

Office of Evidence Based Practice – Specific Care Question: Artificial Sweeteners

Specific Care Question:

In children and adults does the consumption of beverages, including soda sweetened with non nutritive sweeteners (NNS) such as (aspartame, acesulfame K, saccharin, stevia, and sucralose) versus the consumption of beverages, including soda sweetened with nutritive sweeteners (NS) such as sucrose and high fructose corn syrup have an effect on:

- Body weight as evidenced by change in body weight, BMI, or waist circumference
- Risk of blood or solid tumors
- Food intake, satiety
- Hormonal response to foods and metabolic control
- Outcome of pregnancy
- Risk of vascular events (cardio or neurovascular)

Question Originator:

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Plain Language Summary from The Office of Evidence Based Practice: The CDC (2011) recommends limiting the sale of drinks with added sugars as a strategy to “Rethink your Drink” and reduce calories from low nutrient dense foods. As part of the Partnership for a Healthier America Campaign, the sale of sugared beverages (those sweetened with sugar a nutritive sweetener (NS)) was discontinued at Children’s Mercy on January 1, 2013. The question that arose is “are drinks sweetened with non-nutritive sweeteners (NNS) good for you?”

No governmental or professional organization makes a statement preferring beverages with NNS over healthy beverage choices, such as water, low fat/nonfat milk, or 100% juice in 4 oz portions. They have made statements regarding the safety of NNS:

1. The Food and Drug Administration (FDA) set the following limits for intake:

Name	Acceptable Daily Intake (ADI)	Estimated Daily Intake	Number of 12 oz cans containing sweetener to reach the ADI
Aspartame	50 mg/kg BW	0.2-4.1 mg/kg BW	17
Acesulfame K ¹	15 mg/kg BW	0.2-1.7 mg/kg BW	25.6
Saccharin	No ADI	0.1-2 mg/kg BW	2.4
Stevia	4 mg/kg BW	1.3-3.4 mg/kg BW	N/A ²
Sucralose	5 mg/kg BW	0.1-2.0 mg/kg BW	4.8

¹ Acesulfame K is usually mixed with 90 mg aspartame

² Stevia is not widely used in sweetening soda.

2. USDA (2010) states using NNS instead of sugar may reduce calorie intake, but not enough is known about the efficacy of NNS as a weight loss strategy.
3. American Diabetes Association (ADA, 2013) urges consumers to use NNS in compliance with the guidance provided by the FDA.

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4. The Academy of Nutrition and Dietetics (AND, 2012) recommends consumers use NNS within the ADI to sweeten foods without adding unnecessary carbohydrates.
5. The National Cancer Institute (National Cancer Institute, 2009) states in the U.S. as of 2009 there is no clear evidence of NNS being associated with cancer risk.

The literature on this topic is divergent. Randomized control trials are difficult to conduct since the outcomes of interest can take years to develop. Large cohort studies that have addressed these questions can only produce associations. It is known that NS play a role in excess daily calorie intake, and are linked to obesity, but the role of NNS and weight maintenance or loss is not clear (AND, 2012, ADA, 2013, USDA, 2010).

Harm related to the use of NNS is also unclear. Shiffman (2012) comments there are significant gaps in what is known about NNS including the pharmacokinetics, “sweetener-drug” interactions, and the role NNS play in body weight regulation.

Based on the evidence included in this review and the recommendations made by the FDA, USDA, ADA, AND, and the NCI restricting the sale of beverages sweetened with NNS is not warranted at this time. Further research may influence our confidence in the estimate of effect and may change the outcome of this review.

The section below labeled Thumbnails has been added to help the reader; Control/Click on the first author’s name of each article will link to the further figures and details pertaining to that study.

Thumbnails

BMI Weight Change

(de Ruyter, Olthof, Kuijper, & Katan, 2012) USA	Risk of bias was low although subjects were able to tell they were assigned to the NNS group.	Those randomized to the NNS group had significantly greater weight loss than those in the NS beverage group.
(Duffey, Steffen, Van Horn, Jacobs, & Popkin, 2012) USA	Risk of bias is moderate. Large adult cohort study, the CARDIA Study.	Those who did not drink NNS beverages did not have higher risk of elevated fasting blood glucose or blood lipid levels over twenty years.



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(Ebbeling et al., 2012) USA	Risk of bias is low. Adolescents.	There was a significant difference in BMI change in all subjects at 2 years. For those in the NNS beverage group, weight loss was significantly greater. There was a difference between ethnicities. Non Hispanics had higher BMIs at two years, whereas Hispanic subjects who drank NNS beverages had significantly lower BMI at 2 years.
(Tate et al., 2012) USA	Risk of bias is low.	There was no difference between those who drank water and those who drank NNS beverages, outcome weight loss.
(Vanselow et al 2009 USA, Pereira, Neumark-Sztainer, & Raatz, 2009) USA	Risk of bias is high. It is a prospective cohort study of adolescents; follow-up of subjects does not reach 80%.	Low calorie beverage intake was significantly related to weight gain. Intake of sports drinks or soy milk was not evaluated. BMI was calculated on self report, not measured values.

Overall, the strength of the evidence is low. Most evidence comes from cohort studies that produce associations, not cause and effect. Although the risk of bias in these cohort studies is low, by design, the strength of the evidence is low. Furthermore, the results cannot be grouped due to the heterogeneity of treatments, length of treatment and outcomes followed. No recommendation regarding the consumption of NNS beverages and BMI or weight change can be made at this time.

Cancers

(Schernhammer et al., 2012) USA	Risk of bias is moderate. Adults, the Nurses' Health Study and the Health Professionals Follow-up Study.	Consumption of NNS beverage was not associated with the risk of multiple myeloma or non-Hodgkin's lymphoma (NHL) in women. Consumption of NNS beverage was associated with the risk of multiple myeloma and NHL in men Consumption of NNS beverage was associated with the risk of leukemia in both men and women.
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Although this is a large cohort study that was well managed, the results are still associative, not causative. Risk for multiple myeloma, NHL and leukemia vary on amount of NNS beverage consumed. It appears the risk for men is greater than the risk for women. Time to incident diagnosis was not assessed in the study.

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Food intake/ Satiety

(Anton et al., 2010) USA	Risk of bias is high Although it is an RCT, the confidence intervals are wide, and the findings are not precise.	After a preload of NS beverage or NNS beverage, calorie intake at the next two meals (lunch and dinner) was not significantly different.
(Appleton & Blundell, 2007) UK	Risk of bias is moderate. Allocation concealment and blinding are not described.	Habitual high consumers vs. habitual low consumers of NNS beverages did not show difference in energy intake over the rest of one day. There was a difference between the two types of consumers that was independent of pre-load.
(Garnier-Sange, Lebalnc, & Verger, 2001) France	Risk of bias is high. It is a self reported survey.	Children with Type 1 diabetes mellitus were surveyed for 5 day food diaries. Food intake was assessed for amount of 5 different NNS and the Theoretical Maximum Daily Intake (TMDI) was calculated and compared to the Acceptable Daily Intake (ADI). In no instance was the amount consumed by this group, who is likely to consume NNS, near the ADI.
(Tate, et al., 2012) USA	The risk of bias is low.	Consumption of NNS beverage versus water, the sum of calories from all beverage sources over 6 months was not different between groups. Consumption of NNS beverages versus water, the average daily caloric intake was different between groups.

The strength of evidence from the included studies is low. Tate et al (2012) is the stronger of the included studies, but small sample sizes make conclusions difficult to confirm. The data presented by Garnier-Sange et al. (2001) are reassuring that in a likely group of consumers of NNS, the ADI was not reached.

Hormone response/Metabolic Control

(Borstov et al., 2011) USA	Risk of bias is high. Cross-sectional survey Children with Type 1 DM (≥ 10 years)	As NNS beverage intake increase, HbA1c values were higher. As NNS beverage intake increase, serum LDL levels increased. As NNS beverage intake increased, diastolic blood pressure was the same.
(Brown Walter, & Rother, 2009), USA	The risk of bias is low. Crossover design. Oral glucose tolerance test after NNS beverage or NS beverage.	Neither Glucose (AUC), nor Insulin (AUC) were significantly different at 180 minutes between interventions. GLP-1 was significantly higher in the NSS group at 180 minutes. The clinical significance of this finding is unknown.

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(Brown, de Banate, & Rother, 2010) USA	Risk of bias in the included studies is high. Great heterogeneity among the included studies. Systematic review of pediatric cohort studies.	16 studies were included. Nine showed a positive correlation between NNS beverage intake and body weight/BMI. The three interventional studies show no effect of the consumption of NNS beverage on weight loss or BMI. Two of the included studies assess the relationship between NNS beverage on metabolic syndrome and found no causative or associative effects.
(Fgherazzi et al, 2013) France	Risk bias is moderate. It is a well done, large cohort study.	Both the consumption of NS (>11 oz/ week) and NNS (>20/wk) beverages were associated with Type 2 diabetes. Consumption of 100% fruit juice was not. Sensitivity analysis was done and BMI partly mediated the effect. The study included women only.
(De Koning, Malik, Rimm, Willett, & Hu, 2011) USA	Risk of bias is moderate. Large adult cohort study the Health Professionals Follow-up Study.	Consumption of NNS beverages was associated with overall higher diet quality. Intake of NNS was not associated with Type 2 diabetes.
(Lin & Curhan, 2011)	Risk of bias is moderate. It is a well done large cohort study	Two servings or more than 2 servings per day of NNS soda were associated with faster kidney function decline. No association between lower levels of NNS soda intake was associated with decline. No significant associations with MA or eGFR decline were noted for any of the NS soda categories.
(Nettleton et al., 2009) USA	Risk of bias is low Adults	The risk of metabolic syndrome is 36% greater in those who drank ≥ 1 serving of NNS soda per day. However, adjusting for adiposity made the results non significant. If subjects who were positive for any indicator of metabolic syndrome at baseline were excluded, the hazard ratio of subsequently acquiring metabolic syndrome was non-significant.
(Wiebe et al., 2011) Canada	This is a meta analysis of 53 adult RCTs. The risk of bias in the included studies is high. The number of subjects in each study is small and 13/53 studies followed subjects for > 1 week.	Those who drank NNS beverages had greater weight loss. Energy intake over one day was not statistically different between those who drank NS beverages and those who drank NNS beverages, but may have been clinically significant. The consumption of NNS beverages had no effect on HbgA1c or blood lipid levels. Although this is a meta-analysis the included studies are of very low to low quality. The major finding is that adequately powered randomized controlled trials are needed to provide answers.

The studies included in this outcome have high heterogeneity. As such, it is difficult to pool results to strengthen estimates of effect.

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Pregnancy

(Englund-Ogge et al., 2012) Norway	The risk of bias is low. Data is from a large cohort study of women of childbearing age, the Norwegian Mother and Child Cohort Study (1999-2008)	Statistically significant associations were found between the intake of > 1 serving per day NNS beverage (OR 1.11 95% CI [1.00, 1.24]) and NS beverage (OR 1.25 95% CI [1.08, 1.45]) intake and preterm birth. A dose response effect was found. Both NNS and NS increased the risk of preterm delivery. Both NNS and NS beverage intake increased with increasing BMI.
(Halldorsson, Strom, Petersen, & Olsen, 2010), Denmark	The risk of bias is low. Data is from a large cohort study of women of childbearing age, the Danish National Birth Cohort (1996-2002)	No association was seen between NS beverage consumption and preterm delivery. Intake of NNS beverage and preterm birth was strongly associated. Odds ratios increased as number of servings (250ml/serving) increased from < 1 per week to ≥ 4 per day. Women who consumed NNS soft drinks ≥ 1 per day had an adjusted OR of 1.38 95% CI {1.15, 1.65] Preterm delivery was driven by medically induced delivery rather than by spontaneous delivery in this cohort.

The included studies are two well-managed cohort studies. Other factors besides beverage intake are related to preterm birth.

Vascular Disease and Stroke

(Bernstein, de Koning, Flint, Rexrode, & Willett, 2012) USA	The risk of bias is low. Data is from the Nurses' Health Study and the Health Professionals Follow-up Study (Adults)	Increased consumption of NNS <u>AND</u> NS beverages was associated with higher risk of stroke in women.
(Gardener et al., 2012) USA	The risk of bias is low. Data is from a large, adult cohort study, the Northern Manhattan Study	Daily NNS soda consumption was associated with 43% increase risk of vascular events. Those who drank 1 NNS/month to 6/week did not have significantly increased risk.

The included studies show an association between NNS beverage consumption and risk of vascular disease and stroke. Both studies address the concern of reverse causality. Those with increased BMI choose NNS beverages and have increased risk for vascular disease/events independent of beverage choice.

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Search Strategy and Results:

The search of the medical literature was completed on Nov. 14, 2012. 86 citations were returned to the team leaders for them to review and select articles. From this list 36 articles were selected by the team leaders. After close reading of the selected articles by the EBP Scholars, 22 articles are included in this synopsis. (See the Reference list and the Table of Excluded Studies)

Method Used for Appraisal and Synthesis:

The Cochrane Collaborative computer program, Review Manager (RevMan 5.1.7) was used to synthesize 4 of the included studies. The remainder of the studies were analyzed using the Critical Appraisal Skills Programme (CASP) synthesis tools.

Updated February 8 2013 April 4, 2013, April 19 2013, August 5, 2013 August 29, 2013, September 11, 2013

Study Details

Characteristics of included studies- RCTs:

Tables:



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Brown 2009

Methods	Two 75-g oral glucose tolerance tests (OGTTs) on separate days after a 10-h fast. Cross over design
Participants	22 healthy subjects 12–25 years of age; 45% male, 41% Caucasian
Interventions	Intervention: 240 ml of caffeine-free NNS soda (Diet Rite cola) sweetened with sucralose and acesulfame- K 10 min prior to the glucose load. Control: 240 ml unflavored carbonated water, 10 min prior to the glucose load.
Outcomes	Serum glucose Serum insulin Serum GLP-1
Notes	Significance was only found for GLP-1; area under the curve at 180 minutes. The GLP-1 peak was significantly higher with NNS soda versus carbonated water (P= 0.003). Timing of the peak was not changed.

Risk of bias table

Bias	Scholars' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	States carbonated water or NNS soda were given in randomized order, but does not state how randomized.
Allocation concealment (selection bias)	Unclear risk	Does not state who knew which beverage was being served.
Blinding of participants and personnel (performance bias)	Unclear risk	Subjects would be able to tell if they were drinking the NS drink or not.
Blinding of outcome assessment (detection bias)	Low risk	Does not state if lab personnel who drew the lab knew if the subject consumed the intervention or control drink.
Incomplete outcome data (attrition bias)	Low risk	All completed the study, all results are reported.
Selective reporting (reporting bias)	Low risk	Not identified.
Other bias	Unclear risk	

de Ruyter 2012

Methods	Double-blind Randomized Controlled Trial
Participants	Children - 4 years 10 months to 11 years 11 months of age at eight elementary schools near Amsterdam. NNS group N=319. NS group N=322 Data was collected for 20 months: Nov 14 2009 to July 22 2011



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Inclusion criteria:

- Healthy school going boys and girls.
- Children who already habitually consume 250 mL per day or more of NS drinks.

Exclusion criteria:

- Using medication or under medical treatment for obesity.
- Any acute or chronic disease such as diabetes, growth disorders, Celiac disease, or serious gastroenterology (for example inflammatory bowel disease).
- Medical history or surgical events known to interfere with the study.
- Participation in another intervention trial up to 3 months before and during the study if the intervention interferes with the current study.
- Physical disabilities that hamper the measurements.
- Intention to change location of residence and primary school during the study period.

Interventions

NNS group- 1 can per day of a non-caloric, NNS, noncarbonated beverage.

NS group- a sugar-containing noncarbonated beverage was distributed to each child.

Outcomes

Primary outcome: BMI z score for age and sex.

Secondary outcomes waist to height ratio, sum of 4 skin fold measures, fat mass by electrical impedance.

Notes

Intent to treat analysis was preformed.

21% of NNS participants were able to correctly identify they were drinking NNS beverage while only 3% correctly identified their beverage in the NS group.

A total of 26% of the participants stopped consuming the beverages.

Risk of bias table

Bias	Scholars' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	The study used computer generated randomization.
Allocation concealment (selection bias)	Low risk	The study used computer generated randomization.
Blinding of participants and personnel (performance bias)	Unclear risk	21% of the NNS participants were able to correctly identify they were drinking NNS beverage while only 3% correctly identified their beverage in the NS group.
Blinding of outcome assessment (detection bias)	Low risk	Blinding of outcome assessment ensured.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data.

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Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified outcomes that are of interest in the review have been reported.
Other bias	Unclear risk	

Ebbeling 2012

Methods	Randomized control trial
Participants	N: 224; 124 boys and 100 girls; adolescents. Inclusion criteria: consume \geq 12oz serving per day of NS beverage or 100% fruit juice. Subjects were in 9th or 10th grade. BMI above the 85% for sex and age.
Interventions	Experimental: <ul style="list-style-type: none"> • 1-year home delivery of non-caloric beverages every 2 weeks. • Monthly motivation phone calls with parents lasting 30 minutes per call. • 3 check-in visits with subjects lasting 20 minutes per visit. • Written intervention with instruction to drink the beverages which were mailed to participants. • Gift cards were mailed to participants in control group at 4 and 8 months as a retention strategy. Control: \$50.00 supermarket gift cards
Outcomes	Primary outcome: BMI at 2 years
Notes	Performed sub-analysis based on ethnic group

Risk of bias table

Bias	Scholars' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Computer generated stratified random sequence of assignment that created sequences in permuted in blocks of 2 and 4. Separate sequences were generated for each stratum as defined by a combination of recruitment site, sex, and obesity status and stored in the data-management system.
Allocation concealment (selection bias)	Low risk	All personnel are masked to group assignment.
Blinding of participants and personnel (performance bias)	Low risk	Single blinded: subjects know which group they are in by the delivery of the beverages to their homes every 2 weeks.



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Blinding of outcome assessment (detection bias)	Low risk	Those who conducted phone interviews were not aware of group assignment. Used pre-determined open dialog for phone conversations for consistency.
Incomplete outcome data (attrition bias)	Low risk	Retention of subjects was 97% and 93% for years 1 and 2 respectively.
Selective reporting (reporting bias)	Low risk	Results were given for both the 1 and 2 year intervals.
Other bias	Low risk	The study appears to be free of other sources of bias.

Tate 2012

Methods	3-arm, single-center, single-blinded randomized clinical trial.
Participants	318 adults aged 18-65 who consumed ≥ 280 kcal per day in caloric beverages (excluding milk) were enrolled as participants and finished the study.
Interventions	Group 1: Water- replace ≥ 2 servings of NS soda (≥ 200 kcal per serving) with water N= 108 Group 2: NNS beverage - replace ≥ 2 servings of NS soda (≥ 200 kcal per serving) with NNS beverages N= 105 Group 3: Control - monthly group meetings and diet information N= 105
Outcomes	Outcomes were assessed at baseline, 3 months and 6 months <ul style="list-style-type: none"> • BMI • Blood pressure • Fasting blood samples • Urine osmolality • Dietary intake data • looked at weight loss, type of beverage/calories, and total
Notes	Supported by a grant from Nestle Waters USA. Water for the study was provided by Nestle Waters USA

Risk of bias table

Bias	Scholars' Judgment	Support for Judgment
Random sequence generation (selection bias)	Low risk	Computer-generated random-numbers method by the project coordinator.
Allocation concealment (selection bias)	Low risk	Allocation was concealed from the participants and investigators until randomization was revealed at the initial group session.
Blinding of participants and personnel (performance bias)	Low risk	Single blind
Blinding of outcome assessment (detection bias)	Low risk	



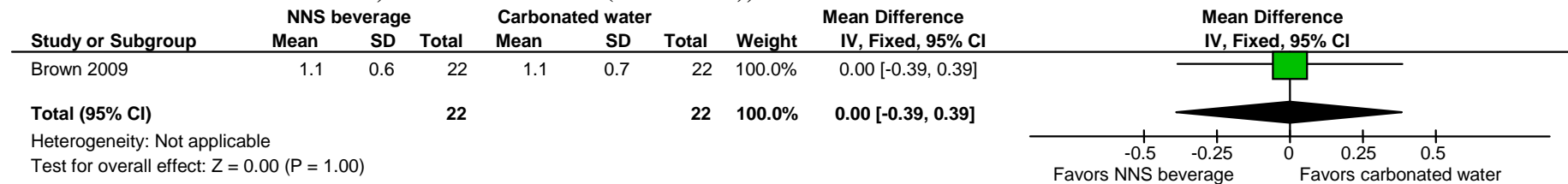
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Incomplete outcome data (attrition bias)	Low risk	84-88% completed the study across groups. However, data was analyzed with “intention to treat” analysis which maintains all initial subjects, minimizing bias.
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	To limit seasonal effects of beverage consumption, the study was conducted in 5 cohorts at different times of the year.

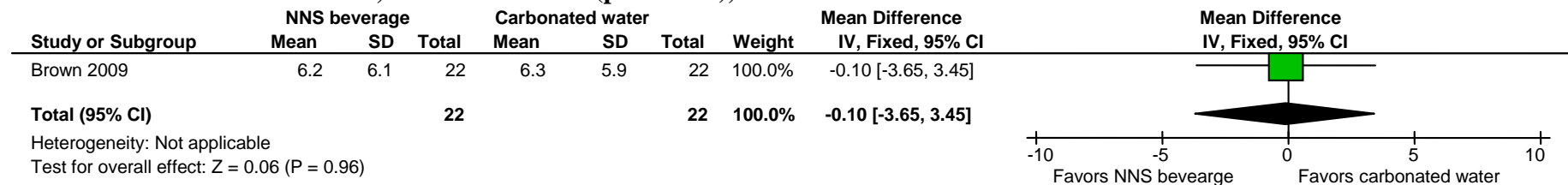
Figures: (For help reading forest plots, see Appendix 1)

Forest Plots of Comparisons

NNS soda vs. carbonated water, outcome: Glucose (mmol/liter), area under the curve at 180 minutes.

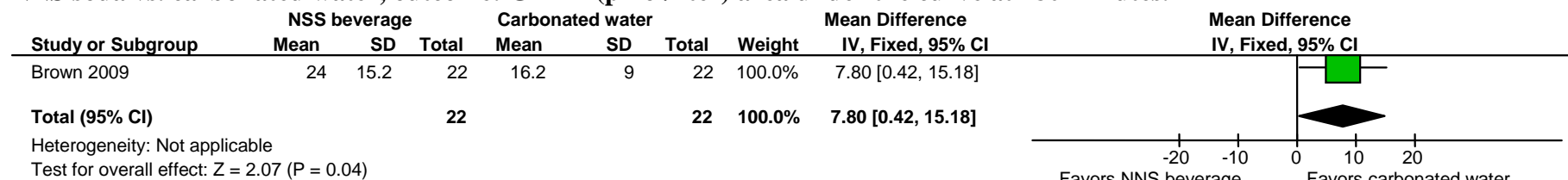


NNS soda vs. carbonated water, outcome: Insulin (pmol/liter), area under the curve at 180 minutes.

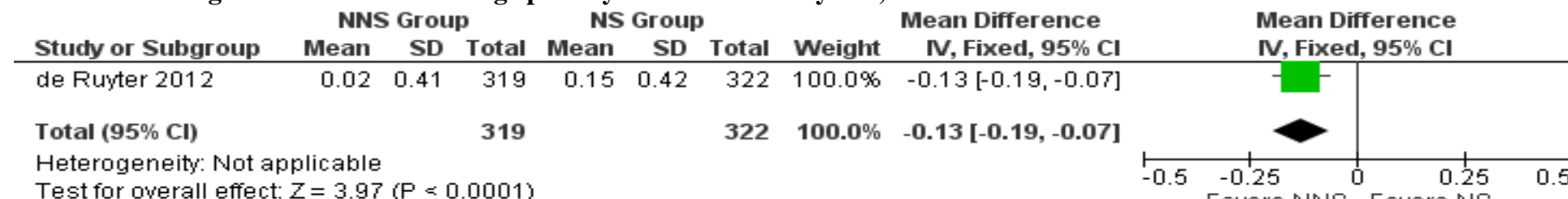


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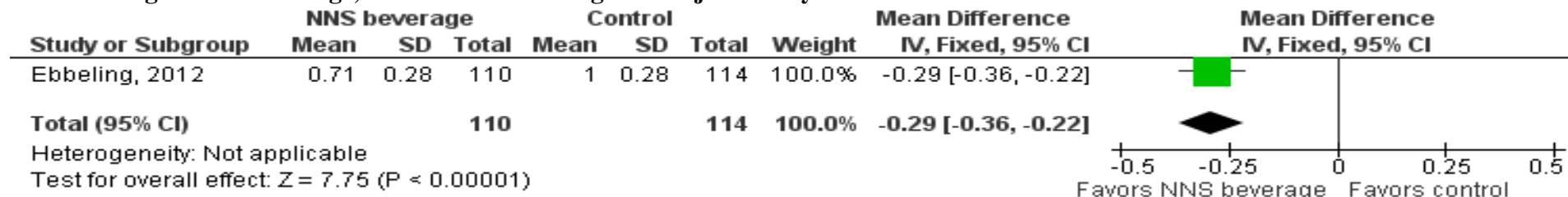
NNS soda vs. carbonated water, outcome: GLP-1 (pmol/liter) area under the curve at 180 minutes.



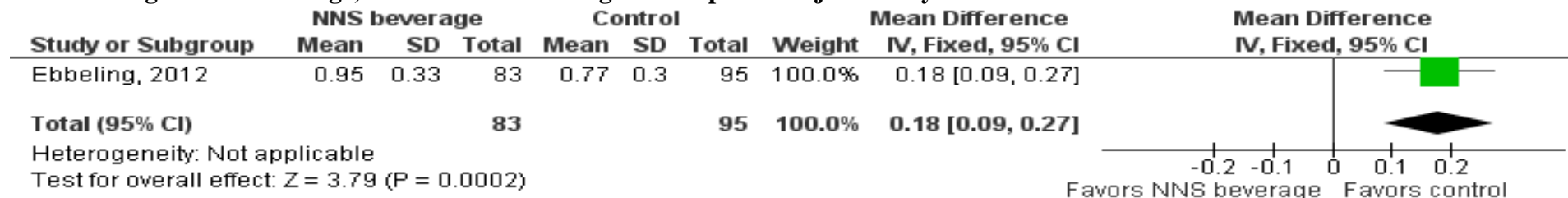
One NNS beverage versus one NS beverage per day in children 4-11 years, outcome: BMI z score at 18 months



NNS beverage vs. NS beverage, outcome: BMI change all subjects at 2 years.

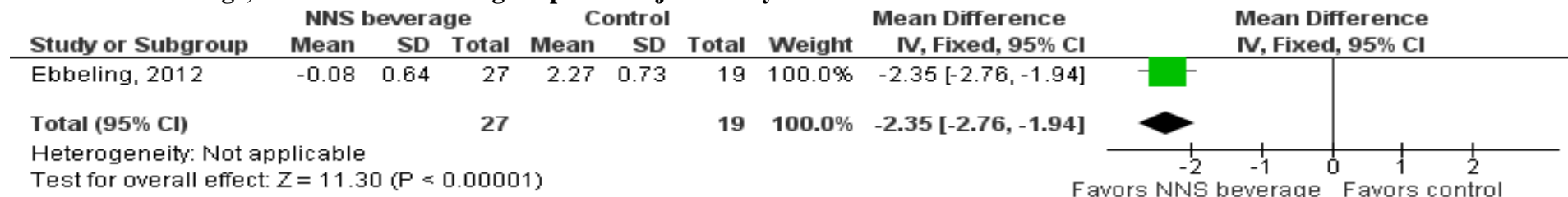


NNS beverage vs. NS beverage, outcome: BMI among non-Hispanic subjects at 2 years.

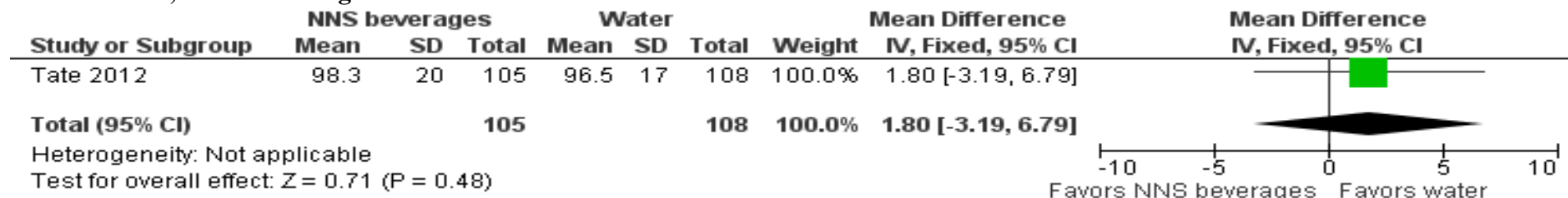


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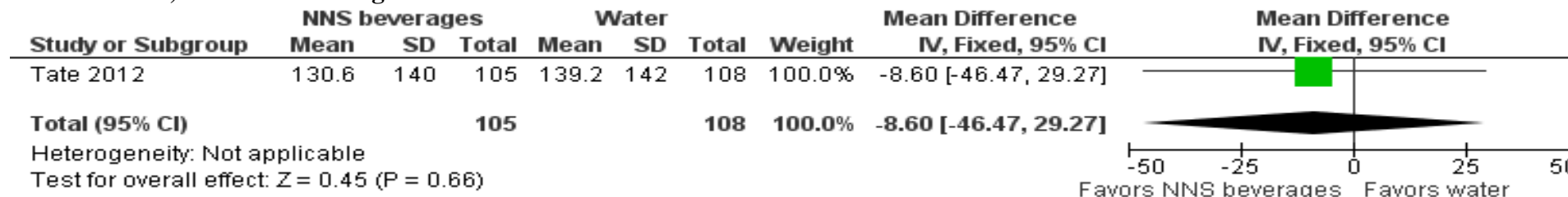
NNS vs. NS beverage, outcome: BMI among Hispanic subjects at 2 years.



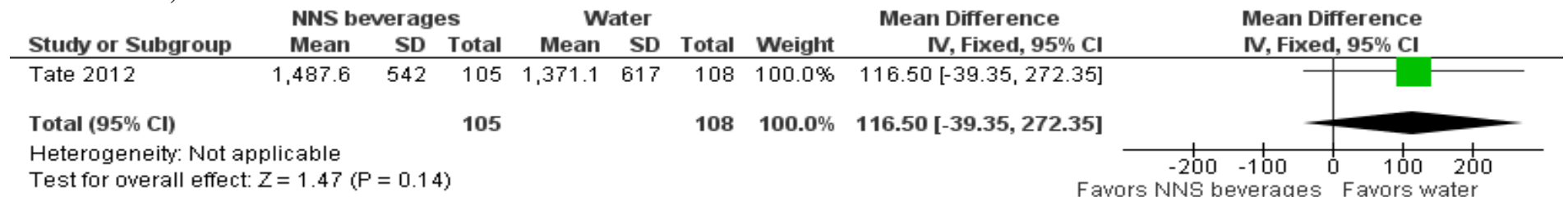
NNS vs. water, outcome: Weight loss.



NNS vs. water, outcome: Beverage calories.



NNS vs. water, outcome: Total calories.



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Critically Appraised Topic (CAT)

Author, date, country	Patient Group	Level of Evidence (Oxford)	Research design	Significant results	Limitations
BMI/Waist Circumference/Body weight					
Duffey 2012, USA	Young adults (18-30 years of age in 1985-1986)	Level 4	Inception cohort with < 80% follow-up (72% follow-up occurred). Young adults from the CARDIA Study. 4 cities in the US. Interviewer administered diet history at 2, 5, 7, 10, 15, and 20 y after baseline.	Subjects were separated into 4 subgroups from 2 groups: Followers of a Western diet (2,383 total): Consumers of NNS beverage (312) Non consumers of NNS beverage (2071) Followers of a Prudent diet (1,778 total): Consumers of NS beverage (613) Non consumers of NNS beverage (1165) Prudent diet is defined as: higher intake of fruit, whole grains, milk, nuts and seeds). Western diet is considered to be a higher intake of fast food, meat and poultry, pizza and snacks. Results were reported as Hazard Ratios (HR) ¹ For the Prudent versus Western diet comparison, for those who followed a Prudent diet there was no greater hazard of having a high waist circumference, high fasting glucose, but there was greater hazard of having low HDL-C, high TGs and high blood pressure 20 years later. For the Non consumer of NNS beverage versus Consumer of NNS beverages comparison, for those who did not consume NNS beverages there was no greater risk of high fasting glucose, low HDL-C, high TGs, or high blood pressure 20 years later. The hazard of metabolic syndrome was lower in both the Prudent diet group and the Non consumer group.	At the outset those who followed a Western diet and were consumers of NNS beverages had a higher BMI than those who either followed a Prudent diet (consumers & non consumers) and those who followed a Western diet and were non consumers.
Vanselow et al 2009 USA	Adolescents from 31 public middle and high schools in MN, USA N= 2,294 Males= 1,032; Females =	Level 2b	Prospective cohort with 78% follow-up Needs 80% follow-up to be considered good follow-up.	Unexpectedly, NS beverages were not shown to be positively associated with weight gain White milk was found to be inversely associated with weight gain There was a significant positive association between low calorie soft drink intake and weight gain. However, it was not present when adjustment for dieting and parental weight related concerns were used for adjustment.	Strengths of this study are it is a 5 year longitudinal evaluation of the associations between beverage consumption and BMI. A variety of beverages were compared; dieting and weight-concerns were taken into account. Limitations of this study are: -data was collected by self report over 5

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	1,262. Mean age 14.9 years.				years -drinks such as sports drinks, soy milk or almond milk were not taken into consideration -BMI was calculated on reported weight/height, not measured values
Cancers					
Schernhammer et al 2012 USA	Men and women in the Health Professionals Follow-up Study and the Nurses' Health Study	Level 1b	Observational Cohort study Data collected from food frequency questionnaires. Total aspartame was calculated from this resource.	<p>Of 121,701 female and 51,529 males who participated, 1,324 non-Hodgkin's lymphomas (1.1%), 285 multiple myelomas (0.2%) and 339 leukemia (0.3%) were identified over 22 years.</p> <p>Multiple versions of modeling were used. Men and women were analyzed separately to examine sex differences. Amount of NNS soda consumed daily and participant age were used as analysis groupings.</p> <p>The mean daily aspartame intake in consumers was 114 mg/d in the Nurses' Health Study and 102 mg/d in the Health Professional Follow up study (ADI is 50 mg/kg/BW in the USA).</p> <p>In men the risk for NHL was significantly increased for subjects who drank ≥ 1 serving of NNS soda per day (RR=1.31, 95% CI [1.01, 1.72] compared with those who reported no consumption. Risk was greater for those who consumed ≥ 2 servings per day RR=1.69, 95% CI [1.17, 2.45].</p> <p>There was no association between NNS soda consumption (≥ 2 servings per day) and risk of all NHL in women. RR=1.12, 95% CI [0.81, 1.56].</p> <p>Multiple myeloma risk was higher in men who drank ≥ 1 servings of NNS soda per day (RR=2.02, 95% CI [1.20,3.40]</p> <p>There was no association with risk of multiple myeloma in women with NNS soda consumption.</p> <p>Leukemia risk was elevated in high intake categories of NNS soda in both men and women. RR= 1.42. 95% CI [1.00, 2.02]</p> <p>Unexpectedly, a higher consumption of ≥ 1 NS</p>	<p>Only studied adults. May not be applicable to children.</p> <p>Relied on self reported food frequency questionnaires. However, they tried to minimize bias by using a prospective approach to collecting this data.</p> <p>Relied on self reported cancer diagnosis as well.</p>

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				soda was associated with higher risk of NHL RR= 1.66. 95% CI [1.10, 2.51] in men but not women.	
Food intake					
Anton et al 2010, USA	19 lean (BMI 20-24.9) and 12 obese (BMI 30-39.9) adults Age 19-50 years	Level 1b: Randomized Control trial with wide confidence intervals.	Cross over intervention study	In the preload with stevia vs. preload with sucrose group, calorie intake at lunch was not different between groups. In the preload with aspartame vs. the preload with sucrose group, calorie intake at lunch was not different between groups.	Wide confidence intervals
Appleton & Blundell 2007, UK	10 women – high consumers of NNS beverages 10 women low consumers of NNS beverages	Level 1b	Pre-load procedure. All subjects were tested with each preload and intake was measured after the preload. Preloads 330 ml of water (W), NNS beverage (NNS), and NS beverage (NS)	Test meal intake (NNS vs. W) - low consumers of NNS beverage consumed more after NNS compared to water. High NNS consumers showed no difference in consumption after an NNS preload compared to water. Test meal intake (NNS vs. NS) – No difference was seen between high and low habitual consumers and meal intake after a preload that contained NS. There was significant difference in intake between high and low consumers of NNS beverages, independent of preload.	Does not state if preloads were randomly assigned to subjects. Does not state if preload administration was blinded.
Garnier -Sagne, Leblanc & Verger, 2001	Survey of 227 children (112 girls, 115 boys) aged 2-20 years with Type 1 diabetes	Level 4: Survey	5 days food diary assessed for NNS intake (all types) from all sources to estimate the Theoretical Maximum Daily Intake (TMDI) and compare to the Acceptable Daily Intake (ADI) as determined by the 1994 European Directive 94/35/CE.	Of the 227 subjects who returned surveys, 192 subjects consumed aspartame. The ADI for aspartame = 40 mg/kg/d. The mean amount taken by the consumer group = 2.4 mg/kg/d (median= 1.1 mg/kg/d; maximum 15.6 mg/kg/d). Of the 227 subjects who returned surveys, 174 consumed saccharin. The ADI for saccharin = 5 mg/kg/d. The mean amount taken by consumers =0.3 mg/kg/d (median 0.1 mg/kg/d; maximum 2.7 mg/kg/d).	Self reported food intake data.

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Metabolic Control					
Borstov et al 2011 USA	Youth (10 years or older) with Type 1 diabetes mellitus (DM) N= 1,806 observations were included.	Level 4b	Cross sectional cohort- subjects completed a valid FFQ for 7 days prior to clinic visit. Blood pressure and fasting blood chemistry values were compared between those with no NNS beverage intake, moderate NNS beverage intake and high NNS beverage intake.	<p>In the previous week: -11% reported no NNS beverage intake -34% reported one serving per day -55% reported one or more serving per day</p> <p>Metabolic Characteristics and CVD risk factors in NNS Beverage intake group: -HgbA1c (%): None 8.7 (8.4-9.1); <1 Glass/d 8.9 (8.6-9.2); 1 Glass/d or more 9.3 (9.0-9.6). - Significantly different even when adjusted for confounding variables.</p> <p>-LDL Chol (mg/dl): None 98 (92-104); <1 Glass/d 101 (96-107); 1 Glass/d or more 104 (99-109). - Significantly different even when adjusted for confounding variables.</p> <p>-Diastolic Blood Pressure (mm Hg): None 67 (65-69); < 1 Glass/d 68 (66-69); 1 Glass/d or more 68(66-70). - No significant difference.</p>	Observational study. Food frequency questionnaires can promote erroneous self reporting. There are many confounding variables too.
Brown et al 2010 USA	Systematic Review	Level 2a	SR of cohort pediatric studies	<p>18 studies were identified: -6 on NNS effect on food intake -3 randomized control trials -3 observational cross sectional studies -6 prospective cohort studies</p> <p>Observational studies on NNS and weight gain- 9 studies addressed this question. One study showed a positive correlation between the intake of NNS beverage use and elevated BMI or % body fat.</p> <p>Interventional studies on NNS and weight gain- 3 studies (small) have shown no effect on weight loss, or BMI.</p> <p>Affect on the metabolic syndrome- two studies address this, and neither found causative or associative effects.</p>	<p>Many confounding factors that are difficult to control.</p> <p>From observational studies, decision to consume NNS is made by those who are concerned about their weight. In children, this decision is made by parents who are concerned.</p> <p>Timing of the NNS beverage prior to a meal is a bigger determinant of food intake than the beverage alone.</p>
De Koning et	Adult men N= 51,529 Aged 40-75	Level 1b	Large cohort study (Health	Consumption of NS beverages (colas) was significantly associated with lower overall diet quality	Participants are only white men, difficult to generalize findings There is potential for confounding by

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al 2011 USA			Professionals Follow up Study)	Consumption of NNS beverages was significantly associated with overall higher diet quality. In a large cohort of men, NNS beverages were not associated with Type 2 diabetes.	factors that were not controlled.
Fagherazzi et al., 2013) France	Adult women N=66,118	Level 1b	Large cohort	Women in the highest quartiles of both NS and NNS beverages had increased risk of Type 2 diabetes. The associations were mediated by BMI.	Participants were only women, difficult to generalize findings.
Lin, et al 2011 USA	Adult women N= 300 Nurses' Health Study	Level 1b	Large cohort	Microalbuminuria no difference was noted between NS and NNS beverage drinkers Estimated GFR no difference was noted between NS and NNS beverage drinkers	A low number of subjects drank > 1 NS beverage/d.
Nettleton et al 2009 USA	6,813 adults, Caucasian, African American, Hispanic, and Chinese aged 45-84 years	Level 1b	Large cohort (MESA Study: Multi-Ethnic Study of Atherosclerosis) Baseline food frequency questionnaire and identification of Type 2 diabetes every other year for 6 years.	Compared with non-consumers, the risk of metabolic syndrome was 36% greater in those consuming 1 or more servings of NNS soda daily. However, adjusting for baseline measurements of adiposity made these results not significant. If subjects with any metabolic component at baseline were excluded, (leaving N = 1,078) the hazard ratio of developing any metabolic syndrome component was not significant. Compared with non-consumers, the risk of Type 2 diabetes was 67% greater. Adjusting for baseline measurements of adiposity slightly attenuated results but they were still significant. Unexpectedly NS soda consumption was not associated with the risk of either metabolic syndrome or Type 2 diabetes (data not shown, just summarized).	Causality cannot be concluded from an observational study. There is possibility of confounding from other lifestyle or dietary practices.
Wiebe et al 2011 Canada	53 studies included	Level 1b	Systematic review with meta analysis.	Outcome: weight management, blood glucose and blood lipids. 3 trials compared NNS (either aspartame, cyclamate or a mixture) to sucrose. Weight One study did not report significant loss in BMI in the NNS group (133 participants, 0.3kg/m ² (-1.1,0.5)). A study in overweight participants, those who consumed NNS had significantly greater loss	Trials were of low quality with a median Jadad score of 1. Jadad scores range from 1-5 with higher being better. Heterogeneity between studies was great, reported to be ≥ 77% for most questions.

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				<p>in BMI over ten weeks (41 participants, -0.9 kg/m² (-1.5,-0.4).</p> <p>Energy intake Two trials reported significant effect of lower energy intake in the NNS groups. [133 participants, (-283 kcals (-414,-153))] and [41 participants (-491 (-806, -177)).</p> <p>Other No effect of NNS type on HbA1c. One trial reported no effect of NNS on total cholesterol, HDL cholesterol or triglycerides in 10 Type 1 diabetics. One trial showed no effect of NNS on triglycerides in 41 overweight subjects.</p>	
Pregnancy					
Englund-Ogge et al 2012 Norway	Norwegian Mother and Child Cohort; N = 60,761 women.	Level 1b	Cohort study. Lifestyle (2 questionnaires, not clear if validated) and food frequency questionnaire (1 questionnaire was validated).	<p>Frequent NNS beverage drinkers (≥ 4 servings per day) had an unadjusted odds ratio for preterm delivery of 1.22 95% CI {1.00, 1.47] relative to never drinkers of NNS beverages, but was not significant after confounders were considered.</p> <p>The highest frequency of NS beverages was also associated with preterm delivery.</p> <p>The trend for NS beverages and preterm delivery at the highest level of intake was stronger than the trend for NNS beverages.</p>	The wording of the outcomes of the study is concerning. The authors state, "a small but significant association between daily intake of NNS beverages and preterm delivery was found (aOR 1.15; 95% CI 1.01,1.32, P-trend 0.07)."
Halldorsson et al 2010 Denmark	Danish National Birth Cohort N= 59,334 pregnant women (1996-2002)	Level 1b	Cohort study mid-pregnancy food frequency questionnaire. The primary outcome was preterm delivery (< 37 weeks gestation).	<p>A greater BMI and difference in energy intake were observed for those who drank NNS soda versus those who drank the NS soda.</p> <p>No association with preterm delivery was observed for NS soda.</p> <p>The intake of NNS soda was strongly associated with an increased risk of preterm delivery. Odds ratio 1.78 (95% CI: 1.19, 2.66).</p> <p>Preterm delivery was driven by medically induced delivery rather than by spontaneous delivery.</p>	
Vascular disease (cardiovascular and neurovascular)					
Bernstein et al, 2012 USA	Nurses' Health Study (80,045 female)	Level 1b	Cohort- all participants completed a 61 item food	<p>Increased consumption of NS <u>AND</u> NNS sodas was associated with higher risk of stroke. The risk was higher in women than in men.</p> <p>The pooled relative risk for stroke if ≥ 1 serving of</p>	This is an observational study. There is potential for residual and unmeasured confounding. The finding of an association between NNS soda and

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	nurses) and the Health Professions Follow up study (43,371 male health professionals)		frequency questionnaire every 2 years. Cohorts were grouped on number of soda servings consumed. Stroke incidence was determined by self report and confirmed by medical imaging. Follow up was 28 years for women and 22 years for men.	NNS soda per day versus none was 1.16 (95% CI: 1.05, 1.28). This finding was independent of dietary and non-dietary cardio-vascular disease risk factors, such as BMI, and energy intake.	stroke risk is a new finding, so it has to be interpreted with caution. New research is likely to change confidence in this effect measure. Due to a low number of hemorrhagic strokes in men, the association needs to be carefully interpreted.
Gardener et al, USA 2012	Adults N=2,564 the Northern Manhattan Study	Level 1b	Population based cohort study. FFQ were evaluated at baseline, and screened annually by telephone for the need for an in person interview. Hospital records were looked at for each subject for morbidity and mortality data (Incident vascular disease).	The mean age of subjects at baseline was 68.6 years of age. Frequent NNS soda consumption was associated with white race, former smoking, hypertension, elevated blood sugar, lower HDL, elevated triglycerides, increased waist circumference, BMI, peripheral vascular disease, previous cardiac disease and the metabolic syndrome. NS soda consumption was associated with male sex, Black race, current smoking, carbohydrate consumption, greater diastolic BP and lower prevalence of diabetes and hypercholesterolemia. No association between NS soda consumption and risk of combined vascular events. Daily NNS soda consumption was associated with 43% increased risk of vascular events. Light NNS soda users did not have significantly increased risk.	The number of daily NNS soda users was small. (163 of 2,564 subjects or 6%) Information on NNS soda consumption was only collected at baseline. If the subject's preference changed it was not known.

¹. Hazard ratio is the ratio of the hazard (chance of something harmful happening) of an event in one group observations divided by the hazard of an event in the other group. A HR of 1 means the event has the same chance occurring in each group. A HR of 3 reveals 3 times the risk.

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Excluded Studies:

Authors	Reason for Exclusion
Anderson, Foreyt, Sigman-Grant, & Allison, 2012	Narrative review
Bloomgarden, 2011	Narrative review
Blum et al., 2008	Does not answer the question
Chen et al., 2009	NS soda only
Elfhag, Tynelius, & Rasmussen, 2007	Does not answer the question
Eshak et al., 2012	NS soda only
Fiorito, et al., 2010	NS soda only
Frank et al., 2008	Does not answer the question
Maersk et al., 2012	NS soda only
Malik & Hu, 2012	Narrative review
Monsivais, Perrigue, & Drewnowski, 2007	Does not answer the question
Nguyen, Choi, Lustic, & Hsu, 2009	NS soda only
Nissinen et al., 2009	NS beverage only
Ogden, 2011	NS beverage only
Park, Blanck, Sherry, Brener, & O'Toole, 2012	Does not answer the question
Polyak et al., 2010	Animal study
Renwick & Molinary, 2010	Narrative review
Reedy & Krebs-Smith, 2010	Does not answer the question
(Skokan, Endler, Wulkersdorfer, Magometschnigg, & Spranger, 2007)	NS only
Swithers, Laboy, Clark, Cooper, & Davidson, 2012	Animal study
Weihrauch & Diehl, 2004	Narrative review
Wojcicki & Heyman, 2012	Narrative review
Yang, 2010	Narrative review

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Appendix 1.

