Supplementary Material

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

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SUPPLEMENTARY TEXT.

Supplementary Methods: Change and Substitution Models Included in the Meta-Analysis.

The change analysis mimicked a quasi-experimental study design to assess the association of the change in low-and no-calorie sweetened beverage (LNCSBs) intake with the concurrent change in outcome during the same time-period. We used the concurrent-change analysis because it shows more robust, consistent, and biologically plausible results in prospective cohort studies compared with the lagged-change analysis(1; 2). The substitution analysis examined the intended use of LNCSBs by assessing the association of substituting LNCSBs for another beverage with the change in outcome. A statistical model was used to estimate the outcome with increasing LNCSB intake while simultaneously decreasing the intake of sugar sweetened beverages (SSBs) or water, matched by beverage volume (1 mL: 1 mL). SSBs were selected as the intended substitution of LCSBs with caloric displacement. Water, the standard of care replacement for SSBs, was selected as the matched substitution of LNCSBs without caloric displacement; therefore, it acted as the 'reference substitution' to SSBs ('intended substitution').

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SUPPLEMENTARY TABLES

Supplementary Table 1. Search strategy for low-and no-calorie sweetened beverages (LNCSBs).

MEDLINE		EMBASE		Cochrane	
1	artifi* sweet*.mp.	1	artifi* sweet*.mp.	1	artifi* sweet*.mp.
2	non-calori*.mp.	2	non-calori*.mp.	2	non-calori*.mp.
3	noncalori*.mp.	3	noncalori*.mp.	3	noncalori*.mp.
4	non-caloric.mp.	4	non-caloric.mp.	4	non-caloric.mp.
5	non-sugar.mp.	5	non-sugar.mp.	5	non-sugar.mp.
6	nonsugar.mp.	6	nonsugar.mp.	6	nonsugar.mp.
7	non-nutritive*.mp.	7	non-nutritive*.mp.	7	non-nutritive*.mp.
8	nonnutritive*.mp.	8	nonnutritive*.mp.	8	nonnutritive*.mp.
9	low-calori*.mp.	9	low-calori*.mp.	9	low-calori*.mp.
10	lowcalori*.mp.	10	lowcalori*.mp.	10	lowcalori*.mp.
11	natural sweet*.mp.	11	natural sweet*.mp.	11	natural sweet*.mp.
12	natural sweetening agent*.mp.	12	natural sweetening agent*.mp.	12	natural sweetening agent*.mp.
13	non-nutritive sweetener/	13	non-nutritive sweetener/	13	non-nutritive sweetener/
14	sweetening agent*.mp.	14	sweetening agent*.mp.	14	sweetening agent*.mp.
15	sugar substitute*.mp.	15	sugar substitute*.mp.	15	sugar substitute*.mp.
16	zero calori*.mp.	16	zero calori*.mp.	16	zero calori*.mp.
17	no calori*.mp.	17	no calori*.mp.	17	no calori*.mp.
18	sugar-free.mp.	18	sugar-free.mp.	18	sugar-free.mp.
19	diet beverage.mp.	19	diet beverage.mp.	19	diet beverage.mp.
20	artificial* sweet* beverage.mp.	20	artificial* sweet* beverage.mp.	20	artificial* sweet* beverage.mp.
21	cohort study.mp.	21	cohort study.mp.	21	cohort study.mp.
22	prospective cohort.mp.	22	prospective cohort.mp.	22	prospective cohort.mp.
23	relative risk:.tw.	23	relative risk:.tw.	23	relative risk:.tw.
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
25	21 or 22 or 23	25	21 or 22 or 23	25	21 or 22 or 23
26	24 and 25	26	24 and 25	26	24 and 25
27	limit 26 to animals	27	limit 26 to animals		
28	26 not 27	28	26 not 27		

Database	**Total**
MEDLINE: June 10, 2021	191
EMBASE: June 10, 2021	235
Cochrane: May, 2021	165
Manual search	85
Total	**676**
Duplicates	**190**
Final Total	**486**

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Supplementary Table 2. Search strategy for water.

To identify studies that examine the substitution of water for sugar-sweetened beverages (SSBs) and cardiometabolic health, an additional search was conducted.

MEDLINE		EMBASE		Cochrane	
1	water*.mp.	1	water*.mp.	1	water*.mp.
2	substitut*.mp.	2	substitut*.mp.	2	substitut*.mp.
3	replac*.mp.	3	replac*.mp.	3	replac*.mp.
4	cohort study.mp.	4	cohort study.mp.	4	cohort study.mp.
5	prospective cohort.mp.	5	prospective cohort.mp.	5	prospective cohort.mp.
6	relative risk:.tw.	6	relative risk:.tw.	6	relative risk:.tw.
7	2 or 3	7	2 or 3	7	2 or 3
8	4 or 5 or 6	8	4 or 5 or 6	8	4 or 5 or 6
9	1 and 7 and 8	9	1 and 7 and 8	9	1 and 7 and 8
10	Limit 9 to animals	10	Limit 9 to animals	10	
11	9 not 10	11	9 not 10	11	

Database	**Total**
MEDLINE: June 10, 2021	95
EMBASE: June 10, 2021	80
Cochrane: May, 2021	18
Manual search	5
Total	**198**
Duplicates	**55**
Final Total	**143**

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Supplementary Table 3. Pre-specified Confounding Variables for Examined Outcomes.

	Measured Outcome(s)		
	Adiposity Measures & Metabolic Syndrome Incidence (5/6†)	**T2D Incidence (4/6†)**	**CVD Incidence & Total Mortality (5/7†)**
Primary Confounding Variable	Age	Age	Age
Secondary Confounding Variables	Sex Markers of adiposity* Smoking Energy intake Family history of metabolic syndrome Physical activity	Sex Markers of adiposity* Smoking Energy intake Family history of T2D Physical activity	Sex Markers of adiposity* Smoking Energy intake Family history of CVD Physical activity Alcohol intake

Abbreviations: CVD, cardiovascular disease; T2D, type 2 diabetes

*Markers of adiposity included baseline body weight, body mass index (BMI), waist circumference, or percent body fat (%BF), or change in body weight in the last 5 y prior to baseline data collection.

†Indicates a minimum number of pre-specified secondary confounding variables needed for one Newcastle-Ottawa Scale point for the comparability of studies.

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Supplementary Table 4A. Analysis of confounding variables among prospective cohorts using change analysis of LNCSBs on cardiometabolic outcomes

Cohort Name (First Author, Year)	HPFS (Drouin-Chartier, 2019 (4))	HPFS (Mozzafarian, 2011 (1))	HPFS (Pan, 2013 (5))	HPFS (Smith, 2015 (2))	NHS (Drouin-Chartier, 2019 (4))	NHS (Mozzafarian, 2011 (1))	NHS (Pan, 2013 (5))	NHS (Smith, 2015 (2))	NHS II (Drouin-Chartier, 2019 (4))	NHS II (Mozzafarian, 2011 (1))	NHS II (Pan, 2013 (5))	NHS II (Smith, 2015 (2))	Mexican Teachers' Cohort (Stern, 2017 (6))	Premier (Chen, 2009 (7))
Number of variables adjusted for in the included model	18	24	27	24	19	24	27	24	20	24	27	24	20	12
PRESPECIFIED VARIABLES														
Age	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sex	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓†	✓
Markers of adiposity*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓§	✓
Smoking	✓‡	✓	✓	✓	✓‡	✓	✓	✓	✓‡	✓	✓	✓	✓‡	
Energy intake	✓				✓				✓					✓
Family history	✓				✓				✓					
Physical activity	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓‡	✓	✓
OTHER CONFOUNDING VARIABLES														
Ethnicity or race	✓				✓				✓					✓
State													✓	
Education														✓
Physical exam	✓				✓				✓					
Marital status														✓
Employment status														✓
Income														✓
Intervention group														✓
TV watching		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Sleep duration		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Fitness level														✓‡
Menopausal status & post-menopausal hormonal therapy use					✓				✓				✓	
Oral contraceptive use									✓				✓	
Calendar time	✓				✓				✓					
DIETARY INTAKE														
AHEI	✓‡				✓‡				✓‡					
Alcohol intake	✓‡	✓	✓	✓	✓‡	✓	✓	✓	✓‡	✓	✓	✓	✓‡	
LNCSBs	✓				✓				✓					
SSBs		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Fruit juice		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Orange or grapefruit juice													✓‡	
Homemade sweetened beverages													✓‡	
Total sugary beverages	✓‡				✓‡				✓‡					

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Coffee	✓‡		✓		✓‡		✓		✓‡		✓			
Tea	✓‡		✓		✓‡		✓		✓‡		✓			
Water	✓‡		✓		✓‡		✓		✓‡		✓			
Dairy										✓			✓ (c)	
Milk	✓‡				✓‡				✓‡					
Whole-fat milk			✓				✓				✓			
Low-fat milk			✓				✓				✓			
Whole-fat dairy products (Butter, cheese, and whole-fat milk)		✓		✓		✓		✓		✓		✓		
Low-fat dairy products (Low-fat or skim milk, and yogurt)		✓		✓		✓		✓		✓		✓		
Yogurt													✓‡	
Fruits		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓‡	
Vegetables		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓‡	
Potatoes (French fries; and boiled, baked, or mashed)		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Whole grains		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Refined grains		✓	✓	✓		✓	✓	✓		✓	✓	✓		
White bread													✓‡	
Corn tortillas													✓‡	
Flour tortillas													✓‡	
Red meats													✓‡	
Unprocessed red meats		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Processed meats		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Sweets and desserts		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Potato chips		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Nuts		✓	✓	✓		✓	✓	✓		✓	✓	✓	✓‡	
Fried foods (consumed at home and away from home)		✓	✓	✓		✓	✓	✓		✓	✓	✓		
Trans fat		✓	✓	✓		✓	✓	✓		✓	✓	✓		

Abbreviations: AHEI, Alternate Healthy Eating Index; Health Professionals Follow-Up Study; LNCSBs, low-and no-calorie sweetened beverages; NHS, Nurses' Health Study; SSBs, Sugar-sweetened beverages

*Markers of obesity included baseline body mass index (BMI).

✓ indicates variables adjusted for in the included model of primary study outcomes in the original article.

✓† indicates variables adjusted due to the nature of the cohort (i.e., single-sex cohort).

✓‡ indicates variables that measured baseline and change from baseline values.

✓§ indicates variables adjusted for during additional data analysis conducted by the authors upon request.

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Supplementary Table 4B. Analysis of confounding variables among prospective cohorts using substitution analysis of LNCSBs on cardiometabolic outcomes.

Cohort Name (Frist Author, year)	A to Z (Stookey, 2008 (8))	ARIC - Females (Keller, 2020 (9))	ARIC - Males (Keller, 2020 (9))	ATBC (Keller, 2020 (9))	EPIC-Norfolk (O' Connor, 2015 (10))	HPFS (Drouin-Chartier, 2019 (4))	HPFS (Keller, 2020 (9))	HPFS & NHS (Bernstein, 2012 (11))	HPFS & NHS (Malik, 2019 (12))	HPFS , NHS, NHS II (Pan, 2013 (5))	IWHS (Keller, 2020 (9))	NHS (Drouin-Chartier, 2019 (4))	NHS80 (Keller, 2020 (9))	NHS86 (Keller, 2020 (9))	NHS II (Drouin-Chartier, 2019 (4))	NHS II (Pan, 2012 (13))	SUN (Frésan, 2016 (14))	WHI (Huang, 2017 (15))	WHS (Keller, 2020 (9))
Number of variables adjusted for in the included model	10	11	11	11	15	18	11	23	14	27	11	19	11	11	20	11	18	22	11
PRESPECIFIED CONFOUNDING VARIABLES																			
Age	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sex	✓§	✓	✓	✓§	✓	✓§	✓§	✓§	✓§	✓§	✓§	✓§	✓§	✓§	✓§	✓§	✓	✓§	✓§
Markers of adiposity*	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Smoking		✓	✓	✓	✓	✓¶	✓	✓	✓	✓	✓	✓¶	✓	✓	✓¶	✓	✓	✓	✓
Energy intake	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓				✓
Family history					✓	✓		✓	✓			✓			✓	✓	✓	✓	
Physical activity†	✓	✓	✓	✓	✓	✓¶	✓	✓	✓	✓¶	✓	✓¶	✓	✓	✓¶	✓	✓	✓	✓
Alcohol intake‡		✓	✓	✓	✓	✓¶	✓	✓	✓	✓	✓	✓¶	✓	✓	✓¶	✓		✓	✓
OTHER CONFOUNDING VARIABLES																			
Age[2]																	✓		
Ethnicity or Race	✓					✓			✓			✓			✓	✓		✓	
Marital status																		✓	
Education		✓	✓	✓	✓		✓				✓		✓	✓				✓	✓
Income																		✓	
Insurance																		✓	
Physical exam						✓						✓			✓				
Occupational social class					✓														
Intervention group	✓									✓									
TV watching										✓									
Sleep duration																			
Sitting time																		✓	
Calendar time						✓		✓				✓			✓				
Menopausal status & post-menopausal hormone therapy use								✓‖	✓‖			✓			✓	✓		✓	
Oral contraceptive use	✓														✓	✓			
DISEASE HISOTRY & MEDICAITONS																			
History of HTN or hypercholesterolemia									✓										
History of OB																	✓		
History of hysterectomy																		✓	
Aspirin or other antihypertensive medications use								✓	✓									✓	
Antihyperlipidemic medications use																		✓	

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Systolic blood pressure																		✓	
DIETARY INTAKE																			
Season of dietary intake data					✓														
Vitamin E use								✓											
Years of multivitamin use								✓	✓										
AHEI						✓¶			✓¶			✓¶			✓¶	✓		✓	
Energy calibration																		✓	
Mediterranean diet adherence																	✓		
Special diet (unspecified)																	✓		
Snacking between meals																	✓		
Macronutrient intake	✓																		
Energy intake from beverages																			
LNCSBs						✓						✓			✓		✓		
SSBs					✓						✓						✓		
Fruit juice					✓						✓						✓		
Total sugary beverages						✓¶						✓¶			✓¶				
Coffee						✓¶					✓	✓¶			✓¶		✓		
Tea						✓¶					✓	✓¶			✓¶				
Sweetened tea or coffee					✓												✓		
Water	✓					✓¶					✓	✓¶			✓¶		✓		
Dairy																	✓		
Milk						✓¶						✓¶			✓¶				
Whole-fat milk											✓								
Low-fat milk											✓								
Whole-fat dairy products (Butter, cheese, and whole-fat milk)								✓											
Low-fat dairy products (Low-fat or skim milk, and yogurt)								✓											
Sweetened-milk beverage					✓														
Other dairy products											✓								
Fruits								✓			✓								
Vegetables								✓			✓								
Potatoes (French fries; and boiled, baked, or mashed)											✓								
Whole grains											✓								
Refined grains											✓								
Cereal fibre		✓		✓			✓	✓		✓			✓	✓					✓
Red meat								✓			✓								
Processed meats																			
Poultry								✓											
Fish								✓											
Sweets and desserts											✓								
Potato chips											✓								
Nuts								✓			✓								
Butter																			
Trans fat		✓		✓			✓	✓		✓	✓		✓	✓					✓
PUFA:SFA ratio		✓		✓			✓			✓			✓	✓					✓

Fried foods (consumed at home and away from home)											✓								
Glycemic index																		✓	
Glycemic load																		✓	

Abbreviations: AHEI, Alternate Healthy Eating Index; ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocophenol and Beta-Carotene Cancer Prevention Study; DASH, Dietary Approaches to Stop Hypertension; DLD, dyslipidemia; EPIC, The European Prospective Investigation of Cancer; HPFS, Health Professionals Follow-Up Study; HTN, hypertension; IWHS, Iowa Women's Health Study; LNCSBs, low- or no-calorie sweetened beverages; NHS, Nurses' Health Study; PUFA, poly-unsaturated fatty acids; SFA, saturated fatty acids; SSBs, Sugar-sweetened beverages; SUN, Sequimiento University of Navarra; WHI, Women's Health Initiative; WHS, Women's Health Study.

*Markers of obesity included baseline body weight, body mass index (BMI), waist circumference, percent body fat (%BF), change in BMI, waist-to-hip ratio, or change in body weight in the last 5 y prior to baseline data collection.

†Physical activity was measured as metabolic equivalent task hours per week, activity metabolic equivalent index score, and total energy expenditure.

‡Alcohol intake was only used as a prespecified variable for studies examining incidence of CVD.

✓ indicates variables adjusted for in the included model of primary study outcomes in the original article.

✓§ indicates variables adjusted due to the nature of the cohort (i.e., single-sex cohort).

✓‖ indicates variables adjusted for only in females.

✓¶ indicates variables that measured baseline and change from baseline values.

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Supplementary Table 5A. Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort comparisons using change analysis presented by cohort comparisons.

Cohort comparison	Selection*	Outcome†	Comparability‡	Total§
HPFS *(Drouin-Chartier (4))*	3	3	2	8
HPFS *(Mozzafarian (1))*	3	2	2	7
HPFS *(Pan (5))*	3	2	2	7
HPFS *(Smith (2))*	3	2	1	6
NHS (*Drouin-Chartier (4)*)	3	3	2	8
NHS *(Mozzafarian (1))*	3	2	2	7
NHS *(Pan (5))*	3	2	2	7
NHS *(Smith (2))*	3	2	1	6
NHS II *(Drouin-Chartier (4))*	3	3	2	8
NHS II *(Mozzafarian (1))*	3	2	2	7
NHS II *(Pan (5))*	3	2	2	7
NHS II *(Smith (2))*	3	2	1	6
Mexican Teachers' Cohort (*Stern (6))*	3	2	1	6
PREMIER *(Chen (7))*	3	3	1	7

Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

*Maximum 4 points were awarded for cohort representativeness, selection of non-exposed cohort, ascertainment of exposure assessment, and demonstration outcome not present at baseline.

†Maximum 3 points were awarded for follow-up length, adequacy of follow-up, and outcome assessment.

‡Maximum 2 points were awarded for controlling for the pre-specified primary confounding variable (age) and additional confounding variables (sex, markers of adiposity, smoking, energy intake, physical activity, family history).

§A maximum of 9 points could be awarded. Cohort were adjudged high (score ≥7), moderate (score = 6) or low (score ≤5) study quality.

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Supplementary Table 5B. Newcastle-Ottawa Scale (NOS) for assessing the quality of cohorts using substitution analysis presented by cohort comparisons.

Cohort comparison	Selection*	Outcome†	Comparability‡	Total§
A to Z *(Stookey (8))*	3	3	1	7
ARIC – Females *(Keller (9))*	3	3	2	8
ARIC – Males *(Keller (9))*	3	3	2	8
ATBC *(Keller (9))*	3	3	2	8
EPIC-Norfolk *(O'Connor (10))*	4	3	2	9
HPFS *(Drouin-Chartier (4))*	3	3	2	8
HPFS *(Keller (9))*	3	3	2	8
HPFS & NHS *(Bernstein (11))*	3	3	2	8
HPFS & NHS *(Malik (12))*	3	3	2	8
HPFS, NHS & NHS II *(Pan (5))*	3	3	2	8
IWHS *(Keller (9))*	3	3	2	8
NHS (Drouin-Chartier (4))	3	3	2	8
NHS80 *(Keller (9))*	3	3	2	8
NHS86 *(Keller (9))*	3	3	2	8
NHS II *(Drouin-Chartier (4))*	3	3	2	8
NHS II *(Pan (13))*	3	3	2	8
SUN *(Fresan (14))*	3	2	2	7
WHI *(Huang (15))*	3	2	2	7
WHS *(Keller (9))*	3	3	2	8

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; ATBC, Alpha-Tocophenol and Beta-Carotene Cancer Prevention Study; EPIC, The European Prospective Investigation of Cancer; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; NHS, Nurses' Health Study; SUN, Sequimiento University of Navarra; WHI, Women's Health Initiative; WHS, Women's Health Study.

*Maximum 4 points awarded for cohort representativeness, selection of non-exposed cohort, ascertainment of exposure assessment, and demonstration outcome not present at baseline.

†Maximum 3 points awarded for follow-up length, adequacy of follow-up, and outcome assessment.

‡Maximum 2 points awarded for controlling for the pre-specified primary confounding variable (age) and additional confounding variables (sex, markers of adiposity, smoking, energy intake, physical activity, family history, alcohol intake).

§A maximum of 9 points could be awarded. Cohort were adjudged high (score ≥7), moderate (score = 6) or low (score ≤5) study quality.

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Supplementary Table 6A. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Assessment for Outcomes using change analysis.

Quality assessment									Effect	Quality Importance
Outcomes	**No. of cohort comparisons**	**No. of participants**	**Risk of bias/study quality**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations including upgrades**	**Effect Estimate[*] [95% CI]**	
Change in LNCSB intake (Increasing 330 mL/day)										
Body Weight (kg/y)	5 (2; 6; 7)	129,210	Not serious	Serious[†]	Not serious	Not serious	Not serious[‡]	Dose-response association[§]	MD: -0.008 [-0.014, -0.002]	⊕⊕⊖⊖ **LOW**[†,§] Due to downgrade for serious inconsistency and upgrade for dose-response association
Waist Circumference (cm/y)	1 (6)	9,294	Not serious	Not serious[††]	Serious[‖]	Serious[¶]	Not serious[‡]	Dose-response association[§]	MD: -1.15 [-2.34, -0.045]	⊕⊕⊖⊖ **LOW**[‖,¶,§] Due to downgrade for serious indirectness and imprecision, and upgrade for dose-response association
Risk of T2D	3 (4)	192,352	Not serious	Not serious[†††]	Serious[‖‖]	Serious[¶¶]	Not serious[‡]	None[§]	RR: 1.02 [0.99, 1.06]	⊕⊖⊖⊖ **VERY LOW**[‖‖,¶¶] Due to downgrade for serious indirectness and imprecision

Abbreviations: MD, mean difference; MID, minimally important difference; RR, risk ratio; T2D, Type 2 Diabetes Mellitus.

[*] Effect estimate was pooled and expressed as mean difference (MD) or risk ratios (RR).

[†] Downgrade for serious inconsistency as there was evidence of substantial heterogeneity (I^2=66%, P_Q=0.02). Although the removal of NHS II (2) (I^2=50%, P_Q=0.11) during sensitivity analysis partially explained the heterogeneity, the presence of residual heterogeneity could not be excluded. The removal of HFS (2) (MD: -0.004 kg/y, [95%CI: -0.011, 0.002]) and NHS (2) (-0.014 kg/y, [-0.022, 0.006]) altered the significance of the association.

[††] No downgrade for inconsistency as only 1 cohort comparison was available for analysis.

[†††] No downgrade for serious inconsistency as the presence of inter-study heterogeneity (I^2=84%, P_Q<0.01) was explained by the removal of NHS II (4) (I^2=0%, P_Q=0.60) during sensitivity analysis.

[‡] No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effects (<10 cohort comparisons included in the meta-analysis).

[§] Change analysis is a dose-response model where the cardiometabolic outcome is assessed against the increasing beverage (1 serving) intake over time. When the association was statistically significant, we applied an upgrade for dose-response association.

[‖] Downgrade for serious indirectness as only 1 cohort comparison of predominantly well-educated, female teachers in Mexico was available for analysis, limiting the generalizability of the outcome to a diverse European population with or at risk for diabetes.

[‖‖] Downgrade for serious indirectness as only 2 cohort comparisons of predominantly Caucasian, well-educated, health professionals in the USA were available for analysis, limiting the generalizability of the outcome to a diverse European population with or at risk for diabetes.

[¶] Downgrade for serious imprecision as the upper bound of 95% CI (MD: 0 cm) includes clinically unimportant effects (MID: -2 cm to 2 cm), while the lower bound of the 95% CI (MD: -2.29 cm) includes clinically important benefit (MID: < -2 cm).

¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 1.06) includes clinically important harm (RR: <1.05), while the lower bound of the 95% CI (RR: 0.99) includes clinically unimportant risk estimates (RR: 0.95 to 1.05).

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Supplementary Table 6B. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Assessment for Outcomes using substitution analysis.

Quality assessment									Effect	Quality Importance
Outcomes	**No. of cohort comparisons**	**No. of participants**	**Risk of bias/study quality**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Other considerations including upgrades**	**Effect Estimate* [95% CI]**	
Substitution of LNCSBs for SSBs ("Intended Substitution")										
Body Weight (kg/y)	3 (8; 13; 14)	165,579	Not serious	Not serious†	Not serious	Not serious	Not serious‡	Dose-response association§	MD: -0.12 [-0.14, -0.10]	⊕⊕⊕⊖ **MODERATE**§ No downgrades and upgrade for dose-response association
Waist Circumference (cm/y)	1 (8)	173	Not serious	Not serious††	Serious‖	Serious¶	Not serious‡	None§	MD: -1.83 [-3.70, 0.05]	⊕⊖⊖⊖ **VERY LOW**‖,¶ Due to downgrade for serious indirectness and imprecision
%BF (%/y)	1 (8)	173	Not serious	Not serious††	Serious‖	Serious¶¶	Not serious‡	None§	MD: -0.96 [-2.32, 0.41]	⊕⊖⊖⊖ **VERY LOW**‖,¶¶ Due to downgrade for serious indirectness and imprecision
OB Incidence**	1 (14)	15,765	Not serious	Not serious††	Serious‖‖	Not serious	Not serious‡	Dose-response association§	RR: 0.88 [0.88, 0.89]	⊕⊕⊖⊖ **LOW**‖‖§ Due to downgrade for serious indirectness
Risk of T2D	5 (4; 10; 13; 15)	281,855	Not serious	Serious†††	Not serious	Not serious	Not serious‡	None§	RR: 0.99 [0.96, 1.01]	⊕⊖⊖⊖ **VERY LOW**††† Due to downgrade for serious inconsistency and upgrade for dose-response association
CHD Events	6 (9)	233,676	Not serious	Not serious††††	Not serious	Serious¶¶¶	Not serious‡	Dose-response association§	RR: 0.89 [0.81, 0.98]	⊕⊕⊖⊖ **LOW**¶¶¶§ Due to downgrade for serious imprecision and upgrade for dose-response analysis
Risk of Stroke	1 (11)	127,456	Not serious	Not serious††	Serious‖‖	Serious¶¶¶	Not serious‡	None§	RR: 1.03 [0.93, 1.14]	⊕⊖⊖⊖ **VERY LOW**‖‖,¶¶¶ Due to downgrade for serious indirectness and imprecision
CHD Mortality	5 (9)	220,805	Not serious	Not serious†††††	Not serious	Serious¶¶¶¶	Not serious‡	None§	RR: 0.95 [0.81, 1.11]	⊕⊖⊖⊖ **VERY LOW**¶¶¶¶ Due to downgrade for serious imprecision
CVD Mortality	1 (12)	118,363	Not serious	Not serious††	Serious‖‖	Serious¶¶¶¶	Not serious‡	Dose-response association§	RR: 0.95 [0.90, 0.99]	⊕⊕⊖⊖ **LOW**‖‖,¶¶¶¶§ Due to downgrade for serious indirectness and imprecision, and upgrade for dose-response association
Total Mortality	1 (12)	118,363	Not serious	Not serious††	Serious‖‖	Serious¶¶¶¶¶	Not serious‡	Dose-response association§	RR: 0.96 [0.94, 0.98]	⊕⊕⊖⊖ **LOW**‖‖,¶¶¶¶¶§ Due to downgrade for serious indirectness and imprecision, and upgrade for dose-response association

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Substitution of Water for SSBs ("Standard of Care Substitution")										
Body Weight (kg/y)	3 (5; 8; 13; 14)	165,579	Not serious	Serious[†††††††]	Not serious	Not serious	Not serious[‡]	Dose-response association[§]	MD: -0.10 [-0.13, -0.06]	⊕⊖⊖⊖ **LOW**[†††††††§] Due to downgrade for serious inconsistency and upgrade for dose-response association
Waist Circumference (cm/y)	1 (8)	173	Not serious	Not serious[††]	Serious[I]	Serious[¶¶¶¶¶¶¶]	Not serious[‡]	Dose-response association[§]	MD: -2.71 [-4.27, -1.15]	⊕⊖⊖⊖ **LOW**[I, ¶¶¶¶¶¶¶§] Due to downgrade for serious indirectness and imprecision, and upgrade for dose-response association
%BF (%)	1 (8)	173	Not serious	Not serious[††]	Serious[I]	Serious[¶¶¶¶¶¶¶¶]	Not serious[‡]	Dose-response association[§]	MD: -1.51 [-2.61, -0.42]	⊕⊖⊖⊖ **LOW**[I, ¶¶¶¶¶¶¶¶§] Due to downgrade for serious indirectness and imprecision, and upgrade for dose-response association
OB[¥] Incidence	1 (14)	15,765	Not serious	Not serious[††]	Serious[II]	Serious[¶¶¶¶¶¶¶¶]	Not serious[‡]	Dose-response association[§]	RR: 0.85 [0.75, 0.97]	⊕⊖⊖⊖ **LOW**[II, ¶¶¶¶¶¶¶¶§] Due to downgrade for serious indirectness and imprecision, and upgrade for dose-response association
Risk of T2D	3 (4; 10; 13; 15)	281,855	Not serious	Not serious[††††††††]	Not serious	Serious[¶¶¶¶¶¶¶¶¶]	Not serious[‡]	Dose-response association[§]	RR: 0.96 [0.94, 0.98]	⊕⊖⊖⊖ **LOW**[¶¶¶¶¶¶¶¶¶§] Due to downgrade for serious imprecision, and upgrade for dose-response association
Risk of Stroke	1 (11)	127,456	Not serious	Not serious[††]	Serious[III]	Serious[¶¶¶¶¶¶¶¶¶]	Not serious[‡]	None[§]	RR: 1.00 [0.94, 1.06]	⊕⊖⊖⊖ **VERY LOW**[III,¶¶¶¶¶¶¶¶¶] Due to downgrade for serious indirectness and imprecision
Substitution of LNCSBs for Water ("Reference Substitution")										
Body Weight (kg/y)	1 (14)	173	Not serious	Not serious[††]	Serious[II]	Not serious	Not serious[‡]	None[§]	MD: 0.08 [-0.11, 0.27]	⊕⊖⊖⊖ **VERY LOW**[II] Due to downgrade for serious indirectness
OB[¥] Incidence	1 (14)	15,765	Not serious	Not serious[††]	Serious[II]	Serious[¶¶¶¶¶¶¶¶¶]	Not serious[‡]	None[§]	RR: 1.19 [0.94, 1.50]	⊕⊖⊖⊖ **VERY LOW**[II,¶¶¶¶¶¶¶¶¶] Due to downgrade for serious indirectness and imprecision
Risk of T2D	4 (4; 15)	257,202	Not serious	Serious[††††††]	Not serious	Not serious	Not serious[‡]	None[§]	RR: 1.00 [0.98, 1.02]	⊕⊖⊖⊖ **VERY LOW**[††††††] Due to downgrade for serious inconsistency
Risk of Stroke	1 (11)	127,456	Not serious	Not serious[††]	Serious[III]	Serious[¶¶¶¶¶¶¶¶¶¶]	Not serious[‡]	None[§]	RR: 1.03 [0.98, 1.09]	⊕⊖⊖⊖ **VERY LOW**[III,¶¶¶¶¶¶¶¶¶¶] Due to downgrade for serious indirectness and imprecision

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Abbreviations: BMI, body mass index; CVD, cardiovascular disease; MD, mean difference; MID, minimally important difference; RR, risk ratio; T2D, Type 2 Diabetes Mellitus; OB, Obesity; %BF, Percent body fat.

* Effect estimate was pooled and expressed as mean difference (MD) or risk ratios (RR).

** OB was defined as having a BMI of ≥30 kg/m^2.

† No downgrade for inconsistency as there was no evidence of substantial inter-study heterogeneity (I^2=17%, P_Q=0.30).

†† No downgrade for inconsistency, as only 1 cohort comparison was available for analysis.

††† Downgrade for serious inconsistency as there was evidence of substantial inter-study heterogeneity (I^2=69%, P_Q=0.01); and sensitivity analysis could not explain the heterogeneity.

†††† No downgrade for serious inconsistency, as there was no evidence of substantial inter-study heterogeneity (I^2=28%, P_Q=0.22).

††††† No downgrade for serious inconsistency, as there was no evidence of substantial inter-study heterogeneity (I^2=36%, P_Q=0.18).

†††††† Downgrade for serious inconsistency as there was evidence of substantial inter-study heterogeneity (I^2=83%, P_Q<0.01); and sensitivity analysis could not explain the heterogeneity.

††††††† Downgrade for serious inconsistency as there was evidence of substantial inter-study heterogeneity (I^2=82%, P_Q<0.01); and sensitivity analysis could not explain the heterogeneity.

†††††††† No downgrade for serious inconsistency as the presence of inter-study heterogeneity (I^2=79%, P_Q<0.01) was explained by the removal of HPFS, NHS, and NHS II cohort comparison (4) (I^2=0%, P_Q=0.76) during sensitivity analysis.

‡ No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effects (<10 cohort comparisons included in the meta-analysis).

§ Substitution analysis is a dose-response model where a potential change is estimated for substituting 1-serving of beverage A against beverage B. It is done by examining the difference between regression coefficients of the two beverages included as continuous (linear) terms of dose-intake. When the association was statistically significant, we applied an upgrade for dose-response association.

‖ Downgrade for serious indirectness as only 1 cohort comparison with obese female participants in a weight-loss trial was available for analysis, limiting the generalizability of the outcome to a diverse European population with or at risk for diabetes.

‖‖ Downgrade for serious indirectness as only 1 cohort comparison with participants from Spain was available for analysis, limiting the generalizability of the outcome to a diverse European population with or at risk for diabetes.

‖‖‖ Downgrade for serious indirectness as only 1 cohort comparison of predominantly Caucasian, well-educated, health professionals in the USA were available for analysis, limiting the generalizability of the outcome to a diverse European population with or at risk for diabetes.

¶ Downgrade for serious imprecision as the upper bound of 95% CI (0.05 cm) includes clinically unimportant effects (MID: -2 cm to 2 cm), while the lower bound of the 95% CI (-3.70 cm) includes clinically important benefit (MID: < -2 cm).

¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (0.41%) includes clinically unimportant effects (MID: -2% to 2%), while the lower bound of 95% CI (-2.32%) includes clinically important benefit (MID: < -2%).

¶¶¶ Downgrade for serious imprecision as the upper bound of the 95% CI (RR: 0.98) includes clinically unimportant risk estimates (RR: 0.95 to 1.05), while the lower bound of 95% CI (RR: 0.81) includes clinically important benefit (RR: <0.95).

¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 1.14) includes clinically important harm (RR >1.05), while the lower bound of 95% CI (RR: 0.93) includes clinically unimportant risk estimates (RR: 0.95 to 1.05).

¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 1.11) includes clinically important harm (RR >1.10), while the lower bound of 95% CI (RR: 0.81) includes clinically important benefit (RR: <0.95).

¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 0.99) includes clinically unimportant risk estimates (RR: 0.95 to 1.05) while the lower bound of 95% CI (RR: 0.90) includes clinically important benefit (RR: <0.95).

¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 0.98) includes clinically unimportant risk estimates (RR: 0.95 to 1.05) while the lower bound of 95% CI (RR: 0.94) includes clinically important benefit (RR: <0.95).

¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 1.50) includes clinically important harm (RR: >1.05), while the lower bound of 95% CI (RR: 0.94) includes clinically important benefit (RR: <0.95).

¶¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 1.09) includes clinically important harm (RR: >1.05), while the lower bound of 95% CI (RR: 0.98) includes clinically unimportant risk estimates (RR: 0.95 to 1.05).

¶¶¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (MD: -1.15 cm) includes clinically unimportant effects (MID: -2 cm to 2 cm), while the lower bound of 95% CI (MD: -4.27%) includes clinically important risk benefit (MID:< -2%).

¶¶¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (MD: -0.42%) includes clinically unimportant effects (MID: -2% to 2%), while the lower bound of 95% CI (MD: -2.61%) includes clinically important risk benefit (MID:< -2%).

¶¶¶¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 0.97) includes clinically unimportant risk estimates (RR: 0.95 to 1.05), while the lower bound of 95% CI (RR: 0.75) includes clinically important benefit (RR: <0.95).

¶¶¶¶¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 0.98) includes clinically unimportant risk estimates (RR: 0.95 to 1.05) while the lower bound of 95% CI (RR: 0.94) includes clinically important benefit (RR: <0.95).

¶¶¶¶¶¶¶¶¶¶¶¶¶ Downgrade for serious imprecision as the upper bound of 95% CI (RR: 1.06) includes clinically important harm (RR: >1.05), while the lower bound of 95% CI (RR: 0.94) includes clinically important benefit (RR: <0.95).

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Supplementary Table 6C. NutriGRADE Assessment for Outcomes using change analysis.

		Quality assessment								Effect	Score
Outcomes	**No. of cohort comparisons**	**Risk of bias, study quality and study limitations***	**Precision****	**Heterogeneity**	**Directness**	**Publication bias**	**Funding bias**	**Effect Size****	**Dose Response**	**Effect Estimate [95% CI]*****	**Meta-evidence (Final point)**
Change in LNCSB intake (Increasing 330 mL/day)											
Body Weight (kg/y)	5 (2; 6; 7)	1 (Mean NOS: 6.2)	1†	0‡	1	0ǀ	1¶	0⁂	1※	MD: -0.008 [-0.014, -0.002]	Low (5)
Waist Circumference (cm/y)	1 (6)	1 (Mean NOS: 6)	0††	0‡‡	0§	0ǀ	1¶	0⁂	1※	MD: -1.15 [-2.34, -0.045]	Very low (3)
Risk of T2D	3 (4)	2 (Mean NOS: 8)	1†††	0‡	0§§	0ǀ	1¶	0⁂	0	RR: 1.02 [0.99, 1.06]	Low (4)

Abbreviations: CI, confidence interval; MD, mean difference; MID, minimally important difference; NOS, Newcastle-Ottawa Scale; RR, risk ratio; T2D, Type 2 Diabetes Mellitus.

* Risk of bias was assessed using NOS shown in Supplementary Table 6A.

** Important benefit was defined as RR of <0.8 and harm RR of > 1.2 (16). For body weight and waist circumference, important benefit was defined as MID shown in **Supplementary Table 4** (i.e., body weight: -0.5 kg to 0.5 kg; waist circumference: -2 cm to 2 cm).

*** Effect estimate was pooled and expressed as mean difference (MD) or risk ratios (RR).

† 1 point was awarded because results from ≥500 participants were included, and the 95% CI excludes the null value.

†† No point was awarded because results from ≥500 participants were included, but 95% CI includes the null value and 95% CI fails to exclude important benefit (MD <-2 cm).

††† 1 point was awarded because ≥500 events were included, but 95% CI overlaps the null value and 95% CI excludes important benefit (RR <0.8) or harm (RR >1.2).

‡ 0 point was awarded for exploring detected heterogeneity with sensitivity analysis (0.3 point) from 3 cohort comparisons (multiplier: 0)

‡‡ No point was awarded because heterogeneity could not be assessed due to only 1 cohort comparison available for analysis.

§ No point was awarded because only 1 cohort comparison with female Mexican teachers was available for analysis.

§§ No point was awarded because only cohort comparisons with US healthcare professionals were available for analysis.

ǀ No point was awarded as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effects.

¶ 1 point was awarded because all studies received funding from academic and/or research institutions.

⁂ No point was awarded because effect estimate showed small effect size (RR: 0.80 - 1.20).

※ Change analysis is a dose-response model where the cardiometabolic outcome is assessed against the increasing beverage (1 serving) intake over time. When the association was statistically significant, 1 point was awarded for the dose-response association.

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Supplementary Table 6D. NutriGRADE Assessment for Outcomes using substitution analysis.

		Quality assessment (points; Max 10)								Effect	Score
Outcomes	**No. of cohort comparisons**	**Risk of bias, study quality and study limitations***	**Precision****	**Heterogeneity**	**Directness**	**Publication bias**	**Funding bias**	**Effect Size****	**Dose Response**	**Effect Estimate [95% CI]*****	**Meta-evidence (Final point)**
Substitution of LNCSBs for SSBs ("Intended Substitution")											
Body Weight (kg/y)	3 (8; 13; 14)	2 (Mean NOS: 7)	1†	0‡	1	0ǁ	1¶	0⁂	1※	MD: -0.12 [-0.14, -0.10]	Moderate (6)
Waist Circumference (cm/y)	1 (8)	2 (Mean NOS: 7)	0††	0‡‡	0§	0ǁ	1¶	0⁂	0	MD: -1.83 [-3.70, 0.05]	Very low (3)
%BF (%/y)	1 (8)	2 (Mean NOS: 7)	0††	0‡‡	0§	0ǁ	1¶	0⁂	0	MD: -0.96 [-2.32, 0.41]	Very low (3)
OB** Incidence**	1 (14)	2 (Mean NOS: 7)	1†	0‡‡	0§§	0ǁ	1¶	0⁂	1※	RR: 0.88 [0.88, 0.89]	Low (5)
Risk of T2D	5 (4; 10; 13; 15)	2 (Mean NOS: 7.75)	1†††	0‡	1	0ǁ	1¶	0⁂	0	RR: 0.99 [0.96, 1.01]	Low (5)
CHD Events	6 (9)	2 (Mean NOS: 8)	1†	0.5‡‡‡	1	0ǁ	1¶	0⁂	1※	RR: 0.89 [0.81, 0.98]	Moderate (6.5)
Risk of Stroke	1 (11)	2 (Mean NOS: 8)	1†††	0‡‡	0§§§	0ǁ	1¶	0⁂	0	RR: 1.03 [0.93, 1.14]	Low (4)
CHD Mortality	5 (9)	2 (Mean NOS: 8)	1†††	0‡‡‡‡	1	0ǁ	1¶	0⁂	0	RR: 0.95 [0.81, 1.11]	Low (5)
CVD Mortality	1 (12)	2 (Mean NOS: 8)	1†	0‡	0§§§	0ǁ	1¶	0⁂	1※	RR: 0.95 [0.90, 0.99]	Low (5)
Total Mortality	1 (12)	2 (Mean NOS: 8)	1†	0‡	0§§§	0ǁ	1¶	0⁂	1※	RR: 0.96 [0.94, 0.98]	Low (5)
Substitution of Water for SSBs ("Standard of Care Substitution")											
Body Weight (kg/y)	3 (5; 8; 13; 14)	2 (Mean NOS: 7.33)	1†	0‡	1	0ǁ	1¶	0⁂	1※	MD: -0.10 [-0.13, -0.06]	Moderate (6)
Waist Circumference (cm/y)	1 (8)	2 (Mean NOS: 7)	0††	0‡‡	0§	0ǁ	1¶	0⁂	1※	MD: -2.71 [-4.27, -1.15]	Low (4)
%BF (%)	1 (8)	2 (Mean NOS: 7)	0††	0‡‡	0§	0ǁ	1¶	0⁂	1※	MD: -1.51 [-2.61, -0.42]	Low (4)
OB** Incidence**	1 (14)	2 (Mean NOS: 7)	1†	0‡‡	0§§	0ǁ	1¶	0⁂	1※	RR: 0.85 [0.75, 0.97]	Low (5)
Risk of T2D	3 (4; 10; 13; 15)	2 (Mean NOS: 7.33)	1†	0‡	1	0ǁ	1¶	0⁂	1※	RR: 0.96 [0.94, 0.98]	Low (6)
Risk of Stroke	1 (11)	2 (Mean NOS: 8)	1†††	0‡‡	0§§§	0ǁ	1¶	0⁂	0	RR: 1.00 [0.94, 1.06]	Low (4)
Substitution of LNCSBs for Water ("Reference Substitution")											
Body Weight (kg/y)	1 (14)	2 (Mean NOS: 7)	1†††	0‡‡	0§§	0ǁ	1¶	0⁂	0	MD: 0.08 [-0.11, 0.27]	Low (4)
OB** Incidence**	1 (14)	2 (Mean NOS: 7)	0††††	0‡‡	0§§	0ǁ	1¶	0⁂	0	RR: 1.19 [0.94, 1.50]	Very low (3)
Risk of T2D	4 (4; 15)	2 (Mean NOS: 7.5)	1†††	0‡	1	0ǁ	1¶	0⁂	0	RR: 1.00 [0.98, 1.02]	Low (5)

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Risk of Stroke	1 (11)	2 (Mean NOS: 8)	1†††	0‡‡	0§§§	0ǀ	1¶	0⁂	0	RR: 1.03 [0.98, 1.09]	Low (4)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; MD, mean difference; MID, minimally important difference; NOS, Newcastle-Ottawa Scale; RR, risk ratio; T2D, Type 2 Diabetes Mellitus; OB, Obesity; %BF, Percent body fat.

* Risk of bias was assessed using NOS shown in Supplementary Table 6A.

** Important benefit was defined as RR of <0.8 and harm RR of > 1.2 (16). For body weight, waist circumference, and %BF, important benefit was defined as MID shown in **Supplementary Table 4** (i.e., body weight: -0.5 kg to 0.5 kg; waist circumference: -2 cm to 2 cm; %BF: -2% to 2%).

*** Effect estimate was pooled and expressed as mean difference (MD) or risk ratios (RR).

**** OB was defined as having a BMI of ≥30 kg/m^2.

† 1 point was awarded because results from ≥500 participants or ≥500 events were included, and the 95% CI excludes the null value.

†† No point was awarded because results from <500 participants were included in the analysis.

††† 1 point was awarded because ≥500 events were included, but 95% CI overlaps the null value and 95% CI excludes important benefit (RR <0.8) or harm (RR >1.2).

†††† No point was awarded because 500 events were included, but 95% CI includes the null value and 95% CI fails to exclude important harm (RR >1.2).

‡ 0 point was awarded for exploring detected heterogeneity with sensitivity analysis (0.3 point) from 2-5 cohort comparisons (multiplier: 0)

‡‡ No point was awarded because heterogeneity could not be assessed due to only 1 cohort comparison available for analysis.

‡‡‡ 0.5 point was awarded for reporting no important heterogeneity (I^2<40%) from 6 cohort comparisons (multiplier: 1).

‡‡‡‡ 0 point was awarded for reporting no important heterogeneity (I^2<40%) from 2-5 cohort comparisons (multiplier: 0).

§ No point was awarded because only 1 cohort comparison with female obese female participants in a weight-loss trial was available for analysis.

§§ No point was awarded because only 1 cohort comparison with graduates from a Spanish university was available for analysis.

§§§ No point was awarded because only cohort comparisons from US healthcare professional was available for analysis.

ǀ No point was awarded as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effects.

¶ 1 point was awarded because all studies received funding from academic and/or research institutions.

⁂ No point was awarded because effect estimate showed small effect size (RR: 0.80 - 1.20).

※ Substitution analysis is a dose-response model where a potential change is estimated for substituting 1-serving of beverage A against beverage B. It is done by examining the difference between regression coefficients of the two beverages included as continuous (linear) terms of dose-intake. When the association was statistically significant, 1 point was awarded for the dose-response association.

Supplementary Material

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

Supplementary Table 7. Minimum Important Difference (MID) used for the imprecision in GRADE assessments

Outcome	MID	Reference
Body weight	0.5 kg	Ge et al. (3)
%Body Fat	2%	Absolute reduction based on 5-7% weight loss being clinically meaningful
BMI	0.2 kg/m^2	Roughly equivalent to 0.5kg
Waist Circumference	2 cm	2 cm=1 full pant size
Risk of OW/OB, diabetes, CVD events, or mortality	RR: 0.95, 1.05	5% change in risk

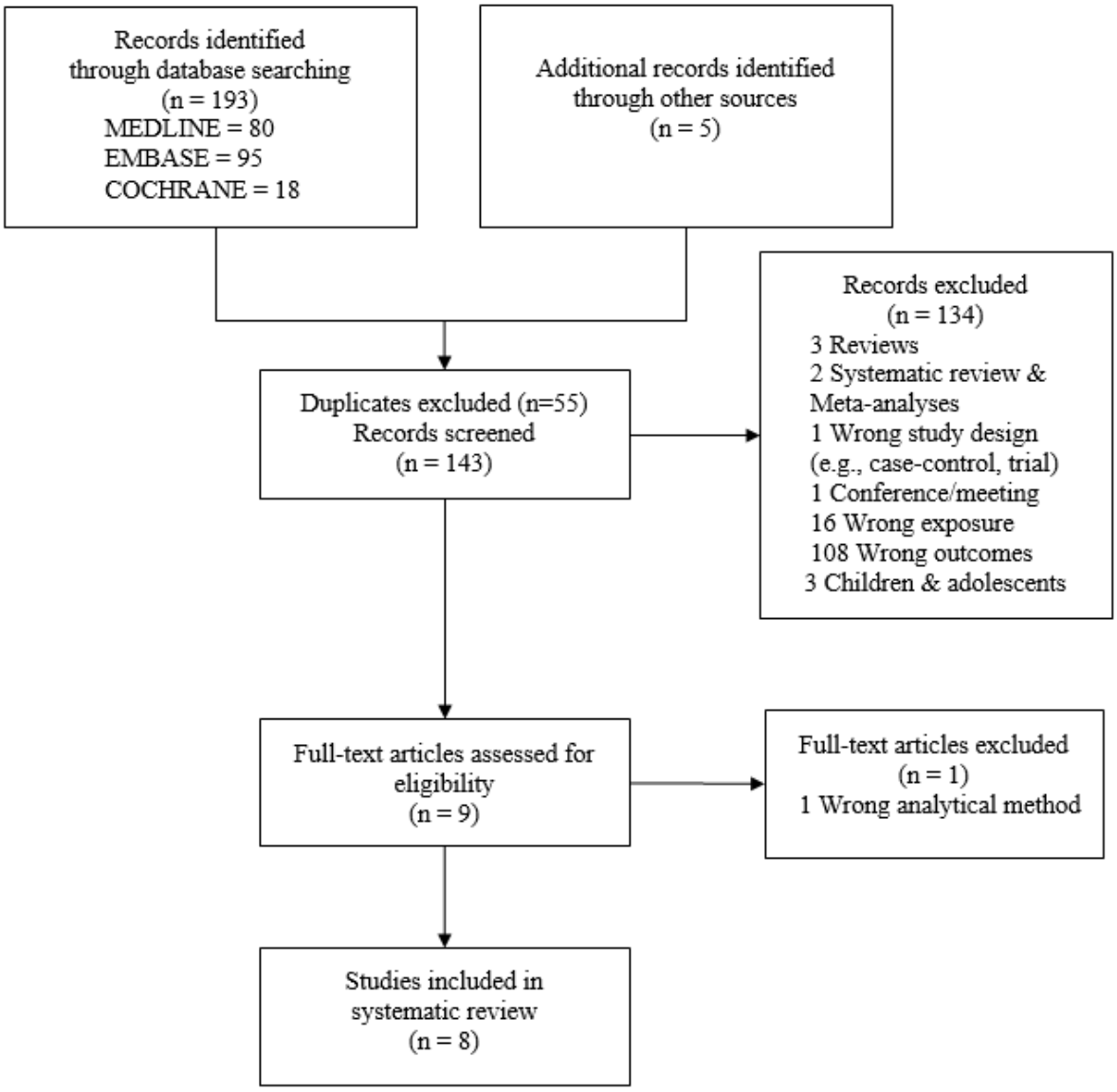
Abbreviations: BMI, body mass index; CVD, Cardiovascular disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MID, Minimally Important Differences; OB, obesity; OW, overweight.

Supplementary Material

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

SUPPLEMENTARY FIGURES

Supplementary Figure 1. Consort diagram outlining the summary of evidence search and selection for water substitution and cardiometabolic outcomes.

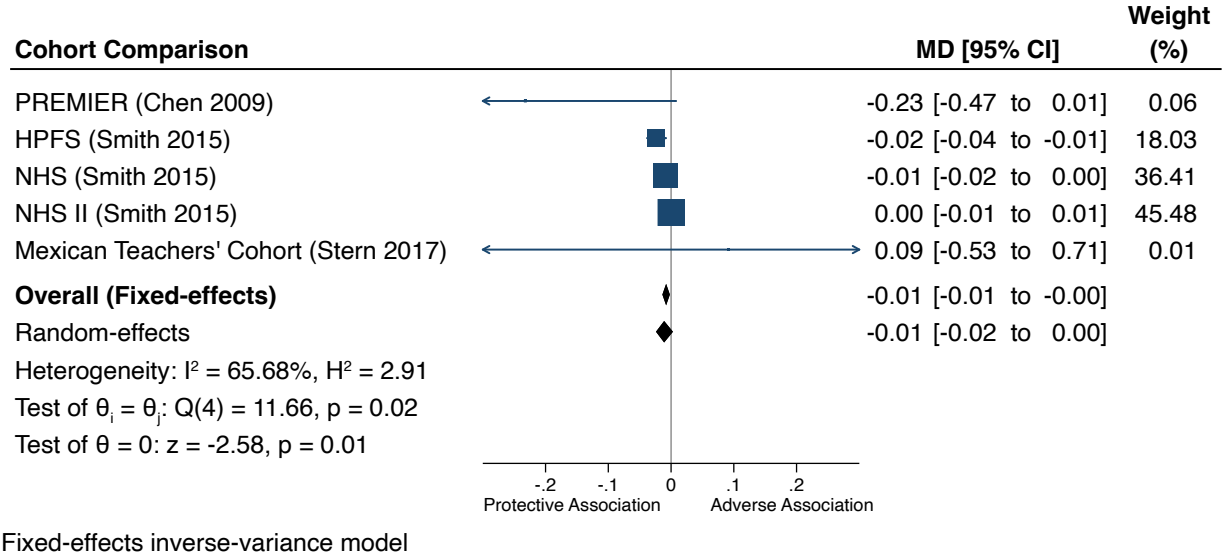


Of the 143 studies screened, 134 were excluded based on title and abstract review. The remaining 9 studies were reviewed in full. A total of 8 studies met the inclusion criteria and qualified for further analysis.

Supplementary Material

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

Supplementary Figure 2A. Relationship between increasing one serving (330 mL) of low-and no-calorie sweetened beverage (LNCSB) intake a day and change in body weight (kg) per year using a fixed-effects model.

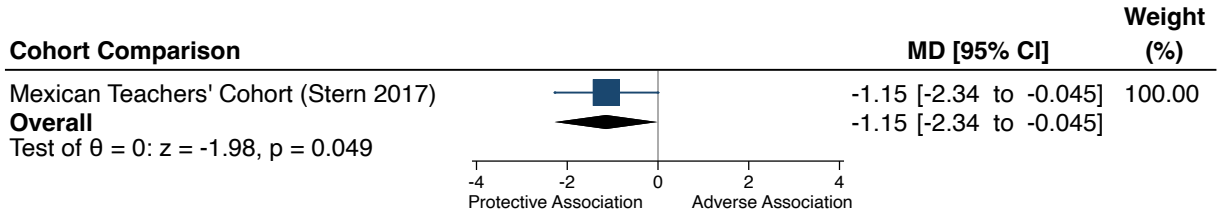


The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as mean difference (MD) in body weight (kg) per year with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 2B. Relationship between increasing one serving (330 mL) of low-and no-calorie sweetened beverage (LNCSB) intake a day and change in waist circumference (cm) per year using a fixed-effects model.

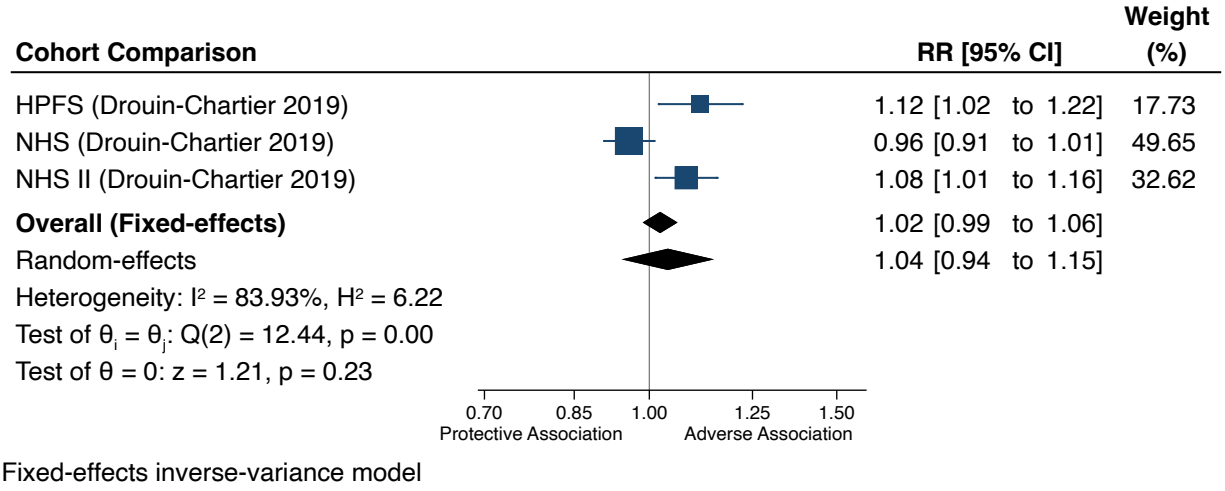


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as mean difference (MD) per year with 95% Confidence Intervals (CI) where estimable.

Supplementary Material

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

Supplementary Figure 2C. Relationship between increasing one serving (330 mL) of low-and no-calorie sweetened beverage (LNCSB) intake a day and type 2 diabetes (T2D) incidence using a fixed-effects model.

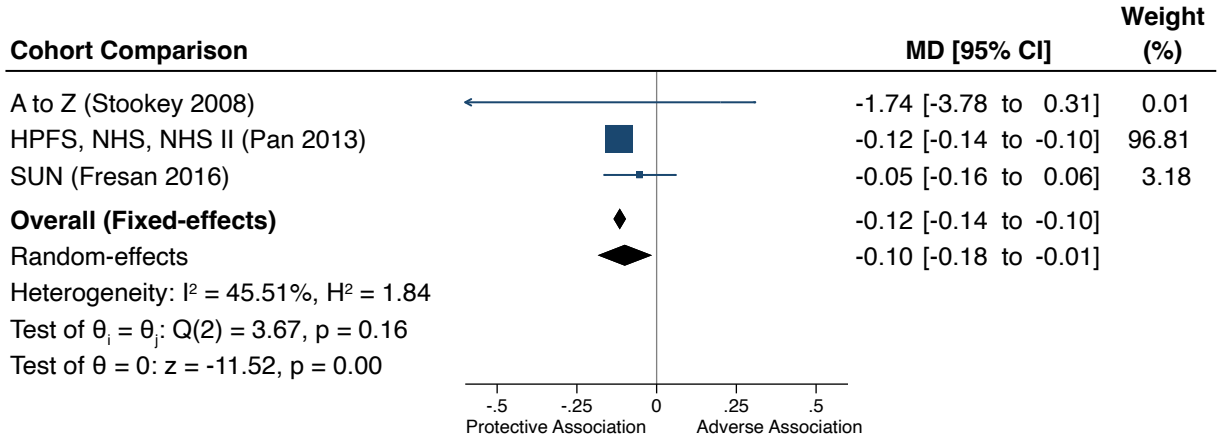


The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 3A. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and change in body weight (kg) per year using a fixed-effects model.

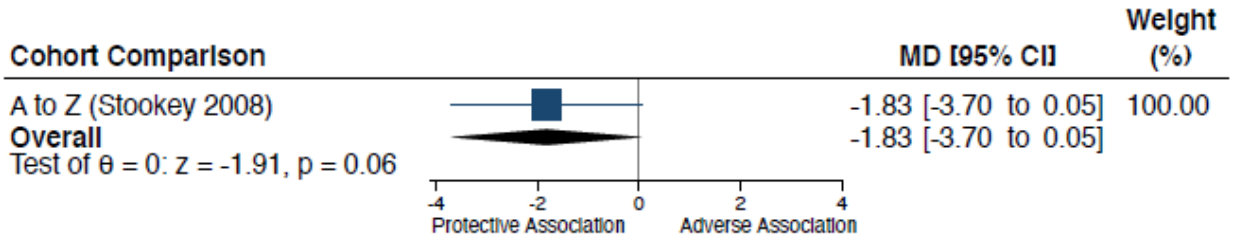


The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as mean difference (MD) in body weight per year with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; SUN, Sequimiento University of Navarra.

Supplementary Material

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

Supplementary Figure 3B. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and change in waist circumference (cm) per year.

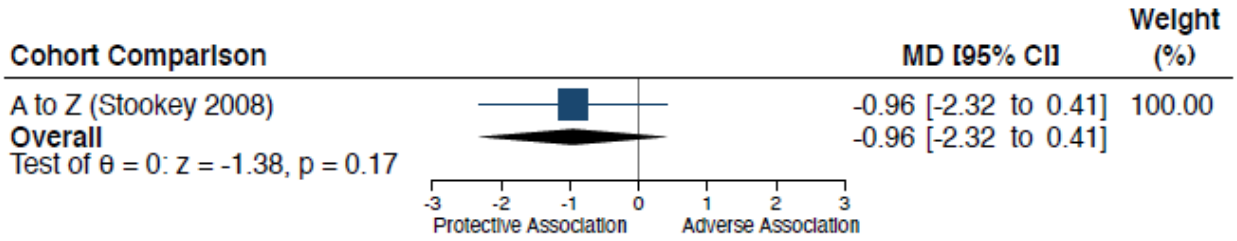


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as mean difference (MD) per year with 95% Confidence Intervals (CI) where estimable.

Supplementary Material

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

Supplementary Figure 3C. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and change in percent body fat (%) per year.

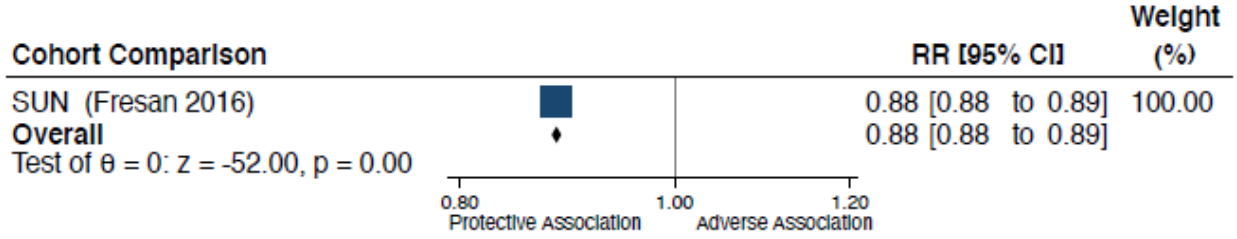


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as mean difference (MD) per year with 95% Confidence Intervals (CI) where estimable.

Supplementary Material

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

Supplementary Figure 3D. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and obesity (OB) incidence.

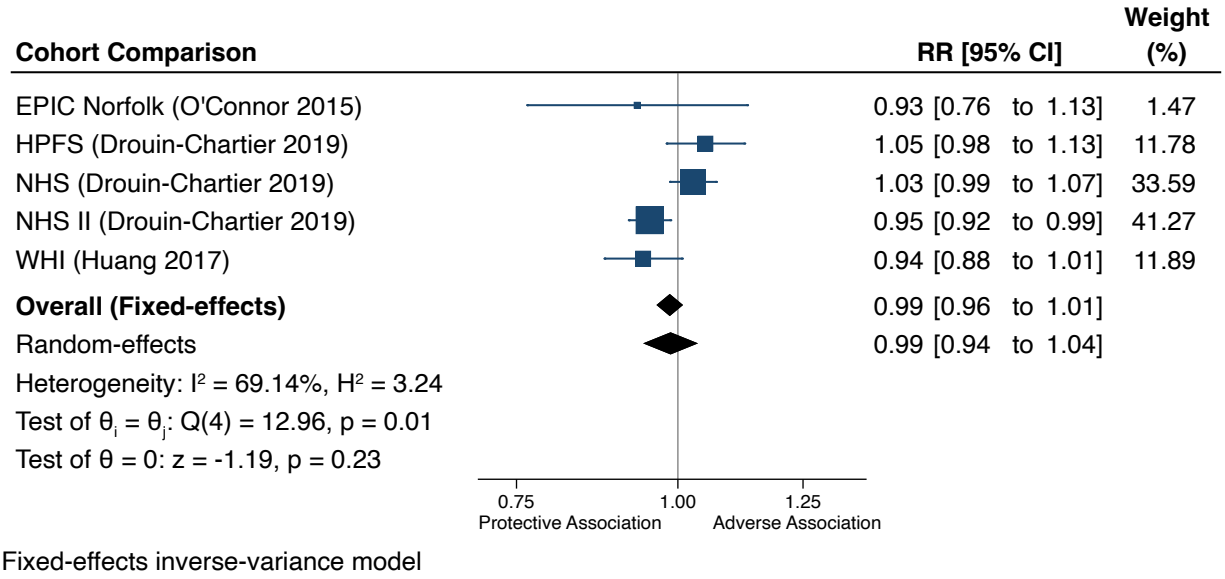


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: SUN, Sequimiento University of Navarra.

Supplementary Material

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

Supplementary Figure 3E. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and type 2 diabetes (T2D) incidence using a fixed-effects model.

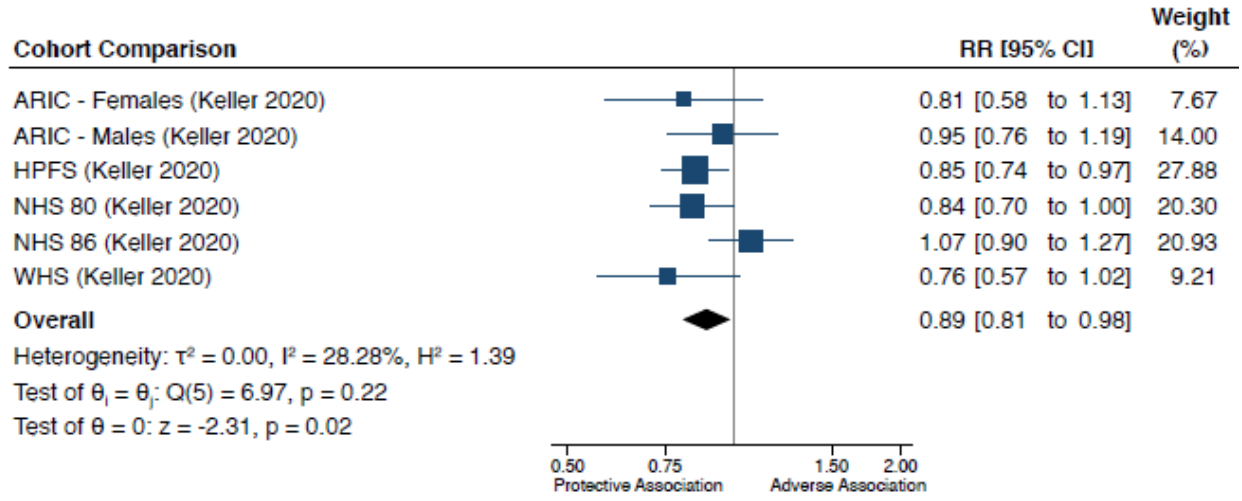


The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: EPIC, The European Prospective Investigation of Cancer; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHI, Women's Health Initiative.

Supplementary Material

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

Supplementary Figure 3F. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and coronary heart disease (CHD) incidence using DerSimonian-Laird random-effects model.



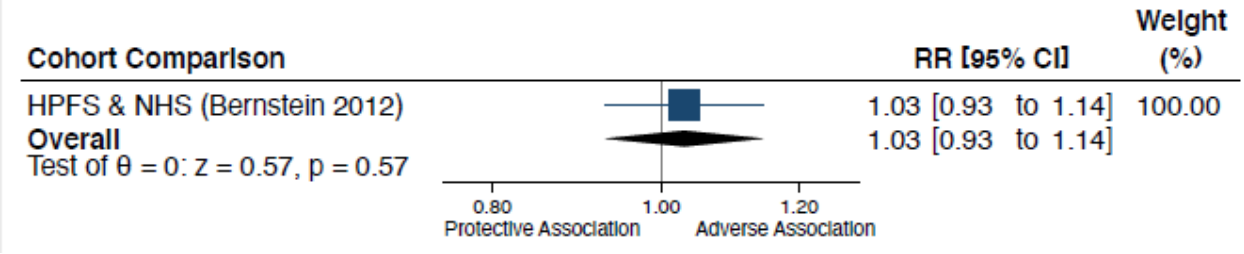
Random-effects DerSimonian-Laird model

The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHS: Women's Health Study.

Supplementary Material

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

Supplementary Figure 3G. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and stroke incidence.

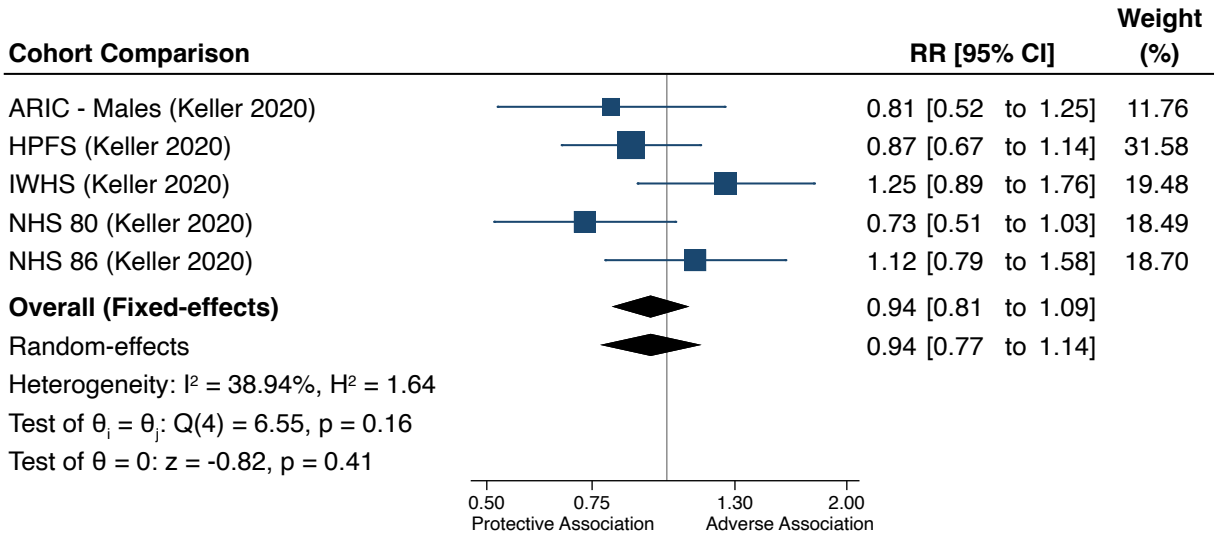


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study

Supplementary Material

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

Supplementary Figure 3H. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and the risk of coronary heart disease (CHD) mortality using a fixed-effects model.



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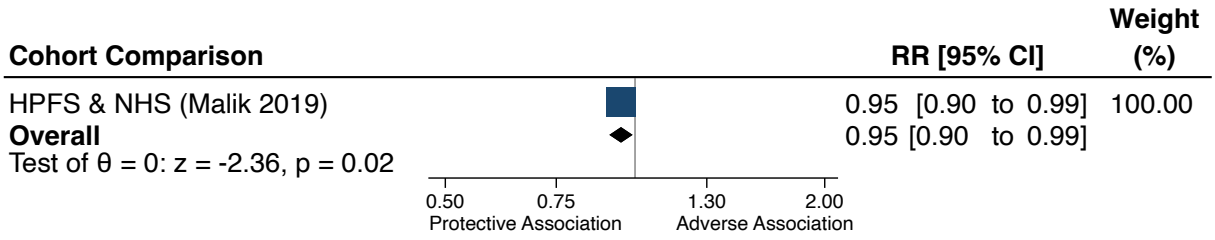
Supplementary Material

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

Supplementary Figure 3I. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and the risk of total cardiovascular disease (CVD) mortality.

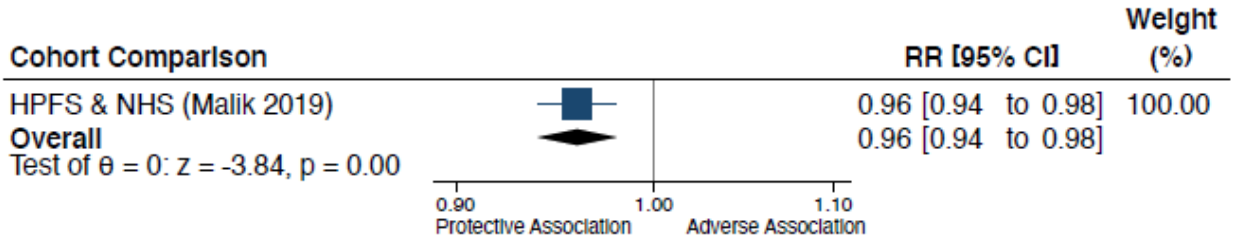


The black diamond represents the pooled summary estimate. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 3J. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and the risk of total mortality.

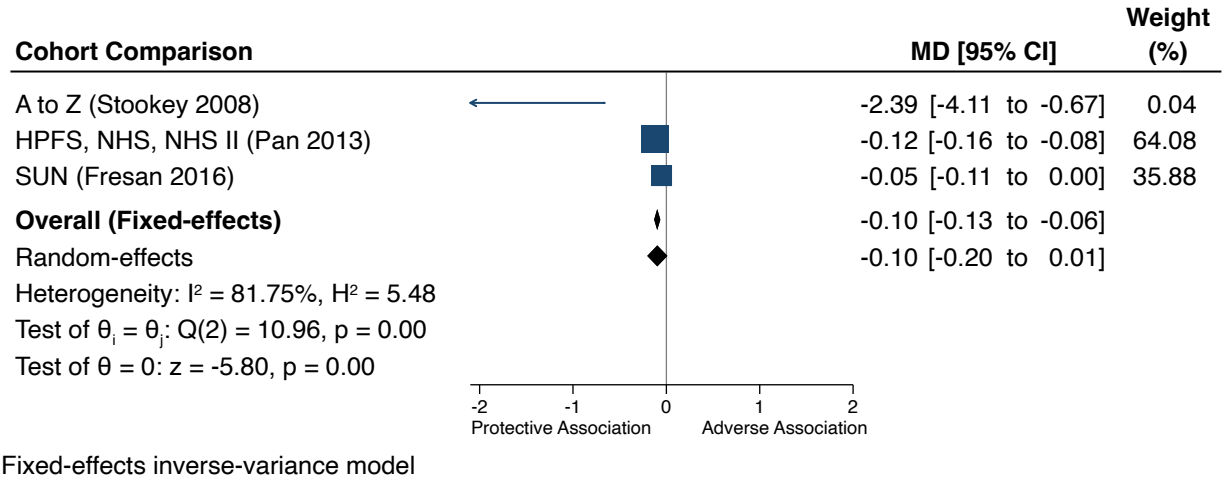


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study

Supplementary Material

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

Supplementary Figure 4A. Relationship between substituting water for sugar-sweetened beverages (SSBs) and change in body weight (kg) per year using a fixed-effects model.

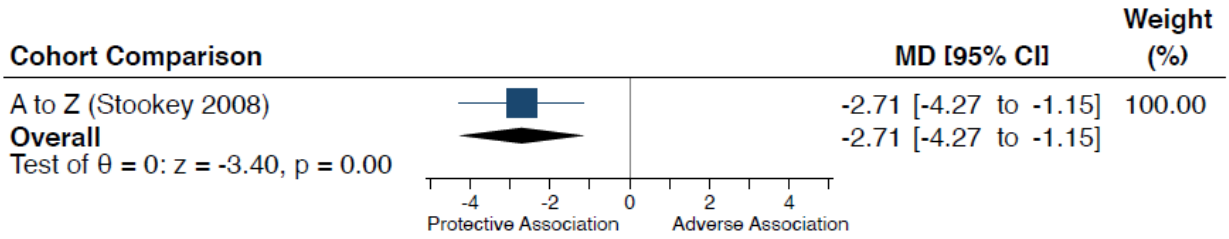


The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (χ^2) at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as mean difference (MD) per year with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; SUN, Sequimiento University of Navarra.

Supplementary Material

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

Supplementary Figure 4B. Relationship between substituting water for sugar-sweetened beverages (SSBs) and change in waist circumference (cm) per year.

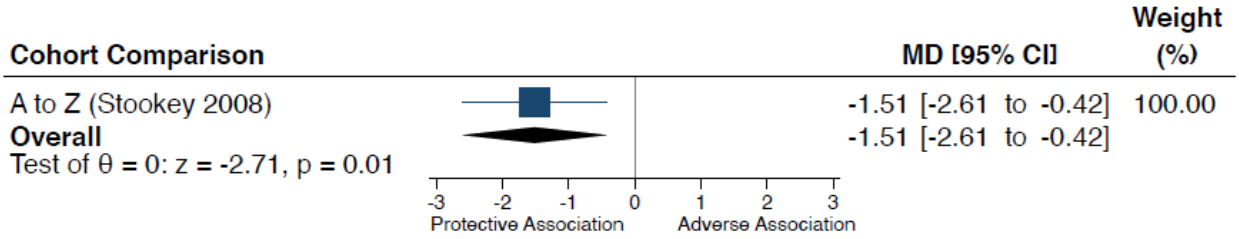


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable.

Supplementary Material

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

Supplementary Figure 4C. Relationship between substituting water for sugar-sweetened beverages (SSBs) and change in percent body fat (%) per year.



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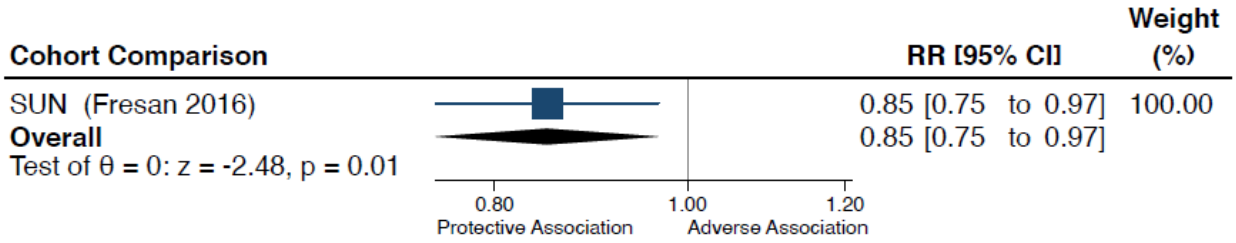
Supplementary Material

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

Supplementary Figure 4D. Relationship between substituting water for sugar-sweetened beverages (SSBs) and obesity (OB) incidence.



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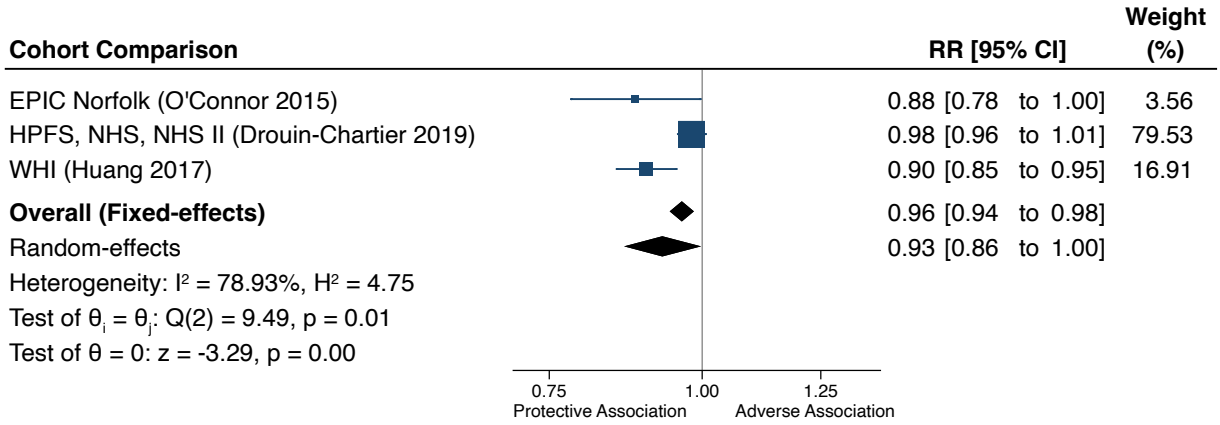
Supplementary Material

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

Supplementary Figure 4E. Relationship between substituting water for sugar-sweetened beverages and the risk of type 2 diabetes (T2D) using a fixed-effects model.



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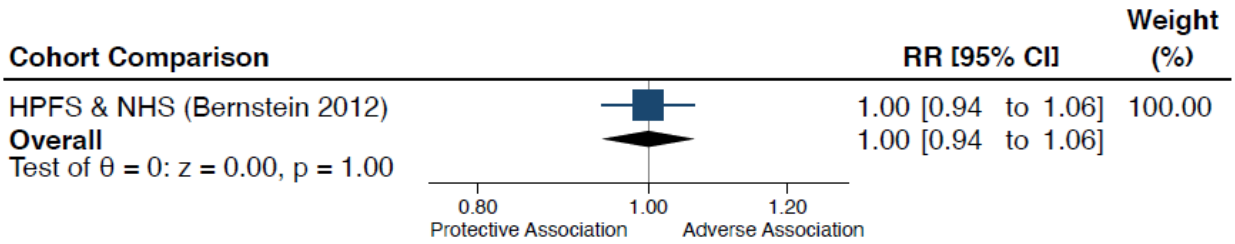
Supplementary Material

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

Supplementary Figure 4F. Relationship between substituting water for sugar-sweetened beverages (SSBs) and stroke incidence.

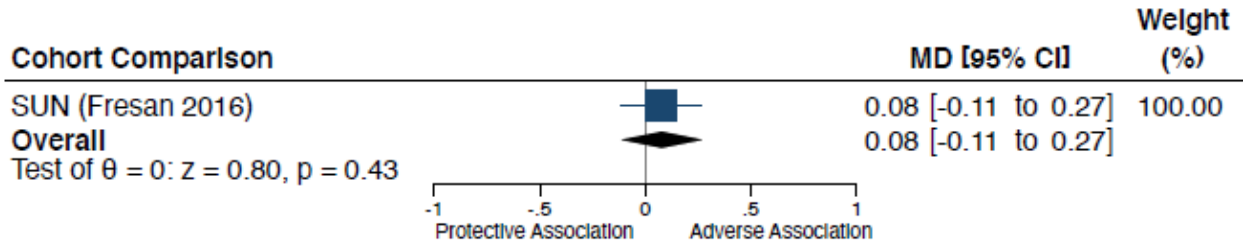


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 5A. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for water and change in body weight (kg) per year.



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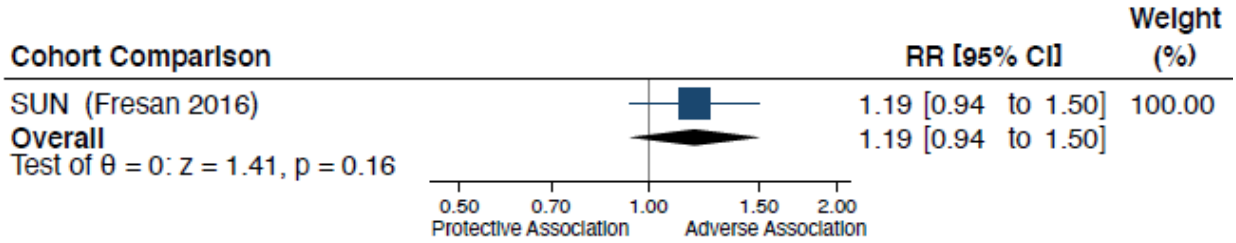
Supplementary Material

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

Supplementary Figure 5B. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for water and obesity (OB) incidence.

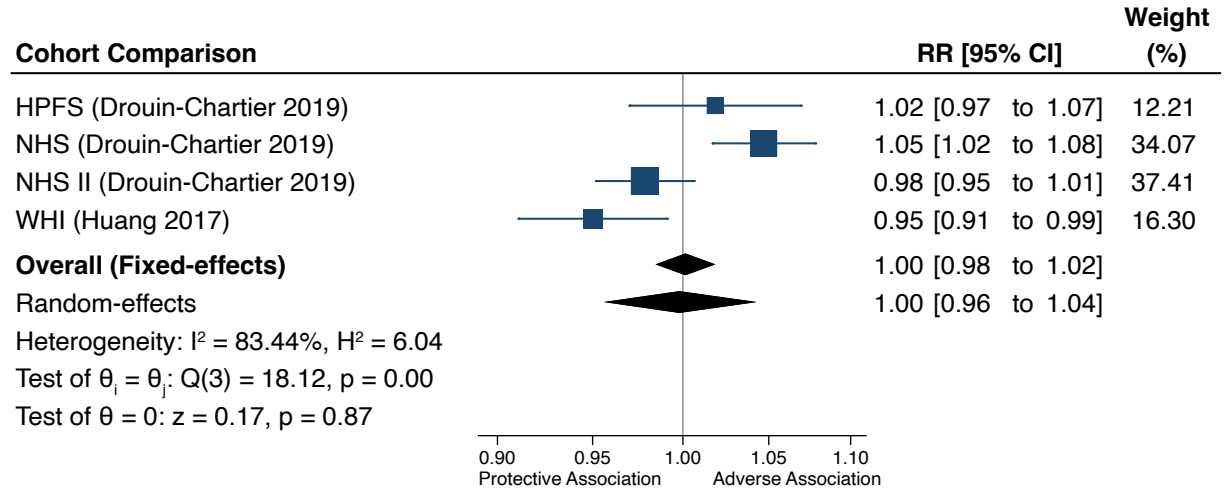


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: SUN, Sequimiento University of Navarra.

Supplementary Material

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

Supplementary Figure 5C. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for water and the risk of type 2 diabetes (T2D) using a fixed-effects model.

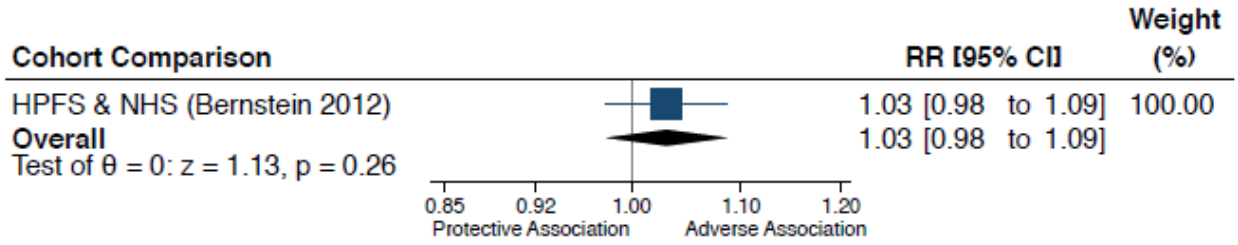


The black diamond represents the pooled summary estimate. Inter-study heterogeneity was tested using the Cochran Q statistic (χ^2) at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic. An I^2 value ≥50% was considered to indicate substantial heterogeneity. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHI, Women's Health Initiative.

Supplementary Material

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

Supplementary Figure 5D. Relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for water and stroke incidence.

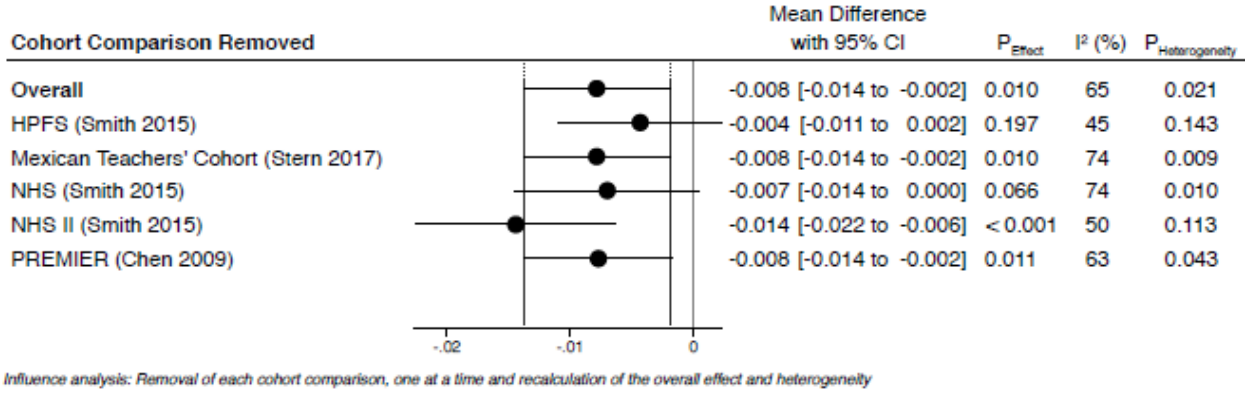


The black diamond represents the pooled summary estimate. Inter-study heterogeneity could not be assessed as only 1 cohort comparison was available for analysis. All results are presented as risk ratio (RR) with 95% Confidence Intervals (CI) where estimable. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 6A. Sensitivity analysis of relationship between change in low-and no-calorie sweetened beverage (LNCSB) intake on change in body weight (kg) per year.

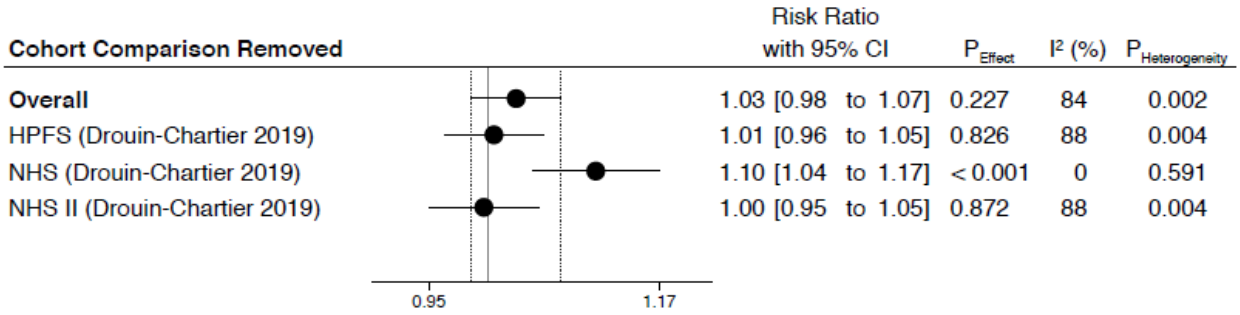


Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study

Supplementary Material

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

Supplementary Figure 6B. Sensitivity analysis of relationship between change in low-and no-calorie sweetened beverage (LNCSB) intake on risk of type 2 diabetes (T2D).



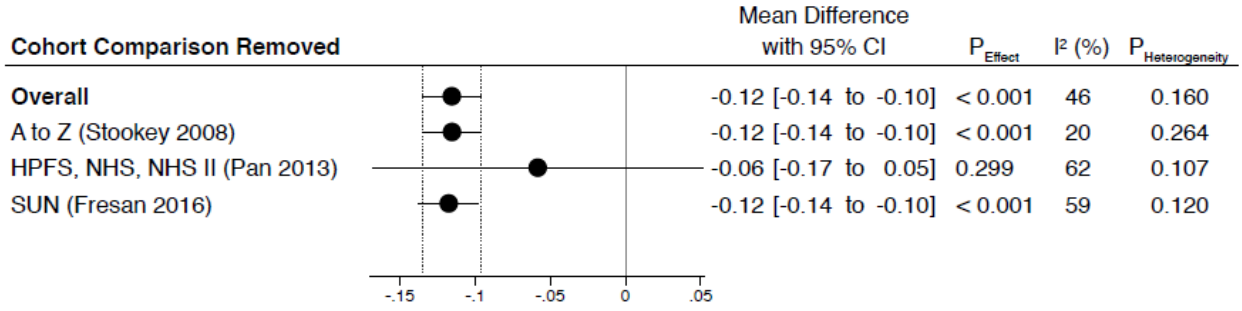
Influence analysis: Removal of each cohort study, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 7A. Sensitivity analysis of relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) on change in body weight (kg) per year.



Influence analysis: Removal of each cohort comparison, one at a time and recalculation of the overall effect and heterogeneity

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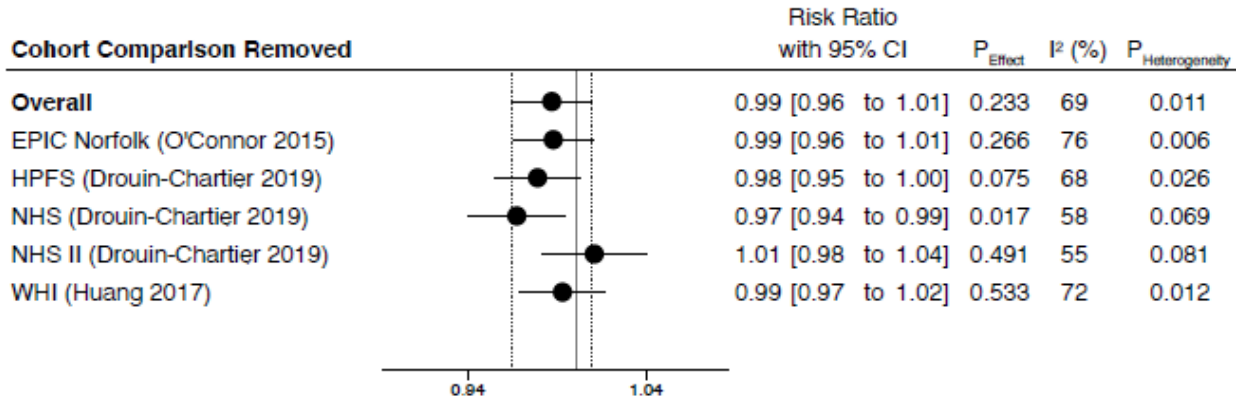
Supplementary Material

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

Supplementary Figure 7B. Sensitivity analysis of relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and risk of type 2 diabetes (T2D).



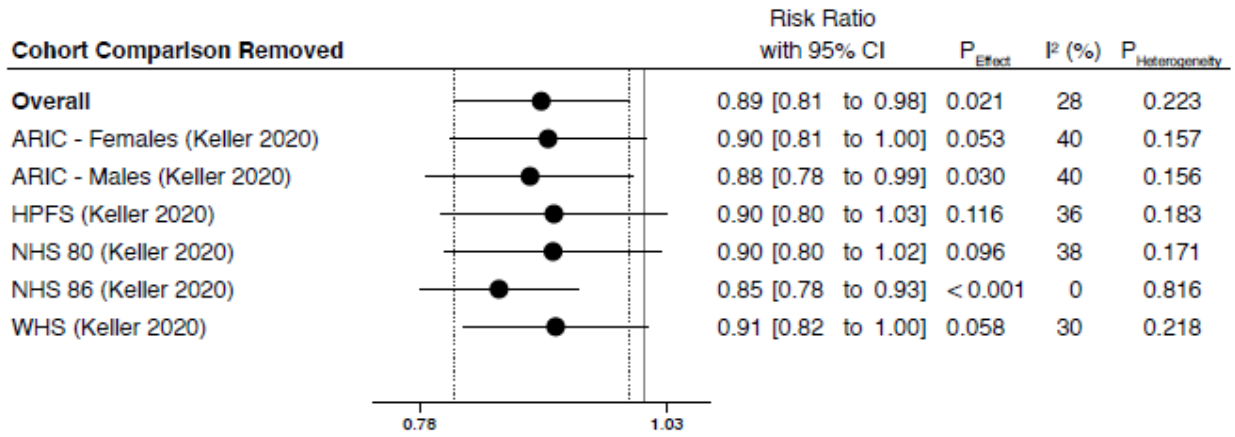
Influence analysis: Removal of each cohort study, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: EPIC, The European Prospective Investigation of Cancer; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHI, Women's Health Initiative.

Supplementary Material

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

Supplementary Figure 7C. Sensitivity analysis of relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and coronary heart disease (CHD) incidence.



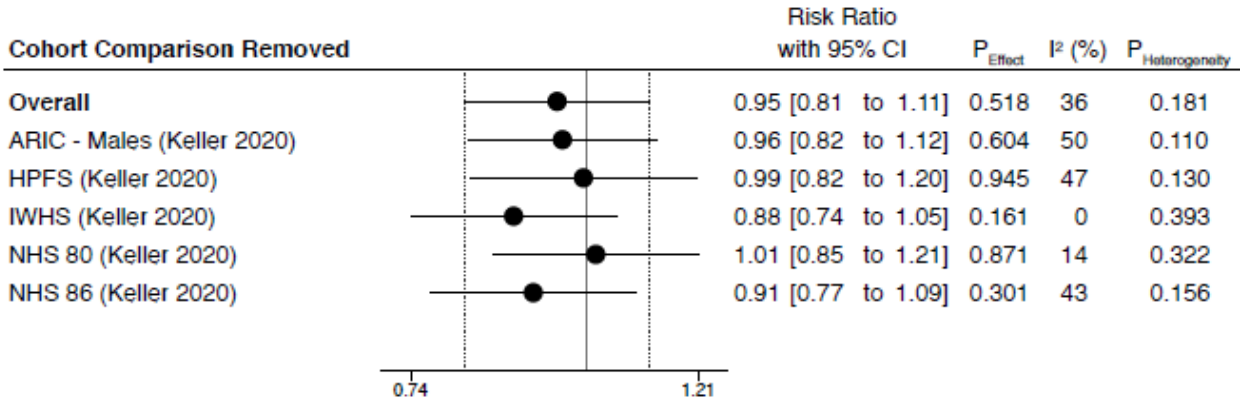
Influence analysis: Removal of each cohort study, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHS: Women's Health Study.

Supplementary Material

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

Supplementary Figure 7D. Sensitivity analysis of relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for sugar-sweetened beverages (SSBs) and risk of coronary heart disease (CHD) mortality.



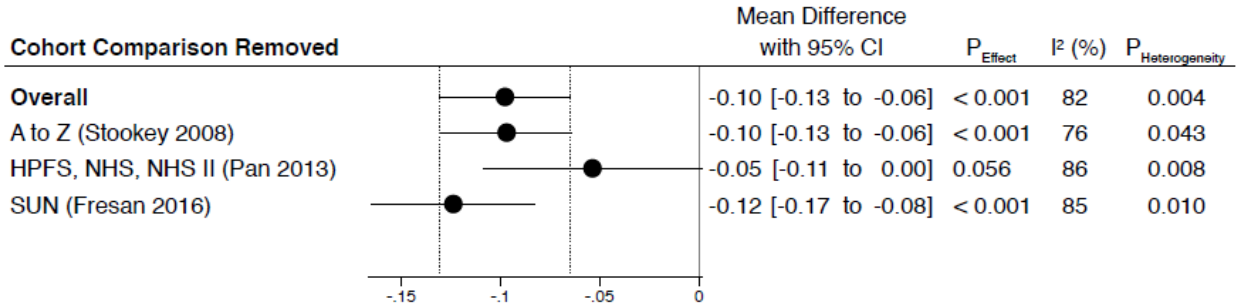
Influence analysis: Removal of each cohort study, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; HPFS, Health Professionals Follow-Up Study; IWHS, Iowa Women's Health Study; NHS, Nurses' Health Study.

Supplementary Material

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

Supplementary Figure 8A. Sensitivity analysis of relationship between substituting water for sugar-sweetened beverages (SSBs) on change in body weight (kg) per year.



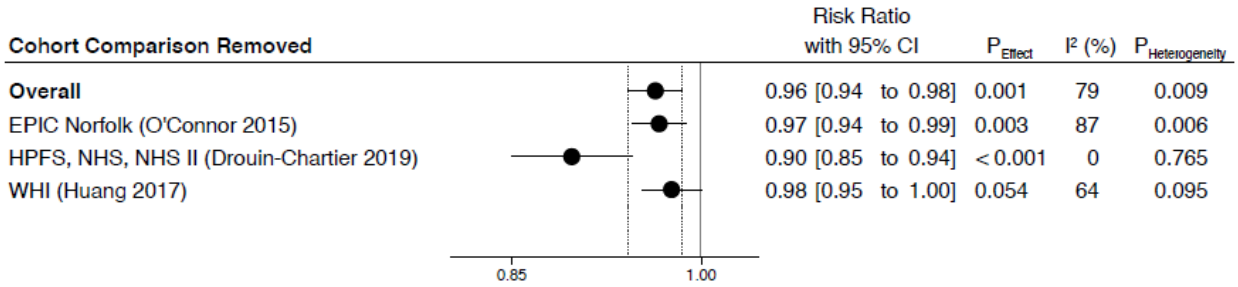
Influence analysis: Removal of each cohort comparison, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; SUN, Sequimiento University of Navarra.

Supplementary Material

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

Supplementary Figure 8B. Sensitivity analysis of relationship between substituting water for sugar-sweetened beverages (SSBs) and risk of type 2 diabetes (T2D).



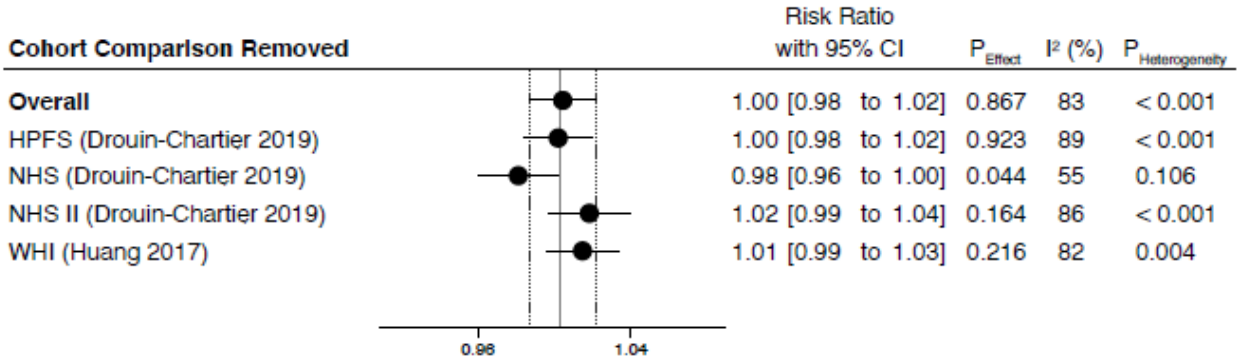
Influence analysis: Removal of each cohort study, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: EPIC, The European Prospective Investigation of Cancer; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHI: Women's Health Initiative.

Supplementary Material

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

Supplementary Figure 9. Sensitivity analysis of relationship between substituting low-and no-calorie sweetened beverages (LNCSBs) for water and risk of type 2 diabetes (T2D).



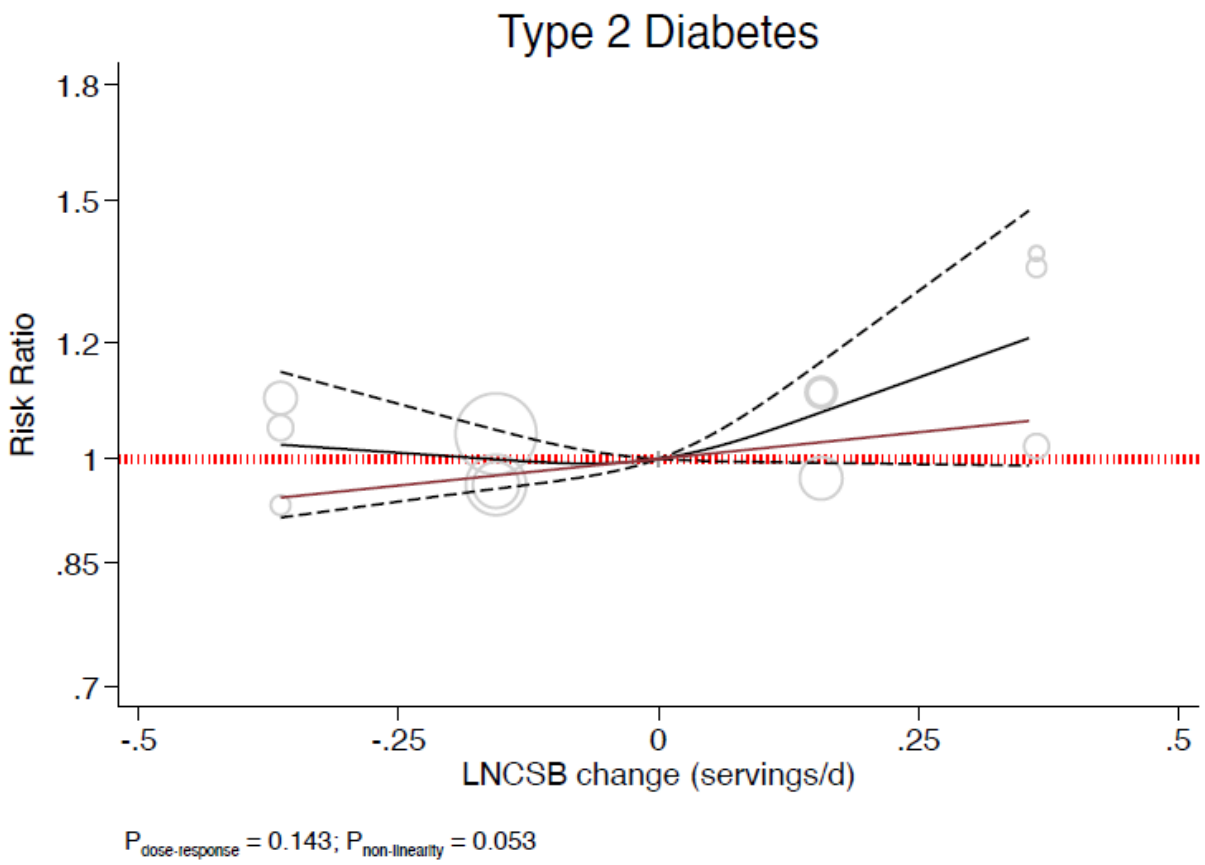
Influence analysis: Removal of each cohort study, one at a time and recalculation of the overall effect and heterogeneity

Each cohort comparison was systematically removed, and summary estimates were recalculated to assess the influence of each cohort comparison. A cohort comparison was considered influential if it changed the direction, or significance of the pooled estimates or the evidence of heterogeneity. Inter-study heterogeneity was tested using the Cochran Q statistic at a significance level of $P_Q<0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered to indicate substantial heterogeneity. Abbreviations: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; WHI: Women's Health Initiative.

Supplementary Material

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

Supplementary Figure 10. Linear and non-linear dose-response relation between increasing low- and no-calorie sweetened beverage (LNCSB) intake and risk of type of 2 diabetes (T2D).



Both linear (solid lines) and non-linear (dashed lines along with 95% confidence intervals) dose-response data were modeled using one-stage linear mixed models. For the non-linear model, the relation was allowed to curve by transforming the exposure using restricted cubic splines with three knots. Individual observations are represented by the circles with the size corresponding to their precision. Red dashed line represents risk ratio of 1.0, indicating no change in risk.

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