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McGlynn ND, Khan TA, Wang L, et al. Association of Low- and No-Calorie Sweetened Beverages as a Replacement for Sugar-Sweetened Beverages With Body Weight and Cardiometabolic Risk: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022;5(3):e222092.

What We Know, Think We Know, or Are Starting to Know

There are certain evergreen controversial topics in nutrition – saturated fat and heart disease, carbs and diabetes – and, drumroll please, artificial sweeteners. And 2022 has been a good year for keeping the sweetener controversy evergreen, with two publications from the French NutriNet-Santé cohort suggesting increased risk of cancer [covered in this *Sigma Nutrition Radio episode*] and cardiovascular disease [covered in a previous Deepdive].

In reconciling apparent controversy within an evidence-base, it is important to have regard for the total body of evidence. For example, if we have a finding from epidemiological data, is there evidence that would lend biological plausibility to that observational association? Is there a mechanism that could explain an association between a given exposure and outcome?

Bringing some rigour to the table with these questions is crucial for the artificial sweeteners' controversy, given that these compounds undergo extensive toxicology and safety assessments in animal models prior to regulatory approval and use in the human food supply [(1–3)]. Thus, observational findings of increased cardiovascular risk, such as that in the NutriNet-Santé cohort, call into question these existing regulatory frameworks.

In relation to biological plausibility and potential mechanisms that could explain an association with increased cardiovascular risk, we can turn to randomised controlled trials in humans. However, whether artificial sweeteners are compared to another non-calorie control [i.e., water], or are compared to a calorie-containing control [i.e., sugar-sweetened beverages (SSB)] is an important factor that may influence the outcomes of RCTs.

In order to deal with the expected differential outcomes related to the control in RCTs on artificial sweeteners, the present study utilised network meta-analysis***** [see *****Geek Box below for further detail] to investigate these different comparisons.

*Geek Box: Network Meta-Analysis

In a traditional meta-analysis, single studies are compiled together to obtain an overall summary of effect for the exposure and outcome being investigated. In a network meta-analysis, the effects of three or more interventions may be compared. This is achieved by combining what is known as "direct" and "indirect" estimates. For example, let's say we have Drug A, Drug B, and Drug C. And let's say that several studies have compared Drug A vs. Drug C; this would be a direct estimate. Now let's say other studies have compared Drug B vs. Drug C; a network meta-analysis would allow for an indirect estimate between Drug A and Drug B, as they had both been compared to Drug C in other studies.

This means that a network meta-analysis is particularly useful for analysing the comparative effects of different interventions and can estimate how these interventions rank in effectiveness. An important assumption for the validity of a network meta-analysis is what is known as "transitivity".

This means that there are no systematic differences in the comparisons other than the treatments being compared, i.e., it is as if participants could have been randomised to any of the treatments in a study and the remaining factors would be similar. Network meta-analysis is a relatively new statistical approach and is a promising method for determining effectiveness of comparative treatments on a specific condition or outcome.

The Study

The present study was a network meta-analysis [see *Geek Box above] of the effect of artificial sweeteners [AS] on cardio-metabolic risk factors based on three comparative interventions:

- AS replacing SSB [i.e., calorie displacement]
- AS replacing water [i.e., no calorie displacement]
- Water replacing SSB [i.e., calorie displacement]

Thus, included studies compared one of either AS, SSB, or water, against another of the three beverages.

To be included, studies were required to fulfil the following criteria:

- **Design and Duration**: RCTs over a minimum of 2-weeks.
- **Population**: Adult men and women [excluding pregnancy or lactation] with or without a diagnosis of type-2 diabetes [T2D].
- **Intervention**: Non-calorie/low-calorie sweeteners [for simplicity here referred to as 'AS'].
- **Comparator**: SSB or water.
- **Outcome**: Primary outcome was change in bodyweight; secondary outcomes included blood lipids, glycaemic control, blood pressure, liver fat, and liver enzymes.

The results were presented as mean difference [MD] and 95% confidence intervals [95% CI]; the outcomes for MD are expressed in the unit of measurement, e.g., bodyweight in kilograms [kg] and can be interpreted in those terms.

Results were also presented as standardised mean difference [SMD], which is important to distinguish from MD because SMD is calculated and interpreted as an effect size: 0.2, 0.6, and 0.8, are considered small, medium, and large effect sizes, respectively.

Results: 17 RCTs were included in the meta-analysis, within which there were 24 different comparisons in total [i.e., AS vs. SSB, SSB vs. water, AS vs. water, etc.]. The total sample size was 1,733 participants [of which 77.4% were women] with an average age of 33yrs, and 22.6% had overweight/obesity.

- ***AS Replacing SSB***: Substituting SSB for AS was associated with a 1.06kg [95% CI 0.41 to 1.71kg] decrease in bodyweight, a 0.32kg/m2 [95% CI 0.07 to 0.58kg/m2] decrease in BMI, and a 0.60% [95% CI 0.18 to 1.03%] decrease in body fat. The SMD for bodyweight, BMI, and body fat, were 0.65, 0.67, and 0.75, respectively, indicating moderate effect sizes for these outcomes. Liver fat was reported as SMD only, and decreased from substituting SSB for AS, with an SMD of 0.42 [95% CI 0.14 to 0.95], a small to moderate effect size.
- ***Water Replacing SSB***: Although the direction of effect for the substitution of SSB with water was similar to substituting SSB for AS, the outcomes were not statistically significant. Liver fat similarly decreased from water replacing SSB, an SMD of 0.36 [95% CI -0.01 to 0.74], while BMI decreased by 0.35kg/m2 [95% CI -0.13 to 0.83kg/m2].
- ***AS Replacing Water***: Substituting water for AS was associated with a 1.07kg [95% CI 0.19 to 1.95kg] decrease in bodyweight, and a 2.63mmHg [95% CI 0.55 to 4.71mmHg] decrease in systolic blood pressure. Compared to AS, water was associated with a 0.21% [95% CI 0.02 to 0.40%] decrease in HbA1c [more under ***Interesting Finding***, below].

The Critical Breakdown

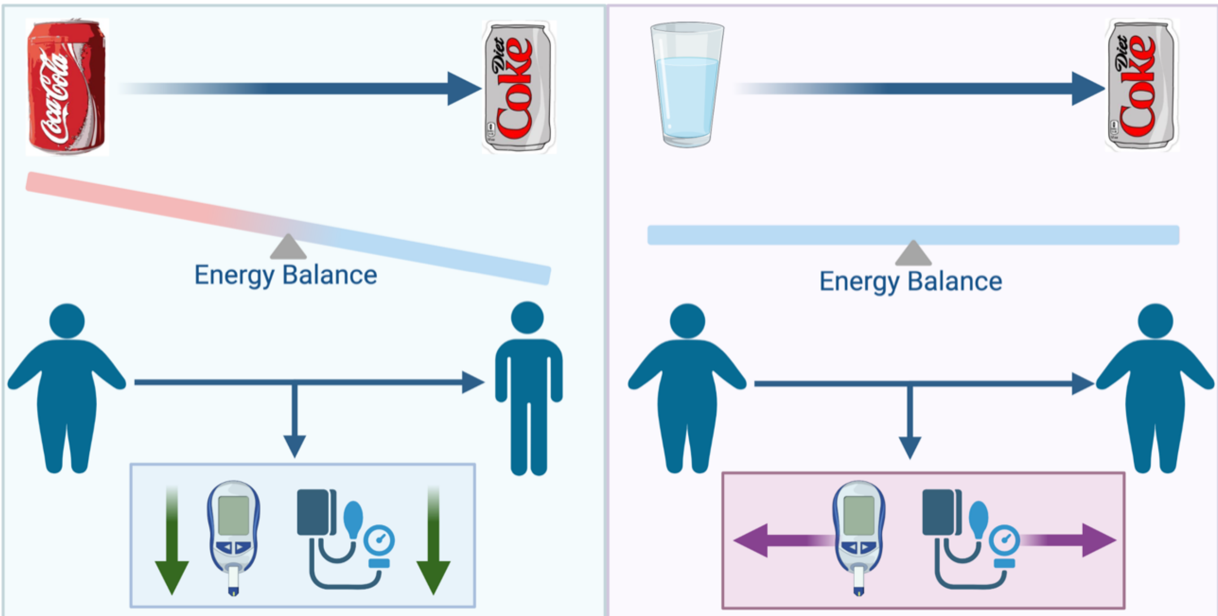
Pros: The inclusion criteria for the primary studies were clearly stated, and the paper clearly outlined the 'PICO' or 'PICOTS' [Population, Intervention, Comparator, Outcome, Time/Duration, Study] criteria for inclusion. The use of a network meta-analysis allowed for the comparisons of three exposures: AS, water, and SSB. This included trials that directly compared two of these in a head-to-head, i.e., the "direct estimates", and the "indirect estimates" of the effect of the third exposure from the comparisons between the other two. The indirect estimate increased the available data pool of the overall meta-analysis, and overall the indirect estimates were similar to the direct estimates.

Cons: Notwithstanding the similarity between direct and indirect estimates, the study is still limited by the small number of direct comparisons for some outcomes, which in turn influences the strength of indirect comparison. For example, if only one trial directly compared water to SSB on blood pressure, and 2 trials directly compared AS to SSB on the same outcome, estimating the indirect effect of water on AS is limited by the lack of direct comparisons. Some comparisons were based on limited sample sizes, e.g., the trials of water replacing SSB had a total of 429 participants. The primary included studies were imbalanced for sex with a majority of female participants, and were largely confined to North America and Europe, limiting generalisability to the potential effects of AS in other populations. No subgroup analyses were conducted to determine the influence of factors like sex, study duration, or funding source.

Key Characteristic

One crucial consideration in the design of RCTs on artificial sweeteners is energy replacement [4]. This is because, as non-calorie [or low-calorie] compounds, artificial sweeteners are conceptually intended to displace energy from the diet, in particular energy from sugar-sweetened beverages [2]. Any potential benefit to artificial sweeteners may primarily reflect the substituting for sugar and/or calories in beverages and food products, reducing total energy intake, facilitating weight loss and, consequently, improvements in cardio-metabolic risk factors [2,4,5].

This means that what artificial sweeteners are compared to in an RCT is important for outcomes; the **figure** below illustrates this point. Compared to water, there is no energy displacement, and consequently there are no expected benefits on cardio-metabolic outcomes. However, compared to SSB, the displacement of energy from SSB by AS products reduces energy intake and facilitates improvements in cardio-metabolic risk factors. Which leads us to the ***Interesting Finding...***

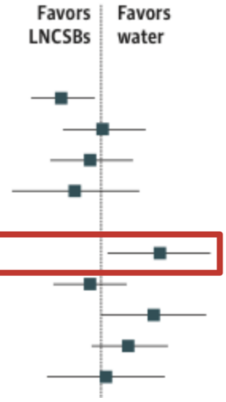


Interesting Finding

In the analysis that compared AS to water, water was associated with a 0.21% [95% CI 0.02 to 0.40%] decrease in HbA1c, i.e., an improvement in glycaemic control compared to AS. However, to the casual observer the way that meta-analysis results are presented could be interpreted as indicating that AS *worsen* HbA1c.

Take a look at the **forest plot** here, with HbA1c in the red rectangle, and you can see this; with the presentation of the effect estimate all to the right of the line, it could be construed as a negative effect of AS on HbA1c.

Outcome	No. of trial comparisons		Total No. of participants		MD (95% CI)	Pooled effect estimates, SMD (95% CI)
	Direct estimate	Network estimate	Direct estimate	Network estimate		
Adiposity						
Body weight, kg	9	24	752	1444	-1.07 (-1.95 to -0.19)	-0.48 (-0.88 to -0.08)
BMI	3	14	174	836	0.02 (-0.46 to 0.51)	0.03 (-0.50 to 0.55)
Body fat, %	4	14	124	559	-0.34 (-1.67 to 1.00)	-0.13 (-0.66 to 0.39)
WC, cm	5	6	628	868	-0.82 (-2.83 to 1.19)	-0.33 (-1.13 to 0.47)
Glycemia						
HbA_{1c}, %	4	9	236	630	0.21 (0.02 to 0.40)	0.72 (0.07 to 1.38)
FPG, mmol/L	9	19	748	1183	-0.02 (-0.08 to 0.04)	-0.14 (-0.59 to 0.31)
2HPP, mmol/L	5	9	286	440	0.19 (0.00 to 0.39)	0.64 (0.00 to 1.31)
FPI, pmol/L	7	16	317	512	7.60 (-2.95 to 18.15)	0.35 (-0.14 to 0.84)
HOMA-IR	4	7	224	265	0.03 (-0.34 to 0.40)	0.07 (-0.67 to 0.81)



However, recall that this is a comparison of effects of each – AS and water – on this outcome. And if we look at the primary included studies from which such a finding was generated, we can see that these effects appear to be driven by weight loss intervention trials that compared AS-sweetened beverage consumption to water [6,7]. And in these trials, *both* water and diet sodas lead to improvements in HbA1c, however, the *magnitude of effect* was greater for water [6,7].

Thus, what this finding was in fact showing was that water had a more beneficial effect on HbA1c during weight loss diets, *not* that AS worsen HbA1c.

Relevance

The appetite of the beast of controversy is insatiable, and so for every NutriNet-Santé study finding, multiple well-conducted studies appear to be required to counteract the controversy. For cardiovascular disease [CVD], the NutriNet-Santé cohort suggested a 9% higher risk of total CVD with higher than median total AS intakes [read the previous Deepdive for the full study breakdown].

However, we also covered in a previous Deepdive a pooled analysis of 6 studies, including 280,886 participants and 4,248 coronary heart disease [CHD] events over 8.2yrs, which showed that the replacement of SSB with AS was associated with a 12% lower risk of CHD events. Thus, with much greater sample sizes and numbers of events, the overall weight of epidemiological research does indicate a benefit to CVD risk from replacing SSB with AS.

The present study adds to this evidence by demonstrating that human RCTs show the replacement of SSB with AS are associated with improved body composition and decreases in liver fat, albeit these differences are modest. These outcomes would be consistent with the biologically plausible explanation that where non/low-calorie alternatives displace calorie-containing beverages/foods from the diet, there is a net reduction in total energy intake that facilitates weight loss [8].

If we look at the direction of effect for blood lipids and blood pressure, we can also see that these risk factors tend to be lower comparing AS to SSB. And, as we discussed under ***Interesting Finding*** above, there is evidence that water may outperform AS in relation to some markers [e.g., HbA1c], but not all [e.g., systolic blood pressure].

Thus, while there may certainly be outlier studies that feed the insatiable beast of controversy, the weight of evidence from both epidemiology and RCTs, supported by the present recent network meta-analysis, indicate that AS are associated with lower CVD risk, a reduction in bodyweight where energy is displaced from the diet, and either neutral or modest improvements in CVD risk factors.

Application to Practice

The main implication from the present study is that energy displacement is a critical concept for the role of AS beverages and foods in the diet. The application of this concept means that AS can certainly be an effective substitution for calorie-containing foods and beverages, provided those calories are not compensated for elsewhere in the diet.

Where this substitution effect is achieved, AS may be useful in facilitating reductions in energy intake, but they should not necessarily be considered a means to improve cardio-metabolic risk factors independent of the wider diet.

In sum, artificial sweeteners may be included in the context of overall nutritional best practices for improving cardio-metabolic health. Fear-mongering over moderate AS consumption is counterproductive and, importantly for healthcare professionals, is not evidence-based advice. Eating more vegetables is more important than the odd Diet Coke.

References

1. Marinovich M, Galli CL, Bosetti C, Gallus S, la Vecchia C. Aspartame, low-calorie sweeteners and disease: Regulatory safety and epidemiological issues. Food and Chem Toxicol. 2013;60:109–15.

2. Gardner C. Non-nutritive sweeteners. Curr Opin Lipidol. 2014 Feb;25(1):80–4.

3. Shankar P, Ahuja S, Sriram K. Non-nutritive sweeteners: Review and update. Nutrition [Internet]. 2013;29(11–12):1293–9.

4. Sievenpiper JL, Khan TA, Ha V, Viguiliouk E, Auyeung R. The importance of study design in the assessment of nonnutritive sweeteners and cardiometabolic health. Can Med Assoc J. 2017 Nov 20;189(46):E1424–5.

5. Gardner C, Wylie-Rosett J, Gidding SS, Steffen LM, Johnson RK, Reader D, et al. Nonnutritive Sweeteners: Current Use and Health Perspectives. Diabetes Care. 2012 Aug 1;35(8):1798–808.

6. Madjd A, Taylor MA, Delavari A, Malekzadeh R, Macdonald IA, Farshchi HR. Beneficial effects of replacing diet beverages with water on type 2 diabetic obese women following a hypo-energetic diet: A randomized, 24-week clinical trial. Diabetes Obes Metab. 2017 Jan;19(1):125–32.

7. 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 Dec 1;102(6):1305–12.

8. Miller PE, Perez V. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. Am J Clin Nutr. 2014 Sep 1;100(3):765–77.