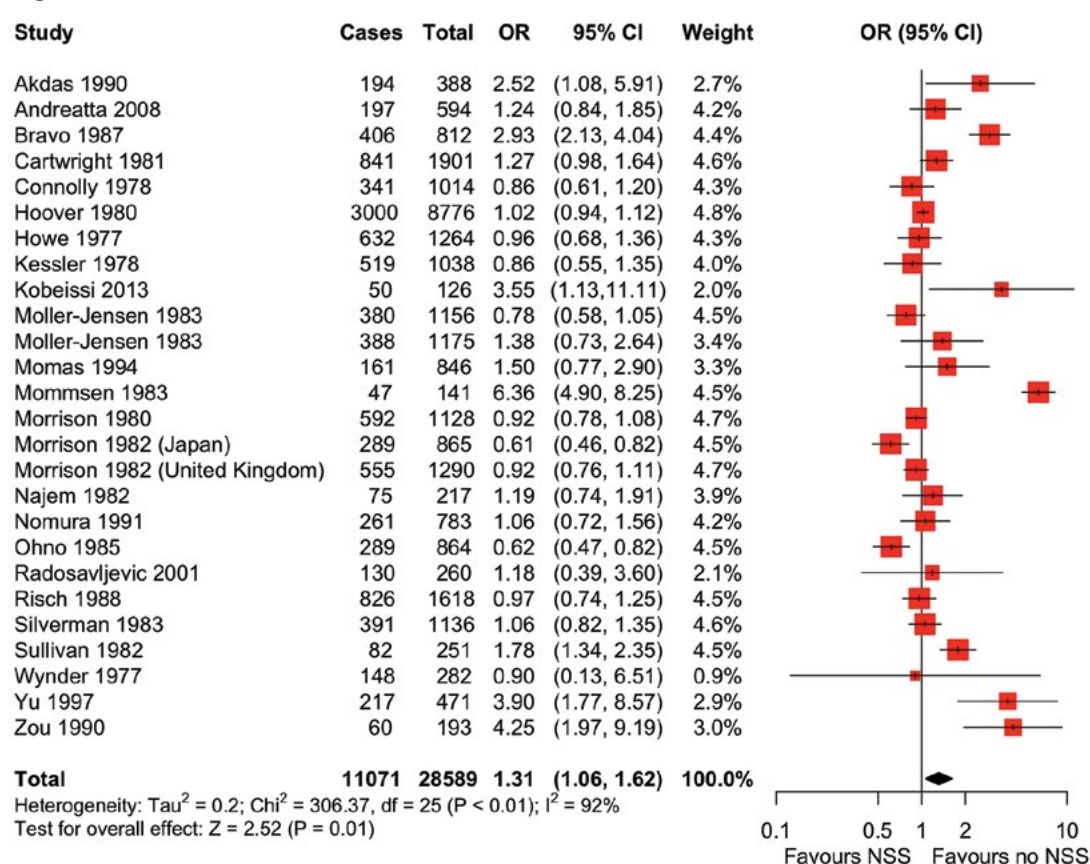
NA: not applicable.

<sup>a</sup> 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,<sup>1</sup> 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<sup>2</sup> ([Annex 9: Fig. A9.52](#)). One prospective study reported an association

<sup>1</sup> 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)

<sup>2</sup> Lin 2011 reported the association between NSS use and decline in estimated glomerular filtration rate (eGFR) of  $\geq 30\%$  (173), and Rebholz 2017 the association between NSS use and chronic kidney disease with one defining characteristic being a  $\geq 25\%$  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 <sup>2</sup> (%)	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.

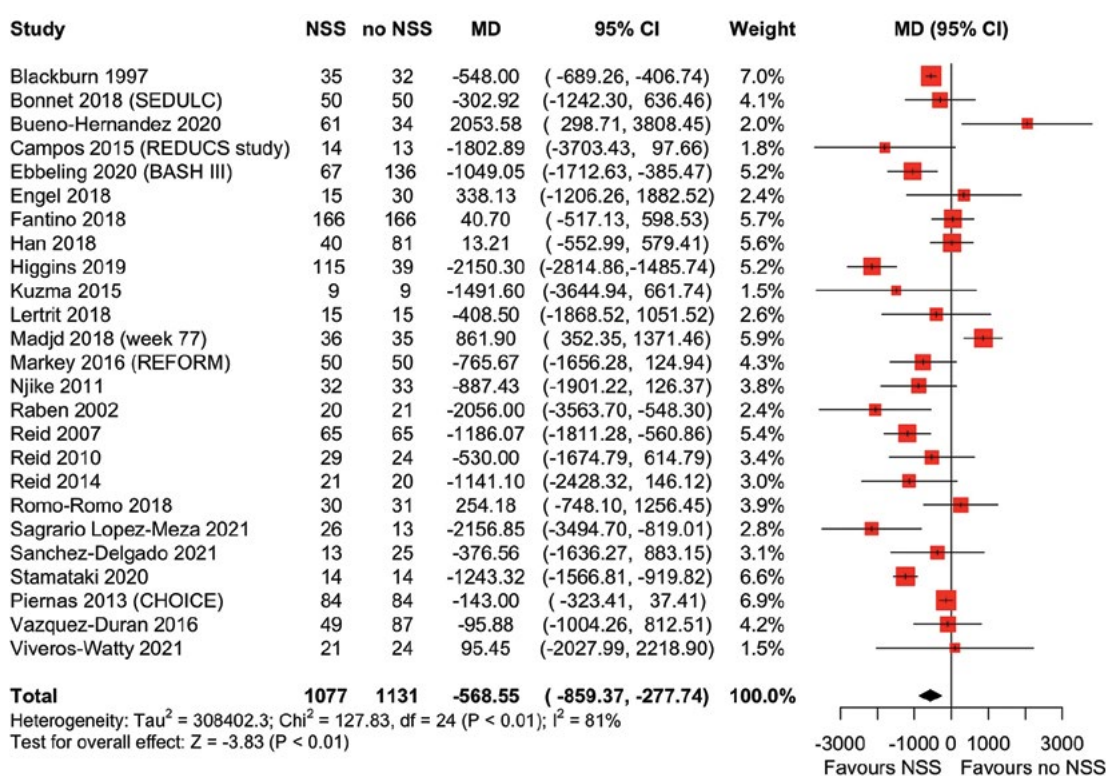
### 3.1.7 Eating behaviour

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

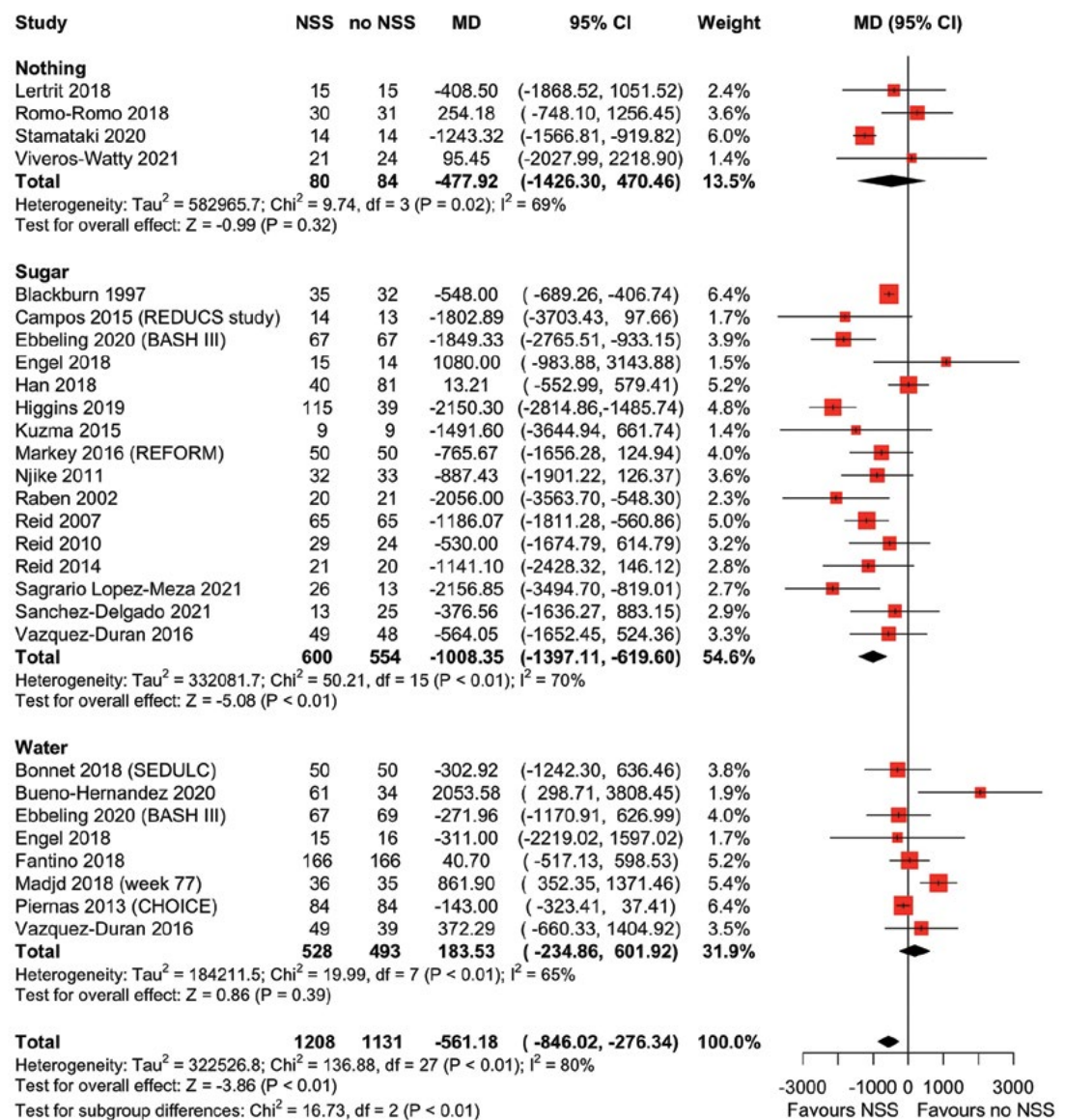
#### 3.1.7.1 Energy intake

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<sup>2</sup> 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

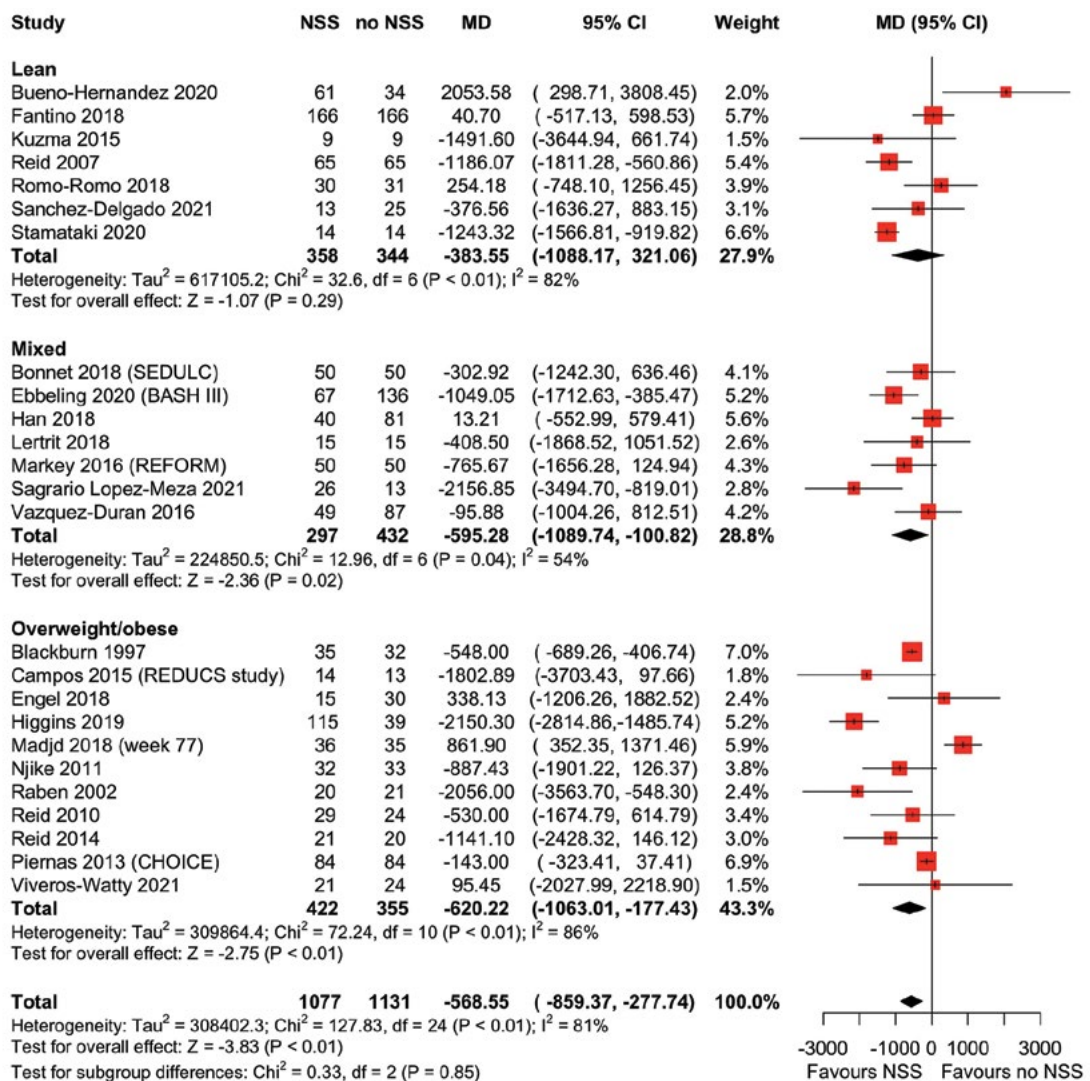
As assessed in RCTs, a small but significant decrease in subjective measures of satiety or fullness was observed with NSS intake (SMD -0.15; 95% CI -0.30, -0.01; three trials with 518 participants;  $I^2$  98%) (Annex 9: Fig. A9.60). In addition, one RCT (41) and one nonrandomized controlled trial (177) 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).

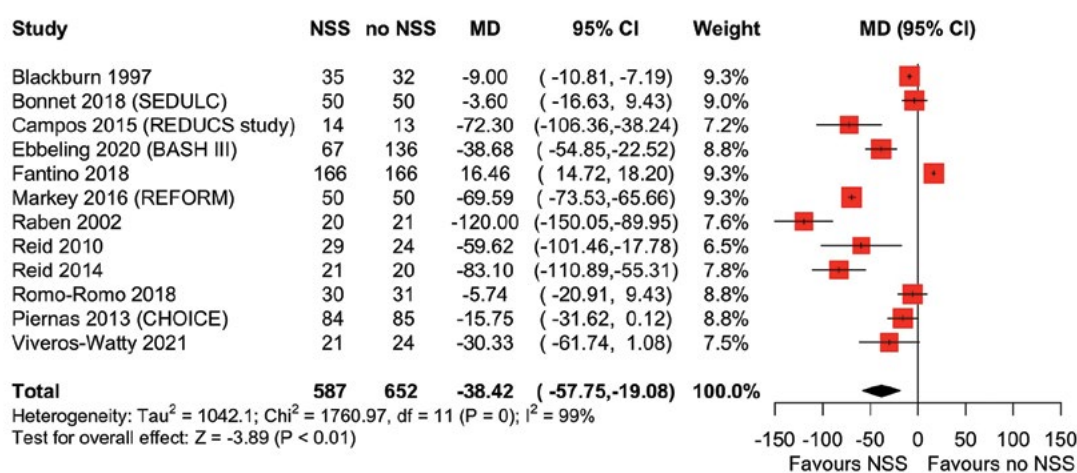
In an analysis of the cross-sectional National Health and Nutrition Examination Survey (NHANES) data, individuals who consumed NSS had more eating episodes per day, which started earlier in the morning and lasted longer across the day, than those who did not (178). Another cross-sectional study comparing 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

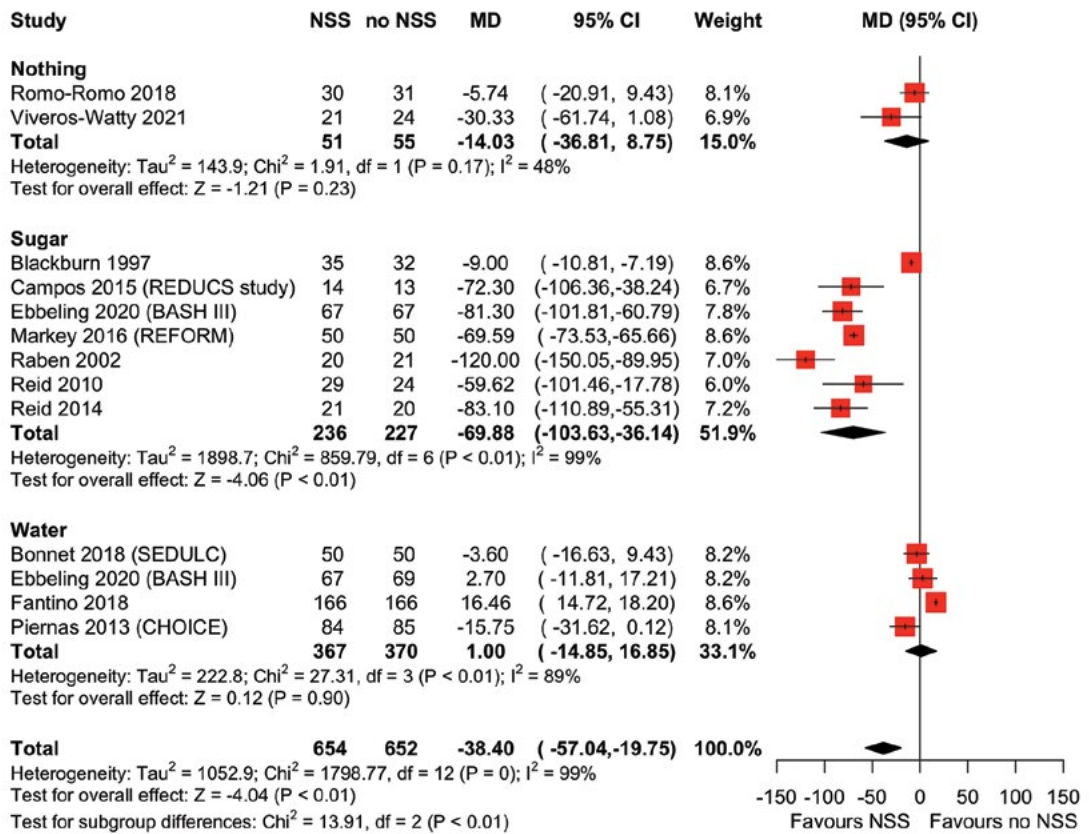
#### 3.1.8.1 Sugars intake

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.

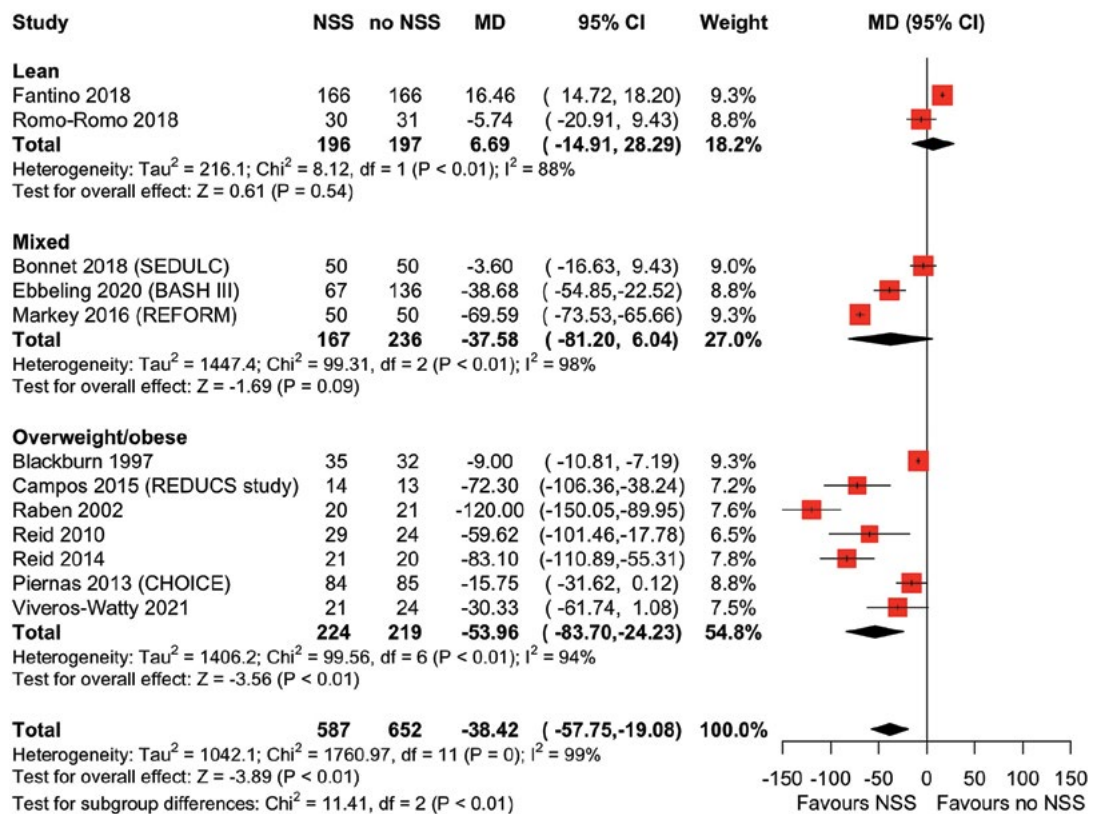
**Fig. 31. Effect of NSS intake on sugars intake (g/day) in randomized controlled trials**



**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<sup>1</sup> score difference:  $b = -0.19$ ; 95% CI  $-0.78, 0.40$ ;  $P = 0.53$ ) (188). In another cohort study, the 10-year

<sup>1</sup> 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 <sup>2</sup> (%)	Figure
Body weight	1 RCT	<b>MD -1.01 (-1.54, -0.48)</b>	NA	NA
	2 cohorts	MD 0.03 (-0.14, 0.21)	0	A9.66
BMI (kg/m <sup>2</sup> )	5 cohorts (cont)	MD 0.08 (-0.01, 0.17)	89	A9.67
	2 cohorts (hvl)	MD 0.04 (-0.32, 0.40)	44	A9.68
BMI z-score	2 RCTs	MD -0.07 (-0.26, 0.11)	48	A9.69
	3 cohorts (cont)	MD -0.23 (-0.70, 0.25)	86	A9.70
	1 cohort (hvl)	MD 0.0 (-0.3, 0.3)	NA	NA
Waist circumference (cm)	1 RCT	<b>MD -0.66 (-1.23, -0.09)</b>	NA	NA
Body fat mass (kg)	1 RCT	<b>MD -0.57 (-1.02, -0.12)</b>	NA	NA
	1 cohort	MD -1.00 (-2.52, 0.52)	NA	NA
Body fat mass (%)	1 RCT	<b>MD -1.07 (-1.99, -0.15)</b>	NA	NA
	2 cohorts	MD -1.53 (-5.73, 2.66)	77	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	<i>n</i>	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	84	2462 (572)
		Initiators of NSSB vs never users	89	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	84	40.2 (11.6)
		Initiators of NSSB vs never users	89	-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 ( $\geq 1$  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 [HVL]) (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,<sup>1</sup> 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 ( $\geq 2$  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).

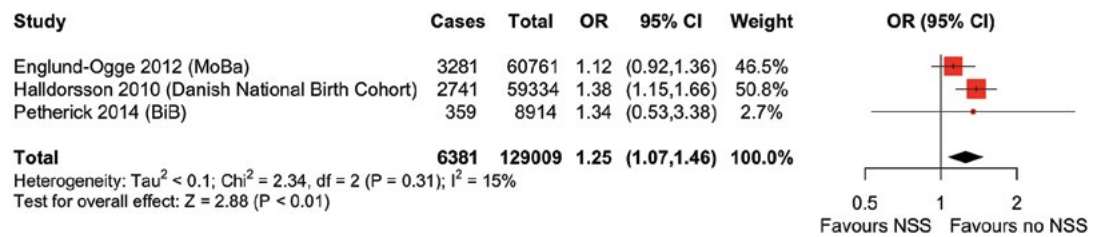
### 3.3.2 Birth outcomes

#### 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).

<sup>1</sup> 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<sup>1</sup> 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,<sup>2</sup> early childhood: -1.2; 95% CI -2.9, 0.5; total WRAVMA,

<sup>1</sup> 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.

<sup>2</sup> 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 ( $\geq 4$  servings/day versus no use; for carbonated beverages, adjusted OR 1.01; 95% CI 0.32, 3.21;  $P_{\text{trend}}$  0.06; for noncarbonated beverages, adjusted OR 1.08; 95% CI 0.65, 1.80;  $P_{\text{trend}}$  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<sup>1</sup>

### 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  $\geq 1$ /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<sup>2</sup> (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).

<sup>1</sup> Not specified a priori.

<sup>2</sup> 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  $P_{\text{trend}}$  value reported a statistically significant  $P_{\text{trend}}$ , 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.<sup>1</sup> 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

<sup>1</sup> 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
<b>Adults</b>	<b>88</b>	<b>74</b>	<b>51</b>	<b>4</b>	<b>2</b>	<b>54</b>	<b>1</b>	<b>8</b>	<b>1</b>	<b>5</b>	<b>7</b>	<b>0</b>	<b>0</b>	<b>45</b>	<b>25</b>	<b>8</b>	<b>0</b>
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
<b>Children</b>	<b>31</b>	<b>4</b>	<b>3</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>5</b>	<b>2</b>	<b>1</b>	<b>2</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>9</b>	<b>6</b>	<b>0</b>	<b>0</b>
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
<b>Mixed</b>	<b>8</b>	<b>2</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>5</b>	<b>3</b>	<b>0</b>	<b>0</b>
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
<b>Pregnant women</b>	<b>8</b>	<b>3</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>8</b>
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
<b>Total</b>	<b>135</b>	<b>83</b>	<b>56</b>	<b>4</b>	<b>2</b>	<b>56</b>	<b>6</b>	<b>10</b>	<b>2</b>	<b>8</b>	<b>8</b>	<b>2</b>	<b>1</b>	<b>59</b>	<b>34</b>	<b>8</b>	<b>8</b>

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	COMPARATOR(S)	DURATION	DESCRIPTION	
<b>ADULTS</b>												
Al-Dujaiti 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) 4x 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	COMPARATOR(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 x 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 x per week.
Campos 2015 (REDUCS study) (27) <sup>1</sup>	Switzerland	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) <sup>2</sup>	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 x over 2 weeks. The separate trial in adolescents was halted based on preliminary results of the trial in adults.
Ebbeling 2020 (BASH III) (180) <sup>3</sup>	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) <sup>4</sup>	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) <sup>5</sup>	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 x 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 x 30 mL), sweetened with either sucralose (2.4 mg/day) or the rare low-energy sugar D-allulose (8 g/day or 1.4 g/day).

STUDY	COUNTRY	STUDY START (YEAR)	DESIGN	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARATOR(S)	DURATION	DESCRIPTION
Higgins 2018 (30)	United States	2016	Parallel	Lean	100 (mixed)	18–60	Aspartame	Drink, capsule	Placebo	12 weeks	Provision of 10 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 (481)	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)	4.7 (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 x 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 x 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	COMPARATOR(S)	DURATION	DESCRIPTION
Madjd 2018 (36) <sup>6</sup>	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 x 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 hyponeurogenic 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, maltodextrin	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 (2x 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) <sup>7</sup>	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	COMPARATOR(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 $\geq 2$ servings per day ( $\geq 200$ 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) <sup>8</sup> 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 ( $\sim 2$ g/kg per day, 1.25–1.75 g/day), or 2) similar drinks and foods containing artificial sweeteners ( $\sim 7$ 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 x 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	COMPARATOR(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 x 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 x 250 mL/day). All participants believed they received sucrose-sweetened beverages.
Romo-Romo 2018 (45)	Mexico	2015	Parallel	Lean	66 (mixed)	18-55	Sucralose	Tabletop	No intervention	14 days	Intervention arm received 3 x 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 (1.00 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).
Stamatakis 2020 (52) <sup>10</sup>	United Kingdom	2019	Parallel	Lean	28 (mixed)	18-40	Stevia	Tabletop	No intervention	12 weeks	The intervention arm consumed 5 stevia drops (2 x 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-Durán <sup>11</sup> 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.
<b>CHILDREN</b>											
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 (1.2 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	COMPARATOR(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.
<b>MIXED (ADULTS AND CHILDREN)</b>											
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.

- 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).
- 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.
- Ebbeling et al. (2020) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Ebbeling et al. (2019) (28).
- 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.
- Fantino et al. (2018) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Fantino et al. (2017) (278).
- Madjid 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 Madjid et al. (2015) (279).
- 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).
- 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).
- 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.
- Stamataki et al. (2020) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Stamataki, Crooks & McLaughlin (2020) (284).
- 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
<b>ADULTS</b>										
Acerio 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 81.7 mL/day vs none	7	FFQ on diet soft drink intake over past 12 months at baseline.
Bassett 2020 (MCCS) (169) <sup>1</sup>	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).
		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) <sup>2</sup>		1980		88 540 (female)	30–55 (baseline)				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		1991	Mixed	97 991 (male)	25–42 (baseline)	Unspecified	Soft drink, fruit drink	≥1/day vs <1/month	16	
NHS II	United States	1986		37 360 (male)	40–76 (baseline)				22	
HPFS										
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) <sup>3</sup>		1986		76 531 (female)	30–55 (baseline)				2 783 210	
NHS		1991	Mixed	81 597 (female)	25–42 (baseline)	Unspecified	Drink	Increase >0.5 serving/day vs no change (and decrease >0.5 serving/day vs no change)	person years	FFQ every 4 years with low-calorie beverages with or without caffeine.
NHS II	United States	1986		34 224 (male)	40–75 (baseline)					
HPFS										
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).
		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. A SBs consisted of all types of low-calorie, sweet, carbonated beverages, such as diet colas and other diet carbonated beverages.
Gardener 2012 (NOMAS) (108) <sup>4</sup>	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, tabletop	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) <sup>a</sup>	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)	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) 14.5 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-García 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. milk shakes, 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 (BWHHS) (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) <sup>7</sup>	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) <sup>8</sup>	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.
HPPS		1986		47 810 (male)	40–75 (baseline)					
Schernhammer 2012 (168) NHS		1984		77 218 (female)	30–55 (baseline)					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).
HPPS	United States	1986	Mixed	47 810 (male)	40–75 (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	

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) <sup>9</sup> 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.
		1991		116 683 (female)	25–42 (baseline)					
		1986		51 530 (male)	40–76 (baseline)					
Stellman 1986 (American Cancer Society study) (67) <sup>10</sup>	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 (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-O5) (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)	≥20 (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.
<b>CHILDREN</b>										
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 x 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 (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).
<b>PREGNANT WOMEN</b>										
Azad 2016 (CHILD) (226) <sup>11</sup>	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 (GeIS) (223)	Germany	2013 <sup>12</sup>	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.
Hrólfsson 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 (YEAR)	PARTICIPANT WEIGHT STATUS	NUMBER OF PARTICIPANTS (SEX)	AGE (YEARS)	NSS	MODE OF DELIVERY	COMPARISON (SERVINGS-HIGHEST VS LOWEST)	FOLLOW-UP (YEARS)	DESCRIPTION
Maslouva 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 <sup>13</sup>	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.

<sup>1</sup> Bassett et al. (2020) is the published version of Bassett et al. (2019) (172), which is a preprint.

<sup>2</sup> 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: Winkelmayr et al. (2005) (288).

<sup>3</sup> 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).

<sup>4</sup> Gardener et al. (2012) is a peer-reviewed publication containing more detailed data than originally reported in the abstract Gardener et al. (2011) (292).

<sup>5</sup> Study includes body mass index data from Russia, Poland and Czech Republic, but the data are only provided longitudinally for Russia.

<sup>6</sup> 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 (IWHHS), Women's Health Study (WHS) and Nurses' Health Study (NHS).

<sup>7</sup> Park et al. (2020) is a prospective cohort study assessing the same population assessed cross-sectionally in Ma et al. (2015) (293).

<sup>8</sup> 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: Bombach et al. (2010) (294).  
<sup>9</sup> 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).

<sup>10</sup> 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).

<sup>11</sup> 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.

<sup>12</sup> This study is a secondary cohort analysis of the GeLiS ("healthy living in pregnancy") RCT, which was initiated in 2013 and completed in 2018.

<sup>13</sup> 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
<b>ADULTS</b>									
Alkdaş 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 or 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.
Iscoovich 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.
Najem 1982 (150)	United States	1978	Mixed	217 (mixed)	67–71 (mean)	Unspecified, saccharin	Drink, tabletop	Used vs non-user	Participants were asked about their use of sugar substitutes added to beverages and foods.
	Japan	1976	Mixed	882 (mixed)	21–89	Unspecified	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
<b>CHILDREN</b>									
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.
<b>PREGNANT WOMEN AND CHILDREN</b>									
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) <sup>1</sup>	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 Agüero 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)	Nicoli 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 [SPANNS]) (212)
Katzmarzyk 2016 (ISCOLE) (342)	Kim 2017 (214)	Lavery 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 (NINPAS) (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)					

<sup>1</sup> 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
<b>ADULTS</b>											
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 (LIAS-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 consume water.
NCT03032640 (STAR-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).
<b>CHILDREN</b>											
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
<b>ADULTS</b>	
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; 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 <sup>2</sup> 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).
Gardner 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.
Gardner 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 $\geq 140/90$ 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-García 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
<b>CHILDREN</b>	
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 (CAP5)	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.
<b>PREGNANT WOMEN</b>	
Azad 2016 (CHLD)	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; pre-pregnancy BMI; household income; child age and sex; child beverage intake.
Gunther 2019 (Gelis)	Pre-pregnancy BMI; age; parity; group assignment.

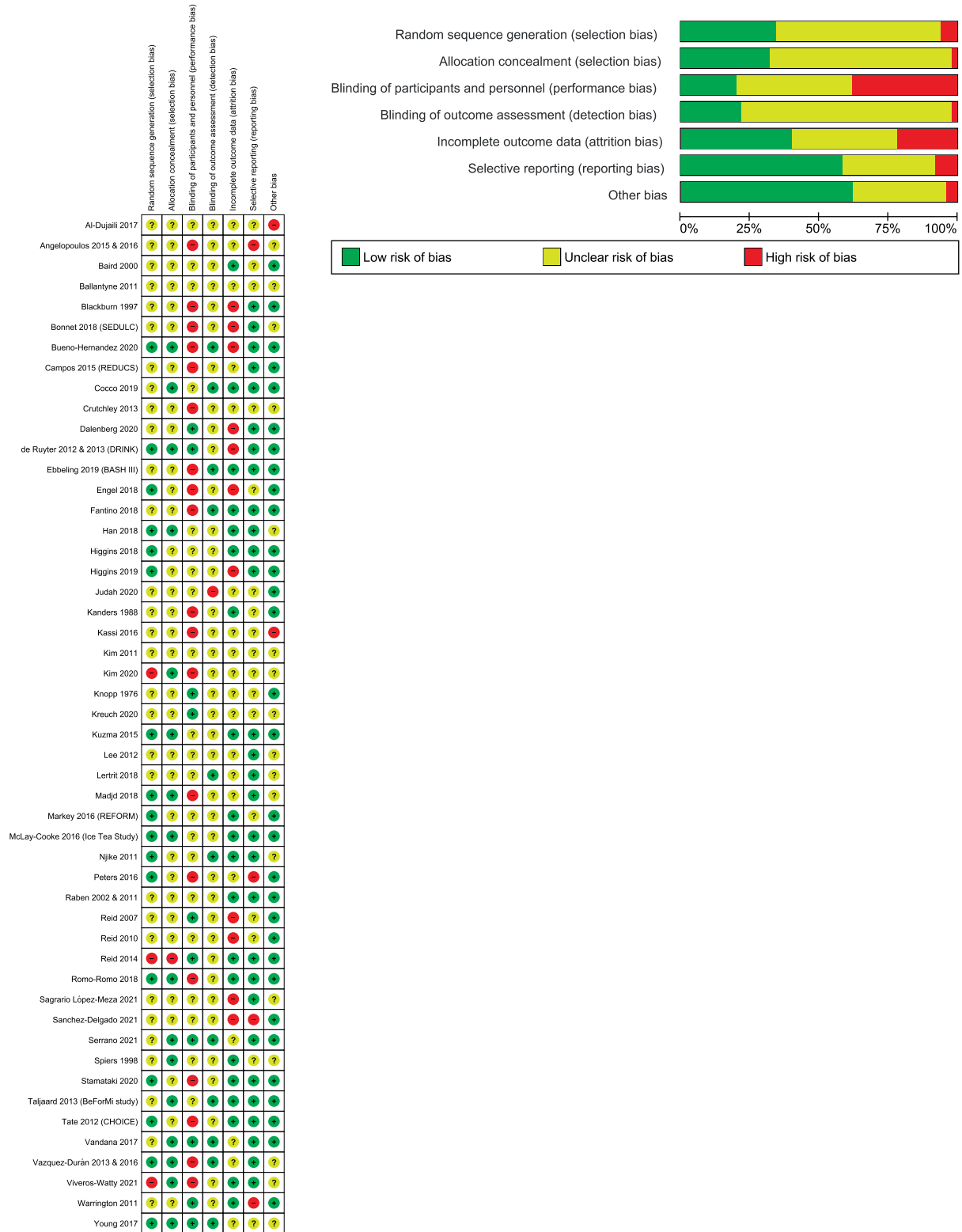
STUDY	ALL COVARIATES ADJUSTED FOR IN MOST ADJUSTED MODEL
Hallforsson 2010 (Danish National Birth Cohort)	Maternal age; height; pre-pregnancy BMI; total energy intake; cohabitant status; parity; smoking during pregnancy; familial socio-occupational status.
Hinkle 2019 (DWH)	Current age; pre-pregnancy 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.
Maslava 2013 (Danish National Birth Cohort)	Maternal age; smoking; parity; pre-pregnancy 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; glycosylated 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
Hirahake 2019 (CARDIA)	*	*	*	*	**	*	*	-	8
Hodge 2018 (MCCS)	*	*	*	*	*	*	*	*	8
Hrolfsdottir 2019 (PREWICE)	-	*	*	-	-	-	*	*	4
Huang 2017 (WHI-O5)	*	*	*	*	**	-	*	-	7
Hur 2021 (NHS II)	-	*	*	*	*	-	*	*	6
InterAct Consortium 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-García 2019 (SUN)	-	*	*	-	**	-	*	*	6
Nettleton 2009 (MESA)	*	*	-	*	*	*	*	*	7
Newby 2004 (North Dakota WIC Program for Children)	-	*	*	*	*	*	*	-	6
O'Connor 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
Stjepien 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	REPRESENTATIVENESS 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

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

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

NO. OF STUDIES/ COHORTS	ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)			EFFECT		CERTAINTY <sup>6</sup>
	STUDY DESIGN <sup>4</sup>	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>2</sup>	IMPRECISION	OTHER <sup>3</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE <sup>5</sup> (95% CI)	ABSOLUTE – PER 1000 <sup>5</sup> (95% CI)			
<b>Diabetes: high fasting glucose</b>													
3	Observational	Not serious <sup>9</sup>	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		
<b>Dental caries</b>													
1	RCT	Serious <sup>24</sup>	Unable to assess <sup>25</sup>	Not serious	Very serious <sup>26</sup>	None	14	15	In a 6-month RCT among adults (26) <sup>27</sup> , 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		
<b>All-cause mortality</b>													
8	Observational	Not serious <sup>9</sup>	Serious <sup>8</sup>	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		
<b>Cardiovascular diseases: cardiovascular disease mortality</b>													
5	Observational	Not serious <sup>9</sup>	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		
<b>Cardiovascular diseases: cardiovascular events</b>													
3	Observational	Not serious <sup>9</sup>	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		
<b>Cardiovascular diseases: coronary heart disease</b>													
4	Observational	Not serious <sup>9</sup>	Serious <sup>8</sup>	Not serious	Serious <sup>44</sup>	None	10104/205455 (4.9%)		HR 1.16 (0.97 to 1.39)	8 more (from 1 fewer to 19 more)	⊕○○○ VERY LOW		
<b>Cardiovascular diseases: stroke</b>													
6	Observational	Not serious <sup>9</sup>	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		

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

ASSESSMENT										NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)			EFFECT		CERTAINTY <sup>6</sup>
NO. OF STUDIES/ COHORTS	STUDY DESIGN <sup>4</sup>	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>2</sup>	IMPRECISION	OTHER <sup>3</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE <sup>5</sup> (95% CI)	ABSOLUTE – PER 1000 <sup>5</sup> (95% CI)					
<b>Cardiovascular diseases: high triglycerides</b>															
4	Observational	Not serious <sup>9</sup>	Not serious	Not serious	Serious <sup>14</sup>	None	6673/12728 (52.4%)		HR 1.03 (0.88 to 1.21)	16 more (from 63 fewer to 110 more)	⊕○○○ VERY LOW				
<b>Cancer: cancer mortality</b>															
4	Observational	Not serious <sup>9</sup>	Serious <sup>8</sup>	Not serious	Serious <sup>14</sup>	None	25494/568175 (4.5%)		HR 1.02 (0.92 to 1.13)	1 more (from 4 fewer to 6 more)	⊕○○○ VERY LOW				
<b>Cancer: incidence (any type)</b>															
7	Observational	Not serious <sup>9</sup>	Not serious	Not serious	Serious <sup>14</sup>	None	27573/942600 (2.9%)		HR 1.02 (0.95 to 1.09)	1 more (from 1 fewer to 3 more)	⊕○○○ VERY LOW				
<b>Cancer: incidence (bladder)</b>															
26	Observational (case-control)	Serious <sup>11</sup>	Serious <sup>8</sup>	Not serious	Not serious	None	11071 cases 28589 controls		OR 1.31 (1.06 to 1.62)	–	⊕○○○ VERY LOW				
<b>Chronic kidney disease: incident disease</b>															
2	Observational	Not serious <sup>9</sup>	Serious <sup>8</sup>	Not serious	Serious <sup>14</sup>	None	3161/18372 (17.2%)		HR 1.41 (0.89 to 2.24)	71 more (from 19 fewer to 213 more)	⊕○○○ VERY LOW				
<b>Chronic kidney disease: creatinine (μmol/L)</b>															
2	RCT	Serious <sup>30</sup>	Serious <sup>8</sup>	Not serious	Very serious <sup>14</sup>	None	93	52	MD 8.80 (–14.65 to 32.25)	–	⊕○○○ VERY LOW				
<b>Chronic kidney disease: albumin (g/L)</b>															
2	RCT	Serious <sup>30</sup>	Not serious	Not serious	Serious <sup>16</sup>	None	93	52	MD 0.00 (–0.56 to 0.56)	–	⊕○○○ LOW				
<b>Energy intake (kJ/day)</b>															
25	RCT	Serious <sup>32</sup>	Serious <sup>8</sup>	Not serious	Not serious	None	1131	1077	MD –569 (–859 to –278)	–	⊕○○○ LOW				
<b>Sugars intake (g/day)</b>															
12	RCT	Serious <sup>33</sup>	Serious <sup>8</sup>	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-1R: 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 =  $1000 \times [\text{event rate} \times (1 - \text{RR})]$ . 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 (>1.5%), 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  $\geq 5$  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  $\leq 5$  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.

- <sup>19</sup> Six out of the 10 comparisons that reported a  $P_{\text{trend}}$  reported a  $P_{\text{trend}}$  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.
- <sup>20</sup> 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.
- <sup>21</sup> 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.
- <sup>22</sup> 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.
- <sup>23</sup> 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.
- <sup>24</sup> 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.
- <sup>25</sup> Unable to assess inconsistency in a single study. Downgraded once.
- <sup>26</sup> Extremely small sample size. Downgraded twice.
- <sup>27</sup> The data for dental caries were reported in the original publication of this trial, Maersk et al. (2012) (183).
- <sup>28</sup> 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 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.
- <sup>29</sup> 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.
- <sup>30</sup> One trial was fairly well reported, and the other was mostly unclear, with concerns about selective reporting of outcomes. Downgraded once.
- <sup>31</sup> The 95% CI crosses the null and includes both significant benefit and harm. Downgraded twice.
- <sup>32</sup> 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.
- <sup>33</sup> 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 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

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

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

<sup>1</sup> 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.

<sup>2</sup> Too few studies to conduct funnel plot analyses.

<sup>3</sup> 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).

<sup>4</sup> 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.

<sup>5</sup> 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

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

NO. OF STUDIES/ COHORTS	STUDY DESIGN <sup>1</sup>	RISK OF BIAS <sup>2</sup>	ASSESSMENT				NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY <sup>4</sup>
			INCONSISTENCY	INDIRECTNESS <sup>2</sup>	IMPRECISION	OTHER <sup>3</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
<b>Adiposity: incident overweight</b>											
2	Observational	Not serious <sup>7</sup>	Not serious	Very serious <sup>14</sup>	None	235/3064 (7.7%)	OR 1.25 (0.43 to 3.66)	19 more (from 44 fewer to 205 more)	⊕○○○ VERY LOW		
<b>Diabetes: intermediate markers</b>											
1	Observational	Serious <sup>12</sup>	Serious <sup>14</sup>	Serious <sup>10</sup>	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			
<b>Dental caries</b>											
2	RCT	Not serious <sup>15</sup>	Not serious	Serious <sup>10</sup>	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 <i>Streptococcus mutans</i> 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		

NO. OF STUDIES/ COHORTS	STUDY DESIGN <sup>1</sup>	ASSESSMENT					NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY <sup>4</sup>
		RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>2</sup>	IMPRECISION	OTHER <sup>3</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
<b>Dental caries (continued)</b>											
1	Observational	Serious <sup>12</sup>	Unable to assess <sup>6</sup>	Not serious	Unable to assess <sup>17</sup>	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
<b>Cardiovascular diseases: blood lipids</b>											
1	Observational	Serious <sup>12</sup>	Unable to assess <sup>6</sup>	Serious <sup>14</sup>	Serious <sup>10</sup>	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
<b>Cancer: brain cancer</b>											
2	Observational (case-control)	Serious <sup>12</sup>	Not serious	Not serious	Serious <sup>10</sup>	None	371 cases 780 controls		<b>OR 1.14</b> (0.80 to 1.63)	<b>2 more</b> (from 2 fewer to 7 more)	⊕○○○ VERY LOW
<b>Energy intake (kJ/day)</b>											
1	RCT	Not serious <sup>18</sup>	Unable to assess <sup>6</sup>	Not serious	Serious <sup>10</sup>	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). <i>Unable to meta-analyse</i> 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).	⊕⊕⊕○ MODERATE
2	Observational	Serious <sup>12</sup>	Unable to assess <sup>17</sup>	Not serious	Unable to assess <sup>17</sup>	None	173 (cohort 1) 2371 (cohort 2)			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

NO. OF STUDIES/ COHORTS	STUDY DESIGN <sup>1</sup>	ASSESSMENT					NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY <sup>4</sup>
		RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>2</sup>	IMPRECISION	OTHER <sup>3</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
<b>Sugars intake (g/day)</b>											
2	Observational	Serious <sup>1,2</sup>	Unable to assess <sup>17</sup>	Not serious	Unable to assess <sup>17</sup>	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
<b>Neurocognition</b>											
1	RCT	Not serious <sup>18</sup>	Unable to assess <sup>6</sup>	Not serious	Serious <sup>10</sup>	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 <sup>7</sup>	Unable to assess <sup>6</sup>	Not serious	Unable to assess <sup>17</sup>	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.

- 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.
- 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.
- Too few studies to conduct funnel plot analyses.
- 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).

- <sup>5</sup> 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.
- <sup>6</sup> Unable to assess inconsistency as there is only a single study. Downgraded once.
- <sup>7</sup> Mean Newcastle–Ottawa Score of >5 with very conservative application of ratings. Not downgraded.
- <sup>8</sup> 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.
- <sup>9</sup>  $I^2 \geq 50\%$ , indicating a significant level of heterogeneity. Downgraded once.
- <sup>10</sup> 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.
- <sup>11</sup> 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.
- <sup>12</sup> Mean Newcastle–Ottawa Score of  $\leq 5$  with very conservative application of ratings. Downgraded once.
- <sup>13</sup> 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.
- <sup>14</sup> The 95% CI crosses the null and includes both significant benefit and harm. Downgraded twice.
- <sup>15</sup> 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.
- <sup>16</sup> 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.
- <sup>17</sup> Unable to assess. Downgraded once.
- <sup>18</sup> 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

NO. OF STUDIES/ COHORTS	STUDY DESIGN	ASSESSMENT						NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY <sup>3</sup>
		RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>1</sup>	IMPRECISION	OTHER <sup>2</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)		
<b>Gestational diabetes</b>												
1	Observational	Not serious <sup>4</sup>	Unable to assess <sup>5</sup>	Not serious	Serious <sup>6</sup>	None	860/13475 (6.4%)		RR 0.92 (0.81 to 1.04)	5 fewer (from 12 fewer to 0 more)	⊕○○○ VERY LOW	
<b>Preterm birth</b>												
3	Observational	Not serious <sup>4</sup>	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	
<b>Birth weight</b>												
3	Observational	Serious <sup>7</sup>	Unable to assess <sup>5</sup>	Not serious	Unable to assess <sup>8</sup>	None	3716				⊕○○○ VERY LOW	
<p><i>Unable to meta-analyse</i></p> <p>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).</p> <p>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; <math>P = 0.002</math>) (224).</p> <p>In a cohort study with women with gestational diabetes in Slovenia, intake of low-calorie beverages<sup>9</sup> was not associated with large for gestational age (Spearman correlation 0.118; <math>P</math> nonsignificant) (225).</p>												

NO. OF STUDIES/ COHORTS	ASSESSMENT							NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY <sup>3</sup>
	STUDY DESIGN	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>1</sup>	IMPRECISION	OTHER <sup>2</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)		
<b>Offspring adiposity</b>												
3	Observational	Not serious <sup>4</sup>	Unable to assess <sup>5</sup>	Not serious	Unable to assess <sup>8</sup>	None	5029		<p><i>Unable to meta-analyse</i></p> <p>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).</p> <p>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).</p> <p>In a prospective cohort study conducted in Denmark, the children of women with gestational diabetes who consumed NSS-sweetened beverages at <math>\geq 1</math>/day (compared with never) had a higher BMI z-score (<math>\beta</math> 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).</p>		⊕○○○ VERY LOW	
<b>Offspring asthma</b>												
1	Observational	Not serious <sup>4</sup>	Unable to assess <sup>5</sup>	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	
<b>Offspring allergies</b>												
1	Observational	Not serious <sup>4</sup>	Unable to assess <sup>5</sup>	Not serious	Serious <sup>6</sup>	None	1855/37971 (4.9%)		OR 1.11 (0.86 to 1.43)	5 more (from 7 fewer to 21 more)	⊕○○○ VERY LOW	



NO. OF STUDIES/ COHORTS	STUDY DESIGN	ASSESSMENT					NO. OF EVENTS/PARTICIPANTS (STUDY EVENT RATE)		EFFECT		CERTAINTY <sup>3</sup>
		RISK OF BIAS	INCONSISTENCY	INDIRECTNESS <sup>1</sup>	IMPRECISION	OTHER <sup>2</sup>	LOWER/NO NSS INTAKE	HIGHER NSS INTAKE	RELATIVE/MEAN DIFFERENCE (95% CI)	ABSOLUTE – PER 1000 (95% CI)	
<b>Offspring neurocognition</b>											
1	Observational	Not serious <sup>4</sup>	Unable to assess <sup>5</sup>	Not serious	Unable to assess <sup>8</sup>	None	1234				<p>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).</p> <p>⊕○○○ VERY LOW</p>

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.

<sup>1</sup> 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.

<sup>2</sup> Too few studies to conduct funnel plot analyses.

<sup>3</sup> 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.

<sup>4</sup> Mean Newcastle-Ottawa Score of >5 with very conservative application of ratings. Not downgraded.

<sup>5</sup> 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.

<sup>6</sup> 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.

<sup>7</sup> Mean Newcastle-Ottawa Score of ≤5 with very conservative application of ratings. Downgraded once.

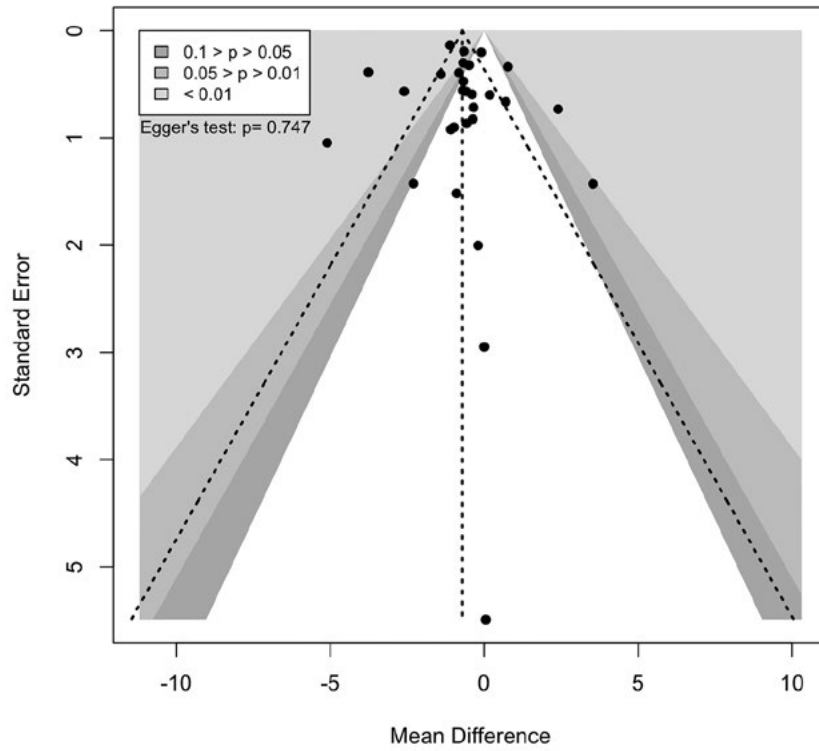
<sup>8</sup> Unable to assess. Downgraded once.

<sup>9</sup> 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.

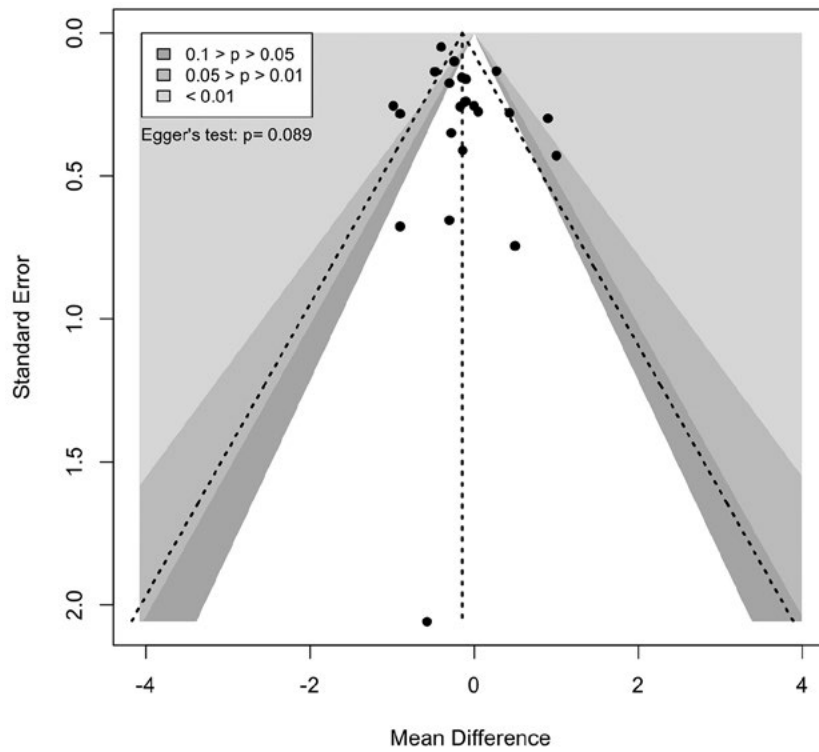
ANNEX 8.

# Funnel plots

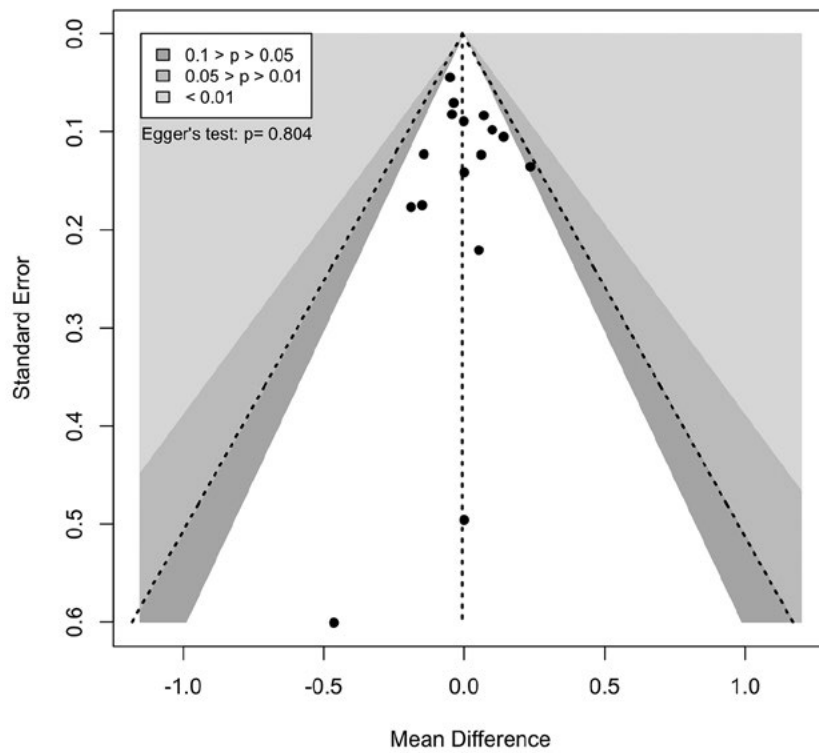
Fig. A8.1 Body weight (kg) among adults in randomized controlled trials



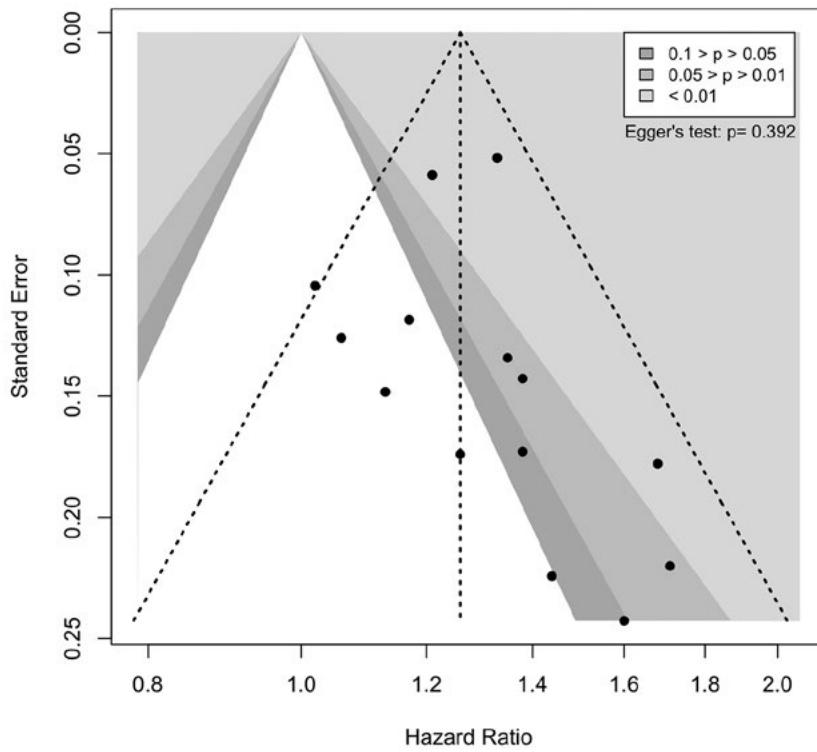
**Fig. A8.2. Body mass index (kg/m<sup>2</sup>) among adults in randomized controlled trials**



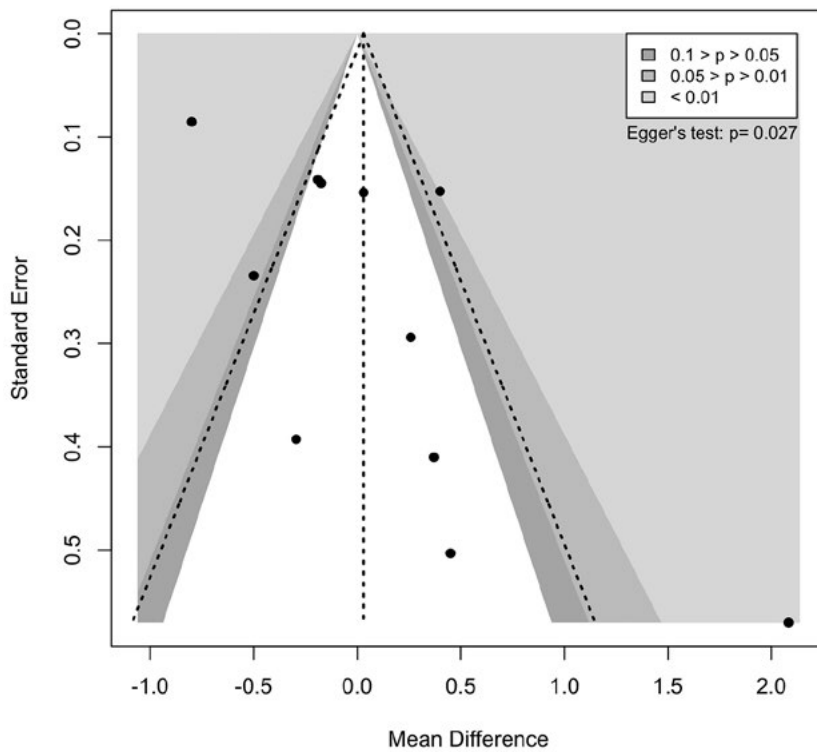
**Fig. A8.3 Fasting glucose (mmol/L) among adults in randomized controlled trials**



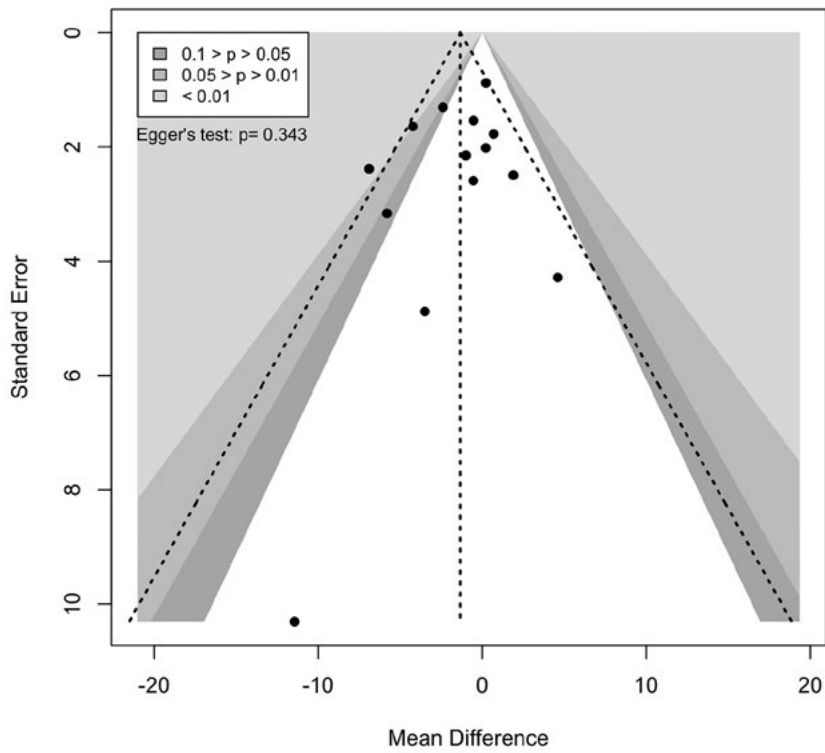
**Fig. A8.4** Type 2 diabetes among adults in cohort studies



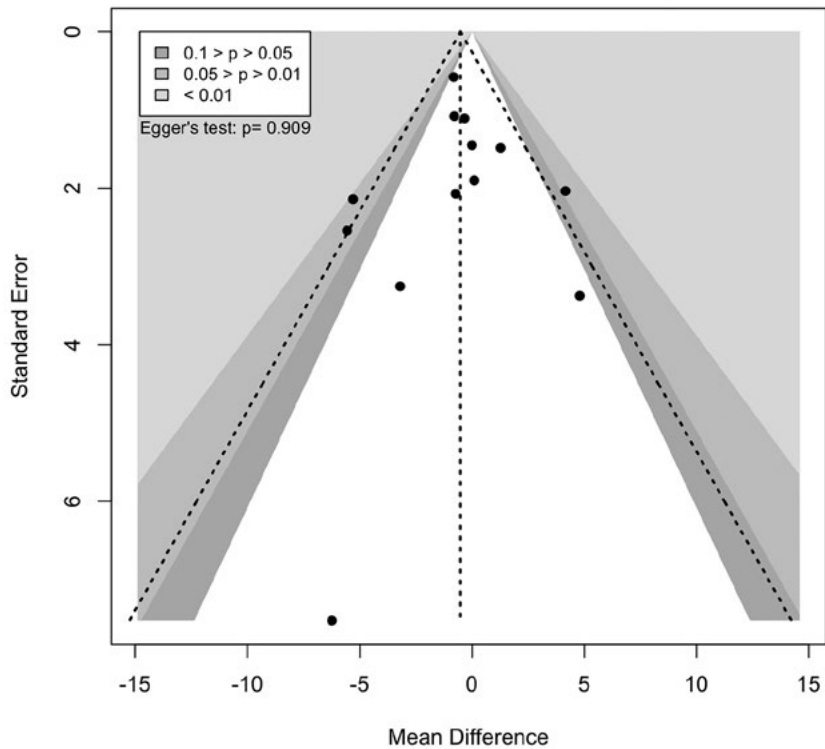
**Fig. A8.5** Funnel plot of HOMA-IR among adults in randomized controlled trials



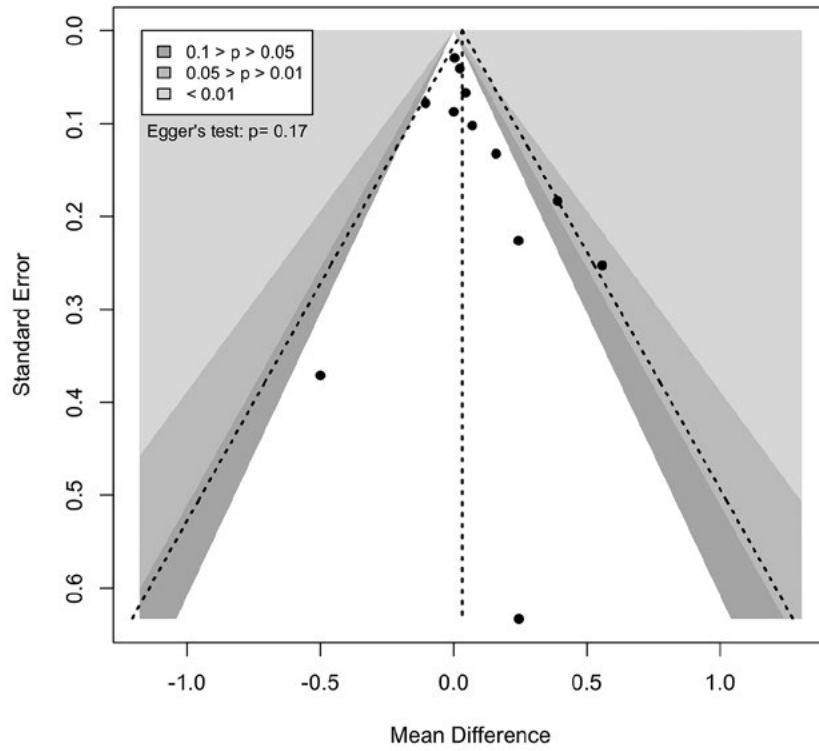
**Fig. A8.6 Systolic blood pressure (mmHg) among adults in randomized controlled trials**



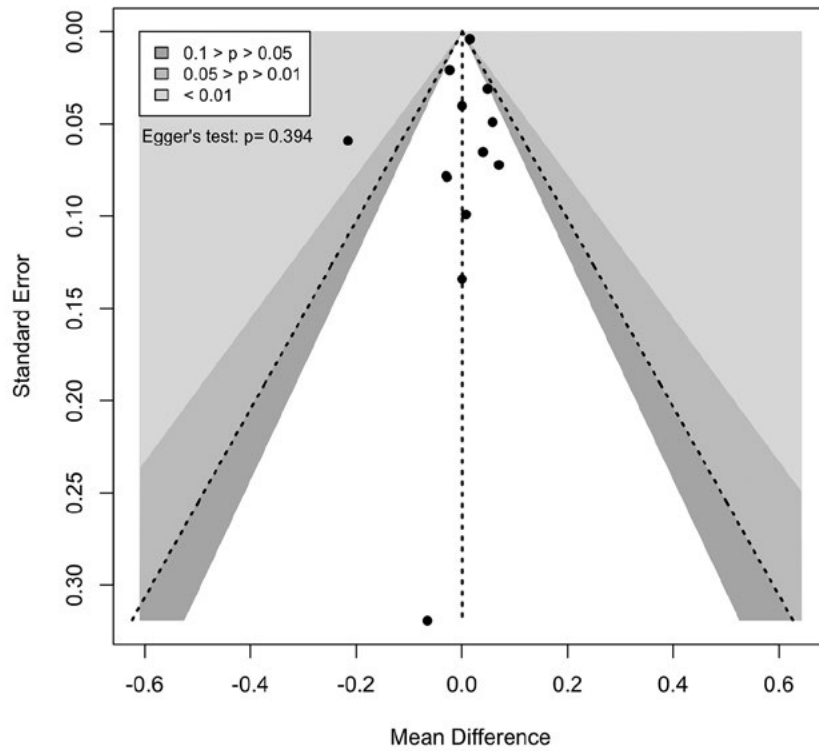
**Fig. A8.7 Diastolic blood pressure (mmHg) among adults in randomized controlled trials**



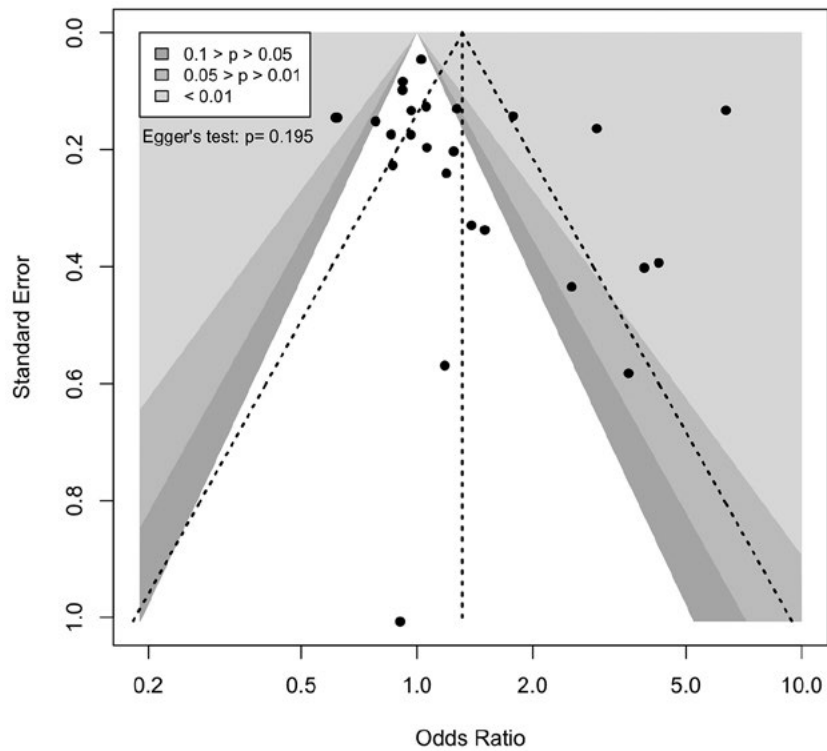
**Fig. A8.8 LDL cholesterol (mmol/L) among adults in randomized controlled trials**



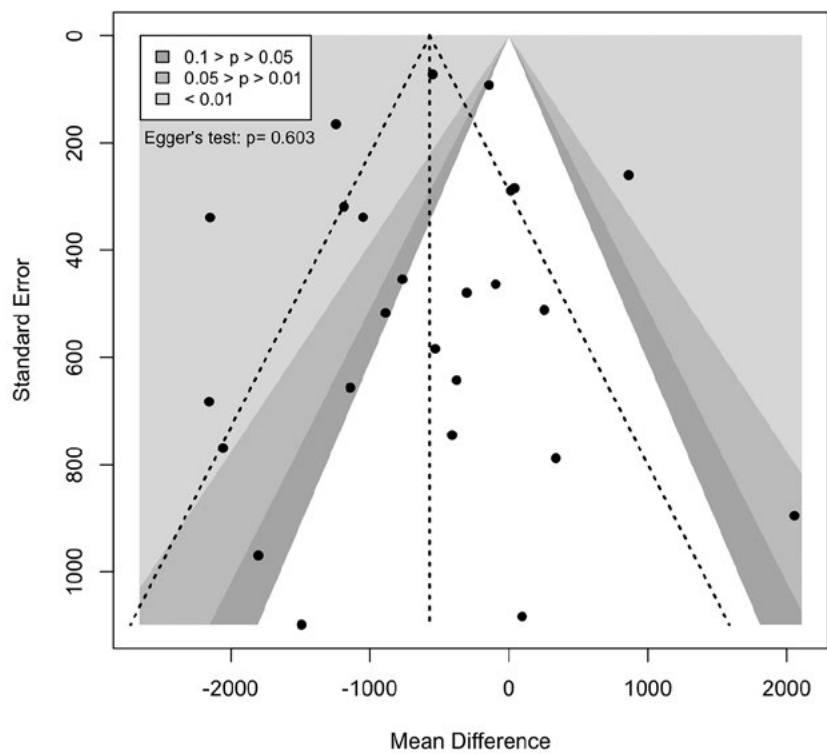
**Fig. A8.9 HDL cholesterol (mmol/L) among adults in randomized controlled trials**



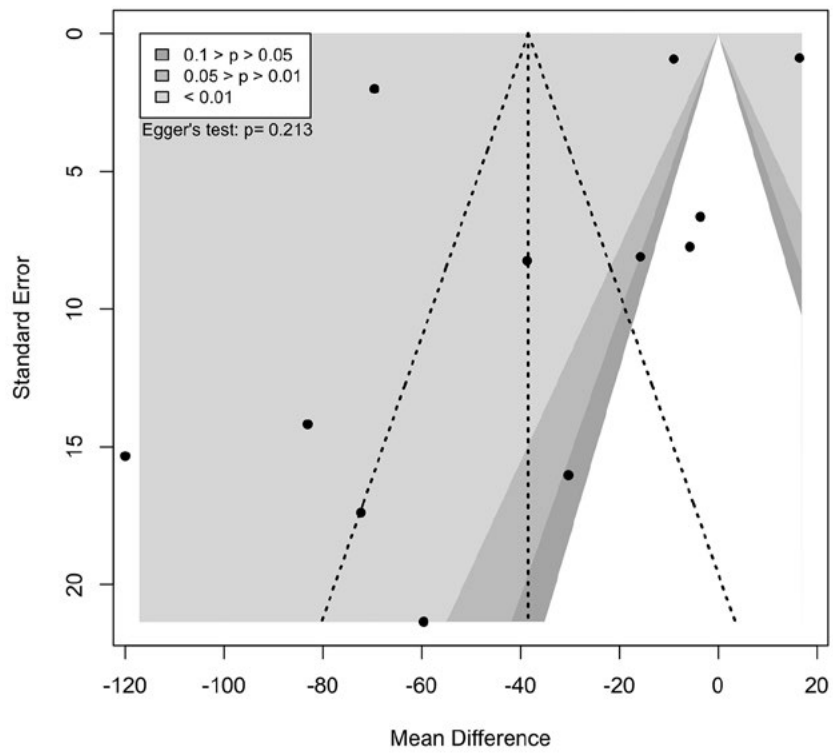
**Fig. A8.10 Bladder cancer among adults in case-control studies**



**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

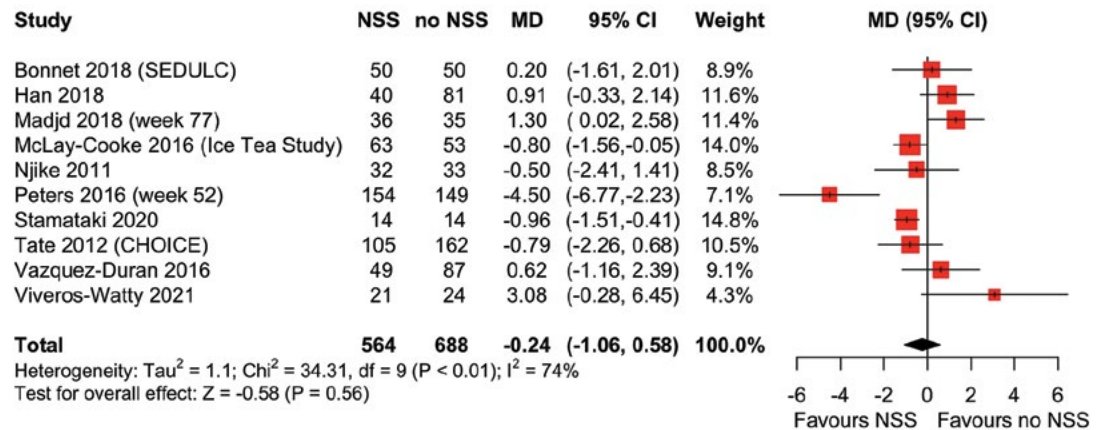




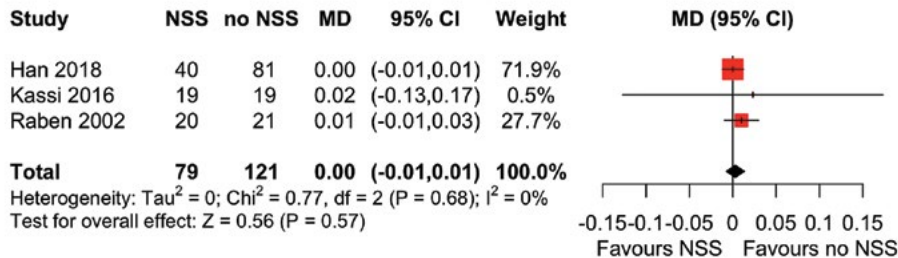
## ANNEX 9.

# Supplementary figures

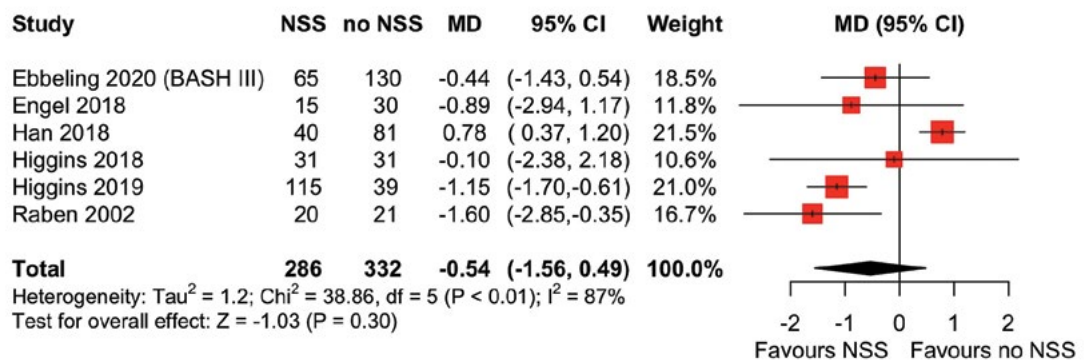
**Fig. A9.1** Effect of NSS on waist circumference (cm) in randomized controlled trials in adults



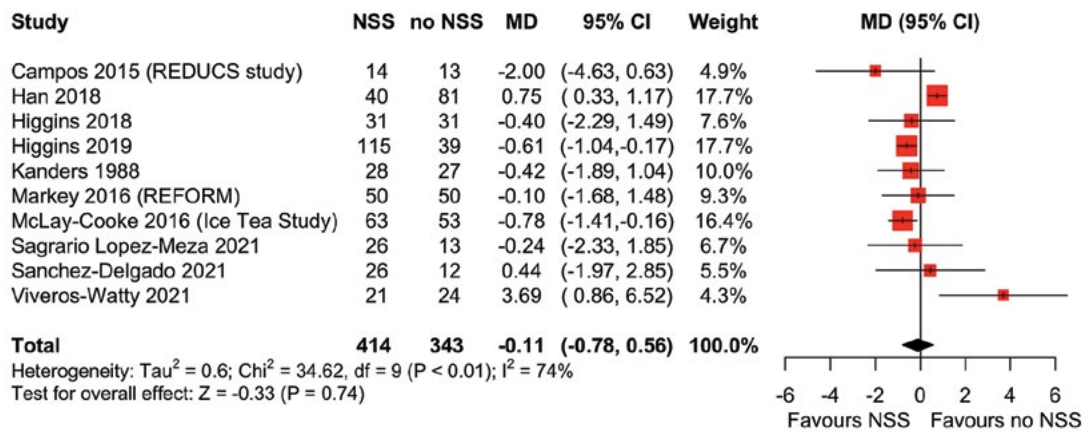
**Fig. A9.2** Effect of NSS on waist-to-hip ratio in randomized controlled trials in adults



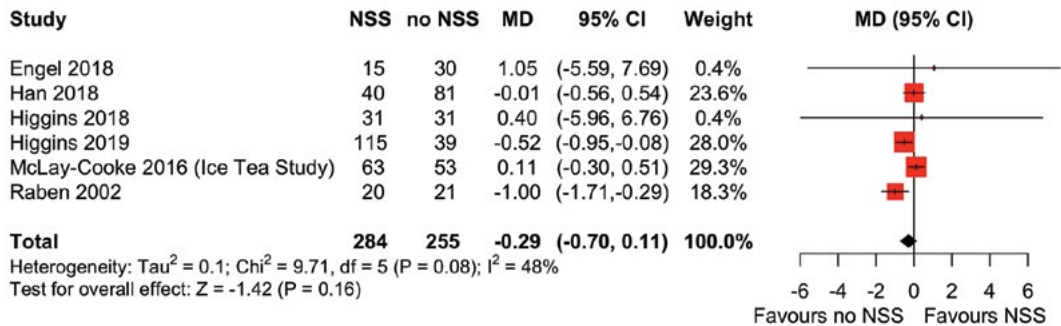
**Fig. A9.3** Effect of NSS on fat mass (kg) in randomized controlled trials in adults



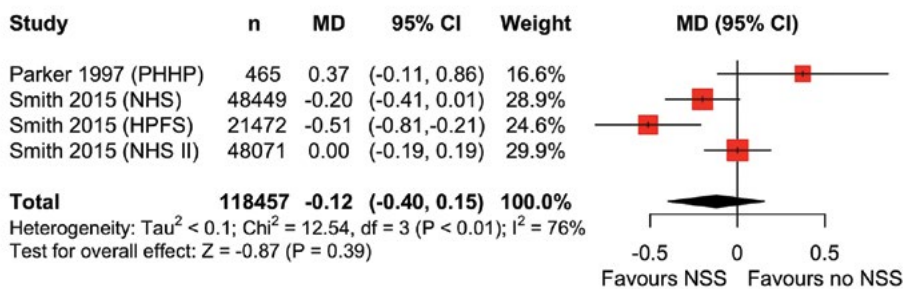
**Fig. A9.4 Effect of NSS on fat mass (%) in randomized controlled trials in adults**



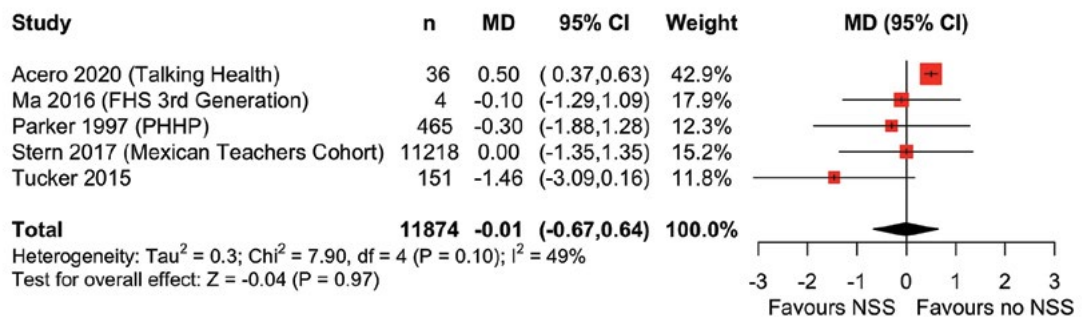
**Fig. A9.5 Effect of NSS on lean mass (kg) in randomized controlled trials in adults**



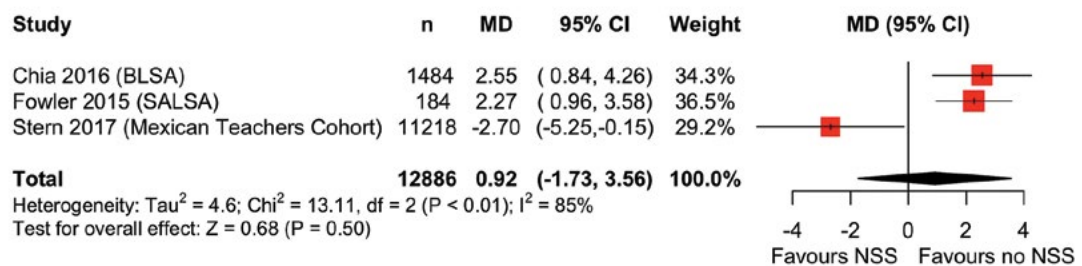
**Fig. A9.6 Association between NSS and body weight (kg) in prospective cohort studies (continuous effect) in adults**



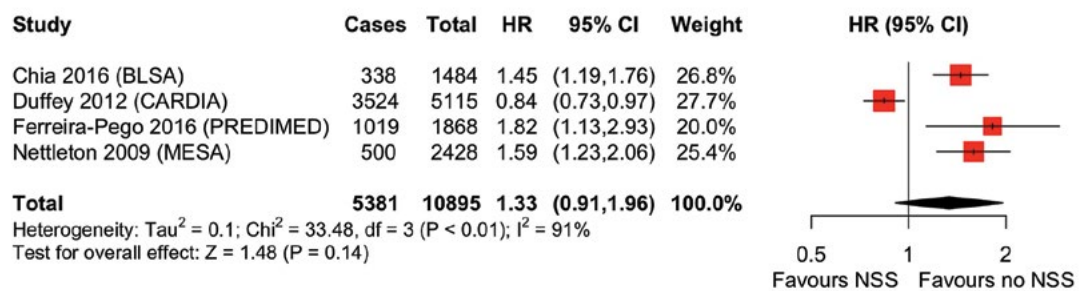
**Fig. A9.7 Association between NSS and body weight (kg) in prospective cohort studies (highest versus lowest) in adults**



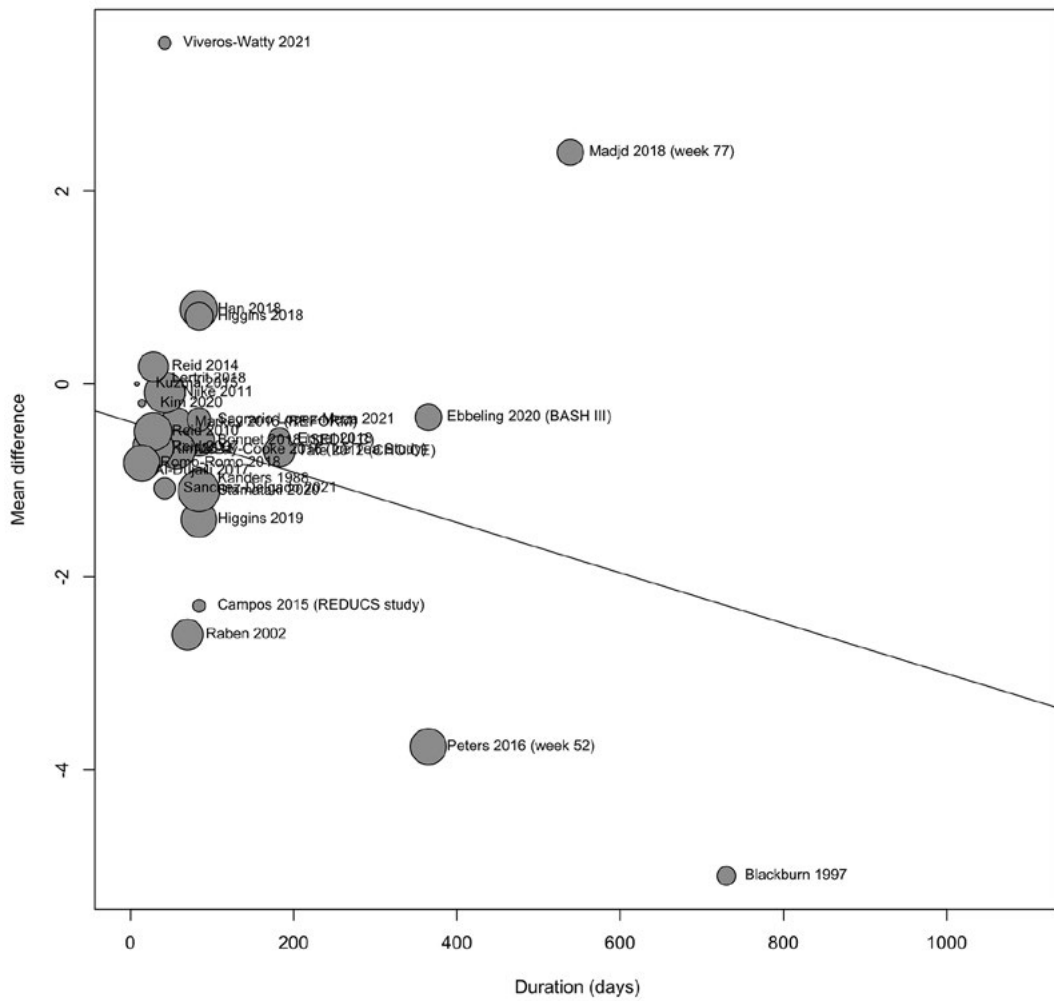
**Fig. A9.8 Association between NSS and waist circumference (cm) in cohort studies (highest versus lowest) in adults**



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

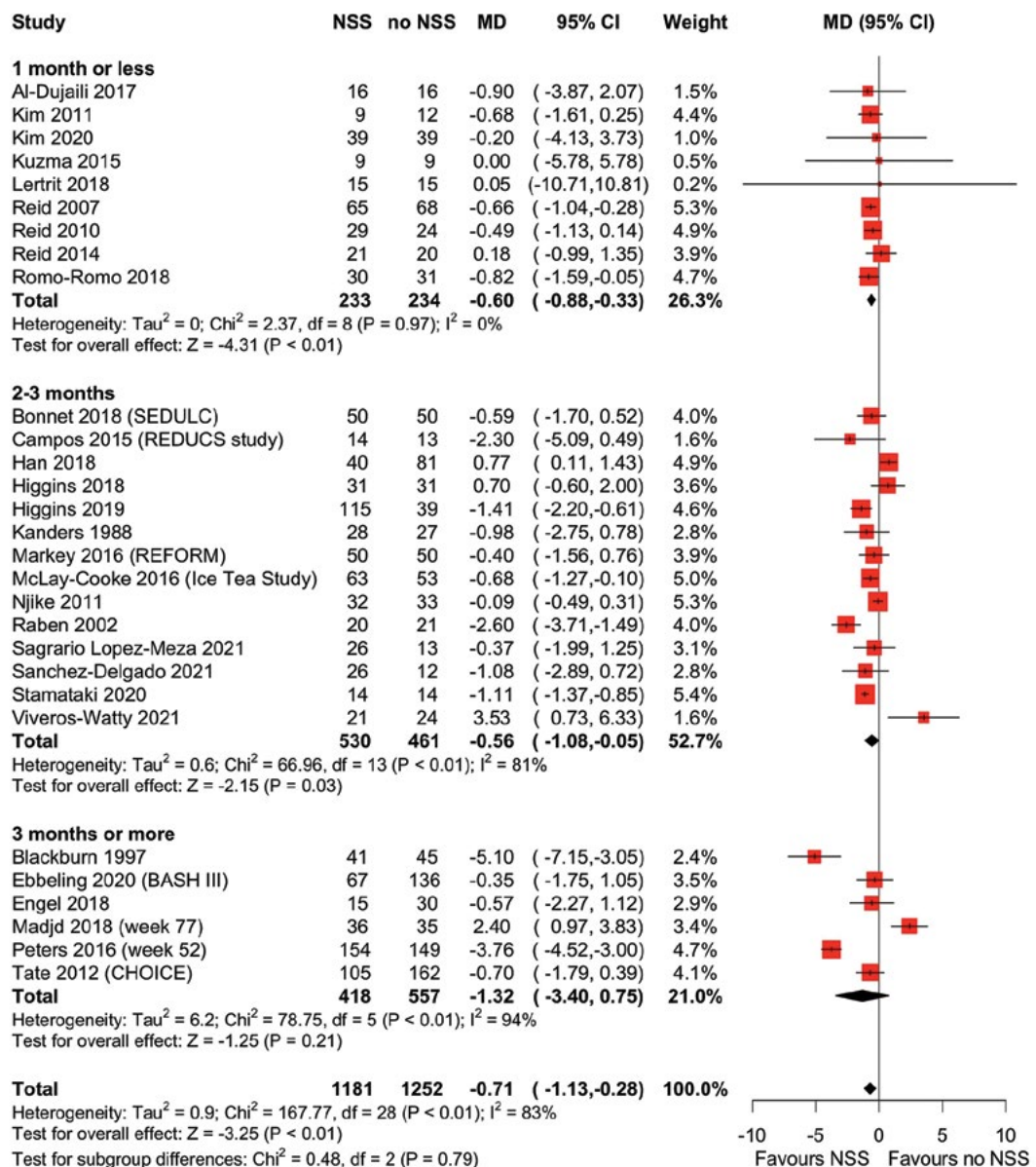


**Fig. A9.10 Meta-regression: body weight results in randomized controlled trials by study duration**

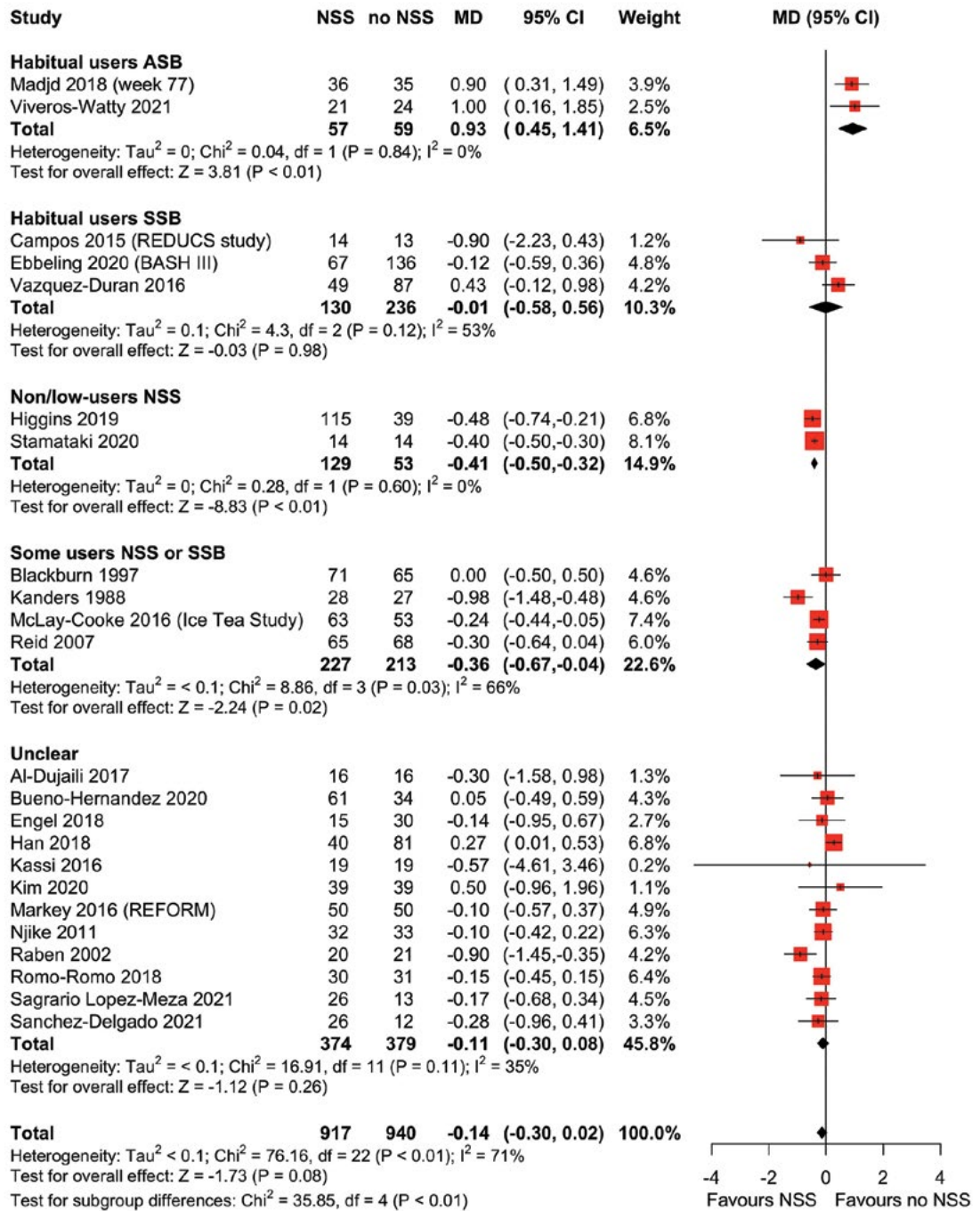


Note: B coefficient = -0.002; P = 0.052.

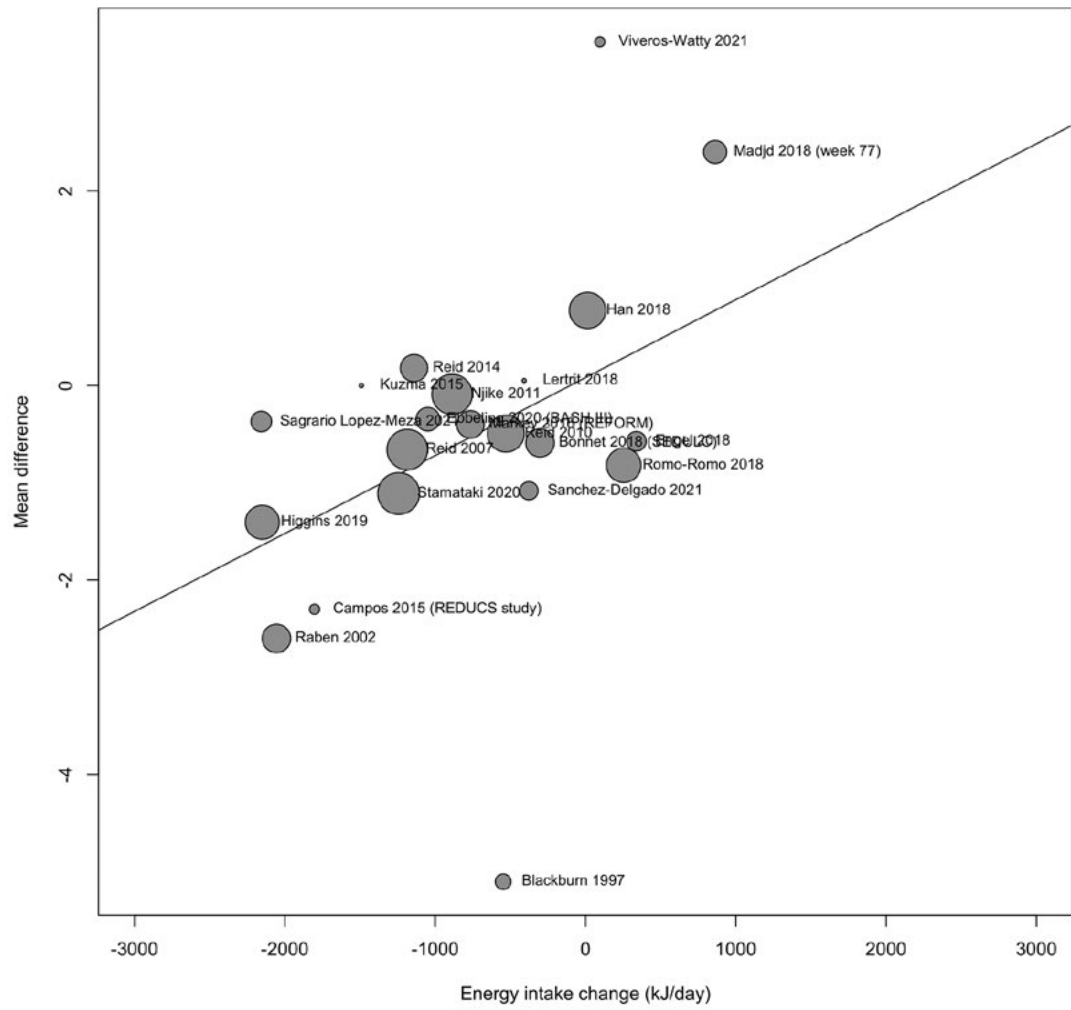
**Fig. A9.11 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by study duration, in adults**



**Fig. A9.12 Effect of NSS on body mass index (kg/m<sup>2</sup>) in randomized controlled trials, subgrouped by consumption pattern, in adults**

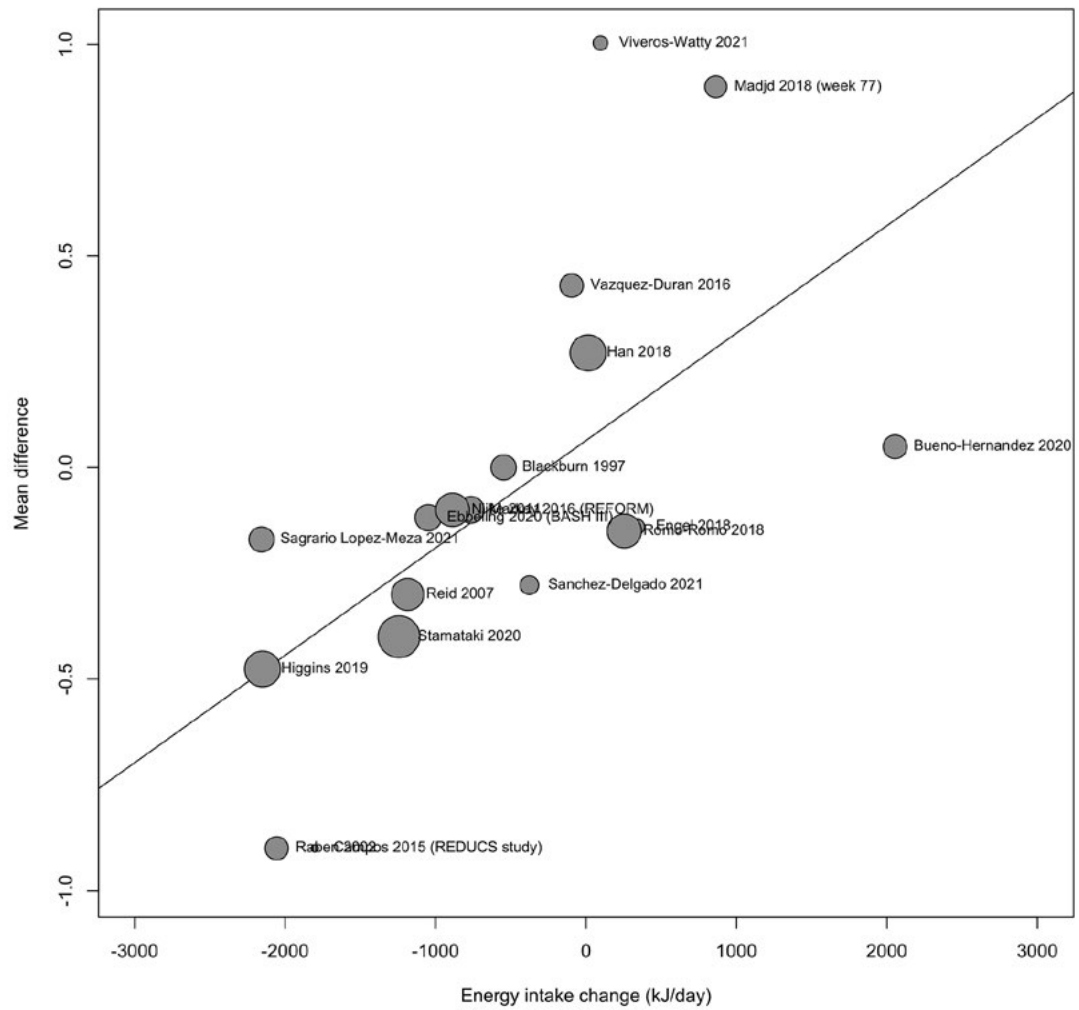


**Fig. A9.13 Meta-regression: body weight by energy intake in randomized controlled trials**



Note: B coefficient = 0.008; P = 0.009.

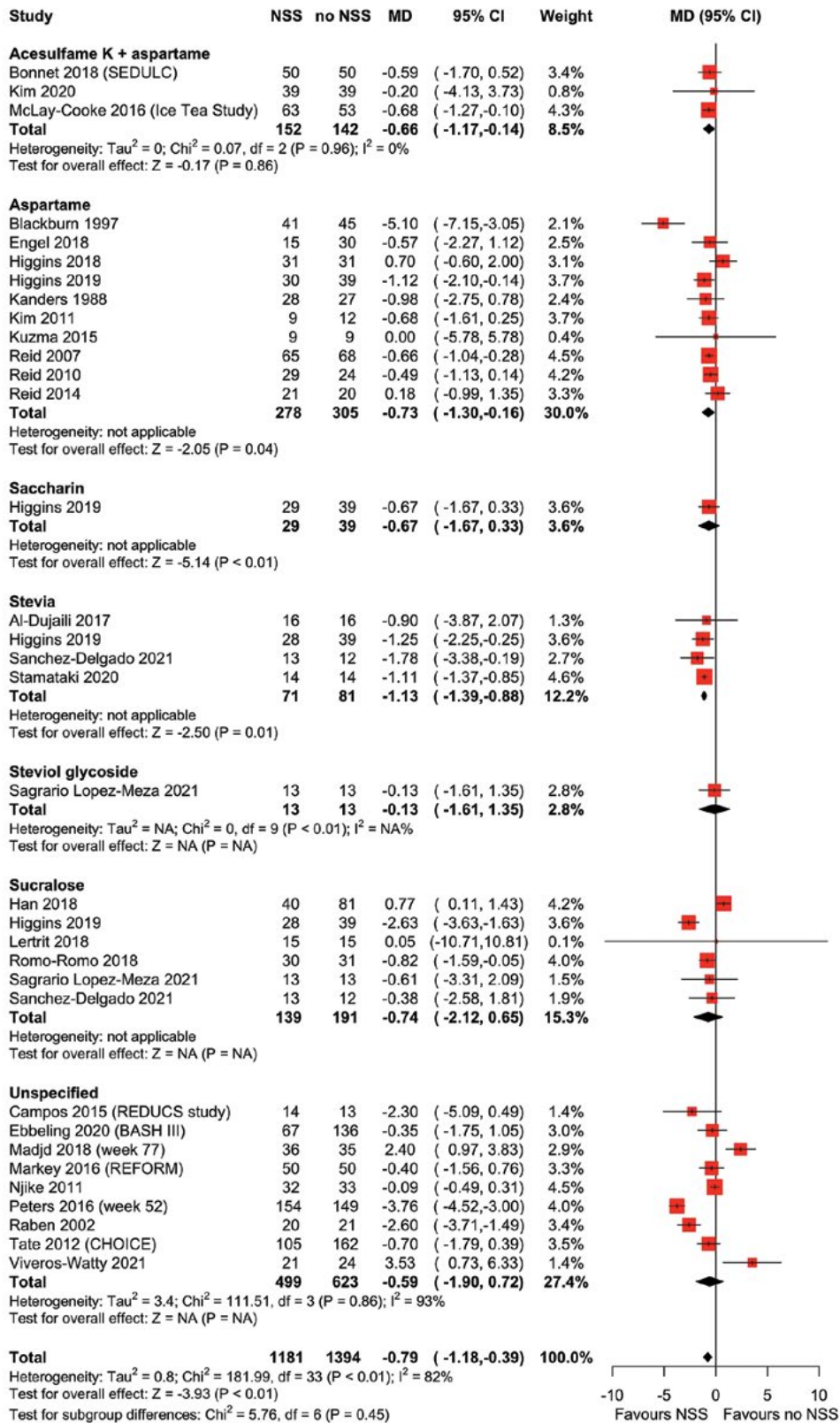
**Fig. A9.14 Meta-regression: body mass index by energy intake in randomized controlled trials**



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

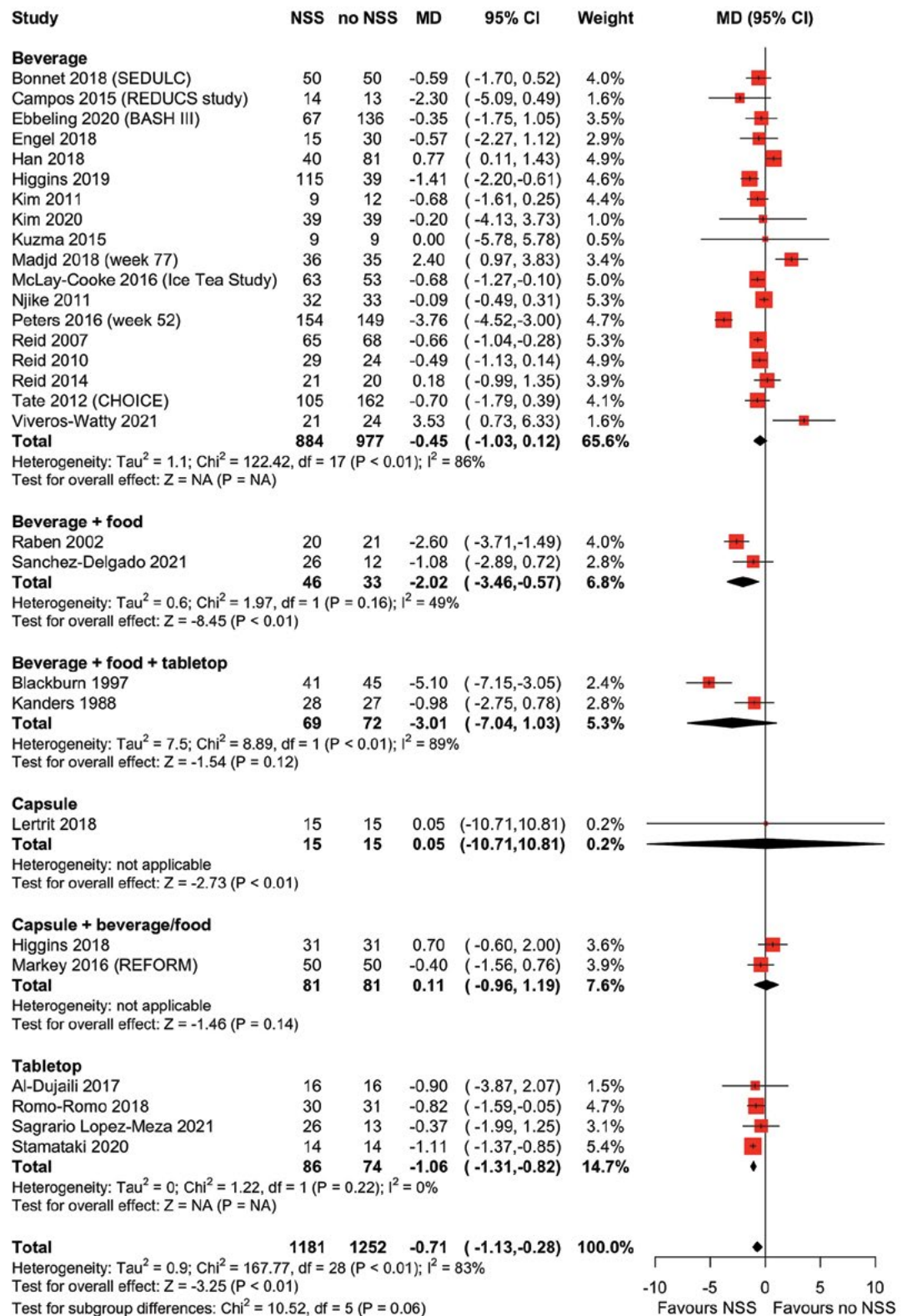


**Fig. A9.15 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by type of NSS, in adults**

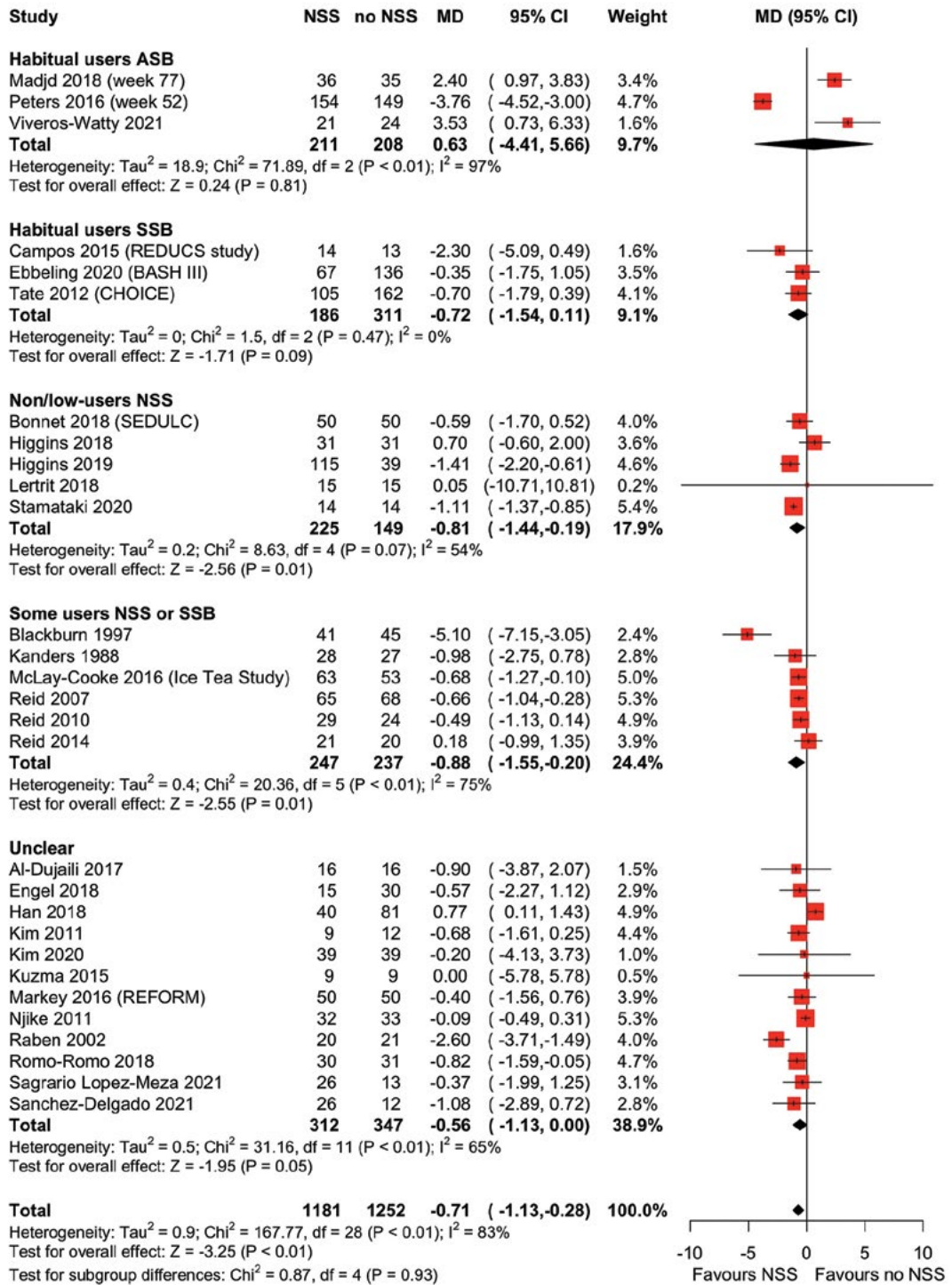


*Note:* Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from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

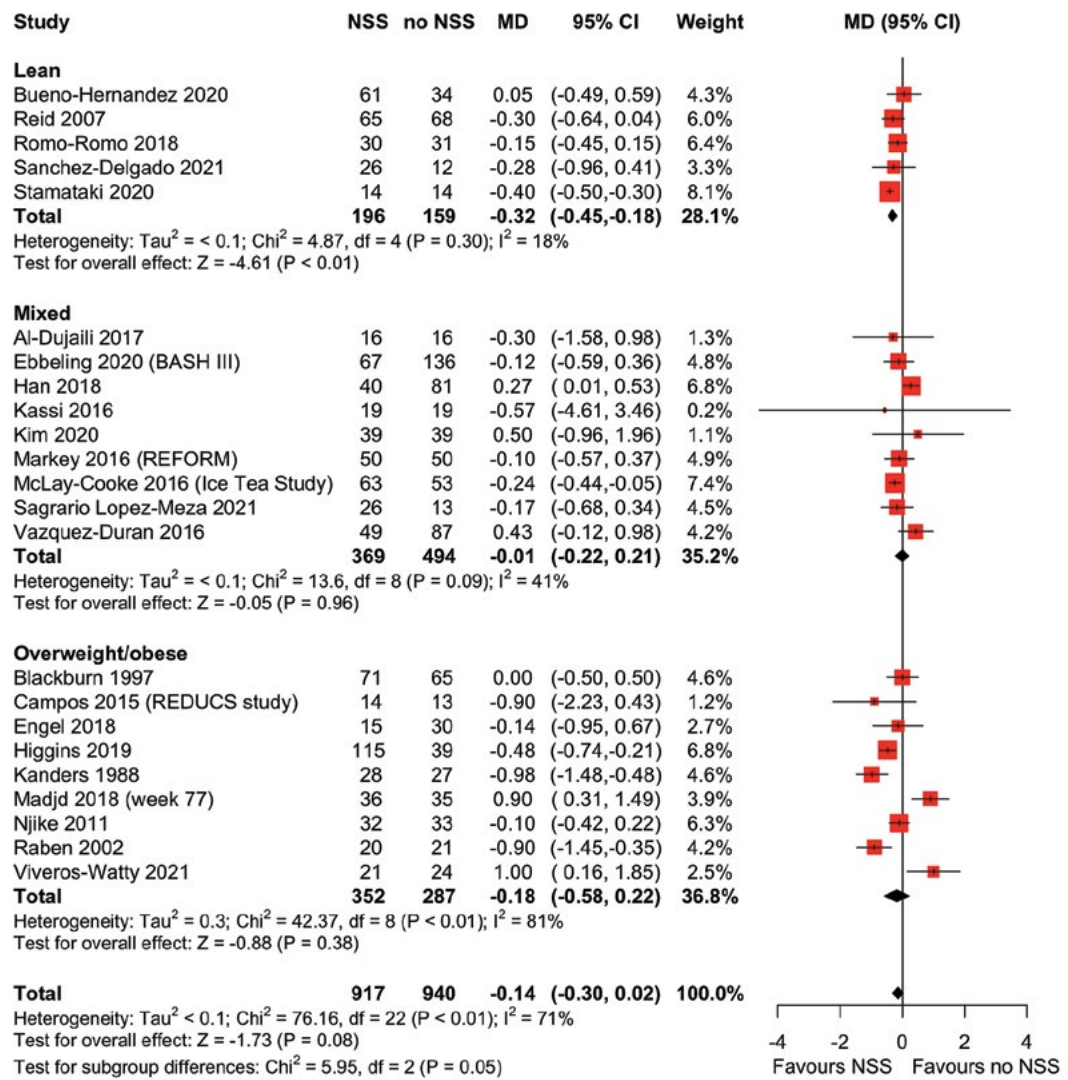
**Fig. A9.16 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by delivery mode, in adults**



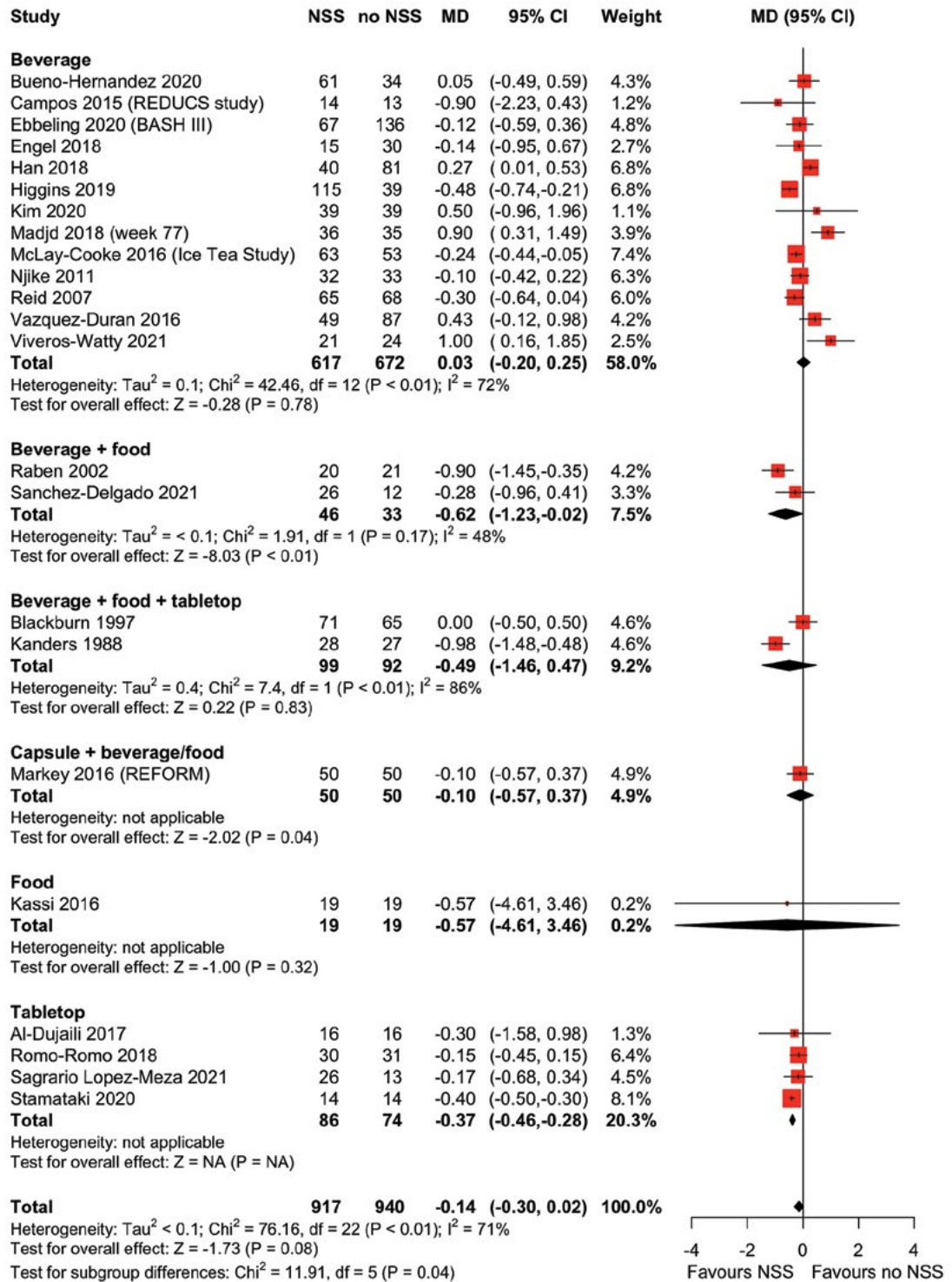
**Fig. A9.17 Effect of NSS intake on body weight (kg) in randomized controlled trials, subgrouped by consumption pattern**



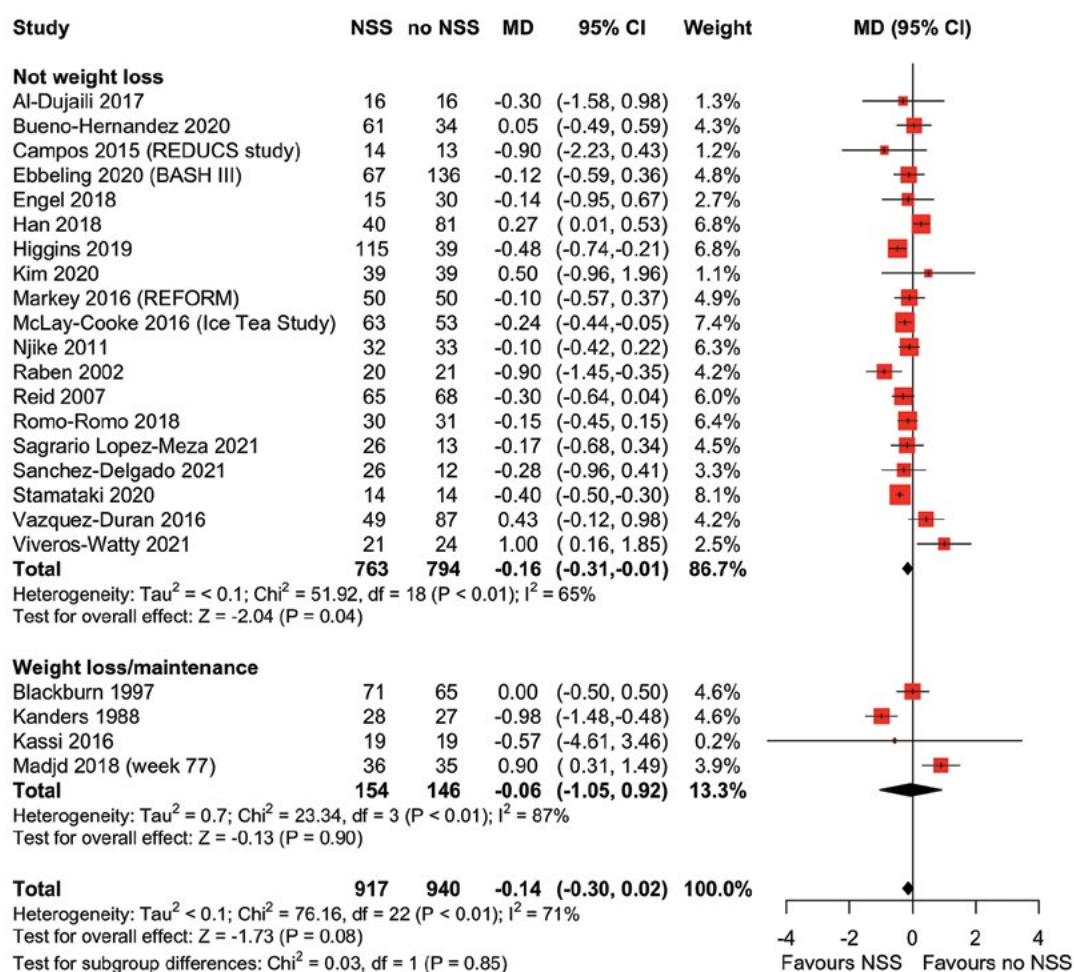
**Fig. A9.18 Effect of NSS on body mass index (kg/m<sup>2</sup>) in randomized controlled trials, subgrouped by weight status, in adults**



**Fig. A9.19 Effect of NSS on body mass index (kg/m<sup>2</sup>) in randomized controlled trials, subgrouped by delivery mode, in adults**

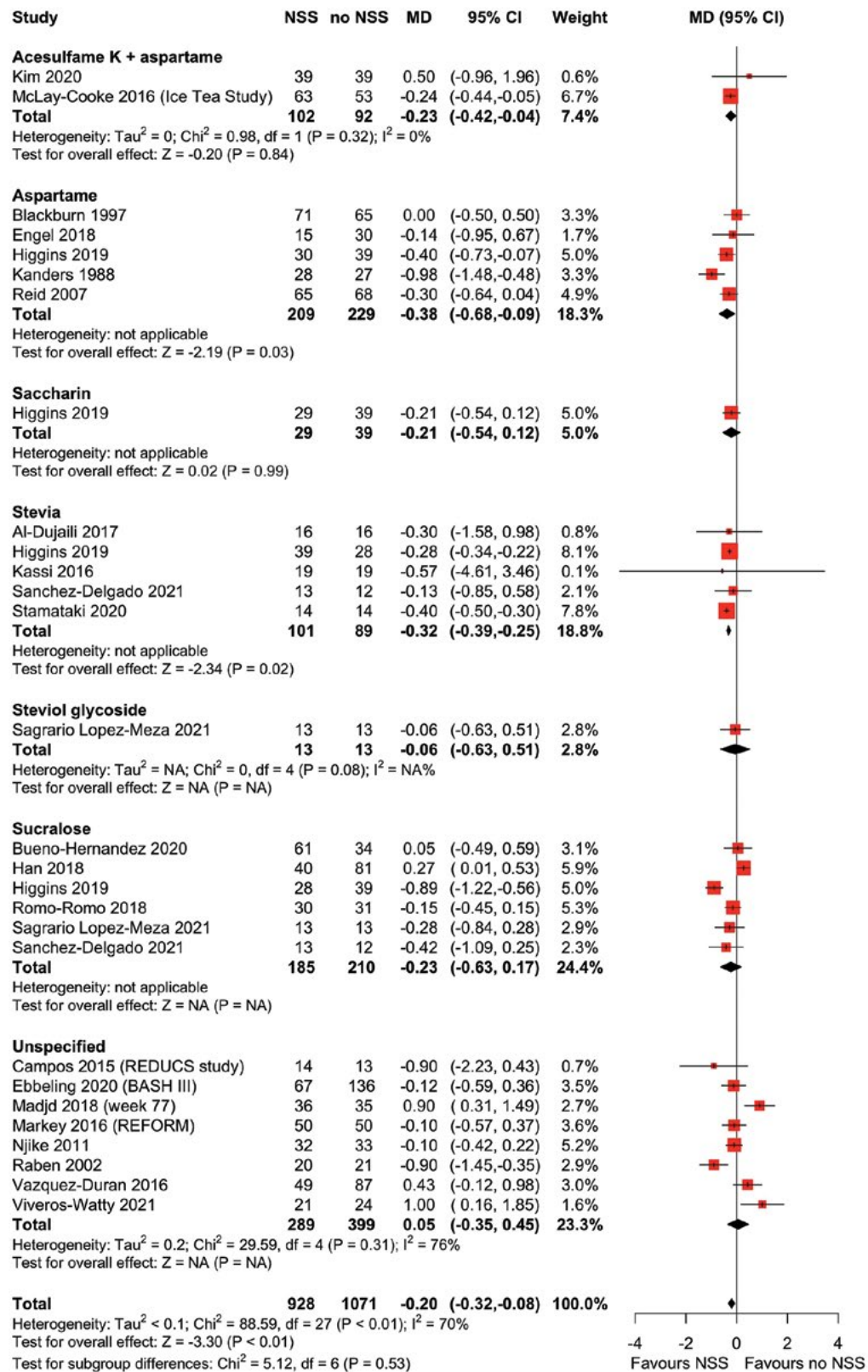


**Fig. A9.20 Effect of NSS on body mass index (kg/m<sup>2</sup>), subgrouped by study design (weight loss studies versus non-weight loss studies), in adults**



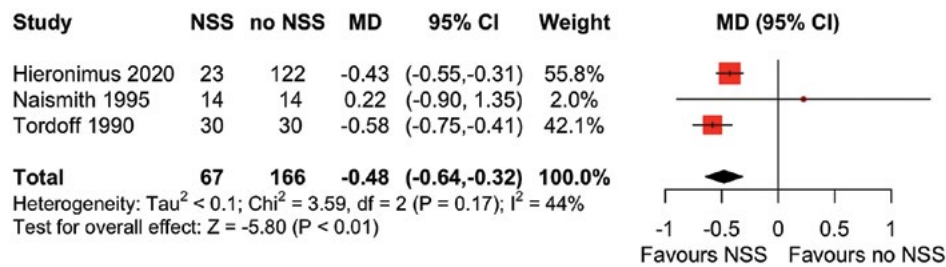
*Note:* Weight loss studies were those in which the participants were instructed to restrict energy intake AND consume NSS or control. Weight maintenance studies were those that followed up participants after active weight loss, with instructions on energy intake designed to prevent weight gain. Non-weight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

**Fig. A9.21 Effect of NSS intake on body mass index (kg/m<sup>2</sup>), subgrouped by NSS type**

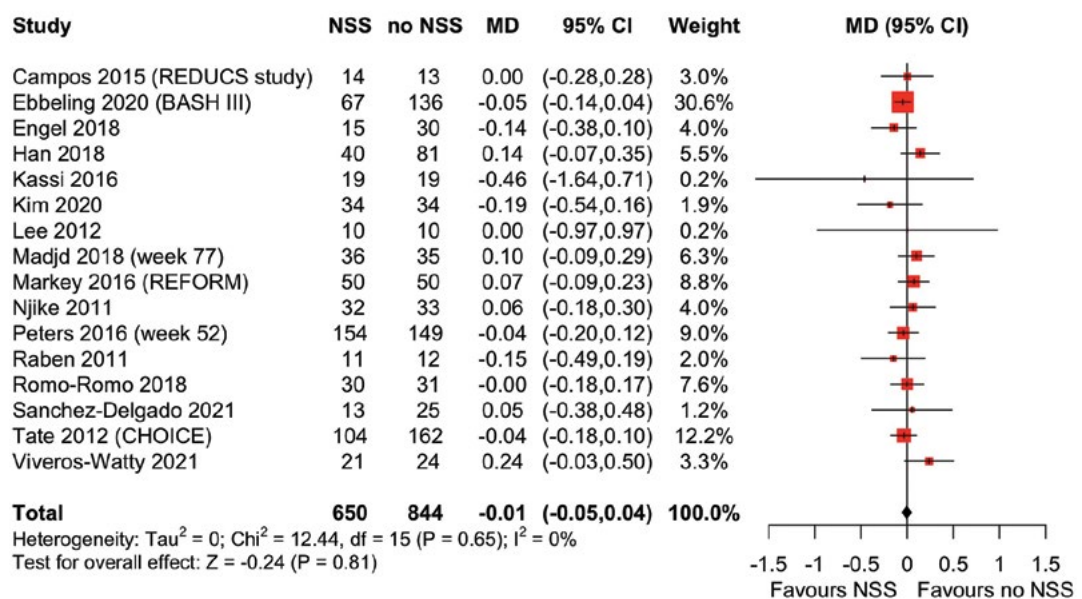


*Note:* Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from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

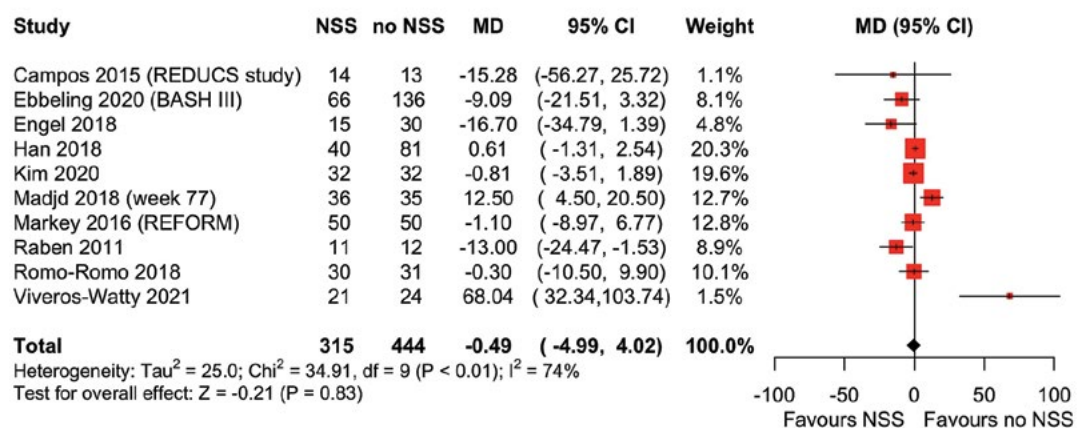
**Fig. A9.22 Effect of NSS on body weight (kg) in nonrandomized controlled trials in adults**



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

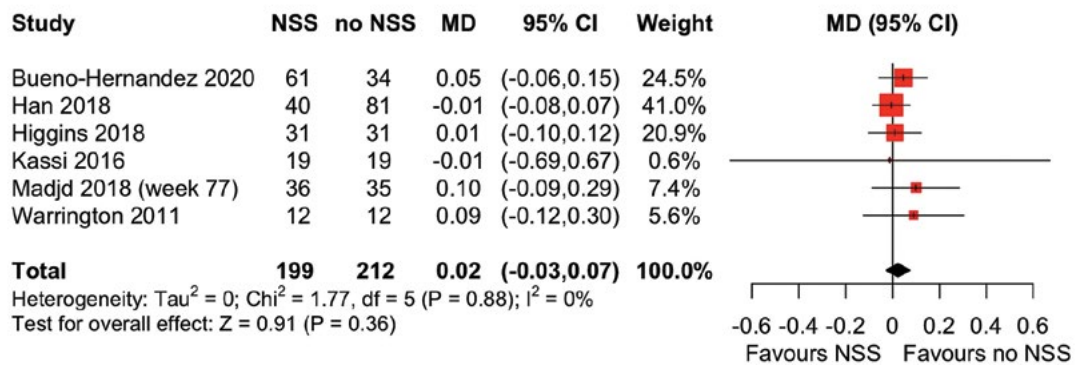


**Fig. A9.24 Effect of NSS on fasting insulin (pmol/L) in randomized controlled trials in adults**

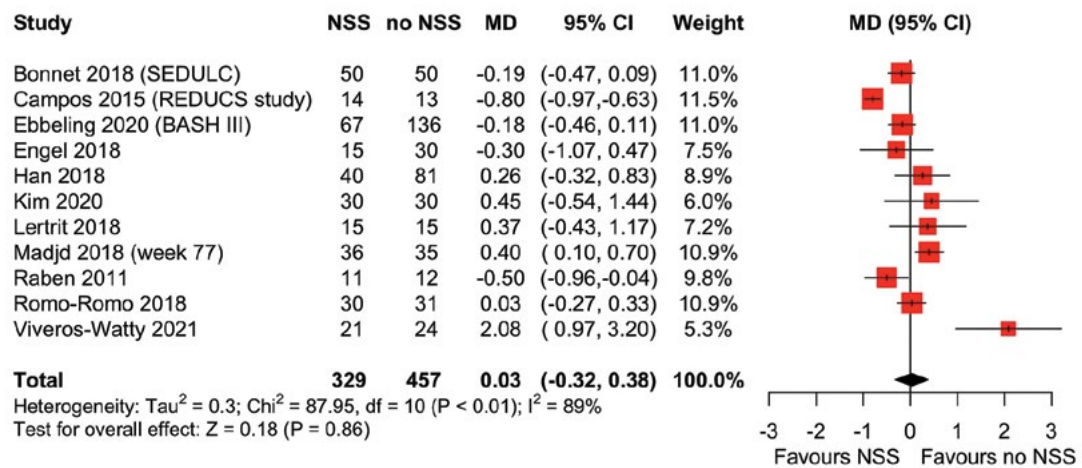




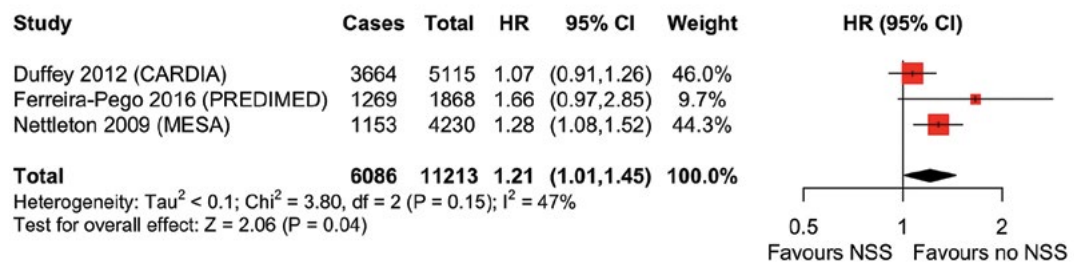
**Fig. A9.25 Effect of NSS on HbA1c (%) in randomized controlled trials in adults**



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

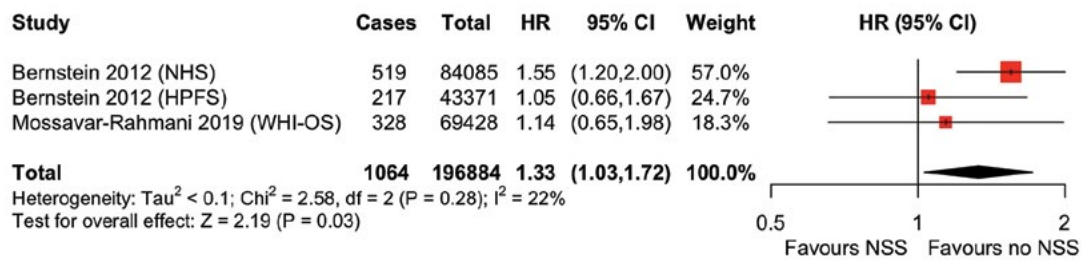


**Fig. A9.27 Association between NSS and high fasting glucose in cohort studies (highest versus lowest) in adults**

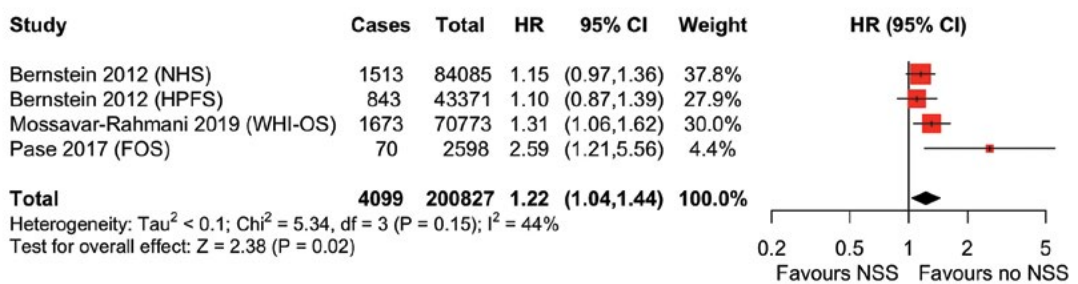


Note: High fasting glucose is defined as  $\geq 5.5$  mmol/L.

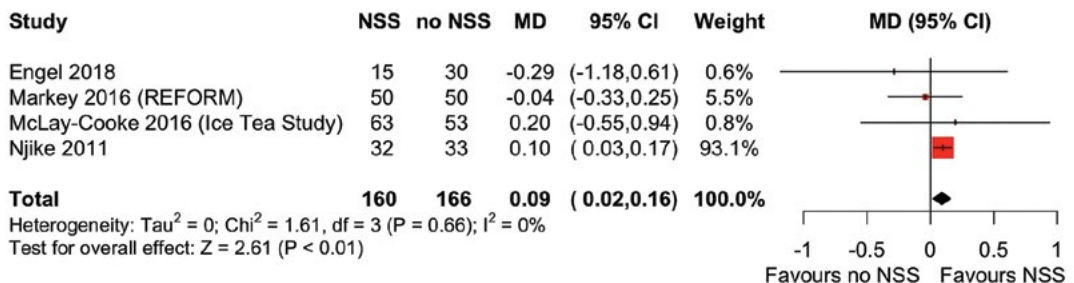
**Fig. A9.28 Association between NSS and haemorrhagic stroke in cohort studies (highest versus lowest) in adults**



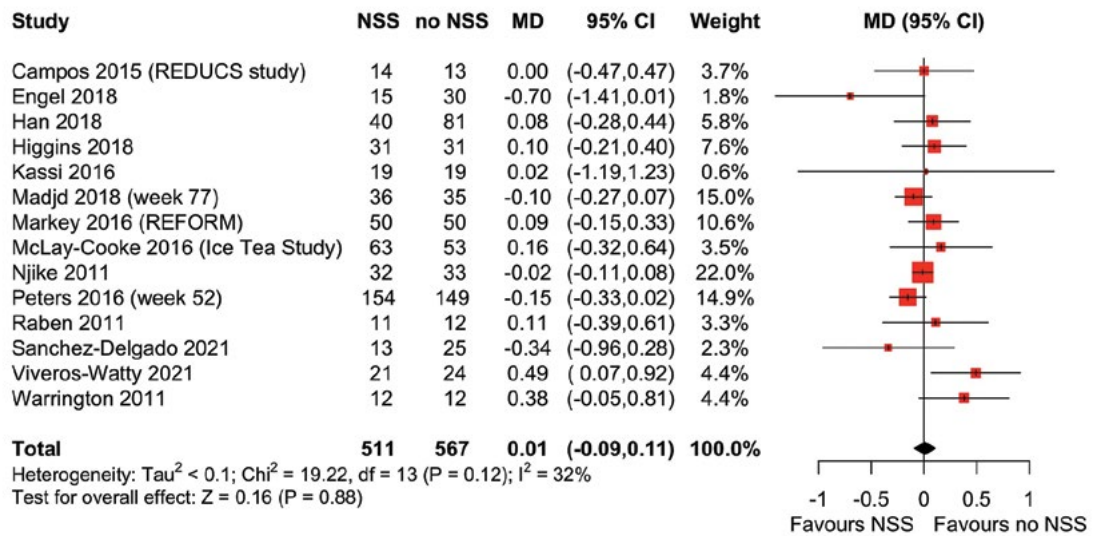
**Fig. A9.29 Association between NSS and ischaemic stroke in cohort studies (highest versus lowest) in adults**



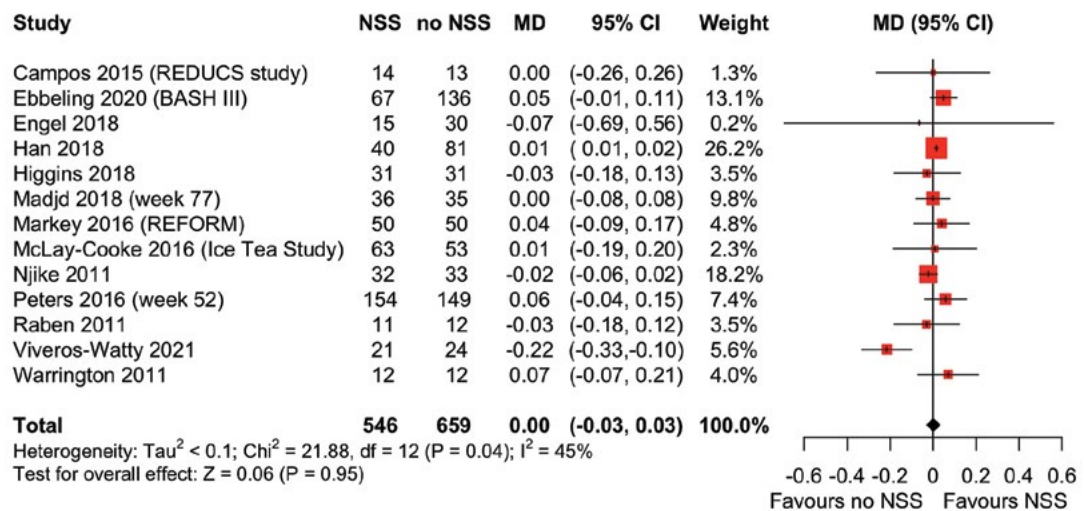
**Fig. A9.30 Effect of NSS on total:HDL cholesterol in randomized controlled trials in adults**



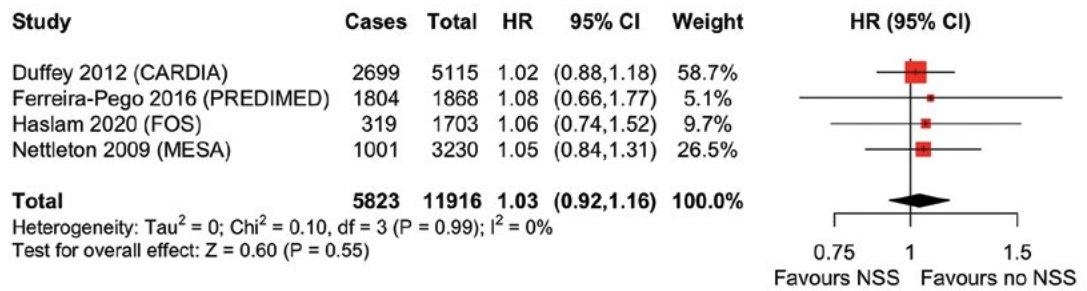
**Fig. A9.31 Effect of NSS on total cholesterol (mmol/L) in randomized controlled trials in adults**



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

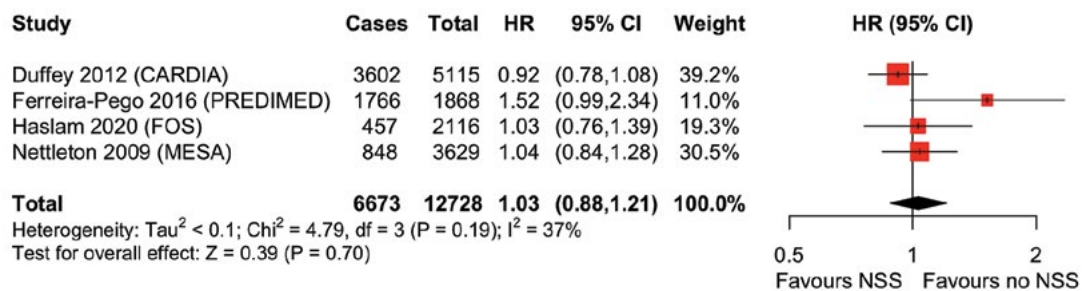


**Fig. A9.33 Association between NSS and low HDL cholesterol in cohort studies (highest versus lowest) in adults**



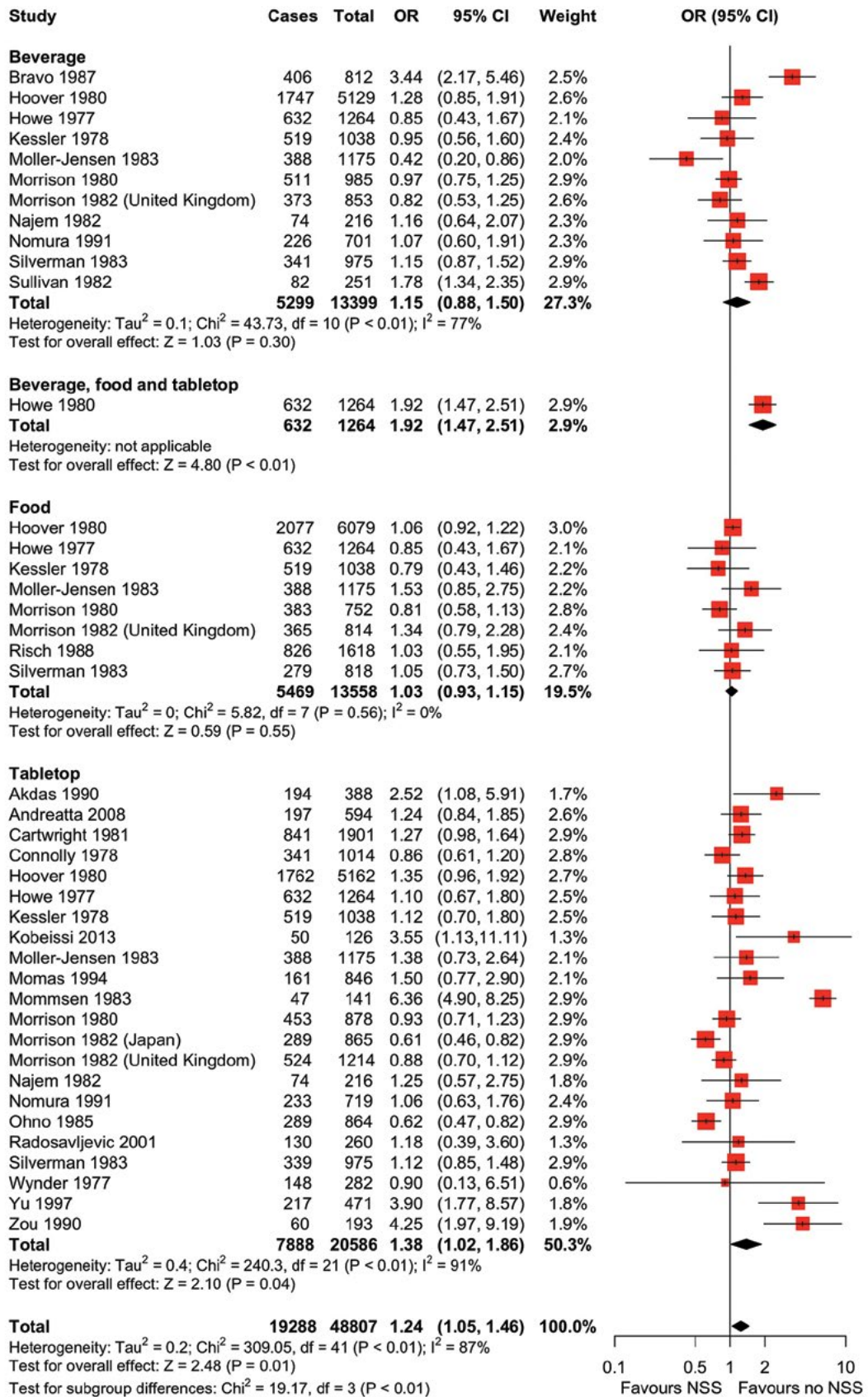
Note: Low HDL cholesterol is defined as  $\geq 5.5$  mmol/L.

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

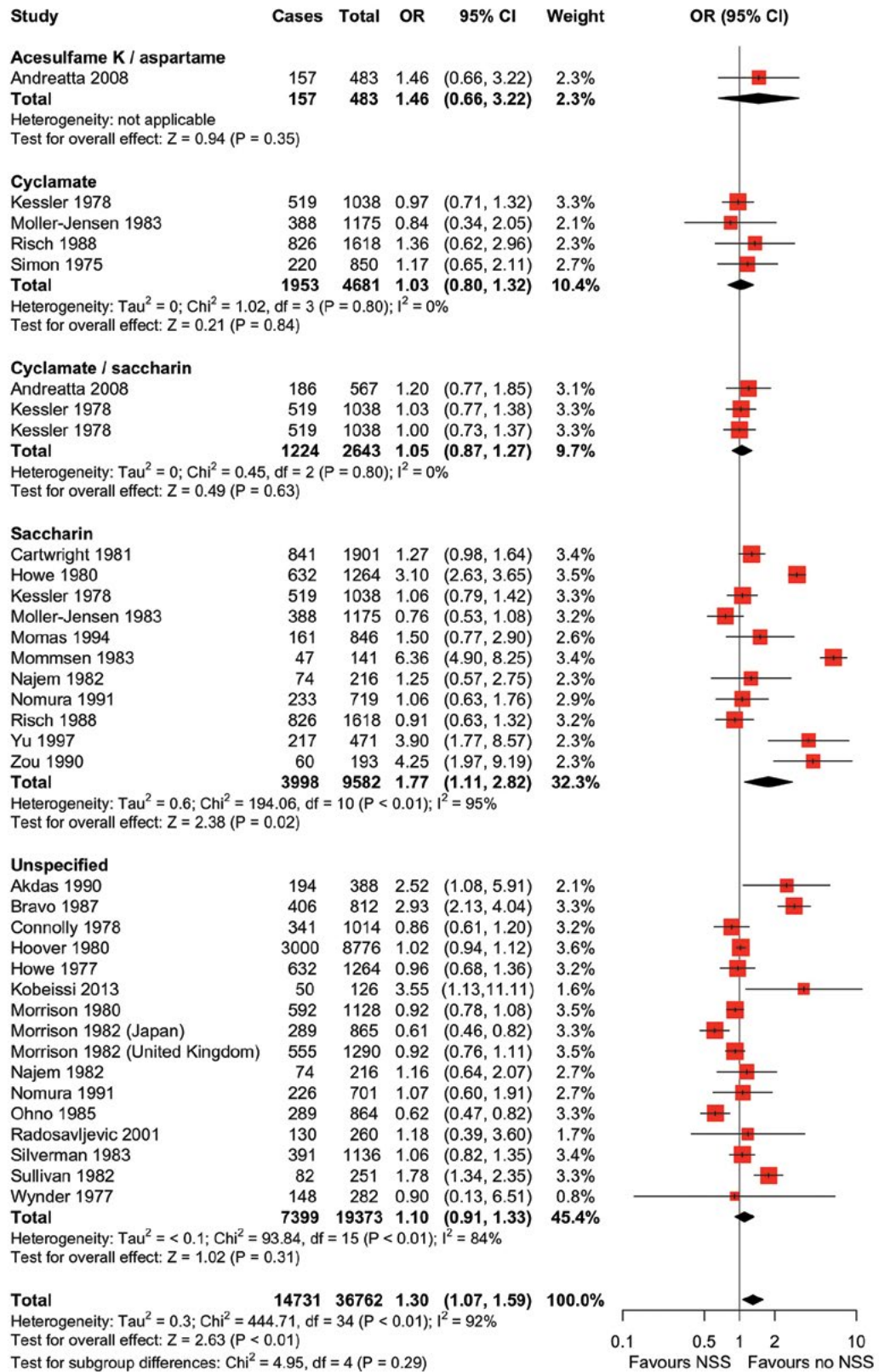


Note: High triglycerides are defined as  $\geq 1.70$  mmol/L.

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

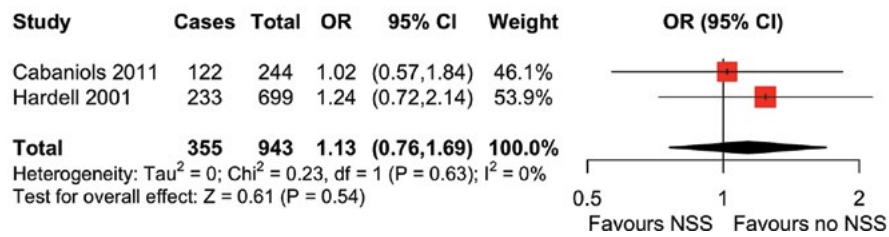


**Fig. A9.36 Association between NSS and bladder cancer in case-control studies, subgrouped by NSS type, in adults**

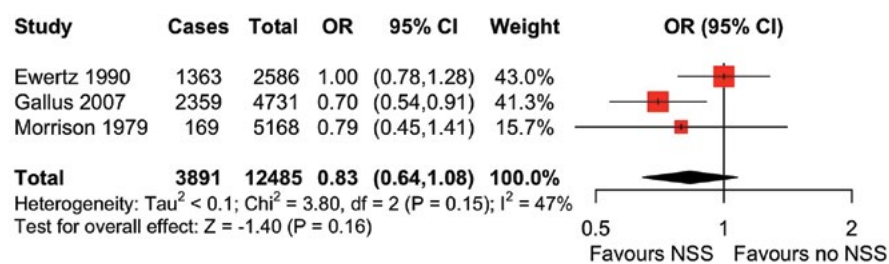


Note: Some studies appear more than once because they had multiple arms (comparing different NSS with a control); therefore, the overall pooled effect is also slightly different from the main effect, and only effects for individual subgroups should be considered.

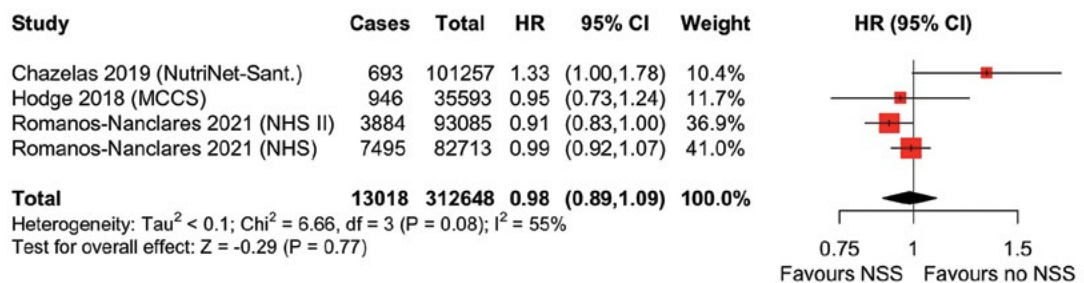
**Fig. A9.37 Association between NSS and brain cancer in case-control studies in adults**



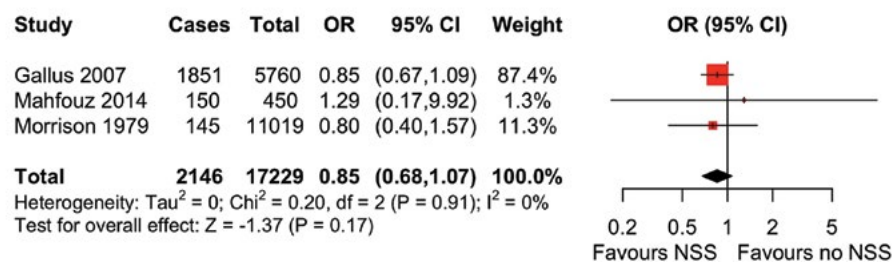
**Fig. A9.38 Association between NSS and breast cancer in case-control studies in adults**



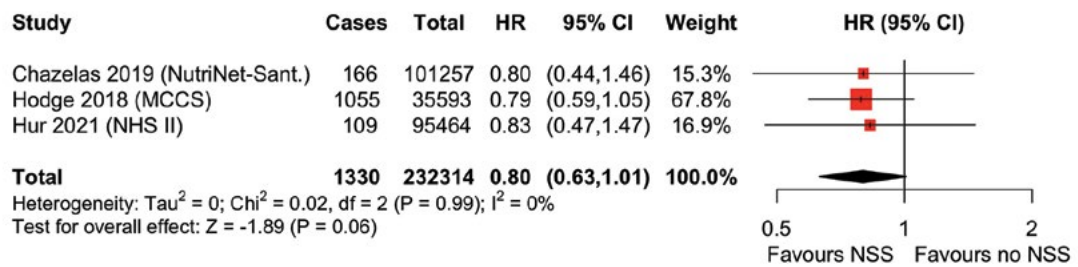
**Fig. A9.39 Association between NSS and breast cancer in prospective cohort studies in adults**



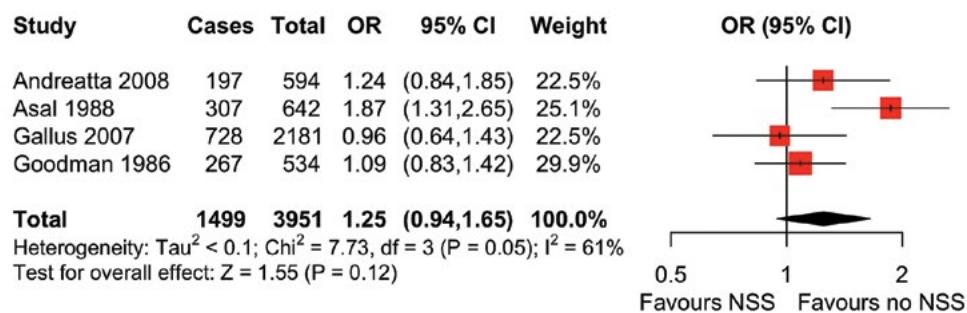
**Fig. A9.40 Association between NSS and colorectal cancer in case-control studies in adults**



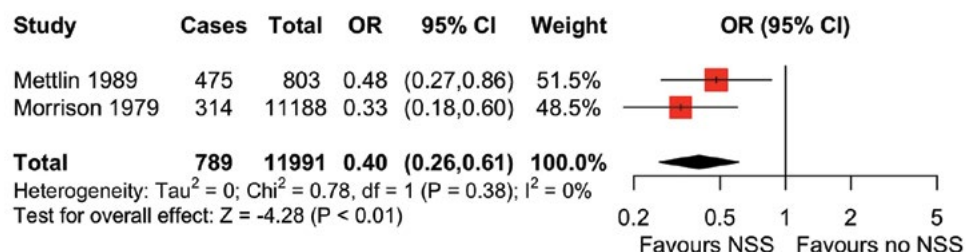
**Fig. A9.41 Association between NSS and colorectal cancer in prospective cohort studies in adults**



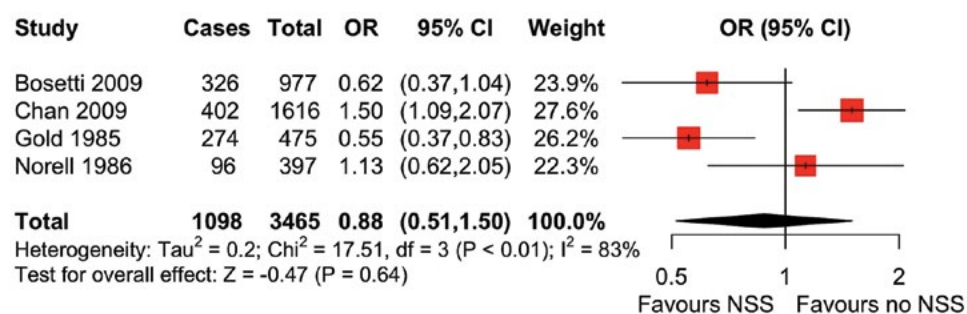
**Fig. A9.42 Association between NSS and renal cancer in case-control studies in adults**



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

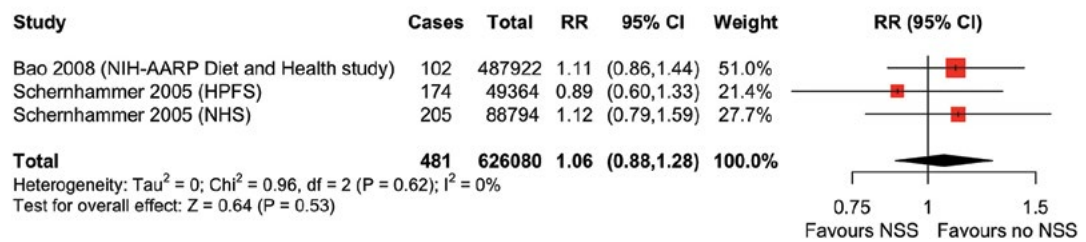


**Fig. A9.44 Association between NSS and pancreatic cancer in case-control studies in adults**

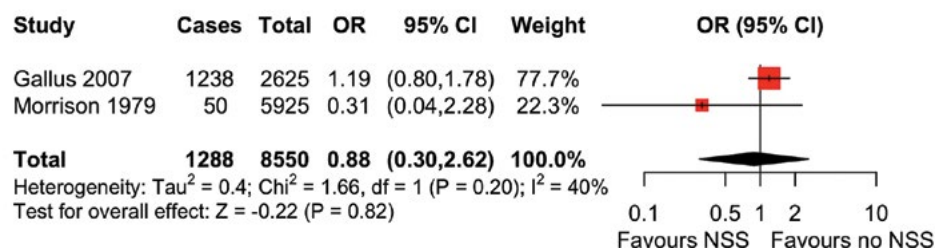




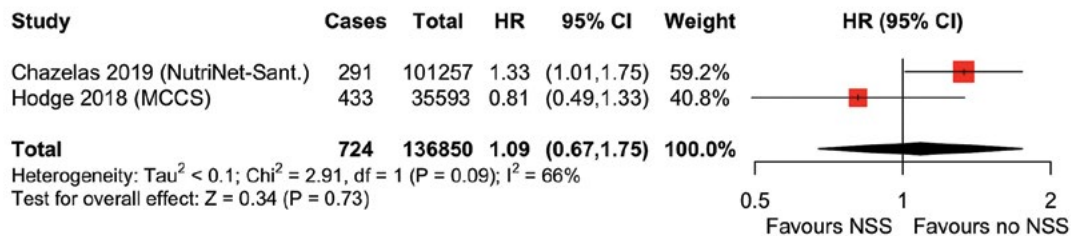
**Fig. A9.45 Association between NSS and pancreatic cancer in prospective cohort studies in adults**



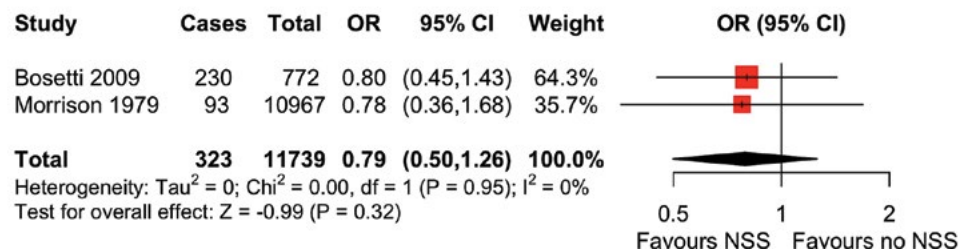
**Fig. A9.46 Association between NSS and prostate cancer in case-control studies in adults**



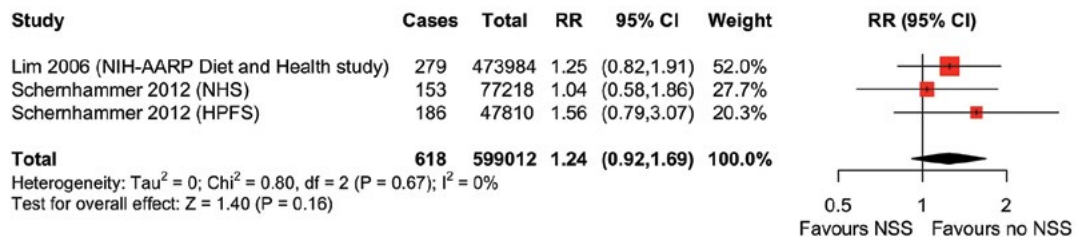
**Fig. A9.47 Association between NSS and prostate cancer in prospective cohort studies in adults**



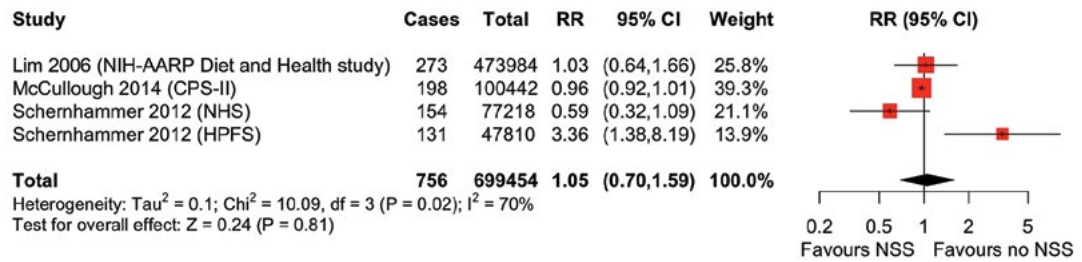
**Fig. A9.48 Association between NSS and gastric cancer in case-control studies in adults**



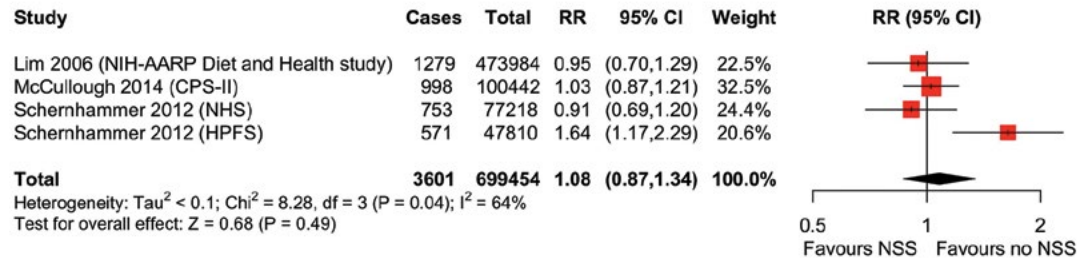
**Fig. A9.49 Association between NSS and leukaemia in cohort studies in adults**



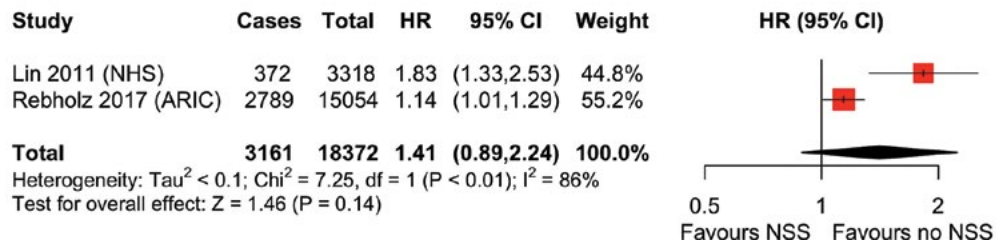
**Fig. A9.50 Association between NSS and multiple myeloma in cohort studies in adults**



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

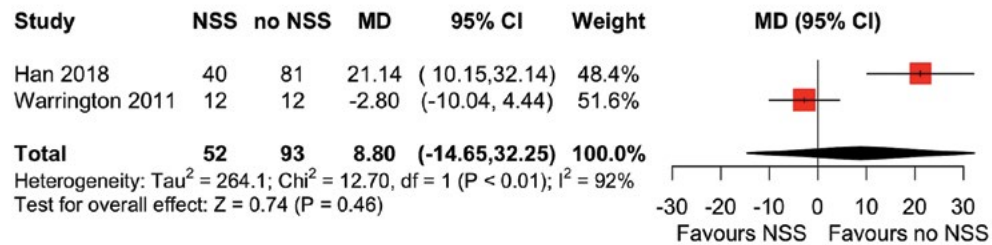


**Fig. A9.52 Association between NSS and chronic kidney disease in cohort studies in adults**

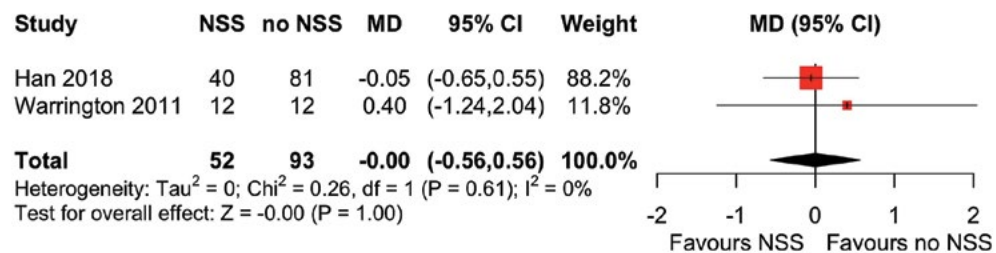


Note: Lin 2011 reported the association between NSS use and decline in estimated glomerular filtration rate (eGFR) of  $\geq 30\%$  (173), and Rebholz 2017, the association between NSS use and chronic kidney disease with one defining characteristic being a  $\geq 25\%$  decline in eGFR (174). Lin 2011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

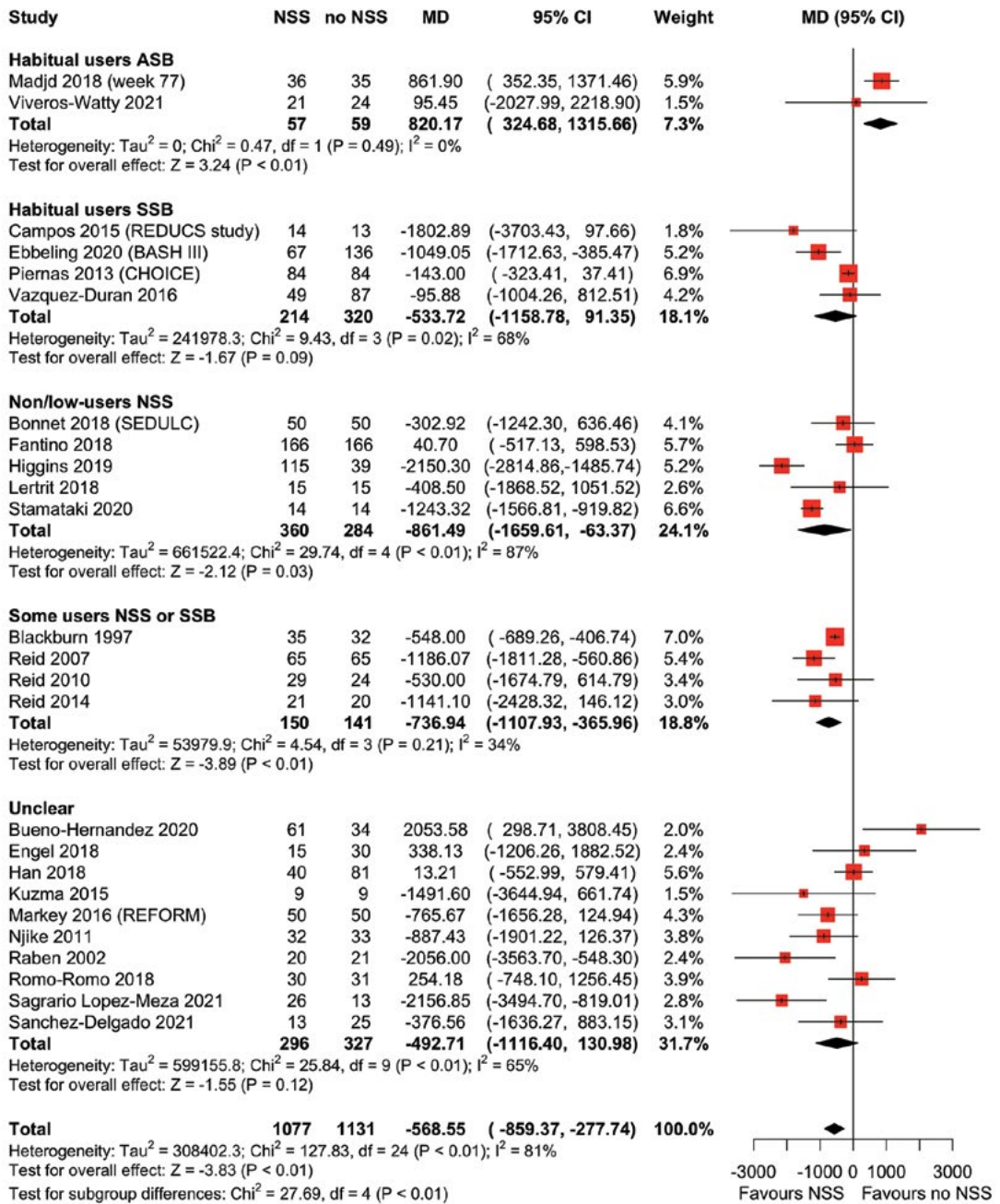
**Fig. A9.53 Effect of NSS on creatinine (mmol/L) in randomized controlled trials in adults**



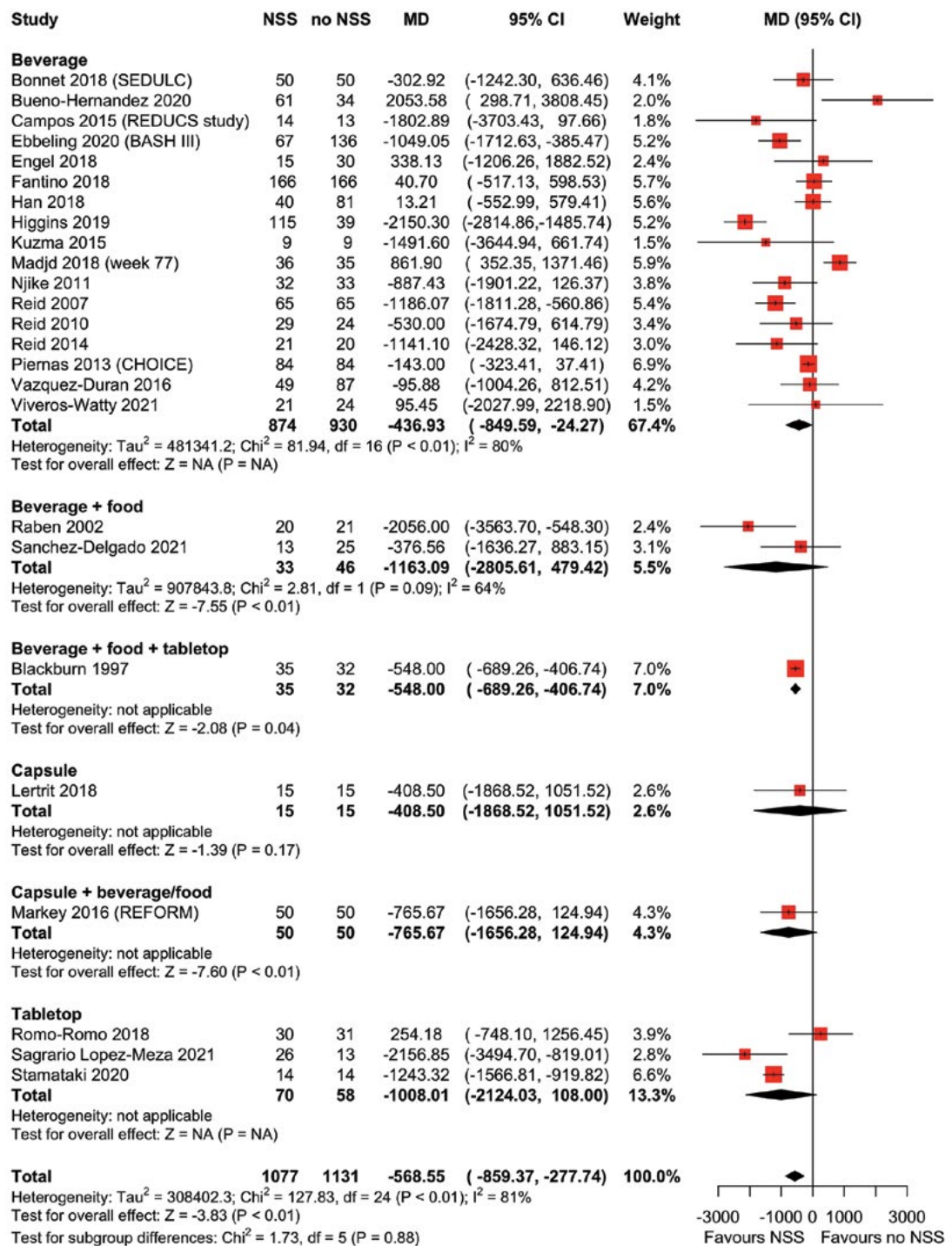
**Fig. A9.54 Effect of NSS on albumin (g/L) in randomized controlled trials in adults**



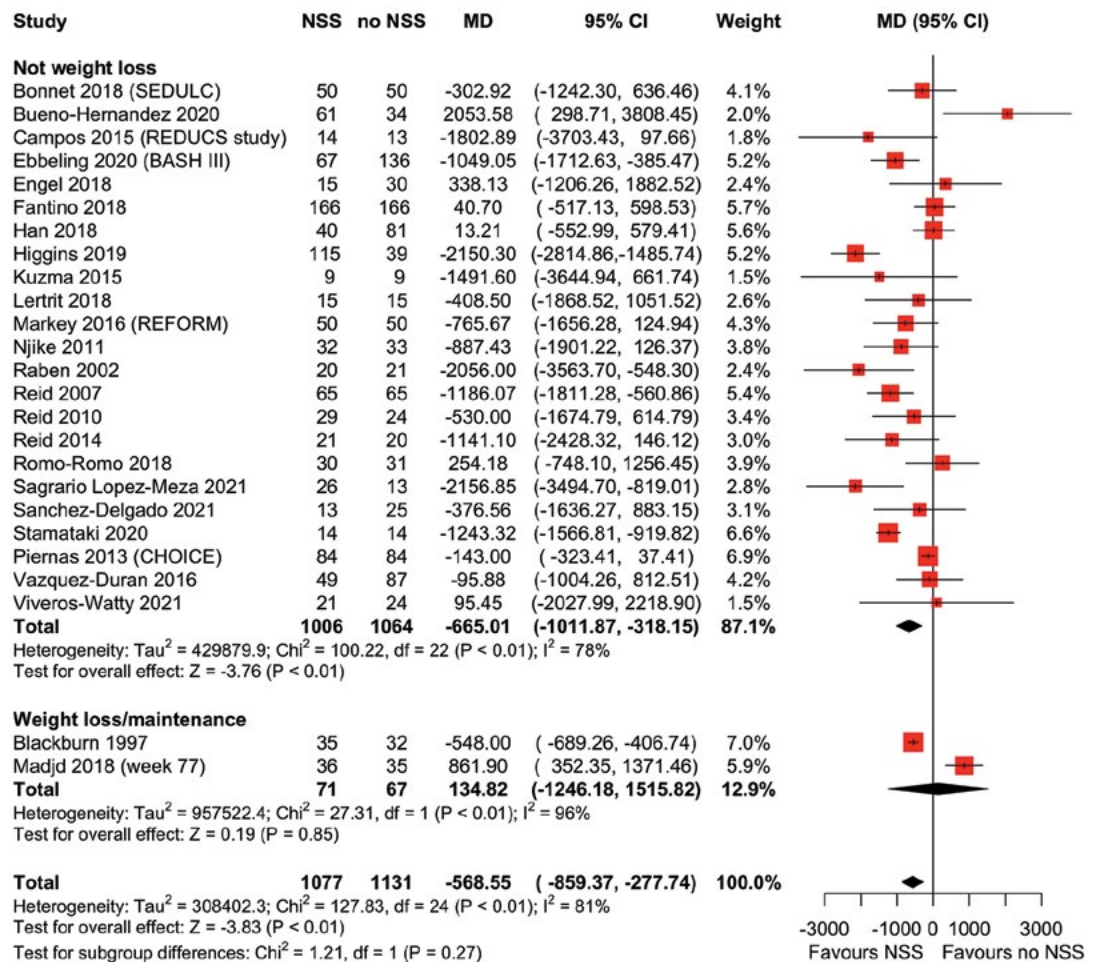
**Fig. A9.55 Effect of NSS on energy intake (kJ/d) in randomized controlled trials, subgrouped by consumption pattern, in adults**



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

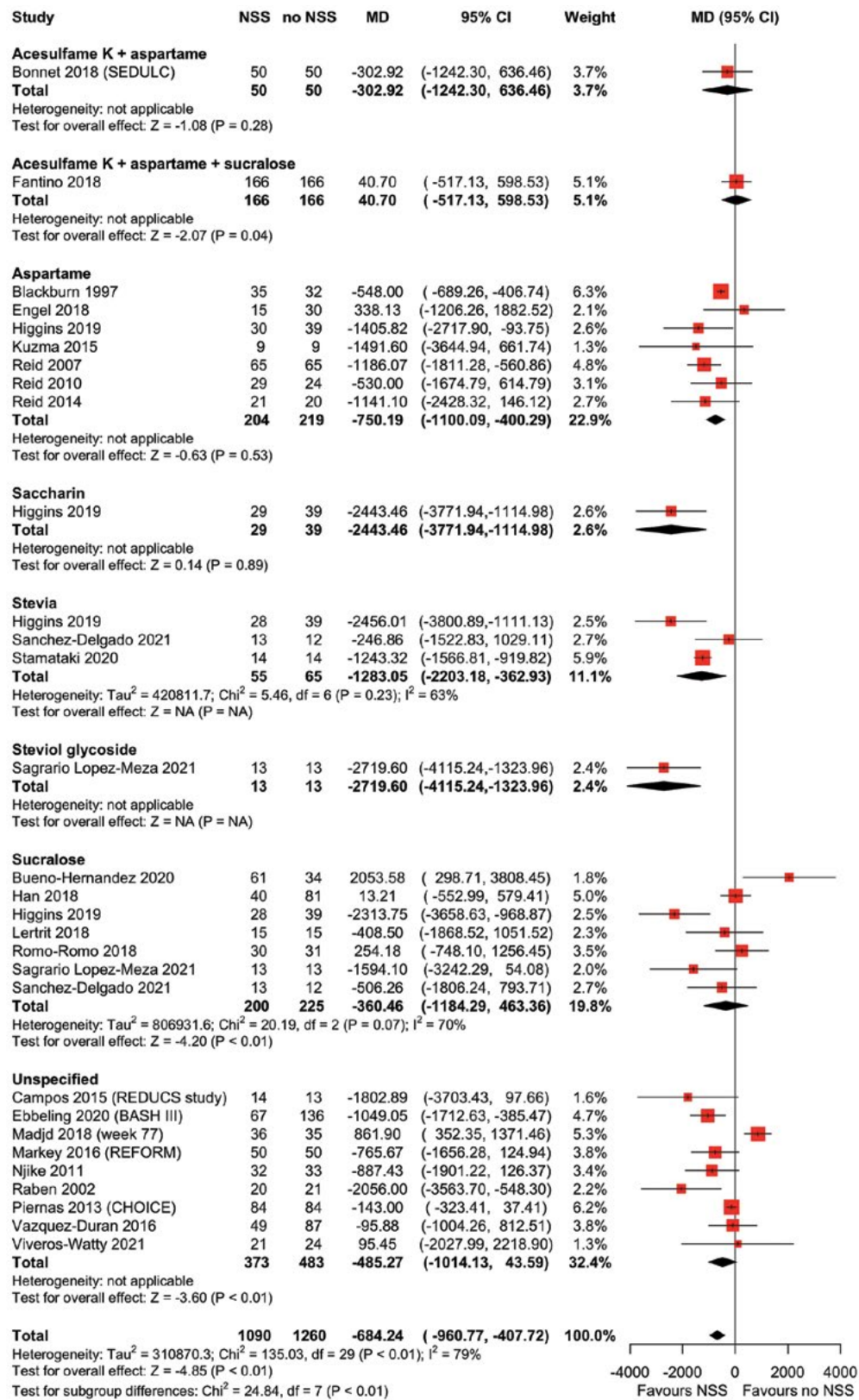


**Fig. A9.57 Effect of NSS on energy intake (kJ/d) in randomized controlled trials, subgrouped by study design (weight loss studies versus non-weight loss studies), in adults**



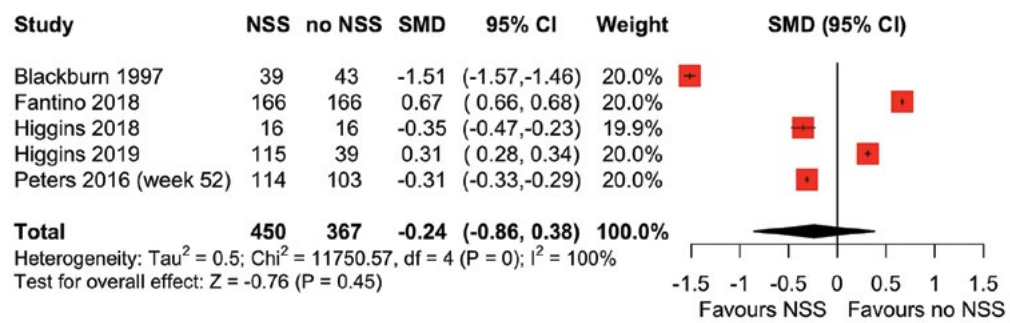
*Note:* Weight loss studies were those in which the participants were instructed to restrict energy intake AND consume NSS or control. Weight maintenance studies were those that followed up participants after active weight loss, with instructions on energy intake designed to prevent weight gain. Non-weight 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**

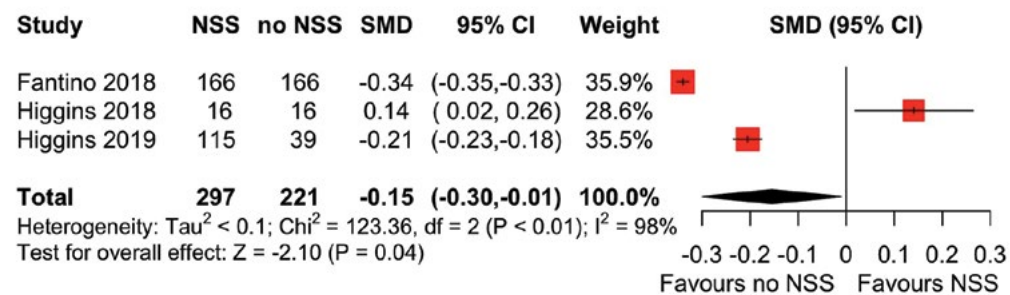


Note: Some studies appear more than once because they had multiple arms (e.g. comparing artificially sweetened beverages with both sugar-sweetened beverages and water, or separately comparing multiple different NSS with a control); therefore, the overall pooled effect is also slightly different from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

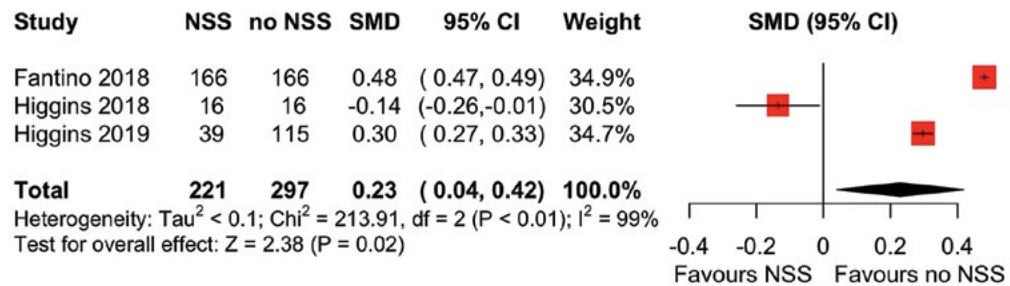
**Fig. A9.59 Effect of NSS on hunger in randomized controlled trials in adults**



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

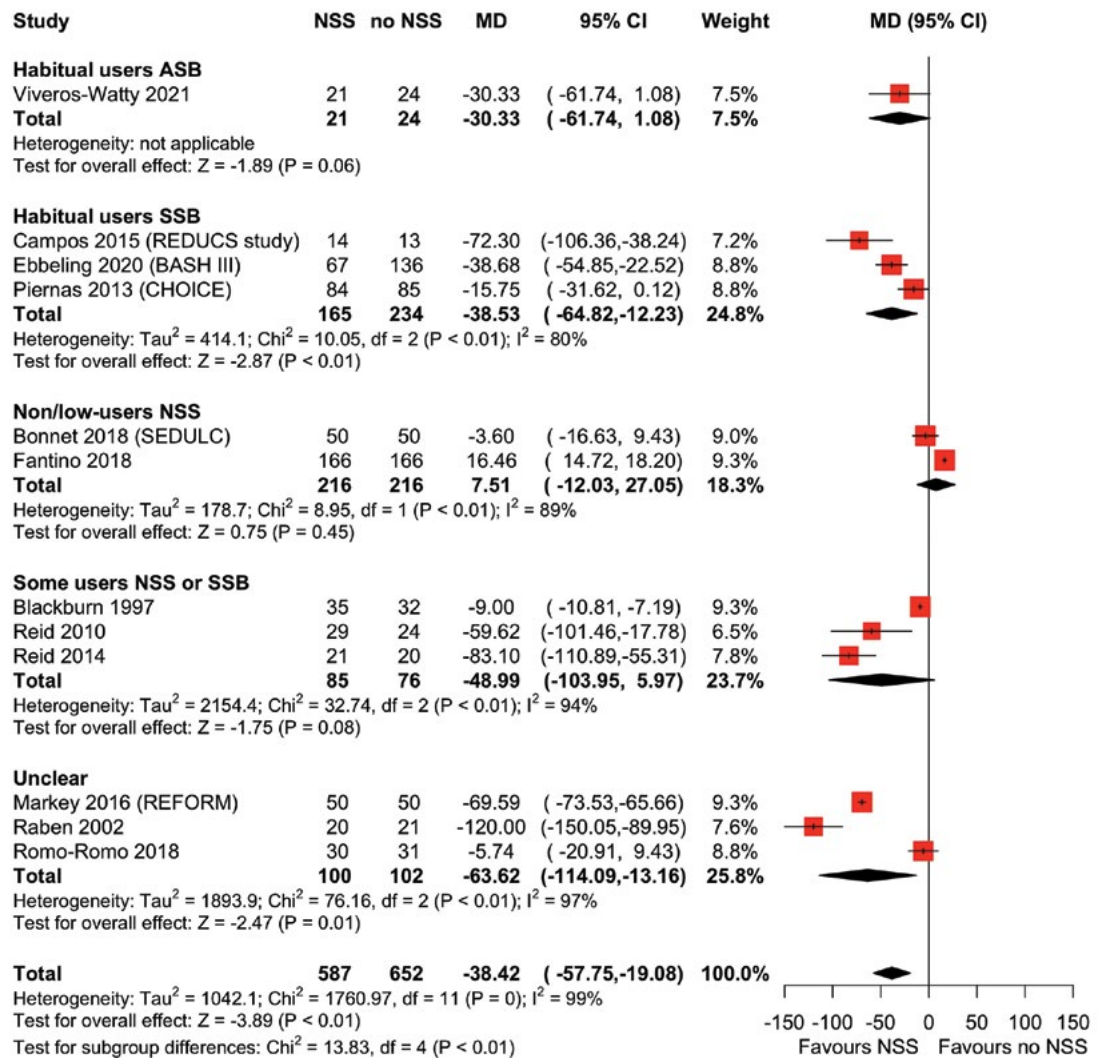


**Fig. A9.61 Effect of NSS on appetite/desire to eat in randomized controlled trials in adults**

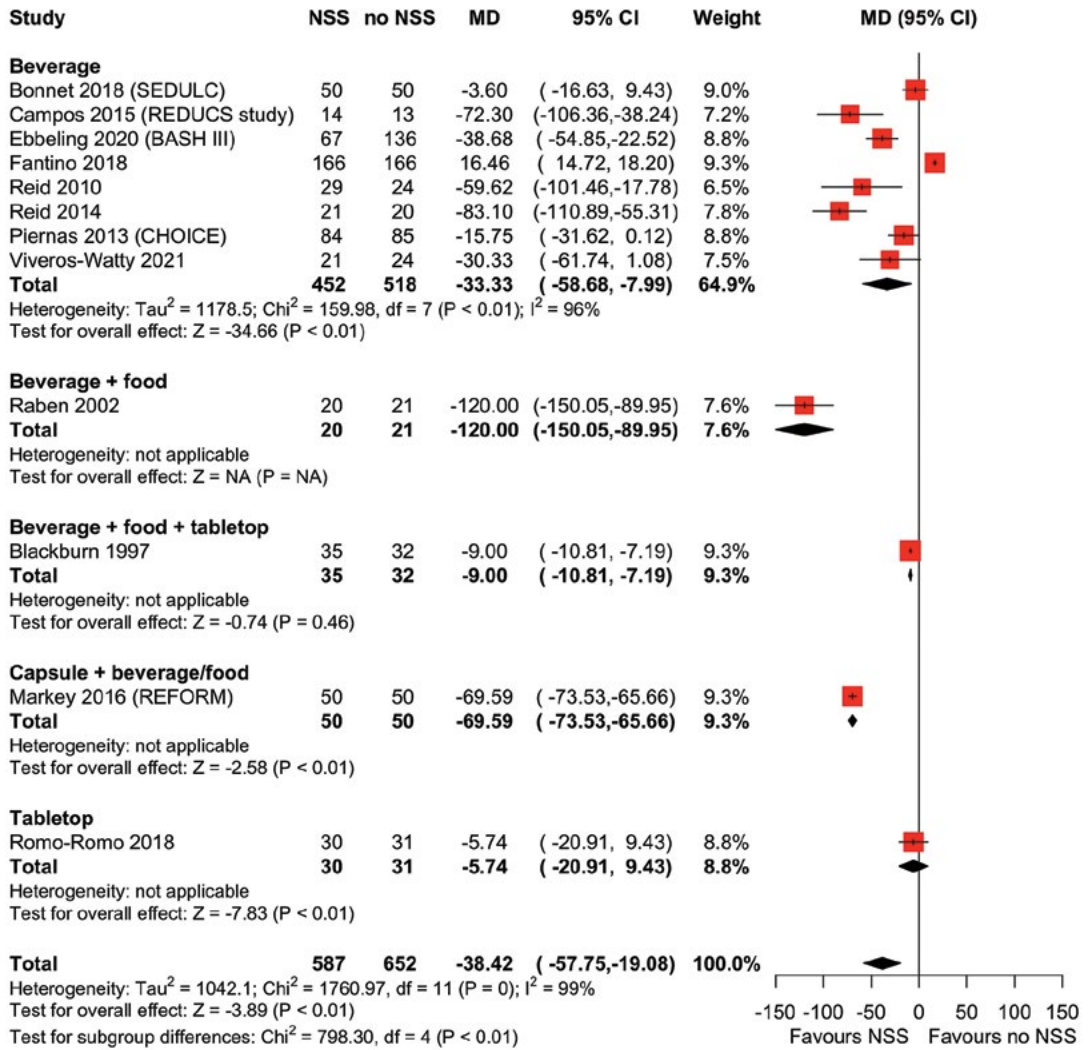




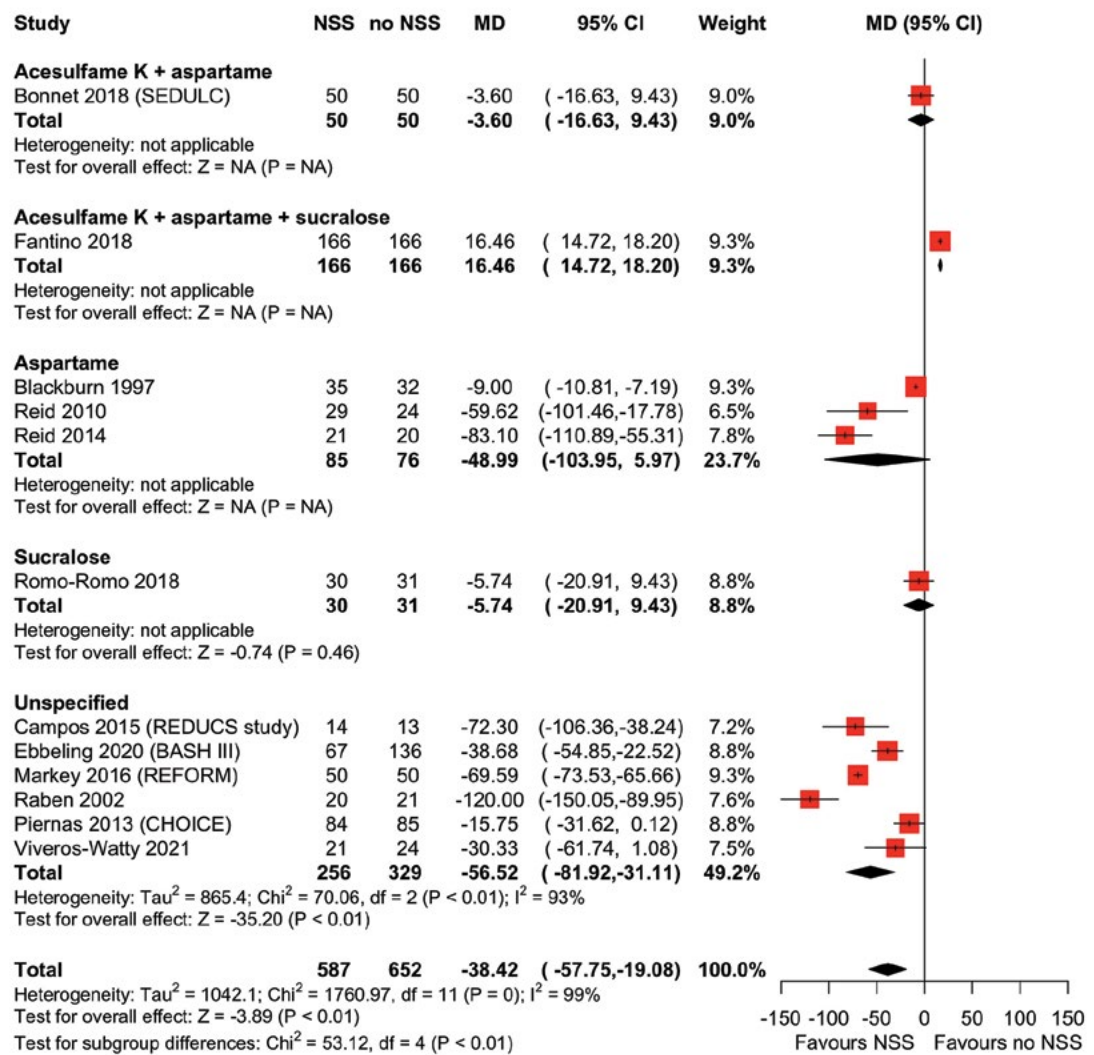
**Fig. A9.62 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by consumption pattern, in adults**



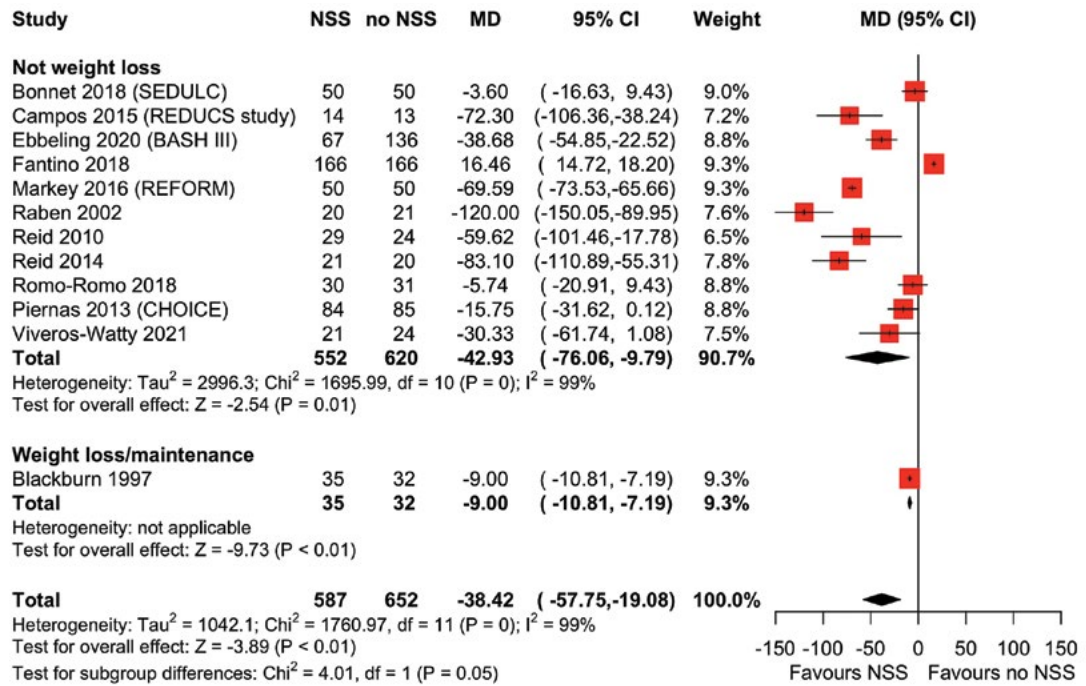
**Fig. A9.63 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by delivery mode, in adults**



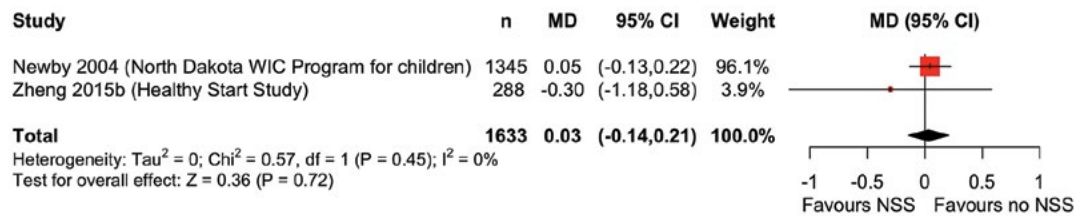
**Fig. A9.64 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by NSS type, in adults**



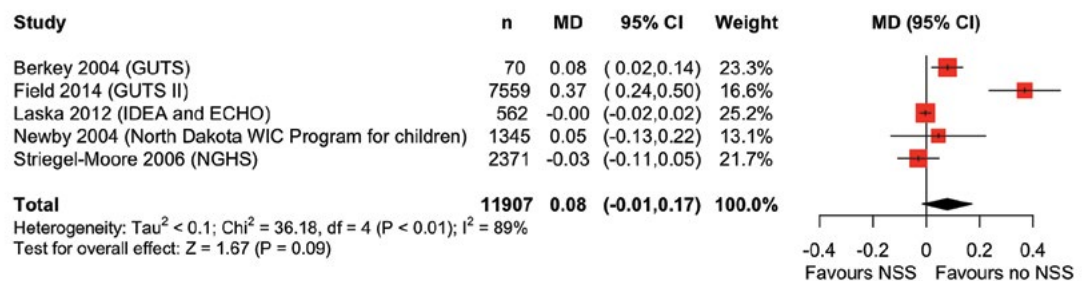
**Fig. A9.65 Effect of NSS on sugars intake (g/day) in randomized controlled trials, subgrouped by study design (weight loss studies versus non-weight loss studies), in adults**



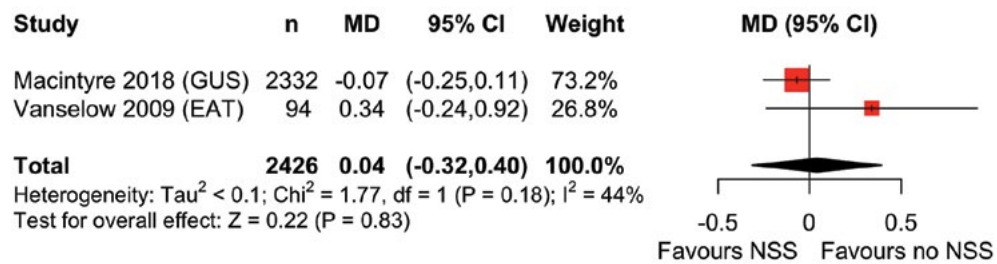
**Fig. A9.66 Association between NSS and body weight (kg) in cohort studies (continuous) in children**



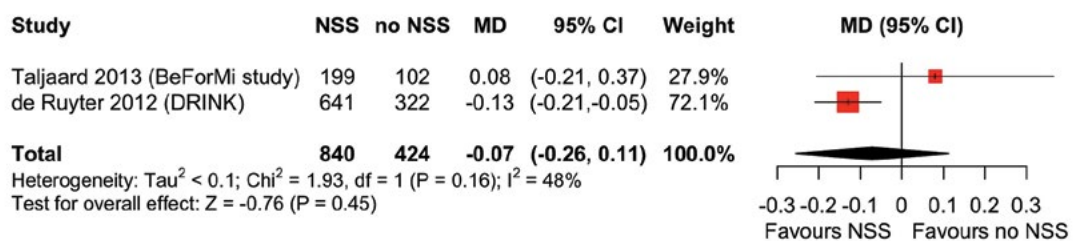
**Fig. A9.67 Association between NSS and body mass index (kg/m<sup>2</sup>) in cohort studies (continuous) in children**



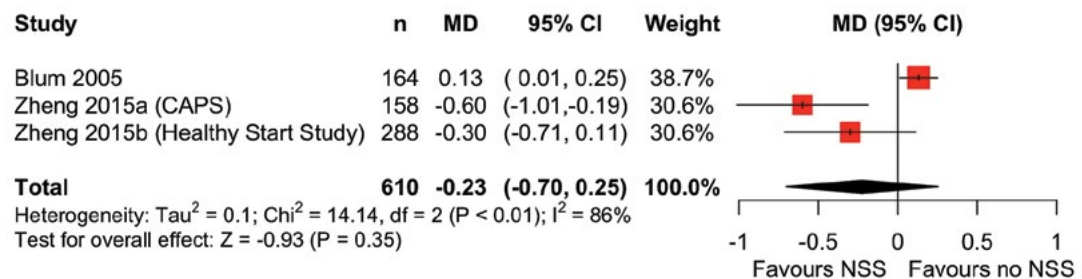
**Fig. A9.68 Association between NSS and body mass index (kg/m<sup>2</sup>) in cohort studies (higher versus lower) in children**



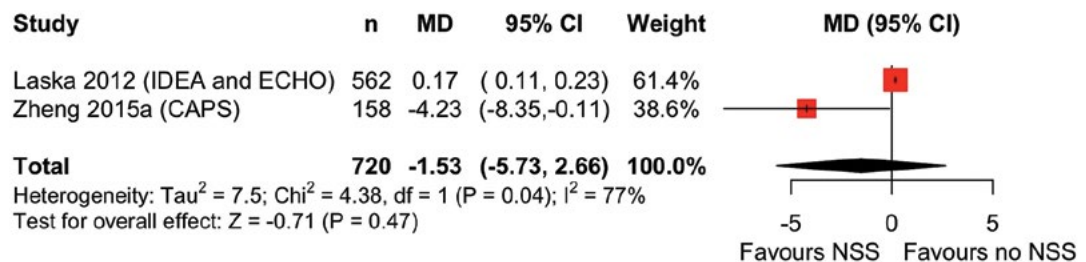
**Fig. A9.69 Effect of NSS on BMI z-score in randomized controlled trials in children**



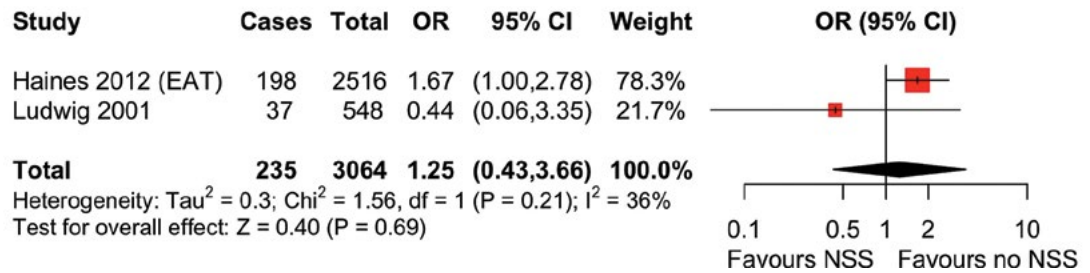
**Fig. A9.70 Association between NSS and BMI z-score in cohort studies (continuous) in children**



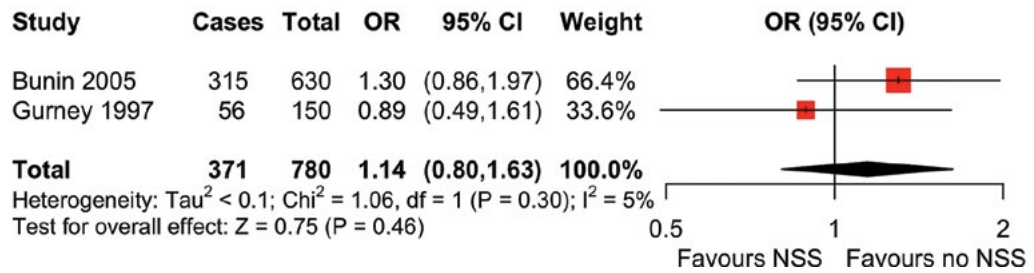
**Fig. A9.71 Association between NSS and body fat mass (%) in cohort studies in children**



**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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 2020 <sup>c</sup> (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

<sup>a</sup> <http://dx.doi.org/10.1016/j.clnesp.2020.09.651>

<sup>b</sup> [https://jglobal.jst.go.jp/en/detail?JGLOBAL\\_ID=202002239574388156](https://jglobal.jst.go.jp/en/detail?JGLOBAL_ID=202002239574388156)

<sup>c</sup> <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
<b>Population</b>	Included general, healthy population of adults ( $\geq 18$ years) or children ( $< 18$ years)  Excluded diseased populations, in vitro studies and animal studies	Also included pregnant women
<b>Intervention/exposure</b>	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
<b>Comparators</b>	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
<b>Outcomes</b>	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
<b>Study design</b>	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
<b>Duration</b>	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

# References

1. Toews I, Lohner S, Küllenberg de Gaudry D, Sommer H, Meerpohl JJ. Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies. *BMJ*. 2019;364:k4718. doi: 10.1136/bmj.k4718.
2. Faruque S, Tong J, Lacmanovic V, Agbonghae C, Minaya DM, Czaja K. T The dose makes the poison: sugar and obesity in the United States – a review. *Pol J Food Nutr Sci*. 2019;69(3):219–33. doi: 10.31883/pjfn/110735.
3. Te Morenga L, Mallard S, Mann J. Dietary sugars and body weight: systematic review and meta-analyses of randomised controlled trials and cohort studies. *BMJ*. 2012;346:e7492. doi: 10.1136/bmj.e7492.
4. Khan TA, Tayyiba M, Agarwal A, Mejia SB, de Souza RJ, Wolever TMS, et al. Relation of total sugars, sucrose, fructose, and added sugars with the risk of cardiovascular disease: a systematic review and dose–response meta-analysis of prospective cohort studies. *Mayo Clin Proc*. 2019;94:2399–414. doi: 10.1016/j.mayocp.2019.05.034.
5. Makarem N, Bandera EV, Nicholson JM, Parekh N. Consumption of sugars, sugary foods, and sugary beverages in relation to cancer risk: a systematic review of longitudinal studies. *Annu Rev Nutr*. 2018;38:17–39. doi: 10.1146/annurev-nutr-082117-051805.
6. Neuenschwander M, Ballon A, Weber KS, Norat T, Aune D, Schwingshackl L, et al. Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies. *BMJ*. 2019;366:l2368. doi: 10.1136/bmj.l2368.
7. Moynihan PJ, Kelly SA. Effect on caries of restricting sugars intake: systematic review to inform WHO guidelines. *J Dent Res*. 2014;93(1):8–18. doi: 10.1177/0022034513508954.
8. Guideline: Sugars intake for adults and children. Geneva: World Health Organization; 2015.
9. Dunford EK, Miles DR, Ng SW, Popkin B. Types and amounts of nonnutritive sweeteners purchased by US households: a comparison of 2002 and 2018 Nielsen Homescan purchases. *J Acad Nutr Diet*. 2020;120:1662–71.e10. doi: 10.1016/j.jand.2020.04.022.
10. Sylvestsky AC, Figueroa J, Rother KI, Goran MI, Welsh JA. Trends in low-calorie sweetener consumption among pregnant women in the United States. *Curr Dev Nutr*. 2019;3:nzz004. doi: 10.1093/cdn/nzz004.
11. Sylvestsky AC, Rother KI. Trends in the consumption of low-calorie sweeteners. *Physiol Behav*. 2016;164:446–50. doi: 10.1016/j.physbeh.2016.03.030.
12. WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 ([http://apps.who.int/iris/bitstream/10665/145714/1/9789241548960\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/145714/1/9789241548960_eng.pdf), accessed 29 January 2021).
13. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;350:g7647. doi: 10.1136/bmj.g7647.
14. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi: 10.1186/2046-4053-4-1.

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi: 10.1136/bmj.b2700.
16. Cochrane handbook for systematic reviews of interventions, version 6.2. Cochrane; 2021 (<https://training.cochrane.org/handbook/current>, accessed 8 November 2021).
17. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva: World Health Organization; 2021 (<https://apps.who.int/food-additives-contaminants-jecfa-database/Search.aspx>, accessed 8 November 2021).
18. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919. doi: 10.1136/bmj.i4919.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629–34. doi: 10.1136/bmj.315.7109.629.
20. Borenstein M, Hedges L, Higgins J, Rothstein H. Introduction to meta-analysis. West Sussex, United Kingdom: John Wiley & Sons, Ltd; 2009.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–88. doi: 10.1016/0197-2456(86)90046-2.
22. Blackburn GL, Kandors BS, Lavin PT, Keller SD, Whatley J. The effect of aspartame as part of a multidisciplinary weight-control program on short- and long-term control of body weight. *Am J Clin Nutr*. 1997;65:409–18. doi: 10.1093/ajcn/65.2.409.
23. Engel S, Tholstrup T, Bruun JM, Astrup A, Richelsen B, Raben A. Effect of high milk and sugar-sweetened and non-caloric soft drink intake on insulin sensitivity after 6 months in overweight and obese adults: a randomized controlled trial. *Eur J Clin Nutr*. 2018;72: 358–66. doi: 10.1038/s41430-017-0006-9.
24. Engel S, Tholstrup T, Bruun JM, Astrup A, Richelsen B, Raben A. Correction: Effect of high milk and sugar-sweetened and noncaloric soft drink intake on insulin sensitivity after 6 months in overweight and obese adults: a randomized controlled trial. *Eur J Clin Nutr*. 2020;74(1):210–13. doi: 10.1038/s41430-019-0531-9.
25. Viveros-Watty PE, López-Franco O, Zepeda RC, Aguirre G, Rodríguez-Alba JC, Gómez-Martínez MA, et al. Effects on cardiometabolic risk factors after reduction of artificially sweetened beverage consumption in overweight subjects: a randomised controlled trial. *Endocrinol Diabetes Nutr*. 2021. doi: 10.1016/j.endinu.2021.03.009.
26. Bonnet F, Tavenard A, Esvan M, Laviolle B, Viltard M, Lepicard EM, et al. Consumption of a carbonated beverage with high-intensity sweeteners has no effect on insulin sensitivity and secretion in nondiabetic adults. *J Nutr*. 2018;148:1293–9. doi: 10.1093/jn/nxy100.
27. Campos V, Despland C, Brandejsky V, Kreis R, Schneiter P, Chiolerio A, et al. Sugar- and artificially sweetened beverages and intrahepatic fat: a randomized controlled trial. *Obesity (Silver Spring)*. 2015;23:2335–9. doi: 10.1002/oby.21310.
28. Ebbeling C, Feldman H, Steltz S, Ludwig D. Differential effects of sugar-sweetened, artificially sweetened, and unsweetened beverages on taste preference but not CVD risk factors in a 12-month RCT. *Circulation*. 2019;139. doi: 10.1161/circ.139.suppl\_1.044.
29. Han Y, Kwon EY, Yu MK, Lee SJ, Kim HJ, Kim SB, et al. A preliminary study for evaluating the dose-dependent effect of D-allulose for fat mass reduction in adult humans: a randomized, double-blind, placebo-controlled trial. *Nutrients*. 2018;10. doi: 10.3390/nu10020160.



30. Higgins KA, Considine RV, Mattes RD. Aspartame consumption for 12 weeks does not affect glycemia, appetite, or body weight of healthy, lean adults in a randomized controlled trial. *J Nutr.* 2018;148:650–7. doi: 10.1093/jn/nxy021.
31. Higgins KA, Mattes RD. A randomized controlled trial contrasting the effects of 4 low-calorie sweeteners and sucrose on body weight in adults with overweight or obesity. *Am J Clin Nutr.* 2019;109:1288–301. doi: 10.1093/ajcn/nqy381.
32. Kanders BS, Lavin PT, Kowalchuk MB, Greenberg I, Blackburn GL. An evaluation of the effect of aspartame on weight loss. *Appetite.* 1988;11 Suppl 1:73–84. doi: 10.1016/S0195-6663(88)80050-3.
33. Kim EJ, Kim M, Kim JS, Cho KD, Han CK, Lee B. Effects of fructooligosaccharides intake on body weight, lipid profiles, and calcium status among Korean college students. *FASEB J.* 2011;25(Suppl 1).
34. Kuzma JN, Cromer G, Hagman DK, Breymeyer KL, Roth CL, Foster-Schubert KE, et al. No difference in ad libitum energy intake in healthy men and women consuming beverages sweetened with fructose, glucose, or high-fructose corn syrup: a randomized trial. *Am J Clin Nutr.* 2015;102:1373–80. doi: 10.3945/ajcn.115.116368.
35. Lertrit A, Srimachai S, Saetung S, Chanprasertyothin S, Chailurkit L-O, Areevut C, et al. Effects of sucralose on insulin and glucagon-like peptide-1 secretion in healthy subjects: a randomized, double-blind, placebo-controlled trial. *Nutrition.* 2018;55–56:125–30. doi: 10.1016/j.nut.2018.04.001.
36. MadjdA, Taylor MA, Delavari A, Malekzadeh R, Macdonald IA, Farshchi HR. Effects of replacing diet beverages with water on weight loss and weight maintenance: 18-month follow-up, randomized clinical trial. *Int J Obes.* 2018;42:835–40. doi: 10.1038/ijo.2017.306.
37. Markey O, Le Jeune J, Lovegrove JA. Energy compensation following consumption of sugar-reduced products: a randomized controlled trial. *Eur J Nutr.* 2016;55:2137–49. doi: 10.1007/s00394-015-1028-5.
38. McLay-Cooke R. Characteristics of obesity resistance and susceptibility. PhD thesis. Dunedin, New Zealand: University of Otago; 2016.
39. Njike VY, Faridi Z, Shuval K, Dutta S, Kay CD, West SG, et al. Effects of sugar-sweetened and sugar-free cocoa on endothelial function in overweight adults. *Int J Cardiol.* 2011;149:83–8. doi: 10.1016/j.ijcard.2009.12.010.
40. Peters JC, Beck J, Cardel M, Wyatt HR, Foster GD, Pan Z, et al. The effects of water and non-nutritive sweetened beverages on weight loss and weight maintenance: a randomized clinical trial. *Obesity (Silver Spring).* 2016;24:297–304. doi: 10.1002/oby.21327.
41. Raben A, Vasilaras T, Moller A, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr.* 2002;76:721–9.
42. Reid M, Hammersley R, Duffy M. Effects of sucrose drinks on macronutrient intake, body weight, and mood state in overweight women over 4 weeks. *Appetite.* 2010;55:130–6. doi: 10.1016/j.appet.2010.05.001.
43. Reid M, Hammersley R, Duffy M, Ballantyne C. Effects on obese women of the sugar sucrose added to the diet over 28 d: a quasi-randomised, single-blind, controlled trial. *Br J Nutr.* 2014;111:563–70. doi: 10.1017/S0007114513002687.
44. Reid M, Hammersley R, Hill AJ, Skidmore P. Long-term dietary compensation for added sugar: effects of supplementary sucrose drinks over a 4-week period. *Br J Nutr.* 2007;97:193–203. doi: 10.1017/S0007114507252705.

45. Romo-Romo A, Aguilar-Salinas CA, Brito-Cordova GX, Gomez-Diaz RA, Almeda-Valdes P. Sucralose decreases insulin sensitivity in healthy subjects: a randomized controlled trial. *Am J Clin Nutr.* 2018;108:485–91. doi: 10.1093/ajcn/nqy152.
46. Tate DF, Turner-McGrievy G, Lyons E, Stevens J, Erickson K, Polzien K, et al. Replacing caloric beverages with water or diet beverages for weight loss in adults: main results of the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. *Am J Clin Nutr.* 2012;95:555–63. doi: 10.3945/ajcn.111.026278.
47. Sanchez-Delgado M, Estrada J, Paredes-Cervantes V, Kaufer-Horwitz M, Contreras I. Changes in nutrient and calorie intake, adipose mass, triglycerides and TNF-alpha concentrations after non-caloric sweetener intake: pilot study. *Int J Vitam Nutr Res.* 2019;1–12. doi: 10.1024/0300-9831/a000611.
48. Al-Dujaili E, Twaij H, Bataineh Y, Arshad U, Amjid F. Effect of stevia consumption on blood pressure, stress hormone levels and anthropometrical parameters in healthy persons. *Am J Pharmacol Toxicol.* 2017;12:7–17. doi: 10.3844/ajtpsp.2017.7.17.
49. Kassi E, Landis G, Pavlaki A, Lambrou G, Mantzou E, Androulakis I, et al. Long-term effects of stevia rebaudiana on glucose and lipid profile, adipocytokines, markers of inflammation and oxidation status in patients with metabolic syndrome. *Endocrine Abstracts.* 2016;37. doi: 10.1210/endo-meetings.2016.CE.5.SUN-577.
50. Vázquez-Durán M, Orea-Tejeda A, Castillo-Martínez L, Cano-García Á, Téllez-Olvera L, Keirns-Davis C. A randomized control trial for reduction of caloric and non-caloric sweetened beverages in young adults: effects in weight, body composition and blood pressure. *Nutr Hosp.* 2016;33:1372–8. doi: 10.20960/nh.797.
51. Kim Y, Keogh JB, Clifton PM. Consumption of a beverage containing aspartame and acesulfame K for two weeks does not adversely influence glucose metabolism in adult males and females: a randomized crossover study. *Int J Environ Res Public Health.* 2020;17. doi: 10.3390/ijerph17239049.
52. Stamataki NS, Crooks B, Ahmed A, McLaughlin JT. Effects of the daily consumption of stevia on glucose homeostasis, body weight, and energy intake: a randomised open-label 12-week trial in healthy adults. *Nutrients.* 2020;12:3049. doi: 10.3390/nu12103049.
53. Bueno-Hernández N, Esquivel-Velázquez M, Alcántara-Suárez R, Gómez-Arauz AY, Espinosa-Flores AJ, de León-Barrera KL, et al. Chronic sucralose consumption induces elevation of serum insulin in young healthy adults: a randomized, double blind, controlled trial. *Nutr J.* 2020;19:32. doi: 10.1186/s12937-020-00549-5.
54. Sagrario Lopez-Meza M, Otero-Ojeda G, Estrada JA, Esquivel-Hernandez FJ, Contreras I. The impact of nutritive and non-nutritive sweeteners on the central nervous system: preliminary study. *Nutr Neurosci.* 2021;1–28. doi: 10.1080/1028415X.2021.1885239.
55. Ma J, McKeown NM, Hwang S-J, Hoffmann U, Jacques PF, Fox CS. Sugar-sweetened beverage consumption is associated with change of visceral adipose tissue over 6 years of follow-up. *Circulation.* 2016;133:370–7. doi: 10.1161/CIRCULATIONAHA.115.018704.
56. Parker DR, Gonzalez S, Derby CA, Gans KM, Lasater TM, Carleton RA. Dietary factors in relation to weight change among men and women from two southeastern New England communities. *Int J Obes Relat Metab Disord.* 1997;21:103–9. doi: 10.1038/sj.ijo.0800373.
57. Smith JD, Hou T, Hu FB, Rimm EB, Spiegelman D, Willett WC, et al. A comparison of different methods for evaluating diet, physical activity, and long-term weight gain in 3 prospective cohort studies. *J Nutr.* 2015;145:2527–34. doi: 10.3945/jn.115.214171.

58. Stern D, Middaugh N, Rice MS, Laden F, Lopez-Ridaura R, Rosner B, et al. Changes in sugar-sweetened soda consumption, weight, and waist circumference: 2-year cohort of Mexican women. *Am J Public Health*. 2017;107:1801–8. doi: 10.2105/AJPH.2017.304008.
59. Tucker LA, Tucker JM, Bailey BW, LeCheminant JD. A 4-year prospective study of soft drink consumption and weight gain: the role of calorie intake and physical activity. *Am J Health Promot*. 2015;29:262–5. doi: 10.4278/ajhp.130619-ARB-315.
60. Chia CW, Shardell M, Tanaka T, Liu DD, Gravenstein KS, Simonsick EM, et al. Chronic low-calorie sweetener use and risk of abdominal obesity among older adults: a cohort study. *PLoS One*. 2016;11:e0167241. doi: 10.1371/journal.pone.0167241.
61. Duffey KJ, Steffen LM, Van Horn L, Jacobs DR, Popkin BM. Dietary patterns matter: diet beverages and cardiometabolic risks in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) study. *Am J Clin Nutr*. 2012;95:909–15. doi: 10.3945/ajcn.111.026682.
62. Ferreira-Pego C, Babio N, Bes-Rastrollo M, Corella D, Estruch R, Ros E, et al. Frequent consumption of sugar- and artificially sweetened beverages and natural and bottled fruit juices is associated with an increased risk of metabolic syndrome in a Mediterranean population at high cardiovascular disease risk. *J Nutr*. 2016;146:1528–36. doi: 10.3945/jn.116.230367.
63. Fowler SP, Williams K, Resendez RG, Hunt KJ, Hazuda HP, Stern MP. Fueling the obesity epidemic? Artificially sweetened beverage use and long-term weight gain. *Obesity (Silver Spring)*. 2008;16:1894–900. doi: 10.1038/oby.2008.284.
64. Fowler SP, Williams K, Hazuda HP. Diet soda intake is associated with long-term increases in waist circumference in a biethnic cohort of older adults: the San Antonio Longitudinal Study of Aging. *J Am Geriatr Soc*. 2015;63:708–15. doi: 10.1111/jgs.13376.
65. Garduno-Alanis A, Malyutina S, Pajak A, Stepaniak U, Kubinova R, Denisova D, et al. Association between soft drink, fruit juice consumption and obesity in eastern Europe: cross-sectional and longitudinal analysis of the HAPIEE study. *Journal Hum Nutr Diet*. 2020;33:66–77. doi: 10.1111/jhn.12696.
66. Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs DR. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*. 2009;32:688–94. doi: 10.2337/dc08-1799.
67. Stellman SD, Garfinkel L. Artificial sweetener use and one-year weight change among women. *Prev Med*. 1986;15:195–202. doi: 10.1016/0091-7435(86)90089-7.
68. Acero D, Zoellner JM, Davy BM, Hedrick VE. Changes in non-nutritive sweetener consumption patterns in response to a sugar-sweetened beverage reduction intervention. *Nutrients*. 2020;12. doi: 10.3390/nu12113428.
69. Anderson JJ, Gray SR, Welsh P, Mackay DF, Celis-Morales CA, Lyall DM, et al. The associations of sugar-sweetened, artificially sweetened and naturally sweet juices with all-cause mortality in 198,285 UK Biobank participants: a prospective cohort study. *BMC Med*. 2020;18:97. doi: 10.1186/s12916-020-01554-5.
70. Baird IM, Shephard NW, Merritt RJ, Hildick-Smith G. Repeated dose study of sucralose tolerance in human subjects. *Food Chem Toxicol*. 2000;38 Suppl 2:S123–9. doi: 10.1016/S0278-6915(00)00035-1.
71. Ballantyne CJ, Hammersley R, Reid M. Effects of sucrose added blind to the diet over eight weeks on body mass and mood in men. *Appetite*. 2011;57:S3. doi: 10.1016/j.appet.2011.05.118.

72. Crutchley PW, Te Morenga L. Effect of sugar-sweetened soft drinks on serum uric acid and associated metabolic risk factors. *FASEB J.* 2013;27:112.8. doi: 10.1096/fasebj.27.1\_supplement.112.8.
73. Angelopoulos TJ, Lowndes J, Rippe JM. No change in indices of glucose regulation or insulin resistance after 6 months of daily consumption of sugar sweetened or diet beverages. *Endocr Rev.* 2016;37. doi: 10.1210/endo-meetings.2016.DGM.8.SUN-688.
74. Angelopoulos T, Lowndes J, Rippe J. Lack of impact of SSB on indices of carbohydrate metabolism. *Ann Nutr Metab.* 2015;67:409–10. doi: 10.1159/000440895.
75. Serrano J, Smith KR, Crouch AL, Sharma V, Yi F, Vargova V, et al. High-dose saccharin supplementation does not induce gut microbiota changes or glucose intolerance in healthy humans and mice. *Microbiome.* 2021;9:11. doi: 10.1186/s40168-020-00976-w.
76. Knopp RH, Brandt K, Arky RA. Effects of aspartame in young persons during weight reduction. *J Toxicol Environ Health.* 1976;2:417–28. doi: 10.1080/15287397609529443.
77. Zheng M, Rangan A, Huang R-C, Beilin LJ, Mori TA, Oddy WH, et al. Modelling the effects of beverage substitution during adolescence on later obesity outcomes in early adulthood: results from the Raine study. *Nutrients.* 2019;11. doi: 10.3390/nu11122928.
78. Gearon E, Peeters A, Hodge A, Backholer K. The role of dietary and physical activity behaviours in educational differences in weight gain among Australian adults: the Melbourne Collaborative Cohort Study. *Obes Res Clin Pract.* 2014;8:35–6. doi: 10.1016/j.orcp.2014.10.065.
79. Bes-Rastrollo M, Sánchez-Villegas A, Gómez-Gracia E, Martínez JA, Pajares RM, Martínez-González MA. Predictors of weight gain in a Mediterranean cohort: the Seguimiento Universidad de Navarra Study 1. *Am J Clin Nutr.* 2006;83:362–70; quiz 94-5. doi: 10.1093/ajcn/83.2.362.
80. Park W, Yiannakou I, Hoffmann U, Ma J. Sugar-sweetened beverage, diet soda, and nonalcoholic fatty liver disease over 6 years of follow-up: the Framingham heart study. *Hepatology.* 2020;72:131A-1159A. doi: 10.1002/hep.31579.
81. Naismith DJ, Rhodes C. Adjustment in energy-intake following the covert removal of sugar from the diet. *J Hum Nutr Diet.* 1995;8:167–75. doi: 10.1111/j.1365-277X.1995.tb00309.x.
82. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. *Am J Clin Nutr.* 1990;51:963–9. doi: 10.1093/ajcn/51.6.963.
83. Hieronimus B, Medici V, Bremer AA, Lee V, Nunez MV, Sigala DM, et al. Synergistic effects of fructose and glucose on lipoprotein risk factors for cardiovascular disease in young adults. *Metabolism.* 2020;112:154356. doi: 10.1016/j.metabol.2020.154356.
84. Drouin-Chartier J-P, Zheng Y, Li Y, Malik V, Pan A, Bhupathiraju SN, et al. Changes in consumption of sugary beverages and artificially sweetened beverages and subsequent risk of type 2 diabetes: results from three large prospective US cohorts of women and men. *Diabetes Care.* 2019;42:2181–9. doi: 10.2337/dc19-0734.
85. Fagherazzi G, Gusto G, Affret A, Mancini FR, Dow C, Balkau B, et al. Chronic consumption of artificial sweetener in packets or tablets and type 2 diabetes risk: evidence from the E3N-European Prospective Investigation into Cancer and Nutrition study. *Ann Nutr Metab.* 2017;70:51–8. doi: 10.1159/000458769.

86. Fagherazzi G, Vilier A, Saes Sartorelli D, Lajous M, Balkau B, Clavel-Chapelon F. Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale–European Prospective Investigation into Cancer and Nutrition cohort. *Am J Clin Nutr.* 2013;97:517–23. doi: 10.3945/ajcn.112.050997.
87. Gardener H, Moon YP, Rundek T, Elkind MSV, Sacco RL. Diet soda and sugar-sweetened soda consumption in relation to incident diabetes in the Northern Manhattan Study. *Curr Dev Nutr.* 2018;2:nzy008. doi: 10.1093/cdn/nzy008.
88. Hirahatake KM, Jacobs DR, Shikany JM, Jiang L, Wong ND, Steffen LM, et al. Cumulative intake of artificially sweetened and sugar-sweetened beverages and risk of incident type 2 diabetes in young adults: the Coronary Artery Risk Development In Young Adults (CARDIA) study. *Am J Clin Nutr.* 2019;110:733–41. doi: 10.1093/ajcn/nqz154.
89. Huang M, Quddus A, Stinson L, Shikany JM, Howard BV, Kutob RM, et al. Artificially sweetened beverages, sugar-sweetened beverages, plain water, and incident diabetes mellitus in postmenopausal women: the prospective Women's Health Initiative observational study. *Am J Clin Nutr.* 2017;106:614–22. doi: 10.3945/ajcn.116.145391.
90. Jensen PN, Howard BV, Best LG, O'Leary M, Devereux RB, Cole SA, et al. Associations of diet soda and non-caloric artificial sweetener use with markers of glucose and insulin homeostasis and incident diabetes: the Strong Heart Family Study. *Eur J Clin Nutr.* 2020;74:322–7. doi: 10.1038/s41430-019-0461-6.
91. O'Connor L, Imamura F, Lentjes MAH, Khaw K-T, Wareham NJ, Forouhi NG. Prospective associations and population impact of sweet beverage intake and type 2 diabetes, and effects of substitutions with alternative beverages. *Diabetologia.* 2015;58:1474–83. doi: 10.1007/s00125-015-3572-1.
92. Palmer JR. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch Inter Med.* 2008;168:1487. doi: 10.1001/archinte.168.14.1487.
93. Sakurai M, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, et al. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. *Eur J Nutr.* 2014;53:251–8. doi: 10.1007/s00394-013-0523-9.
94. InterAct Consortium, Romaguera D, Norat T, Wark PA, Vergnaud AC, Schulze MB, et al. Consumption of sweet beverages and type 2 diabetes incidence in European adults: results from EPIC-InterAct. *Diabetologia.* 2013;56:1520–30. doi: 10.1007/s00125-013-2899-8.
95. Lee B, Kim E, Kim M, Cho K, Han C, Lee B. Effect of fructooligosaccharides on improvement of blood glucose, calcium status and habitual bowel movement among college students in Korea. *FASEB J.* 2012;26.
96. Raben A, Moller B, Flint A, Vasilaras T, Moller A, Holst J, et al. Increased postprandial glycaemia, insulinemia, and lipidemia after 10 weeks' sucrose-rich diet compared to an artificially sweetened diet: a randomised controlled trial. *Food Nutr Res.* 2011;55.
97. Warrington S, Lee C, Otabe A, Narita T, Polnjak O, Pirags V, et al. Acute and multiple-dose studies to determine the safety, tolerability, and pharmacokinetic profile of advantame in healthy volunteers. *Food Chem Toxicol.* 2011;49 Suppl 1:577–83. doi: 10.1016/j.fct.2011.06.043.
98. Chia CW, Shardell M, Gravenstein KS, Carlson OD, Simonsick EM, Ferrucci L, et al. Regular low-calorie sweetener consumption is associated with increased secretion of glucose-dependent insulinotropic polypeptide. *Diabetes Obes Metab.* 2018;20:2282–5. doi: 10.1111/dom.13328.

99. Kreuch D, Ivey K, Mobegi FM, Leong L, Isaacs NJ, Pezos N, et al. Mechanisms linking low-calorie sweeteners to impaired glycaemic control. *Neurogastroenterol Motil.* 2020;32. doi: 10.1111/nmo.13816.
100. Dalenberg JR, Patel BP, Denis R, Veldhuizen MG, Nakamura Y, Vinke PC, et al. Short-term consumption of sucralose with, but not without, carbohydrate impairs neural and metabolic sensitivity to sugar in humans. *Cell Metab.* 2020;31:493–502.e7. doi: 10.1016/j.cmet.2020.01.014.
101. Serrano J, Smith KR, Crouch AL, Sharma V, Yi F, Vargova V, et al. High-dose saccharin supplementation does not induce gut microbiota changes or glucose intolerance in healthy humans and mice. *Microbiome.* 2021;9. doi: 10.1186/s40168-020-00976-w.
102. Malik VS, Li Y, Pan A, De Koning L, Schernhammer E, Willett WC, et al. Long-term consumption of sugar-sweetened and artificially sweetened beverages and risk of mortality in US adults. *Circulation.* 2019;139:2113–25. doi: 10.1161/CIRCULATIONAHA.118.037401.
103. Mossavar-Rahmani Y, Kamensky V, Manson JE, Silver B, Rapp SR, Haring B, et al. Artificially sweetened beverages and stroke, coronary heart disease, and all-cause mortality in the Women’s Health Initiative. *Stroke.* 2019;50:555–62. doi: 10.1161/STROKEAHA.118.023100.
104. Mullee A, Romaguera D, Pearson-Stuttard J, Viallon V, Stepien M, Freisling H, et al. Association between soft drink consumption and mortality in 10 European countries. *JAMA Intern Med.* 2019. doi: 10.1001/jamainternmed.2019.2478.
105. Paganini-Hill A, Kawas CH, Corrada MM. Non-alcoholic beverage and caffeine consumption and mortality: the Leisure World Cohort Study. *Prev Med.* 2007;44:305–10. doi: 10.1016/j.ypmed.2006.12.011.
106. Farvid MS, Spence ND, Rosner BA, Chen WY, Eliassen AH, Willett WC, et al. Consumption of sugar-sweetened and artificially sweetened beverages and breast cancer survival. *Cancer.* 2021;127:2762–73. doi: 10.1002/cncr.33461.
107. Zhang YB, Chen JX, Jiang YW, Xia PF, Pan A. Association of sugar-sweetened beverage and artificially sweetened beverage intakes with mortality: an analysis of US National Health and Nutrition Examination Survey. *Eur J Nutr.* 2021;60:1945–55. doi: 10.1007/s00394-020-02387-x.
108. Gardener H, Rundek T, Markert M, Wright CB, Elkind MSV, Sacco RL. Diet soft drink consumption is associated with an increased risk of vascular events in the Northern Manhattan Study. *J Gen Intern Med.* 2012;27:1120–6. doi: 10.1007/s11606-011-1968-2.
109. Vyas A, Rubenstein L, Robinson J, Seguin RA, Vitolins MZ, Kazlauskaitė R, et al. Diet drink consumption and the risk of cardiovascular events: a report from the Women’s Health Initiative. *J Gen Intern Med.* 2015;30:462–8. doi: 10.1007/s11606-014-3098-0.
110. Chazelas E, Debras C, Srour B, Fezeu LK, Julia C, Hercberg S, et al. Sugary drinks, artificially-sweetened beverages, and cardiovascular disease in the NutriNet-Santé cohort. *J Am Coll Cardiol.* 2020;76:2175–7. doi: 10.1016/j.jacc.2020.08.075.
111. de Koning L, Malik VS, Kellogg MD, Rimm EB, Willett WC, Hu FB. Sweetened beverage consumption, incident coronary heart disease, and biomarkers of risk in men. *Circulation.* 2012;125:1735–41, S1. doi: 10.1161/CIRCULATIONAHA.111.067017.
112. Fung TT, Malik V, Rexrode KM, Manson JE, Willett WC, Hu FB. Sweetened beverage consumption and risk of coronary heart disease in women. *Am J Clin Nutr.* 2009;89:1037–42. doi: 10.3945/ajcn.2008.27140.

113. Bernstein AM, de Koning L, Flint AJ, Rexrode KM, Willett WC. Soda consumption and the risk of stroke in men and women. *Am J Clin Nutr.* 2012;95:1190–9. doi: 10.3945/ajcn.111.030205.
114. Pase MP, Himali JJ, Beiser AS, Aparicio HJ, Satizabal CL, Vasani RS, et al. Sugar- and artificially sweetened beverages and the risks of incident stroke and dementia: a prospective cohort study. *Stroke.* 2017;48:1139–46. doi: 10.1161/STROKEAHA.116.016027.
115. Cohen L, Curhan G, Forman J. Association of sweetened beverage intake with incident hypertension. *J Gen Intern Med.* 2012;27:1127–34. doi: 10.1007/s11606-012-2069-6.
116. Haslam DE, Peloso GM, Herman MA, Dupuis J, Lichtenstein AH, Smith CE, et al. Beverage consumption and longitudinal changes in lipoprotein concentrations and incident dyslipidemia in US adults: the Framingham Heart Study. *J Am Heart Assoc.* 2020;9:e014083. doi: 10.1161/JAHA.119.014083.
117. Wang D, Karvonen-Gutierrez CA, Jackson EA, Elliott MR, Appelhans BM, Barinas-Mitchell E, et al. Prospective associations between beverage intake during the midlife and subclinical carotid atherosclerosis: the Study of Women’s Health Across the Nation. *PloS One.* 2019;14:e0219301. doi: 10.1371/journal.pone.0219301.
118. Keller A, O’Reilly EJ, Malik V, Buring JE, Andersen I, Steffen L, et al. Substitution of sugar-sweetened beverages for other beverages and the risk of developing coronary heart disease: results from the Harvard Pooling Project of Diet and Coronary Disease. *Prev Med.* 2020;131:105970. doi: 10.1016/j.ypmed.2019.105970.
119. Akdaş A, Kirkali Z, Bilir N. Epidemiological case–control study on the etiology of bladder cancer in Turkey. *Eur Urol.* 1990;17:23–6. doi: 10.1159/000463993.
120. Andreatta MM, Muñoz SE, Lantieri MJ, Eynard AR, Navarro A. Artificial sweetener consumption and urinary tract tumors in Cordoba, Argentina. *Prev Med.* 2008;47:136–9. doi: 10.1016/j.ypmed.2008.03.015.
121. Asal NR, Risser DR, Kadmani S, Geyer JR, Lee ET, Cherg N. Risk factors in renal cell carcinoma: I. Methodology, demographics, tobacco, beverage use, and obesity. *Cancer Detect Prev.* 1988;11:359–77.
122. Bosetti C, Gallus S, Talamini R, Montella M, Franceschi S, Negri E, et al. Artificial sweeteners and the risk of gastric, pancreatic, and endometrial cancers in Italy. *Cancer Epidemiol Biomarkers Prev.* 2009;18:2235–8. doi: 10.1158/1055-9965.EPI-09-0365.
123. Bravo MP, Del Rey-Calero J, Conde M. Risk factors of bladder cancer in Spain. *Neoplasma.* 1987;34:633–7.
124. Bravo P, Del Rey Calero J, Sánchez J, Conde M. [Artificial sweeteners as a risk factor for cancer of the bladder]. *Rev Sanid Hig Publica (Madr).* 1987;61:301–7 (in Spanish).
125. Cabaniols C, Giorgi R, Chinot O, Ferahta N, Spinelli V, Alla P, et al. Links between private habits, psychological stress and brain cancer: a case–control pilot study in France. *J Neurooncol.* 2011;103:307–16. doi: 10.1007/s11060-010-0388-1.
126. Cartwright RA, Adib R, Glashan R, Gray BK. The epidemiology of bladder cancer in West Yorkshire: a preliminary report on non-occupational aetiologies. *Carcinogenesis.* 1981;343–7. doi: 10.1093/carcin/2.4.343.
127. Chan JM, Wang F, Holly EA. Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case–control study. *Cancer Causes Control.* 2009;20:835–46. doi: 10.1007/s10552-009-9323-1.
128. Connolly JG, Rider WD, Rosenbaum L, Chapman JA. Relation between the use of artificial sweeteners and bladder cancer. *Can Med Assoc J.* 1978;119:408.

129. Ewertz M, Gill C. Dietary factors and breast-cancer risk in Denmark. *Int J Cancer*. 1990;46:779–84. doi: 10.1002/ijc.2910460505.
130. Gallus S, Scotti L, Negri E, Talamini R, Franceschi S, Montella M, et al. Artificial sweeteners and cancer risk in a network of case–control studies. *Ann Oncol*. 2007;18:40–4. doi: 10.1093/annonc/mdl346.
131. Gold EB, Gordis L, Diener MD, Seltser R, Boitnott JK, Bynum TE, et al. Diet and other risk factors for cancer of the pancreas. *Cancer*. 1985;55:460–7. doi: 10.1002/1097-0142(19850115)55:2<460::aid-cncr2820550229>3.0.co;2-v.
132. Goodman MT, Morgenstern H, Wynder EL. A case–control study of factors affecting the development of renal cell cancer. *Am J Epidemiol*. 1986;124:926–41. doi: 10.1093/oxfordjournals.aje.a114482.
133. Hardell L, Mild KH, Pålsson A, Hallquist A. Ionizing radiation, cellular telephones and the risk for brain tumours. *Eur J Cancer Prev*. 2001;10:523–9. doi: 10.1097/00008469-200112000-00007.
134. Hoover RN, Strasser PH. Artificial sweeteners and human bladder cancer: preliminary results. *Lancet*. 1980;1:837–40. doi: 10.1016/s0140-6736(80)91350-1.
135. Howe GR, Burch JD, Miller AB, Cook GM, Esteve J, Morrison B, et al. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *J Natl Cancer Inst*. 1980;64:701–13.
136. Howe GR, Burch JD, Miller AB, Morrison B, Gordon P, Weldon L, et al. Artificial sweeteners and human bladder cancer. *Lancet*. 1977;2:578–81. doi: 10.1016/s0140-6736(77)91428-3.
137. Kantor AF, Hartge P, Hoover RN, Fraumeni JF. Familial and environmental interactions in bladder cancer risk. *Int J Cancer*. 1985;35:703–6. doi: 10.1002/ijc.2910350602.
138. Kessler II. Non-nutritive sweeteners and human bladder cancer: preliminary findings. *J Urol*. 1976;115:143–6. doi: 10.1016/s0022-5347(17)59104-1.
139. Kessler II, Clark JP. Saccharin, cyclamate, and human bladder cancer: no evidence of an association. *JAMA*. 1978;240:349–55.
140. Kobeissi LH, Yassine IA, Jabbour ME, Moussa MA, Dhaini HR. Urinary bladder cancer risk factors: a Lebanese case–control study. *Asian Pac J Cancer Prev*. 2013;14:3205–11. doi: 10.7314/apjcp.2013.14.5.3205.
141. Mahfouz EM, Sadek RR, Abdel-Latif WM, Mosallem FA-H, Hassan EE. The role of dietary and lifestyle factors in the development of colorectal cancer: case control study in Minia, Egypt. *Cent Eur J Public Health*. 2014;22:215–22. doi: 10.21101/cejph.a3919.
142. Mettlin C. Milk drinking, other beverage habits, and lung cancer risk. *Int J Cancer*. 1989;43:608–12.
143. Møller-Jensen O, Knudsen JB, Sørensen BL, Clemmesen J. Artificial sweeteners and absence of bladder cancer risk in Copenhagen. *Int J Cancer*. 1983;32:577–82. doi: 10.1002/ijc.2910320510.
144. Momas I, Daurès JP, Festy B, Bontoux J, Grémy F. Relative importance of risk factors in bladder carcinogenesis: some new results about Mediterranean habits. *Cancer Causes Control*. 1994;5:326–32. doi: 10.1007/bf01804983.
145. Mommsen S, Aagaard J, Sell A. A case–control study of female bladder cancer. *Eur J Cancer Clin Oncol*. 1983;19:725–9. doi: 10.1016/0277-5379(83)90005-6.
146. Morgan RW, Jain MG. Bladder cancer: smoking, beverages and artificial sweeteners. *Can Med Assoc J*. 1974;111:1067–70.



147. Morrison AS. Use of artificial sweeteners by cancer patients. *J Natl Cancer Inst.* 1979;62:1397–9.
148. Morrison AS, Buring JE. Artificial sweeteners and cancer of the lower urinary tract. *New Engl J Med.* 1980;302:537–41. doi: 10.1056/NEJM198003063021001.
149. Morrison AS, Verhoek WG, Leck I, Aoki K, Ohno Y, Obata K. Artificial sweeteners and bladder cancer in Manchester, UK, and Nagoya, Japan. *Br J Cancer.* 1982;45:332–6. doi: 10.1038/bjc.1982.59.
150. Najem GR, Louria DB, Seebode JJ, Thind IS, Prusakowski JM, Ambrose RB, et al. Life time occupation, smoking, caffeine, saccharine, hair dyes and bladder carcinogenesis. *Int J Epidemiol.* 1982;11:212–17. doi: 10.1093/ije/11.3.212.
151. Nomura AM, Kolonel LN, Hankin JH, Yoshizawa CN. Dietary factors in cancer of the lower urinary tract. *Int J Cancer.* 1991;48:199–205. doi: 10.1002/ijc.2910480208.
152. Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, et al. Diet and pancreatic cancer: a case–control study. *Am J Epidemiol.* 1986;124:894–902. doi: 10.1093/oxfordjournals.aje.a114479.
153. Ohno Y, Aoki K, Obata K, Morrison AS. Case–control study of urinary bladder cancer in metropolitan Nagoya. *Natl Cancer Inst Monogr.* 1985;69:229–34.
154. Radosavljević V, Jankovic S, Marinkovic J, Djokić M. Some habits as risk factors for bladder cancer. *J BUON.* 2001;6:435–9.
155. Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR. Dietary factors and the incidence of cancer of the urinary bladder. *Am J Epidemiol.* 1988;127:1179–91. doi: 10.1093/oxfordjournals.aje.a114911.
156. Silverman DT, Hoover RN, Swanson GM. Artificial sweeteners and lower urinary tract cancer: hospital vs. population controls. *Am J Epidemiol.* 1983;117:326–34. doi: 10.1093/oxfordjournals.aje.a113545.
157. Simon D, Yen S, Cole P. Coffee drinking and cancer of the lower urinary tract. *J Natl Cancer Inst.* 1975;54:587–91.
158. Sullivan JW. Epidemiologic survey of bladder cancer in greater New Orleans. *J Urol.* 1982;128:281–3. doi: 10.1016/s0022-5347(17)52886-4.
159. Wynder EL, Goldsmith R. The epidemiology of bladder cancer: a second look. *Cancer.* 1977;40:1246–68. doi: 10.1002/1097-0142(197709)40:3<1246::aid-cnrcr2820400340>3.0.co;2-5.
160. Wynder EL, Stellman SD. Artificial sweetener use and bladder cancer: a case–control study. *Science.* 1980;207:1214–16. doi: 10.1126/science.7355283.
161. Yu Y, Hu J, Wang PP, Zou Y, Qi Y, Zhao P, et al. Risk factors for bladder cancer: a case–control study in northeast China. *Eur J Cancer Prev.* 1997;6:363–9. doi: 10.1097/00008469-199708000-00008.
162. Zou YH. [Research into risk factors of bladder cancer in Heilongjiang]. *Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi.* 1990;11:217–20 (in Chinese).
163. Bao Y, Stolzenberg-Solomon R, Jiao L, Silverman DT, Subar AF, Park Y, et al. Added sugar and sugar-sweetened foods and beverages and the risk of pancreatic cancer in the National Institutes of Health–AARP Diet and Health Study. *Am J Clin Nutr.* 2008;88:431–40. doi: 10.1093/ajcn/88.2.431.
164. Chazelas E, Srouf B, Desmetz E, Kesse-Guyot E, Julia C, Deschamps V, et al. Sugary drink consumption and risk of cancer: results from NutriNet-Sante prospective cohort. *BMJ.* 2019;366:l2408. doi: 10.1136/bmj.l2408.

165. Hodge AM, Bassett JK, Milne RL, English DR, Giles GG. Consumption of sugar-sweetened and artificially sweetened soft drinks and risk of obesity-related cancers. *Public Health Nutr.* 2018;21:1618–26. doi: 10.1017/S1368980017002555.
166. Lim U, Subar AF, Mouw T, Hartge P, Morton LM, Stolzenberg-Solomon R, et al. Consumption of aspartame-containing beverages and incidence of hematopoietic and brain malignancies. *Cancer Epidemiol Biomarkers Prev.* 2006;15:1654–9. doi: 10.1158/1055-9965.EPI-06-0203.
167. McCullough ML, Teras LR, Shah R, Diver WR, Gaudet MM, Gapstur SM. Artificially and sugar-sweetened carbonated beverage consumption is not associated with risk of lymphoid neoplasms in older men and women. *J Nutr.* 2014;144:2041–9. doi: 10.3945/jn.114.197475.
168. Schernhammer ES, Bertrand KA, Birmann BM, Sampson L, Willett WC, Feskanich D. Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. *Am J Clin Nutr.* 2012;96:1419–28. doi: 10.3945/ajcn.111.030833.
169. Bassett JK, Milne RL, English DR, Giles GG, Hodge AM. Consumption of sugar-sweetened and artificially sweetened soft drinks and risk of cancers not related to obesity. *Int J Cancer.* 2020;146:3329–34. doi: 10.1002/ijc.32772.
170. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. *Gut.* 2021. doi: 10.1136/gutjnl-2020-323450.
171. Romanos-Nanclares A, Collins LC, Hu FB, Willett WC, Rosner BA, Toledo E, et al. Sugar-sweetened beverages, artificially sweetened beverages, and breast cancer risk: results from 2 prospective US cohorts. *J Nutr.* 2021;151(9):2768–79. doi: 10.1093/jn/nxab172.
172. Bassett JK, Milne RL, English DR, Giles GG, Hodge AM. Consumption of sugar-sweetened and artificially sweetened soft drinks and risk of cancers not related to obesity. *Int J Cancer.* 2019;146(12):3329–34. doi: 10.1002/ijc.32772.
173. Lin J, Curhan GC. Associations of sugar and artificially sweetened soda with albuminuria and kidney function decline in women. *Clin J Am Soc Nephrol.* 2011;6:160–6. doi: 10.2215/CJN.03260410.
174. Rebholz CM, Grams ME, Steffen LM, Crews DC, Anderson CAM, Bazzano LA, et al. Diet soda consumption and risk of incident end stage renal disease. *Clin J Am Soc Nephrol.* 2017;12:79–86. doi: 10.2215/CJN.03390316.
175. Fantino M, Fantino A, Matray M, Mistretta F. Beverages containing low energy sweeteners do not differ from water in their effects on appetite, energy intake and food choices in healthy, non-obese French adults. *Appetite.* 2018;125:557–65. doi: 10.1016/j.appet.2018.03.007.
176. Piernas C, Tate DF, Wang X, Popkin BM. Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. *Am J Clin Nutr.* 2013;97:604–11. doi: 10.3945/ajcn.112.048405.
177. Appleton KM, Blundell JE. Habitual high and low consumers of artificially-sweetened beverages: effects of sweet taste and energy on short-term appetite. *Physiol Behav.* 2007;92:479–86. doi: 10.1016/j.physbeh.2007.04.027.
178. Pergrin Marriott B, Hunt KJ, Malek AM, Greenberg D, St. Peter J. Eating episodes and low calorie sweetener intake in the US adult population: NHANES 2007–2012. *FASEB J.* 2016.

179. Appleton KM, Conner MT. Body weight, body-weight concerns and eating styles in habitual heavy users and non-users of artificially sweetened beverages. *Appetite*. 2001;37:225–30. doi: 10.1006/appe.2001.0435.
180. Ebbeling CB, Feldman HA, Steltz SK, Quinn NL, Robinson LM, Ludwig DS. Effects of sugar-sweetened, artificially sweetened, and unsweetened beverages on cardiometabolic risk factors, body composition, and sweet taste preference: a randomized controlled trial. *J Am Heart Assoc*. 2020;9:e015668. doi: 10.1161/jaha.119.015668.
181. Judah G, Mullan B, Yee M, Johansson L, Allom V, Liddelow C. A habit-based randomised controlled trial to reduce sugar-sweetened beverage consumption: the impact of the substituted beverage on behaviour and habit strength. *Int J Behav Med*. 2020;27:623–35. doi: 10.1007/s12529-020-09906-4.
182. Mahar A, Duizer LM. The effect of frequency of consumption of artificial sweeteners on sweetness liking by women. *J Food Sci*. 2007;72:S714–8. doi: 10.1111/j.1750-3841.2007.00573.x.
183. Maersk M, Belza A, Stødkilde-Jørgensen H, Ringgaard S, Chabanova E, Thomsen H, et al. Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. *Am J Clin Nutr*. 2012;95:283–9. doi: 10.3945/ajcn.111.022533.
184. Spiers PA, Sabounjian L, Reiner A, Myers DK, Wurtman J, Schomer DL. Aspartame: neuropsychologic and neurophysiologic evaluation of acute and chronic effects. *Am J Clin Nutr*. 1998;68:531–7. doi: 10.1093/ajcn/68.3.531.
185. Guo X, Park Y, Freedman ND, Sinha R, Hollenbeck AR, Blair A, et al. Sweetened beverages, coffee, and tea and depression risk among older US adults. *PloS One*. 2014;9:e94715. doi: 10.1371/journal.pone.0094715.
186. Lana A, Lopez-Garcia E, Rodríguez-Artalejo F. Consumption of soft drinks and health-related quality of life in the adult population. *Eur J Clin Nutr*. 2015;69:1226–32. doi: 10.1038/ejcn.2015.103.
187. Ángeles Pérez-Ara M, Gili M, Visser M, Penninx B, Brouwer IA, Watkins E, et al. Associations of non-alcoholic beverages with major depressive disorder history and depressive symptoms clusters in a sample of overweight adults. *Nutrients*. 2020;12. doi: 10.3390/nu12103202.
188. Munoz-Garcia MI, Martinez-Gonzalez MA, Martin-Moreno JM, Razquin C, Cervantes S, Guillen-Grima F, et al. Sugar-sweetened and artificially-sweetened beverages and changes in cognitive function in the SUN project. *Nutr Neurosci*. 2019:1–9. doi: 10.1080/1028415X.2019.1580919.
189. de Ruyter JC, Olthof MR, Seidell JC, Katan MB. A trial of sugar-free or sugar-sweetened beverages and body weight in children. *New Engl J Med*. 2012;367:1397–406. doi: 10.1056/NEJMoa1203034.
190. Taljaard C, Covic NM, van Graan AE, Kruger HS, Smuts CM, Baumgartner J, et al. Effects of a multi-micronutrient-fortified beverage, with and without sugar, on growth and cognition in South African schoolchildren: a randomised, double-blind, controlled intervention. *Br J Nutr*. 2013;110:2271–84. doi: 10.1017/S000711451300189X.
191. Berkey CS, Rockett HRH, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. *Obes Res*. 2004;12:778–88. doi: 10.1038/oby.2004.94.
192. Blum JW, Jacobsen DJ, Donnelly JE. Beverage consumption patterns in elementary school aged children across a two-year period. *J Am Coll Nutr*. 2005;24:93–8. doi: 10.1080/07315724.2005.10719449.

193. Davis JN, Asigbee FM, Markowitz AK, Landry MJ, Vandyousefi S, Khazaei E, et al. Consumption of artificial sweetened beverages associated with adiposity and increasing HbA1c in Hispanic youth. *Clin Obes*. 2018;8:236–43. doi: 10.1111/cob.12260.
194. Field AE, Sonneville KR, Falbe J, Flint A, Haines J, Rosner B, et al. Association of sports drinks with weight gain among adolescents and young adults: sports drinks intake predicts weight gain. *Obesity*. 2014;22:2238–43. doi: 10.1002/oby.20845.
195. Haines J, Neumark-Sztainer D, Wall M, Story M. Personal, behavioral, and environmental risk and protective factors for adolescent overweight. *Obesity*. 2012;15:2748–60. doi: 10.1038/oby.2007.327.
196. Laska MN, Murray DM, Lytle LA, Harnack LJ. Longitudinal associations between key dietary behaviors and weight gain over time: transitions through the adolescent years. *Obesity (Silver Spring)*. 2012;20:118–25. doi: 10.1038/oby.2011.179.
197. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001;357:505–8. doi: 10.1016/S0140-6736(00)04041-1.
198. Macintyre AK, Marryat L, Chambers S. Exposure to liquid sweetness in early childhood: artificially-sweetened and sugar-sweetened beverage consumption at 4–5 years and risk of overweight and obesity at 7–8 years. *Pediatr Obes*. 2018;13:755–65. doi: 10.1111/ijpo.12284.
199. Newby PK, Peterson KE, Berkey CS, Leppert J, Willett WC, Colditz GA. Beverage consumption is not associated with changes in weight and body mass index among low-income preschool children in North Dakota. *J Am Diet Assoc*. 2004;104:1086–94. doi: 10.1016/j.jada.2004.04.020.
200. Striegel-Moore RH, Thompson D, Affenito SG, Franko DL, Obarzanek E, Barton BA, et al. Correlates of beverage intake in adolescent girls: the National Heart, Lung, and Blood Institute Growth and Health Study. *J Pediatr*. 2006;148:183–7. doi: 10.1016/j.jpeds.2005.11.025.
201. Vanselow MS, Pereira MA, Neumark-Sztainer D, Ratz SK. Adolescent beverage habits and changes in weight over time: findings from Project EAT. *Am J Clin Nutr*. 2009;90:1489–95. doi: 10.3945/ajcn.2009.27573.
202. Zheng M, Allman-Farinelli M, Heitmann BL, Toelle B, Marks G, Cowell C, et al. Liquid versus solid energy intake in relation to body composition among Australian children. *J Hum Nutr Diet*. 2015;28 Suppl 2:70–9. doi: 10.1111/jhn.12223.
203. Zheng M, Rangan A, Allman-Farinelli M, Rohde J, Olsen N, Heitmann B. Replacing sugary drinks with milk is inversely associated with weight gain among young obesity-predisposed children. *Br J Nutr*. 2015;114:1448–55. doi: 10.1017/S0007114515002974.
204. Kral TVE, Stunkard AJ, Berkowitz RI, Stallings VA, Moore RH, Faith MS. Beverage consumption patterns of children born at different risk of obesity. *Obesity (Silver Spring)*. 2008;16:1802–8. doi: 10.1038/oby.2008.287.
205. Wolraich ML, Lindgren SD, Stumbo PJ, Stegink LD, Appelbaum MI, Kiritsy MC. Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children. *New Engl J Med*. 1994;330:301–7. doi: 10.1056/NEJM199402033300501.
206. Bunin GR, Kushi LH, Gallagher PR, Rorke-Adams LB, McBride ML, Cnaan A. Maternal diet during pregnancy and its association with medulloblastoma in children: a Children's Oncology Group study (United States). *Cancer Causes Control*. 2005;16:877–91. doi: 10.1007/s10552-005-3144-7.

207. Gurney JG, Pogoda JM, Holly EA, Hecht SS, Preston-Martin S. Aspartame consumption in relation to childhood brain tumor risk: results from a case-control study. *J Natl Cancer Inst.* 1997;89:1072-4. doi: 10.1093/jnci/89.14.1072.
208. de Ruyter JC, Katan MB, Kuijper LDJ, Liem DG, Olthof MR. The effect of sugar-free versus sugar-sweetened beverages on satiety, liking and wanting: an 18 month randomized double-blind trial in children. *PLoS One.* 2013;8:e78039. doi: 10.1371/journal.pone.0078039.
209. Cocco F, Cagetti MG, Livesu R, Camoni N, Pinna R, Lingstrom P, et al. Effect of a daily dose of snacks containing maltitol or stevia rebaudiana as sweeteners in high caries risk schoolchildren: a double-blind RCT study. *Oral Health Prev Dent.* 2019;17:515-22. doi: 10.3290/j.ohpd.a43329.
210. Vandana K, Reddy VC, Sudhir KM, Kumar K, Raju SH, Babu JN. Effectiveness of stevia as a mouthrinse among 12-15-year-old schoolchildren in Nellore district, Andhra Pradesh: a randomized controlled trial. *J Indian Soc Periodontol.* 2017;21:37-43. doi: 10.4103/jisp.jisp\_54\_17.
211. Marshall TA, Levy SM, Broffitt B, Warren JJ, Eichenberger-Gilmore JM, Burns TL, et al. Dental caries and beverage consumption in young children. *Pediatrics.* 2003;112:e184-91. doi: 10.1542/peds.112.3.e184.
212. Hardy LL, Bell J, Bauman A, Mhrshahi S. Association between adolescents' consumption of total and different types of sugar-sweetened beverages with oral health impacts and weight status. *Aust N Z J Public Health.* 2018;42:22-6. doi: 10.1111/1753-6405.12749.
213. Serra Majem L, García Closas R, Ramón JM, Manau C, Cuenca E, Krasse B. Dietary habits and dental caries in a population of Spanish schoolchildren with low levels of caries experience. *Caries Res.* 1993;27:488-94. doi: 10.1159/000261586.
214. Kim JY, Kang HL, Kim D-K, Kang SW, Park YK. Eating habits and food additive intakes are associated with emotional states based on EEG and HRV in healthy Korean children and adolescents. *J Am Coll Nutr.* 2017;36:335-41. doi: 10.1080/07315724.2017.1281774.
215. Cohen JFW, Rifas-Shiman SL, Young J, Oken E. Associations of prenatal and child sugar intake with child cognition. *Am J Prev Med.* 2018;54:727-35. doi: 10.1016/j.amepre.2018.02.020.
216. Berentzen NE, van Stokkom VL, Gehring U, Koppelman GH, Schaap LA, Smit HA, et al. Associations of sugar-containing beverages with asthma prevalence in 11-year-old children: the PIAMA birth cohort. *Eur J Clin Nutr.* 2015;69:303-8. doi: 10.1038/ejcn.2014.153.
217. Chen L, Hu FB, Yeung E, Willett W, Zhang C. Prospective study of pre-gravid sugar-sweetened beverage consumption and the risk of gestational diabetes mellitus. *Diabetes Care.* 2009;32:2236-41. doi: 10.2337/dc09-0866.
218. Perez M, Raghuraman N, Kelly J, Foeller M, Zhang F, England SK, et al. Consumption of sugar sweetened and artificially sweetened beverages and pregnancy outcomes. *American J Obstet Gynecol.* 2021;224:S473-4. doi: 10.1016/j.ajog.2020.12.779.
219. Nicoli F, Prete A, Citro F, Bertolotto A, Aragona M, de Gennaro G, et al. Use of non-nutritive-sweetened soft drink and risk of gestational diabetes. *Diabetes Res Clin Pract.* 2021;178. doi: 10.1016/j.diabres.2021.108943.
220. Englund-Ögge L, Brantsæter AL, Haugen M, Sengpiel V, Khatibi A, Myhre R, et al. Association between intake of artificially sweetened and sugar-sweetened beverages and preterm delivery: a large prospective cohort study. *Am J Clin Nutr.* 2012;96:552-9. doi: 10.3945/ajcn.111.031567.

221. Halldorsson TI, Strøm M, Petersen SB, Olsen SF. Intake of artificially sweetened soft drinks and risk of preterm delivery: a prospective cohort study in 59,334 Danish pregnant women. *Am J Clin Nutr.* 2010;92:626–33. doi: 10.3945/ajcn.2009.28968.
222. Petherick ES, Goran MI, Wright J. Relationship between artificially sweetened and sugar-sweetened cola beverage consumption during pregnancy and preterm delivery in a multi-ethnic cohort: analysis of the Born in Bradford cohort study. *Eur J Clin Nutr.* 2014;68:404–7. doi: 10.1038/ejcn.2013.267.
223. Gunther J, Hoffmann J, Spies M, Meyer D, Kunath J, Stecher L, et al. Associations between the prenatal diet and neonatal outcomes: a secondary analysis of the cluster-randomised GeliS Trial. *Nutrients.* 2019;11. doi: 10.3390/nu11081889.
224. Salavati N, Vinke PC, Lewis F, Bakker MK, Erwich JJHM, van der Beek EM. Offspring birth weight is associated with specific preconception maternal food group intake: data from a linked population-based birth cohort. *Nutrients.* 2020;12. doi: 10.3390/nu12103172.
225. Munda A, Starčič Erjavec M, Molan K, Ambrožič Avguštin J, Žgur-Bertok D, Pongrac Barlovič D. Association between pre-pregnancy body weight and dietary pattern with large-for-gestational-age infants in gestational diabetes. *Diabetol Metab Syndr.* 2019;11:68. doi: 10.1186/s13098-019-0463-5.
226. Azad MB, Sharma AK, de Souza RJ, Dolinsky VW, Becker AB, Mandhane PJ, et al. Association between artificially sweetened beverage consumption during pregnancy and infant body mass index. *JAMA Pediatr.* 2016;170:662–70. doi: 10.1001/jamapediatrics.2016.0301.
227. Gillman MW, Rifas-Shiman SL, Fernandez-Barres S, Kleinman K, Taveras EM, Oken E. Beverage intake during pregnancy and childhood adiposity. *Pediatrics.* 2017;140. doi: 10.1542/peds.2017-0031.
228. Zhu Y, Olsen SF, Mendola P, Halldorsson TI, Rawal S, Hinkle SN, et al. Maternal consumption of artificially sweetened beverages during pregnancy, and offspring growth through 7 years of age: a prospective cohort study. *Int J Epidemiol.* 2017;46:1499–508. doi: 10.1093/ije/dyx095.
229. Maslova E, Strøm M, Olsen SF, Halldorsson TI. Consumption of artificially-sweetened soft drinks in pregnancy and risk of child asthma and allergic rhinitis. *PloS One.* 2013;8:e57261. doi: 10.1371/journal.pone.0057261.
230. Dale MTG, Magnus P, Leirgul E, Holmstrom H, Gjessing HK, Brodwall K, et al. Intake of sucrose-sweetened soft beverages during pregnancy and risk of congenital heart defects (CHD) in offspring: a Norwegian pregnancy cohort study. *Eur J Epidemiol.* 2019;34:383–96. doi: 10.1007/s10654-019-00480-y.
231. Schmidt AB, Lund M, Corn G, Halldorsson TI, Øyen N, Wohlfahrt J, et al. Dietary glycemic index and glycemic load during pregnancy and offspring risk of congenital heart defects: a prospective cohort study. *Am J Clin Nutr.* 2020;111:526–35. doi: 10.1093/ajcn/nqz342.
232. Kline J, Stein ZA, Susser M, Warburton D. Spontaneous abortion and the use of sugar substitutes (saccharin). *Am J Obstet Gynecol.* 1978;130:708–11. doi: 10.1016/0002-9378(78)90333-2.
233. Renault K, Carlsen E, Norgaard K, Nilas L, Pryds O, Secher N, et al. Intake of sweets, snacks and soft drinks predicts weight gain in obese pregnant women: detailed analysis of the results of a randomised controlled trial. *PLoS One.* 2015;10. doi: 10.1371/journal.pone.0133041.
234. Hrolfsdottir L, Halldorsson TI, Birgisdottir BE, Hreidarsdottir IT, Hardardottir H, Gunnarsdottir I. Development of a dietary screening questionnaire to predict excessive weight gain in pregnancy. *Matern Child Nutr.* 2019;15:e12639. doi: 10.1111/mcn.12639.

235. Hinkle SN, Rawal S, Bjerregaard AA, Halldorsson TI, Li M, Ley SH, et al. A prospective study of artificially sweetened beverage intake and cardiometabolic health among women at high risk. *Am J Clin Nutr*. 2019;110:221–32. doi: 10.1093/ajcn/nqz094.
236. Pan A, Hu FB. Effects of carbohydrates on satiety: differences between liquid and solid food. *Curr Opin Clin Nutr Metab Care*. 2011;14:385–90. doi: 10.1097/MCO.0b013e328346df36.
237. Malik VS. Non-sugar sweeteners and health. *BMJ*. 2019;364:k5005. doi: 10.1136/bmj.k5005.
238. Mela DJ, McLaughlin J, Rogers PJ. Perspective: Standards for research and reporting on low-energy (“artificial”) sweeteners. *Adv Nutr*. 2020;11:484–91. doi: 10.1093/advances/nmz137.
239. Mosdøl A, Vist GE, Svendsen C, Dirven H, Lillegaard ITL, Mathisen GH, et al. Hypotheses and evidence related to intense sweeteners and effects on appetite and body weight changes: a scoping review of reviews. *PLoS One*. 2018;13:e0199558. doi: 10.1371/journal.pone.0199558.
240. Gardner C, Wylie-Rosett J, Gidding SS, Steffen LM, Johnson RK, Reader D, et al. Nonnutritive sweeteners: current use and health perspectives: a scientific statement from the American Heart Association and the American Diabetes Association. *Diabetes Care*. 2012;35:1798–808. doi: 10.2337/dc12-9002.
241. An R. Beverage consumption in relation to discretionary food intake and diet quality among US adults, 2003 to 2012. *J Acad Nutr Diet*. 2016;116:28–37. doi: 10.1016/j.jand.2015.08.009.
242. Sylvestsky AC, Figueroa J, Zimmerman T, Swithers SE, Welsh JA. Consumption of low-calorie sweetened beverages is associated with higher total energy and sugar intake among children, NHANES 2011–2016. *Pediatr Obes*. 2019;14:e12535. doi: 10.1111/ijpo.12535.
243. Laffitte A, Neiers F, Briand L. Functional roles of the sweet taste receptor in oral and extraoral tissues. *Curr Opin Clin Nutr Metab Care*. 2014;17:379–85. doi: 10.1097/mco.000000000000058.
244. Rother KI, Conway EM, Sylvestsky AC. How non-nutritive sweeteners influence hormones and health. *Trends Endocrinol Metab*. 2018;29:455–67. doi: 10.1016/j.tem.2018.04.010.
245. Ahmad R, Dalziel JE. G protein-coupled receptors in taste physiology and pharmacology. *Front Pharmacol*. 2020;11:587664. doi: 10.3389/fphar.2020.587664.
246. Pang MD, Goossens GH, Blaak EE. The impact of artificial sweeteners on body weight control and glucose homeostasis. *Front Nutr*. 2020;7:598340. doi: 10.3389/fnut.2020.598340.
247. Reuber MD. Carcinogenicity of saccharin. *Environ Health Perspect*. 1978;25:173–200. doi: 10.1289/ehp.7825173.
248. Chappel CI. A review and biological risk assessment of sodium saccharin. *Regul Toxicol Pharmacol*. 1992;15:253–70. doi: 10.1016/0273-2300(92)90037-a.
249. Mishra A, Ahmed K, Froghi S, Dasgupta P. Systematic review of the relationship between artificial sweetener consumption and cancer in humans: analysis of 599,741 participants. *Int J Clin Pract*. 2015;69:1418–26. doi: 10.1111/ijcp.12703.
250. Azad MB, Archibald A, Tomczyk MM, Head A, Cheung KG, de Souza RJ, et al. Nonnutritive sweetener consumption during pregnancy, adiposity, and adipocyte differentiation in offspring: evidence from humans, mice, and cells. *Int J Obes (Lond)*. 2020;44:2137–48. doi: 10.1038/s41366-020-0575-x.

251. Ou-Yang MC, Sun Y, Liebowitz M, Chen CC, Fang ML, Dai W, et al. Accelerated weight gain, prematurity, and the risk of childhood obesity: a meta-analysis and systematic review. *PLoS One*. 2020;15:e0232238. doi: 10.1371/journal.pone.0232238.
252. Rogers PJ, Appleton KM. The effects of low-calorie sweeteners on energy intake and body weight: a systematic review and meta-analyses of sustained intervention studies. *Int J Obes (Lond)*. 2021;45:464–78. doi: 10.1038/s41366-020-00704-2.
253. Laviada-Molina H, Molina-Segui F, Pérez-Gaxiola G, Cuello-García C, Arjona-Villicaña R, Espinosa-Marrón A, et al. Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: systematic review and meta-analysis. *Obes Rev*. 2020;21:e13020. doi: 10.1111/obr.13020.
254. Stanhope KL, Medici V, Bremer AA, Lee V, Lam HD, Nunez MV, et al. A dose–response study of consuming high-fructose corn syrup-sweetened beverages on lipid/lipoprotein risk factors for cardiovascular disease in young adults. *Am J Clin Nutr*. 2015;101:1144–54. doi: 10.3945/ajcn.114.100461.
255. Frey GH. Use of aspartame by apparently healthy children and adolescents. *J Toxicol Environ Health*. 1976;2:401–15. doi: 10.1080/15287397609529442.
256. Koyuncu BU, Balci MK. Metabolic effects of dissolved aspartame in the mouth before meals in prediabetic patients: a randomized controlled cross-over study. *J Endocrinol Diabetes Obes*. 2014; 2:1-6.
257. Ebbeling CB, Feldman HA, Chomitz VR, Antonelli TA, Gortmaker SL, Osganian SK, et al. A randomized trial of sugar-sweetened beverages and adolescent body weight. *N Engl J Med*. 2012;367:1407–16. doi: 10.1056/NEJMoa1203388.
258. Ebbeling CB, Feldman HA, Osganian SK, Chomitz VR, Ellenbogen SJ, Ludwig DS. Effects of decreasing sugar-sweetened beverage consumption on body weight in adolescents: a randomized, controlled pilot study. *Pediatrics*. 2006;117:673–80. doi: 10.1542/peds.2005-0983.
259. Karalexi MA, Mitrogiorgou M, Georgantzi GG, Papaevangelou V, Fessatou S. Non-nutritive sweeteners and metabolic health outcomes in children: a systematic review and meta-analysis. *J Pediatr*. 2018;197:128–33.e2. doi: 10.1016/j.jpeds.2018.01.081.
260. Li H, Liang H, Yang H, Zhang X, Ding X, Zhang R, et al. Association between intake of sweetened beverages with all-cause and cause-specific mortality: a systematic review and meta-analysis. *J Public Health (Oxf)*. 2021. doi: 10.1093/pubmed/fdab069.
261. Zhang YB, Jiang YW, Chen JX, Xia PF, Pan A. Association of consumption of sugar-sweetened beverages or artificially sweetened beverages with mortality: a systematic review and dose–response meta-analysis of prospective cohort studies. *Adv Nutr*. 2021;12:374–83. doi: 10.1093/advances/nmaa110.
262. Pan B, Ge L, Lai H, Wang Q, Wang Q, Zhang Q, et al. Association of soft drink and 100% fruit juice consumption with all-cause mortality, cardiovascular diseases mortality, and cancer mortality: a systematic review and dose–response meta-analysis of prospective cohort studies. *Crit Rev Food Sci Nutr*. 2021:1–12. doi: 10.1080/10408398.2021.1937040.
263. Jatho A, Cambia JM, Myung SK. Consumption of artificially sweetened soft drinks and risk of gastrointestinal cancer: a meta-analysis of observational studies. *Public Health Nutr*. 2021:1–15. doi: 10.1017/s136898002100104x.
264. Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, et al. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. *Can Med Assoc J*. 2017;189:E929–39. doi: 10.1503/cmaj.161390.



265. Nichol AD, Holle MJ, An R. Glycemic impact of non-nutritive sweeteners: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr.* 2018;72:796–804. doi: 10.1038/s41430-018-0170-6.
266. Lo WC, Ou SH, Chou CL, Chen JS, Wu MY, Wu MS. Sugar- and artificially-sweetened beverages and the risks of chronic kidney disease: a systematic review and dose–response meta-analysis. *J Nephrol.* 2021. doi: 10.1007/s40620-020-00957-0.
267. Cai C, Sivak A, Davenport MH. Effects of prenatal artificial sweeteners consumption on birth outcomes: a systematic review and meta-analysis. *Public Health Nutr.* 2021;24(15):5024–33. doi: 10.1017/s1368980021000173.
268. Reid AE, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, et al. Early exposure to nonnutritive sweeteners and long-term metabolic health: a systematic review. *Pediatrics.* 2016;137:e20153603. doi: 10.1542/peds.2015-3603.
269. Angelopoulos T, Lowndes J, Rippe JM. No changes in uric acid or blood pressure after 6 months of daily consumption of sugar sweetened or diet beverages. *J Am Soc Hypertens.* 2016;10:e56. doi: 10.1016/j.jash.2016.03.136.
270. López-Meza MS, Otero-Ojeda G, Estrada JA, Esquivel-Hernández FJ, Contreras I. The impact of nutritive and non-nutritive sweeteners on the central nervous system: preliminary study. *Nutr Neurosci.* 2021:1–10. doi: 10.1080/1028415x.2021.1885239.
271. Sánchez-Delgado M, Estrada JA, Paredes-Cervantes V, Kaufer-Horwitz M, Contreras I. Changes in nutrient and calorie intake, adipose mass, triglycerides and TNF- $\alpha$  concentrations after non-caloric sweetener intake: a pilot study. *Int J Vitam Nutr Res.* 2021;91:87–98. doi: 10.1024/0300-9831/a000611.
272. Serrano J, Smith KR, Crouch AL, Sharma V, Yi F, Vargova V, et al. High-dose saccharin supplementation does not induce gut microbiota changes or glucose intolerance in healthy humans and mice. *Microbiome.* 2021;9:11. doi: 10.1186/s40168-020-00976-w.
273. Young RL, Isaacs NJ, Schober G, Wu T, Cvijanovic N, Pezos N, et al. Impact of artificial sweeteners on glycaemic control in healthy humans. *Diabetologia.* 2017;60:S91. doi: 10.1007/s00125-017-4350-z.
274. de Ruyter JC, Olthof MR, Kuijper LDJ, Katan MB. Effect of sugar-sweetened beverages on body weight in children: design and baseline characteristics of the Double-blind, Randomized INtervention study in Kids. *Contemp Clin Trials.* 2012;33:247–57. doi: 10.1016/j.cct.2011.10.007.
275. de Ruyter JC, Katan MB, Kuijper LD, Liem DG, Olthof MR. The effect of sugar-free versus sugar-sweetened beverages on satiety, liking and wanting: an 18 month randomized double-blind trial in children. *PLoS One.* 2013;8:e78039. doi: 10.1371/journal.pone.0078039.
276. Campos V, Despland C, Schneiter P, Brandejsky V, Kreis R, Boesch C, et al. A randomized control trial of sugar-sweetened and artificially sweetened beverages and intrahepatic fat in overweight subjects. *FASEB J.* 2015; 29(S1):Experimental Biology 2015 Meeting Abstracts. doi: 10.1096/fasebj.29.1\_supplement.602.5.
277. Campos V, Despland C, Brandejsky V, Kreis R, Schneiter P, Boesch C, et al. Metabolic effects of replacing sugar-sweetened beverages with artificially-sweetened beverages in overweight subjects with or without hepatic steatosis: a randomized control clinical trial. *Nutrients.* 2017;9:202. doi: 10.3390/nu9030202.
278. Fantino M, Fantino A, Mistretta F, Bottiglioli D. Acute or long term consumption of beverages containing low calorie sweeteners do not alter appetite, energy intake or macronutrient selection in healthy adults: a non-inferiority comparison with water. 2017;71:871. doi: 10.1159/000480486.

279. Madjd A, Taylor MA, Delavari A, Malekzadeh R, Macdonald IA, Farshchi HR. Effects on weight loss in adults of replacing diet beverages with water during a hypoenergetic diet: a randomized, 24-wk clinical trial. *Am J Clin Nutr.* 2015;102:1305–12. doi: 10.3945/ajcn.115.109397.
280. Peters JC, Wyatt HR, Foster GD, Pan Z, Wojtanowski AC, Vander Veur SS, et al. The effects of water and non-nutritive sweetened beverages on weight loss during a 12-week weight loss treatment program. *Obesity (Silver Spring).* 2014;22:1415–21. doi: 10.1002/oby.20737.
281. Raben A, Moller AC, Vasilaras TH, Astrup A. A randomized 10 week trial of sucrose vs artificial sweeteners on body weight and blood pressure after 10 weeks. *Obes Res.* 2001;9:865.
282. Sørensen L, Vasilaras T, Astrup A, Raben A. Sucrose compared with artificial sweeteners: a clinical intervention study of effects on energy intake, appetite, and energy expenditure after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr.* 2014;100:36–45. doi: 10.3945/ajcn.113.081554.
283. Romo-Romo A, Aguilar-Salinas CA, López-Carrasco MG, Guillén-Pineda LE, Brito-Córdova GX, Gómez-Díaz RA, et al. Sucralose consumption over 2 weeks in healthy subjects does not modify fasting plasma concentrations of appetite-regulating hormones: a randomized clinical trial. *J Acad Nutr Diet.* 2020;120:1295–304. doi: 10.1016/j.jand.2020.03.018.
284. Stamatakis N, Crooks B, McLaughlin J. Daily consumption of stevia drops effects on glycemia, body weight and energy intake: results from a 12-week, open-label, randomized controlled trial in healthy adults. *Curr Dev Nutr.* 2020;4(Suppl. 2):663. doi: 10.1093/cdn/nzaa049\_056.
285. Vázquez-Durán M, Castillo-Martínez L, Orea-Tejeda A, Téllez-Olvera L, Delgado Perez L, Marquez Zepeda B, et al. Effect of decreasing the consumption of sweetened caloric and non-caloric beverages on weight, body composition and blood pressure in young adults. *Eur J Prev Cardiol.* 2013;1:S120.
286. Schernhammer ES, Hu FB, Giovannucci E, Michaud DS, Colditz GA, Stampfer MJ, et al. Sugar-sweetened soft drink consumption and risk of pancreatic cancer in two prospective cohorts. *Cancer Epidemiol Biomarkers Prev.* 2005;14:2098–105. doi: 10.1158/1055-9965.epi-05-0059.
287. Stepien M, Duarte-Salles T, Fedirko V, Trichopoulou A, Lagiou P, Bamia C, et al. Consumption of soft drinks and juices and risk of liver and biliary tract cancers in a European cohort. *Eur J Nutr.* 2016;55:7–20. doi: 10.1007/s00394-014-0818-5.
288. Winkelmayr WC, Stampfer MJ, Willett WC, Curhan GC. Habitual caffeine intake and the risk of hypertension in women. *JAMA.* 2005;294:2330–5. doi: 10.1001/jama.294.18.2330.
289. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA.* 2004;292:927–34. doi: 10.1001/jama.292.8.927.
290. de Koning L, Malik VS, Rimm EB, Willett WC, Hu FB. Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men. *Am J Clin Nutr.* 2011;93:1321–7. doi: 10.3945/ajcn.110.007922.
291. Bhupathiraju SN, Pan A, Malik VS, Manson JE, Willett WC, van Dam RM, et al. Caffeinated and caffeine-free beverages and risk of type 2 diabetes. *Am J Clin Nutr.* 2013;97:155–66. doi: 10.3945/ajcn.112.048603.
292. Gardener H, Rundek T, Wright C, Vieira J, Elkind MS, Sacco RL. Soda consumption and risk of vascular events in the northern Manhattan study. *Stroke.* 2011;42:e273. doi: 10.1161/STR.0b013e3182074d9b.

293. Ma J, Fox CS, Jacques PF, Speliotes EK, Hoffmann U, Smith CE, et al. Sugar-sweetened beverage, diet soda, and fatty liver disease in the Framingham Heart Study cohorts. *J Hepatol.* 2015;63:462–9. doi: 10.1016/j.jhep.2015.03.032.
294. Bombback AS, Derebail VK, Shoham DA, Anderson CA, Steffen LM, Rosamond WD, et al. Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. *Kidney Int.* 2010;77:609–16. doi: 10.1038/ki.2009.500.
295. Colditz GA, Willett WC, Stampfer MJ, London SJ, Segal MR, Speizer FE. Patterns of weight change and their relation to diet in a cohort of healthy women. *Am J Clin Nutr.* 1990;51:1100–5. doi: 10.1093/ajcn/51.6.1100.
296. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. *New Engl J Med.* 2011;364:2392–404. doi: 10.1056/NEJMoa1014296.
297. Pan A, Malik VS, Hao T, Willett WC, Mozaffarian D, Hu FB. Changes in water and beverage intake and long-term weight changes: results from three prospective cohort studies. *Int J Obes (Lond).* 2013;37:1378–85. doi: 10.1038/ijo.2012.225.
298. Stellman SD, Garfinkel L. Patterns of artificial sweetener use and weight change in an American Cancer Society prospective study. *Appetite.* 1988;11 Suppl 1:85–91.
299. Iscovich J, Castelletto R, Estève J, Muñoz N, Colanzi R, Coronel A, et al. Tobacco smoking, occupational exposure and bladder cancer in Argentina. *Int J Cancer.* 1987;40:734–40. doi: 10.1002/ijc.2910400604.
300. Arrais PSD, Perdigao de Negreiros Vianna M, Zaccolo AV, Moreira LIM, The PMP, Quidute ARP, et al. [Use of artificial sweeteners in Brazil: a household survey approach]. *Cadernos de saude publica.* 2019;35:e00010719 (in Portuguese). doi: 10.1590/0102-311X00010719.
301. Barrett P, Imamura F, Brage S, Griffin SJ, Wareham NJ, Forouhi NG. Sociodemographic, lifestyle and behavioural factors associated with consumption of sweetened beverages among adults in Cambridgeshire, UK: the Fenland Study. *Public Health Nutr.* 2017;20:2766–77. doi: 10.1017/S136898001700177X.
302. Bleich SN, Wolfson JA, Vine S, Wang YC. Diet-beverage consumption and caloric intake among US adults, overall and by body weight. *Am J Public Health.* 2014;104:e72–8. doi: 10.2105/AJPH.2013.301556.
303. Bouchard DR, Ross R, Janssen I. Coffee, tea and their additives: association with BMI and waist circumference. *Obes Facts.* 2010;3:345–52. doi: 10.1159/000322915.
304. Bragg MA, White MA. Examining the relationship between soda consumption and eating disorder pathology. *Adv Eat Disord.* 2013;1. doi: 10.1080/21662630.2013.742317.
305. Brunkwall L, Almgren P, Hellstrand S, Orho-Melander M, Ericson U. Commonly consumed beverages associate with different lifestyle and dietary intakes. *Int J Food Sci Nutr.* 2019;70:88–97. doi: 10.1080/09637486.2018.1466272.
306. Carroll HA, Betts JA, Johnson L. An investigation into the relationship between plain water intake and glycated Hb (HbA1c): a sex-stratified, cross-sectional analysis of the UK National Diet and Nutrition Survey (2008–2012). *Br J Nutr.* 2016;1–11. doi: 10.1017/S0007114516003688.
307. Chen LN, Parham ES. College students' use of high-intensity sweeteners is not consistently associated with sugar consumption. *J Am Diet Assoc.* 1991;91:686–90.
308. Crichton G, Alkerwi Aa, Elias M. Diet soft drink consumption is associated with the metabolic syndrome: a two sample comparison. *Nutrients.* 2015;7:3569–86. doi: 10.3390/nu7053569.

309. de Castro JM. When, how much and what foods are eaten are related to total daily food intake. *Br J Nutr.* 2009;102:1228–37. doi: 10.1017/S0007114509371640.
310. den Biggelaar LJ, Sep SJS, Mari A, Ferrannini E, van Dongen MCJM, Wijckmans NEG, et al. Association of artificially sweetened and sugar-sweetened soft drinks with beta-cell function, insulin sensitivity, and type 2 diabetes: the Maastricht Study. *Eur J Nutr.* 2020;59:1717–27. doi: 10.1007/s00394-019-02026-0.
311. Deshmukh-Taskar PR, Mendoza JA, Nicklas TA, Liu Y, Berenson GS. Dietary & health predictors associated with overweight & obesity in young adults: the Bogalusa Heart Study. *FASEB J.* 2009;23.
312. Drewnowski A, Rehm CD. The use of low-calorie sweeteners is associated with self-reported prior intent to lose weight in a representative sample of US adults. *Nutr Diabetes.* 2016;6:e202. doi: 10.1038/nutd.2016.9.
313. Durán Agüero S, Vásquez Leiva A, Morales Illanes G, Schifferli Castro I, Sanhueza Espinoza C, Encina Vega C, et al. [Association between stevia sweetener consumption and nutritional status in university students]. *Nutr Hosp.* 2015;32:362–6 (in Spanish). doi: 10.3305/nh.2015.32.1.8961.
314. Fernandes J, Arts J, Dimond E, Hirshberg S, Lofgren IE. Dietary factors are associated with coronary heart disease risk factors in college students. *Nutr Res.* 2013;33:647–52. doi: 10.1016/j.nutres.2013.05.013.
315. Fitzgerald N, Damio G, Segura-Perez S, Perez-Escamilla R. Nutrition knowledge, food label use, and food intake patterns among Latinas with and without type 2 diabetes. *J Am Diet Assoc.* 2008;108:960–7. doi: 10.1016/j.jada.2008.03.016.
316. Geraldo APG, Pinto-e-Silva MEM. Factors associated with diet soda consumption by employees of public universities in Sao Paulo state (Brazil). *Obes Facts.* 2013;6:150–1.
317. Gomez Roig MD, Mazarico E, Ferrero S, Montejo R, Ibanez L, Grima F, et al. Differences in dietary and lifestyle habits between pregnant women with small fetuses and appropriate-for-gestational-age fetuses. *J Obstet Gynecol Res.* 2017;43:1145–51. doi: 10.1111/jog.13330.
318. Hartman T, Haardorfer R, Greene B, Parulekar S, Kegler M. Beverage consumption patterns among overweight and obese African American women. *Nutrients.* 2017;9:1344. doi: 10.3390/nu9121344.
319. Hedrick VE, Passaro EM, Davy BM, You W, Zoellner JM. Characterization of non-nutritive sweetener intake in rural southwest Virginian adults living in a health-disparate region. *Nutrients.* 2017;9. doi: 10.3390/nu9070757.
320. Hess EL, Myers EA, Swithers SE, Hedrick VE. Associations between nonnutritive sweetener intake and metabolic syndrome in adults. *J Am Coll Nutr.* 2018;37:487–93. doi: 10.1080/07315724.2018.1440658.
321. Hunt KJ, St Peter JV, Malek AM, Vrana-Diaz C, Marriott BP, Greenberg D. Daily eating frequency in US adults: associations with low-calorie sweeteners, body mass index, and nutrient intake (NHANES 2007–2016). *Nutrients.* 2020;12. doi: 10.3390/nu12092566.
322. Kuk JL, Brown RE. Aspartame intake is associated with greater glucose intolerance in individuals with obesity. *Appl Physiol Nutr Metab.* 2016;41:795–8. doi: 10.1139/apnm-2015-0675.
323. Leahy M, Ratliff JC, Riedt CS, Fulgoni VL. Consumption of low-calorie sweetened beverages compared to water is associated with reduced intake of carbohydrates and sugar, with no adverse relationships to glycemic responses: results from the 2001–2012 National Health and Nutrition Examination Surveys. *Nutrients.* 2017;9. doi: 10.3390/nu9090928.

324. Mackenzie T, Brooks B, O'Connor G. Beverage intake, diabetes, and glucose control of adults in America. *Ann Epidemiol.* 2006;16:688–91. doi: 10.1016/j.annepidem.2005.11.009.
325. Malek AM, Hunt KJ, DellaValle DM, Greenberg D, St Peter JV, Marriott BP. Reported consumption of low-calorie sweetener in foods, beverages, and food and beverage additions by US adults: NHANES 2007–2012. *Curr Dev Nutr.* 2018;2:nzy054. doi: 10.1093/cdn/nzy054.
326. Marques-Vidal P, Vollenweider P, Grange M, Guessous I, Waeber G. Dietary intake of subjects with diabetes is inadequate in Switzerland: the CoLaus study. *Eur J Nutr.* 2017;56:981–9. doi: 10.1007/s00394-015-1146-0.
327. Miller C, Ettridge K, Wakefield M, Pettigrew S, Coveney J, Roder D, et al. Consumption of sugar-sweetened beverages, juice, artificially-sweetened soda and bottled water: an Australian population study. *Nutrients.* 2020;12. doi: 10.3390/nu12030817.
328. Mostad IL, Langaas M, Grill V. Central obesity is associated with lower intake of whole-grain bread and less frequent breakfast and lunch: results from the HUNT study, an adult all-population survey. *Appl Physiol Nutr Metab.* 2014;39:819–28. doi: 10.1139/apnm-2013-0356.
329. Shoham DA, Durazo-Arvizu R, Kramer H, Luke A, Vupputuri S, Kshirsagar A, et al. Sugary soda consumption and albuminuria: results from the National Health and Nutrition Examination Survey, 1999–2004. *PloS One.* 2008;3:e3431. doi: 10.1371/journal.pone.0003431.
330. Tamez M, Monge A, Lopez-Ridaura R, Fagherazzi G, Rinaldi S, Ortiz-Panoso E, et al. Soda intake is directly associated with serum C-reactive protein concentration in Mexican women. *J Nutr.* 2018;148:117–24. doi: 10.1093/jn/nxx021.
331. Wensel C, Harper K, Trude A, Poirier L, Redmond L, Gittelsohn J. Associations between sodium, potassium, sugar and non-caloric sweetener intake and hypertension in Native American adults (P04-127-19). *Curr Dev Nutr.* 2019;3. doi: 10.1093/cdn/nzz051.P04-127-19.
332. Winther R, Aasbrenn M, Farup PG. Intake of non-nutritive sweeteners is associated with an unhealthy lifestyle: a cross-sectional study in subjects with morbid obesity. *BMC Obes.* 2017;4:41. doi: 10.1186/s40608-017-0177-x.
333. Wulaningsih W, Van Hemelrijck M, Tsilidis KK, Tzoulaki I, Patel C, Rohrmann S. Investigating nutrition and lifestyle factors as determinants of abdominal obesity: an environment-wide study. *Int J Obes (Lond).* 2017;41:340–7. doi: 10.1038/ijo.2016.203.
334. Yarmolinsky J, Duncan BB, Chambless LE, Bensenor IM, Barreto SM, Goulart AC, et al. Artificially sweetened beverage consumption is positively associated with newly diagnosed diabetes in normal-weight but not in overweight or obese Brazilian adults. *J Nutr.* 2016;146:290–7. doi: 10.3945/jn.115.220194.
335. Yoshida M, McKeown NM, Rogers G, Meigs JB, Saltzman E, D'Agostino R, et al. Surrogate markers of insulin resistance are associated with consumption of sugar-sweetened drinks and fruit juice in middle and older-aged adults. *J Nutr.* 2007;137:2121–7. doi: 10.1093/jn/137.9.2121.
336. Yu ZM, Parker L, Dummer TJB. Associations of coffee, diet drinks, and non-nutritive sweetener use with depression among populations in eastern Canada. *Sci Rep.* 2017;7:6255. doi: 10.1038/s41598-017-06529-w.
337. Yu Z, Ley SH, Sun Q, Hu FB, Malik VS. Cross-sectional association between sugar-sweetened beverage intake and cardiometabolic biomarkers in US women. *Br J Nutr.* 2018;119:570–80. doi: 10.1017/S0007114517003841.

338. Beck AL, Tschann J, Butte NF, Penilla C, Greenspan LC. Association of beverage consumption with obesity in Mexican American children. *Public Health Nutr.* 2014;17:338–44. doi: 10.1017/S1368980012005514.
339. Duran Agüero S, Oñate G, Haro Rivera P. Consumption of non-nutritive sweeteners and nutritional status in 10-16 year old students. *Arch Argent Pediatr.* 2014;112:207–14. doi: 10.5546/aap.2014.207.
340. Forshee RA, Storey ML. Total beverage consumption and beverage choices among children and adolescents. *Int J Food Sci Nutr.* 2003;54:297–307. doi: 10.1080/09637480120092143.
341. Giammattei J, Blix G, Marshak HH, Wollitzer AO, Pettitt DJ. Television watching and soft drink consumption: associations with obesity in 11- to 13-year-old schoolchildren. *Arch Pediatr Adolesc Med.* 2003;157:882–6. doi: 10.1001/archpedi.157.9.882.
342. Katzmarzyk PT, Broyles ST, Champagne CM, Chaput J-P, Fogelholm M, Hu G, et al. Relationship between soft drink consumption and obesity in 9–11 years old children in a multi-national study. *Nutrients.* 2016;8. doi: 10.3390/nu8120770.
343. Lavery AA, Magee L, Monteiro CA, Saxena S, Millett C. Sugar and artificially sweetened beverage consumption and adiposity changes: national longitudinal study. *Int J Behav Nutr Phys Act.* 2015;12:137. doi: 10.1186/s12966-015-0297-y.
344. Ledoux TA, Watson K, Barnett A, Nguyen NT, Baranowski JC, Baranowski T. Components of the diet associated with child adiposity: a cross-sectional study. *J Am Coll Nutr.* 2011;30:536–46.
345. Mariscal-Arcas M, Monteagudo C, Hernandez-Elizondo J, Benhammou S, Lorenzo ML, Olea-Serrano F. Differences in food intake and nutritional habits between Spanish adolescents who engage in ski activity and those who do not. *Nutr Hosp.* 2014;31:936–43. doi: 10.3305/nh.2015.31.2.8267.
346. Milla Tobarra M, Martinez-Vizcaino V, Lahoz Garcia N, Garcia-Prieto JC, Arias-Palencia NM, Garcia-Hermoso A. The relationship between beverage intake and weight status in children: the Cuenca study. *Nutr Hosp.* 2014;30:818–24. doi: 10.3305/nh.2014.30.4.7666.
347. O'Connor TM, Yang S-J, Nicklas TA. Beverage intake among preschool children and its effect on weight status. *Pediatrics.* 2006;118:e1010–8. doi: 10.1542/peds.2005-2348.
348. Skeie G, Sandvaer V, Grimnes G. Intake of sugar-sweetened beverages in adolescents from Troms, Norway: the Tromso Study: Fit Futures. *Nutrients.* 2019;11. doi: 10.3390/nu11020211.
349. da SN Souza B, Cunha DB, Pereira RA, Sichieri R. Soft drink consumption, mainly diet ones, is associated with increased blood pressure in adolescents. *J Hypertens.* 2016;34:221–5. doi: 10.1097/HJH.0000000000000800.
350. Venegas Hargous C, Reyes M, Smith Taillie L, González CG, Corvalán C. Consumption of non-nutritive sweeteners by pre-schoolers of the food and environment Chilean cohort (FECHIC) before the implementation of the Chilean food labelling and advertising law. *Nutr J.* 2020;19:69. doi: 10.1186/s12937-020-00583-3.
351. Barraij LM, Bi X, Murphy MM, Scrafford CG, Tran NL. Comparisons of nutrient intakes and diet quality among water-based beverage consumers. *Nutrients.* 2019;11. doi: 10.3390/nu11020314.
352. French S, Rosenberg M, Wood L, Maitland C, Shilton T, Pratt IS, et al. Soft drink consumption patterns among Western Australians. *J Nutr Educ Behav.* 2013;45:525–32. doi: 10.1016/j.jneb.2013.03.010.

353. Grech A, Kam CO, Gemming L, Rangan A. Diet-quality and socio-demographic factors associated with non-nutritive sweetener use in the Australian population. *Nutrients*. 2018;10. doi: 10.3390/nu10070833.
354. Jones AC, Kirkpatrick SI, Hammond D. Beverage consumption and energy intake among Canadians: analyses of 2004 and 2015 national dietary intake data. *Nutr J*. 2019;18:60. doi: 10.1186/s12937-019-0488-5.
355. Serra-Majem L, Ribas L, Inglès C, Fuentes M, Lloveras G, Salleras L. Cyclamate consumption in Catalonia, Spain (1992): relationship with the body mass index. *Food Addit Contam*. 1996;13:695–703. doi: 10.1080/02652039609374455.
356. Silva Monteiro L, Kulik Hassan B, Melo Rodrigues PR, Massae Yokoo E, Sichieri R, Alves Pereira R. Use of table sugar and artificial sweeteners in Brazil: National Dietary Survey 2008–2009. *Nutrients*. 2018;10. doi: 10.3390/nu10030295.
357. Sylvetsky AC, Jin Y, Clark EJ, Welsh JA, Rother KI, Talegawkar SA. Consumption of low-calorie sweeteners among children and adults in the United States. *J Acad Nutr Diet*. 2017;117:441–8.e2. doi: 10.1016/j.jand.2016.11.004.
358. Hieronimus B, Medici V, Lee V, Nunez M, Havel PJ, Stanhope KL. Coingestion of glucose and fructose has synergistic effects on lipoprotein risk factors for cardiovascular disease in healthy young adults. *Diabetes*. 2019;68. doi: 10.2337/db19-1920-P.
359. Rippe JM. The effect of sugar sweetened and diet beverages consumed as part of a weight-maintenance diet on fat storage (NCT02252952). 2014 (<https://clinicaltrials.gov/ct2/show/NCT02252952>, accessed 8 November 2021).
360. Pfeiffer AFH. Immediate and long-term induction of incretin release by artificial sweeteners 2 (ILIAS-2) (NCT02487537). 2015.
361. Havel PJ. Adverse metabolic effects of dietary sugar (NCT02548767). 2015 (<https://clinicaltrials.gov/ct2/show/NCT02548767>, accessed 8 November 2021).
362. Friel JK. Effects of artificial sweeteners on gut microbiota and glucose metabolism (NCT02569762). 2015 (<https://clinicaltrials.gov/ct2/show/NCT02569762>, accessed 8 November 2021).
363. Nilsson A. On the impact of common sweetening agents on glucose regulation, cognitive functioning and gut microbiota (NCT02580110). 2015 (<https://clinicaltrials.gov/ct2/show/NCT02580110>, accessed 8 November 2021).
364. Halford J. EffectS of Non-nutritive sSweetened Beverages on appetITe During aCtive weight Loss (SWITCH) (NCT02591134). 2015 (<https://clinicaltrials.gov/ct2/show/NCT02591134>, accessed 8 November 2021).
365. Kyriazis G. Interactions of human gut microbiota with intestinal sweet taste receptors (ISTAR-micro) (NCT03032640). 2016 (<https://clinicaltrials.gov/ct2/show/NCT03032640>, accessed 8 November 2021).
366. Vohl M-C. Effect of non-nutritive sweeteners of high sugar sweetened beverages on metabolic health and gut microbiome (NCT03259685). 2017 (<https://clinicaltrials.gov/ct2/show/NCT03259685>, accessed 8 November 2021).
367. Rother KI. Effects of sucralose on drug absorption and metabolism (the SweetMeds Study) (NCT03407079). 2018 (<https://clinicaltrials.gov/ct2/show/NCT03407079>, accessed 8 November 2021).
368. Sievenpiper JL. Strategies to oppose sugars with non-nutritive sweeteners or water (STOP Sugars NOW) trial (NCT03543644). 2018.

369. Elinav E. Microbiome and non-caloric sweeteners in humans (NCT03708939). 2017 (<https://clinicaltrials.gov/ct2/show/NCT03708939>, accessed 8 November 2021).
370. Villaño D. Evaluation of new beverages rich in bioactive compounds for the modulation of energetic metabolism in overweight adults (NCT04016337). 2019 (<https://clinicaltrials.gov/ct2/show/NCT04016337>, accessed 8 November 2021).
371. Almeda-Valdés P. Effects of sucralose in insulin sensitivity, intestinal microbiota and postprandial GLP-1 (NCT04182464). 2019 (<https://clinicaltrials.gov/ct2/show/NCT04182464>, accessed 8 November 2021).
372. Örkü SE. Effects of low/no calorie sweeteners on glucose tolerance (NCT04904133). 2021 (<https://clinicaltrials.gov/ct2/show/NCT04904133>, accessed 8 November 2021).
373. Small DM. The effect of artificial sweeteners (AFS) on sweetness sensitivity, preference and brain response in adolescents (NCT02499705). 2015 (<https://clinicaltrials.gov/ct2/show/NCT02499705>, accessed 8 November 2021).
374. Huber T. Study of the reversibility of glucose intolerance caused by chronic aspartame consumption (NCT02520258). 2015 (<https://clinicaltrials.gov/ct2/show/NCT02520258>, accessed 8 November 2021).
375. Steffen LM. Sucralose, stevia, gut microbiome and glucose metabolism (NCT02800707). 2016 (<https://clinicaltrials.gov/ct2/show/NCT02800707>, accessed 8 November 2021).
376. Afonso M, Moreira P, Carmo I, Raposo J. Food and nutritional intake of Portuguese adolescents with and without type 1 diabetes. *Pediatr Diabetes*. 2013;14:92.
377. Agüero SD, Díaz W. Noncaloric sweeteners, good or bad that the evidence says. *Revista Española de Nutrición Humana y Dietética*. 2019;23:18–19.
378. Ahmad SY, Friel JK, MacKay DS. The effect of the artificial sweeteners on glucose metabolism in healthy adults: a randomized, double-blinded, crossover clinical trial. *Appl Physiol Nutr Metab*. 2020;45:606–12. doi: 10.1139/apnm-2019-0359.
379. Ahmad SY, Friel J, Mackay D. The effects of non-nutritive artificial sweeteners, aspartame and sucralose, on the gut microbiome in healthy adults: secondary outcomes of a randomized double-blinded crossover clinical trial. *Nutrients*. 2020;12. doi: 10.3390/nu12113408.
380. Akhavan T, Luhovyy BL, Anderson GH. Effect of drinking compared with eating sugars or whey protein on short-term appetite and food intake. *Int J Obes (Lond)*. 2011;35:562–9. doi: 10.1038/ijo.2010.163.
381. Ali F. Consumption of artificial sweeteners in pregnancy increased overweight risk in infants. *Arch Dis Child Educ Pract Ed*. 2017;102:277. doi: 10.1136/archdischild-2017-312618.
382. Alsubaie ASR. Consumption and correlates of sweet foods, carbonated beverages, and energy drinks among primary school children in Saudi Arabia. *Saudi Med J*. 2017;38:1045–50. doi: 10.15537/smj.2017.10.19849.
383. Alviso-Orellana C, Estrada-Tejada D, Carrillo-Larco RM, Bernabe-Ortiz A. Sweetened beverages, snacks and overweight: findings from the Young Lives cohort study in Peru. *Public Health Nutr*. 2018;21:1627–33. doi: 10.1017/S1368980018000320.
384. Anonymous. New concerns about diet sodas. *Harv Health Lett*. 2015;40:5.
385. Anonymous. Replace diet drinks with water to lose weight. *Nurs Stand*. 2016;31:17.
386. Anonymous. NewsCAP: Higher intake of diet drinks may increase health risks in postmenopausal women. *Am J Nurs*. 2019;119:13. doi: 10.1097/01.NAJ.0000557898.05866.85.



387. Appelhans BM, Bleil ME, Waring ME, Schneider KL, Nackers LM, Busch AM, et al. Beverages contribute extra calories to meals and daily energy intake in overweight and obese women. *Physiol Behav.* 2013;122:129–33. doi: 10.1016/j.physbeh.2013.09.004.
388. Appelhans BM, Baylin A, Huang M-H, Li H, Janssen I, Kazlauskaitė R, et al. Beverage intake and metabolic syndrome risk over 14 years: the Study of Women’s Health Across the Nation. *J Aca Nutr Diet.* 2017;117:554–62. doi: 10.1016/j.jand.2016.10.011.
389. Armstrong B, Doll R. Bladder cancer mortality in England and Wales in relation to cigarette smoking and saccharin consumption. *Br J Prev Soc Med.* 1974;28:233–40. doi: 10.1136/jech.28.4.233.
390. Barraj L, Scrafford C, Bi X, Tran N. Intake of low and no-calorie sweeteners (LNCS) by the Brazilian population. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess.* 2021;38:181–94. doi: 10.1080/19440049.2020.1846083.
391. Barriocanal LA, Palacios M, Benitez G, Benitez S, Jimenez JT, Jimenez N, et al. Apparent lack of pharmacological effect of steviol glycosides used as sweeteners in humans: a pilot study of repeated exposures in some normotensive and hypotensive individuals and in type 1 and type 2 diabetics. *Regul Toxicol Pharmacol.* 2008;51:37–41. doi: 10.1016/j.yrtph.2008.02.006.
392. Bawa SH, Rupert N, Webb M. The link between the consumption of sweetened beverages and the development of overweight and obesity among students of the University of the West Indies, St Augustine campus in Trinidad and Tobago. *Roczniki Panstwowego Zakladu Higieny.* 2018;69:251–5.
393. Bawadi H, Khataybeh T, Obeidat B, Kerkadi A, Tayyem R, Banks AD, et al. Sugar-sweetened beverages contribute significantly to college students’ daily caloric intake in Jordan: soft drinks are not the major contributor. *Nutrients.* 2019;11. doi: 10.3390/nu11051058.
394. Beck AL, Fernandez A, Rojina J, Cabana M. Randomized controlled trial of a clinic-based intervention to promote healthy beverage consumption among Latino children. *Clin Pediatr (Phila).* 2017;56:838–44. doi: 10.1177/0009922817709796.
395. Bellisle F, Altenburg de Assis MA, Fieux B, Preziosi P, Galan P, Guy-Grand B, et al. Use of “light” foods and drinks in French adults: biological, anthropometric and nutritional correlates. *J Hum Nutr Diet.* 2001;14:191–206. doi: 10.1046/j.1365-277x.2001.00289.x.
396. Bolt-Evensen K, Vik FN, Stea TH, Klepp K-I, Bere E. Consumption of sugar-sweetened beverages and artificially sweetened beverages from childhood to adulthood in relation to socioeconomic status: 15 years follow-up in Norway. *Int J Behav Nutr Phys Act.* 2018;15:8. doi: 10.1186/s12966-018-0646-8.
397. Agostoni C, Salari P, Riva E. Metabolic needs, utilization and dietary sources of fatty acids in childhood. *Prog Food Nutr Sci.* 1992;16:1–49.
398. Chen WL, Li SC, Chen CM, Weng YL, Chen O, Mu SC. Association of beverage consumption types with weight, height, and body mass index in grade 3 children in northern Taiwan: a cross-sectional study. *Nutrition.* 2021;90:111173. doi: 10.1016/j.nut.2021.111173.
399. Cochrane Central Register of Controlled Trials. Effects of non-nutritive sweeteners intake on the glycemic response in general population. 2017 (<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01885715/full>, accessed 8 November 2021).
400. Cohen BL. Relative risks of saccharin and calorie ingestion. *Science.* 1978;199:983. doi: 10.1126/science.622580.
401. Conway M, Malhotra S, Crandall KA, Sylvetsky AC, Staat BC, Rother KI. Maternal and infant exposure to non-nutritive sweeteners: effects on gut and breast milk microbiome. *Horm Res Paediatr.* 2017;88:323. doi: 10.1159/000481424.

402. Conway MC, Cawley S, Geraghty AA, Walsh NM, O'Brien EC, McAuliffe FM. The consumption of low-calorie sweetener containing foods during pregnancy: results from the ROLO study. *Eur J Clin Nutr.* 2021. doi: 10.1038/s41430-021-00935-0.
403. Creighton S, Jay M. Are non-nutritive sweetened beverages comparable to water in weight loss trials? *J Clin Outcomes Manag.* 2014;21:490–2.
404. Creze C, Notter-Bielser M-L, Knebel J-F, Campos V, Tappy L, Murray M, et al. The impact of replacing sugar- by artificially-sweetened beverages on brain and behavioral responses to food viewing: an exploratory study. *Appetite.* 2018;123:160–8. doi: 10.1016/j.appet.2017.12.019.
405. Cros J, Bidlingmeyer L, Rosset R, Seyssel K, Creze C, Stefanoni N, et al. Effect of nutritive and non-nutritive sweeteners on hemodynamic responses to acute stress: a randomized crossover trial in healthy women. *Nutr Diabetes.* 2020;10:1. doi: 10.1038/s41387-019-0104-y.
406. Cullen M, Nolan J, Cullen M, Moloney M, Kearney J, Lambe J, et al. Effect of high levels of intense sweetener intake in insulin dependent diabetics on the ratio of dietary sugar to fat: a case–control study. *Eur J Clin Nutr.* 2004;58:1336–41. doi: 10.1038/sj.ejcn.1601969.
407. DeChristopher LR, Tucker KL. Excess free fructose, high-fructose corn syrup and adult asthma: the Framingham Offspring Cohort. *Br J Nutr.* 2018;119:1157–67. doi: 10.1017/S0007114518000417.
408. de Ruyter JC, Olthof MO, Kuijper LDJ, Liem G, Seidell JC, Katan MB. Short-term satiety and long-term weight effects of sugarfree and sugar-sweetened beverages in children. *Obes Facts.* 2013;6:33.
409. De Sagrario Lopez-Meza M, Estrada JA, Otero-Ojeda GA, Esquivel-Hernandez FJ, Contreras I. Alterations in attention and memory in people with normal body mass index related to frequent sucralose or sucrose intake. *FASEB J.* 2018;32. doi: 10.1096/fasebj.2018.32.1\_supplement.lb450.
410. den Biggelaar L, Sep SJS, Mari A, Ferrannini E, van Dongen M, Wijckmans NEG, et al. Association of artificially sweetened and sugar-sweetened soft drinks with  $\beta$ -cell function, insulin sensitivity, and type 2 diabetes: the Maastricht Study. *Eur J Nutr.* 2020;59:1717–27. doi: 10.1007/s00394-019-02026-0.
411. Deschamps I, Tichet J, Lestrade H. [Influence of cyclamate on blood sugar in normal and diabetic children]. *Le Diabete.* 1971;19:21–3 (in French).
412. Fantino M, Fantino A, Matray M, Mistretta F. Reprint of "Beverages containing low energy sweeteners do not differ from water in their effects on appetite, energy intake and food choices in healthy, non-obese French adults". *Appetite.* 2018;129:103–12. doi: 10.1016/j.appet.2018.06.036.
413. Farr OM. Acute diet soda consumption alters brain responses to food cues in humans: a randomized, controlled, cross-over pilot study. *Nutr Health.* 2021;260106021993753. doi: 10.1177/0260106021993753.
414. Forster H. [Influence of the sweetening agent aspartame on appetite]. *Aktuelle Ernährungsmedizin Klinik und Praxis.* 1993;18:331–7 (in German).
415. Franchi F, Yaranov DM, Rollini F, Rivas A, Rivas Rios J, Been L, et al. Effects of D-allulose on glucose tolerance and insulin response to a standard oral sucrose load: results of a prospective, randomized, crossover study. *BMJ Open Diabetes Res Care.* 2021;9. doi: 10.1136/bmjdr-2020-001939.
416. Friedhoff R, Simon JA, Friedhoff AJ. Sucrose solution vs. no-calorie sweetener vs. water in weight gain. *J Am Diet Assoc.* 1971;59:485–6.

417. Fritschka E. Intensive Zuckersenkung wirkt nicht nach. *Fortschr Med.* 2019;161:40. doi: 10.1007/s15006-019-1120-5.
418. Fuentealba Arevalo F, Espinoza Espinoza J, Salazar Ibacache C, Duran Aguero S. Consumption of non-caloric sweeteners among pregnant Chileans: a cross-sectional study. *Nutr Hosp.* 2019;36:890–7. doi: 10.20960/nh.2431.
419. Gehring F. [Caries prevention by use of sugar substitutes]. *Zahnärztl Mitt.* 1990;80:900–10 (in German).
420. Gibson SA, Horgan GW, Francis LE, Gibson AA, Stephen AM. Low calorie beverage consumption is associated with energy and nutrient intakes and diet quality in British adults. *Nutrients.* 2016;8. doi: 10.3390/nu8010009.
421. Ginieis R, Franz EA, Oey I, Peng M. The “sweet” effect: comparative assessments of dietary sugars on cognitive performance. *Physiol Behav.* 2018;184:242–7. doi: 10.1016/j.physbeh.2017.12.010.
422. Gligore V, Fekete T, Lucaciu O, Ticlete I, Motocu M. [Therapeutic value of a calorie-free diet in obesity]. *Medicina Interna.* 1971;23:1065–72 (in Romanian).
423. Goto R, Masuoka H, Yoshida K, Mori M, Miyake H. [A case control study of cancer of the pancreas]. *Gan No Rinsho.* 1990;Spec No:344–50 (in Japanese).
424. Griffioen-Roose S, Smeets PAM, Weijzen PLG, van Rijn I, van den Bosch I, de Graaf C. Effect of replacing sugar with non-caloric sweeteners in beverages on the reward value after repeated exposure. *PLoS One.* 2013;8:e81924. doi: 10.1371/journal.pone.0081924.
425. Grotz VL, Pi-Sunyer X, Porte D, Jr., Roberts A, Richard Trout J. A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis. *Regul Toxicol Pharmacol.* 2017;88:22–33. doi: 10.1016/j.yrtph.2017.05.011.
426. Gui Z-H, Zhu Y-N, Cai L, Sun F-H, Ma Y-H, Jing J, et al. Sugar-sweetened beverage consumption and risks of obesity and hypertension in Chinese children and adolescents: a national cross-sectional analysis. *Nutrients.* 2017;9:1302. doi: 10.3390/nu9121302.
427. He B, Long W, Li X, Yang W, Chen Y, Zhu Y. Sugar-sweetened beverages consumption positively associated with the risks of obesity and hypertriglyceridemia among children aged 7–18 years in south China. *J Atheroscler Thromb.* 2018;25:81–9. doi: 10.5551/jat.38570.
428. Heckenmueller S, Ferriday D, Brunstrom JM, Potter C, Rogers PJ. Different effects of sweet and low-sweet drinks on expected snack intake: the role of sensory-specific satiety and drink energy content. *Appetite.* 2021;157:104948. doi: 10.1016/j.appet.2020.104948.
429. Hennon DK. Low-caloric beverages and dental health. *J Indiana Dent Assoc.* 1965;44:275.
430. Hong J, Whelton H, Douglas G, Kang J. Consumption frequency of added sugars and UK children’s dental caries. *Community Dent Oral Epidemiol.* 2018;46:457–64. doi: 10.1111/cdoe.12413.
431. Hu Y, Costenbader KH, Gao X, Al-Daabil M, Sparks JA, Solomon DH, et al. Sugar-sweetened soda consumption and risk of developing rheumatoid arthritis in women. *Am J Clin Nutr.* 2014;100:959–67. doi: 10.3945/ajcn.114.086918.
432. Cochrane Registry of Controlled Trials. Comparing the tendency to tea sweetened with stevia to sugar (Ircct20140310016925N). 2018 (<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01906206/full>, accessed 8 November 2021).
433. Ismail AI, Burt BA, Eklund SA. The cariogenicity of soft drinks in the United States. *J Am Dent Assoc.* 1984;109:241–5.

434. Jensen OM, Kamby C. Intra-uterine exposure to saccharin and risk of bladder cancer in man. *Int J Cancer*. 1982;29:507–9. doi: 10.1002/ijc.2910290504.
435. Johnson L, Mander AP, Jones LR, Emmett PM, Jebb SA. Is sugar-sweetened beverage consumption associated with increased fatness in children? *Nutrition*. 2007;23:557–63. doi: 10.1016/j.nut.2007.05.005.
436. Kant AK. Interaction of body mass index and attempt to lose weight in a national sample of US adults: association with reported food and nutrient intake, and biomarkers. *Eur J Clin Nutr*. 2003;57:249–59. doi: 10.1038/sj.ejcn.1601549.
437. Kenney EL, Gortmaker SL. United States adolescents' television, computer, videogame, smartphone, and tablet use: associations with sugary drinks, sleep, physical activity, and obesity. *J Pediatr*. 2017;182:144–9. doi: 10.1016/j.jpeds.2016.11.015.
438. Kim H, Hu EA, Rebholz CM. Ultra-processed food intake and mortality in the USA: results from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994). *Public Health Nutr*. 2019;22:1777–85. doi: 10.1017/S1368980018003890.
439. Koebnick C, Black MH, Wu J, Shu Y-H, MacKay AW, Watanabe RM, et al. A diet high in sugar-sweetened beverage and low in fruits and vegetables is associated with adiposity and a pro-inflammatory adipokine profile. *Br J Nutr*. 2018;120:1230–9. doi: 10.1017/S0007114518002726.
440. Kruesi MJ, Rapoport JL, Cummings EM, Berg CJ, Ismond DR, Flament M, et al. Effects of sugar and aspartame on aggression and activity in children. *Am J Psychiatry*. 1987;144:1487–90. doi: 10.1176/ajp.144.11.1487.
441. Laforest-Lapointe I, Becker AB, Mandhane PJ, Turvey SE, Moraes TJ, Sears MR, et al. Maternal consumption of artificially sweetened beverages during pregnancy is associated with infant gut microbiota and metabolic modifications and increased infant body mass index. *Gut Microbes*. 2021;13:1–15. doi: 10.1080/19490976.2020.1857513.
442. Larsson SC, Akesson A, Wolk A. Sweetened beverage consumption is associated with increased risk of stroke in women and men. *J Nutr*. 2014;144:856–60. doi: 10.3945/jn.114.190546.
443. Larsson SC, Giovannucci EL, Wolk A. Sweetened beverage consumption and risk of biliary tract and gallbladder cancer in a prospective study. *J Natl Cancer Inst*. 2016;108. doi: 10.1093/jnci/djw125.
444. Lemeshow AR, Rimm EB, Hasin DS, Gearhardt AN, Flint AJ, Field AE, et al. Food and beverage consumption and food addiction among women in the Nurses' Health Studies. *Appetite*. 2018;121:186–97. doi: 10.1016/j.appet.2017.10.038.
445. Lertrit A, Srimachai S, Saetung S, Chanprasertyothin S, Chailurkit LO, Areevut C, et al. Effects of sucralose on insulin secretion, GLP-1 release and gut microbiota in healthy subjects: a randomized double-blind, placebo controlled trial. *Cochrane Central Register of Controlled Trials*. 2017;38. doi: 10.1002/central/CN-01399975/full.
446. Lertrit A, Srimachai S, Saetung S, Chanprasertyothin S, Chailurkit LO, Areevut C, et al. Effects of sucralose on insulin and glucagon-like peptide-1 secretion in healthy subjects: a randomized, double-blind, placebo-controlled trial. *Nutrition*. 2018;55 56:125–30. doi: 10.1016/j.nut.2018.04.001.
447. Leung CW, DiMatteo SG, Gosliner WA, Ritchie LD. Sugar-sweetened beverage and water intake in relation to diet quality in US children. *Am J Prev Med*. 2018;54:394–402. doi: 10.1016/j.amepre.2017.11.005.
448. Lindseth GN, Coolahan SE, Petros TV, Lindseth PD. Neurobehavioral effects of aspartame consumption. *Res Nurs Health*. 2014;37:185–93. doi: 10.1002/nur.21595.

449. Lodefalk M, Aman J. Food habits, energy and nutrient intake in adolescents with type 1 diabetes mellitus. *Diabet Med.* 2006;23:1225–32. doi: 10.1111/j.1464-5491.2006.01971.x.
450. Lotto M, Strieder AP, Ayala Aguirre PE, Oliveira TM, Andrade Moreira Machado MA, Rios D, et al. Parental-oriented educational mobile messages to aid in the control of early childhood caries in low socioeconomic children: a randomized controlled trial. *J Dent.* 2020;101:103456. doi: 10.1016/j.jdent.2020.103456.
451. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation.* 2008;117:754–61. doi: 10.1161/CIRCULATIONAHA.107.716159.
452. Lutsey PL, Steffen LM, Virnig BA, Folsom AR. Diet and incident venous thromboembolism: the Iowa Women's Health Study. *Am Heart J.* 2009;157:1081–7. doi: 10.1016/j.ahj.2009.04.003.
453. Maillot M, Vieux F, Rehm CD, Rose CM, Drewnowski A. Consumption patterns of milk and 100% juice in relation to diet quality and body weight among United States children: analyses of NHANES 2011–16 data. *Front Nutr.* 2019;6:117. doi: 10.3389/fnut.2019.00117.
454. Maki KC, Curry LL, Carakostas MC, Tarka SM, Reeves MS, Farmer MV, et al. The hemodynamic effects of rebaudioside A in healthy adults with normal and low-normal blood pressure. *Food Chem Toxicol.* 2008;46 Suppl 7:S40–6. doi: 10.1016/j.fct.2008.04.040.
455. Maloney NG, Christiansen P, Harrold JA, Halford JCG, Hardman CA. Do low-calorie sweetened beverages help to control food cravings? Two experimental studies. *Physiol Behav.* 2019;208:112500. doi: 10.1016/j.physbeh.2019.03.019.
456. Markus CR, Rogers PJ. Effects of high and low sucrose-containing beverages on blood glucose and hypoglycemic-like symptoms. *Physiol Behav.* 2020;222:112916. doi: 10.1016/j.physbeh.2020.112916.
457. Marshall TA, Van Buren JM, Warren JJ, Cavanaugh JE, Levy SM. Beverage consumption patterns at age 13 to 17 years are associated with weight, height, and body mass index at age 17 years. *J Acad Nutr Diet.* 2017;117:698–706. doi: 10.1016/j.jand.2017.01.010.
458. Marshall TA, Curtis AM, Cavanaugh JE, VanBuren JM, Warren JJ, Levy SM. Description of child and adolescent beverage and anthropometric measures according to adolescent beverage patterns. *Nutrients.* 2018;10. doi: 10.3390/nu10080958.
459. Marshall T, Curtis A, Cavanaugh J, Warren J, Levy S. Associations between child and adolescent beverage intakes and age 17-year percent body fat (P21-064-19). *Curr Dev Nutr.* 2019;3. doi: 10.1093/cdn/nzz041.P21-064-19.
460. Marshall TA, Curtis AM, Cavanaugh JE, Warren JJ, Levy SM. Child and adolescent sugar-sweetened beverage intakes are longitudinally associated with higher body mass index z scores in a birth cohort followed 17 years. *J Acad Nutr Diet.* 2019;119:425–34. doi: 10.1016/j.jand.2018.11.003.
461. Marshall TA, Curtis AM, Cavanaugh JE, Warren JJ, Levy SM. Beverage intakes and toothbrushing during childhood are associated with caries at age 17 years. *J Acad Nutr Diet.* 2021;121:253–60. doi: 10.1016/j.jand.2020.08.087.
462. Mayasari NR, Susetyowati, Wahyuningsih MSH, Probosuseno. Antidiabetic effect of rosella-stevia tea on prediabetic women in Yogyakarta, Indonesia. *J Am Coll Nutr.* 2018;37:373–9. doi: 10.1080/07315724.2017.1400927.
463. McNaughton SA, Mishra GD, Brunner EJ. Dietary patterns, insulin resistance, and incidence of type 2 diabetes in the Whitehall II Study. *Diabetes Care.* 2008;31:1343–8. doi: 10.2337/dc07-1946.

464. Meyer-Gerspach AC, Biesiekierski JR, Deloosse E, Clevers E, Rotondo A, Rehfeld JF, et al. Effects of caloric and noncaloric sweeteners on antroduodenal motility, gastrointestinal hormone secretion and appetite-related sensations in healthy subjects. *Am J Clin Nutr*. 2018;107:707–16. doi: 10.1093/ajcn/nqy004.
465. Miguel-Berges ML, Santaliestra-Pasias A, Iglesia-Altaba I, Flores-Barrantes P, Samper P, Moreno LA, et al. Association between beverages consumption and total diet quality index with sedentary behaviours in Spanish children: Calina study. *Proc Nutr Soc*. 2020;79:E468. doi: 10.1017/S0029665120004164.
466. Miranda Lora A, López Martínez B, Vilchis Ordoñez A, Klünder Klünder M. Effects of cola drinks with nutritive and nonnutritive sweeteners on glucose and gastrointestinal, pancreatic and adipose derived hormones: crossover trial. *Endocr Rev*. 2018;39. doi: 10.1093/edrv/39.suppl.1.
467. Mirghani H, Alali N, Albalawi H, Alselaimy R. Diet sugar-free carbonated soda beverage, non-caloric flavors consumption, and diabetic retinopathy: any linkage. *Diabetes Metab Syndr Obes*. 2021;14:2309–15. doi: 10.2147/dmso.s309029.
468. Morin C, Gandy J, Brazeilles R, Moreno LA, Kavouras SA, Martinez H, et al. Fluid intake patterns of children and adolescents: results of six Liq.In7 national cross-sectional surveys. *Eur J Nutr*. 2018;57:113–23. doi: 10.1007/s00394-018-1725-y.
469. Mullie P, Clarys P. Consumption of artificially sweetened beverages during pregnancy is associated with a twofold higher risk of infant being overweight at 1 year. *Evid Based Nurs*. 2017;20:11. doi: 10.1136/eb-2016-102558.
470. Nazari SSH, Mokhayeri Y, Mansournia MA, Khodakarim S, Soori H. Associations between dietary risk factors and ischemic stroke: a comparison of regression methods using data from the Multi-Ethnic Study of Atherosclerosis. *Epidemiol Health*. 2018;40:e2018021. doi: 10.4178/epih.e2018021.
471. Cochrane Central Register of Controlled Trials. Reducing sugar-sweetened beverage consumption in overweight adolescents. 2006 (<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02020326/full>, accessed 8 November 2021).
472. Cochrane Central Register of Controlled Trials. Chronic study on body composition, training, performance, and recovery. 2020 (<https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02054115/full>, accessed 8 November 2021).
473. Papakonstantinou A. Effects of sugar-free products with added sweeteners on glycemic responses (NCT04857554). 2021 (<https://clinicaltrials.gov/ct2/show/NCT04857554>, accessed 8 November 2021).
474. NejadSadeghi E, Sadeghi R, Shojaeizadeh D, Yekaninejad MS, Djazayeri A, Majlesi F. Influence of lifestyle factors on body mass index in preschoolers in Behbahan city, southwest Iran, 2016. *Electron Physician*. 2018;10:6725–32. doi: 10.19082/6725.
475. Nicklas TA, Yang S-J, Baranowski T, Zakeri I, Berenson G. Eating patterns and obesity in children: the Bogalusa Heart Study. *Am J Prev Med*. 2003;25:9–16. doi: 10.1016/s0749-3797(03)00098-9.
476. Nissensohn M, Sánchez-Villegas A, Serra-Majem L. Beverage consumption habits amongst the Spanish population: association with total water and energy intake – findings of the ANIBES study. *Nutr Hosp*. 2015;32 Suppl 2:10325. doi: 10.3305/nh.2015.32.sup2.10325.
477. Patel L, Alicandro G, La Vecchia C. Low-calorie beverage consumption, diet quality and cardiometabolic risk factors in British adults. *Nutrients*. 2018;10. doi: 10.3390/nu10091261.

478. Petersen SB, Rasmussen MA, Olsen SF, Vestergaard P, Mølgaard C, Halldorsson TI, et al. Maternal dietary patterns during pregnancy in relation to offspring forearm fractures: prospective study from the Danish National Birth Cohort. *Nutrients*. 2015;7:2382–400. doi: 10.3390/nu7042382.
479. Porikos KP, Booth G, Van Itallie TB. Effect of covert nutritive dilution on the spontaneous food intake of obese individuals: a pilot study. *Am J Clin Nutr*. 1977;30:1638–44. doi: 10.1093/ajcn/30.10.1638.
480. Porikos KP, Hesser MF, Van Itallie TB. Caloric regulation in normal-weight men maintained on a palatable diet of conventional foods. *Physiol Behav*. 1982;29:293–300. doi: 10.1016/0031-9384(82)90018-x.
481. Qiu C, Hou M. Association between food preferences, eating behaviors and socio-demographic factors, physical activity among children and adolescents: a cross-sectional study. *Nutrients*. 2020;12. doi: 10.3390/nu12030640.
482. Rusmevichientong P, Mitra S, McEligot AJ, Navajas E. The association between types of soda consumption and overall diet quality: evidence from National Health and Nutrition Examination Survey (NHANES). *Calif J Health Promot*. 2018;16:24–35.
483. Samman M, Kaye E, Cabral H, Scott T, Sohn W. The effect of diet drinks on caries among US children: cluster analysis. *J Am Dent Assoc*. 2020;151:502–9. doi: 10.1016/j.adaj.2020.03.013.
484. Shaywitz BA, Sullivan CM, Anderson GM, Gillespie SM, Sullivan B, Shaywitz SE. Aspartame, behavior, and cognitive function in children with attention deficit disorder. *Pediatrics*. 1994;93:70–5.
485. Shin S, Kim S-A, Ha J, Lim K. Sugar-sweetened beverage consumption in relation to obesity and metabolic syndrome among Korean adults: a cross-sectional study from the 2012–2016 Korean National Health and Nutrition Examination Survey (KNHANES). *Nutrients*. 2018;10. doi: 10.3390/nu10101467.
486. Soparkar PM, Newman MB, Hein JW. Comparable effects of saccharin and aspartame sweetened sugarless chewing gums on plaque pH. *J Dent Res*. 1978;57:196.
487. Stamatakis NS, Scott C, Elliott R, McKie S, Bosscher D, McLaughlin JT. Stevia beverage consumption prior to lunch reduces appetite and total energy intake without affecting glycemia or attentional bias to food cues: a double-blind randomized controlled trial in healthy adults. *J Nutr*. 2020;150:1126–34. doi: 10.1093/jn/nxaa038.
488. Stookey JD, Constant F, Gardner CD, Popkin BM. Replacing sweetened caloric beverages with drinking water is associated with lower energy intake. *Obesity (Silver Spring)*. 2007;15:3013–22. doi: 10.1038/oby.2007.359.
489. Storey KE, Forbes LE, Fraser SN, Spence JC, Plotnikoff RC, Raine KD, et al. Diet quality, nutrition and physical activity among adolescents: the Web-SPAN (Web-Survey of Physical Activity and Nutrition) project. *Public Health Nutr*. 2009;12:2009–17. doi: 10.1017/S1368980009990292.
490. Sushanthi S, Leelavathi L, Indiran MA, Rathinavelu PK, Rajesh Kumar S. Assessing the effect of natural sweetener on salivary pH and *Streptococcus mutans* growth: an in vivo study. *Int J Res Pharm Sci*. 2021;12:180–5. doi: 10.26452/ijrps.v12i1.3975.
491. Sylvestsky AC, Chandran A, Talegawkar SA, Welsh JA, Drews K, El Ghormli L. Consumption of beverages containing low-calorie sweeteners, diet, and cardiometabolic health in youth with type 2 diabetes. *J Acad Nutr Diet*. 2020;120:1348–58.e6. doi: 10.1016/j.jand.2020.04.005.

492. Sylvetsky AC, Sen S, Merkel P, Dore F, Stern DB, Henry CJ, et al. Consumption of diet soda sweetened with sucralose and acesulfame-potassium alters inflammatory transcriptome pathways in females with overweight and obesity. *Mol Nutr Food Res*. 2020;64:e1901166. doi: 10.1002/mnfr.201901166.
493. Tey SL, Salleh NB, Henry J, Forde CG. Effects of aspartame-, monk fruit-, stevia- and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *Int J Obes (Lond)*. 2017;41:450–7. doi: 10.1038/ijo.2016.225.
494. Thomson P, Santibanez R, Aguirre C, Galgani JE, Garrido D. Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults. *Br J Nutr*. 2019;122:856–62. doi: 10.1017/S0007114519001570.
495. Tucker KL, Morita K, Qiao N, Hannan MT, Cupples LA, Kiel DP. Colas, but not other carbonated beverages, are associated with low bone mineral density in older women: the Framingham Osteoporosis Study. *Am J Clin Nutr*. 2006;84:936–42. doi: 10.1093/ajcn/84.4.936.
496. Turner-McGrievy G, Wang X, Popkin B, Tate DF. Tasting profile affects adoption of caloric beverage reduction in a randomized weight loss intervention. *Obes Sci Pract*. 2016;2:392–8. doi: 10.1002/osp4.64.
497. van den Eeden SK. A randomized crossover trial of aspartame and sleep. *Am J Clin Nutr*. 1991;53:30.
498. Walker AM, Dreyer NA, Friedlander E, Loughlin J, Rothman KJ, Kohn HI. An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. *Am J Public Health*. 1982;72:376–81. doi: 10.2105/ajph.72.4.376.
499. Walton RG, Hudak R, Green-Waite RJ. Adverse reactions to aspartame: double-blind challenge in patients from a vulnerable population. *Biol Psychiatry*. 1993;34:13–17. doi: 10.1016/0006-3223(93)90251-8.
500. Wang Q-P, Simpson SJ, Herzog H, Neely GG. Chronic sucralose or L-glucose ingestion does not suppress food intake. *Cell Metab*. 2017;26:279–80. doi: 10.1016/j.cmet.2017.07.002.
501. Williams RD, Jr., Housman JM, Odum M, Rivera AE. Energy drink use linked to high-sugar beverage intake and BMI among teens. *Am J Health Behav*. 2017;41:259–65. doi: 10.5993/AJHB.41.3.5.
502. Wilson JF. Lunch eating behavior of preschool children: effects of age, gender, and type of beverage served. *Physiol Behav*. 70:27–33. doi: 10.1016/s0031-9384(00)00230-4.
503. Yao R, Couch S, Khoury J, Lee SY. The association between beverage consumption and food security status in US adults: findings from NHANES 2009–2010. *FASEB J*. 2014;28:805.17. doi: 10.1096/fasebj.28.1\_supplement.805.17.
504. Young RL, Kreuch D, Mobegi FM, Leong L, Schober G, Isaacs NJ, et al. Low-calorie sweeteners disrupt the gut microbiome in healthy subjects in association with impaired glycaemic control. *Diabetologia*. 2018;61:S123. doi: 10.1007/s00125-018-4693-0.
505. Zanela NLM, Bijella MFTB, Pereira da Silva RO. The influence of mouthrinses with antimicrobial solutions on the inhibition of dental plaque and on the levels of mutans streptococci in children. *Braz Oral Res*. 2002;16:101–6. doi: 10.1590/s1517-74912002000200002.
506. Zhang S, Gu Y, Bian S, Lu Z, Zhang Q, Liu L, et al. Soft drink consumption and risk of nonalcoholic fatty liver disease: results from the Tianjin Chronic Low-Grade Systemic Inflammation and Health (TCLSIH) cohort study. *Am J Clin Nutr*. 2021;113:1265–74. doi: 10.1093/ajcn/nqaa380.
507. Zollner N, Pieper M. [Concluding report of a 3-year clinical study on cyclamate]. *Arzneimittelforschung*. 1971;21:431–2 (in German).







**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](mailto:nutrition@who.int)**

**<https://www.who.int/teams/nutrition-and-food-safety>**

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