Evidence on Low- and Non-Calorie Sweeteners on Cardiometabolic Outcomes

"The WHO Guideline and the Need for an Update"

Tauseef A. Khan, MBBS, PhD

Senior Research Associate, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto

Toronto 3D Risk Factor Modification and Clinical Trials Unit, St Michael's Hospital, Toronto

Workshop on Reformulation

Ankara, Turkey

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Disclosures (past 24 months)

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– Canadian Institutes of Health Research (CIHR)

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– Institute for the Advancement of Food and Nutrition Sciences (IAFNS) [Previously ILSI North America]

Honoraria or Speaker Fees

– IFIC (International Food Information Council)

– IAFNS

Advisory Board

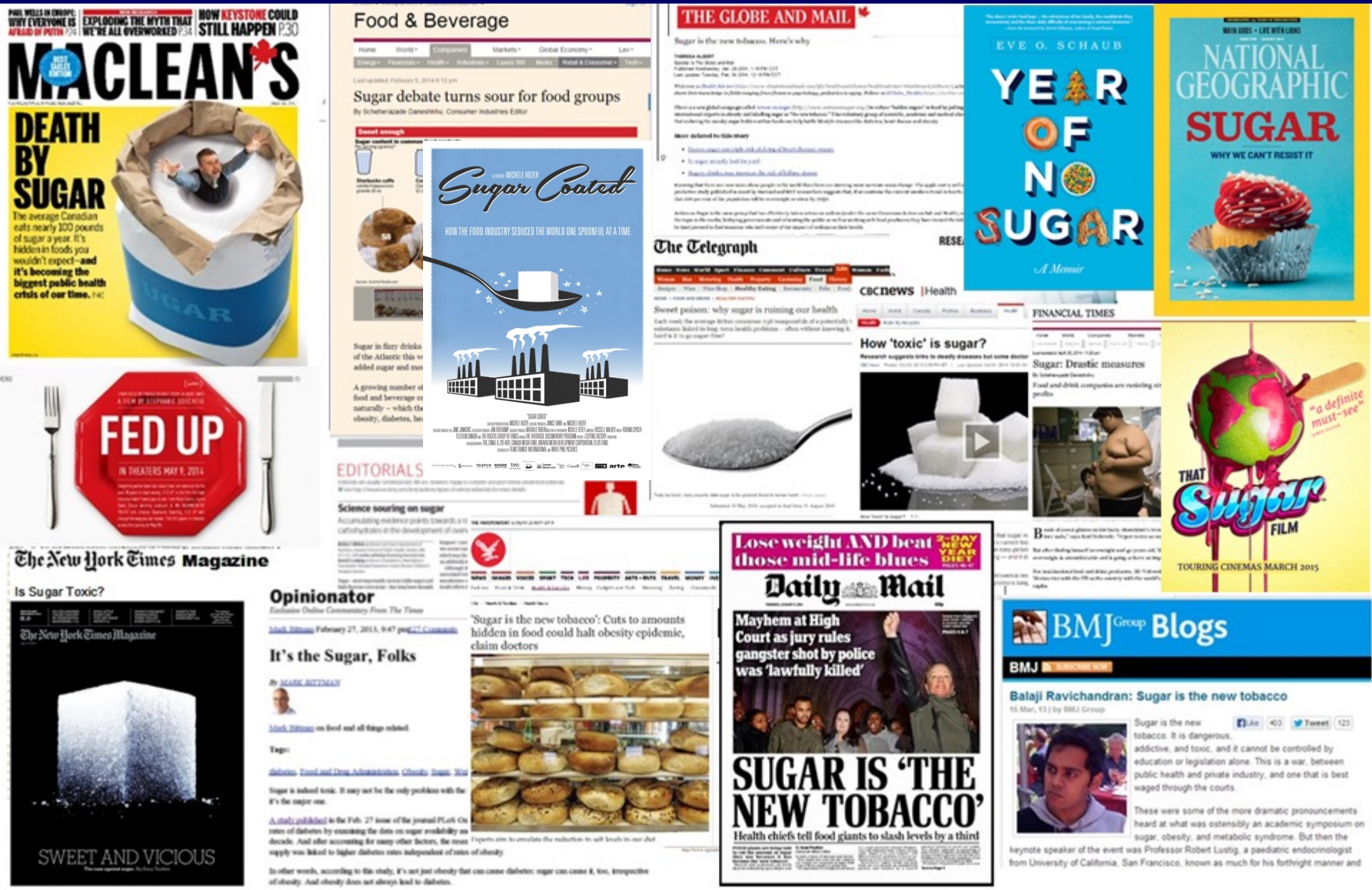
— Nuradec

Other conflicts

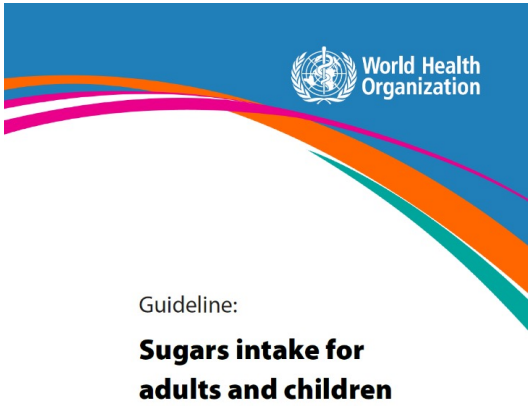
— Wrote a response to the WHO guideline on Non-Sugar Sweeteners which has been accepted in EJCN

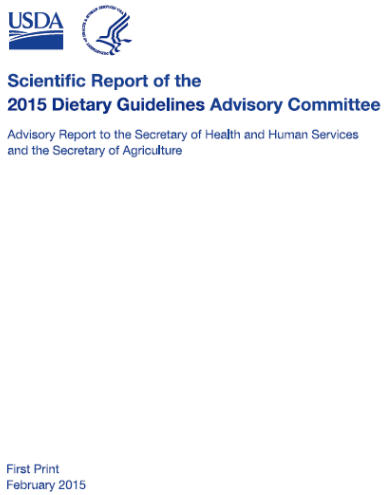
— Consumer of low-calorie sweetened beverages

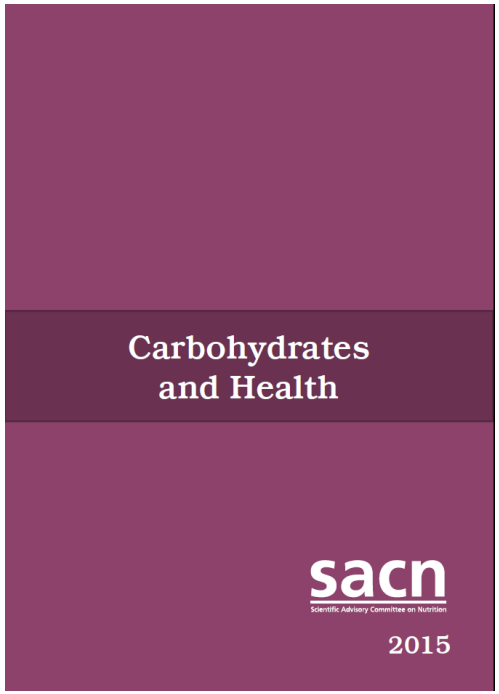
Sugars the new dominant public health concern



Sugars the new dominant public health concern:
Dietary guidelines recommend <5-10% energy from sugars







<10% energy
<5% energy (conditional)

≤10% energy

≤5% energy

http://www.who.int/nutrition/publications/guidelines/sugars_intake/en/
http://www.health.gov/dietaryguidelines/2015-scientific-report/
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf

Low- and Non-Calorie Sweeteners

As a strategy to reduce excess calories from sugars

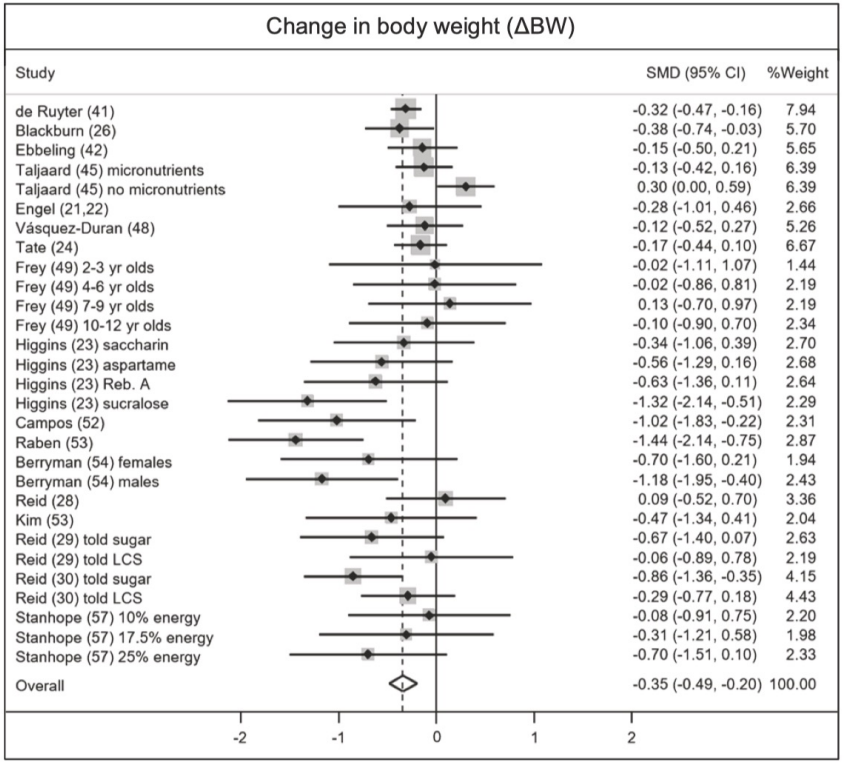
Non- and Low-Calorie Sweeteners

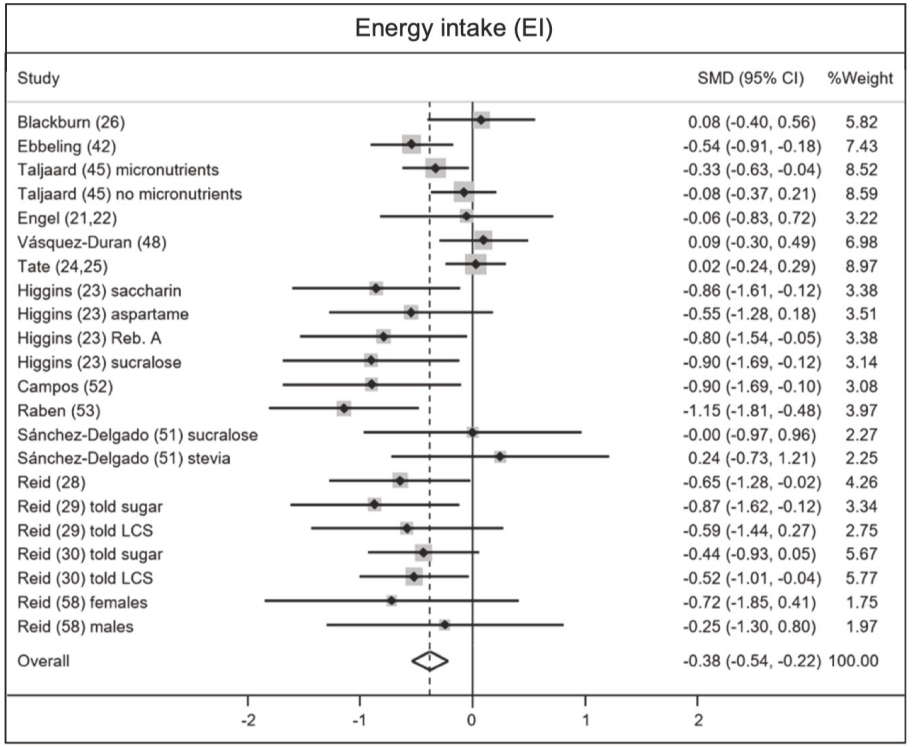
- **Non- and low-calorie sweeteners (LNCS)** are **sugar substitutes** used as a replacement for sugar in food and beverages.
- They are also known as **artificial sweeteners**, **sugar alternatives**, **high-intensity sweeteners, low-calorie sweeteners, non-sugar sweeteners,** or **non-nutritive sweeteners.**
- They contain virtually no calories or very low calories.
- Common non-caloric sweeteners include **aspartame**, **acesulfame potassium** (**ace-K**), **saccharin**, **sucralose**, advantame, neotame, cyclamate, **stevia**, thaumatin etc. [More than 20]
- They elicit **sweet taste** and some are many times (200x – 600x) sweeter than sucrose, require very small amounts.
- They are **popular among people** who are looking to reduce their calorie intake or manage their blood sugar levels.

Non- and Low-Calorie Sweeteners

- Each sweetener has **different characteristics, metabolism** and **fate** in the body
- Have been extensively tested **by FAO/WHO Joint Expert Committee on Food Additives (JECFA)**, **US Food and Drug Administration (FDA)** and **European Food Safety Authority (EFSA)** for their **safety**.
- Evidence shows they be **beneficial for weight management** as it replaces sugars in diet
- **No concrete evidence of adverse effect on sweet preference**, **appetite** or **glucose** control
- Useful **strategy to control sugar intake** in people with **diabetes**
- Effect on **gut microbiota is limited** and no evidence that the effect on gut health at doses relevant to human use

Benefit on Weight and calories– LNCS vs Sugar
29 Trials, 2267 participants



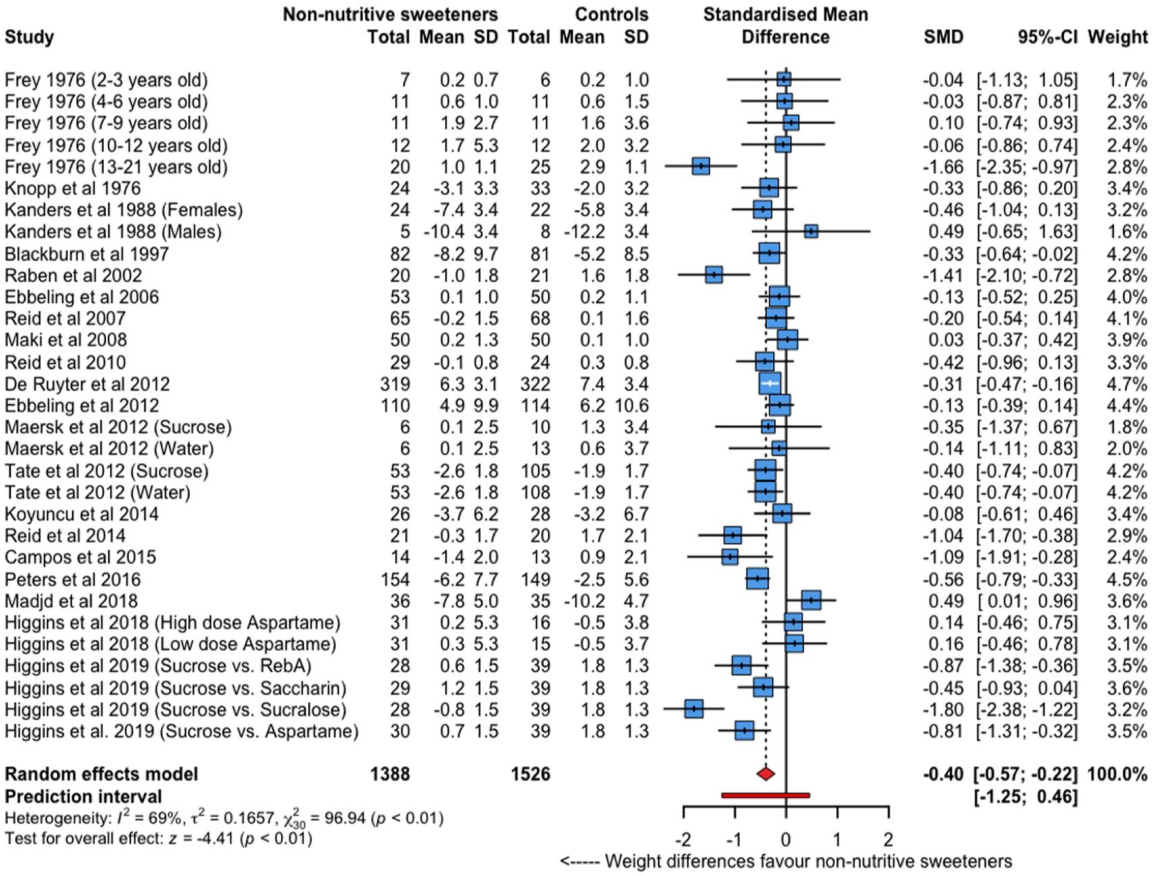


BW change, −1.06 kg, 95% CI −1.50 to −0.62

Energy intake change
−224.56 kcal/day, 95% CI −320.07 to −129.37

Rogers and Appleton. Int.J.Obesity. 2021.

Benefit on Weight – LNCS vs Sugars
22 Trials, 2914 participants



BW change, −0.4 kg, 95% CI −0.57 to −0.22 – LNCS vs All

BW change, −0.56 kg, 95% CI −0.79 to −0.34 — LNCS vs Sucrose

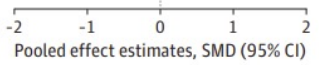
Laviada-Molina. Int.J.Obesity. 2021.

LNCSBs for SSBs ("Intended substitution"):
Network meta-analysis 17 RCTs, N=1,733, FU=3-52 wk

Nema McGlynn

Figure 2. Substitution of Low- and No-Calorie Sweetened Beverages (LNCSBs) for Sugar-Sweetened Beverages (SSBs)

Outcome	No. of trial comparisons: Direct estimate	No. of trial comparisons: Network estimate	Total No. of participants: Direct estimate	Total No. of participants: Network estimate	MD (95% CI)	Pooled effect estimates, SMD (95% CI)	GRADE certainty of the evidence
Adiposity							
Body weight, kg	12	24	467	1444	-1.06 (-1.71 to -0.41)	-0.65 (-1.05 to -0.25)	◆◆◆◇ Moderate
BMI	9	14	437	836	-0.32 (-0.58 to -0.07)	-0.67 (-1.19 to -0.14)	◆◆◇◇ Low
Body fat, %	7	14	210	559	-0.60 (-1.03 to -0.18)	-0.74 (-1.27 to -0.22)	◆◆◆◇ Moderate
WC, cm	0	6	0	868	-0.52 (-4.98 to 3.94)	-0.09 (-0.89 to 0.71)	◆◆◇◇ Low
Glycemia							
HbA_{1c}, %	4	9	154	630	0.12 (-0.08 to 0.32)	0.39 (-0.26 to 1.05)	◆◆◆◇ Moderate
FPG, mmol/L	7	19	210	1183	-0.06 (-0.16 to 0.03)	-0.32 (-0.77 to 0.13)	◆◆◆◇ Moderate
2HPP, mmol/L	4	9	154	440	0.29 (-0.45 to 1.03)	0.26 (-0.40 to 0.91)	◆◆◆◇ Moderate
FPI, pmol/L	7	16	210	512	-9.79 (-29.99 to 10.40)	-0.24 (-0.73 to 0.25)	◆◆◇◇ Low
HOMA-IR	2	7	56	265	-0.10 (-0.71 to 0.51)	-0.12 (-0.86 to 0.62)	◆◆◆◇ Moderate
Lipids, mmol/L							
LDL-C	6	16	183	894	-0.01 (-0.15 to 0.12)	-0.08 (-0.57 to 0.41)	◆◆◆◇ Moderate
Non-HDL-C	6	14	210	923	-0.08 (-0.25 to 0.09)	-0.25 (-0.77 to 0.28)	◆◆◆◇ Moderate
Triglycerides	7	17	210	923	-0.13 (-0.29 to 0.03)	-0.40 (-0.87 to 0.08)	◆◆◆◇ Moderate
HDL-C[a]	7	17	210	923	-0.05 (-0.10 to 0.01)	-0.41 (-0.88 to 0.07)	◆◆◆◇ Moderate
Total cholesterol	6	14	210	923	-0.10 (-0.35 to 0.15)	-0.21 (-0.73 to 0.31)	◆◆◇◇ Low
Blood pressure, mm Hg							
Systolic BP	3	10	56	706	-2.44 (-5.20 to 0.33)	-0.55 (-1.17 to 0.07)	◆◆◆◇ Moderate
Diastolic BP	3	9	56	483	-1.84 (-4.07 to 0.39)	-0.54 (-0.19 to 0.12)	◆◆◇◇ Low
Liver							
IHCL, SMD	2	4	49	62	-0.42 (-0.70 to -0.14)	-0.42 (-0.70 to -0.14)	◆◆◆◇ Moderate
ALT, U/L	2	6	27	143	-6.67 (-16.20 to 2.86)	-0.56 (-1.36 to 0.24)	◆◆◇◇ Low
AST, U/L	1	3	27	120	-1.50 (-7.87 to 4.87)	-0.27 (-1.40 to 0.87)	◆◆◇◇ Low
Uric acid							
Uric acid, mmol/L	3	7	49	62	-0.02 (-0.05 to 0.02)	-1.16 (-1.06 to 0.42)	◆◆◆◇ Moderate



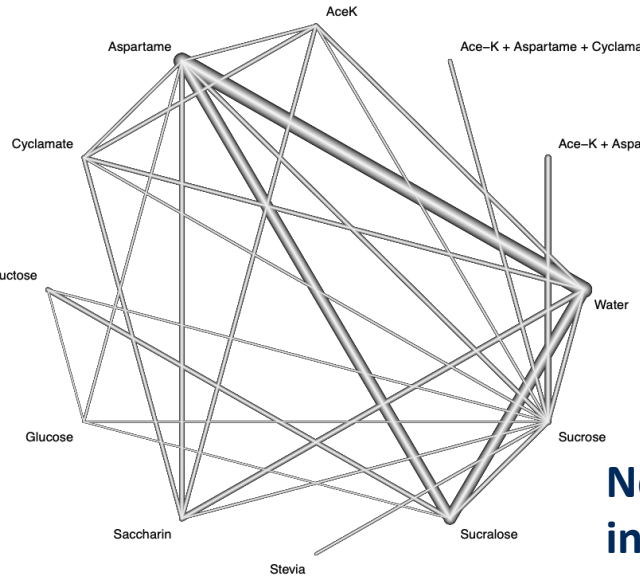
Acute Glucose Response [2 hours]

Comparing LNCS to Caloric Sweeteners

Network meta-analysis 14 RCTs, N=151 (NGT)

Network Plot

14 Trials | 151 Participants (Healthy)



	Individual NNS					NNS Blends		Water	Caloric Sweeteners		
Ace-K (1 trial, N=14)	2.031 (-30.925, 34.988) ⊕⊕⊕	-2.280 (-39.616, 35.056) ⊕⊕⊕	9.113 (-26.058, 44.285) ⊕⊕⊕	45.809 (-14.059, 105.676) ⊕⊕	-0.649 (-35.623, 34.325) ⊕⊕⊕	**56.642 (7.942, 105.342) ⊕⊕⊕⊕**	50.982 (-8.321, 110.284) ⊕⊕⊕	-7.439 (-39.580, 24.701) ⊕⊕⊕	**239.847 (175.749, 303.945) ⊕⊕⊕⊕**	**104.809 (63.114, 146.503) ⊕⊕⊕**	40.553 (-1.824, 82.931) ⊕⊕⊕⊕
	Aspartame (8 trials, N=82)	-4.311 (-37.410, 28.787) ⊕⊕⊕	7.082 (-19.550, 33.714) ⊕⊕⊕⊕	43.777 (-9.944, 97.498) ⊕⊕⊕⊕	-2.680 (-20.680, 15.319) ⊕⊕⊕⊕	**54.611 (13.703, 95.519) ⊕⊕⊕**	48.950 (-4.141, 102.041) ⊕⊕⊕	-9.471 (-20.895, 1.953) ⊕⊕⊕⊕	**237.816 (182.307, 293.324) ⊕⊕⊕⊕**	**102.777 (70.525, 135.030) ⊕⊕⊕⊕**	**38.522 (8.565, 68.479) ⊕⊕⊕⊕**
		Cyclamate (1 trial, N=14)	11.393 (-23.912, 46.698) ⊕⊕⊕	48.089 (-11.857, 108.035) ⊕⊕	1.631 (-33.477, 36.739) ⊕⊕⊕	**58.922 (10.126, 107.718) ⊕⊕⊕⊕**	53.262 (-6.120, 112.643) ⊕⊕⊕	-5.159 (-37.446, 27.127) ⊕⊕⊕	**242.127 (177.956, 306.299) ⊕⊕⊕⊕**	**107.089 (65.282, 148.896) ⊕⊕⊕**	**42.833 (0.345, 85.321) ⊕⊕⊕⊕**
			Saccharin (2 trials, N=24)	36.696 (-20.775, 94.166) ⊕⊕	-9.762 (-39.340, 19.815) ⊕⊕⊕⊕	**47.529 (1.808, 93.249) ⊕⊕⊕⊕**	41.868 (-15.013, 98.750) ⊕⊕⊕	-16.553 (-42.664, 9.559) ⊕⊕⊕	**230.734 (169.572, 291.896) ⊕⊕⊕⊕**	95.695 (57.523, 133.868) ⊕⊕⊕	31.440 (-6.609, 69.490) ⊕⊕⊕⊕
				Stevia (2 trials, N=34)	-46.458 (-100.190, 7.275) ⊕⊕	10.833 (-38.956, 60.623) ⊕⊕⊕⊕	5.173 (-55.028, 65.373) ⊕⊕⊕⊕	**-53.248 (-106.064, -0.432) ⊕⊕**	194.038 (117.465, 270.612) ⊕⊕⊕⊕	59.000 (16.038, 101.962) ⊕⊕⊕	-5.255 (-64.012, 53.502) ⊕⊕⊕⊕
					Sucralose (3 trials, N=29)	**57.291 (16.368, 98.214) ⊕⊕⊕**	51.630 (-1.472, 104.733) ⊕⊕⊕	-6.790 (-21.191, 7.610) ⊕⊕⊕⊕	**240.496 (183.900, 297.092) ⊕⊕⊕⊕**	**105.458 (73.186, 137.729) ⊕⊕⊕⊕**	**41.202 (17.206, 65.199) ⊕⊕⊕⊕**
						Ace-K + Aspartame (1 trial, N=9)	-5.660 (-54.769, 43.448) ⊕⊕⊕⊕	**-64.081 (-103.794, -24.369) ⊕⊕⊕⊕**	183.205 (115.007, 251.404) ⊕⊕⊕⊕	48.167 (23.002, 73.331) ⊕⊕⊕⊕	-16.089 (-63.416, 31.239) ⊕⊕⊕⊕
							Ace-K + Aspartame + Cyclamate (2 trials, N=20)	**-58.421 (-110.596, -6.246) ⊕⊕⊕**	188.866 (112.733, 264.998) ⊕⊕⊕⊕	53.827 (11.656, 95.998) ⊕⊕⊕	-10.428 (-68.609, 47.753) ⊕⊕⊕⊕
								Water (5 trials, N=44)	**247.287 (191.300, 303.273) ⊕⊕⊕⊕**	**112.248 (81.526, 142.970) ⊕⊕⊕⊕**	**47.993 (20.043, 75.943) ⊕⊕⊕⊕**
									Glucose (5 trials, N=61)	**-135.038 (-198.425, -71.652) ⊕⊕⊕⊕**	**-199.294 (-260.661, -137.927) ⊕⊕⊕⊕**
										Sucrose (7 trials, N=81)	**-64.255 (-104.338, -24.172) ⊕⊕⊕⊕**
											Fructose (1 trial, N=15)

No effect on appetite hormones including insulin, GIP, GLP-1, Ghrelin, PYY and Glucagon

Zhang et al, Nutrients. 2023

Roselyn Zhang, MSc, RD

Jarvis Noronha, MSc, MD (candidate)

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LNCS effect on Microbiome

- **Saccharin intake associated with impaired glucose tolerance through changes in the microbiome [Suez et al Nature 2014]**

- **Aspartame and sucralose intake is NOT associated with impaired glucose tolerance through changes in microbiome [Ahmad et al App Phys Nut Met 2020]**

- **Sucralose intake is NOT associated with impaired glucose tolerance through changes in microbiome [Thompson et al Brit J Nutrition. 2019]**

- **Saccharin intake is NOT associated with impaired glucose tolerance through changes in microbiome [Serrano et al Mirobiome 2021]**

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

606

NRC Research Press

ARTICLE

The effect of the artificial sweeteners on glucose metabolism in healthy adults: a randomized, double-blinded, crossover clinical trial

Samar Y. Ahmad, James K. Friel, and Dylan S. MacKay

British Journal of Nutrition (2019), 122, 856–862
© The Authors 2019

doi:10.1017/S0007114519001570

Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults

Serrano et al. Microbiome (2021) 9:11
https://doi.org/10.1186/s40168-020-00976-w

Microbiome

RESEARCH Open Access

High-dose saccharin supplementation does not induce gut microbiota changes or glucose intolerance in healthy humans and mice

Check for updates

What do guidelines say about LNCS?

Guidelines in general are supportive of LNCS

USDA Scientific Report of the 2020 Dietary Guidelines Advisory Committee

*…recommends **these food ingredients [LCS]** be considered as an option for managing body weight*

*"The use of nonnutritive sweeteners may have the **potential to reduce overall calorie intake***

American Diabetes Association. Diabetes Care 2022; 45 (Suppl 1): S60–S82

American Diabetes Association®

***have shown a weight loss benefit when non-nutritive sweeteners are used to displace excess calories** from added sugars*

Sievenpiper et al. Can J Diabetes. 2018;42 Suppl 1:S64-S79

DIABETES CANADA

*"…**low-calorie sweeteners** in **substitution for sugars** …, may have **advantages like those of water or other strategies intended to displace excess calories** from added sugars."*

Wharton S, et al. CMAJ. 2020;192:E875-E891

obesity canada

*"For those looking to **reduce** free or added **sugars** intake, **replacement** with **non-nutritive sweeteners (NNS)** may be an **appropriate strategy."***

DNSG Guideline Group. Diabetologia, May 2023

EASD

The WHO Guideline on LNCS 2023

Released yesterday May 15th

WHO b guideline: Use of non-sugar sweeteners

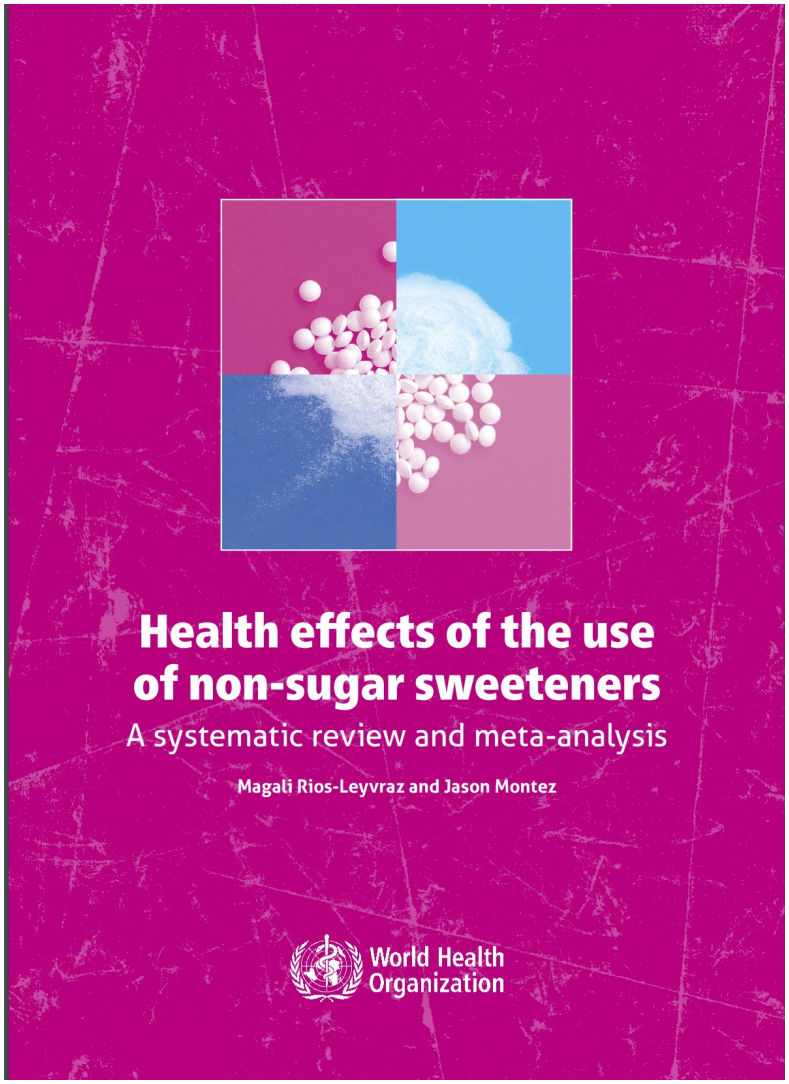
Nutrition Guidance and Advisory Group (NUGAG)

*"WHO suggests that **NSS not** be used as a means of achieving **weight control** or **reducing risk of noncommunicable diseases** (conditional recommendation)[2]"*

[2] Conditional recommendations are those recommendations for which the WHO guideline development group is **uncertain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are small.** Policymaking related to conditional recommendations therefore may require **substantial debate** and **involvement of various stakeholders**.

https://www.who.int/publications/i/item/9789240073616

Why is there a discordance from other recommendations?



APRIL 2022

JULY 2022

Summary of results

Randomized controlled trials

Adiposity
- ↓ Body weight −0.71 kg *(low)*
- ↓ BMI −0.14 kg/m² *(low)*

Mostly in NSS→sugars

- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 (*moderate*)
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake −569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake −38 *(low)*

Pregnancy
No data

Rios-Leyvraz M, Mon ; 2022
https://apps.who.int

Summary of results: Body Weight

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sugars

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- ↓ Energy intake –569 *(low)*

Mostly in NSS→sugars

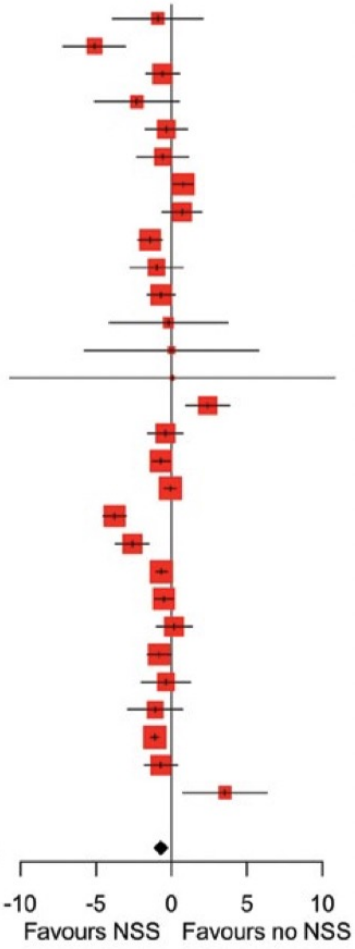
Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

Pregnancy
No data

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

Study	NSS	no NSS	MD	95% CI	Weight
Al-Dujaili 2017	16	16	-0.90	(-3.87, 2.07)	1.5%
Blackburn 1997	41	45	-5.10	(-7.15,-3.05)	2.4%
Bonnet 2018 (SEDULC)	50	50	-0.59	(-1.70, 0.52)	4.0%
Campos 2015 (REDUCS study)	14	13	-2.30	(-5.09, 0.49)	1.6%
Ebbeling 2020 (BASH III)	67	136	-0.35	(-1.75, 1.05)	3.5%
Engel 2018	15	30	-0.57	(-2.27, 1.12)	2.9%
Han 2018	40	81	0.77	(0.11, 1.43)	4.9%
Higgins 2018	31	31	0.70	(-0.60, 2.00)	3.6%
Higgins 2019	115	39	-1.41	(-2.20,-0.61)	4.6%
Kanders 1988	28	27	-0.98	(-2.75, 0.78)	2.8%
Kim 2011	9	12	-0.68	(-1.61, 0.25)	4.4%
Kim 2020	39	39	-0.20	(-4.13, 3.73)	1.0%
Kuzma 2015	9	9	0.00	(-5.78, 5.78)	0.5%
Lertrit 2018	15	15	0.05	(-10.71,10.81)	0.2%
Madjd 2018 (week 77)	36	35	2.40	(0.97, 3.83)	3.4%
Markey 2016 (REFORM)	50	50	-0.40	(-1.56, 0.76)	3.9%
McLay-Cooke 2016 (Ice Tea Study)	63	53	-0.68	(-1.27,-0.10)	5.0%
Njike 2011	32	33	-0.09	(-0.49, 0.31)	5.3%
Peters 2016 (week 52)	154	149	-3.76	(-4.52,-3.00)	4.7%
Raben 2002	20	21	-2.60	(-3.71,-1.49)	4.0%
Reid 2007	65	68	-0.66	(-1.04,-0.28)	5.3%
Reid 2010	29	24	-0.49	(-1.13, 0.14)	4.9%
Reid 2014	21	20	0.18	(-0.99, 1.35)	3.9%
Romo-Romo 2018	30	31	-0.82	(-1.59,-0.05)	4.7%
Sagrario Lopez-Meza 2021	26	13	-0.37	(-1.99, 1.25)	3.1%
Sanchez-Delgado 2021	26	12	-1.08	(-2.89, 0.72)	2.8%
Stamataki 2020	14	14	-1.11	(-1.37,-0.85)	5.4%
Tate 2012 (CHOICE)	105	162	-0.70	(-1.79, 0.39)	4.1%
Viveros-Watty 2021	21	24	3.53	(0.73, 6.33)	1.6%
Total	**1181**	**1252**	**-0.71**	**(-1.13,-0.28)**	**100.0%**

Heterogeneity: $Tau^2 = 0.9$; $Chi^2 = 167.77$, df = 28 ($P < 0.01$); $I^2 = 83\%$
Test for overall effect: $Z = -3.25$ ($P < 0.01$)



Rios-Leyvraz M, Montez JM. World Health Organization; 2022
https://apps.who.int/iris/ handle/10665/353064)

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Summary of results: Body Weight

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sugars

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 *(moderate)*
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake –569 *(low)*

Mostly in NSS→sugars

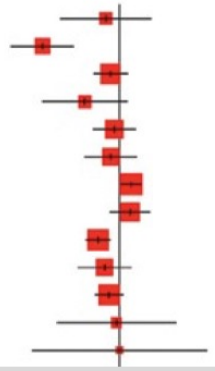
Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

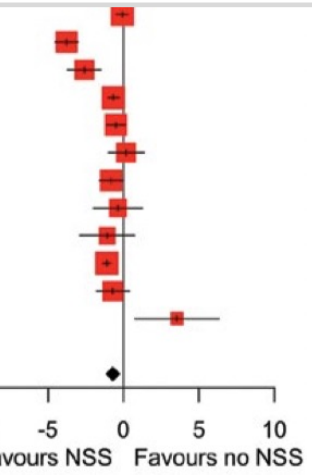
Pregnancy
No data

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

Study	NSS	no NSS	MD	95% CI	Weight
Al-Dujaili 2017	16	16	-0.90	(-3.87, 2.07)	1.5%
Blackburn 1997	41	45	-5.10	(-7.15,-3.05)	2.4%
Bonnet 2018 (SEDULC)	50	50	-0.59	(-1.70, 0.52)	4.0%
Campos 2015 (REDUCS study)	14	13	-2.30	(-5.09, 0.49)	1.6%
Ebbeling 2020 (BASH III)	67	136	-0.35	(-1.75, 1.05)	3.5%
Engel 2018	15	30	-0.57	(-2.27, 1.12)	2.9%
Han 2018	40	81	0.77	(0.11, 1.43)	4.9%
Higgins 2018	31	31	0.70	(-0.60, 2.00)	3.6%
Higgins 2019	115	39	-1.41	(-2.20,-0.61)	4.6%
Kanders 1988	28	27	-0.98	(-2.75, 0.78)	2.8%
Kim 2011	9	12	-0.68	(-1.61, 0.25)	4.4%
Kim 2020	39	39	-0.20	(-4.13, 3.73)	1.0%
Kuzma 2015	9	9	0.00	(-5.78, 5.78)	0.5%
Njike 2011	32	33	-0.09	(-0.49, 0.31)	5.3%
Peters 2016 (week 52)	154	149	-3.76	(-4.52,-3.00)	4.7%
Raben 2002	20	21	-2.60	(-3.71,-1.49)	4.0%
Reid 2007	65	68	-0.66	(-1.04,-0.28)	5.3%
Reid 2010	29	24	-0.49	(-1.13, 0.14)	4.9%
Reid 2014	21	20	0.18	(-0.99, 1.35)	3.9%
Romo-Romo 2018	30	31	-0.82	(-1.59,-0.05)	4.7%
Sagrario Lopez-Meza 2021	26	13	-0.37	(-1.99, 1.25)	3.1%
Sanchez-Delgado 2021	26	12	-1.08	(-2.89, 0.72)	2.8%
Stamataki 2020	14	14	-1.11	(-1.37,-0.85)	5.4%
Tate 2012 (CHOICE)	105	162	-0.70	(-1.79, 0.39)	4.1%
Viveros-Watty 2021	21	24	3.53	(0.73, 6.33)	1.6%
Total	**1181**	**1252**	**-0.71**	**(-1.13,-0.28)**	**100.0%**

Heterogeneity: $Tau^2 = 0.9$; $Chi^2 = 167.77$, df = 28 ($P < 0.01$); $I^2 = 83\%$
Test for overall effect: $Z = -3.25$ ($P < 0.01$)





Body Weight: MD -0.71 kg [-1.13, -0.28]

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BODY WT

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sugars

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 *(moderate)*
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake –569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

Pregnancy
No data

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

Study	NSS	no NSS	MD	95% CI	Weight
Nothing					
Higgins 2018	31	31	0.70	(-0.60, 2.00)	3.4%
Kanders 1988	28	27	-0.98	(-2.75, 0.78)	2.6%
Lertrit 2018	15	15	0.05	(-10.71,10.81)	0.1%
Romo-Romo 2018	30	31	-0.82	(-1.59,-0.05)	4.4%
Stamataki 2020	14	14	-1.11	(-1.37,-0.85)	5.1%
Viveros-Watty 2021	21	24	3.53	(0.73, 6.33)	1.5%
Total	**139**	**142**	**-0.29**	**(-1.20, 0.62)**	**17.3%**
Heterogeneity: Tau^2 = 0.7; Chi^2 = 17.53, df = 5 (P < 0.01); I^2 = 71%					
Test for overall effect: Z = -0.62 (P = 0.54)					
Sugar					
Al-Dujaili 2017	16	16	-0.90	(-3.87, 2.07)	1.4%
Blackburn 1997	41	45	-5.10	(-7.15,-3.05)	2.3%
Campos 2015 (REDUCS study)	14	13	-2.30	(-5.09, 0.49)	1.5%
Ebbeling 2020 (BASH III)	67	67	-0.60	(-2.26, 1.06)	2.8%
Engel 2018	15	14	-1.00	(-3.30, 1.30)	2.0%
Han 2018	40	81	0.77	(0.11, 1.43)	4.6%
Higgins 2019	115	39	-1.41	(-2.20,-0.61)	4.4%
Kim 2011	9	12	-0.68	(-1.61, 0.25)	4.1%
Kuzma 2015	9	9	0.00	(-5.78, 5.78)	0.5%
Markey 2016 (REFORM)	50	50	-0.40	(-1.56, 0.76)	3.7%
McLay-Cooke 2016 (Ice Tea Study)	63	53	-0.68	(-1.27,-0.10)	4.7%
Njike 2011	32	33	-0.09	(-0.49, 0.31)	5.0%
Raben 2002	20	21	-2.60	(-3.71,-1.49)	3.8%
Reid 2007	65	68	-0.66	(-1.04,-0.28)	5.0%
Reid 2010	29	24	-0.49	(-1.13, 0.14)	4.7%
Reid 2014	21	20	0.18	(-0.99, 1.35)	3.7%
Sagrario Lopez-Meza 2021	26	13	-0.37	(-1.99, 1.25)	2.9%
Sanchez-Delgado 2021	26	12	-1.08	(-2.89, 0.72)	2.6%
Tate 2012 (CHOICE)	105	75	-0.70	(-1.99, 0.59)	3.4%
Total	**763**	**665**	**-0.76**	**(-1.18,-0.34)**	**62.9%**
Heterogeneity: Tau^2 = 0.5; Chi^2 = 61.31, df = 18 (P < 0.01); I^2 = 71%					
Test for overall effect: Z = -3.56 (P < 0.01)					
Water					
Bonnet 2018 (SEDULC)	50	50	-0.59	(-1.70, 0.52)	3.8%
Ebbeling 2020 (BASH III)	67	69	-0.10	(-1.63, 1.43)	3.0%
Engel 2018	15	16	-0.20	(-3.61, 3.21)	1.1%
Kim 2020	39	39	-0.20	(-4.13, 3.73)	0.9%
Madjd 2018 (week 77)	36	35	2.40	(0.97, 3.83)	3.2%
Peters 2016 (week 52)	154	149	-3.76	(-4.52,-3.00)	4.4%
Tate 2012 (CHOICE)	105	87	-0.70	(-2.05, 0.65)	3.3%
Total	**466**	**445**	**-0.51**	**(-2.40, 1.37)**	**19.8%**
Heterogeneity: Tau^2 = 5.4; Chi^2 = 70.83, df = 6 (P < 0.01); I^2 = 92%					
Test for overall effect: Z = -0.53 (P = 0.59)					
Total	**1368**	**1252**	**-0.70**	**(-1.11,-0.29)**	**100.0%**
Heterogeneity: Tau^2 = 0.8; Chi^2 = 168.29, df = 31 (P < 0.01); I^2 = 82%					
Test for overall effect: Z = -3.36 (P < 0.01)					
Test for subgroup differences: Chi^2 = 0.90, df = 2 (P = 0.64)					

MD (95% CI)

-10 -5 0 5 10

Favours NSS Favours no NSS

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BODY WT

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*

Mostly in NSS→sugars

- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 *(moderate)*
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake –569 *(low)*

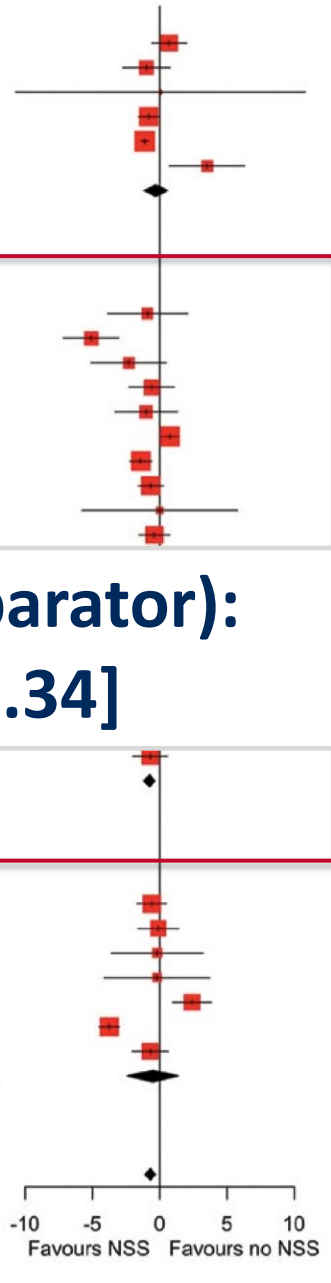
Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

Pregnancy
No data

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

Study	NSS	no NSS	MD	95% CI	Weight
Nothing					
Higgins 2018	31	31	0.70	(-0.60, 2.00)	3.4%
Kanders 1988	28	27	-0.98	(-2.75, 0.78)	2.6%
Lertrit 2018	15	15	0.05	(-10.71,10.81)	0.1%
Romo-Romo 2018	30	31	-0.82	(-1.59,-0.05)	4.4%
Stamataki 2020	14	14	-1.11	(-1.37,-0.85)	5.1%
Viveros-Watty 2021	21	24	3.53	(0.73, 6.33)	1.5%
Total	**139**	**142**	**-0.29**	**(-1.20, 0.62)**	**17.3%**
Heterogeneity: $Tau^2 = 0.7$; $Chi^2 = 17.53$, df = 5 (P < 0.01); $I^2 = 71\%$					
Test for overall effect: Z = -0.62 (P = 0.54)					
Sugar					
Al-Dujaili 2017	16	16	-0.90	(-3.87, 2.07)	1.4%
Blackburn 1997	41	45	-5.10	(-7.15,-3.05)	2.3%
Campos 2015 (REDUCS study)	14	13	-2.30	(-5.09, 0.49)	1.5%
Ebbeling 2020 (BASH III)	67	67	-0.60	(-2.26, 1.06)	2.8%
Engel 2018	15	14	-1.00	(-3.30, 1.30)	2.0%
Han 2018	40	81	0.77	(0.11, 1.43)	4.6%
Higgins 2019	115	39	-1.41	(-2.20,-0.61)	4.4%
Kim 2011	9	12	-0.68	(-1.61, 0.25)	4.1%
Kuzma 2015	9	9	0.00	(-5.78, 5.78)	0.5%
Markey 2016 (REFORM)	50	50	-0.40	(-1.56, 0.76)	3.7%
Tate 2012 (CHOICE)	105	75	-0.70	(-1.99, 0.59)	3.4%
Total	**763**	**665**	**-0.76**	**(-1.18,-0.34)**	**62.9%**
Heterogeneity: $Tau^2 = 0.5$; $Chi^2 = 61.31$, df = 18 (P < 0.01); $I^2 = 71\%$					
Test for overall effect: Z = -3.56 (P < 0.01)					
Water					
Bonnet 2018 (SEDULC)	50	50	-0.59	(-1.70, 0.52)	3.8%
Ebbeling 2020 (BASH III)	67	69	-0.10	(-1.63, 1.43)	3.0%
Engel 2018	15	16	-0.20	(-3.61, 3.21)	1.1%
Kim 2020	39	39	-0.20	(-4.13, 3.73)	0.9%
Madjd 2018 (week 77)	36	35	2.40	(0.97, 3.83)	3.2%
Peters 2016 (week 52)	154	149	-3.76	(-4.52,-3.00)	4.4%
Tate 2012 (CHOICE)	105	87	-0.70	(-2.05, 0.65)	3.3%
Total	**466**	**445**	**-0.51**	**(-2.40, 1.37)**	**19.8%**
Heterogeneity: $Tau^2 = 5.4$; $Chi^2 = 70.83$, df = 6 (P < 0.01); $I^2 = 92\%$					
Test for overall effect: Z = -0.53 (P = 0.59)					
Total	**1368**	**1252**	**-0.70**	**(-1.11,-0.29)**	**100.0%**
Heterogeneity: $Tau^2 = 0.8$; $Chi^2 = 168.29$, df = 31 (P < 0.01); $I^2 = 82\%$					
Test for overall effect: Z = -3.36 (P < 0.01)					
Test for subgroup differences: $Chi^2 = 0.90$, df = 2 (P = 0.64)					



Body Weight (sugar comparator): MD -0.76 kg [-1.18, -0.34]

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ONTO

BMI

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sugars

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 (*moderate*)
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

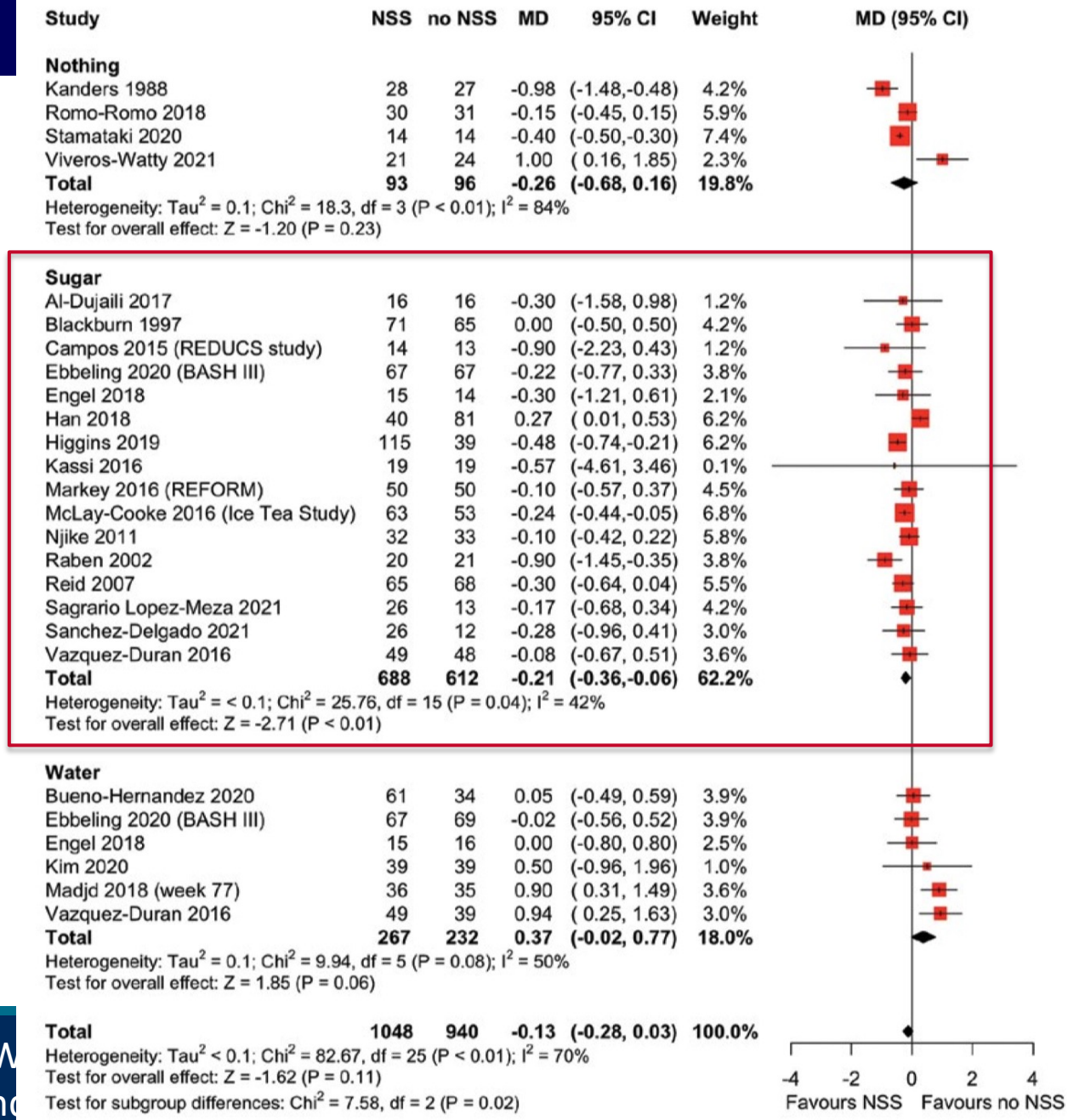
Total energy intake (kJ/day)
- ↓ Energy intake –569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

Pregnancy
No data

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



BMI

Randomized controlled trials

Adiposity
- Body weight –0.71 kg *(low)*
- BMI –0.14 kg/m² *(low)*

Mostly in NSS→sugars

- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- Total:HDL cholesterol +0.09 (*moderate*
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- Energy intake –569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- Sugars intake –38 *(low)*

Pregnancy
No data

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

Study	NSS	no NSS	MD	95% CI	Weight
Nothing					
Kanders 1988	28	27	-0.98	(-1.48,-0.48)	4.2%
Romo-Romo 2018	30	31	-0.15	(-0.45, 0.15)	5.9%
Stamataki 2020	14	14	-0.40	(-0.50,-0.30)	7.4%
Viveros-Watty 2021	21	24	1.00	(0.16, 1.85)	2.3%
Total	**93**	**96**	**-0.26**	**(-0.68, 0.16)**	**19.8%**
Heterogeneity: Tau^2 = 0.1; Chi^2 = 18.3, df = 3 (P < 0.01); I^2 = 84%					
Test for overall effect: Z = -1.20 (P = 0.23)					
Sugar					
Al-Dujaili 2017	16	16	-0.30	(-1.58, 0.98)	1.2%
Blackburn 1997	71	65	0.00	(-0.50, 0.50)	4.2%
Campos 2015 (REDUCS study)	14	13	-0.90	(-2.23, 0.43)	1.2%
Ebbeling 2020 (BASH III)	67	67	-0.22	(-0.77, 0.33)	3.8%
Engel 2018	15	14	-0.30	(-1.21, 0.61)	2.1%
Han 2018	40	81	0.27	(0.01, 0.53)	6.2%
Higgins 2019	115	39	-0.48	(-0.74,-0.21)	6.2%
Kassi 2016	19	19	-0.57	(-4.61, 3.46)	0.1%
Vazquez-Duran 2016	49	48	-0.08	(-0.67, 0.51)	3.6%
Total	**688**	**612**	**-0.21**	**(-0.36,-0.06)**	**62.2%**
Heterogeneity: Tau^2 = < 0.1; Chi^2 = 25.76, df = 15 (P = 0.04); I^2 = 42%					
Test for overall effect: Z = -2.71 (P < 0.01)					
Water					
Bueno-Hernandez 2020	61	34	0.05	(-0.49, 0.59)	3.9%
Ebbeling 2020 (BASH III)	67	69	-0.02	(-0.56, 0.52)	3.9%
Engel 2018	15	16	0.00	(-0.80, 0.80)	2.5%
Kim 2020	39	39	0.50	(-0.96, 1.96)	1.0%
Madjd 2018 (week 77)	36	35	0.90	(0.31, 1.49)	3.6%
Vazquez-Duran 2016	49	39	0.94	(0.25, 1.63)	3.0%
Total	**267**	**232**	**0.37**	**(-0.02, 0.77)**	**18.0%**
Heterogeneity: Tau^2 = 0.1; Chi^2 = 9.94, df = 5 (P = 0.08); I^2 = 50%					
Test for overall effect: Z = 1.85 (P = 0.06)					
Total	**1048**	**940**	**-0.13**	**(-0.28, 0.03)**	**100.0%**
Heterogeneity: Tau^2 < 0.1; Chi^2 = 82.67, df = 25 (P < 0.01); I^2 = 70%					
Test for overall effect: Z = -1.62 (P = 0.11)					
Test for subgroup differences: Chi^2 = 7.58, df = 2 (P = 0.02)					

MD (95% CI)

-4 -2 0 2 4

Favours NSS Favours no NSS

BMI (sugar comparator):
MD -0.21 [-0.36, -0.06]

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Energy and sugar reduction

Randomized controlled trials

Adiposity
- ↓ Body weight –0.71 kg *(low)*
- ↓ BMI –0.14 kg/m² *(low)*

Mostly in NSS→sugars

- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 *(moderate)*
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

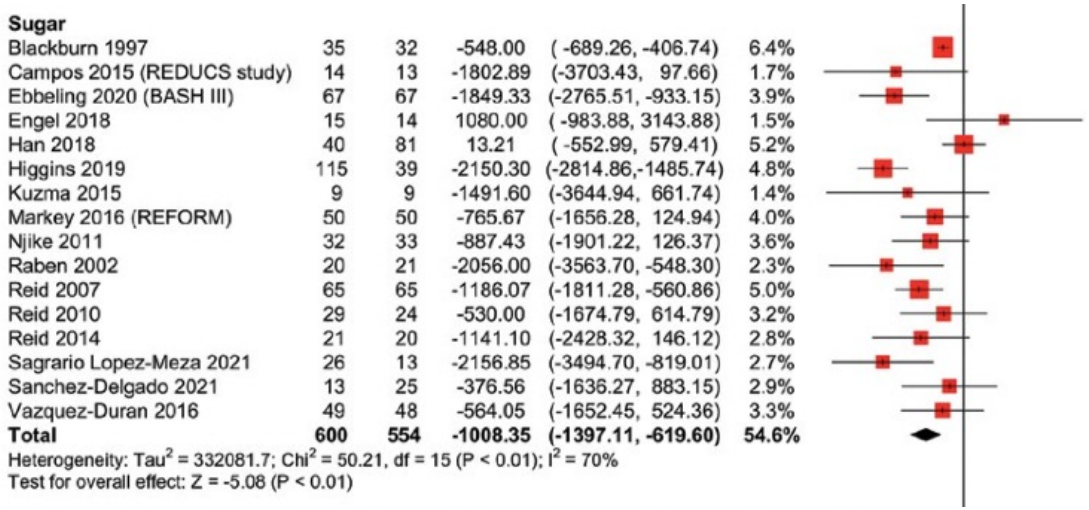
Total energy intake (kJ/day)
- ↓ Energy intake –569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake –38 *(low)*

Pregnancy
No data

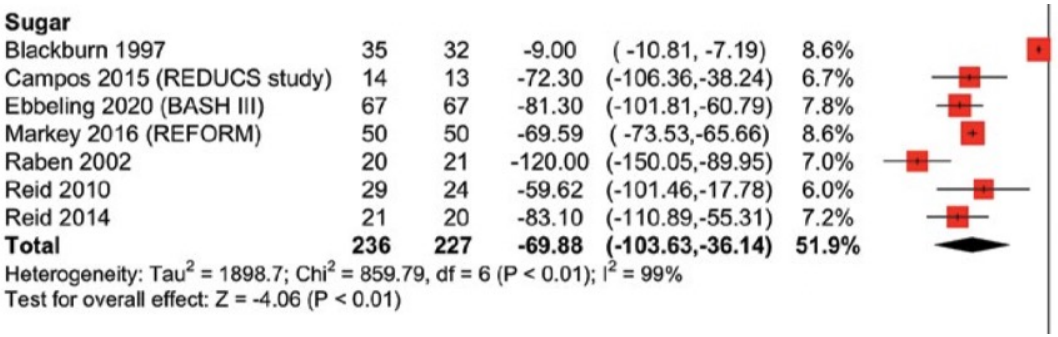
Fig. 29. Effect of NSS intake on total energy intake (kJ/day) in randomized controlled trials, subgrouped by comparator



Sugar					
Blackburn 1997	35	32	-548.00	(-689.26, -406.74)	6.4%
Campos 2015 (REDUCS study)	14	13	-1802.89	(-3703.43, 97.66)	1.7%
Ebbeling 2020 (BASH III)	67	67	-1849.33	(-2765.51, -933.15)	3.9%
Engel 2018	15	14	1080.00	(-983.88, 3143.88)	1.5%
Han 2018	40	81	13.21	(-552.99, 579.41)	5.2%
Higgins 2019	115	39	-2150.30	(-2814.86,-1485.74)	4.8%
Kuzma 2015	9	9	-1491.60	(-3644.94, 661.74)	1.4%
Markey 2016 (REFORM)	50	50	-765.67	(-1656.28, 124.94)	4.0%
Njike 2011	32	33	-887.43	(-1901.22, 126.37)	3.6%
Raben 2002	20	21	-2056.00	(-3563.70, -548.30)	2.3%
Reid 2007	65	65	-1186.07	(-1811.28, -560.86)	5.0%
Reid 2010	29	24	-530.00	(-1674.79, 614.79)	3.2%
Reid 2014	21	20	-1141.10	(-2428.32, 146.12)	2.8%
Sagrario Lopez-Meza 2021	26	13	-2156.85	(-3494.70, -819.01)	2.7%
Sanchez-Delgado 2021	13	25	-376.56	(-1636.27, 883.15)	2.9%
Vazquez-Duran 2016	49	48	-564.05	(-1652.45, 524.36)	3.3%
Total	**600**	**554**	**-1008.35**	**(-1397.11, -619.60)**	**54.6%**

Heterogeneity: $Tau^2 = 332081.7$; $Chi^2 = 50.21$, df = 15 ($P < 0.01$); $I^2 = 70\%$
Test for overall effect: $Z = -5.08$ ($P < 0.01$)

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



Sugar					
Blackburn 1997	35	32	-9.00	(-10.81, -7.19)	8.6%
Campos 2015 (REDUCS study)	14	13	-72.30	(-106.36,-38.24)	6.7%
Ebbeling 2020 (BASH III)	67	67	-81.30	(-101.81,-60.79)	7.8%
Markey 2016 (REFORM)	50	50	-69.59	(-73.53,-65.66)	8.6%
Raben 2002	20	21	-120.00	(-150.05,-89.95)	7.0%
Reid 2010	29	24	-59.62	(-101.46,-17.78)	6.0%
Reid 2014	21	20	-83.10	(-110.89,-55.31)	7.2%
Total	**236**	**227**	**-69.88**	**(-103.63,-36.14)**	**51.9%**

Heterogeneity: $Tau^2 = 1898.7$; $Chi^2 = 859.79$, df = 6 ($P < 0.01$); $I^2 = 99\%$
Test for overall effect: $Z = -4.06$ ($P < 0.01$)

Rios-Leyvraz M, Montez JM. World Health Organization; 2022
https://apps.who.int/iris/ handle/10665/353064)

Energy and sugar reduction

Randomized controlled trials

Adiposity
- Body weight –0.71 kg *(low)*
- BMI –0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sug

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- Total:HDL cholesterol +0.09 (*moderate*)
- Ø 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)*

Mostly in NSS→sugars

Pregnancy
No data

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

Energy intake (sugar comparator):
MD -1008 kjoules/d [-1397, -619]
MD -241 kcal/d [-333, -147]

Reid 2014	21	20	-1141.10	(-2428.32, 146.12)	2.8%
Sagrario Lopez-Meza 2021	26	13	-2156.85	(-3494.70, -819.01)	2.7%
Sanchez-Delgado 2021	13	25	-376.56	(-1636.27, 883.15)	2.9%
Vazquez-Duran 2016	49	48	-564.05	(-1652.45, 524.36)	3.3%
Total	**600**	**554**	**-1008.35**	**(-1397.11, -619.60)**	**54.6%**

Heterogeneity: Tau^2 = 332081.7; Chi^2 = 50.21, df = 15 (P < 0.01); I^2 = 70%
Test for overall effect: Z = -5.08 (P < 0.01)

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

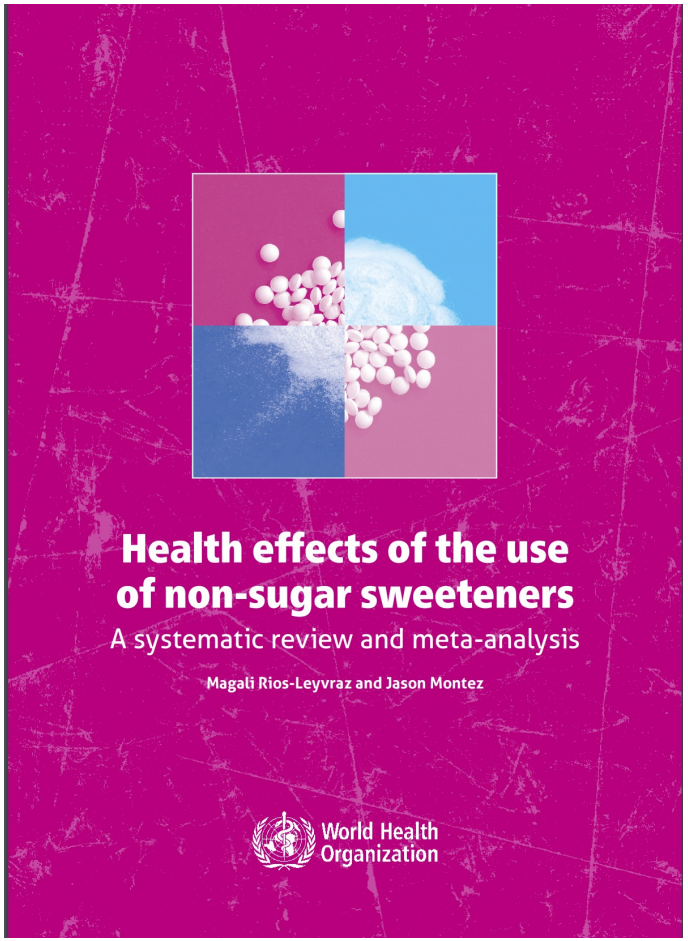
Sugar intake (sugar comparator):
MD –70 g/d [-103, -36]

Reid 2014	21	20	-83.10	(-110.89,-55.31)	7.2%
Total	**236**	**227**	**-69.88**	**(-103.63,-36.14)**	**51.9%**

Heterogeneity: Tau^2 = 1898.7; Chi^2 = 859.79, df = 6 (P < 0.01); I^2 = 99%
Test for overall effect: Z = -4.06 (P < 0.01)

Rios-Leyvraz M, Montez JM. World Health Organization; 2022
https://apps.who.int/iris/ handle/10665/353064)

Updated/expanded WHO-commissioned SRMA of non-sugar sweeteners shows weight loss in RCTs:
SRMA of 55 RCTs/NRCTs, 213 observational studies



- In RCTs, those consuming **NSS had lower body weight and BMI at the end of the trials**, particularly when compared with sugars
- Consuming **NSS** also exhibited a **significant reduction in energy intake**, primarily when NSS were compared to sugars.
- **NSS** may be **effective at assisting with short-term weight loss when their use leads to a reduction in total energy intake and sugar intake.**

https://www.who.int/publications/i/item/9789240046429

Summary of results

Randomized controlled trials

Adiposity
- ↓ Body weight −0.71 kg *(low)*
- ↓ BMI −0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sugars

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 (*moderate*)
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake −569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake −38 *(low)*

Pregnancy
No data

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
- ↑ High fasting glucose HR 1.21 *(low)*
- Ø 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)*
- Ø CHD *(very low)*
- ↑ Stroke HR 1.19 *(low)*
- ↑ Hypertension HR 1.13 *(low)*

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

Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

Rios-Leyvraz M, Mon … h; 2 … ONTO
https://apps.who.int …

Cohort studies

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
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- Ø Other measures

All-cause mortality
- ↑ Mortality HR 1.12 *(very low)*

Cardiovascular diseases
- ↑ CVD mortality HR 1.19 *(low)*
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- Ø Mortality *(very low)*
- Ø Incidence: any type *(very low)*
- ↑ Bladder cancer OR 1.31 *(very low)* — Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

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

Measure of adiposity (unit)	No. of studies/cohorts	Effect estimate (95% CI)	I^2 (%)
Weight (kg)	29 RCTs	**MD –0.71 (–1.13, –0.28)**	83
	4 cohorts (cont)	MD –0.12 (–0.40, 0.15)	76
	5 cohorts (hvl)	MD –0.01 (–0.67, 0.64)	49
BMI (kg/m²)	23 RCTs	MD –0.14 (–0.30, 0.02)	71
	5 cohorts (hvl)	**MD 0.14 (0.03, 0.25)**	79
Incident obesity	2 cohorts (hvl)	**HR 1.76 (1.25, 2.49)**	0

orld Health Organization; 2022
dle/10665/353064)

Cohort studies

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
- ↑ High fasting glucose HR 1.21 *(low)*
- Ø 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)*
- Ø CHD *(very low)*
- ↑ Stroke HR 1.19 *(low)*
- ↑ Hypertension HR 1.13 *(low)*

Cancer
- Ø Mortality *(very low)*
- Ø Incidence: any type *(very low)*
- ↑ Bladder cancer OR 1.31 *(very low)* — Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

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)	I² (%)
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	5 cohorts (hvl)	MD –0.01 (–0.67, 0.64)	49
BMI (kg/m²)	23 RCTs	MD –0.14 (–0.30, 0.02)	71
	5 cohorts (hvl)	**MD 0.14 (0.03, 0.25)**	79
Incident obesity	2 cohorts (hvl)	**HR 1.76 (1.25, 2.49)**	0

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)	I² (%)
Incident type 2 diabetes (beverages)	13 cohorts	**HR 1.23 (1.14, 1.32)**	6
Incident type 2 diabetes (tabletop)	2 cohorts	**HR 1.34 (1.21, 1.48)**	0

orld Health Organization; 2022
dle/10665/353064)

Cohort studies

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
- ↑ High fasting glucose HR 1.21 *(low)*
- Ø 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)*
- Ø CHD *(very low)*
- ↑ Stroke HR 1.19 *(low)*
- ↑ Hypertension HR 1.13 *(low)*

Cancer
- Ø Mortality *(very low)*
- Ø Incidence: any type *(very low)*
- ↑ Bladder cancer OR 1.31 *(very low)* — Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

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)	I² (%)
Weight (kg)	29 RCTs	**MD –0.71 (–1.13, –0.28)**	83
	4 cohorts (cont)	MD –0.12 (–0.40, 0.15)	76
	5 cohorts (hvl)	MD –0.01 (–0.67, 0.64)	49
BMI (kg/m²)	23 RCTs	MD –0.14 (–0.30, 0.02)	71
	5 cohorts (hvl)	**MD 0.14 (0.03, 0.25)**	79
Incident obesity	2 cohorts (hvl)	**HR 1.76 (1.25, 2.49)**	0

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

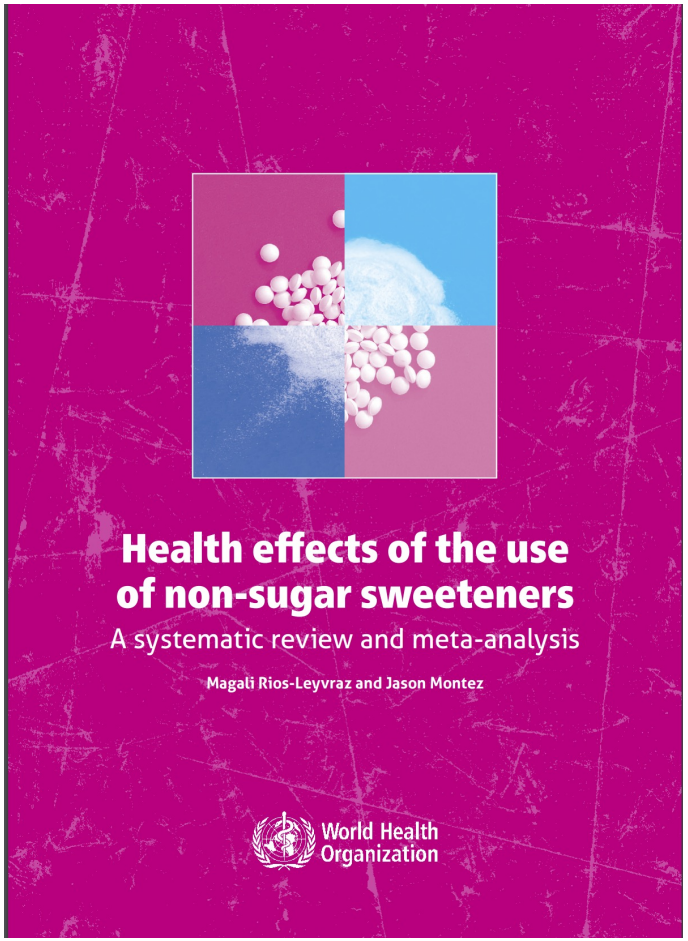
Measure of type 2 diabetes (unit)	No. of studies/ cohorts	Effect estimate (95% CI)	I² (%)
Incident type 2 diabetes (beverages)	13 cohorts	**HR 1.23 (1.14, 1.32)**	6
Incident type 2 diabetes (tabletop)	2 cohorts	**HR 1.34 (1.21, 1.48)**	0

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

Measure of CVD (unit)	Number of studies/cohorts	Effect estimate (95% CI)	I² (%)
CVD mortality	5 cohorts	**HR 1.19 (1.07, 1.32)**	25
Cardiovascular events	3 cohorts	**HR 1.32 (1.17, 1.50)**	0
Coronary heart disease	4 cohorts	HR 1.16 (0.97, 1.39)	75
Stroke	6 cohorts	**HR 1.19 (1.09, 1.29)**	0
Hypertension	6 cohorts	**HR 1.13 (1.09, 1.17)**	48

Updated/expanded WHO-commissioned SRMA of non-sugar sweeteners shows adverse associations in cohorts:

SRMA of 55 RCTs/NRCTs, 213 observational studies

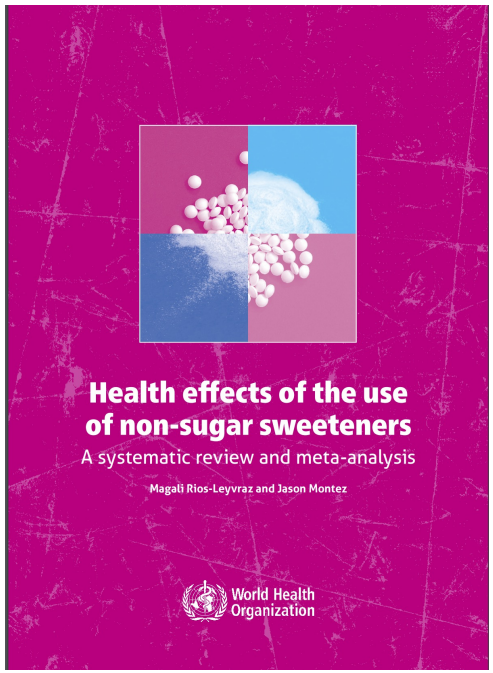


- Results from **prospective cohort studies** suggest the **possibility of long-term harm** in the form of increased **risk of obesity**, **type 2 diabetes**, **cardiovascular diseases** and **mortality**.

- Further **research** is **needed** to determine whether the observed associations are **genuine** or a result of **reverse causation and/or residual confounding**.

https://www.who.int/publications/i/item/9789240046429

WHO guideline: Evidence to Recommendations



APRIL 2022

JULY 2022

MAY 2023

GRADE methodology was used to assess the certainty (i.e. confidence) in the evidence identified in the systematic reviews

WHO guideline: Use of non-sugar sweeteners

Nutrition Guidance and Advisory Group (NUGAG)

*"WHO suggests that **NSS not** be used as a means of achieving **weight control** or **reducing risk of noncommunicable diseases** (conditional recommendation)*"*

* *Conditional recommendations are those recommendations for which the WHO guideline development group is **uncertain that the desirable consequences of implementing the recommendation outweigh the undesirable consequences or when the anticipated net benefits are small.** Policymaking related to conditional recommendations therefore may require **substantial debate** and **involvement of various stakeholders**.*

https://www.who.int/publications/i/item/9789240073616

WHO guideline: Use of non-sugar sweeteners

Not applicable to subjects with diabetes

— With the exception of individuals with diabetes (as noted below), this recommendation is relevant for everyone

Recommendations relevant to all NSS

— the evidence is currently insufficient to make recommendations for individual NSS.

WHO guideline on use of non-sugar sweeteners

Issue 1: Observational (prospective cohort) studies given more weight in recommendation

— Ignored established hierarchy of evidence
— Disregarded trial evidence including long-term studies

WHO guideline on use of non-sugar sweeteners

Issue 1: Observational studies given more weight in recommendation

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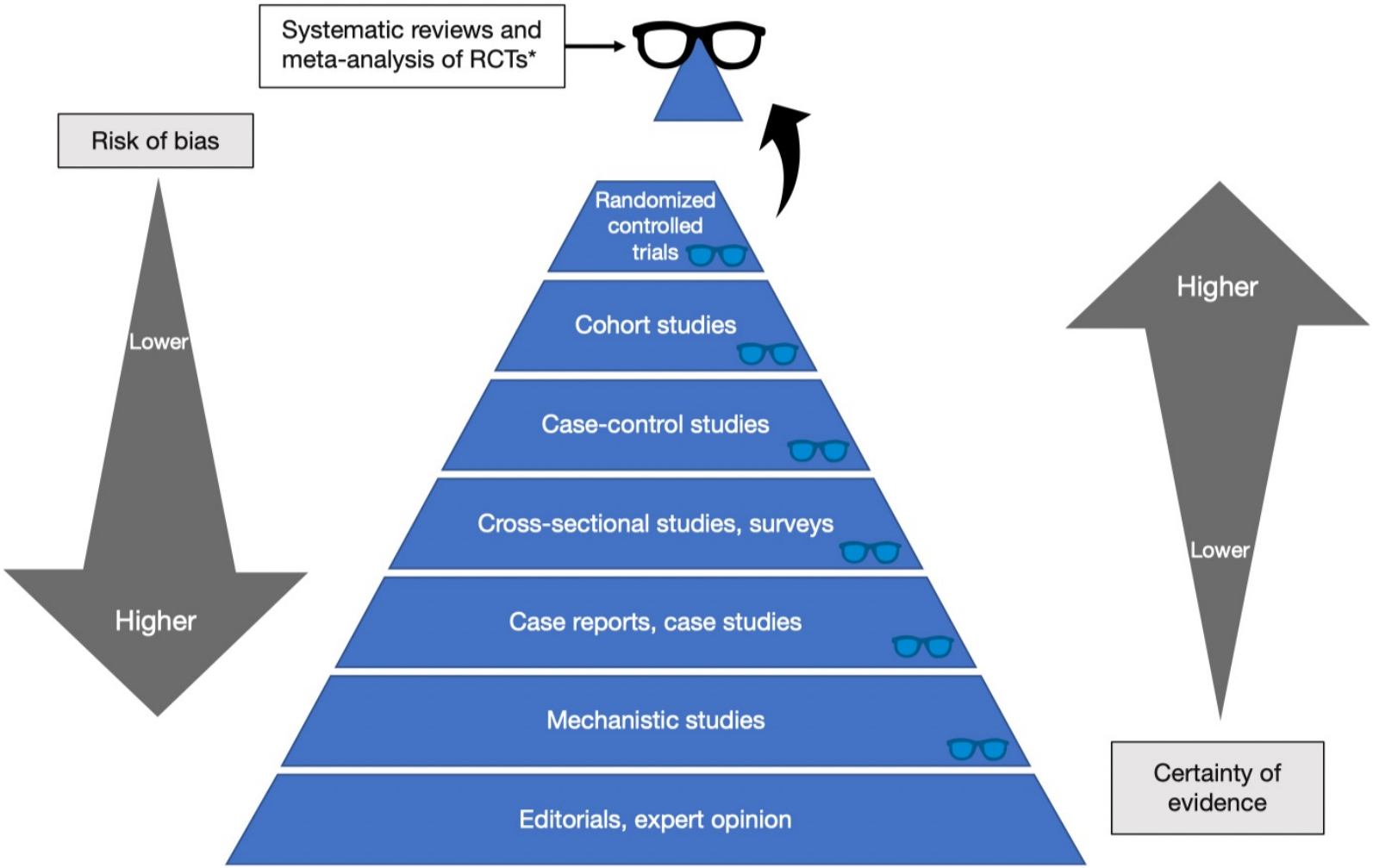
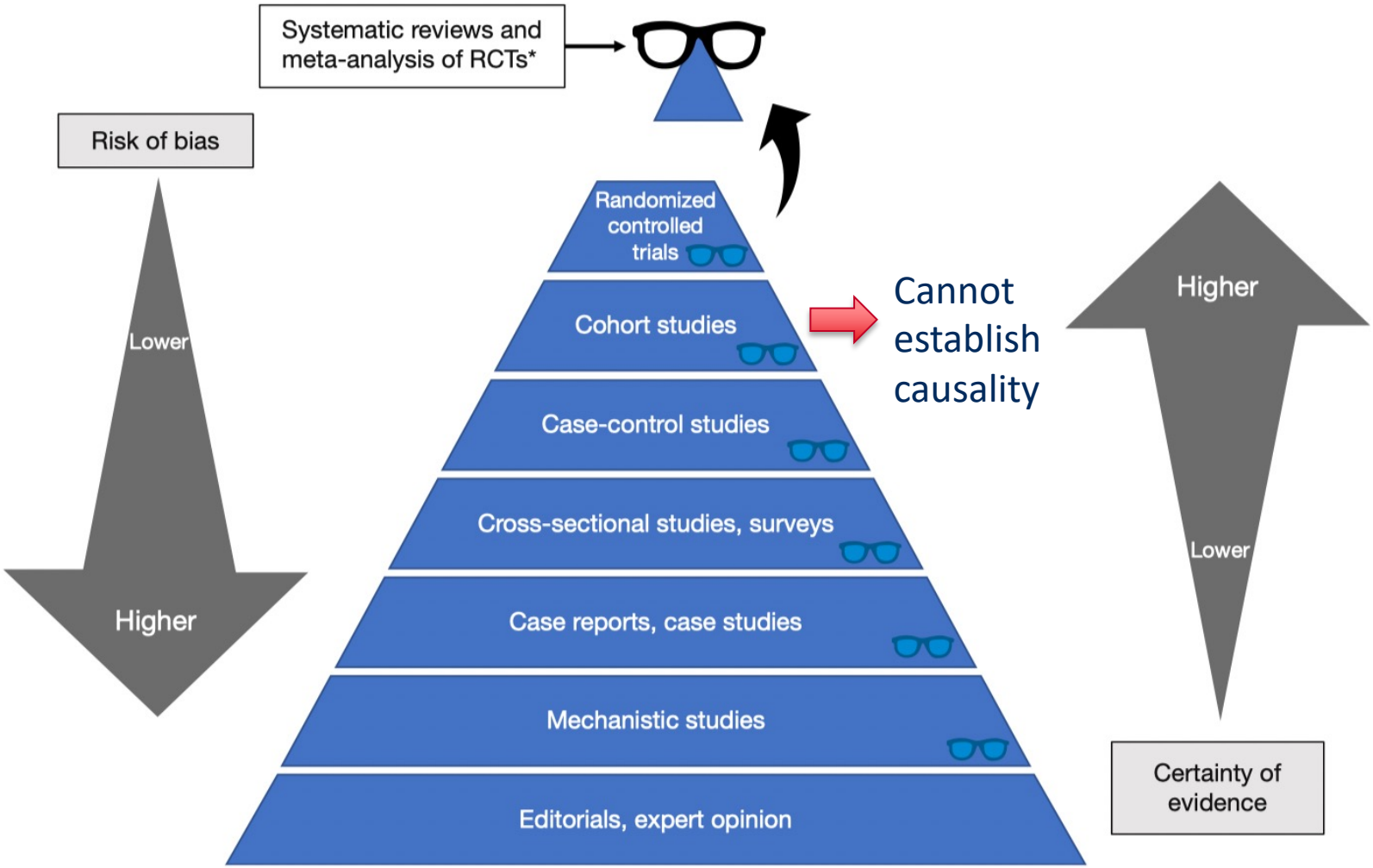
WHO guideline: Hierarchy of Evidence

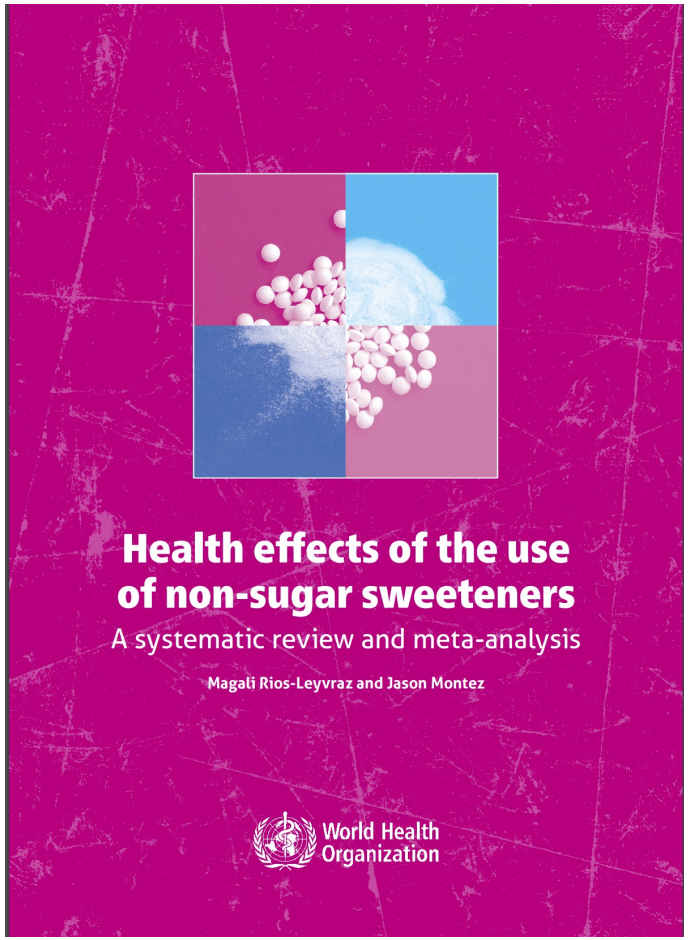


WHO guideline: Hierarchy of Evidence



Updated/expanded WHO-commissioned SRMA of non-sugar sweeteners weighted RCTs > cohorts:

SRMA of 55 RCTs/NRCTs, 213 observational studies



https://www.who.int/publications/i/item/9789240046429

Randomized controlled trials

Adiposity
- ↓ Body weight −0.71 kg *(low)*
- ↓ BMI −0.14 kg/m² *(low)*

Mostly in NSS→sugars

- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 (*moderate*)
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake −569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake −38 *(low)*

Pregnancy
No data

Low to moderate certainty

>

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
- ↑ High fasting glucose HR 1.21 *(low)*
- Ø 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)*
- Ø CHD *(very low)*
- ↑ Stroke HR 1.19 *(low)*
- ↑ Hypertension HR 1.13 *(low)*

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

Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

Very low to low certainty

WHO guideline on use of non-sugar sweeteners:
New interpretation with weighting of prospective cohorts > RCTs

Randomized controlled trials

Adiposity
- ↓ Body weight −0.71 kg *(low)*
- ↓ BMI −0.14 kg/m² *(low)*
- Ø Other measures (waist-to-hip ratio, waist circumference, fat/lean mass)

Mostly in NSS→sugars

Type 2 diabetes
- Ø Intermediate markers (glucose, insulin, HOMA-IR, HbA1c)

All-cause mortality
No data

Cardiovascular diseases
- ↑ Total:HDL cholesterol +0.09 (*moderate*)
- Ø Blood pressure, cholesterol (total, LDL, HDL), triglycerides)

Cancer
No data

Total energy intake (kJ/day)
- ↓ Energy intake −569 *(low)*

Mostly in NSS→sugars

Sugars intake (g/day)
- ↓ Sugars intake −38 *(low)*

Pregnancy
No data

Low to moderate certainty

<

Cohort/case–control studies

Adiposity
- ↑ Incident obesity HR 1.76 *(low)*
- ↑ BMI +0.14 kg/m² *(very low)*
- Ø Other measures

Type 2 diabetes
- ↑ Disease (beverage) HR 1.23 *(low)*
- ↑ Disease (tabletop) HR 1.34 *(low)*
- ↑ High fasting glucose HR 1.21 *(low)*
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All-cause mortality
- ↑ Mortality HR 1.12 *(very low)*

Cardiovascular diseases
- ↑ CVD mortality HR 1.19 *(low)*
- ↑ CV events HR 1.32 *(low)*
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- ↑ Hypertension HR 1.13 *(low)*

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

Mostly in saccharin

Total energy intake (kJ/day)
No data

Sugars intake (g/day)
No data

Pregnancy
- ↑ Preterm birth HR 1.25 *(low)*

Very low to low certainty

WHO guideline on use of non-sugar sweeteners

Issue 1: Observational studies given more weight in recommendation

— Ignored established hierarchy of evidence
— Disregarded trial evidence including long-term studies

WHO guideline on use of non-sugar sweeteners

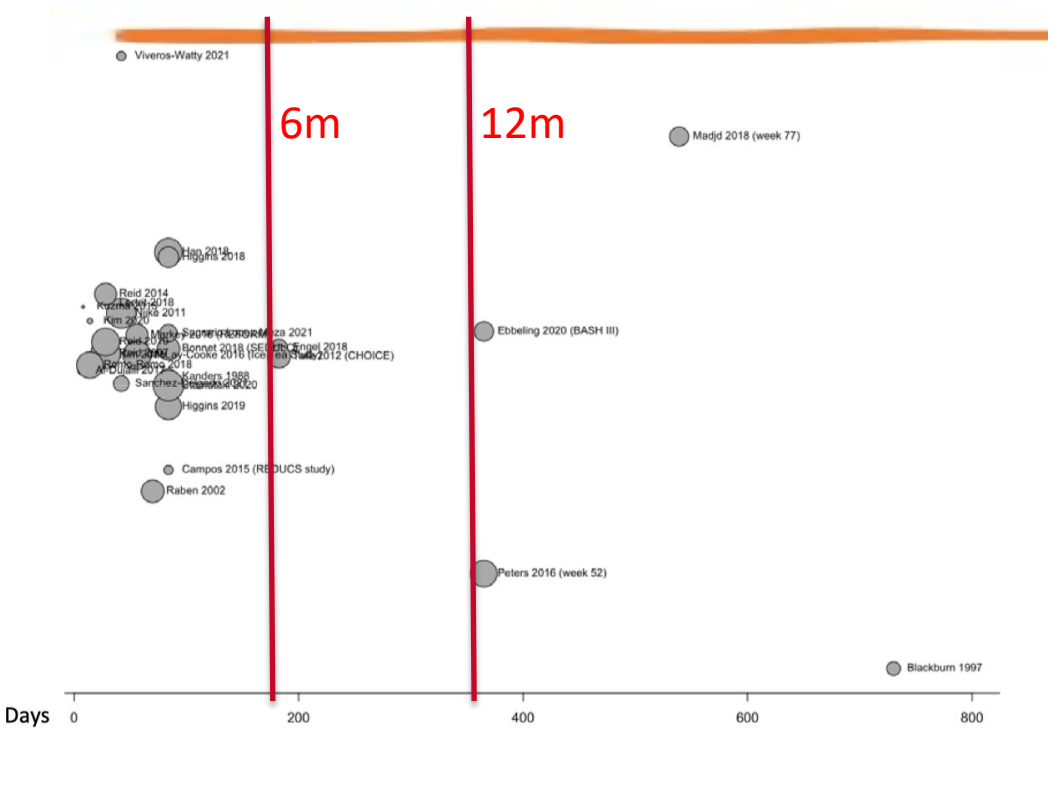
Overall certainty of the evidence

*"The **overall certainty** in the **evidence** was considered **low** and is based on **undesirable effects of NSS** use on **prioritized health outcomes** observed in **prospective cohort studies** which were individually considered to be **very low to low**."*

*"The **discordant results** between the **randomized controlled trials** and **prospective cohort studies** suggest that the **small amount of weight loss** resulting from NSS use in short-term experimental settings may **not** be **relevant** to the **effects of long-term NSS use** in the general population."*

Updated Systematic Review

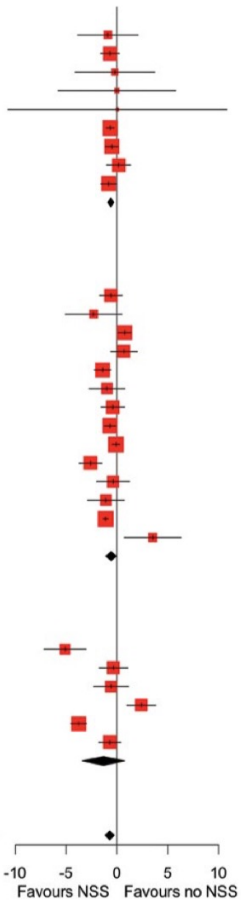
Results: RCT study duration



https://www.who.int/publications/i/item/9789240046429

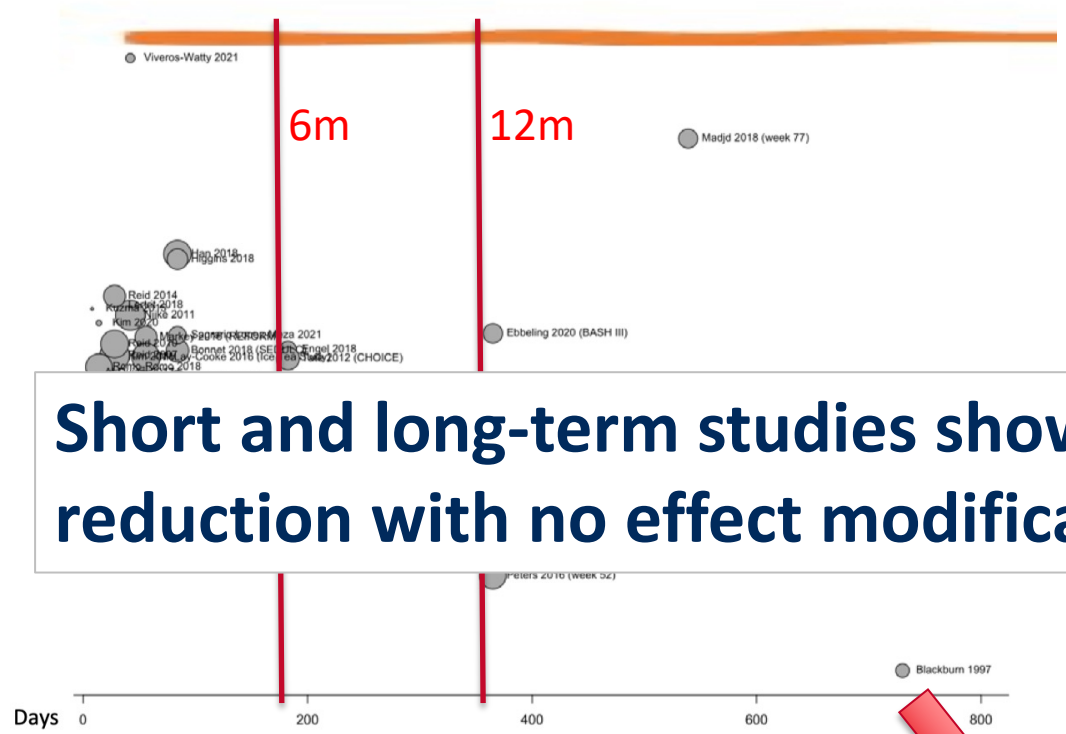
Fig. A9.11 Effect of NSS on body weight (kg) in randomized controlled trials, subgrouped by study duration, in adults

Study	NSS	no NSS	MD	95% CI	Weight
1 month or less					
Al-Dujaili 2017	16	16	-0.90	(-3.87, 2.07)	1.5%
Kim 2011	9	12	-0.68	(-1.61, 0.25)	4.4%
Kim 2020	39	39	-0.20	(-4.13, 3.73)	1.0%
Kuzma 2015	9	9	0.00	(-5.78, 5.78)	0.5%
Lertrit 2018	15	15	0.05	(-10.71,10.81)	0.2%
Reid 2007	65	68	-0.66	(-1.04,-0.28)	5.3%
Reid 2010	29	24	-0.49	(-1.13, 0.14)	4.9%
Reid 2014	21	20	0.18	(-0.99, 1.35)	3.9%
Romo-Romo 2018	30	31	-0.82	(-1.59,-0.05)	4.7%
Total	**233**	**234**	**-0.60**	**(-0.88,-0.33)**	**26.3%**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.37$, df = 8 (P = 0.97); $I^2 = 0\%$					
Test for overall effect: Z = -4.31 (P < 0.01)					
2-3 months					
Bonnet 2018 (SEDULC)	50	50	-0.59	(-1.70, 0.52)	4.0%
Campos 2015 (REDUCS study)	14	13	-2.30	(-5.09, 0.49)	1.6%
Han 2018	40	81	0.77	(0.11, 1.43)	4.9%
Higgins 2018	31	31	0.70	(-0.60, 2.00)	3.6%
Higgins 2019	115	39	-1.41	(-2.20,-0.61)	4.6%
Kanders 1988	28	27	-0.98	(-2.75, 0.78)	2.8%
Markey 2016 (REFORM)	50	50	-0.40	(-1.56, 0.76)	3.9%
McLay-Cooke 2016 (Ice Tea Study)	63	53	-0.68	(-1.27,-0.10)	5.0%
Njike 2011	32	33	-0.09	(-0.49, 0.31)	5.3%
Raben 2002	20	21	-2.60	(-3.71,-1.49)	4.0%
Sagrario Lopez-Meza 2021	26	13	-0.37	(-1.99, 1.25)	3.1%
Sanchez-Delgado 2021	26	12	-1.08	(-2.89, 0.72)	2.8%
Stamataki 2020	14	14	-1.11	(-1.37,-0.85)	5.4%
Viveros-Watty 2021	21	24	3.53	(0.73, 6.33)	1.6%
Total	**530**	**461**	**-0.56**	**(-1.08,-0.05)**	**52.7%**
Heterogeneity: $Tau^2 = 0.6$; $Chi^2 = 66.96$, df = 13 (P < 0.01); $I^2 = 81\%$					
Test for overall effect: Z = -2.15 (P = 0.03)					
3 months or more					
Blackburn 1997	41	45	-5.10	(-7.15,-3.05)	2.4%
Ebbeling 2020 (BASH III)	67	136	-0.35	(-1.75, 1.05)	3.5%
Engel 2018	15	30	-0.57	(-2.27, 1.12)	2.9%
Madjd 2018 (week 77)	36	35	2.40	(0.97, 3.83)	3.4%
Peters 2016 (week 52)	154	149	-3.76	(-4.52,-3.00)	4.7%
Tate 2012 (CHOICE)	105	162	-0.70	(-1.79, 0.39)	4.1%
Total	**418**	**557**	**-1.32**	**(-3.40, 0.75)**	**21.0%**
Heterogeneity: $Tau^2 = 6.2$; $Chi^2 = 78.75$, df = 5 (P < 0.01); $I^2 = 94\%$					
Test for overall effect: Z = -1.25 (P = 0.21)					
Total	**1181**	**1252**	**-0.71**	**(-1.13,-0.28)**	**100.0%**
Heterogeneity: $Tau^2 = 0.9$; $Chi^2 = 167.77$, df = 28 (P < 0.01); $I^2 = 83\%$					
Test for overall effect: Z = -3.25 (P < 0.01)					
Test for subgroup differences: $Chi^2 = 0.48$, df = 2 (P = 0.79)					



Updated Systematic Review

Results: RCT study duration

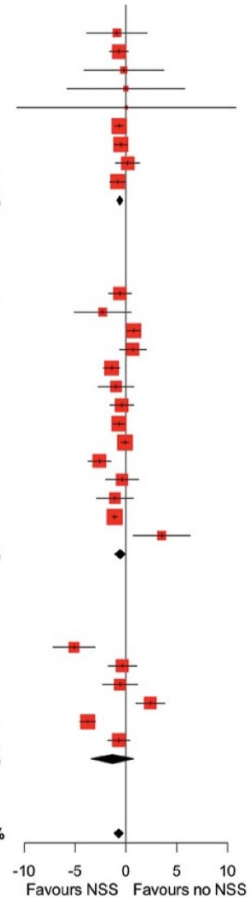


Short and long-term studies showed similar reduction with no effect modification

https://www.who.int/publications/i/item/9789240046429

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

Study	NSS	no NSS	MD	95% CI	Weight
1 month or less					
Al-Dujaili 2017	16	16	-0.90	(-3.87, 2.07)	1.5%
Kim 2011	9	12	-0.68	(-1.61, 0.25)	4.4%
Kim 2020	39	39	-0.20	(-4.13, 3.73)	1.0%
Kuzma 2015	9	9	0.00	(-5.78, 5.78)	0.5%
Lertrit 2018	15	15	0.05	(-10.71,10.81)	0.2%
Reid 2007	65	68	-0.66	(-1.04,-0.28)	5.3%
Reid 2010	29	24	-0.49	(-1.13, 0.14)	4.9%
Reid 2014	21	20	0.18	(-0.99, 1.35)	3.9%
Romo-Romo 2018	30	31	-0.82	(-1.59,-0.05)	4.7%
Total	**233**	**234**	**-0.60**	**(-0.88,-0.33)**	**26.3%**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 2.37$, df = 8 (P = 0.97); $I^2 = 0\%$					
Test for overall effect: Z = -4.31 (P < 0.01)					
2-3 months					
Bonnet 2018 (SEDULC)	50	50	-0.59	(-1.70, 0.52)	4.0%
Campos 2015 (REDUCS study)	14	13	-2.30	(-5.09, 0.49)	1.6%
Han 2018	40	81	0.77	(0.11, 1.43)	4.9%
Higgins 2018	31	31	0.70	(-0.60, 2.00)	3.6%
			1.41	(-2.20,-0.61)	4.6%
			0.98	(-2.75, 0.78)	2.8%
			0.40	(-1.56, 0.76)	3.9%
			0.68	(-1.27,-0.10)	5.0%
			0.09	(-0.49, 0.31)	5.3%
			2.60	(-3.71,-1.49)	4.0%
			0.37	(-1.99, 1.25)	3.1%
			1.08	(-2.89, 0.72)	2.8%
			1.11	(-1.37,-0.85)	5.4%
			3.53	(0.73, 6.33)	1.6%
			0.56	**(-1.08,-0.05)**	**52.7%**
6 months or more					
Blackburn 1997	41	45	-5.10	(-7.15,-3.05)	2.4%
Ebbeling 2020 (BASH III)	67	136	-0.35	(-1.75, 1.05)	3.5%
Engel 2018	15	30	-0.57	(-2.27, 1.12)	2.9%
Madjd 2018 (week 77)	36	35	2.40	(0.97, 3.83)	3.4%
Peters 2016 (week 52)	154	149	-3.76	(-4.52,-3.00)	4.7%
Tate 2012 (CHOICE)	105	162	-0.70	(-1.79, 0.39)	4.1%
Total	**418**	**557**	**-1.32**	**(-3.40, 0.75)**	**21.0%**
Heterogeneity: $Tau^2 = 6.2$; $Chi^2 = 78.75$, df = 5 (P < 0.01); $I^2 = 94\%$					
Test for overall effect: Z = -1.25 (P = 0.21)					
Total	**1181**	**1252**	**-0.71**	**(-1.13,-0.28)**	**100.0%**
Heterogeneity: $Tau^2 = 0.9$; $Chi^2 = 167.77$, df = 28 (P < 0.01); $I^2 = 83\%$					
Test for subgroup differences: $Chi^2 = 0.48$, df = 2 (P = 0.79)					



WHO guideline on use of non-sugar sweeteners

Issue 1: Observational studies given more weight in recommendation

— Ignored established hierarchy of evidence
— Disregarded trial evidence including long-term studies

WHO guideline on use of non-sugar sweeteners

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1. Conventional understanding of nutrition research
2. Best practices in evidence synthesis

WHO guideline on use of non-sugar sweeteners

Issue 1: Observational studies given more weight in recommendation

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— Relied on prospective cohort studies — *Prone to bias and cannot infer causality.* This is a methodologically flawed approach! Goes against:

1. Conventional understanding of nutrition research
2. Best practices in evidence synthesis

No sound biological reasoning for adiposity-related benefits from trials would develop into long-term harm

WHO guideline on use of non-sugar sweeteners

Issue 2: Discounting evidence from prospective cohort studies which applied methodologies to reduce bias

WHO guideline on use of non-sugar sweeteners

Issue 2: Discounting evidence from prospective cohort studies which applied methodologies to reduce bias

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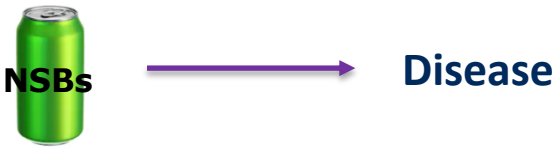
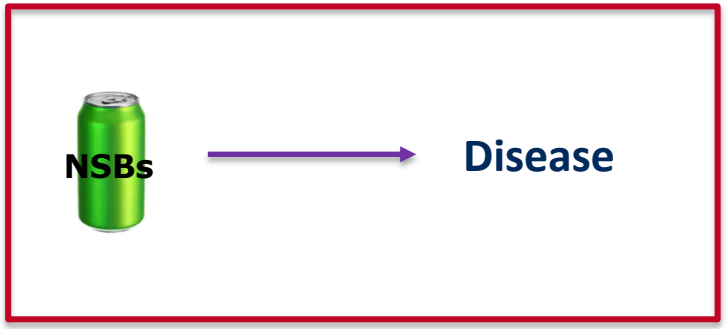
WHO guideline on use of non-sugar sweeteners

Issue 2: Discounting evidence from prospective cohort studies which applied methodologies to reduce bias

— Relied on **PREVALENT** prospective cohort studies

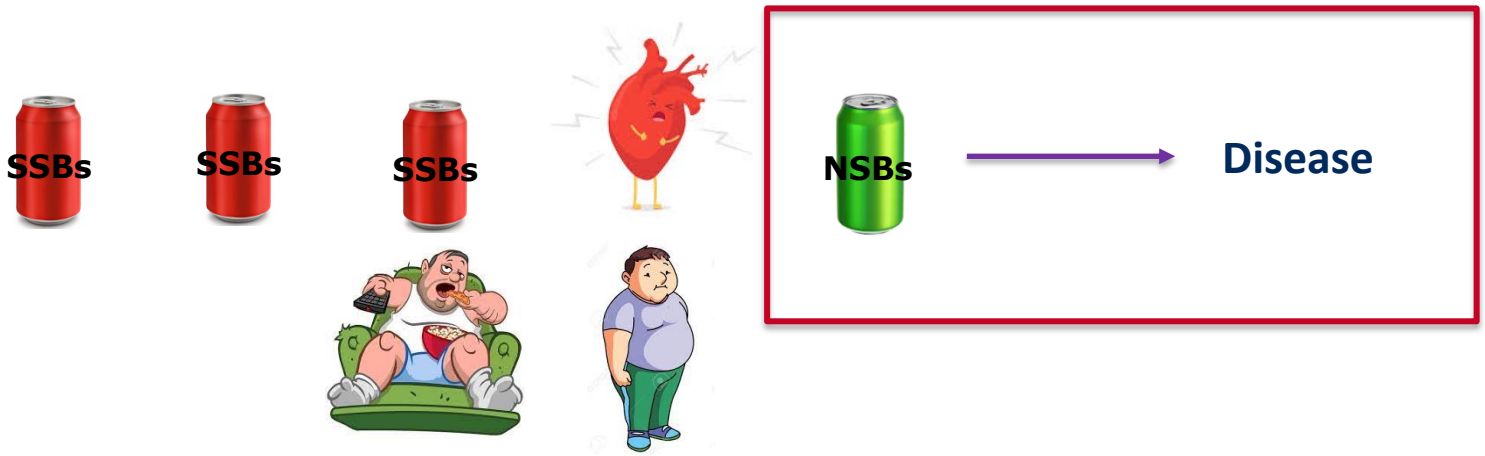


Prevalent or Baseline Analysis



- Prospective cohort studies using prevalent or baseline analysis for LNCS are at **high risk of bias**
- **Bias due to behaviour clustering, residual confounding and reverse causality**

Prevalent or Baseline Analysis



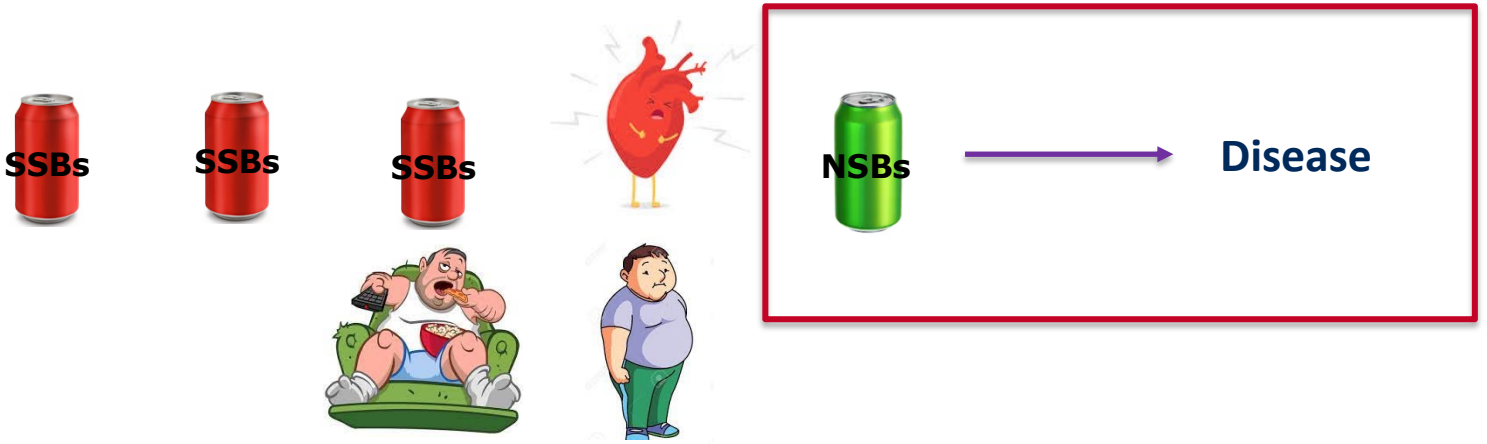
- Prospective cohort studies using prevalent or baseline analysis for LNCS are at **high risk of bias**
- **Bias due to behaviour clustering, residual confounding and reverse causality**

- **Reverse causality: Being at high risk for obesity, type 2 diabetes or CVD leads to increased LNCS intake as a risk reduction strategy**

Prevalent or Baseline Analysis

Research community and dietary guidelines are in agreement:

Prospective cohort studies on LNCS are prone to high risk of bias due to behaviour clustering, residual confounding and reverse causality



Research community

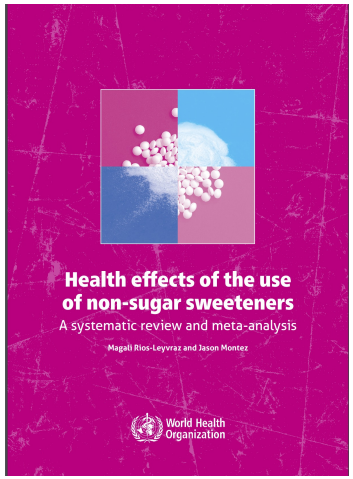
1. Bright OJM et al. Research Priorities for Studies Linking Intake of Low-Calorie Sweeteners and Potentially Related Health Outcomes. Curr Dev Nutr. 2017. 1(7):e000547.
2. Sievenpiper JL, Khan TA et al. The importance of study design in the assessment of nonnutritive sweeteners and cardiometabolic health. CMAJ. 2017 Nov 20;189(46):E1424–5
3. Khan TA, Malik VS, Sievenpiper JL. Letter on Artificially Sweetened Beverages and Stroke, Coronary Heart Disease, and All-Cause Mortality in the Women's Health Initiative. Stroke. 2019 Jun;50(6):e167–8.
4. Malik VS. Non-sugar sweeteners and health. BMJ. 2019 Jan 3;364:k5005.
5. Khan TA, Sievenpiper JL. Low-energy sweeteners and cardiometabolic health: is there method in the madness? Am J Clin Nutr. 2020 Oct 1;112(4):917–9.
6. Mela DJ, McLaughlin J, Rogers PJ. Perspective: Standards for Research and Reporting on Low-Energy ("Artificial") Sweeteners. Adv Nutr. 2020 May 1 [cited 2022 Aug 9];11(3):484–91

Guidelines and Expert Consensus

1. Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition Therapy. Can J Diabetes. 2018 Apr;42:S64–79.
2. United States Department of Agriculture (USDA), United States Department of Health and Human Services (HHS). Dietary Guidelines for Americans 2020-2025. 2020.
3. DNSG Guidelines Committee. Evidence-based European recommendations for the dietary management of diabetes: The DNSG of the EASD Guideline Development Group. Diabetologia. 2023.
4. Ashwell M et al. Expert consensus on low-calorie sweeteners: facts, research gaps and suggested actions. Nutr Res Rev. 2020 Jun;33(1):145–54.

Updated/expanded WHO-commissioned SRMA of non-sugar sweeteners shows adverse associations in cohorts:

SRMA of 55 RCTs/NRCTs, 213 observational studies



Further **research** is **needed** to determine whether the observed associations are **genuine** or a result of **reverse causation and/or residual confounding**.

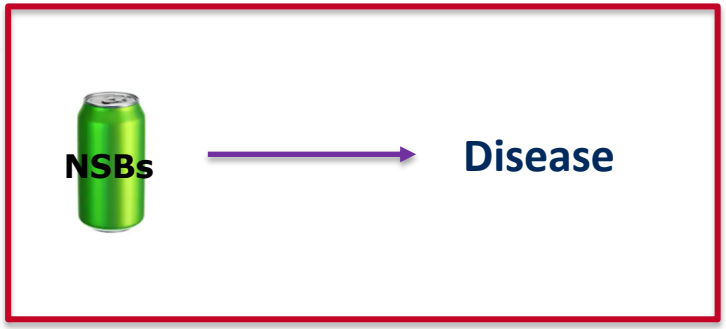
Reverse causation and residual confounding may be contributing factors, the available evidence suggests that the associations observed between NSS use and health outcomes in observational studies **cannot be dismissed** as being solely a result of reverse causation or residual confounding.

https://www.who.int/publications/i/item/9789240046429

Observational Cohorts

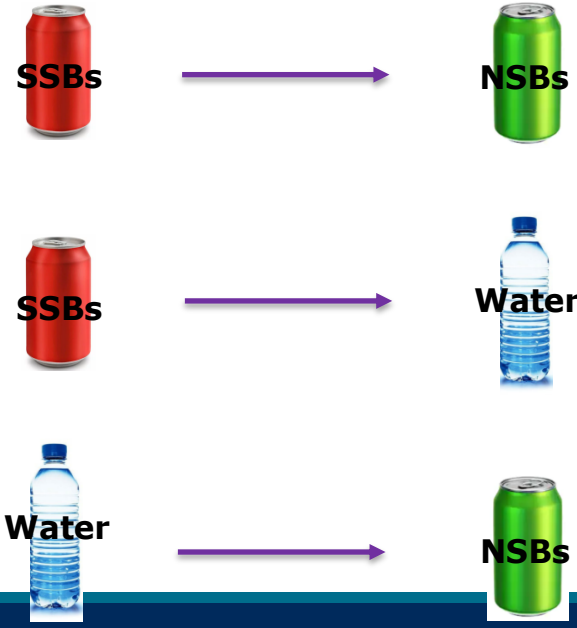
Are there more robust methods that can control for risk of bias

Prevalent or Baseline Analysis of LNCS

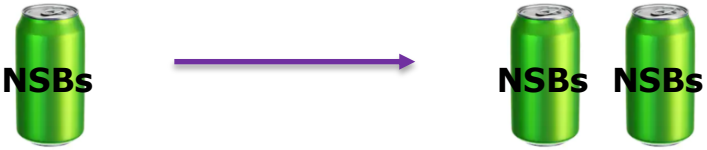


Prevalent or Baseline Analysis of LNCS

Substitution analyses



Change analyses



Approach: Substitution and change analyses

3 prespecified comparisons of clinical/public health importance

Change in intake (increase in 1 serving [330mL] per day)

Jennifer Lee

Diabetes Care Volume 45, August 2022 1917

Relation of Change or Substitution of Low- and No-Calorie Sweetened Beverages With Cardiometabolic Outcomes: A Systematic Review and Meta-analysis of Prospective Cohort Studies

Diabetes Care 2022;45:1917–1930 | https://doi.org/10.2337/dc21-2130

Jennifer J. Lee,[1] Tauseef A. Khan,[1,2] Nema McGlynn,[1,2] Vasanti S. Malik,[1,3] James O. Hill,[4] Lawrence A. Leiter,[1,2,5–7] Per Bendix Jeppesen,[8] Dario Rahelić,[9–11] Hana Kahleová,[12,13] Jordi Salas-Salvadó,[14,15] Cyril W.C. Kendall,[1,2,16] and John L. Sievenpiper[1,2,5–7]

BACKGROUND

Adverse associations of low- and no-calorie sweetened beverages (LNCSB) with cardiometabolic outcomes in observational studies may be explained by reverse causality and residual confounding.

PURPOSE

To address these limitations we used change analyses of repeated measures of intake and substitution analyses to synthesize the association of LNCSB with cardiometabolic outcomes.

DATA SOURCES

MEDLINE, Embase, and the Cochrane Library were searched up to 10 June 2021 for prospective cohort studies with ≥1 year of follow-up duration in adults.

STUDY SELECTION

Outcomes included changes in clinical measures of adiposity, risk of overweight/obesity, metabolic syndrome, type 2 diabetes (T2D), cardiovascular disease, and total mortality.

DATA EXTRACTION

Two independent reviewers extracted data, assessed study quality, and assessed certainty of evidence using GRADE. Data were pooled with a random-effects model and expressed as mean difference (MD) or risk ratio (RR) and 95% CI.

DATA SYNTHESIS

A total of 14 cohorts (416,830 participants) met the eligibility criteria. Increase in LNCSB intake was associated with lower weight (5 cohorts, 130,020 participants; MD −0.008 kg/year [95% CI −0.014, −0.002]). Substitution of LNCSB for sugar-sweetened beverages (SSB) was associated with lower weight (three cohorts, 165,579 participants; MD, −0.12 [−0.14, −0.10,] kg/y) and lower incidence of obesity (OB) (one cohort, 15,765 participants; RR 0.88 [95% CI 0.88, 0.89]), coronary heart disease (six cohorts, 233,676 participants; 0.89 [0.81, 0.98]), cardiovascular disease mortality (one cohort, 118,363 participants; 0.95 [0.90, 0.99]), and

[1]Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[2]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada
[3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA
[4]Department of Nutrition Sciences, The University of Alabama at Birmingham, Birmingham, AL
[5]Division of Endocrinology and Metabolism, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada
[6]LI Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
[7]Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[8]Department of Clinical Medicine, Aarhus University, Aarhus University Hospital, Aarhus, Denmark
[9]Vuk Vrhovac University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Merkur University Hospital, Zagreb, Croatia
[10]Catholic University of Croatia School of Medicine, Zagreb, Croatia
[11]Josip Juraj Strossmayer University of Osijek School of Medicine, Osijek, Croatia
[12]Institute for Clinical and Experimental Medicine, Diabetes Centre, Prague, Czech Republic
[13]Physicians Committee for Responsible Medicine,

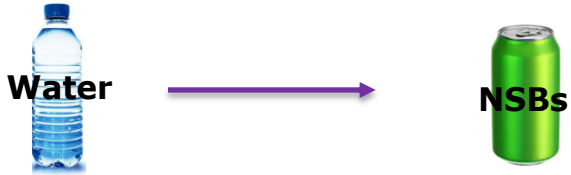
META-ANALYSIS

Substitution analyses

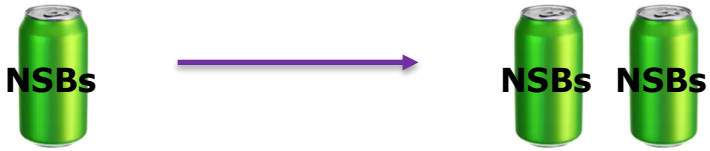
LNCSBs for SSBs ("intended substitution")

Water for SSBs ("standard of care substitution")

LNCSBs for Water ("reference substitution")



Change analyses



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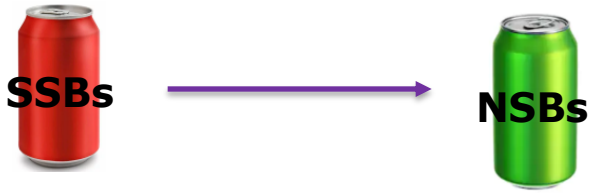
Intended substitution

LNCSBs for SSBs ("intended substitution")



LNCSBs for SSBs ("Intended substitution"):

SRMA of 14 unique prospective cohorts; n=416,830; FU=17.5y

Outcome	Cohort Comparisons	N	Estimate	Pooled Estimate [95% CI]	Heterogeneity I^2	Heterogeneity P_Q	GRADE: Downgrade: Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade: Dose response	Large effect size	Attenuation	Certainty of Evidence
Substituted Beverages: LNCSBs for SSBs ('Intended Substitution')															
Body Weight (kg/y)	3	165,579	MD	-0.12 [-0.14, -0.10]	46%	0.16	□	□	□	□	□	■	□	□	⊕⊕⊕◯ Moderate
Waist Circumference* (cm/y)	1	173	MD	-1.83 [-3.70, 0.05]	N/A	N/A	□	□	■	■	□	□	□	□	⊕◯◯◯ Very Low
% Body Fat* (%/y)	1	173	MD	-0.96 [-2.32, 0.41]	N/A	N/A	□	□	■	■	□	□	□	□	⊕◯◯◯ Very Low
OB Incidence	1	15,765	RR	0.88 [0.88, 0.89]	N/A	N/A	□	□	■	□	□	■	□	□	⊕⊕◯◯ Low
T2D Incidence	5	281,855	RR	0.99 [0.96, 1.01]	69%	0.01	□	■	□	□	□	□	□	□	⊕◯◯◯ Very Low
CHD Incidence	6	233,676	RR	0.89 [0.81, 0.98]	28%	0.22	□	□	□	■	□	■	□	□	⊕⊕◯◯ Low
Stroke Incidence	1	127,456	RR	1.03 [0.93, 1.14]	N/A	N/A	□	□	■	■	□	□	□	□	⊕◯◯◯ Very Low
CHD Mortality	5	220,805	RR	0.95 [0.81, 1.11]	36%	0.18	□	□	□	■	□	□	□	□	⊕◯◯◯ Very Low
CVD Mortality	1	118,363	RR	0.95 [0.90, 0.99]	N/A	N/A	□	□	■	■	□	■	□	□	⊕⊕◯◯ Low
Total Mortality	1	118,363	RR	0.96 [0.94, 0.98]	N/A	N/A	□	□	■	■	□	■	□	□	⊕⊕◯◯ Low

Pooled estimates represented as SMD

-0.20 -0.10 0.00 0.10 0.20

Protective Association

Adverse Association

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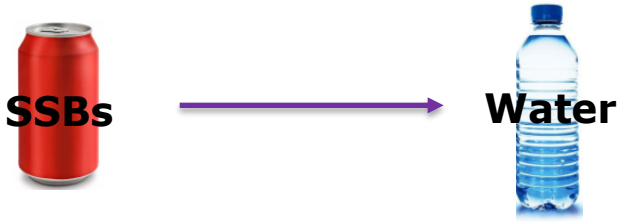
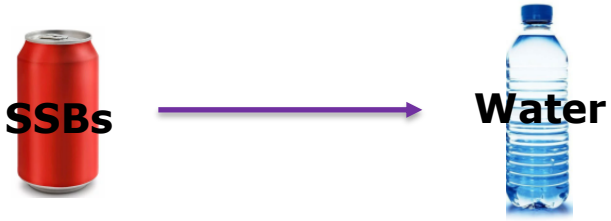
Standard of care substitution

Water for SSBs (“standard of care substitution”)

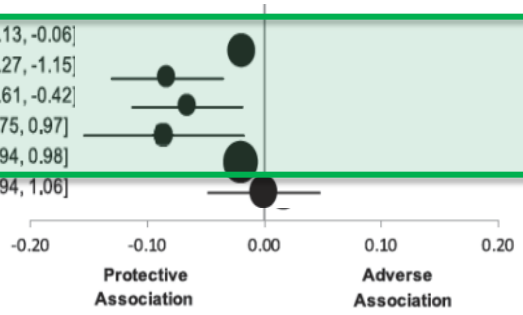


Water for SSBs ("standard of care substitution"):
SRMA of 14 unique prospective cohorts; n=416,830; FU=17.5y



Outcome	Cohort Comparisons	N	Estimate	Pooled Estimate [95% CI]	I^2	P_Q	GRADE: Downgrade (Risk of Bias, Inconsistency, Indirectness, Imprecision, Publication bias) / Upgrade (Dose response, Large effect size, Attenuation)	Certainty of Evidence
Substituted Beverages: Water for SSBs ('Standard of Care Substitution')								
Body Weight (kg/y)	3	165,579	MD	-0.10 [-0.13, -0.06]	82%	<0.01	■ /	⊕⊕◯◯ Low
Waist Circumference* (cm/y)	1	173	MD	-2.71 [-4.27, -1.15]	N/A	N/A	■■ /	⊕⊕◯◯ Low
% Body Fat* (%/y)	1	173	MD	-1.51 [-2.61, -0.42]	N/A	N/A	■■ /	⊕⊕◯◯ Low
OB Incidence	1	15,765	RR	0.85 [0.75, 0.97]	N/A	N/A	■■ /	⊕⊕◯◯ Low
T2D Incidence	3	281,855	RR	0.96 [0.94, 0.98]	79%	<0.01	■■ /	⊕⊕◯◯ Low
Stroke Incidence	1	127,456	RR	1.00 [0.94, 1.06]	N/A	N/A	■■ /	⊕◯◯◯ Very Low

Pooled estimates represented as SMD



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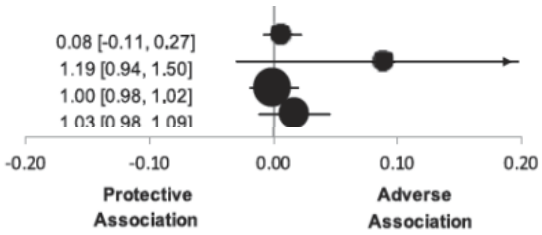
Reference substitution

LNCSBs for Water ("reference substitution")

Relation of substitution of LNCSBs for water ("reference substitution") with cardiometabolic outcomes

SRMA of 14 unique prospective cohorts; n=416,830; FU=17.5y

Outcome	Cohort Comparisons	N	Estimat	Pooled estimates represented as SMD	Heterogeneity I^2	Heterogeneity P_Q	GRADE: Downgrade (Risk of Bias, Inconsistency, Indirectness, Imprecision, Publication bias)	GRADE: Upgrade (Dose response, Large effect size, Attenuation)	Certainty of Evidence
Substituted Beverages: LNCSBs for Water ('Reference Substitution')									
Body Weight (kg/y)	1	173	MD	0.08 [-0.11, 0.27]	N/A	N/A	□□■□□	□□□	⊕○○○ Very Low
OB Incidence	1	15,765	RR	1.19 [0.94, 1.50]	N/A	N/A	□□■■□	□□□	⊕○○○ Very Low
T2D Incidence	3	257,202	RR	1.00 [0.98, 1.02]	83%	<0.01	□■□□□	□□□	⊕○○○ Very Low
Stroke Incidence	1	127,456	RR	1.03 [0.98, 1.09]	N/A	N/A	□□■■□	□□□	⊕○○○ Very Low



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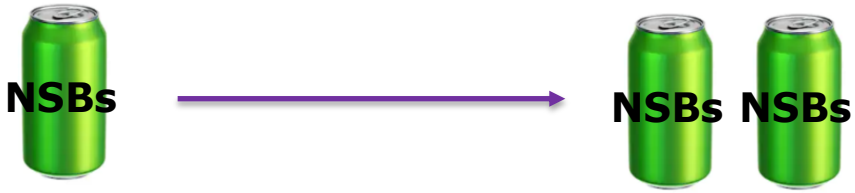
Change analyses

Relation of change in intake (per 330 mL serving per day) of LNCSBs with cardiometabolic outcomes

SRMA of 14 unique prospective cohorts; n=416,830; FU=17.5y

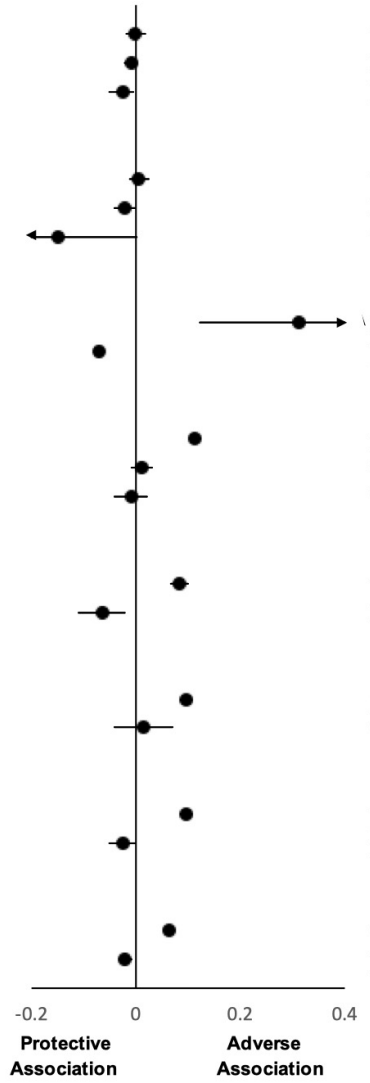


Outcome	Cohort Comparisons	N	Estimate	Pooled Estimate [95% CI]	P-value	Pooled estimates represented as SMD: SMD [95% CI]	Heterogeneity: I^2	Heterogeneity: P_Q	GRADE: Downgrade: Risk of Bias, Inconsistency, Indirectness, Imprecision, Publication bias	GRADE: Upgrade: Dose response, Large effect size, Attenuation	Certainty of Evidence
Body Weight (kg/y)	5	136,206	MD	-0,008 [-0.014, -0.002]	0.01	-0.01 [-0.02, -0.004]	66%	0.02	☐■☐☐☐	■☐☐	⊕⊕◯◯ Low
Waist Circumference (cm/y)	1	9,294	MD	-1.15 [-2.34, -0.045]	0.04	-0.02 [-0.04, -0.002]	N/A	N/A	☐☐■■☐	■☐☐	⊕⊕◯◯ Low
T2D Incidence	3	117,992	RR	1.02 [0.99, 1.06]	0.23	0.01 [-0.01, 0.03]	84%	<0.01	☐☐■■☐	☐☐☐	⊕◯◯◯ Very Low

Lee et al. Diabetes Care, Diabetes Care. 2022;45:1917-1930

Prevalent, Change and Substitution analysis in Cohort studies

Outcome Analysis (no. of cohorts)	N	Pooled Estimate [95% CI]	Certainty of Evidence
Body Weight* (MD)			
Prevalent (5)	11,874	-0.01 [-0.67, 0.64]	Very Low
Change (5)	130,020	-0.01 [-0.01, 0.00]	Low
Substitution (3)	165,579	-0.12 [-0.14, -0.10]	Moderate
Waist Circumference† (MD)			
Prevalent (3)	12,886	0.92 [-1.73, 3.56]	Very Low
Change (1)	9,294	-1.15 [-2.34, -0.05]	Low
Substitution (1)	173	-1.83 [-3.70, 0.05]	Very Low
Obesity Incidence (RR)			
Prevalent (2)	1,668	1.76 [1.25, 2.49]	Low
Substitution (1)	15,765	0.88 [0.88, 0.89]	Low
T2D Incidence (RR)			
Prevalent (13)	408,609	1.23 [1.14, 1.32]	Low
Change (3)	192,352	1.02 [0.99, 1.06]	Very Low
Substitution (5)	281,855	0.99 [0.96, 1.01]	Very Low
CHD Incidence (RR)			
Prevalent (4)	205,455	1.16 [0.97, 1.39]	Very Low
Substitution (6)	233,676	0.89 [0.81, 0.98]	Low
Stroke Incidence (RR)			
Prevalent (6)	655,953	1.19 [1.09, 1.29]	Low
Substitution (1)	127,456	1.03 [0.93, 1.14]	Very Low
CVD Mortality (RR)			
Prevalent (5)	598,951	1.19 [1.07, 1.32]	Low
Substitution (1)	118,363	0.95 [0.90, 0.99]	Low
Total Mortality (RR)			
Prevalent (8)	860,873	1.12 [1.05, 1.19]	Very Low
Substitution (1)	118,363	0.96 [0.94, 0.98]	Low



Data from

- **Prevalence** — **WHO** Rios-Leyvraz M, Montez J. World Health Organization. 2022
- **Change** — Lee et al. Diabetes Care, Diabetes Care. 2022
- **Substitution** — Lee et al. Diabetes Care, Diabetes Care. 2022

Khan 2023. EJCN. Under Review

Prevalent, Change and Substitution analysis in Cohort studies

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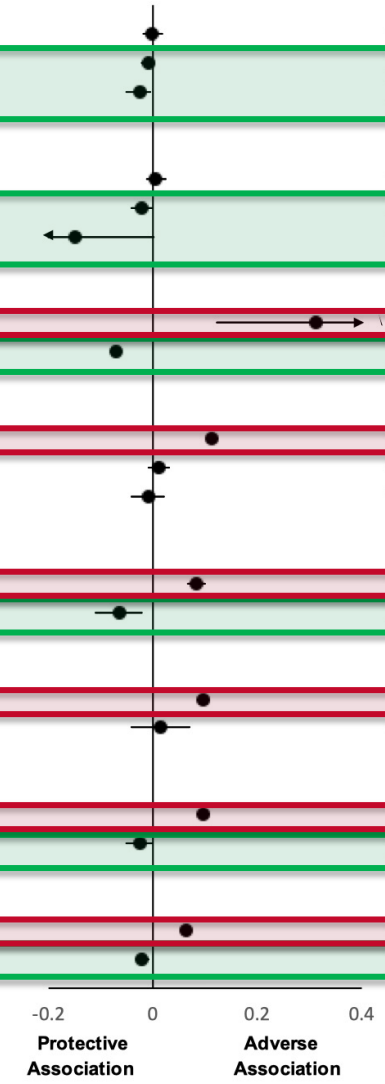


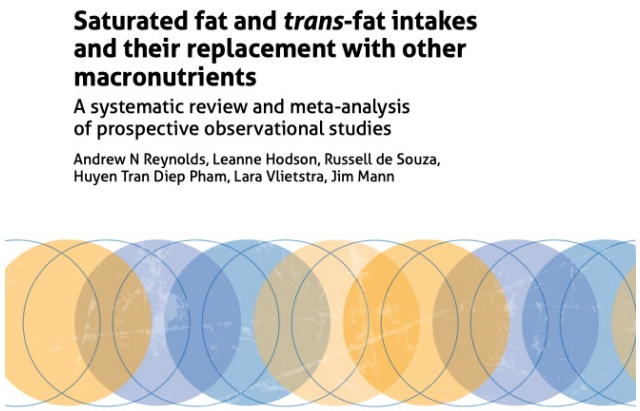
Data from

- **Prevalence** — **WHO** Rios-Leyvraz M, Montez J. World Health Organization. 2022
- **Change** — Lee et al. Diabetes Care, Diabetes Care. 2022
- **Substitution** — Lee et al. Diabetes Care, Diabetes Care. 2022

Khan 2023. EJCN. Under Review

WHO has taken this approach before!

WHO SRMA on Saturated and trans-fat intakes and their replacement with other macronutrients



Results of replacing Saturated Fatty Acids (SFA)

*— **replacement** of these fats with other **macronutrients** allowed us to consider this topic in **more detail than any other previous work on this topic**.*

World Health Organization

Reynolds AN et al. Saturated fat and trans-fat intakes and their replacement with other macronutrients: a systematic review and meta-analysis of prospective observational studies. 2022 https://www.who.int/publications/i/item/9789240061668

WHO guideline
Call for more robust exposure assessments

Research gaps and future initiatives

Elaboration and refinement of prospective cohort studies *including:*
*— **more robust exposure assessment** (e.g. multiple, sequential assessments of exposure [i.e. change])*
*— further **efforts to address reverse causation** [i.e. change and substitution analysis]*

WHO guideline
There are other ways of sugar reduction!

*— **reduction in free sugars intake** can be achieved and corresponding desirable health benefits realized **without the use of NSS.***

*— Use **of NSS is not the only way** to achieve a reduction in free sugars intake; **viable alternatives** exist that are compatible with features of a healthy diet including consumption of foods with naturally occurring sugars, such as **fruit, and unsweetened foods and beverages.***

*— **Individuals switching from NSS** to free sugars would **not be a widespread occurrence**.*

https://www.who.int/publications/i/item/9789240073616

WHO guideline on use of non-sugar sweeteners: Updating the guideline

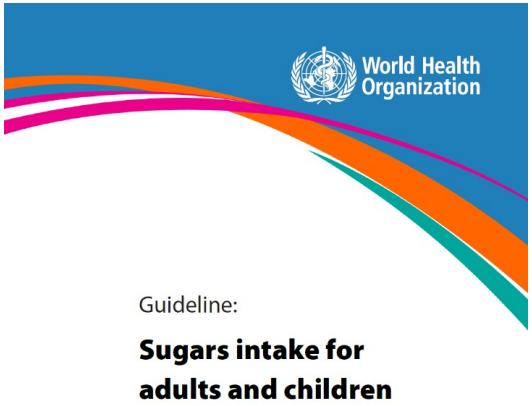
Updating the guideline

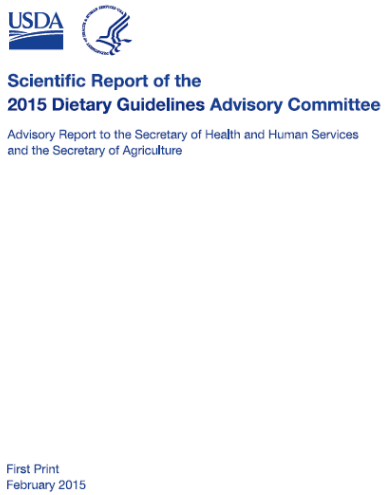
"Because the evidence base for NSS use is rapidly evolving, the literature will be monitored on a regular basis.

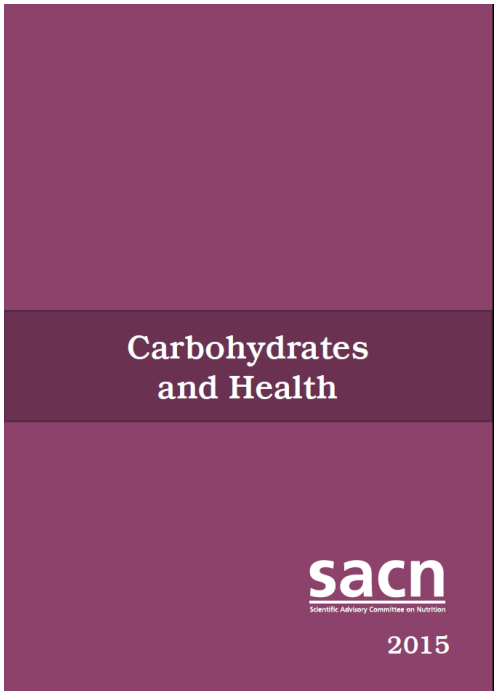
It is planned that the recommendation in this guideline will be reviewed when ***new data and information become available*** *that might alter the* ***overall body of evidence such that it would need to be re-evaluated****."*

Importance of values and preferences?

Sugars the new dominant public health concern:
Dietary guidelines recommend <5-10% energy from sugars







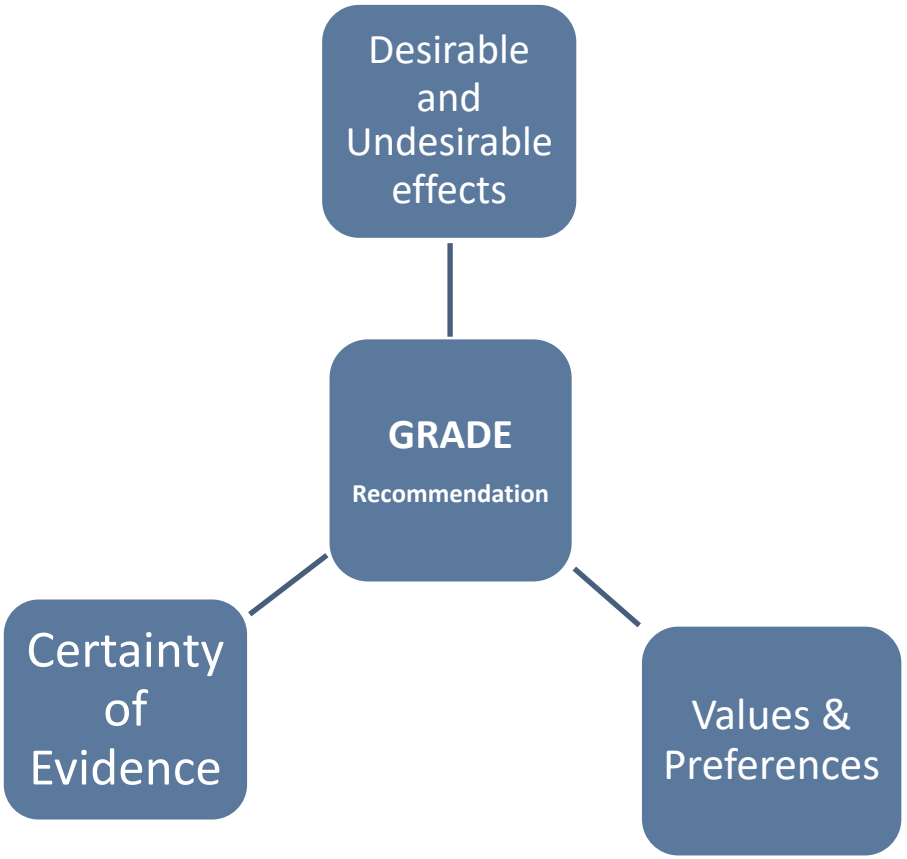
<10% energy
<5% energy (conditional)

≤10% energy

≤5% energy

http://www.who.int/nutrition/publications/guidelines/sugars_intake/en/
http://www.health.gov/dietaryguidelines/2015-scientific-report/
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/445503/SACN_Carbohydrates_and_Health.pdf

Values and Preferences



- *Values and preferences refer to the **attitudes, beliefs, and preferences of end-users, decision makers**, and other **stakeholders** re the outcomes and trade-offs of the intervention.*
- *Individuals' and stakeholders' values and preferences, **should be taken into account when making a recommendation.***
- *Ensures that the **recommendations are not solely based on the evidence but also take into account the unique circumstances and preferences, cost options in different settings, feasibility, and acceptability**.*

Most important reason people provide for consuming LNCS is to cut sugars and calories:

2020 survey, N=919 users (MarketLab, unpublished observations)

FEATURE ARTICLE

Practical Strategies to Help Reduce Added Sugars Consumption to Support Glycemic and Weight Management Goals

Hope Warshaw[1] and Steven V. Edelman[2,3]

Overconsumption of added sugars is a key contributor to the growing obesity, prediabetes, and type 2 diabetes pandemics. The nutrition therapy guidance of the American Diabetes Association recognizes that using low- and no-calorie sweeteners (LNCS) to reduce consumption of added sugars can reduce low–nutrient-density sources of calories and carbohydrate to beneficially affect glycemia, weight, and cardiometabolic health. This article provides information for primary care providers, diabetes care and education specialists, and other diabetes clinicians on the safety of LNCS and summarizes research evidence on the role of LNCS in glycemic and weight management. It also provides practical strategies for counseling individuals about how to integrate LNCS into their healthy eating pattern.

The increasing number of adults and children/adolescents who are overweight and obese in the United States is a national health concern. Numerous studies have shown that overweight and obesity are significant risk factors for several interrelated health conditions, including prediabetes, type 2 diabetes, cardiovascular and cerebrovascular disease, hypertension, stroke, and other significant health conditions of increasing concern (1,2), such as nonalcoholic steatohepatitis and nonalcoholic fatty liver disease (3). Excessive weight is a concern in individuals with type 1 or type 2 diabetes and is a leading risk factor for prediabetes (4) because it decreases insulin sensitivity, which creates additional challenges in achieving and maintaining management of glycemia and other cardiometabolic health metrics (5).

Given the growing pandemics of type 1 and type 2 diabetes, prediabetes, and obesity and their associated costs (6), it is imperative that primary care providers (PCPs), diabetes care and education specialists, and other diabetes clinicians provide people who have or are at risk for developing diabetes with practical strategies for weight management and healthier eating. For many people, the most challenging part of their diabetes care plan is knowing what to eat and adhering to a healthy eating plan over time (7). Some individuals can achieve some success by reducing consumption of added sugars by choosing foods and beverages sweetened with low- and no-calorie sweeteners (LNCS) and using their preferred type and forms of table-top LNCS to sweeten foods and beverages. LNCS, the term used throughout this publication, are also referred to as low-calorie sweeteners, nonnutritive sweeteners, sugar substitutes, and high-intensity sweeteners (8). As sweetening ingredients, LNCS add no or negligible calories to foods and beverages.

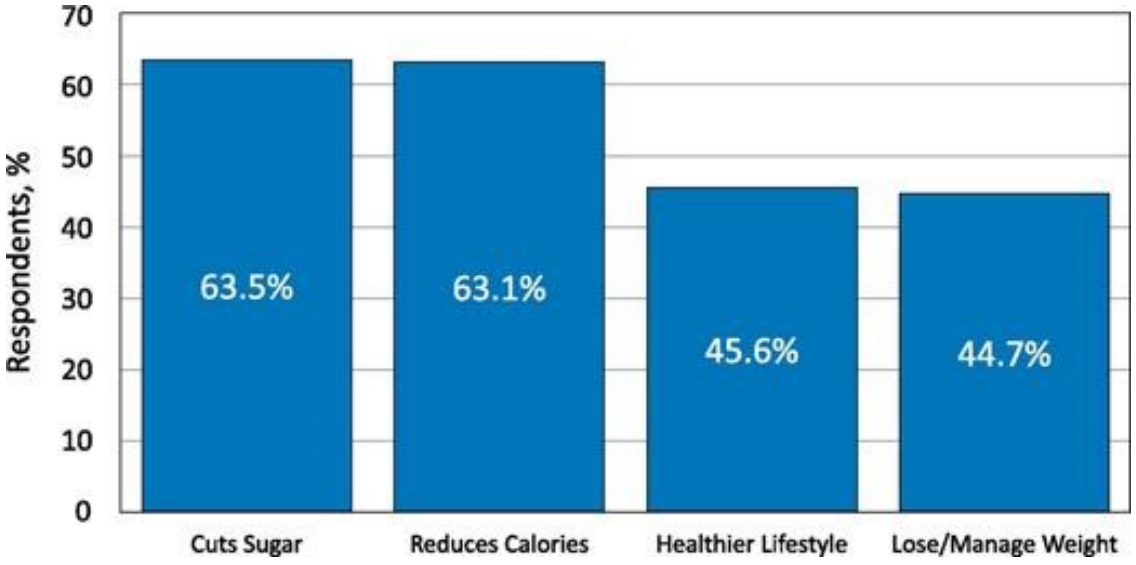
This article reviews evidence supporting the safety and efficacy of LNCS in glycemic and weight management. It also provides practical strategies for clinicians to help people with diabetes and prediabetes effectively use LNCS to replace full-calorie sources of added sugars to assist with weight management and glycemic goals.

Scope of the Problem

The National Center for Health Statistics reports that the prevalence of obesity was 42.4% in 2017–2018 (9). The prevalence of obesity among children and adolescents is estimated to be 18.5% (10).

Overconsumption of various sources of added sugars is one contributor to the growing obesity pandemic. Several recent meta-analyses confirm the strong relationship between the consumption of added sugars, including

[1]Hope Warshaw Associates, Asheville, NC; [2]University of California San Diego, San Diego, CA; [3]Taking Control of Your Diabetes, San Diego, CA
Corresponding author: Hope Warshaw, hope@hopewarshaw.com
https://doi.org/10.2337/cd20-0034



Warshaw H et al. Clin Diabetes 2021;39(1):45–56

LNCSBs are widely consumed (as part of a broader lifestyle modification) in successful longterm weight loss maintenance: *National Weight Control Registry*, n=434 (≥13.6kg weight loss, maintained for >1 year)

Original Article
EPIDEMIOLOGY/GENETICS

Obesity

Low/No Calorie Sweetened Beverage Consumption in the National Weight Control Registry

Victoria A. Catenacci[1], Zhaoxing Pan[2], J. Graham Thomas[3], Lorraine G. Ogden[4], Susan A. Roberts[5], Holly R. Wyatt[1], Rena R. Wing[3] and James O. Hill[6]

Objective: The aim of this cross-sectional study was to evaluate prevalence of and strategies behind low/no calorie sweetened beverage (LNCSB) consumption in successful weight loss maintainers.
Methods: An online survey was administered to 434 members of the National Weight Control Registry (NWCR, individuals who have lost ≥13.6 kg and maintained weight loss for > 1 year).
Results: While few participants (10%) consume sugar-sweetened beverages on a regular basis, 53% regularly consume LNCSB. The top five reasons for choosing LNCSB were for taste (54%), to satisfy thirst (40%), part of routine (27%), to reduce calories (22%) and to go with meals (21%). The majority who consume LNCSB (78%) felt they helped control total calorie intake. Many participants considered changing patterns of beverage consumption to be very important in weight loss (42%) and maintenance (40%). Increasing water was by far the most common strategy, followed by reducing regular calorie beverages.
Conclusions: Regular consumption of LNCSB is common in successful weight loss maintainers for various reasons including helping individuals to limit total energy intake. Changing beverage consumption patterns was felt to be very important for weight loss and maintenance by a substantial percentage of successful weight loss maintainers in the NWCR.

Obesity (2014) **22**, 2244–2251. doi:10.1002/oby.20834

Introduction

Low/no calorie sweetened beverages (LNCSB) are beverages sweetened with one or more high intensity sweeteners in place of energy yielding sugars. These beverages are widely available and consumed; recent National Health and Nutrition Examination Survey (NHANES) data suggests 28% of US adults consume beverages sweetened with low/no calorie sweeteners on a daily basis (1). It is likely many individuals consume these products in the belief that they will help them limit their total calorie intake and/or control their weight. However, the role of these products in aiding weight loss or weight loss maintenance is controversial. While a few short-term laboratory based feeding studies in humans have suggested low/no calorie sweeteners may stimulate hunger (2-4), most other studies have found consumption of low/no calorie sweetened foods or beverages did not increase hunger or subsequent food intake (5-9). Some longitudinal studies have linked low/no calorie sweeteners with weight gain and increased cardio-metabolic risk (10-13), leading to concerns that these products may be contributing to the obesity epidemic (14). However, several interventional studies have shown that low/no calorie sweeteners can be an effective part of weight loss (15-19) and weight loss maintenance (15) programs.

Phelan et al (20) compared the use of fat- and sugar-modified foods and beverages in weight loss maintainers (n=172) and always-normal weight controls (n=131) using 24 hour dietary recalls. Compared to normal weight controls, weight loss maintainers reported consuming three times more daily servings of artificially sweetened soft drinks suggesting these products may be an important weight

[1] Division of Endocrinology, Metabolism, and Diabetes, Department of Medicine, Anschutz Health and Wellness Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA. Correspondence: Victoria A. Catenacci (vicki.catenacci@ucdenver.edu) [2] Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA [3] Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, Brown University, Providence, Rhode Island, USA [4] Anschutz Health and Wellness Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA [5] Global Scientific and Regulatory Affairs, The Coca-Cola Company, Atlanta, Georgia, USA [6] Department of Medicine and Pediatrics, Anschutz Health and Wellness Center, University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA

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Additional Supporting Information may be found in the online version of this article.
Received: 23 May 2014; **Accepted:** 20 June 2014; **Published online 19 June 2014. doi:10.1002/oby.20834**

*"**53% regularly [≥ 1 per day] consume LNCSBs**. The top five reasons for choosing LNCSB were for **taste (54%),** to satisfy **thirst (40%),** part of **routine (27%),** to **reduce calories (22%)** and to go with **meals (21%)**.*

*The **majority** who consume LNCSB **(78%)** felt they **helped control total calorie intake**. Many participants considered changing patterns of beverage consumption to be **very important in weight loss (42%) and maintenance (40%)**."*

Catenacci VA et al. Obesity (Silver Spring). 2014;22:2244-51

CONCLUSIONS

Conclusions

1. **The results of meta-analysis of of randomized controlled trials results** support the use of **LNCS in clinical and public health strategies** for reducing **caloric intake, while** achieving short and long-term **weight loss benefits**.
2. Prospective cohort studies on **LNCS** using **prevalent analysis** are subject to serious **methodological limitations** including **residual confounding**, **behaviour clustering**, and **reverse causality**.
3. The **WHO guideline recommendation against the use of LNCS** relies solely on evidence from **prospective cohort studies with prevalent assessment** of LNCS while ignoring the beneficial trial results.
4. **Prospective cohort studies**, utilizing **methods to reduce bias that includes substitution and change analysis,** give consistent results with trials and demonstrate **reductions** in incident **obesity**, **CHD**, and **total mortality**.
5. The **consistency between trial results and analytically rigorous prospective cohort studies,** and the need to **consider values and preferences of users and stakeholders** may warrant an **update** of the **WHO's** evidence base and **recommendation for use of LNCS** for **weight loss** and **subsequent risk reduction of chronic disease**.

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Current lab members

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Dr. Laura Chiavaroli, PhD (Assistant Professor)
Dr. Andreea Zurbau, MBBS, PhD (Research Associate)
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Dr. Andrea Glenn, PhD, RD (PhD, US)
Mr. Rodney Au Yeung, MSc (PhD student)
Ms. Sabrina Ayoub-Charette, HBSc (PhD student)
Ms. Meaghan Kavanagh, MSc (PhD student)
Ms. Madeline Erlich, RD (PhD student)
Ms. Diana Ghidanac, RD (MSc student)
Ms. Victoria Chen (MSc student)
Ms. Julianah Oguntala (Summer student)
Ms. Gabriella Viscardi (MSc student)
Ms. Songhee Back (Msc student)

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