

SUPPLEMENTARY TABLES

Table S1. Search strategy.....	10
Table S2. PICOTS framework	11
Table S3. Characteristics of UNCOUPLING INTERVENTIONS.....	12
Table S4. Characteristics of COUPLING INTERVENTIONS	14
Table S5. Characteristics of DELAYED COUPLING INTERVENTIONS	15
Table S6. OVERALL CIneMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants.....	17
Table S7. OVERALL CIneMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES	18
Table S8. OVERALL CIneMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	19
Table S9. OVERALL CIneMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES	20
Table S10. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	21
Table S11. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	22
Table S12. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GHRELIN response in HEALTHY participants.....	23
Table S13. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants	24
Table S14. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with	

caloric sweeteners on postprandial blood GLUCAGON response in participants with TYPE 2 DIABETES	25
Table S15. GRADE assessments of COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood GLUCOSE response in HEALTHY participants	26
Table S16. GRADE assessments of COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood INSULIN response in HEALTHY participants	27
Table S17. OVERALL CInEMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLUCOSE response in HEALTHY participants.....	28
Table S18. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES.....	29
Table S19. OVERALL CInEMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood INSULIN response in HEALTHY participants	30
Table S20. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood INSULIN response in participants with TYPE 2 DIABETES.....	31
Table S21. OVERALL CInEMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLP-1 response in HEALTHY participants	32
Table S22. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLP-1 response in participants with TYPE 2 DIABETES	33
Table S23. OVERALL CInEMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GIP response in HEALTHY participants	34
Table S24. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLUCAGON response in HEALTHY participants	35
Table S25. GRADE assessments for outcomes with single direct trial comparisons.....	36

SUPPLEMENTARY FIGURES

Figure S1. Formulas used to compute incremental area under the curve (iAUC) for primary and secondary outcomes	37
Figure S2. Flow of literature	38
Figure S3. Individual (top) and summary (bottom) risk of bias assessments of studies with UNCOUPLING INTERVENTIONS	39
Figure S4. Individual (top) and summary (bottom) risk of bias assessment of studies with COUPLING INTERVENTIONS	40
Figure S5. Individual (top) and summary (bottom) risk of bias assessment of studies with DELAYED COUPLING INTERVENTIONS	41
Figure S6. Risk of bias assessment of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants	42
Figure S7. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants	44
Figure S8. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants	47
Figure S9. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants	51
Figure S10. Risk of bias assessment of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES ..	53
Figure S11. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES	54
Figure S12. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES	55

Figure S13. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES	56
Figure S14. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	57
Figure S15. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	59
Figure S16. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants	61
Figure S17. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants	64
Figure S18. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants	67
Figure S19. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES.....	70
Figure S20. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES	71
Figure S21. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES	72

Figure S22. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES	73
Figure S23. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES	74
Figure S24. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	75
Figure S25. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	76
Figure S26. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	77
Figure S27. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	78
Figure S28. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GHRELIN response in HEALTHY participants.....	79
Figure S29. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GHRELIN response in HEALTHY participants.....	80
Figure S30. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants	81
Figure S31. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants	82
Figure S32. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of	

non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in participants with TYPE 2 DIABETES	83
Figure S33. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in participants with TYPE 2 DIABETES	84
Figure S34. Risk of bias assessment of COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood GLUCOSE response in HEALTHY participants.	85
Figure S35. Network plot and meta-analysis of COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood INSULIN response in HEALTHY participants.	86
Figure S36. Risk of bias assessment of COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood INSULIN response in HEALTHY participants.	87
Figure S37. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants.....	88
Figure S38. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants.....	89
Figure S39. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants.....	91
Figure S40. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants.....	93
Figure S41. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES	94

Figure S42. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	95
Figure S43. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	97
Figure S44. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	98
Figure S45. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	100
Figure S46. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants.....	101
Figure S47. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES.....	102
Figure S48. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES.....	103
Figure S49. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	104
Figure S50. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	106
Figure S51. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened	

beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	107
Figure S52. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	109
Figure S53. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants	110
Figure S54. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in participants with TYPE 2 DIABETES	111
Figure S55. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in participants with TYPE 2 DIABETES	112
Figure S56. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	113
Figure S57. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	114
Figure S58. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	115
Figure S59. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	116
Figure S60. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened	

beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants	117
Figure S61. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants	118
Figure S62. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants	119

Table S1. Search strategy

MEDLINE	EMBASE	Cochrane Central Register of Controlled Trials
<ol style="list-style-type: none"> 1. exp Non-Nutritive Sweeteners/ 2. exp Aspartame/ 3. aspartame.mp. 4. exp Saccharin/ 5. saccharin.mp. 6. sucralose.mp. 7. acesulfame.mp. 8. neotame.mp. 9. advantame.mp. 10. alitame.mp. 11. exp Cyclamates/ 12. cyclamate.mp. 13. exp Stevia/ 14. stevia.mp. 15. steviol glycoside.mp. 16. rebaudioside.mp. 17. stevioside.mp. 18. siraitia grosvenorii.mp. 19. luo han guo.mp. 20. monk fruit.mp. 21. exp Postprandial Period/ 22. postprandial.mp. 23. acute.mp. 24. exp Blood Glucose/ 25. exp Glucose Tolerance Test/ 26. glucose.mp. 27. glycemia.mp. 28. glycaemia.mp. 29. glycemie.mp. 30. glycaemic.mp. 31. exp Insulin/ 32. insulin.mp. 33. exp Glucagon-Like Peptide 1/ 34. glucagon-like peptide 1.mp. 35. glp-1.mp. 36. exp Peptide YY/ 37. peptide yy.mp. 38. PYY.mp. 39. exp Gastric Inhibitory Polypeptide/ 40. gastric inhibitory polypeptide.mp. 41. GIP.mp. 42. exp Ghrelin/ 43. ghrelin.mp. 44. exp Leptin/ 45. leptin.mp. 46. exp Glucagon/ 47. glucagon.mp. 48. or/1-20 49. or/21-47 50. 48 and 49 51. limit 50 to animals 52. 50 not 51 	<ol style="list-style-type: none"> 1. exp nonnutritive sweetener/ 2. exp aspartame/ 3. aspartame.mp. 4. exp saccharin/ 5. saccharin.mp. 6. exp sucralose/ 7. sucralose.mp. 8. exp acesulfame/ 9. acesulfame.mp. 10. exp neotame/ 11. neotame.mp. 12. advantame.mp. 13. exp alitame/ 14. alitame.mp. 15. exp cyclamate sodium/ 16. cyclamate.mp. 17. exp Stevia/ 18. stevia.mp. 19. steviol glycoside.mp. 20. rebaudioside.mp. 21. stevioside.mp. 22. exp Siraitia grosvenorii/ 23. luo han guo.mp. 24. monk fruit.mp. 25. exp postprandial state/ 26. postprandial.mp. 27. acute.mp. 28. exp glucose blood level/ 29. exp glucose tolerance test/ 30. glucose.mp. 31. glycemia.mp. 32. glycaemia.mp. 33. glycemie.mp. 34. glycaemic.mp. 35. exp insulin/ 36. insulin.mp. 37. exp glucagon like peptide 1/ 38. glucagon-like peptide 1.mp. 39. glp-1.mp. 40. exp peptide YY/ 41. peptide yy.mp. 42. PYY.mp. 43. exp gastric inhibitory polypeptide/ 44. gastric inhibitory polypeptide.mp. 45. GIP.mp. 46. exp ghrelin/ 47. ghrelin.mp. 48. exp leptin/ 49. leptin.mp. 50. exp glucagon/ 51. glucagon.mp. 52. or/1-24 53. or/25-51 54. 52 and 53 55. limit 54 to animals 56. 54 not 55 	<ol style="list-style-type: none"> 1. exp Non-Nutritive Sweeteners/ 2. exp Aspartame/ 3. aspartame.mp. 4. exp Saccharin/ 5. saccharin.mp. 6. sucralose.mp. 7. acesulfame.mp. 8. neotame.mp. 9. advantame.mp. 10. exp Cyclamates/ 11. cyclamate.mp. 12. exp Stevia/ 13. stevia.mp. 14. steviol glycoside.mp. 15. rebaudioside.mp. 16. stevioside.mp. 17. luo han guo.mp. 18. monk fruit.mp. 19. exp Postprandial Period/ 20. postprandial.mp. 21. acute.mp. 22. exp Blood Glucose/ 23. exp Glucose Tolerance Test/ 24. glucose.mp. 25. glycemia.mp. 26. glycaemia.mp. 27. glycemie.mp. 28. glycaemic.mp. 29. exp Insulin/ 30. insulin.mp. 31. exp Glucagon-Like Peptide 1/ 32. glucagon-like peptide 1.mp. 33. GLP-1.mp. 34. exp Peptide YY/ 35. peptide yy.mp. 36. PYY.mp. 37. exp Gastric Inhibitory Polypeptide/ 38. gastric inhibitory polypeptide.mp. 39. GIP.mp. 40. exp Ghrelin/ 41. ghrelin.mp. 42. exp Leptin/ 43. leptin.mp. 44. exp Glucagon/ 45. glucagon.mp. 46. or/1-18 47. or/19-45 48. 46 and 47

Table S2. PICOTS framework

Participants	Intervention	Comparison	Outcomes	Time	Study Design
Males and females of all health backgrounds and ages (i.e., adults and children), excluding pregnant or breastfeeding women	NNS beverages sweetened single or blends of NNS, water, or SSBs sweetened with caloric sugars	NNS beverages sweetened single or blends of NNS, water, or SSBs sweetened with caloric sugars	Glucose iAUC Insulin iAUC GLP-1 iAUC PYY iAUC GIP iAUC Ghrelin iAUC Glucagon iAUC	2 hours	Acute, randomized and non-randomized, controlled, feeding trials

NNS beverage, non-nutritive sweetened beverage; NNS, non-nutritive sweetener; SSBs, sugar-sweetened beverage; iAUC, incremental area under the curve; GLP-1, glucagon-like peptide 1; PYY, peptide YY; GIP, gastric inhibitory peptide. NNS include, aspartame, acesulfame potassium (Ace-K), Luo Han Guo (monk) fruit extract, neotame, saccharin, stevia, sucralose and advantame (1)

Table S3. Characteristics of UNCOUPLING INTERVENTIONS

First author, year (reference)	Arm description	Study Design	Participants	Health status	Age, years	BMI, kg/m ²	Duration (mins)	Outcomes extracted	Funding source	Country
Shigeta, 1985 (2) Aspartame Glucose	225mg oral aspartame loading test 75g OGTT	NRS	15 (10M, 5F)	DM2	62.9 (12.8)	-	180	Glucose Insulin	-	Japan
Okuno, 1986 (3) Aspartame Glucose	500mg aspartame in 300ml water 100g glucose in 300ml water	NRS	7 6 8 8	Healthy DM2 DM2 DM2	46.7 (31-60) 47.3 (18-64) 50.3 (38-60) 46.5 (46-54)	-	180	Glucose Insulin Glucagon	-	Japan
Horwitz, 1988 (4) Aspartame Saccharin Water	300ml Kool-Aid sweetened with 400mg aspartame 300ml Kool-Aid sweetened with 135mg saccharin 300ml unsweetened Kool-Aid	RCT	12 (0M, 12F) 10 (5M, 5F)	Healthy DM2	28.0 (8.0) 57.0 (8.0)	22.5 33.7	180	Glucose Insulin Glucagon	Industry	USA
Moller, 1991 (5) Aspartame Water	1g aspartame dissolved in 200ml water 200ml water	RCT	6 (6M, 0F)	Healthy	29 (22-37)	-	240	Glucose Insulin	Agency	Denmark
Härtel, 1993 (6) Aspartame Ace-K Cyclamate Saccharin Sucrose Water	165mg aspartame in 330ml water 165mg ace-K in 330ml water 800mg cyclamate in 330ml water 75mg saccharin in 330ml water 33g sucrose in 330ml water 330ml water	NRS	14 (6M, 8F)	Healthy	19-52	-	120	Glucose Insulin	-	Germany
Nguyen, 1998 (7) Aspartame Glucose	250mg aspartame dissolved in 250ml water 75g glucose dissolved in 250ml water	RCT	7 (4M, 3F)	Healthy	30-47	-	120	Glucose Insulin	-	USA
Coppola, 2004 (8) Aspartame Glucose	250mg aspartame dissolved in 250ml water 75g glucose dissolved in 250ml water	RCT	20 (10M, 10F) 20 (10M, 10F)	Healthy IGT	68.0 (8.0) 69.0 (11.0)	26.4 (3.0) 27.0 (3.6)	120	Glucose Insulin	-	Italy
Berlin, 2005 (9) Aspartame Glucose	0.6g aspartame in 200ml water 75g glucose in 200ml water	RCT	12 (7M, 5F)	Healthy	28.6 (7.9)	21.2 (0.4)	300	Glucose Insulin	Agency	France
Ford, 2011 (10) Sucralose Water	50ml sucralose (0.083% w/v, 2mmol/L) 50ml water	RCT	8 (1M, 7F)	Healthy	22-27	18.8-23.9	120	Glucose Insulin GLP-1 PYY	Agency	UK
Maersk, 2012 (11) Aspartame Sucrose Water	500ml aspartame-sweetened diet cola (Coca Cola) 500ml sucrose-sweetened regular cola (Coca Cola) 500ml bottled still water (Aqua d'or mineral water)	RCT	24 (12M, 12F)	Healthy	33.5 (9.2)	31.4 (3.1)	240	Ghrelin GLP-1 GIP	Agency	Denmark
Hazali, 2014 (12) Stevia (500mg) Stevia (1000mg) Sucrose	500mg stevia in 100ml water 1000mg stevia in 100ml water 20g sucrose in 100ml water	NRS	32 (4M, 28F)	Healthy	21.3 (1.1)	21.6 (3.3)	120	Glucose	Agency	Malaysia
Bloomer, 2016 (13) Aspartame Sucralose Sucrose Water	20oz aspartame sweetened soda (Sunkist) 20oz splenda/sucralose sweetened soda (Diet Rite) 20oz HFCS and sugar sweetened soda (Sunkist) 20oz carbonated water	RCT	12 (12M, 0F)	Healthy	26.8 (7.6)	27.1 (2.8)	120	Glucose Insulin	Agency	USA

Gonzalez, 2017 (14)		RCT	10 (10M, 0F)	Healthy	22-26	20-24	120	Glucose Insulin	-	Spain
Ace-K+Asp+Cycl	330ml of Coke Zero with caffeine but without sugar									
Ace-K+Asp+Cycl	330ml of caffeine-free Coke Zero without sugar									
Sucrose	330ml of Regular Coke with sugar and caffeine									
Sucrose	330ml of Regular Coke with sugar but without caffeine									
Goza, 2018 (15)		RCT	10 (5M, 5F)	Healthy	27.4 (3.5)	23.5 (2.6)	120	Glucose Insulin	Agency	Chile
Ace-K+Aspartame	350ml beverage with 84mg aspartame and 56mg Ace-K									
Sucrose	350ml beverage with 38.7g sucrose									
Eckstein 2021 (16)		RCT	15 (10M, 5F)	Healthy	25.4 (2.5)	23.7 (1.7)	120	Glucose Insulin	-	Germany
Sucralose	300mL water with 0.2g sucralose									
Glucose	300mL water with 1g/kg BM glucose									
Fructose	300mL water with 1g/kg BM fructose									
Sucrose	300mL water with 0.5g/kg BM glucose and fructose (each)									

Ace-K, acesulfame potassium; Asp, aspartame; Cycl, cyclamate; RCT, randomized controlled trial; NRS, non-randomized study; OGTT, oral glucose tolerance test; iAUC, incremental area under the curve; M, male; F, female; DM2, type 2 diabetes; N, normal; IGT, impaired glucose tolerance; HFCS, high-fructose corn syrup; BM, body mass

Table S4. Characteristics of COUPLING INTERVENTIONS

First author, year (reference)	Meal description	Study Design	Participants	Health status	Age, years	BMI, kg/m2	Duration (mins)	Outcomes extracted	Funding source	Country
Wolf-Novak, 1988 (17)		NRS	7 (2M, 5F)	Healthy	27.0 (3.0)	-	360	Glucose Insulin	Agency	USA
Aspartame	12oz cherry-flavored beverage sweetened with 200mg aspartame and 60g CHO (partial hydrolysate of starch)									
Control	12oz cherry-flavored beverage with 60g CHO (partial hydrolysate of starch)									
Melchoir, 1991 (18)		RCT	10 (3M, 7F)	Healthy	21.7 (20-25)	20.6 (18.9-23.5)	180	Glucose Insulin	Agency	France
Aspartame	400ml chocolate drink sweetened with 80mg aspartame									
Control	400ml chocolate drink sweetened with 50g sucrose									
Solomi, 2019 (19)		NRS	10 (4M, 6F)	Healthy	27.2 (6.9)	23.9 (2.4)	120	Glucose	Agency	UK
Ace-K+Aspartame	25g glucose in 125ml water consumed with 236ml diet cola sweetened with aspartame and ace-K (Caffeine-Free Diet Coke)									
Control	25g glucose in 125ml water consumed with 236ml water									

RCT, randomized controlled trial; NRS, non-randomized study; OGTT, oral glucose tolerance test; iAUC, incremental area under the curve; M, male; F, female; DM2, type 2 diabetes; N, normal; IGT, impaired glucose tolerance; HFCS, high-fructose corn syrup; CHO, carbohydrate; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus

Table S5. Characteristics of DELAYED COUPLING INTERVENTIONS

First author, year (reference)	Meal description	Study Design	Participants	Health status	Age, years	BMI, kg/m ²	Duration (mins)	Outcomes extracted	Funding source	Country
Brown, 2012 (20)		RCT	25 (13M, 12F)	Healthy	18.8 (4.4)	25.7 (4.6)	180	Glucose	Agency	USA
Diet Soda	240ml of diet soda (Diet Rite Cola containing sucralose and ace-K) consumed 10mins prior to 75g OGTT		9 (3M, 6F)	DM1	18.2 (3.4)	21.7 (2.4)		Insulin		
Carbonated water	240ml of carbonated water (Zazz Seltzer) consumed 10mins prior to 75g OGTT		10 (1M, 9F)	DM2	17.9 (3.13)	35.0 (6.8)		Glucagon GLP-1 GIP PYY		
Pepino, 2013 (21)		RCT	17 (2M, 15F)	Healthy	35.1 (4.1)	41.0 (6.2)	300	Glucose	Agency	USA
Sucralose	60ml solution containing 48mg sucralose was consumed 10mins before ingestion of 75g glucose solution							Insulin		
Water	60ml of distilled water was consumed 10mins prior to ingestion of 75g glucose solution							GLP-1 GIP		
Temizkhan, 2014 (22)		RCT	8 (4M, 4F)	Healthy	45.0 (4.1)	30.3 (4.5)	120	Glucose	-	Turkey
Aspartame	72mg aspartame in 200ml water was consumed 15mins prior to 75g OGTT		8 (4M, 4F)	DM2	51.5 (9.2)	33.7 (5.4)		Insulin		
Sucralose	24mg sucralose in 200ml water was consumed 15mins prior to 75g OGTT							GLP-1		
Water	200ml water was consumed 15mins prior to 75g OGTT									
Sylvetsky, 2016 (23)		RCT	30 (14M, 16F)	Healthy	29.7 (7.6)	25.8 (4.2)	120	Glucose	Agency	USA
Sucralose (68mg)	A drink containing 68mg sucralose mixed with 355ml water was consumed 10mins prior to 75g OGTT							Insulin		
Sucralose (170mg)	A drink containing 170mg sucralose mixed with 355ml water was consumed 10mins prior to 75g OGTT							Glucagon		
Arm 1 Sucralose (250mg)	A drink containing 250mg sucralose mixed with 355ml water was consumed 10mins prior to 75g OGTT							GLP-1		
Water	A drink containing 355ml water was consumed 10mins prior to 75g OGTT							GIP PYY		
Diet Rite Cola	355ml caffeine-free Diet Rite Cola sweetened with 68mg sucralose and 41mg ace-K was consumed 10mins prior to 75g OGTT	RCT	31 (14M, 17F)	Healthy	27.4 (6.7)	26.3 (7.5)	120	Glucose	Agency	USA
Arm 2 Diet Mountain Dew	355ml caffeine-free Diet Mountain Dew sweetened with 18mg sucralose, 18mg ace-K and 57mg aspartame was consumed 10mins prior to 75g OGTT							Insulin		
NNS solution	A drink containing 68mg sucralose and 41mg ace-K in 355ml water was consumed 10mins prior to 75g OGTT							GLP-1		
Water	355ml water was consumed 10mins prior to 75g OGTT							GIP PYY		
Kariman Azari, 2017 (24)		RCT	10 (3M, 7F)	Healthy	33.5 (11.1)	22.4 (2.5)	120	Glucose	Agency	USA
Saccharin	A drink containing 18mg saccharin dissolved in 60ml water was consumed 10mins prior to glucose solution (75g glucose in 600ml water)							Insulin		
Water	60ml distilled water was consumed 10mins prior to glucose solution (75g glucose in 600ml water)							Glucagon GLP-1 GIP		
Nichol, 2019 (25)		RCT	10 (3M, 7F)	Lean	27.0 (4.2)	22.8 (0.9)	300	Glucose	Agency	USA
Sucralose	60ml solution containing 48mg sucralose was consumed 10mins prior to 75g OGTT		11 (1M, 10F)	Obese	29.5 (4.0)	37.7 (5.5)		Insulin		
Water	60ml distilled water was consumed 10mins prior to 75g OGTT							GIP		

Solomi, 2020 (26)		NRS	10 (5M, 5F)	Healthy	26.9 (3.3)	24.7 (1.1)	120	Glucose	-	USA
Diet cola	250ml diet soda (Caffeine-Free Diet Coke) sweetened with aspartame and ace-K was consumed 10mins prior to beverage containing 25g glucose									
Carbonated water	250ml carbonated water was consumed 10mins prior to beverage containing 25g glucose									

RCT, randomized controlled trial; NRS, non-randomized study; OGTT, oral glucose tolerance test; iAUC, incremental area under the curve; M, male; F, female; DM2, type 2 diabetes; N, normal; IGT, impaired glucose tolerance; HFCS, high-fructose corn syrup; CHO, carbohydrate; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus

Table S6. OVERALL CInEMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Ace-K + Aspartame:Sucrose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame + Cyclamate:Sucrose	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
AceK:Aspartame	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
AceK:Cyclamate	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
AceK:Saccharin	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
AceK:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
AceK:Water	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Aspartame:Cyclamate	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Aspartame:Glucose	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Saccharin	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Sucralose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Sucrose	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Water	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Cyclamate:Saccharin	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Cyclamate:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Cyclamate:Water	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Fructose:Glucose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Sucralose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Sucrose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Sucralose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Sucrose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Saccharin:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Saccharin:Water	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Stevia:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Sucralose:Sucrose	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Sucralose:Water	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Sucrose:Water	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
INDIRECT EVIDENCE									
Ace-K + Aspartame:Ace-K + Aspartame + Cyclamate	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Ace-K + Aspartame	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Aspartame	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame:Cyclamate	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Saccharin	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Stevia	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Sucralose	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame:Water	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Ace-K + Aspartame + Cyclamate	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Cyclamate:Aspartame	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Cyclamate:Cyclamate	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Cyclamate:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame + Cyclamate:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame + Cyclamate:Saccharin	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame + Cyclamate:Stevia	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame + Cyclamate:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Cyclamate:Water	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
AceK:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Stevia	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low	Within-study bias, Imprecision
AceK:Sucralose	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Aspartame:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Stevia	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low	Within-study bias, Heterogeneity
Cyclamate:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Cyclamate:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Cyclamate:Stevia	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low	Within-study bias, Imprecision
Cyclamate:Sucralose	0	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Fructose:Saccharin	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Stevia	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Water	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Saccharin	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Stevia	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Water	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Saccharin:Stevia	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low	Within-study bias, Heterogeneity
Saccharin:Sucralose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Stevia:Sucralose	0	Some concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Low	Within-study bias, Imprecision
Stevia:Water	0	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low	Within-study bias, Heterogeneity

Table S7. OVERALL CInEMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Aspartame:Glucose	4	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Low	Within-study bias, Incoherence
Aspartame:Saccharin	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	Imprecision, Incoherence
Aspartame:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	Imprecision, Incoherence
Saccharin:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	Imprecision, Incoherence
INDIRECT EVIDENCE									
Glucose:Saccharin	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Low	Heterogeneity, Incoherence
Glucose:Water	0	No concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Low	Heterogeneity, Incoherence

Table S8. OVERALL CIneMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Ace-K + Aspartame:Sucrose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame + Cyclamate:Sucrose	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Aspartame	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
AceK:Cyclamate	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
AceK:Saccharin	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
AceK:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
AceK:Water	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
Aspartame:Cyclamate	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
Aspartame:Glucose	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Saccharin	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Aspartame:Sucralose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Sucrose	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Aspartame:Water	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Cyclamate:Saccharin	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
Cyclamate:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Cyclamate:Water	1	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
Fructose:Glucose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Sucralose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Sucrose	1	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
Glucose:Sucralose	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Sucrose	1	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Moderate	Incoherence
Saccharin:Sucrose	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Saccharin:Water	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Sucralose:Sucrose	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Sucralose:Water	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Sucrose:Water	2	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
INDIRECT EVIDENCE									
Ace-K + Aspartame:Ace-K + Aspartame + Cyclamate	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
AceK:Ace-K + Aspartame	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias, Imprecision, Heterogeneity
Ace-K + Aspartame:Aspartame	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame:Cyclamate	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias, Imprecision, Heterogeneity
Ace-K + Aspartame:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame:Saccharin	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame:Water	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
AceK:Ace-K + Aspartame + Cyclamate	0	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
Ace-K + Aspartame + Cyclamate:Aspartame	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame + Cyclamate:Cyclamate	0	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias, Imprecision, Heterogeneity
Ace-K + Aspartame + Cyclamate:Fructose	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame + Cyclamate:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Ace-K + Aspartame + Cyclamate:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Ace-K + Aspartame + Cyclamate:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame + Cyclamate:Water	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
AceK:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
AceK:Sucralose	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
Aspartame:Fructose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Cyclamate:Fructose	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Cyclamate:Glucose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Cyclamate:Sucralose	0	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Within-study bias, Heterogeneity
Fructose:Saccharin	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Fructose:Water	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Saccharin	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Glucose:Water	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Saccharin:Sucralose	0	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	Heterogeneity

Table S9. OVERALL CInEMA assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Aspartame:Glucose	4	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low	["Within-study bias", "Heterogeneity", "Incoherence"]
Aspartame:Saccharin	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision", "Incoherence"]
Aspartame:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision", "Incoherence"]
Saccharin:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Low	["Imprecision", "Incoherence"]
INDIRECT EVIDENCE									
Glucose:Saccharin	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	["Imprecision", "Heterogeneity", "Incoherence"]
Glucose:Water	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	["Imprecision", "Heterogeneity", "Incoherence"]

Table S10. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Sucrose	262.15 (-12.991, 537.291)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	-86.97 (-345.469, 171.529)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Water	0.00 (-3251.947, 3251.947)	-	-	↓	↓	-	-	LOW ⊕⊕
Water vs. Sucrose	349.12 (63.721, 634.519)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Sucralose	-86.97 (-3349.174, 3175.234)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Sucrose	349.12 (-2915.326, 3613.566)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 82 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood GLP-1 incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29) [xx]. Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of GLP-1 iAUC by taking 20% of 412 pmol*mins/L which is the median of the difference in GLP-1 iAUC among healthy participants (~95 pmol*mins/L) and those with type 2 diabetes (~633 pmol*mins/L) after a glucose or meal tolerance test (30). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S11. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Sucrose	1007.80 (675.588, 1340.012)	-	-	↓	-	-	-	MODERATE ⊕⊕
Aspartame vs. Water	23.21 (-238.591, 285.011)	-		↓	↓	-	-	LOW ⊕⊕
Water vs. Sucrose	984.59 (649.367, 1319.813)	-	-	↓	-	-	-	MODERATE ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 94 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood GIP incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of GIP iAUC by taking 20% of 468 pmol*mins/L which is the median of the difference in GIP iAUC among healthy participants (~168 pmol*mins/L) and those with type 2 diabetes (~768 pmol*mins/L) after a glucose or meal tolerance test (31). Significant results are bolded in white. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S12. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GHRELIN response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Sucrose	-29.56 (-357.818, 298.698)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	19.40 (-330.006, 368.806)	-	-	↓	↓	-	-	LOW ⊕⊕
Water vs. Sucrose	-48.96 (-425.914, 327.994)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28) (reference). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 9.8 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood ghrelin incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of ghrelin iAUC by taking 20% of 20% of -49.0 pmol*min/L (sucrose vs. water comparison) which was -9.8 pmol*mins/L. Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S13. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Saccharin	-1203.101 (-7381.296, 4975.093)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	914.930 (-4370.027, 6199.888)	-	-	↓	↓	-	-	LOW ⊕⊕
Saccharin vs. Water	2118.032 (-3598.818, 7834.882)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Glucose	59.273 (-1170.323, 1288.868)	-	-	↓	↓	-	-	LOW ⊕⊕
Saccharin vs. Glucose	1262.374 (-5036.991, 7561.739)	-	-	↓	↓	-	-	LOW ⊕⊕
Water vs. Glucose	-855.658 (-6281.769, 4570.453)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 205 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood glucagon incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of glucagon iAUC by taking 20% of 1025 pmol*mins/L which is the median value of glucagon iAUC (water vs. glucose comparisons) in healthy individuals (~850 pmol*mins/L) and those with type 2 diabetes (~1200 pmol*mins/L). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S14. GRADE assessments of UNCOUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in participants with TYPE 2 DIABETES

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Saccharin	-140.368 (-4533.755, 4253.019)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	1003.800 (-4010.785, 6018.385)	-	-	↓	↓	-	-	LOW ⊕⊕
Saccharin vs. Water	1144.168 (-3847.925, 6136.261)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Glucose	-198.894 (-975.641, 577.854)	-	-	↓	↓	-	-	LOW ⊕⊕
Saccharin vs. Glucose	-58.526 (-4520.048, 4402.997)	-	-	↓	↓	-	-	LOW ⊕⊕
Water vs. Glucose	-1202.694 (-6277.080, 3871.693)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28) (reference). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 205 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood glucagon incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of glucagon iAUC by taking 20% of 1025 pmol*mins/L which is the median value of glucagon iAUC (water vs. glucose comparisons) in healthy individuals (~850 pmol*mins/L) and those with type 2 diabetes (~1200 pmol*mins/L). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S15. GRADE assessments of COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood GLUCOSE response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Aspartame+Ace-K	31.639 (-33.462, 96.739)	↓	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Control	32.538 (-24.927, 90.004)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame+Ace-K vs. Control	0.900 (-29.689, 31.489)	↓	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 100 mmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood glucose incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Thus, we calculated the MID of glucose iAUC by taking 20% of 500 mmol*mins/L which is the median of glucose iAUC in healthy participants (~300 mmol*mins/L) and those with type 2 diabetes (~700 mmol*mins/L) after a 75-g oral glucose tolerance test (32-34). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S16. GRADE assessments of COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood INSULIN response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Unsweetened Control	1718.16 (-2926.557, 6362.877)	↓	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Sucrose	33234.84 (-9197.392, 75667.071)	-	-	↓	↓	-	-	LOW ⊕⊕
Unsweetened Control vs. Sucrose	31516.68 (-11169.005, 74202.364)	↓	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 2250 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood insulin incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of insulin iAUC by taking 20% of 11250 pmol*mins/L which is the median of insulin iAUC in participants with type 2 diabetes (~6200 pmol*mins/L) and healthy participants (~16300 pmol*mins/L) after a 75-g oral glucose tolerance test (32-34). Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S17. OVERALL CIneMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLUCOSE response in HEALTHY participants

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Ace-K + Aspartame:Water	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	Within-study bias
Ace-K + Aspartame + Sucralose:Ace-K + Sucralose	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame + Sucralose:Water	1	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Sucralose:Water	2	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Sucralose	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Aspartame:Water	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Saccharin:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Sucralose:Water	4	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
INDIRECT EVIDENCE									
Ace-K + Aspartame:Ace-K + Aspartame + Sucralose	0	No concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame:Ace-K + Sucralose	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame:Aspartame	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame:Sucralose	0	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Ace-K + Aspartame + Sucralose:Aspartame	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Aspartame	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
Aspartame:Saccharin	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Saccharin:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity

Table S18. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Sucralose	-33.230 (-263.439, 196.979)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Sucralose+Ace-K	43.516 (-264.436, 351.467)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	-9.950 (-269.812, 249.912)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Sucralose+Ace-K	76.746 (-206.631, 360.122)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Water	23.280 (-206.929, 253.489)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose+Ace-K vs. Water	-53.466 (-218.711, 111.780)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 100 mmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood glucose incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Thus, we calculated the MID of glucose iAUC by taking 20% of 500 mmol*mins/L which is the median of glucose iAUC in healthy participants (~300 mmol*mins/L) and those with type 2 diabetes (~700 mmol*mins/L). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S19. OVERALL CINeMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood INSULIN response in HEALTHY participants

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Ace-K + Aspartame + Sucralose:Ace-K + Sucralose	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Water	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Aspartame:Sucralose	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Aspartame:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Saccharin:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Sucralose:Water	4	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
INDIRECT EVIDENCE									
Ace-K + Aspartame + Sucralose:Aspartame	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Aspartame	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Aspartame:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Saccharin:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision

Table S20. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood INSULIN response in participants with TYPE 2 DIABETES

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Sucralose	-6897.480 (-26800.86, 13005.90)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Sucralose+Ace-K	-1254.645 (-33264.83, 30755.54)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	3700.840 (-18897.51, 26299.19)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Sucralose+Ace-K	5642.835 (-25142.04, 36427.71)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Water	10598.320 (-10228.15, 31424.79)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose+Ace-K vs. Water	4955.485 (-17715.34, 27626.31)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 2250 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood insulin incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of insulin iAUC by taking 20% of 11250 pmol*mins/L which is the median of insulin iAUC in participants with type 2 diabetes (~6200 pmol*mins/L) and healthy participants (~16300 pmol*mins/L) after a 75-g oral glucose tolerance test (32-34). Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S21. OVERALL CInEMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLP-1 response in HEALTHY participants

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Ace-K + Aspartame + Sucralose:Ace-K + Sucralose	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Aspartame + Sucralose:Water	1	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Sucralose:Water	2	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Aspartame:Sucralose	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Aspartame:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Saccharin:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Sucralose:Water	3	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
INDIRECT EVIDENCE									
Ace-K + Aspartame + Sucralose:Aspartame	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Ace-K + Sucralose:Aspartame	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	Imprecision, Heterogeneity
Aspartame:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Saccharin:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision

Table S22. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLP-1 response in participants with TYPE 2 DIABETES

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Aspartame vs. Sucralose	-483.260 (-1314.391, 347.871)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Sucralose+Ace-K	-332.706 (-1360.600, 695.188)	-	-	↓	↓	-	-	LOW ⊕⊕
Aspartame vs. Water	-156.770 (-1127.779, 814.239)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Sucralose+Ace-K	150.554 (-790.271, 1091.379)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Water	326.490 (-551.829, 1204.809)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose+Ace-K vs. Water	175.936 (-161.268, 513.141)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 82 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood GLP-1 incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of GLP-1 iAUC by taking 20% of 412 pmol*mins/L which is the median of the difference in GLP-1 iAUC among healthy participants (~95 pmol*mins/L) and those with type 2 diabetes (~633 pmol*mins/L) after a glucose or meal tolerance test (30). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S23. OVERALL CIneMA assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GIP response in HEALTHY participants

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
DIRECT EVIDENCE									
Ace-K + Aspartame + Sucralose:Ace-K + Sucralose	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Water	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Saccharin:Water	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Sucralose:Water	2	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
INDIRECT EVIDENCE									
Ace-K + Aspartame + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Aspartame + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Saccharin	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Ace-K + Sucralose:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision
Saccharin:Sucralose	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Imprecision

Table S24. GRADE assessments of DELAYED COUPLING INTERVENTIONS examining the effect of non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS) and water on postprandial blood GLUCAGON response in HEALTHY participants

Treatments	Effect Estimate	GRADE Assessments						Overall
		1	2	3	4	5	6	
Saccharin vs. Sucralose	-37.122 (-480.123, 405.879)	-	-	↓	↓	-	-	LOW ⊕⊕
Saccharin vs. Sucralose+Ace-K	-183.248 (-722.058, 355.561)	-	-	↓	↓	-	-	LOW ⊕⊕
Saccharin vs. Water	18.340 (-336.407, 373.087)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Sucralose+Ace-K	-146.126 (-630.765, 338.512)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose vs. Water	55.462 (-209.876, 320.800)	-	-	↓	↓	-	-	LOW ⊕⊕
Sucralose+Ace-K vs. Water	201.588 (-203.961, 607.137)	-	-	↓	↓	-	-	LOW ⊕⊕

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trial data, the CINeMA (Confidence in Network Meta-Analysis) web application was unable to make judgements for the six domains. Thus, manual judgements were made based on the CINeMA framework (27, 28). GRADE domains refer to: (1), within-study bias; (2), reporting bias; (3), indirectness; (4), imprecision; (5) heterogeneity; and (6) incoherence. The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was downgraded for imprecision if 95% CIs overlapped the minimally important difference of 205 pmol*min/L. Evidence was downgraded for indirectness due lack of available trial data. There is no general consensus on a clinically important size difference for 2-hour blood glucagon incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of glucagon iAUC by taking 20% of 1025 pmol*mins/L which is the median value of glucagon iAUC (water vs. glucose comparisons) in healthy individuals (~850 pmol*mins/L) and those with type 2 diabetes (~1200 pmol*mins/L). Significant results are bolded in black. Non-significant results are grey and not bolded. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (>1 MID) have a light blue background; moderate effects (>2 MID) have a darker blue background; large effects (>5 to <10 MID) have a purple background; very large effects (>10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕

Table S25. GRADE assessments for outcomes with single direct trial comparisons

Outcome	Population	Treatments	Effect Estimate	GRADE Assessments					
				1	2	3	4	5	Overall
Uncoupling interventions (Beverages were consumed without added energy or nutrients)									
Glucose (mmol*min/L)	IGT (N=20)	Aspartame vs. Glucose	357.7 [-25.1, 740.4]	-	↓	-	↓	-	⊕⊕ LOW
Insulin (pmol*min/L)	IGT (N=20)	Aspartame vs. Glucose	25335.8 [-13636.3, 64307.7]	-	↓	-	↓	-	⊕⊕ LOW
PYY (pmol*min/L)	Healthy (N=8)	Sucralose vs. Water	0.1 [-442.8, 442.8]	-	↓	-	↓	-	⊕⊕ LOW
Delayed coupling interventions (Beverages were consumed as a preload prior to added energy and nutrients as carbohydrate)									
Glucose (mmol*min/L)	PLWO (N=11)	Sucralose vs. Water	-30.0 [-87.3, 27.3]	-	↓	-	↓	-	⊕⊕ LOW
	T1D (N=9)	Ace-K+Sucralose vs. Water	-64.0 [-233.1, 105.3]	-	↓	-	↓	-	⊕⊕ LOW
Insulin (pmol*min/L)	PLWO (N=11)	Sucralose vs. Water	-8200.0 [-31642.4, 15242.4]	-	↓	-	↓	-	⊕⊕ LOW
	T1D (N=9)	Ace-K+Sucralose vs. Water	-543.9 [-1779.2, 691.5]	-	↓	-	↓	-	⊕⊕ LOW
GLP-1 (pmol*min/L)	T1D (N=9)	Ace-K+Sucralose vs. Water	-433.5 [-1134.4, 267.5]	-	↓	-	↓	-	⊕⊕ LOW
GIP (pmol*min/L)	T1D (N=9)	Ace-K+Sucralose vs. Water	-934.8 [-2215.7, 346.1]	-	↓	-	↓	-	⊕⊕ LOW
	T2D (N=9)	Ace-K+Sucralose vs. Water	-479.8 [-2181.5, 1222.1]	-	↓	-	↓	-	⊕⊕ LOW
Glucagon (pmol*min/L)	T1D (N=9)	Ace-K+Sucralose vs. Water	-20.3 [-97.4, 46.8]	-	↓	-	↓	-	⊕⊕ LOW
	T2D (N=10)	Ace-K+Sucralose vs. Water	241.9 [-38.8, 522.5]	-	↓	-	↓	-	⊕⊕ LOW

Data reported as mean difference with 95% confidence intervals (CIs). Due to lack of available trials, the CINeMA (Confidence in Network Meta-Analysis) web application could not be utilized. Confidence in the effect estimates were assessed using the traditional GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach (35). GRADE domains refer to: (1), risk of bias; (2), imprecision; (3), inconsistency; (4), indirectness; and (5), publication bias. The following minimally important differences (MID) were utilized: glucose (100 mmol*min/L), insulin (2250 pmol*mins/L), GLP-1 (82 pmol*mins/L), GIP (94 pmol*mins/L), glucagon (205 pmol*mins/L) and PYY (200 pmol*mins/L). The risk of bias domain was assessed using the Cochrane RoB2 tool (no downgrade if there was no concern for overall risk of bias; downgraded if there was some or major concern for overall risk of bias). Evidence was double downgraded for imprecision due to availability of only a single trial. Inconsistency and publication bias could not be assessed due to limited trial data and thus, no downgrades were applied. ↓ downgrade; “-”, no downgrade. IGT, impaired glucose tolerance; PLWO, participants living with obesity; T1D, type 1 diabetes; T2D, type 2 diabetes. 2

Figure S1. Formulas used to compute incremental area under the curve (iAUC) for primary and secondary outcomes

Incremental area under the curve (iAUC)

$$iAUC = \frac{(A + B) \times t}{2} + \frac{(B + C) \times t}{2} + \frac{(C + D) \times t}{2} + \frac{(D + E) \times t}{2} \text{ etc ...}$$

Standard error (SE) computation for iAUC

$$SE \text{ of } iAUC = \sqrt{t^2 + \text{average } SE^2}$$

The iAUC for glucose and insulin was calculated geometrically using the trapezoid rule (36) where A, B, C, D, and E represent positive glucose and insulin increments, and t is the time interval between blood samples. The standard error of the iAUC was computed using the propagation of error approach for area (37). t represents the duration of follow-up and average SE is the average of the SE at individual time points on the glucose and insulin curves.

Figure S2. Flow of literature

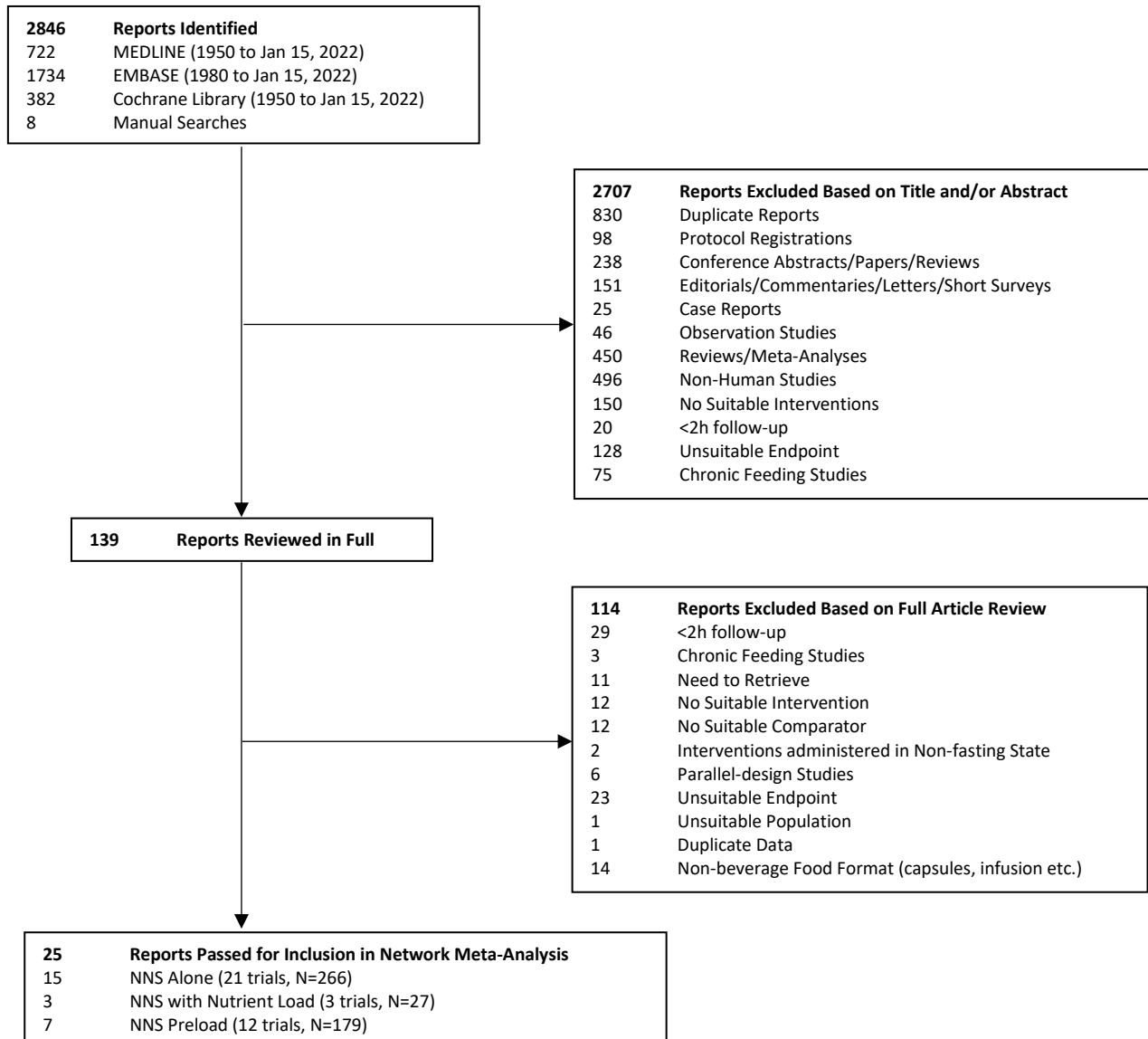


Figure S3. Individual (top) and summary (bottom) risk of bias assessments of studies with UNCOUPLING INTERVENTIONS



Figure S4. Individual (top) and summary (bottom) risk of bias assessment of studies with COUPLING INTERVENTIONS

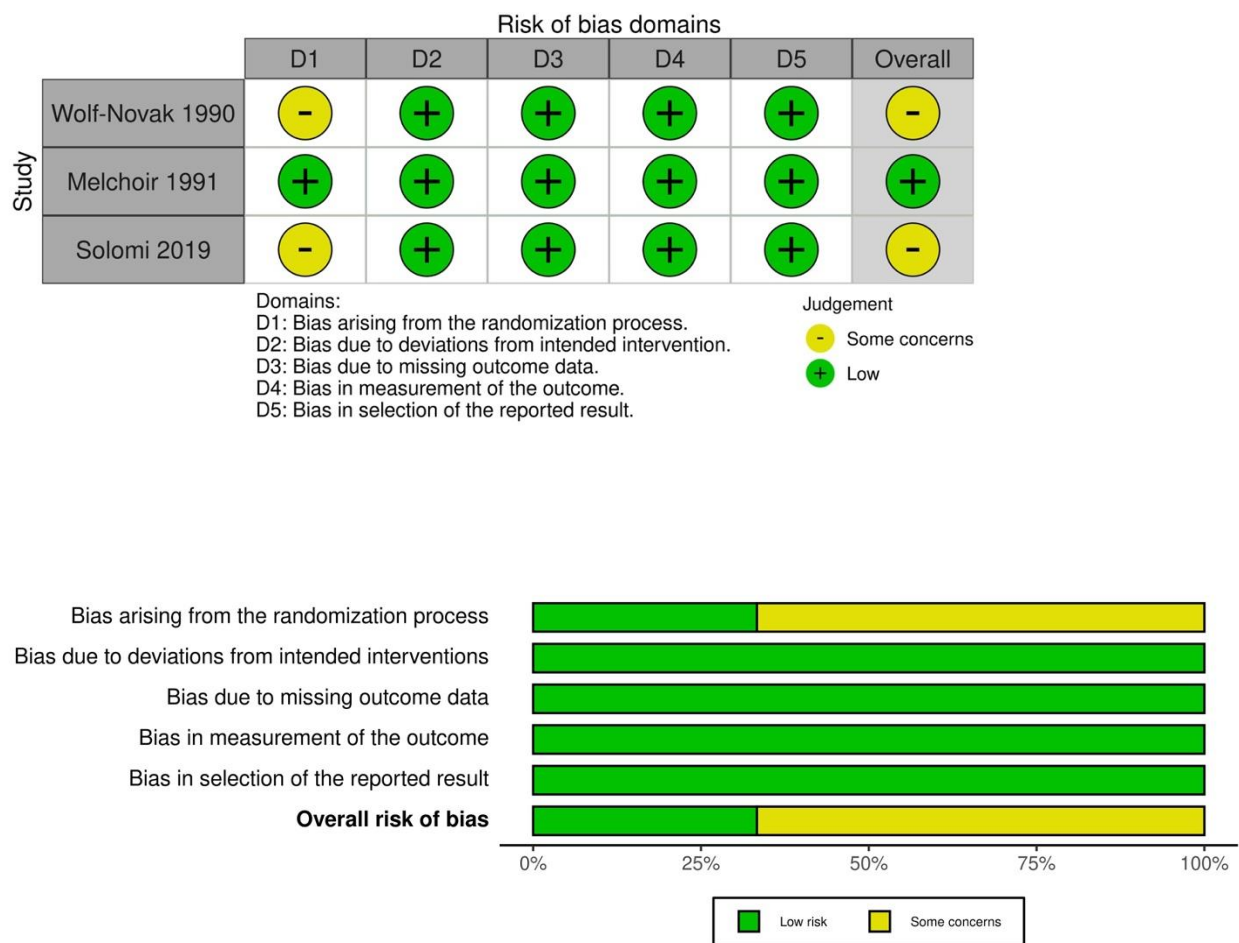


Figure S5. Individual (top) and summary (bottom) risk of bias assessment of studies with DELAYED COUPLING INTERVENTIONS

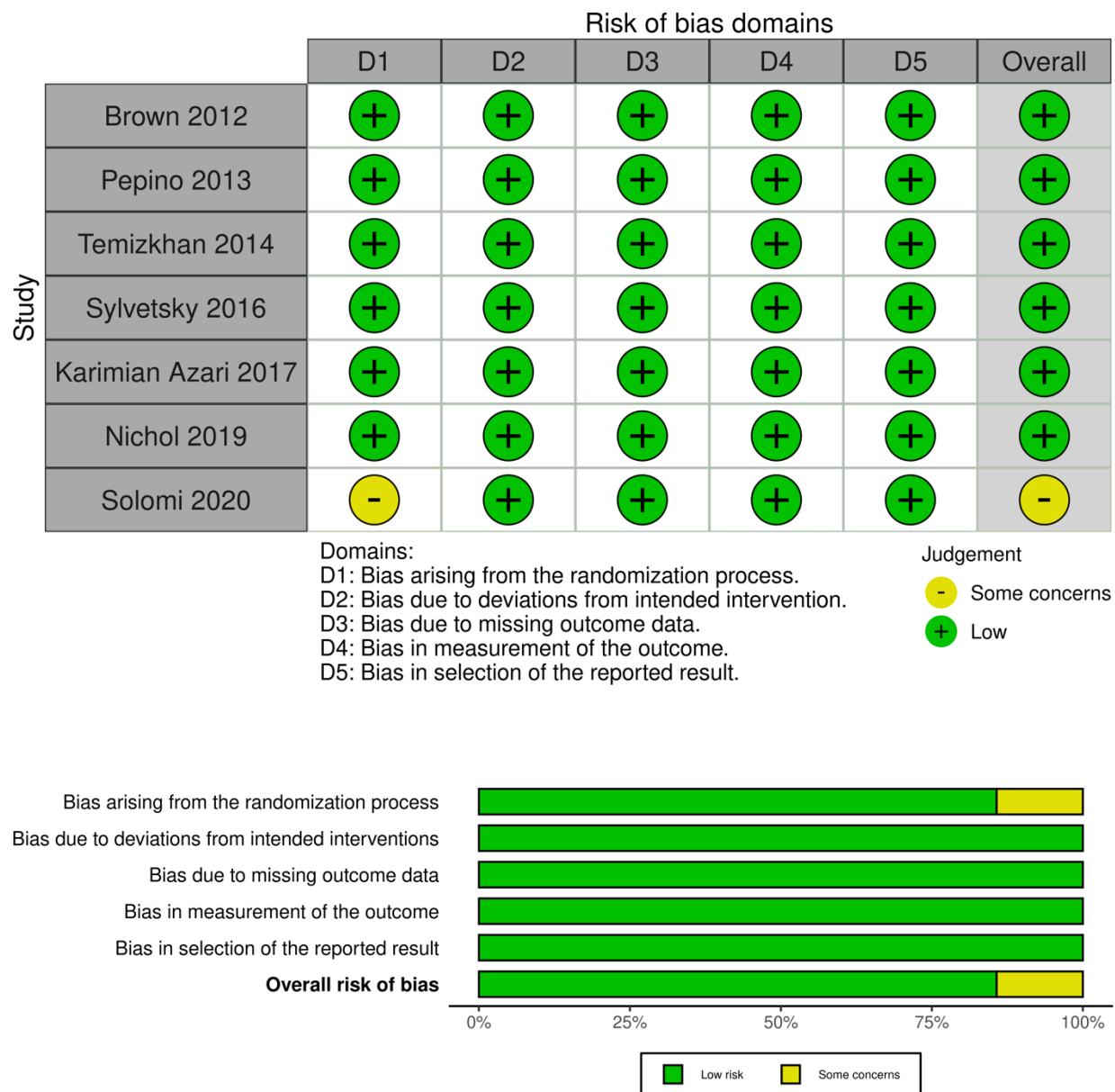
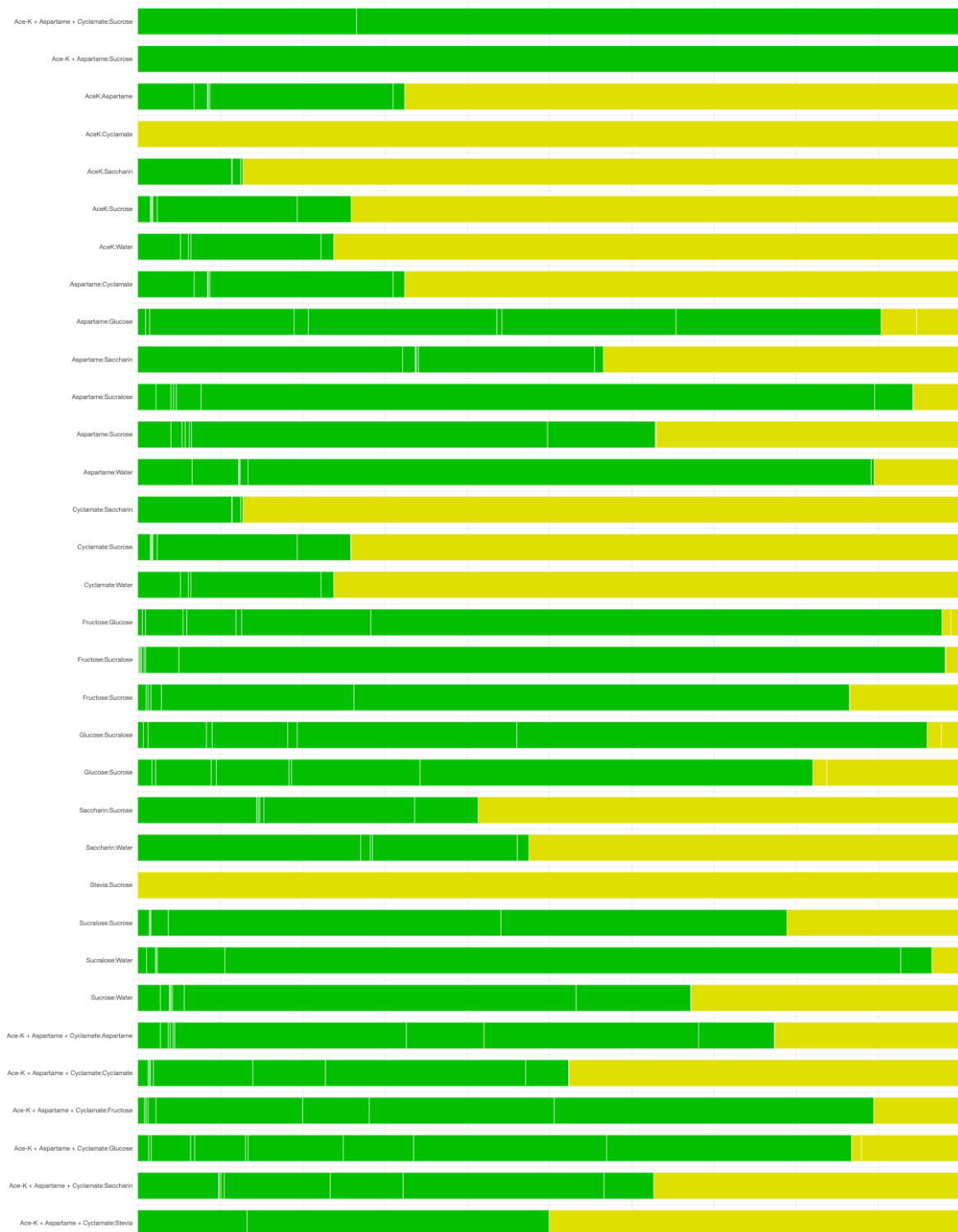
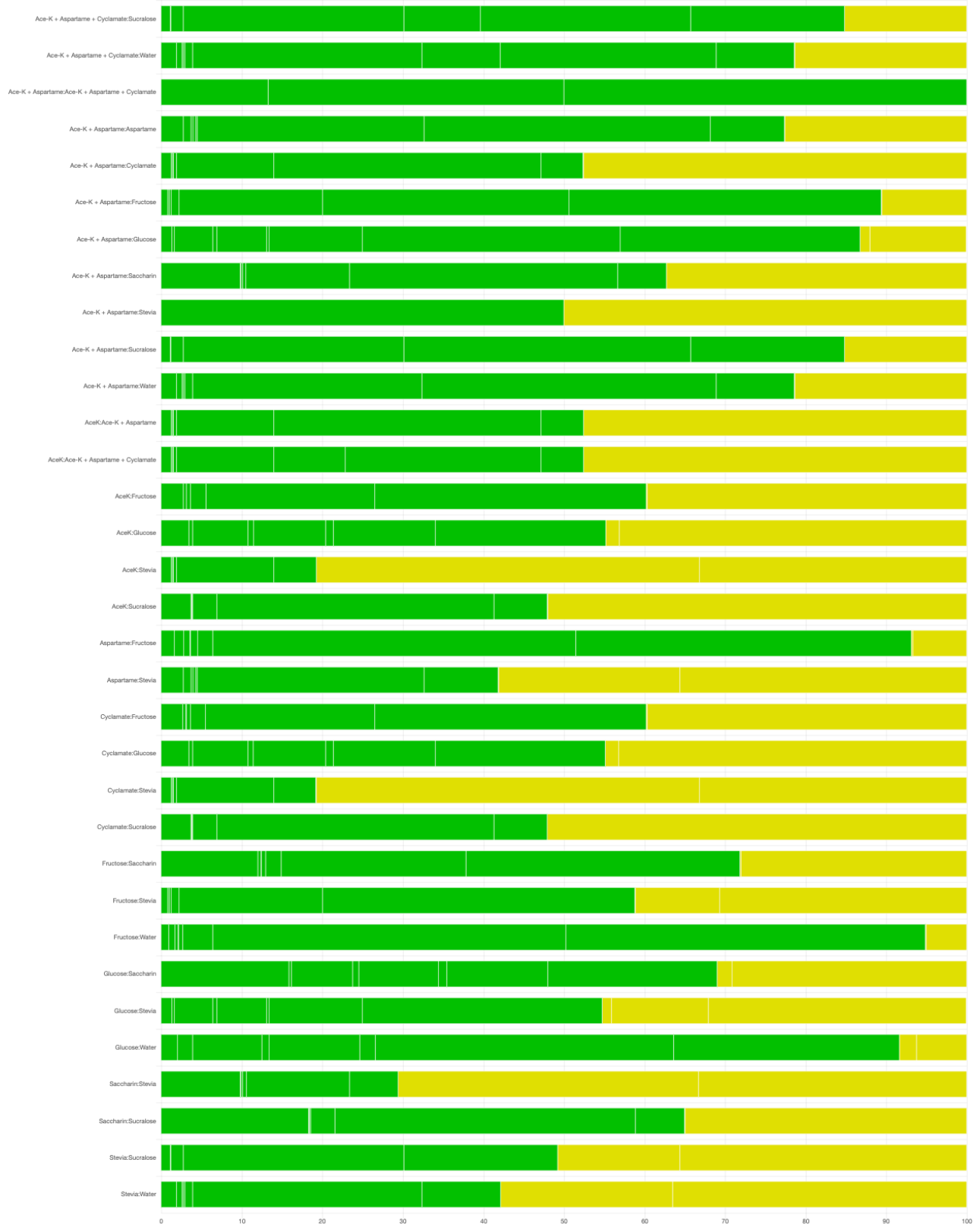


Figure S6. Risk of bias assessment of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants





Green = no concerns; yellow = some concerns; red = major concerns

Figure S7. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants



<p>Comparison Sucralose:Sucrose Evidence: mixed</p> <p>NMA estimate: -105.458 95% Confidence interval: Confidence interval (-137.729,-73.186) interval does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Sucralose:Water Evidence: mixed</p> <p>NMA estimate: 6.790 95% Confidence interval: Confidence interval (-7.610,21.191) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Sucrose:Water Evidence: mixed</p> <p>NMA estimate: 112.248 95% Confidence interval: Confidence interval (81.526,142.970) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Ace-K + Aspartame + Cyclamate Evidence: indirect</p> <p>NMA estimate: 5.660 95% Confidence interval: Confidence interval (-43.448,54.769) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>
<p>Comparison Evidence: Ace-K:Ace-K + Aspartame indirect</p> <p>NMA estimate: -56.642 95% Confidence interval: Confidence interval (-105.342,-7.942) interval does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Aspartame Evidence: indirect</p> <p>NMA estimate: 54.611 95% Confidence interval: Confidence interval (13.703,95.519) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Cyclamate Evidence: indirect</p> <p>NMA estimate: 58.922 95% Confidence interval: Confidence interval (10.126,107.718) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Fructose Evidence: indirect</p> <p>NMA estimate: 16.089 95% Confidence interval: Confidence interval (-31.239,63.416) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>
<p>Comparison Ace-K + Aspartame:Glucose Evidence: indirect</p> <p>NMA estimate: -183.205 95% Confidence interval: Confidence interval (-251.404,-115.007) interval does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Saccharin Evidence: indirect</p> <p>NMA estimate: 47.529 95% Confidence interval: Confidence interval (1.808,93.249) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Evidence: Ace-K + Aspartame:Stevia indirect</p> <p>NMA estimate: 10.833 95% Confidence interval: Confidence interval (-38.956,60.623) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Sucralose Evidence: indirect</p> <p>NMA estimate: 57.291 95% Confidence interval: Confidence interval (16.368,98.214) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>
<p>Comparison Evidence: Ace-K + Aspartame:Water indirect</p> <p>NMA estimate: 64.081 95% Confidence interval: Confidence interval (24.369,103.794) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K:Ace-K + Aspartame + Cyclamate Evidence: indirect</p> <p>NMA estimate: -50.982 95% Confidence interval: Confidence interval (-110.284,8.321) extends into clinically important effects</p> <p>Imprecision judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Aspartame Evidence: indirect</p> <p>NMA estimate: 48.950 95% Confidence interval: Confidence interval (-4.141,102.041) extends into clinically important effects</p> <p>Imprecision judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Cyclamate Evidence: indirect</p> <p>NMA estimate: 53.262 95% Confidence interval: Confidence interval (-6.120,112.643) extends into clinically important effects</p> <p>Imprecision judgment Some concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Fructose Evidence: indirect</p> <p>NMA estimate: 10.428 95% Confidence interval: Confidence interval (-47.753,68.609) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Glucose Evidence: indirect</p> <p>NMA estimate: -188.866 95% Confidence interval: Confidence interval (-264.998,-112.733) interval does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Saccharin Evidence: indirect</p> <p>NMA estimate: 41.868 95% Confidence interval: Confidence interval (-15.013,98.750) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Stevia Evidence: indirect</p> <p>NMA estimate: 5.173 95% Confidence interval: Confidence interval (-55.028,65.373) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Sucralose Evidence: indirect</p> <p>NMA estimate: 51.630 95% Confidence interval: Confidence interval (-1.472,104.733) extends into clinically important effects</p> <p>Imprecision judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Water Evidence: indirect</p> <p>NMA estimate: 58.421 95% Confidence interval: Confidence interval (6.246,110.596) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K:Fructose Evidence: indirect</p> <p>NMA estimate: -40.553 95% Confidence interval: Confidence interval (-82.931,1.824) does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>	<p>Comparison Ace-K:Glucose Evidence: indirect</p> <p>NMA estimate: -239.847 95% Confidence interval: Confidence interval (-303.945,-175.749) interval does not cross clinically important effect</p> <p>Imprecision judgment No concerns</p>

Comparison AceK:Stevia Evidence: indirect NMA estimate: -45.809 95% Confidence interval: (-105.676,14.059) <i>interval extends into clinically important effects</i> Imprecision judgment Some concerns ▼	Comparison AceK:Sucralose Evidence: indirect NMA estimate: 0.649 95% Confidence interval: (-34.325,35.623) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Aspartame:Fructose Evidence: indirect NMA estimate: -38.522 95% Confidence interval: (-68.479,-8.565) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Aspartame:Stevia Evidence: indirect NMA estimate: -43.777 95% Confidence interval: (-97.498,9.944) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼
Comparison Cyclamate:Fructose Evidence: indirect NMA estimate: -42.833 95% Confidence interval: (-85.321,-0.345) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Cyclamate:Glucose Evidence: indirect NMA estimate: -242.127 95% Confidence interval: (-306.299,-177.956) <i>interval does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Cyclamate:Stevia Evidence: indirect NMA estimate: -48.089 95% Confidence interval: (-108.035,11.857) <i>interval extends into clinically important effects</i> Imprecision judgment Some concerns ▼	Comparison Cyclamate:Sucralose Evidence: indirect NMA estimate: -1.631 95% Confidence interval: (-36.739,33.477) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼
Comparison Fructose:Saccharin Evidence: indirect NMA estimate: 31.440 95% Confidence interval: (-6.609,69.490) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Fructose:Stevia Evidence: indirect NMA estimate: -5.255 95% Confidence interval: (-64.012,53.502) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Fructose:Water Evidence: indirect NMA estimate: 47.993 95% Confidence interval: (20.043,75.943) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Glucose:Saccharin Evidence: indirect NMA estimate: 230.734 95% Confidence interval: (169.572,291.896) <i>interval does not cross clinically important effect</i> Imprecision judgment No concerns ▼
Comparison Glucose:Stevia Evidence: indirect NMA estimate: 194.038 95% Confidence interval: (117.465,270.612) <i>interval does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Glucose:Water Evidence: indirect NMA estimate: 247.287 95% Confidence interval: (191.300,303.273) <i>interval does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Saccharin:Stevia Evidence: indirect NMA estimate: -36.696 95% Confidence interval: (-94.166,20.775) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Saccharin:Sucralose Evidence: indirect NMA estimate: 9.762 95% Confidence interval: (-19.815,39.340) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼
Comparison Stevia:Sucralose Evidence: indirect NMA estimate: 46.458 95% Confidence interval: (-7.275,100.190) <i>extends into clinically important effects</i> Imprecision judgment Some concerns ▼	Comparison Stevia:Water Evidence: indirect NMA estimate: 53.248 95% Confidence interval: (0.432,106.064) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼		

Relative effect estimates below -100.0 and above 100.0 mmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CiNEMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood glucose incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Thus, we calculated the MID of glucose iAUC by taking 20% of 500 mmol*mins/L which is the median of glucose iAUC in healthy participants (~300 mmol*mins/L) and those with type 2 diabetes (~700 mmol*mins/L) after a 75-g oral glucose tolerance test (32-34).

Figure S8. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants



(continued on next page)

<p>Comparison Fructose:Glucose Evidence: mixed</p> <p>NMA estimate: -199.294 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-260.661,-137.927) interval: (-268.207,-130.380)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Fructose:Sucralose Evidence: mixed</p> <p>NMA estimate: 41.202 95% intervals for NMA estimate</p> <p>Confidence interval: (17.206,65.199) Prediction interval: (14.255,68.150)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Fructose:Sucrose Evidence: mixed</p> <p>NMA estimate: -64.255 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-104.338,-24.172) interval: (-109.267,-19.243)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Glucose:Sucralose Evidence: mixed</p> <p>NMA estimate: 240.496 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (183.900,297.092) interval: (176.940,304.052)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Glucose:Sucrose Evidence: mixed</p> <p>NMA estimate: 135.038 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction interval:(71.652,198.425) interval: (63.858,206.220)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Saccharin:Sucrose Evidence: mixed</p> <p>NMA estimate: -95.695 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-133.868,-57.523) interval: (-138.562,-52.829)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Saccharin:Water Evidence: mixed</p> <p>NMA estimate: 16.553 95% intervals for NMA estimate</p> <p>Confidence interval: (-9.559,42.664) Prediction interval: (-12.770,45.875)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Stevia:Sucrose Evidence: mixed</p> <p>NMA estimate: -59.000 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-101.962,-16.038) interval: (-107.245,-10.755)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Sucralose:Sucrose Evidence: mixed</p> <p>NMA estimate: -105.458 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-137.729,-73.186) interval: (-141.698,-69.218)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Sucralose:Water Evidence: mixed</p> <p>NMA estimate: 6.790 95% intervals for NMA estimate</p> <p>Confidence interval: (-7.610,21.191) Prediction interval: (-9.381,22.962)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Sucrose:Water Evidence: mixed</p> <p>NMA estimate: 112.248 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction interval:(81.526,142.970) interval: (77.748,146.748)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Ace-K + Aspartame + Cyclamate Evidence: indirect</p> <p>NMA estimate: 5.660 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction interval: (-43.448,54.769) interval: (-49.487,60.808)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Ace-K + Aspartame:Glucose Evidence: indirect</p> <p>NMA estimate: -56.642 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-105.342,-7.942) interval: (-111.330,-1.954)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Aspartame Evidence: indirect</p> <p>NMA estimate: 54.611 95% intervals for NMA estimate</p> <p>Confidence interval: (13.703,95.519) Prediction interval: (8.672,100.549)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame:Cyclamate Evidence: indirect</p> <p>NMA estimate: 58.922 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction interval:(10.126,107.718) interval: (4.125,113.719)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Fructose Evidence: indirect</p> <p>NMA estimate: 16.089 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction interval: (-31.239,63.416) interval: (-37.059,69.236)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Ace-K + Aspartame:Glucose Evidence: indirect</p> <p>NMA estimate: -183.205 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction (-251.404,-115.007) interval: (-259.790,-106.620)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Saccharin Evidence: indirect</p> <p>NMA estimate: 47.529 95% intervals for NMA estimate</p> <p>Confidence interval: (1.808,93.249) Prediction interval: (-3.814,98.872)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Evidence:Ace-K + Aspartame:Stevia Evidence: indirect</p> <p>NMA estimate: 10.833 95% intervals for NMA estimate</p> <p>Confidence interval: Prediction interval: (-38.956,60.623) interval: (-45.078,66.745)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Sucralose Evidence: indirect</p> <p>NMA estimate: 57.291 95% intervals for NMA estimate</p> <p>Confidence interval: (16.368,98.214) Prediction interval: (11.336,103.246)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>

(continued on next page)

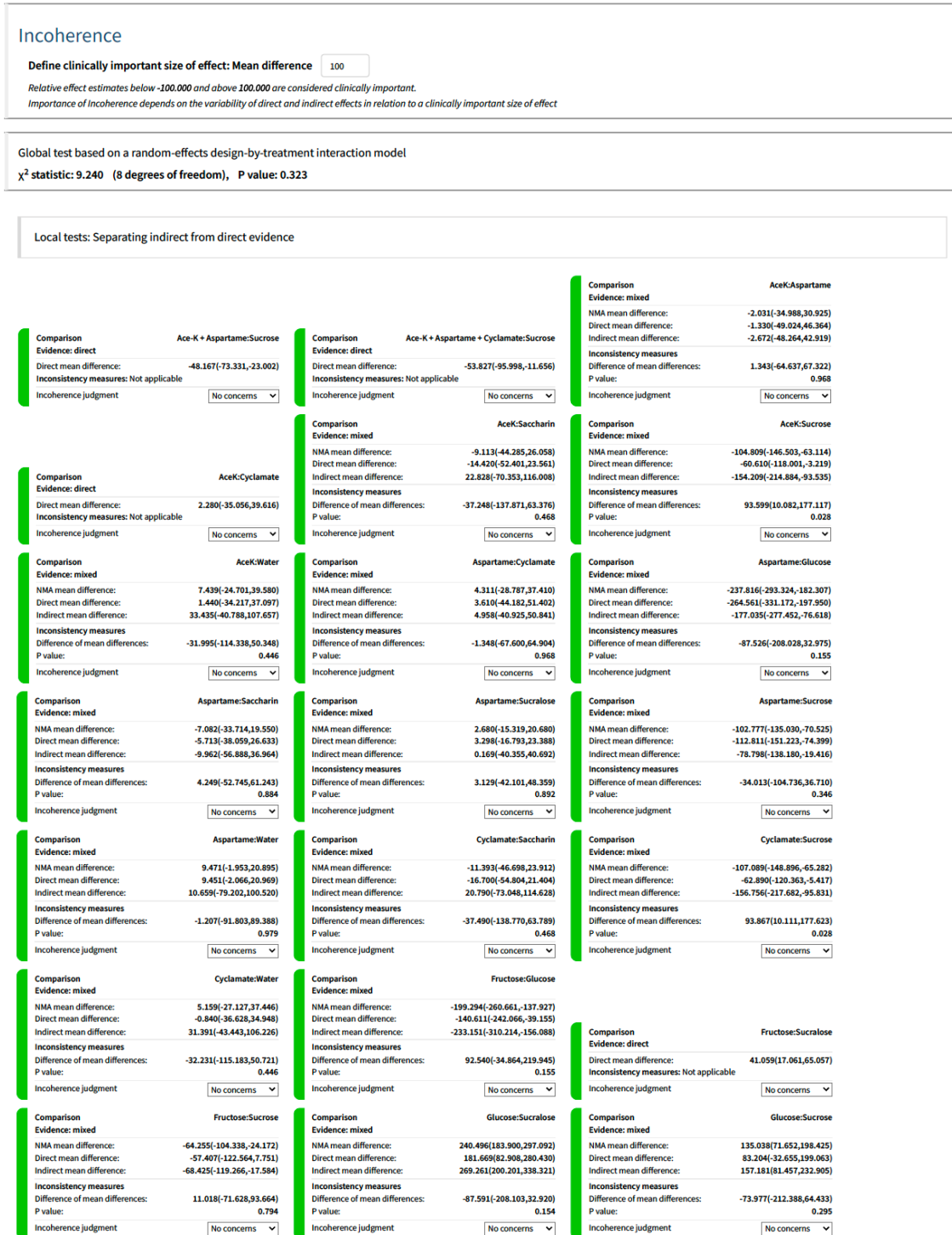
<p>Comparison Evidence: Ace-K + Aspartame:Water indirect</p> <p>NMA estimate: 64.081 95% intervals for NMA estimate Confidence interval: Prediction interval:(24.369,103.794) Confidence and (19.485,108.677) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison AceK:Ace-K + Aspartame + Cyclamate Evidence: indirect</p> <p>NMA estimate: -50.982 95% intervals for NMA estimate Confidence interval: Prediction interval: (-110.284,8.321) Confidence and (-117.577,15.614) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Aspartame Evidence: indirect</p> <p>NMA estimate: 48.950 95% intervals for NMA estimate Confidence interval: Prediction interval: (-4.141,102.041) Confidence and (-10.669,108.569) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Cyclamate Evidence: indirect</p> <p>NMA estimate: 53.262 95% intervals for NMA estimate Confidence interval: Prediction interval: (-6.120,112.643) Confidence and (-13.422,119.946) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Fructose Evidence: indirect</p> <p>NMA estimate: 10.428 95% intervals for NMA estimate Confidence interval: Prediction interval: (-47.753,68.609) Confidence and (-54.907,75.764) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Glucose Evidence: indirect</p> <p>NMA estimate: -188.866 95% intervals for NMA estimate Prediction interval: (-264.998,-112.733) interval: (-274.361,-103.371) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Saccharin Evidence: indirect</p> <p>NMA estimate: 41.868 95% intervals for NMA estimate Confidence interval: Prediction interval: (-15.013,98.750) Prediction interval (-22.008,105.745) <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Stevia Evidence: indirect</p> <p>NMA estimate: 5.173 95% intervals for NMA estimate Confidence interval: Prediction interval: (-55.028,65.373) Confidence and (-62.431,72.776) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Sucralose Evidence: indirect</p> <p>NMA estimate: 51.630 95% intervals for NMA estimate Confidence interval: Prediction interval: (-1.472,104.733) Confidence and (-8.002,111.263) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Water Evidence: indirect</p> <p>NMA estimate: 58.421 95% intervals for NMA estimate Confidence interval: (6.246,110.596) Prediction interval: (-0.170,117.012) Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison AceK:Fructose Evidence: indirect</p> <p>NMA estimate: -40.553 95% intervals for NMA estimate Confidence interval: (-82.931,1.824) Prediction interval: (-88.142,7.035) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison AceK:Glucose Evidence: indirect</p> <p>NMA estimate: -239.847 95% intervals for NMA estimate Confidence interval: Prediction interval: (-303.945,-175.749) interval: (-311.828,-167.867) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison AceK:Stevia Evidence: indirect</p> <p>NMA estimate: -45.809 95% intervals for NMA estimate Confidence interval: Prediction interval: (-105.676,14.059) interval: (-113.038,21.421) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison AceK:Sucralose Evidence: indirect</p> <p>NMA estimate: 0.649 95% intervals for NMA estimate Confidence interval: Prediction interval: (-34.325,35.623) Confidence and (-38.626,39.924) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Aspartame:Fructose Evidence: indirect</p> <p>NMA estimate: -38.522 95% intervals for NMA estimate Confidence interval: (-68.479,-8.565) Prediction interval: (-72.162,-4.881) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Aspartame:Stevia Evidence: indirect</p> <p>NMA estimate: -43.777 95% intervals for NMA estimate Confidence interval: (-97.498,9.944) Prediction interval: Prediction interval (-104.105,16.550) <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>
<p>Comparison Cyclamate:Fructose Evidence: indirect</p> <p>NMA estimate: -42.833 95% intervals for NMA estimate Confidence interval: (-85.321,-0.345) Prediction interval: (-90.546,4.880) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Cyclamate:Glucose Evidence: indirect</p> <p>NMA estimate: -242.127 95% intervals for NMA estimate Confidence interval: Prediction interval: (-306.299,-177.956) interval: (-314.190,-170.065) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Cyclamate:Stevia Evidence: indirect</p> <p>NMA estimate: -48.089 95% intervals for NMA estimate Confidence interval: Prediction interval: (-108.035,11.857) interval: (-115.406,19.229) Confidence and prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Cyclamate:Sucralose Evidence: indirect</p> <p>NMA estimate: -1.631 95% intervals for NMA estimate Confidence interval: Prediction interval: (-36.739,33.477) Confidence and (-41.056,37.794) prediction intervals <i>agree</i> in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>

(continued on next page)

<p>Comparison Fructose:Saccharin</p> <p>Evidence: indirect</p> <p>NMA estimate: 31.440</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (-6.609,69.490)</p> <p>Prediction interval: (-11.289,74.169)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>	<p>Comparison Fructose:Stevia</p> <p>Evidence: indirect</p> <p>NMA estimate: -5.255</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (-64.012,53.502)</p> <p>Prediction interval: (-71.238,60.727)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>	<p>Comparison Fructose:Water</p> <p>Evidence: indirect</p> <p>NMA estimate: 47.993</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (20.043,75.943)</p> <p>Prediction interval: (16.606,79.380)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>	<p>Comparison Glucose:Saccharin</p> <p>Evidence: indirect</p> <p>NMA estimate: 230.734</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (169.572,291.896)</p> <p>Prediction interval: (162.051,299.417)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>
<p>Comparison Glucose:Stevia</p> <p>Evidence: indirect</p> <p>NMA estimate: 194.038</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (117.465,270.612)</p> <p>Prediction interval: (108.048,280.029)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>	<p>Comparison Glucose:Water</p> <p>Evidence: indirect</p> <p>NMA estimate: 247.287</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (191.300,303.273)</p> <p>Prediction interval: (184.415,310.158)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>	<p>Comparison Saccharin:Stevia</p> <p>Evidence: indirect</p> <p>NMA estimate: -36.696</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (-94.166,20.775)</p> <p>Prediction interval: (-101.233,27.842)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment</p> <p>Some concerns ▼</p>	<p>Comparison Saccharin:Sucralose</p> <p>Evidence: indirect</p> <p>NMA estimate: 9.762</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (-19.815,39.340)</p> <p>Prediction interval: (-23.452,42.977)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>
<p>Comparison Stevia:Sucralose</p> <p>Evidence: indirect</p> <p>NMA estimate: 46.458</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (-13.882,106.798)</p> <p>Prediction interval: (-7.275,100.190)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment</p> <p>No concerns ▼</p>	<p>Comparison Stevia:Water</p> <p>Evidence: indirect</p> <p>NMA estimate: 53.248</p> <p>95% intervals for NMA estimate</p> <p>Confidence interval: (0.432,106.064)</p> <p>Prediction interval: (-6.063,112.559)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment</p> <p>Some concerns ▼</p>		

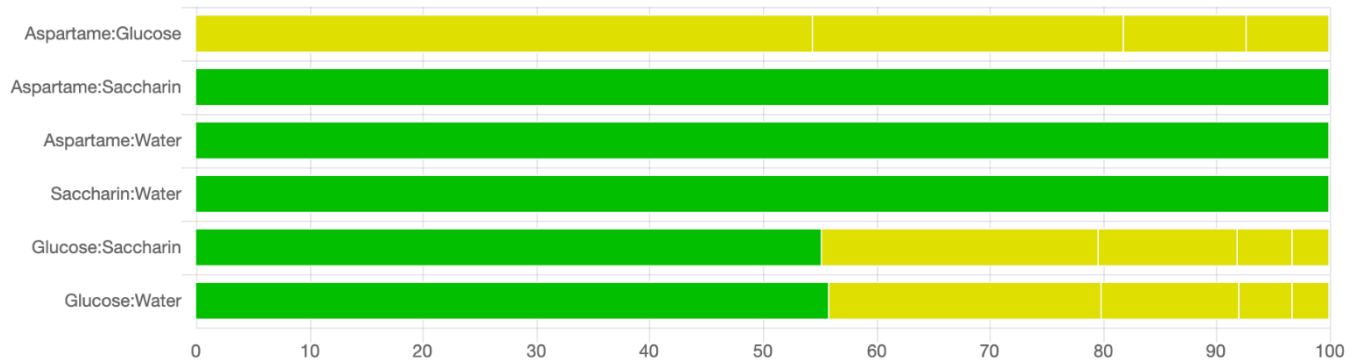
Judgements for were assigned by the CiNEMA algorithm (27, 28).

Figure S9. CIneMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants



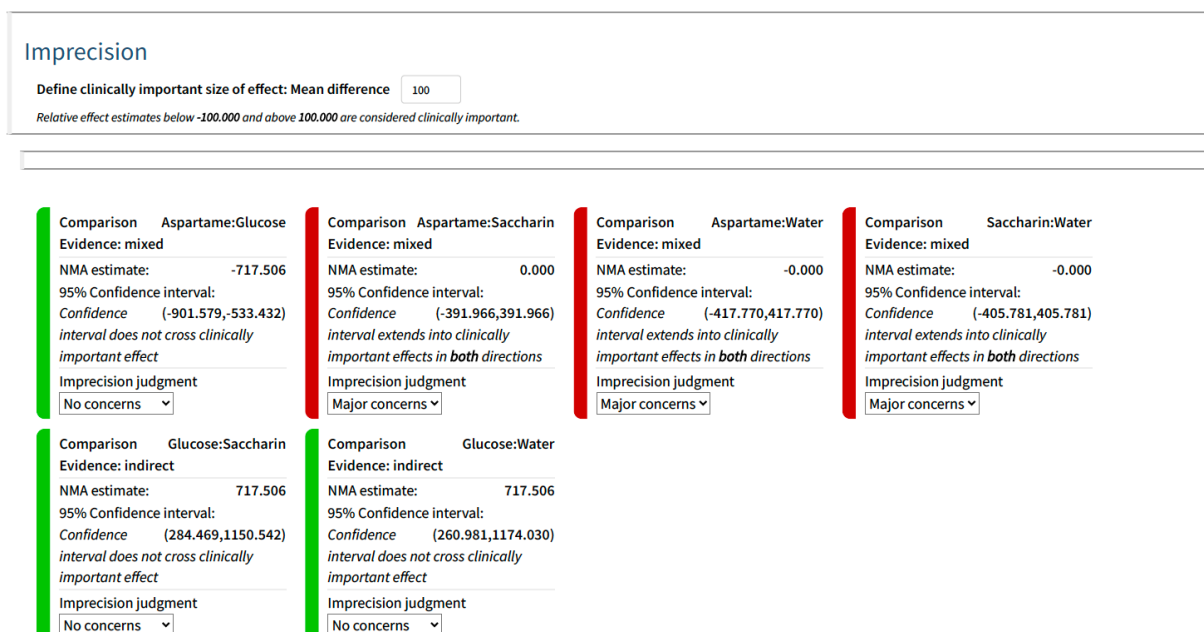
Comparison Evidence: mixed NMA mean difference: -95.695(-133.868,-57.523) Direct mean difference: -46.190(-104.084,11.704) Indirect mean difference: -133.769(-184.541,-82.998) Inconsistency measures Difference of mean differences: 87.579(10.576,164.583) P value: 0.026 Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 16.553(-9.559,42.664) Direct mean difference: 9.847(-19.181,38.875) Indirect mean difference: 44.982(-14.788,104.753) Inconsistency measures Difference of mean differences: -35.135(-101.582,31.311) P value: 0.300 Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: direct Direct mean difference: -59.000(-101.962,-16.038) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: mixed NMA mean difference: -105.458(-137.729,-73.186) Direct mean difference: -127.048(-165.034,-89.062) Indirect mean difference: -49.458(-110.635,11.720) Inconsistency measures Difference of mean differences: -77.590(-149.602,-5.579) P value: 0.035 Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 6.790(-7.610,21.191) Direct mean difference: 5.194(-9.615,20.002) Indirect mean difference: 34.584(-27.202,96.369) Inconsistency measures Difference of mean differences: -29.390(-92.925,34.145) P value: 0.365 Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 112.248(81.526,142.970) Direct mean difference: 116.172(80.477,151.868) Indirect mean difference: 101.035(40.699,161.372) Inconsistency measures Difference of mean differences: 15.137(-54.968,85.242) P value: 0.672 Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 5.660(-43.448,54.769) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -56.642(-105.342,-7.942) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 54.611(13.703,95.519) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 58.922(10.126,107.718) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 16.089(-31.239,63.416) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -183.205(-251.404,-115.007) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 47.529(1.808,93.249) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 10.833(-38.956,60.623) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 57.291(16.368,98.214) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 64.081(24.369,103.794) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -50.982(-110.284,8.321) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 48.950(-4.141,102.041) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 53.262(-6.120,112.643) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 10.428(-47.753,68.609) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -188.866(-264.998,-112.733) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 41.868(-15.013,98.750) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 5.173(-55.028,65.373) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 51.630(-147.102,733) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 58.421(6.246,110.596) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -40.553(-82.931,1.824) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -239.847(-303.945,-175.749) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -45.809(-105.676,14.059) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 0.649(-34.325,35.623) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -38.522(-68.479,-8.565) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -43.777(-97.498,9.944) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -42.833(-85.321,-0.345) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -242.127(-306.299,-177.956) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -48.089(-108.035,11.857) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -1.631(-36.739,33.477) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 31.440(-6.609,69.490) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -5.255(-64.012,53.502) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 47.993(20.043,75.943) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 230.734(169.572,291.896) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 194.038(117.465,270.612) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 247.287(191.300,303.273) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -36.696(-94.166,20.775) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 9.762(-19.815,39.340) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 46.458(-7.275,100.190) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 53.248(0.432,106.064) Inconsistency measures: Not applicable Incoherence judgment <input type="button" value="No concerns"/>

Figure S10. Risk of bias assessment of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES



Green = no concerns; yellow = some concerns; red = major concerns

Figure S11. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES



Relative effect estimates below -100.0 and above 100.0 mmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CINeMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood glucose incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Thus, we calculated the MID of glucose iAUC by taking 20% of 500 mmol*mins/L which is the median of glucose iAUC in healthy participants (~300 mmol*mins/L) and those with type 2 diabetes (~700 mmol*mins/L) after a 75-g oral glucose tolerance test (32-34).

Figure S12. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES

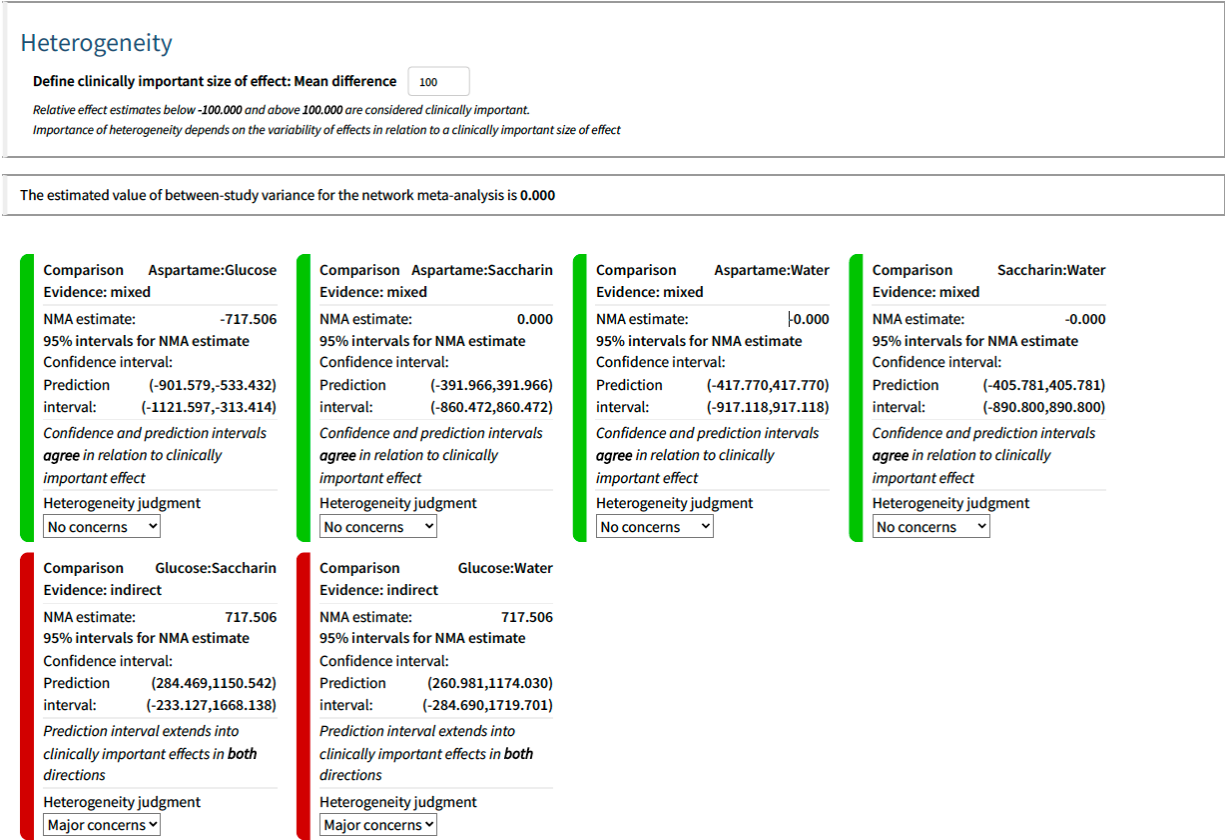
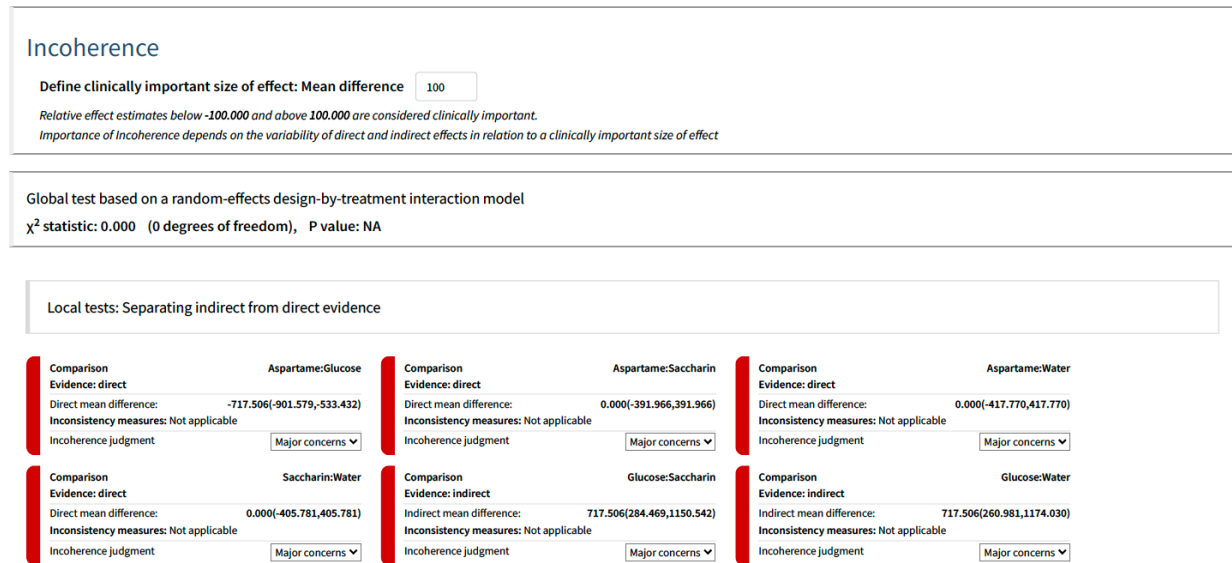
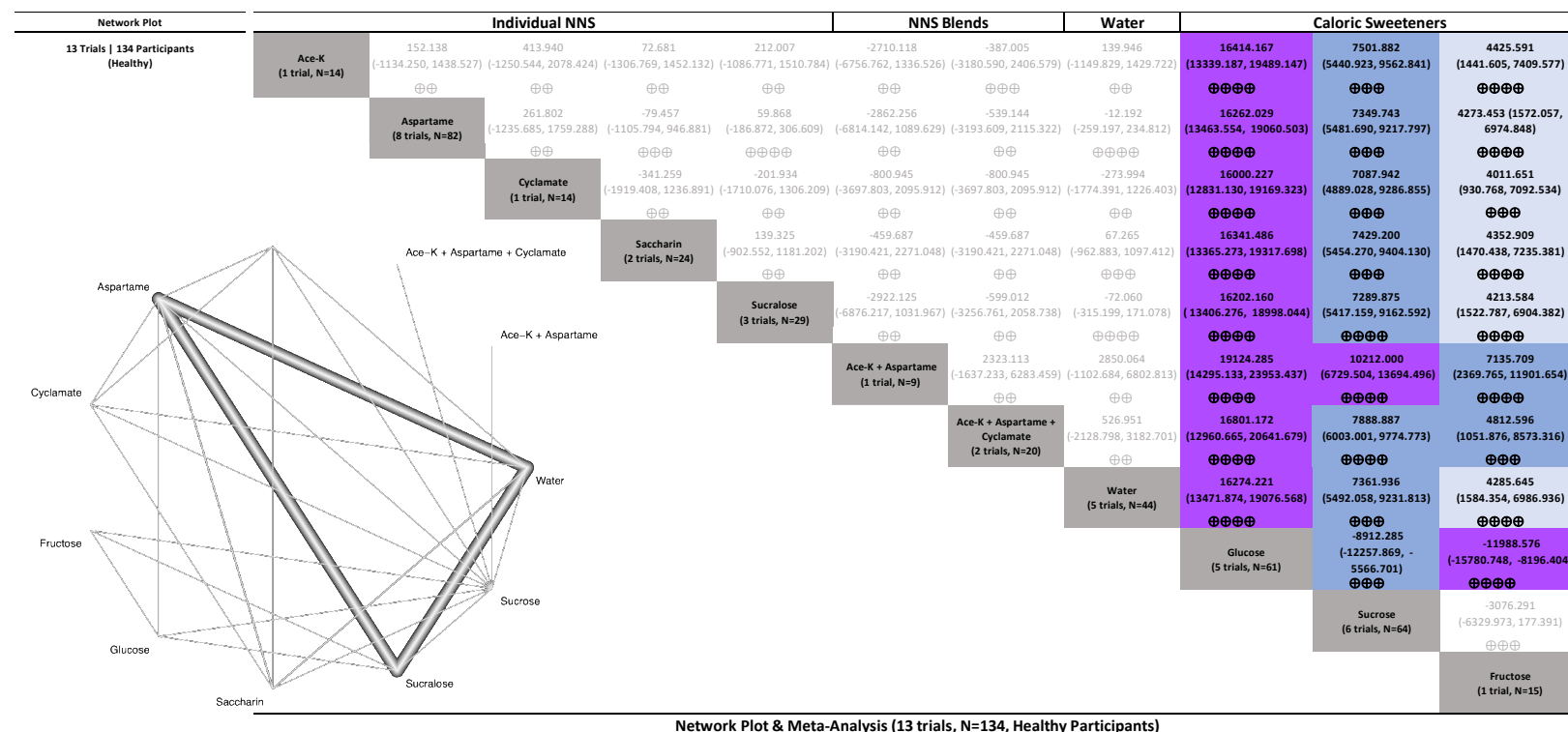


Figure S13. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS examining non-nutritive sweetened beverages (NNS beverages) sweetened with individual or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES



Judgements for were assigned by the CiNeMA algorithm (27, 28).

Figure S14. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants

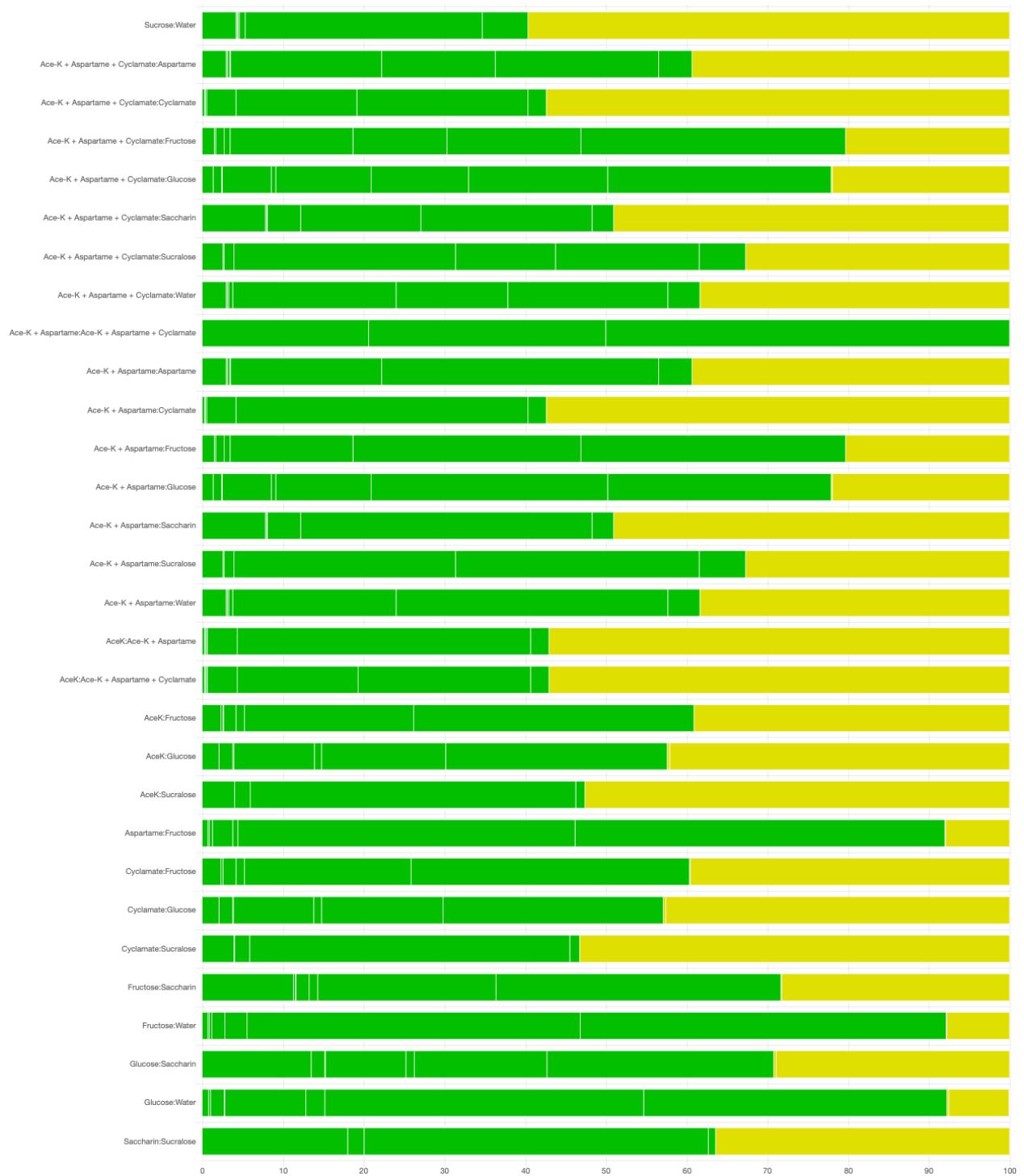


Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial insulin response is 2250 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects

(≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 8 and Figures 15-18** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S15. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants





Green = no concerns; yellow = some concerns; red = major concerns

Figure S16. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants



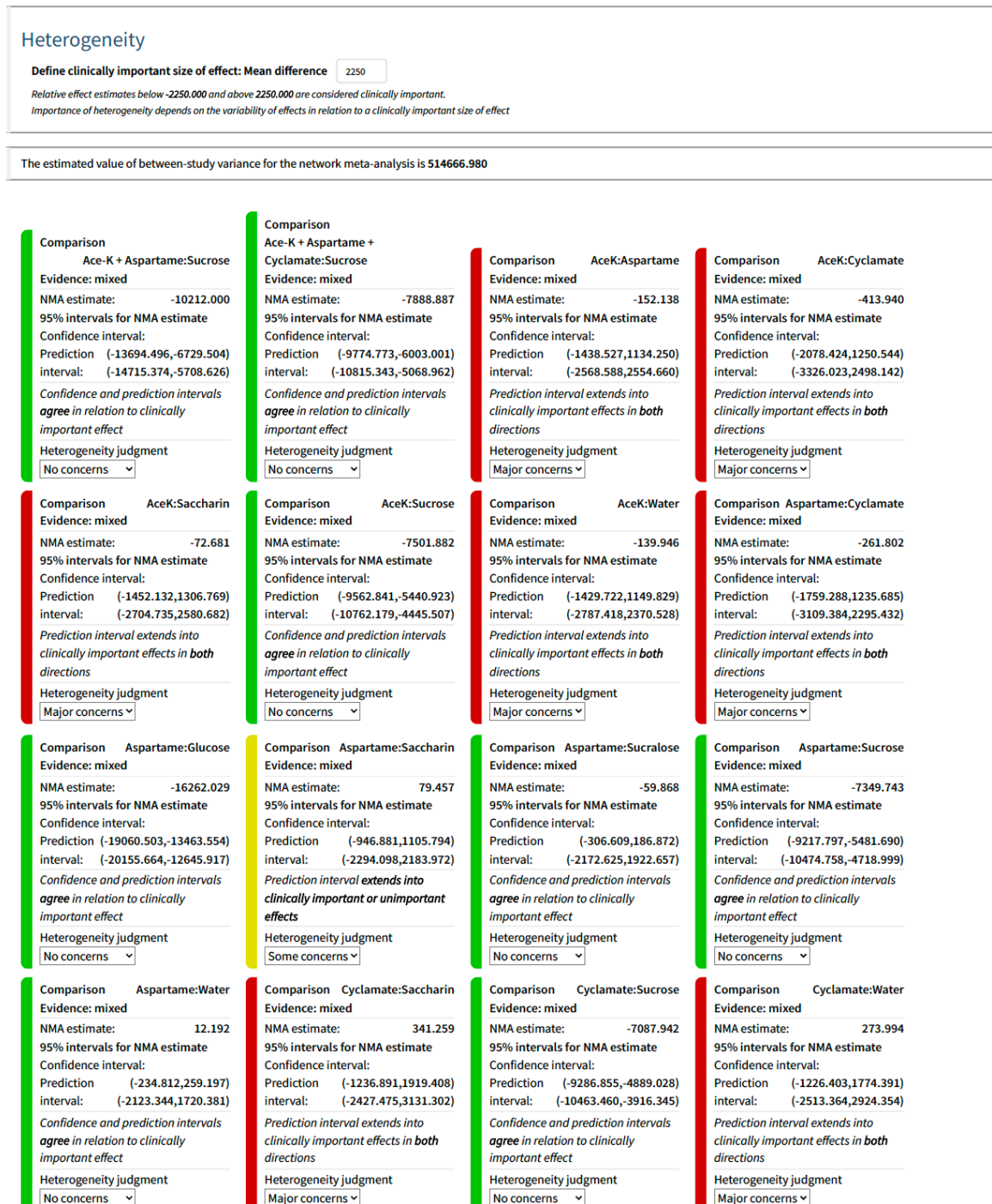
<p>Comparison Sucralose:Water</p> <p>Evidence: mixed</p> <p>NMA estimate: 72.060</p> <p>95% Confidence interval: (-171.078,315.199)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison Sucrose:Water</p> <p>Evidence: mixed</p> <p>NMA estimate: 7361.936</p> <p>95% Confidence interval: (5492.058,9231.813)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison Ace-K + Aspartame:Ace-K + Aspartame + Cyclamate</p> <p>Evidence: indirect</p> <p>NMA estimate: -2323.113</p> <p>95% Confidence interval: (-6283.459,1637.233)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison AceK:Ace-K + Aspartame</p> <p>Evidence: indirect</p> <p>NMA estimate: 2710.118</p> <p>95% Confidence interval: (-1336.526,6756.762)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>
<p>Comparison Ace-K + Aspartame:Aspartame</p> <p>Evidence: indirect</p> <p>NMA estimate: -2862.256</p> <p>95% Confidence interval: (-6814.142,1089.629)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Ace-K + Aspartame:Cyclamate</p> <p>Evidence: indirect</p> <p>NMA estimate: -3124.058</p> <p>95% Confidence interval: (-7242.674,994.558)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Ace-K + Aspartame:Fructose</p> <p>Evidence: indirect</p> <p>NMA estimate: -7135.709</p> <p>95% Confidence interval: (-11901.654,-2369.765)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison Ace-K + Aspartame:Glucose</p> <p>Evidence: indirect</p> <p>NMA estimate: -19124.285</p> <p>95% Confidence interval: (-23953.437,-14295.133)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>
<p>Comparison Ace-K + Aspartame:Saccharin</p> <p>Evidence: indirect</p> <p>NMA estimate: -2782.800</p> <p>95% Confidence interval: (-6786.314,1220.715)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Ace-K + Aspartame:Sucralose</p> <p>Evidence: indirect</p> <p>NMA estimate: -2922.125</p> <p>95% Confidence interval: (-6876.217,1031.967)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Evidence: Ace-K + Aspartame:Water</p> <p>Evidence: indirect</p> <p>NMA estimate: -2850.064</p> <p>95% Confidence interval: (-6802.813,1102.684)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison AceK:Ace-K + Aspartame + Cyclamate</p> <p>Evidence: indirect</p> <p>NMA estimate: 387.005</p> <p>95% Confidence interval: (-2406.579,3180.590)</p> <p><i>interval extends into clinically important effects in both directions</i></p> <p>Imprecision judgment</p> <p>Major concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Aspartame</p> <p>Evidence: indirect</p> <p>NMA estimate: -539.144</p> <p>95% Confidence interval: (-3193.609,2115.322)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Cyclamate</p> <p>Evidence: indirect</p> <p>NMA estimate: -800.945</p> <p>95% Confidence interval: (-3697.803,2095.912)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Fructose</p> <p>Evidence: indirect</p> <p>NMA estimate: -4812.596</p> <p>95% Confidence interval: (-8573.316,-1051.876)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Glucose</p> <p>Evidence: indirect</p> <p>NMA estimate: -16801.172</p> <p>95% Confidence interval: (-20641.679,-12960.665)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Saccharin</p> <p>Evidence: indirect</p> <p>NMA estimate: -459.687</p> <p>95% Confidence interval: (-3190.421,2271.048)</p> <p><i>interval extends into clinically important effects in both directions</i></p> <p>Imprecision judgment</p> <p>Major concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Sucralose</p> <p>Evidence: indirect</p> <p>NMA estimate: -599.012</p> <p>95% Confidence interval: (-3256.761,2058.738)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Water</p> <p>Evidence: indirect</p> <p>NMA estimate: -526.951</p> <p>95% Confidence interval: (-3182.701,2128.798)</p> <p><i>interval extends into clinically important effects</i></p> <p>Imprecision judgment</p> <p>Some concerns</p>	<p>Comparison AceK:Fructose</p> <p>Evidence: indirect</p> <p>NMA estimate: -4425.591</p> <p>95% Confidence interval: (-7409.577,-1441.605)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>
<p>Comparison AceK:Glucose</p> <p>Evidence: indirect</p> <p>NMA estimate: -16414.167</p> <p>95% Confidence interval: (-19489.147,-13339.187)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison AceK:Sucralose</p> <p>Evidence: indirect</p> <p>NMA estimate: -212.007</p> <p>95% Confidence interval: (-1510.784,1086.771)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison Aspartame:Fructose</p> <p>Evidence: indirect</p> <p>NMA estimate: -4273.453</p> <p>95% Confidence interval: (-6974.848,-1572.057)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>	<p>Comparison Cyclamate:Fructose</p> <p>Evidence: indirect</p> <p>NMA estimate: -4011.651</p> <p>95% Confidence interval: (-7092.534,-930.768)</p> <p><i>interval does not cross clinically important effect</i></p> <p>Imprecision judgment</p> <p>No concerns</p>

(continued on next page)

Comparison Cyclamate:Glucose Evidence: indirect NMA estimate: -16000.227 95% Confidence interval: Confidence (-19169.323,-12831.130) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>	Comparison Cyclamate:Sucralose Evidence: indirect NMA estimate: 201.934 95% Confidence interval: Confidence (-1306.209,1710.076) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>	Comparison Fructose:Saccharin Evidence: indirect NMA estimate: 4352.909 95% Confidence interval: Confidence (1470.438,7235.381) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>	Comparison Fructose:Water Evidence: indirect NMA estimate: 4285.645 95% Confidence interval: Confidence (1584.354,6986.936) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>
Comparison Glucose:Saccharin Evidence: indirect NMA estimate: 16341.486 95% Confidence interval: Confidence (13365.273,19317.698) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>	Comparison Glucose:Water Evidence: indirect NMA estimate: 16274.221 95% Confidence interval: Confidence (13471.874,19076.568) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>	Comparison Saccharin:Sucralose Evidence: indirect NMA estimate: -139.325 95% Confidence interval: Confidence (-1181.202,902.552) <i>interval does not cross clinically important effect</i> Imprecision judgment <input type="button" value="No concerns"/>	

Relative effect estimates below -2250.0 and above 2250.0 pmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CiNEMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood insulin incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of insulin iAUC by taking 20% of 11250 pmol*mins/L which is the median of insulin iAUC in participants with type 2 diabetes (~6200 pmol*mins/L) and healthy participants (~16300 pmol*mins/L) after a 75-g oral glucose tolerance test (32-34).

Figure S17. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants



(continued on next page)

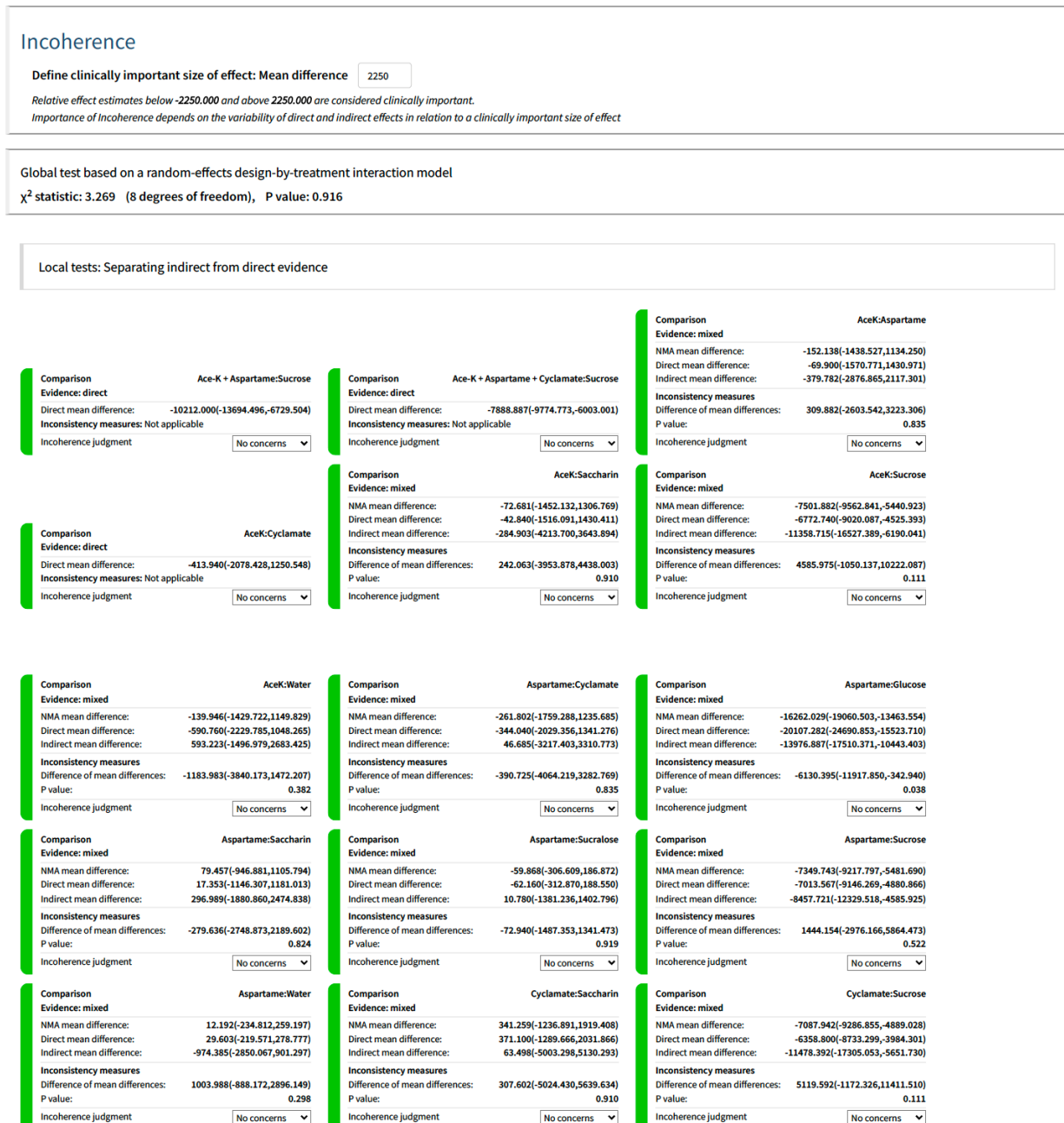
<p>Comparison Fructose:Glucose Evidence: mixed</p> <p>NMA estimate: -11988.576 95% intervals for NMA estimate Confidence interval: Prediction (-15780.748,-8196.404) interval: (-16802.681,-7223.754)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Fructose:Sucralose Evidence: mixed</p> <p>NMA estimate: 4213.584 95% intervals for NMA estimate Confidence interval: Prediction (1522.787,6904.382) interval: (523.537,8001.642)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Fructose:Sucrose Evidence: mixed</p> <p>NMA estimate: -3076.291 95% intervals for NMA estimate Confidence interval: Prediction (-6329.973,177.391) interval: (-7616.677,1198.067)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Glucose:Sucralose Evidence: mixed</p> <p>NMA estimate: 16202.160 95% intervals for NMA estimate Confidence interval: Prediction (13406.276,18998.044) interval: (12560.371,19991.243)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Glucose:Sucrose Evidence: mixed</p> <p>NMA estimate: 8912.285 95% intervals for NMA estimate Confidence interval: Prediction (5566.701,12257.869) interval: (4473.325,13134.499)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Saccharin:Sucrose Evidence: mixed</p> <p>NMA estimate: -7429.200 95% intervals for NMA estimate Confidence interval: Prediction (-9404.130,-5454.270) interval: (-10547.703,-4535.929)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Saccharin:Water Evidence: mixed</p> <p>NMA estimate: -67.265 95% intervals for NMA estimate Confidence interval: Prediction (-1097.412,962.883) interval: (-2404.156,2111.319)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Sucralose:Sucrose Evidence: mixed</p> <p>NMA estimate: -7289.875 95% intervals for NMA estimate Confidence interval: Prediction (-9162.592,-5417.159) interval: (-10428.627,-4515.162)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Sucralose:Water Evidence: mixed</p> <p>NMA estimate: 72.060 95% intervals for NMA estimate Confidence interval: Prediction (-171.078,315.199) interval: (-2033.877,1880.883)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Sucrose:Water Evidence: mixed</p> <p>NMA estimate: 7361.936 95% intervals for NMA estimate Confidence interval: Prediction (5492.058,9231.813) interval: (4515.164,10275.630)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Ace-K + Aspartame + Cyclamate Evidence: indirect</p> <p>NMA estimate: -2323.113 95% intervals for NMA estimate Confidence interval: Prediction (-6283.459,1637.233) interval: (-7373.021,2833.326)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Evidence: AceK:Ace-K + Aspartame indirect</p> <p>NMA estimate: 2710.118 95% intervals for NMA estimate Confidence interval: Prediction (-1336.526,6756.762) interval: (-2660.831,7877.146)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>
<p>Comparison Ace-K + Aspartame:Aspartame Evidence: indirect</p> <p>NMA estimate: -2862.256 95% intervals for NMA estimate Confidence interval: Prediction (-6814.142,1089.629) interval: (-7720.936,2490.693)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame:Cyclamate Evidence: indirect</p> <p>NMA estimate: -3124.058 95% intervals for NMA estimate Confidence interval: Prediction (-7242.674,994.558) interval: (-8360.949,2316.754)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame:Fructose Evidence: indirect</p> <p>NMA estimate: -7135.709 95% intervals for NMA estimate Confidence interval: Prediction (-11901.654,-2369.765) interval: (-13102.866,-902.524)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame:Glucose Evidence: indirect</p> <p>NMA estimate: -19124.285 95% intervals for NMA estimate Confidence interval: Prediction (-23953.437,-14295.133) interval: (-25060.839,-12970.986)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Ace-K + Aspartame:Saccharin Evidence: indirect</p> <p>NMA estimate: -2782.800 95% intervals for NMA estimate Confidence interval: Prediction (-6786.314,1220.715) interval: (-7849.230,2508.862)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame:Sucralose Evidence: indirect</p> <p>NMA estimate: -2922.125 95% intervals for NMA estimate Confidence interval: Prediction (-6876.217,1031.967) interval: (-7890.777,2410.566)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Evidence: Ace-K + Aspartame:Water indirect</p> <p>NMA estimate: -2850.064 95% intervals for NMA estimate Confidence interval: Prediction (-6802.813,1102.684) interval: (-7923.745,2290.539)</p> <p>Prediction interval extends into clinically important or unimportant effects</p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison AceK:Ace-K + Aspartame + Cyclamate Evidence: indirect</p> <p>NMA estimate: 387.005 95% intervals for NMA estimate Confidence interval: Prediction (-2406.579,3180.590) interval: (-3628.690,4305.310)</p> <p>Confidence and prediction intervals agree in relation to clinically important effect</p> <p>Heterogeneity judgment No concerns</p>

(continued on next page)

<p>Comparison Ace-K + Aspartame + Cyclamate:Aspartame Evidence: indirect</p> <p>NMA estimate: -539.144 95% intervals for NMA estimate Confidence interval: Prediction (-3193.609,2115.322) interval: (-4092.833,3402.284)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Cyclamate Evidence: indirect</p> <p>NMA estimate: -800.945 95% intervals for NMA estimate Confidence interval: Prediction (-3697.803,2095.912) interval: (-4811.583,3307.082)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Fructose Evidence: indirect</p> <p>NMA estimate: -4812.596 95% intervals for NMA estimate Confidence interval: Prediction (-8573.316,-1051.876) interval: (-9751.506,285.810)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Glucose Evidence: indirect</p> <p>NMA estimate: -16801.172 95% intervals for NMA estimate Confidence interval: Prediction (-20641.679,-12960.665) interval: (-21697.427,-11794.703)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Ace-K + Aspartame + Cyclamate:Saccharin Evidence: indirect</p> <p>NMA estimate: -459.687 95% intervals for NMA estimate Confidence interval: Prediction (-3190.421,2271.048) interval: (-4247.071,3446.397)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Sucralose Evidence: indirect</p> <p>NMA estimate: -599.012 95% intervals for NMA estimate Confidence interval: Prediction (-3256.761,2058.738) interval: (-4278.705,3338.189)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison Ace-K + Aspartame + Cyclamate:Water Evidence: indirect</p> <p>NMA estimate: -526.951 95% intervals for NMA estimate Confidence interval: Prediction (-3182.701,2128.798) interval: (-4296.122,3202.611)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>	<p>Comparison AceK:Fructose Evidence: indirect</p> <p>NMA estimate: -4425.591 95% intervals for NMA estimate Confidence interval: Prediction (-7409.577,-1441.605) interval: (-8710.891,-78.184)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison AceK:Glucose Evidence: indirect</p> <p>NMA estimate: -16414.167 95% intervals for NMA estimate Confidence interval: Prediction (-19489.147,-13339.187) interval: (-20605.599,-12209.911)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison AceK:Sucralose Evidence: indirect</p> <p>NMA estimate: -212.007 95% intervals for NMA estimate Confidence interval: Prediction (-1510.784,1086.771) interval: (-2863.423,2599.527)</p> <p>Prediction interval <i>extends into clinically important effects in both directions</i></p> <p>Heterogeneity judgment Major concerns</p>	<p>Comparison Aspartame:Fructose Evidence: indirect</p> <p>NMA estimate: -4273.453 95% intervals for NMA estimate Confidence interval: Prediction (-6974.848,-1572.057) interval: (-8314.656,-460.492)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Cyclamate:Fructose Evidence: indirect</p> <p>NMA estimate: -4011.651 95% intervals for NMA estimate Confidence interval: Prediction (-7092.534,-930.768) interval: (-8381.961,420.766)</p> <p>Prediction interval <i>extends into clinically important or unimportant effects</i></p> <p>Heterogeneity judgment Some concerns</p>
<p>Comparison Cyclamate:Glucose Evidence: indirect</p> <p>NMA estimate: -16000.227 95% intervals for NMA estimate Confidence interval: Prediction (-19169.323,-12831.130) interval: (-20279.020,-11708.609)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Cyclamate:Sucralose Evidence: indirect</p> <p>NMA estimate: 201.934 95% intervals for NMA estimate Confidence interval: Prediction (-1306.209,1710.076) interval: (-2581.930,3145.914)</p> <p>Prediction interval <i>extends into clinically important effects in both directions</i></p> <p>Heterogeneity judgment Major concerns</p>	<p>Comparison Fructose:Saccharin Evidence: indirect</p> <p>NMA estimate: 4352.909 95% intervals for NMA estimate Confidence interval: Prediction (1470.438,7235.381) interval: (192.725,8472.297)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Fructose:Water Evidence: indirect</p> <p>NMA estimate: 4285.645 95% intervals for NMA estimate Confidence interval: Prediction (1584.354,6986.936) interval: (294.621,8077.563)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>
<p>Comparison Glucose:Saccharin Evidence: indirect</p> <p>NMA estimate: 16341.486 95% intervals for NMA estimate Confidence interval: Prediction (13365.273,19317.698) interval: (12332.184,20359.272)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Glucose:Water Evidence: indirect</p> <p>NMA estimate: 16274.221 95% intervals for NMA estimate Confidence interval: Prediction (13471.874,19076.568) interval: (12409.777,19988.842)</p> <p>Confidence and prediction intervals <i>agree in relation to clinically important effect</i></p> <p>Heterogeneity judgment No concerns</p>	<p>Comparison Saccharin:Sucralose Evidence: indirect</p> <p>NMA estimate: -139.325 95% intervals for NMA estimate Confidence interval: Prediction (-1181.202,902.552) interval: (-2506.110,2366.267)</p> <p>Prediction interval <i>extends into clinically important effects in both directions</i></p> <p>Heterogeneity judgment Major concerns</p>	

Judgements for were assigned by the CiNEMA algorithm (27, 28).

Figure S18. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants



(continued on next page)

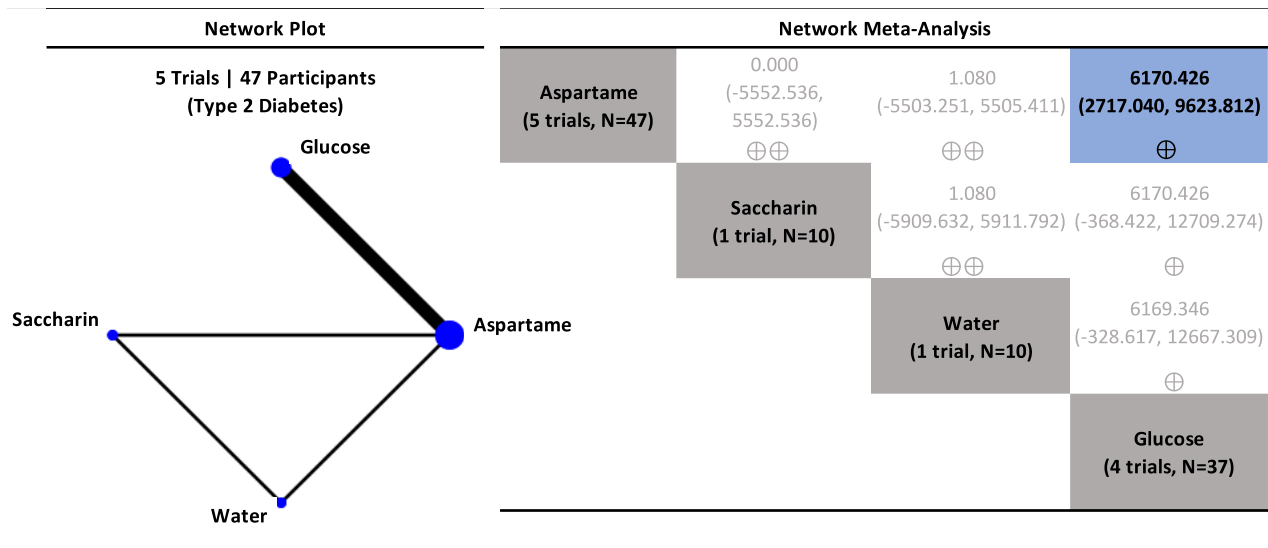
Comparison Evidence: mixed NMA mean difference: 273.994(-1226.403,1774.391) Direct mean difference: -176.820(-1986.262,1632.622) Indirect mean difference: 1266.171(-1418.180,3950.523) Inconsistency measures Difference of mean differences: -1442.991(-4680.247,1794.264) P value: 0.382 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: -11988.576(-15780.748,-8196.404) Direct mean difference: -9812.530(-14125.289,-5499.771) Indirect mean difference: -19404.153(-27365.748,-11442.559) Inconsistency measures Difference of mean differences: 9591.623(536.963,18646.284) P value: 0.038 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 4213.584(1522.787,6904.382) Direct mean difference: 4185.320(1490.947,6879.693) Indirect mean difference: 14755.722(-37280.641,66792.085) Inconsistency measures Difference of mean differences: -10570.402(-62676.473,41535.670) P value: 0.691 Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: mixed NMA mean difference: -3076.291(-6329.973,177.391) Direct mean difference: -6118.220(-11581.148,-655.292) Indirect mean difference: -1404.068(-5454.510,2646.374) Inconsistency measures Difference of mean differences: -4714.152(-11514.862,2086.558) P value: 0.174 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 16202.160(13406.276,18998.044) Direct mean difference: 13997.850(10471.257,17524.443) Indirect mean difference: 19931.674(15344.448,24518.900) Inconsistency measures Difference of mean differences: -5933.824(-11719.971,-147.677) P value: 0.044 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 8912.285(5566.701,12257.869) Direct mean difference: 3694.310(-2223.527,9612.147) Indirect mean difference: 11363.304(7307.377,15419.231) Inconsistency measures Difference of mean differences: -7668.994(-14843.347,-494.642) P value: 0.036 Incoherence judgment: <input type="button" value="Some concerns"/>
Comparison Evidence: mixed NMA mean difference: -7429.200(-9404.130,-5454.270) Direct mean difference: -6729.900(-8974.492,-4485.308) Indirect mean difference: -9826.303(-13982.045,-5670.561) Inconsistency measures Difference of mean differences: 3096.403(-1626.772,7819.578) P value: 0.199 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: -67.265(-1097.412,962.883) Direct mean difference: -321.082(-1572.876,930.711) Indirect mean difference: 465.292(-1347.939,2278.523) Inconsistency measures Difference of mean differences: -786.374(-2989.734,1416.985) P value: 0.484 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: -7289.875(-9162.592,-5417.159) Direct mean difference: -9979.606(-13849.114,-6110.099) Indirect mean difference: -6467.180(-8607.217,-4327.143) Inconsistency measures Difference of mean differences: -3512.427(-7934.287,909.434) P value: 0.119 Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: mixed NMA mean difference: 72.060(-171.078,315.199) Direct mean difference: 78.873(-165.877,323.623) Indirect mean difference: -440.272(-2562.704,1682.160) Inconsistency measures Difference of mean differences: 519.145(-1617.352,2655.643) P value: 0.634 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed NMA mean difference: 7361.936(5492.058,9231.813) Direct mean difference: 6583.525(4372.751,8794.299) Indirect mean difference: 9318.438(5813.499,12823.378) Inconsistency measures Difference of mean differences: -2734.913(-6878.840,1409.013) P value: 0.196 Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -2323.113(-6283.459,1637.233) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 2710.118(-1336.526,6756.762) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -2862.256(-6814.142,1089.629) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -3124.058(-7242.674,994.558) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -7135.709(-11901.654,-2369.765) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -19124.285(-23953.437,-14295.133) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -2782.800(-6786.314,1220.715) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -2922.125(-6876.217,1031.967) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -2850.064(-6802.813,1102.684) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 387.005(-2406.579,3180.590) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>

(continued on next page)

Comparison Evidence: indirect Indirect mean difference: -539.144(-3193.609,2115.322) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -800.945(-3697.803,2095.912) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -4812.596(-8573.316,-1051.876) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -16801.172(-20641.679,-12960.665) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -459.687(-3190.421,2271.048) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -599.012(-3256.761,2058.738) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -526.951(-3182.701,2128.798) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -4425.591(-7409.577,-1441.605) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -16414.167(-19489.147,-13339.187) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -212.007(-1510.784,1086.771) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -4273.453(-6974.848,-1572.057) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: -4011.651(-7092.534,-930.768) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -16000.227(-19169.323,-12831.130) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 201.934(-1306.209,1710.076) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 4352.909(1470.438,7235.381) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: 4285.645(1584.354,6986.936) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 16341.486(13365.273,19317.698) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Indirect mean difference: 16274.221(13471.874,19076.568) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>
Comparison Evidence: indirect Indirect mean difference: -139.325(-1181.202,902.552) Inconsistency measures: Not applicable Incoherence judgment: <input type="button" value="No concerns"/>		

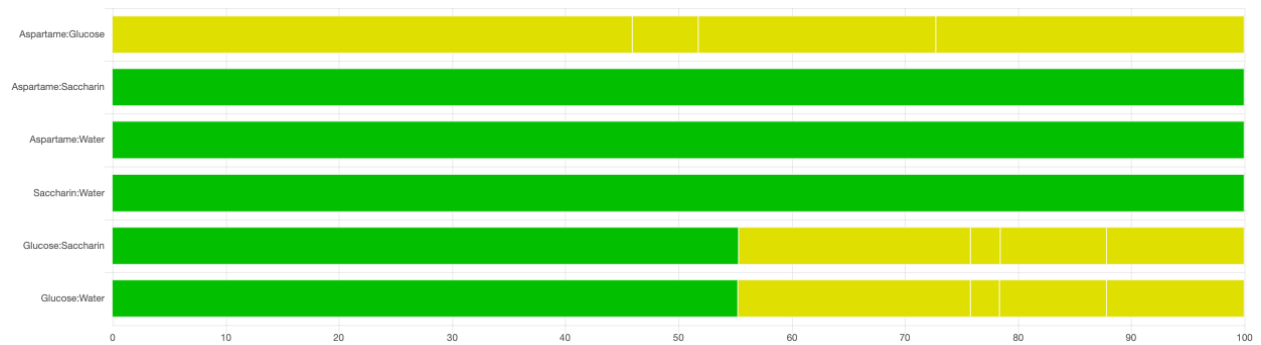
Judgements for were assigned by the CiNEMA algorithm (27, 28).

Figure S19. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



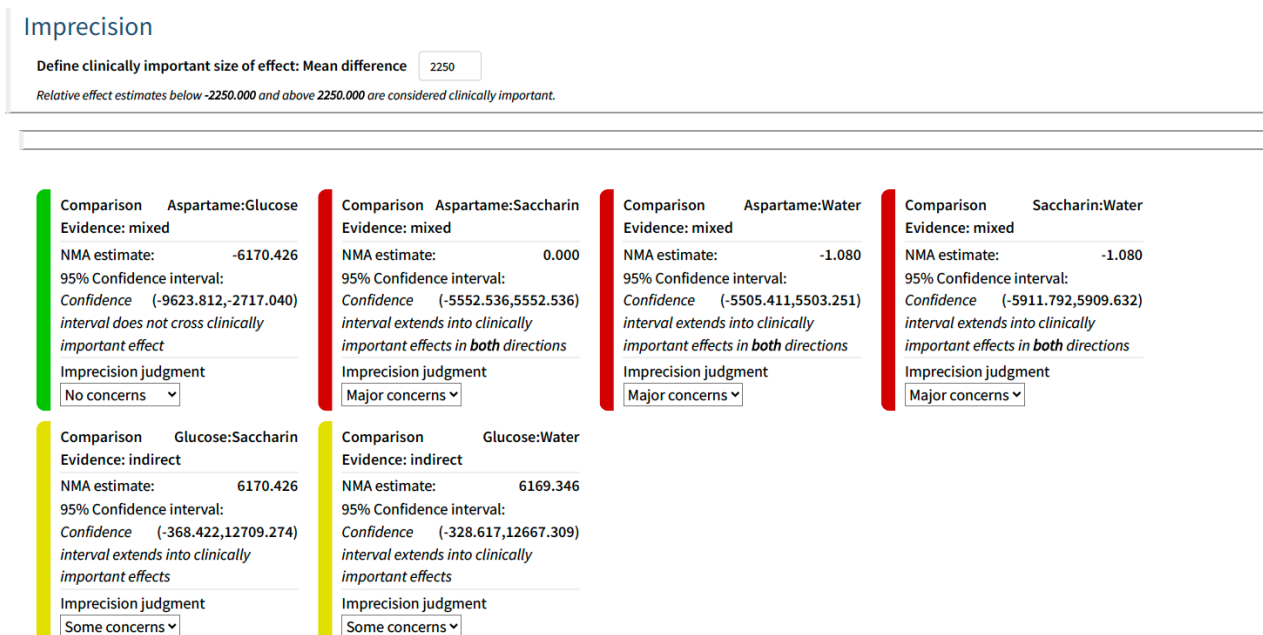
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 2250 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 9 and Figures 20-23** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S20. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



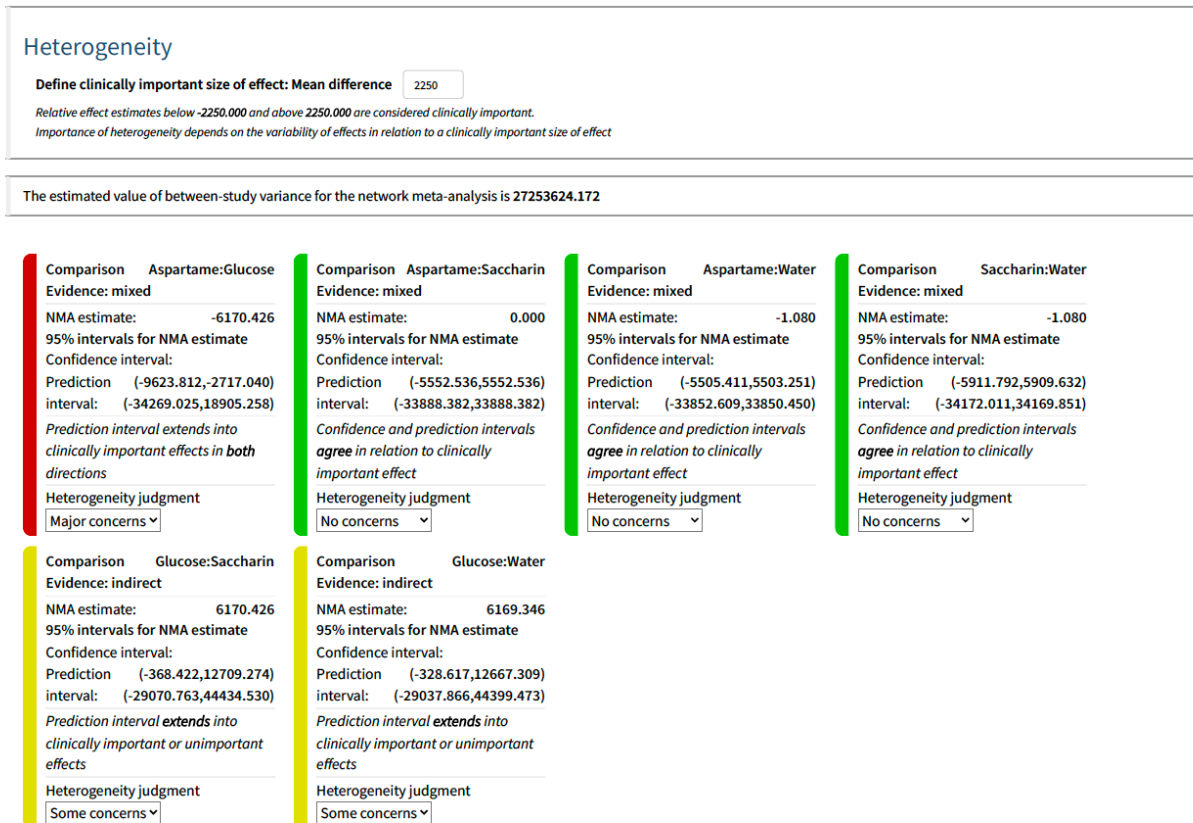
Green = no concerns; yellow = some concerns; red = major concerns

Figure S21. CINeMA output for the IMPRECISION domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



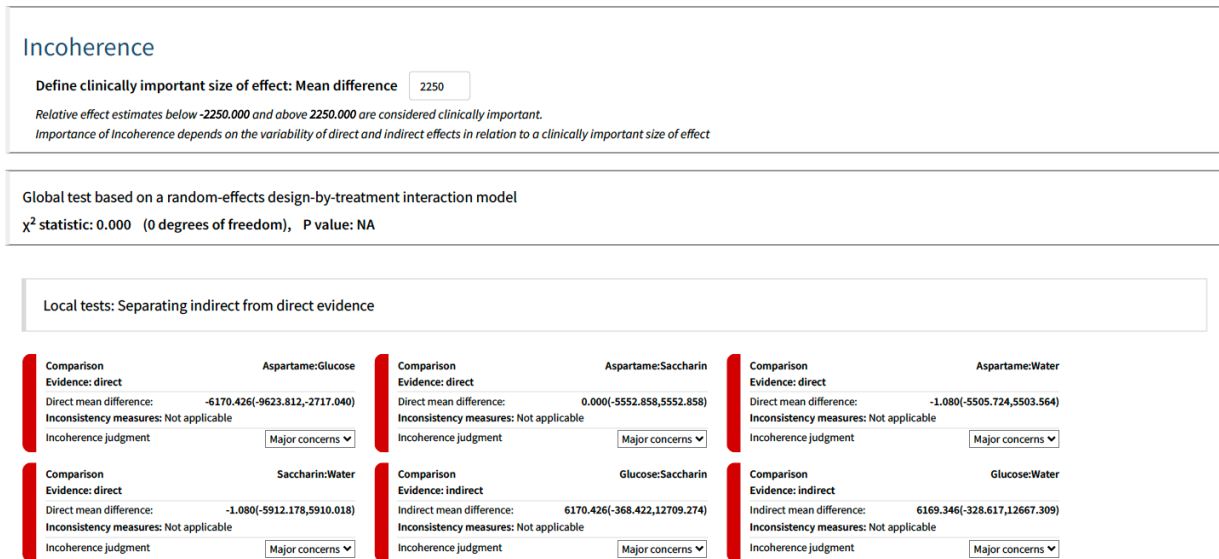
Relative effect estimates below -2250.0 and above 2250.0 pmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CiNEMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood insulin incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of insulin iAUC by taking 20% of 11250 pmol*mins/L which is the median of insulin iAUC in participants with type 2 diabetes (~6200 pmol*mins/L) and healthy participants (~16300 pmol*mins/L) after a 75-g oral glucose tolerance test (32-34).

Figure S22. CINeMA output for the HETEROGENEITY domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



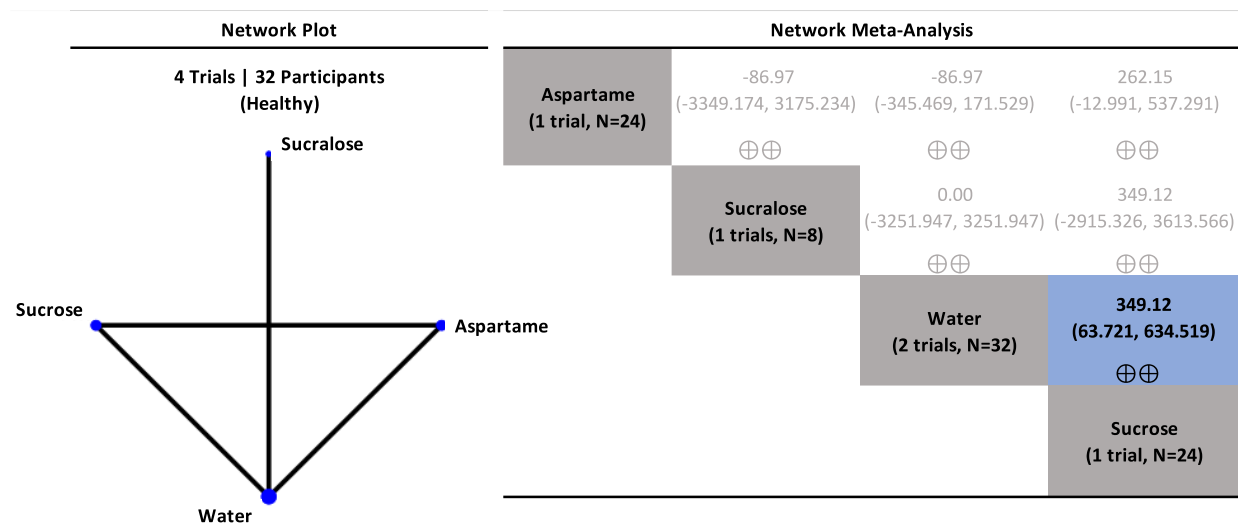
Judgements for were assigned by the CiNeMA algorithm (27, 28).

Figure S23. CINeMA output for the INCOHERENCE domain of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



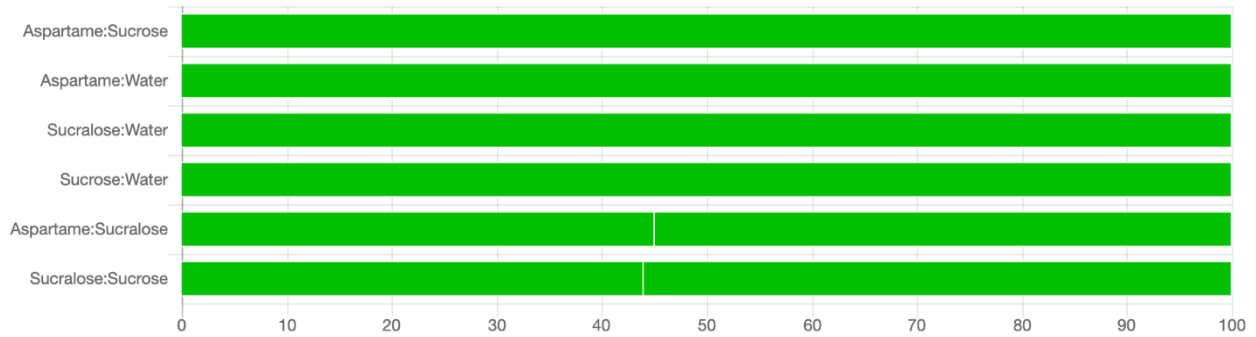
Judgements for were assigned by the CiNEMA algorithm (27, 28).

Figure S24. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants



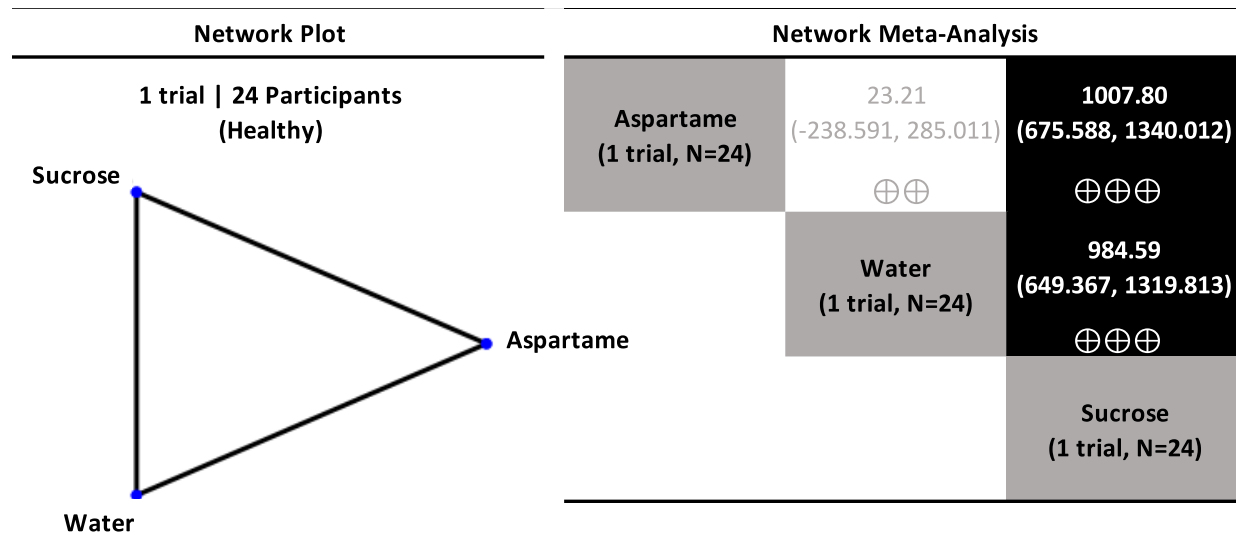
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 82 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 10 and Figure 25** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S25. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants



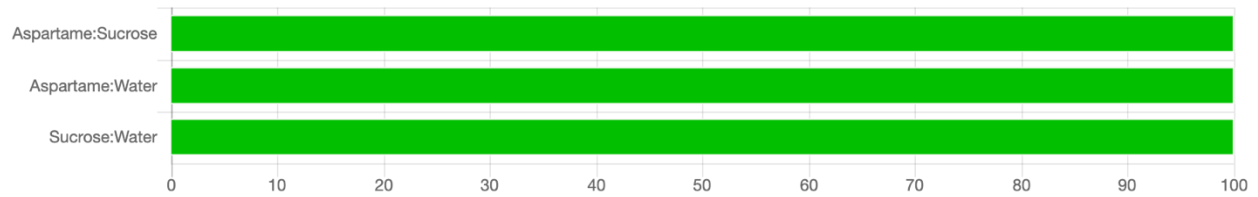
Green = no concerns; yellow = some concerns; red = major concerns

Figure S26. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants



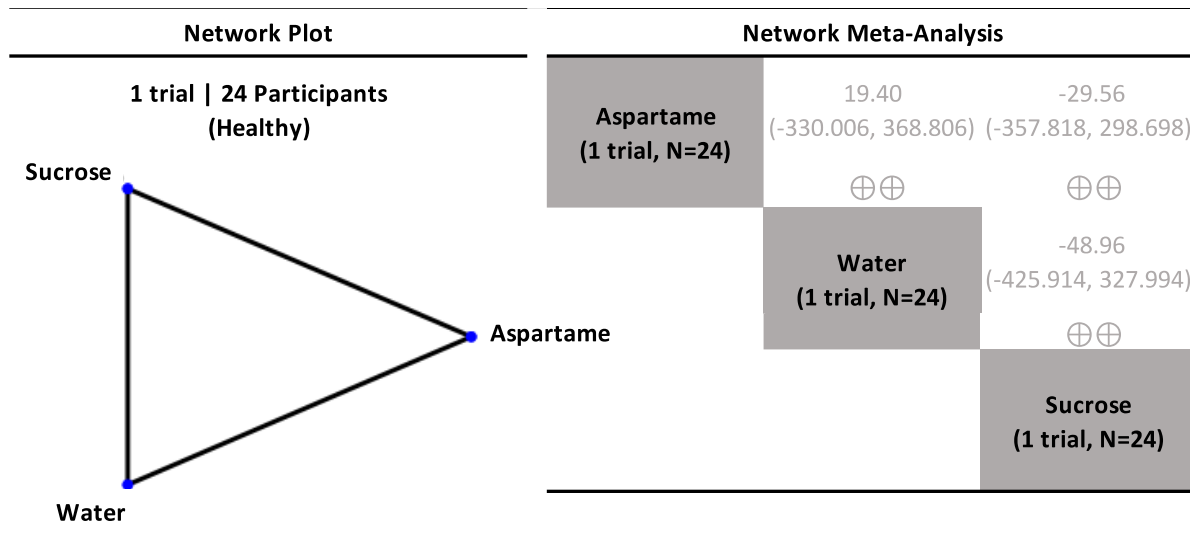
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in white. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 82 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥1 MID) have a light blue background; moderate effects (≥2 MID) have a darker blue background; large effects (≥5 to <10 MID) have a purple background; very large effects (≥10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 11 and Figure 27** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S27. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants



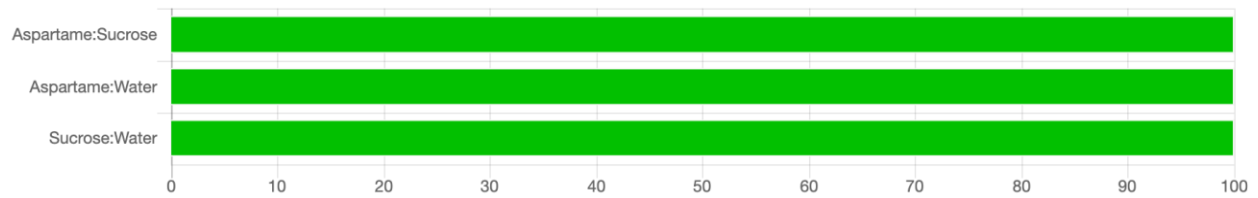
Green = no concerns; yellow = some concerns; red = major concerns

Figure S28. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GHRELIN response in HEALTHY participants



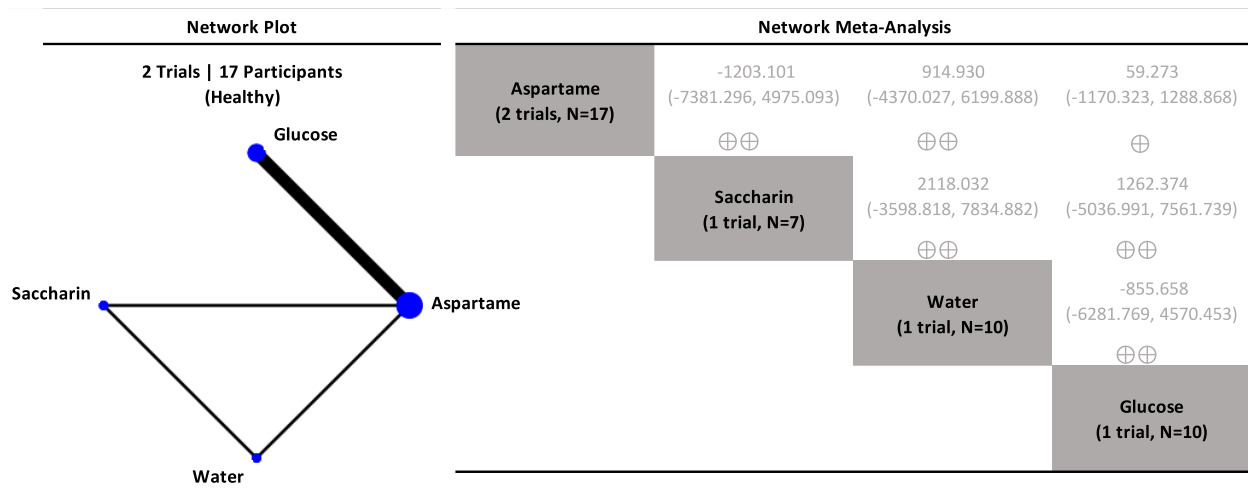
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in white. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 10 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 12 and Figure 29** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S29. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GHRELIN response in HEALTHY participants



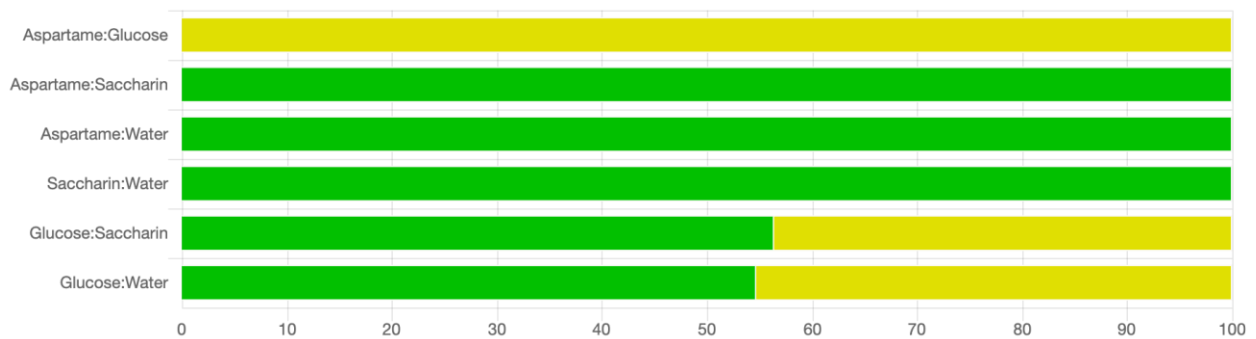
Green = no concerns; yellow = some concerns; red = major concerns

Figure S30. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants



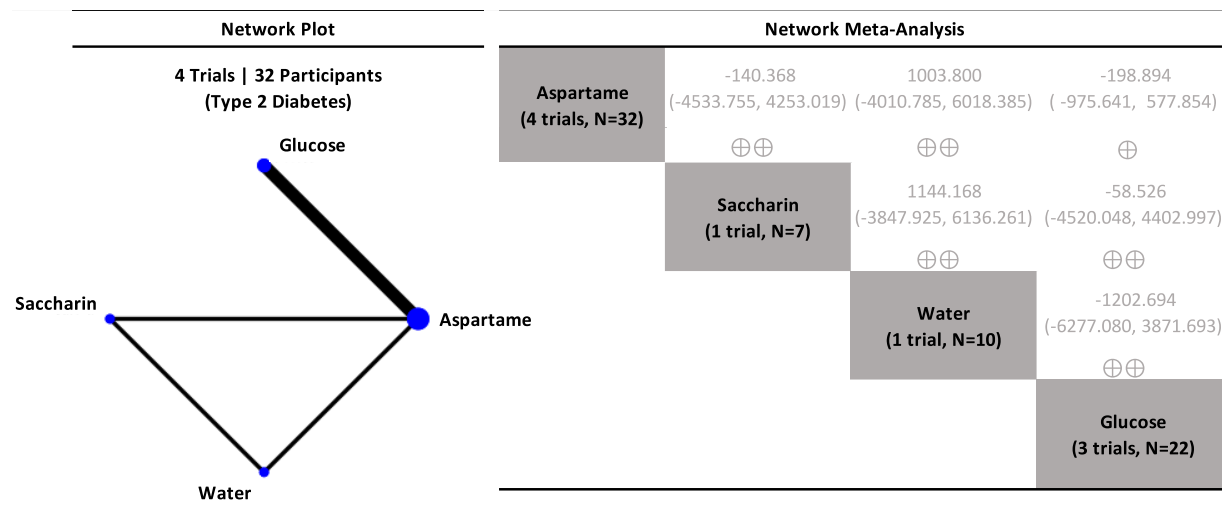
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in white. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 205 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥1 MID) have a light blue background; moderate effects (≥2 MID) have a darker blue background; large effects (≥5 to <10 MID) have a purple background; very large effects (≥10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 13** and **Figure 31** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S31. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants



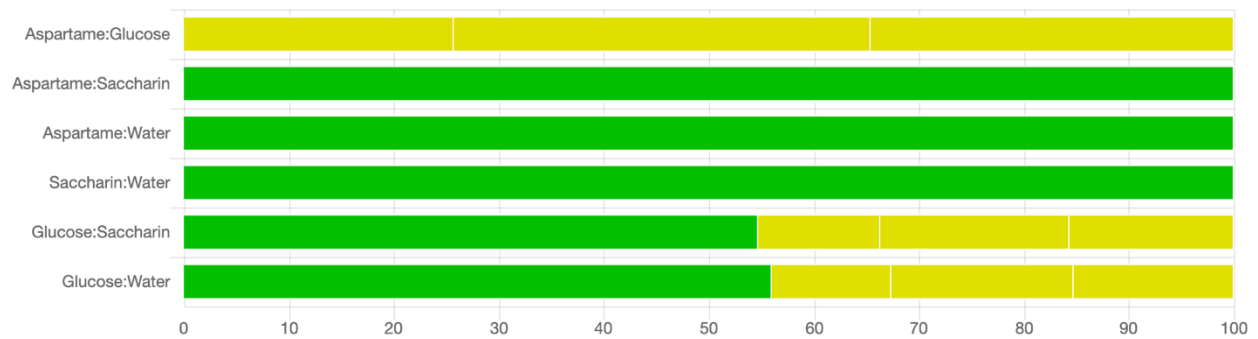
Green = no concerns; yellow = some concerns; red = major concerns

Figure S32. Network plot and meta-analysis of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in participants with TYPE 2 DIABETES



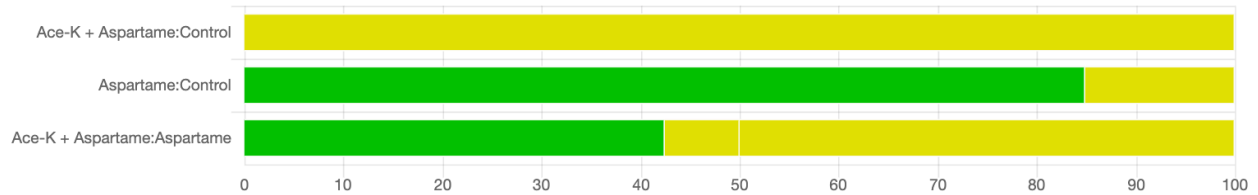
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in white. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 205 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 14** and **Figure 33** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S33. Risk of bias assessment of UNCOUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in participants with TYPE 2 DIABETES



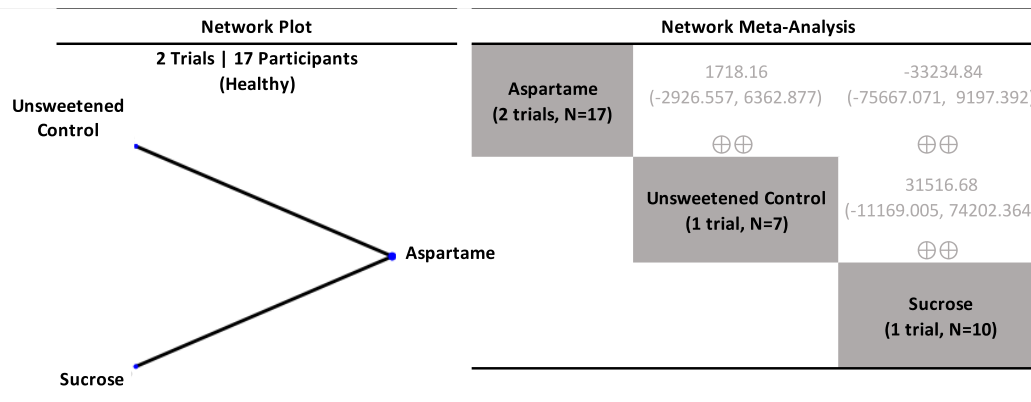
Green = no concerns; yellow = some concerns; red = major concerns

Figure S34. Risk of bias assessment of COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood GLUCOSE response in HEALTHY participants.



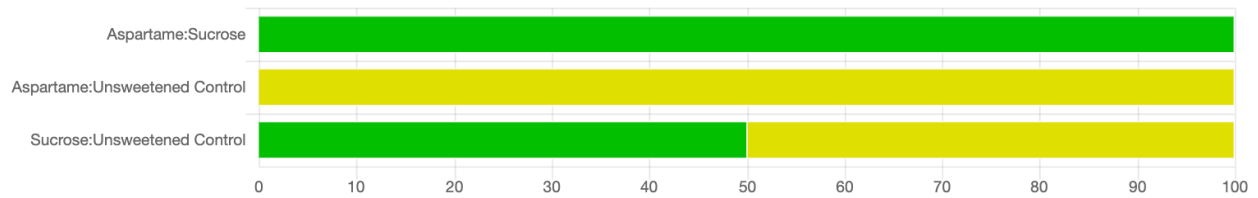
Green = no concerns; yellow = some concerns; red = major concerns

Figure S35. Network plot and meta-analysis of COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood INSULIN response in HEALTHY participants.



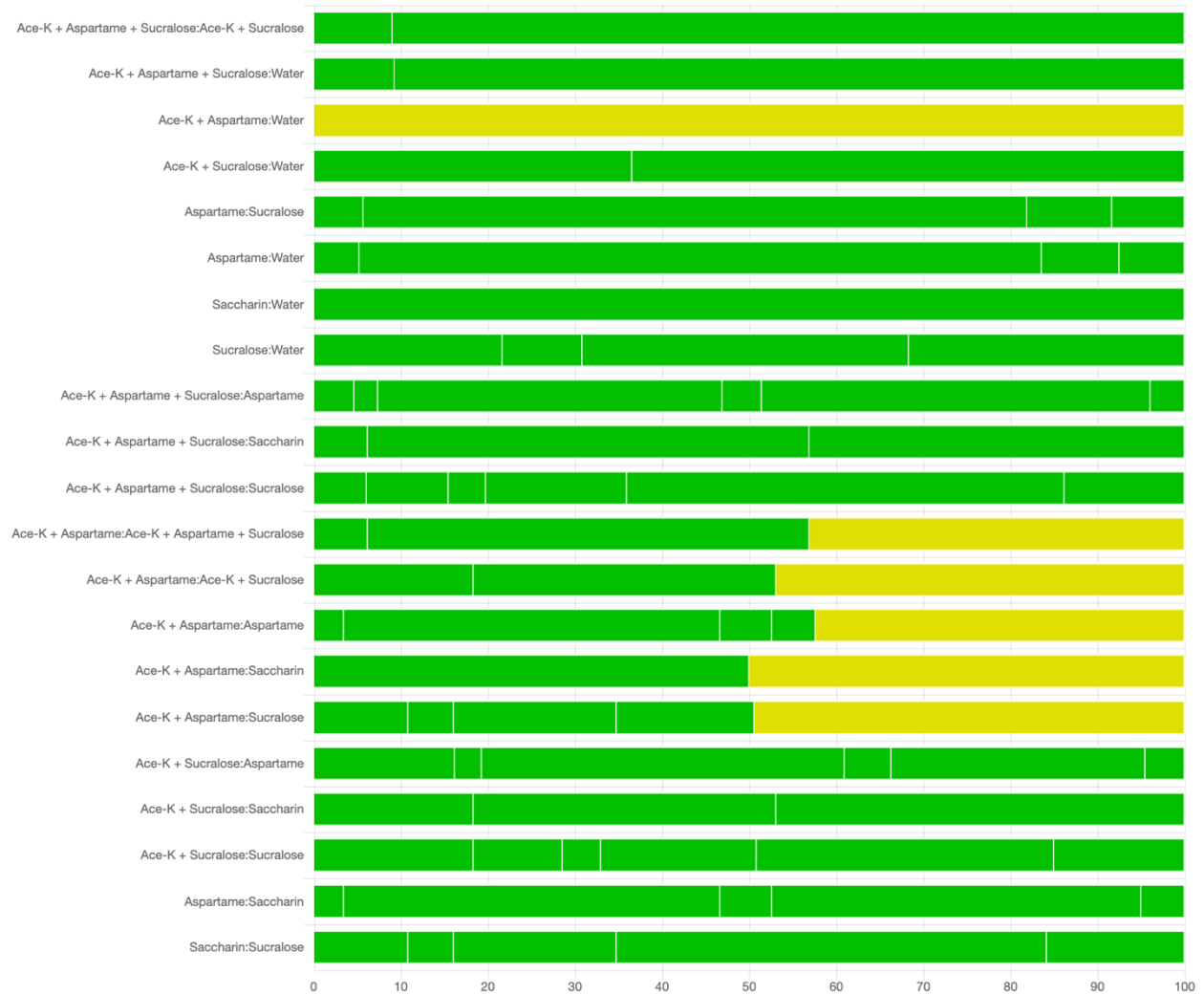
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (mmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 2250 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 16 and Figures 36-40** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S36. Risk of bias assessment of COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS) and controls on postprandial blood INSULIN response in HEALTHY participants.



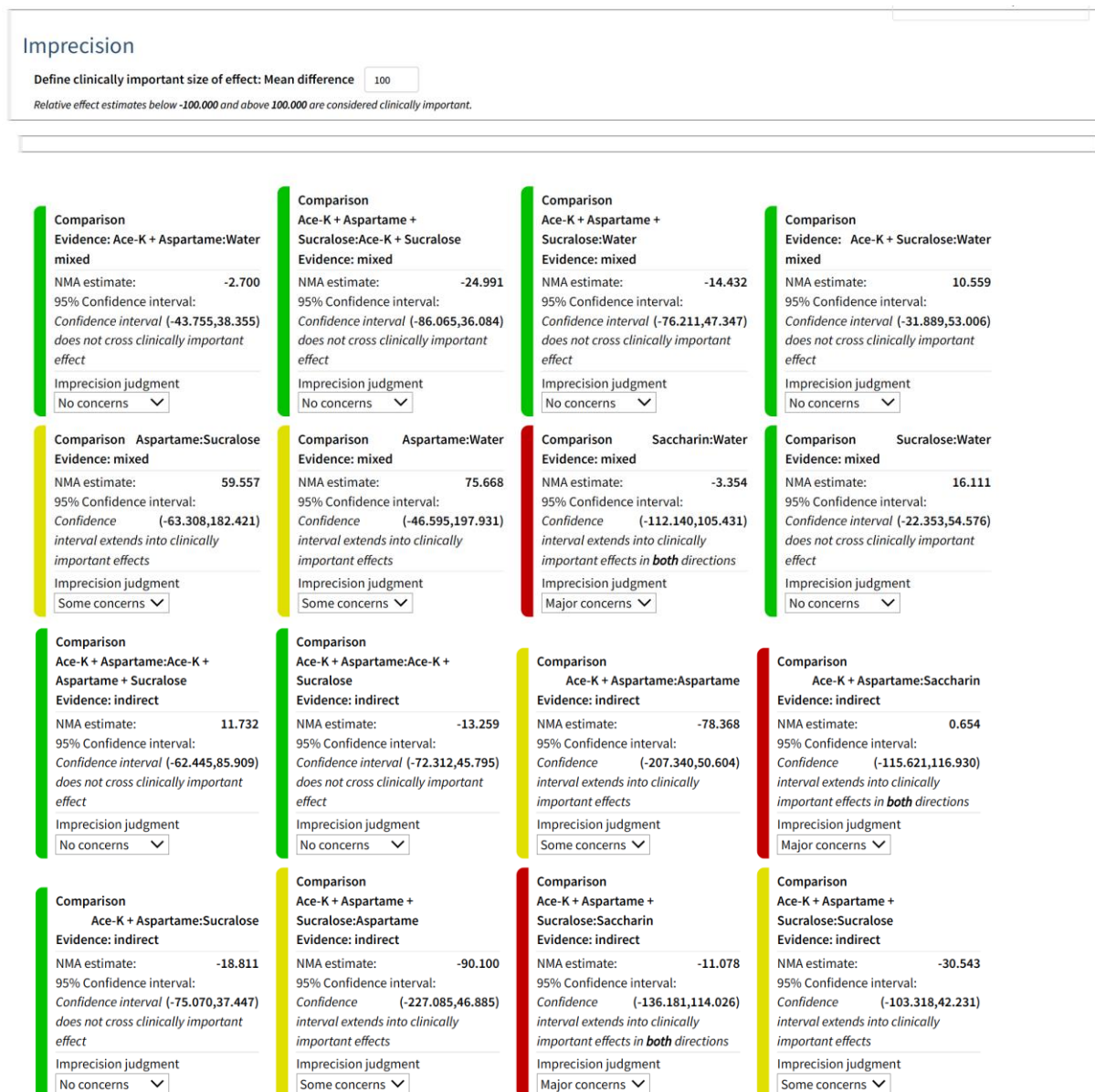
Green = no concerns; yellow = some concerns; red = major concerns

Figure S37. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants



Green = no concerns; yellow = some concerns; red = major concerns

Figure S38. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants



(continued on next page)

Comparison Ace-K + Sucralose:Aspartame Evidence: indirect NMA estimate: -65.109 95% Confidence interval: Confidence (-194.531,64.312) <i>interval extends into clinically important effects</i> Imprecision judgment Some concerns ▼	Comparison Ace-K + Sucralose:Saccharin Evidence: indirect NMA estimate: 13.913 95% Confidence interval: Confidence (-102.861,130.687) <i>interval extends into clinically important effects in both directions</i> Imprecision judgment Major concerns ▼	Comparison Ace-K + Sucralose:Sucralose Evidence: indirect NMA estimate: -5.553 95% Confidence interval: Confidence interval (-62.835,51.730) <i>does not cross clinically important effect</i> Imprecision judgment No concerns ▼	Comparison Aspartame:Saccharin Evidence: indirect NMA estimate: 79.022 95% Confidence interval: Confidence (-84.631,242.676) <i>interval extends into clinically important effects</i> Imprecision judgment Some concerns ▼
Comparison Saccharin:Sucralose Evidence: indirect NMA estimate: -19.466 95% Confidence interval: Confidence (-134.851,95.920) <i>interval extends into clinically important effects</i> Imprecision judgment Some concerns ▼			

Relative effect estimates below -100.0 and above 100.0 mmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CiNEMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood glucose incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Thus, we calculated the MID by taking 20% of 500 mmol*mins/L which is the median of glucose iAUC in healthy participants (~300 mmol*mins/L) and those with type 2 diabetes (~700 mmol*mins/L) after a 75-g oral glucose tolerance test (32-34).

Figure S39. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants



Comparison Ace-K + Sucralose:Aspartame
Evidence: indirect
NMA estimate: -65.109
95% intervals for NMA estimate
Confidence interval:
Prediction (-194.531,64.312)
interval: (-275.255,145.036)
Prediction interval **extends** into clinically important or unimportant effects
Heterogeneity judgment
Some concerns ▼

Comparison Ace-K + Sucralose:Saccharin
Evidence: indirect
NMA estimate: 13.913
95% intervals for NMA estimate
Confidence interval:
Prediction (-102.861,130.687)
interval: (-175.696,203.522)
Confidence and prediction intervals **agree** in relation to clinically important effect
Heterogeneity judgment
No concerns ▼

Comparison Ace-K + Sucralose:Sucralose
Evidence: indirect
NMA estimate: -5.553
95% intervals for NMA estimate
Confidence interval:
Prediction interval: (-62.835,51.730)
Confidence and prediction intervals **agree** in relation to clinically important effect
Heterogeneity judgment
No concerns ▼

Comparison Aspartame:Saccharin
Evidence: indirect
NMA estimate: 79.022
95% intervals for NMA estimate
Confidence interval:
Prediction (-84.631,242.676)
interval: (-186.707,344.752)
Prediction interval **extends** into clinically important or unimportant effects
Heterogeneity judgment
Some concerns ▼

Comparison Saccharin:Sucralose
Evidence: indirect
NMA estimate: -19.466
95% intervals for NMA estimate
Confidence interval:
Prediction (-134.851,95.920)
interval: (-206.821,167.889)
Prediction interval **extends** into clinically important or unimportant effects
Heterogeneity judgment
Some concerns ▼

Figure S40. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in HEALTHY participants

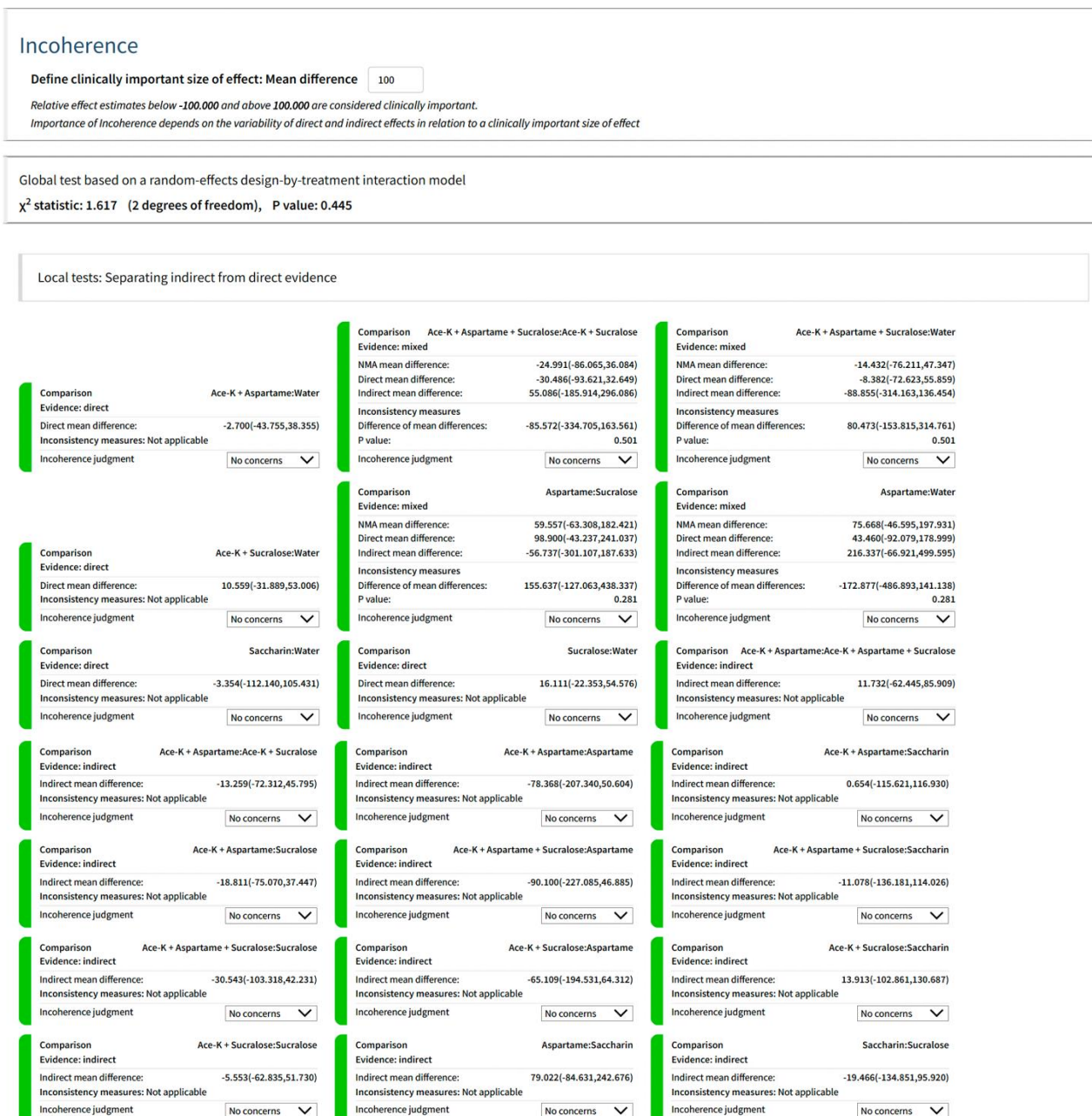
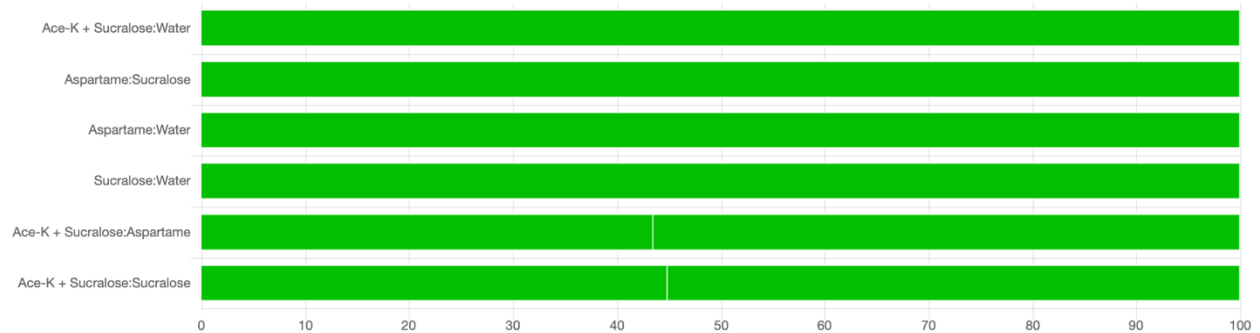
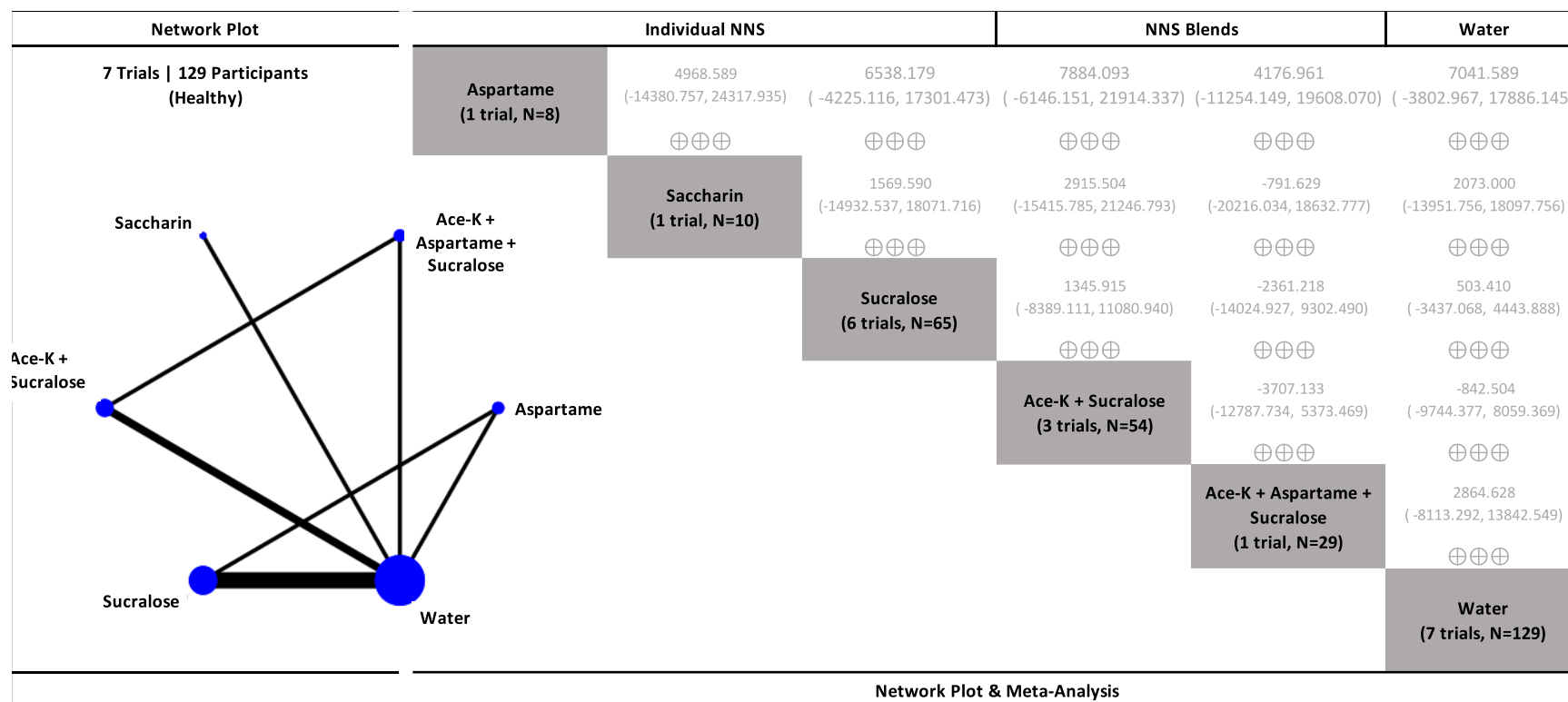


Figure S41. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCOSE response in participants with TYPE 2 DIABETES



Green = no concerns; yellow = some concerns; red = major concerns

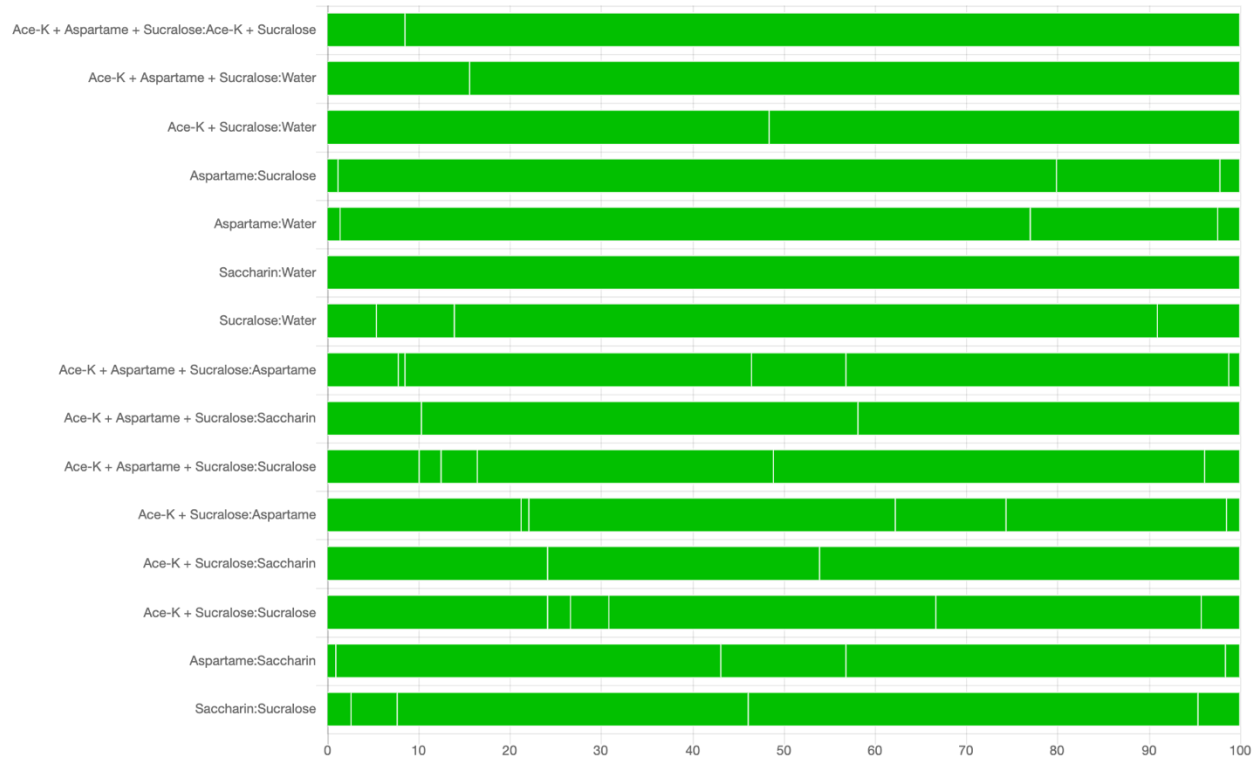
Figure S42. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants



Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 2250 pmol*min/L. Trivial

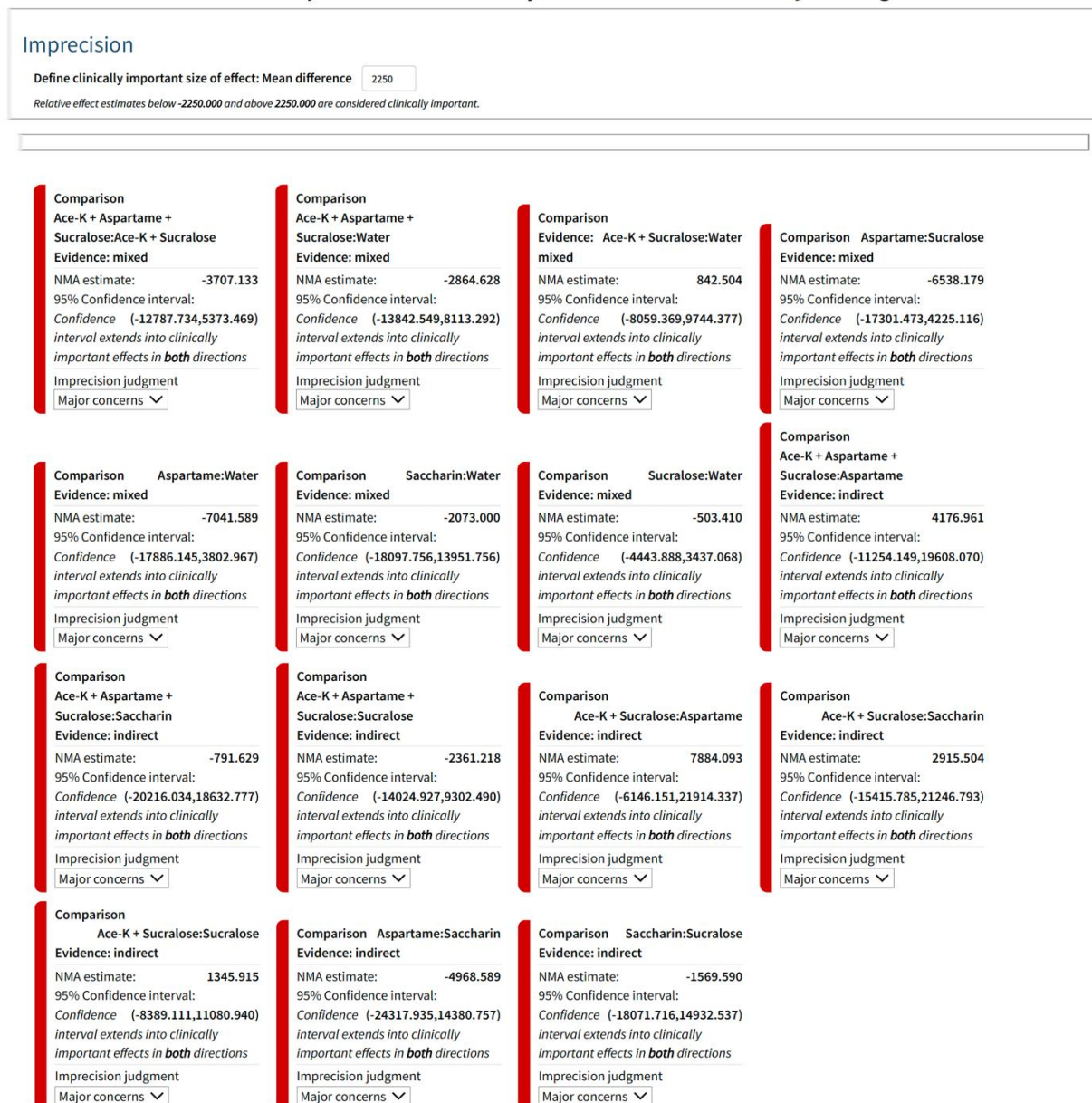
(significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 19 and Figures 43-46** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S43. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants



Green = no concerns; yellow = some concerns; red = major concerns

Figure S44. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants



Relative effect estimates below -2250.0 and above 2250.0 pmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CiNEMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood insulin incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated

the MID of insulin iAUC by taking 20% of 11250 pmol*mins/L which is the median of insulin iAUC in participants with type 2 diabetes (~6200 pmol*mins/L) and healthy participants (~16300 pmol*mins/L) after a 75-g oral glucose tolerance test (32-34).

Figure S45. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants

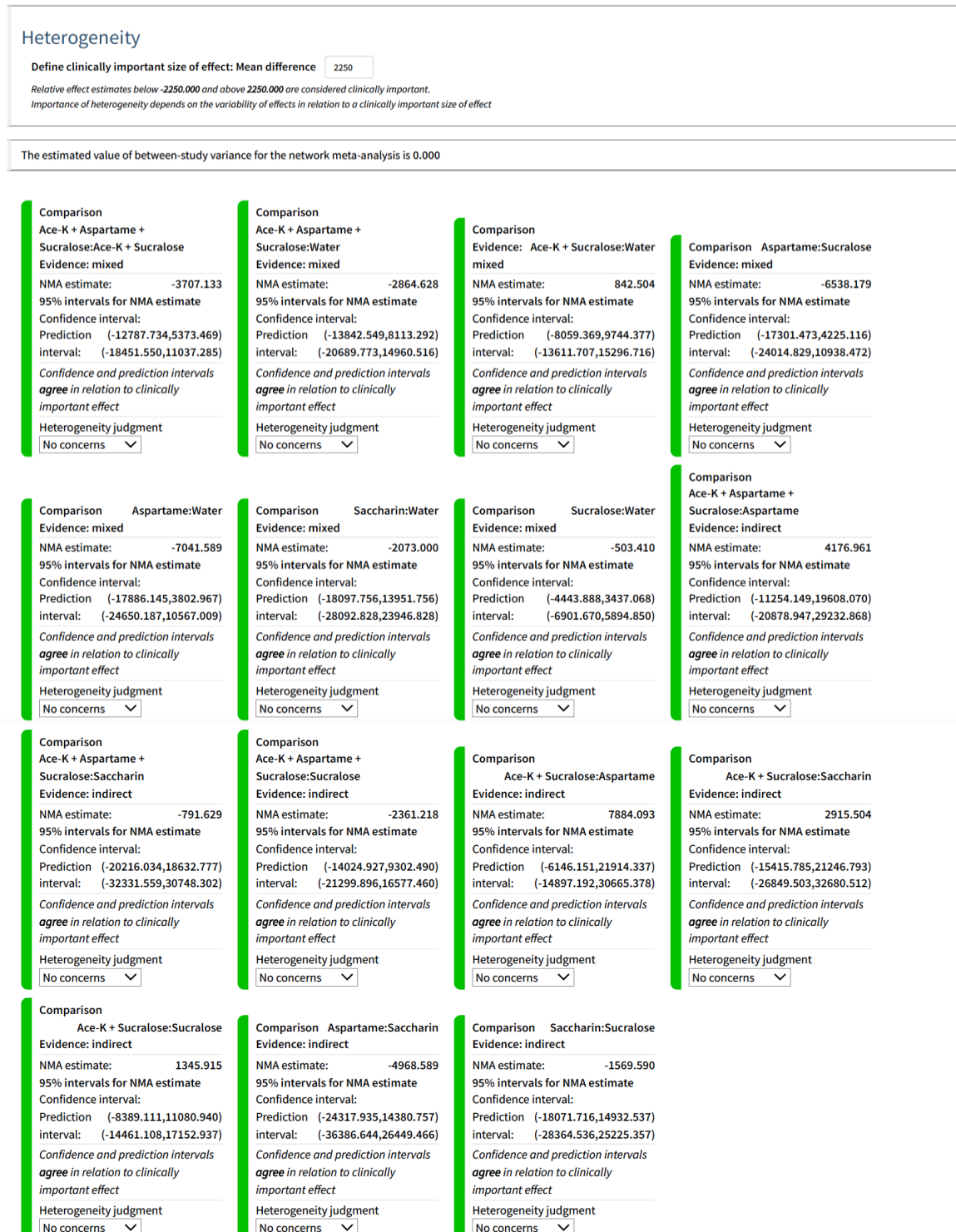


Figure S46. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in HEALTHY participants

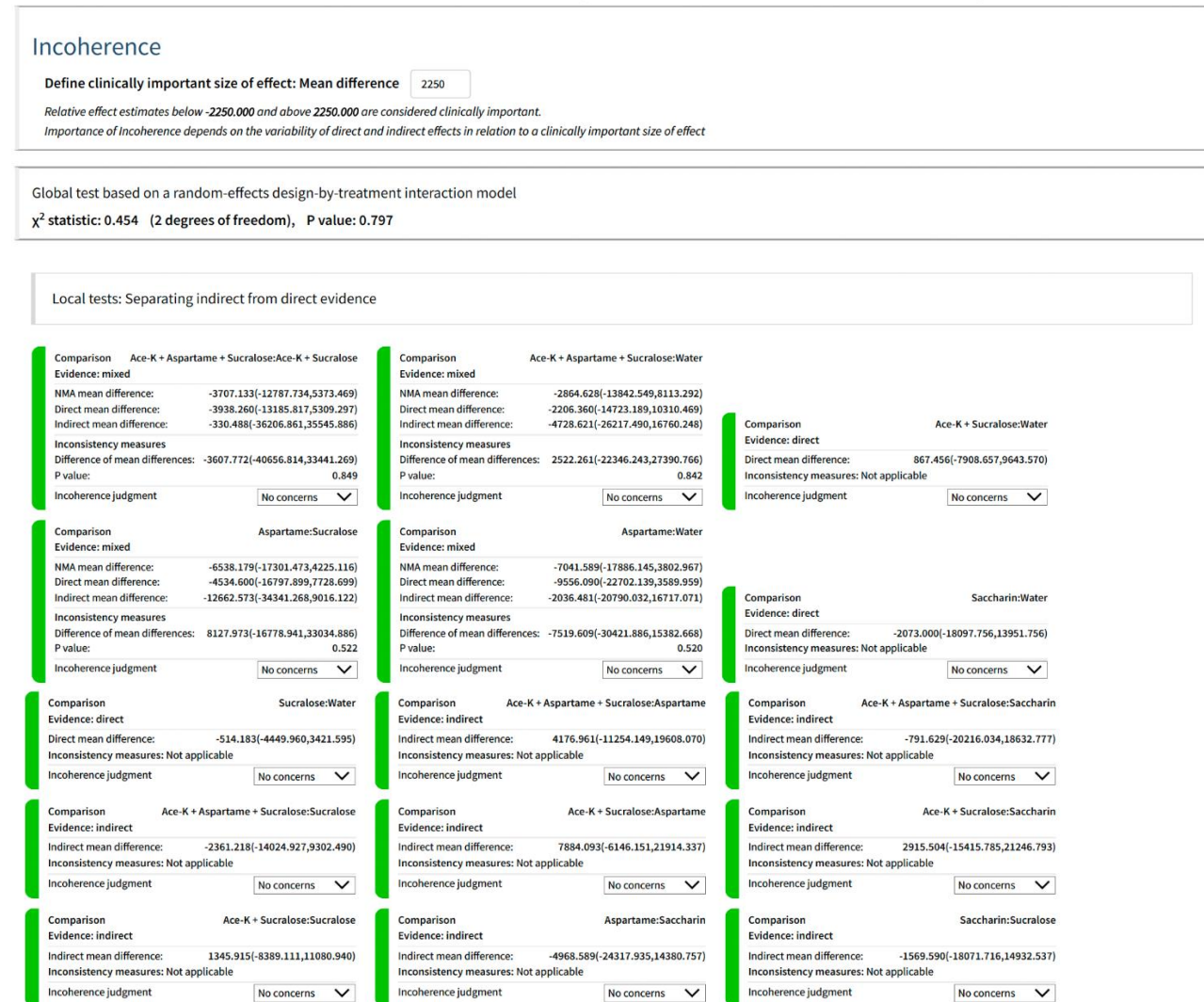
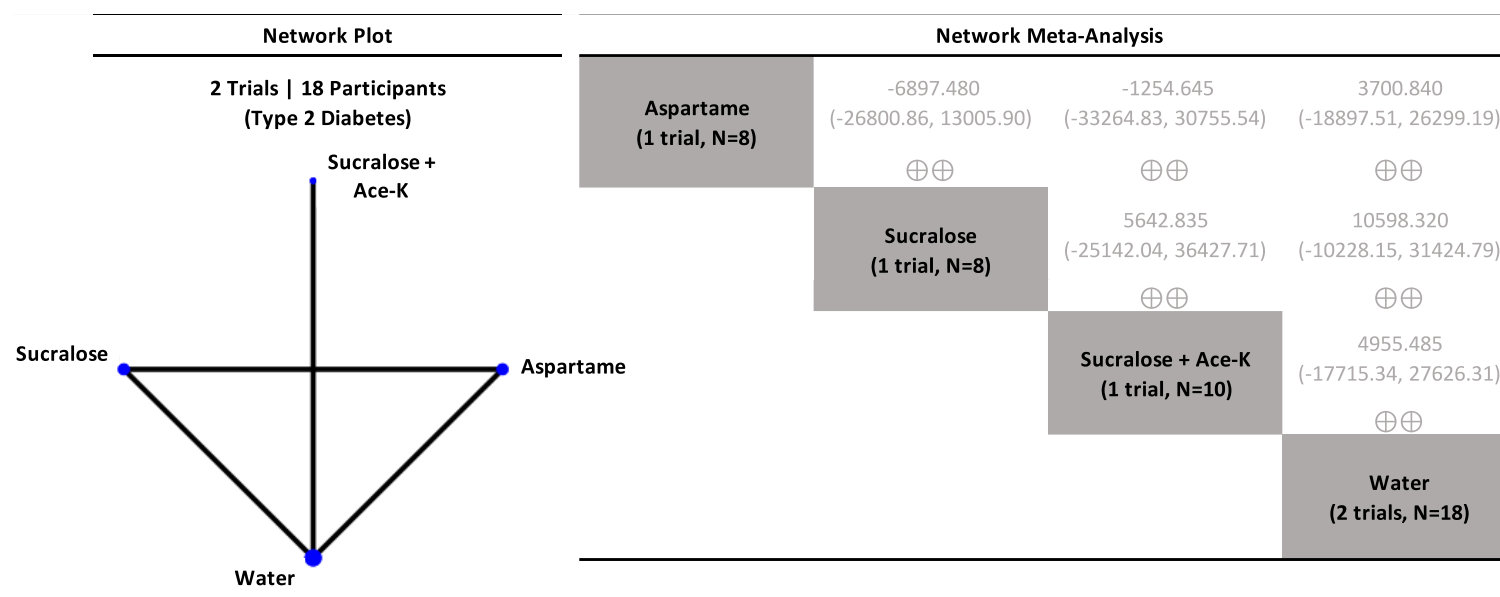
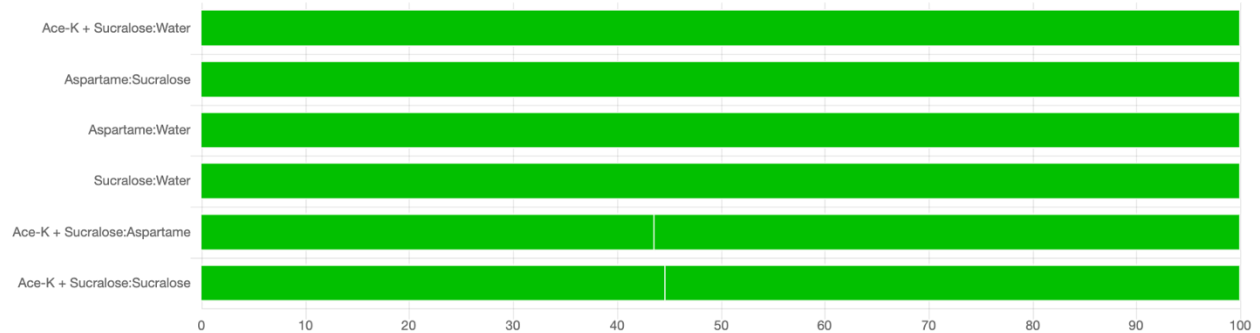


Figure S47. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



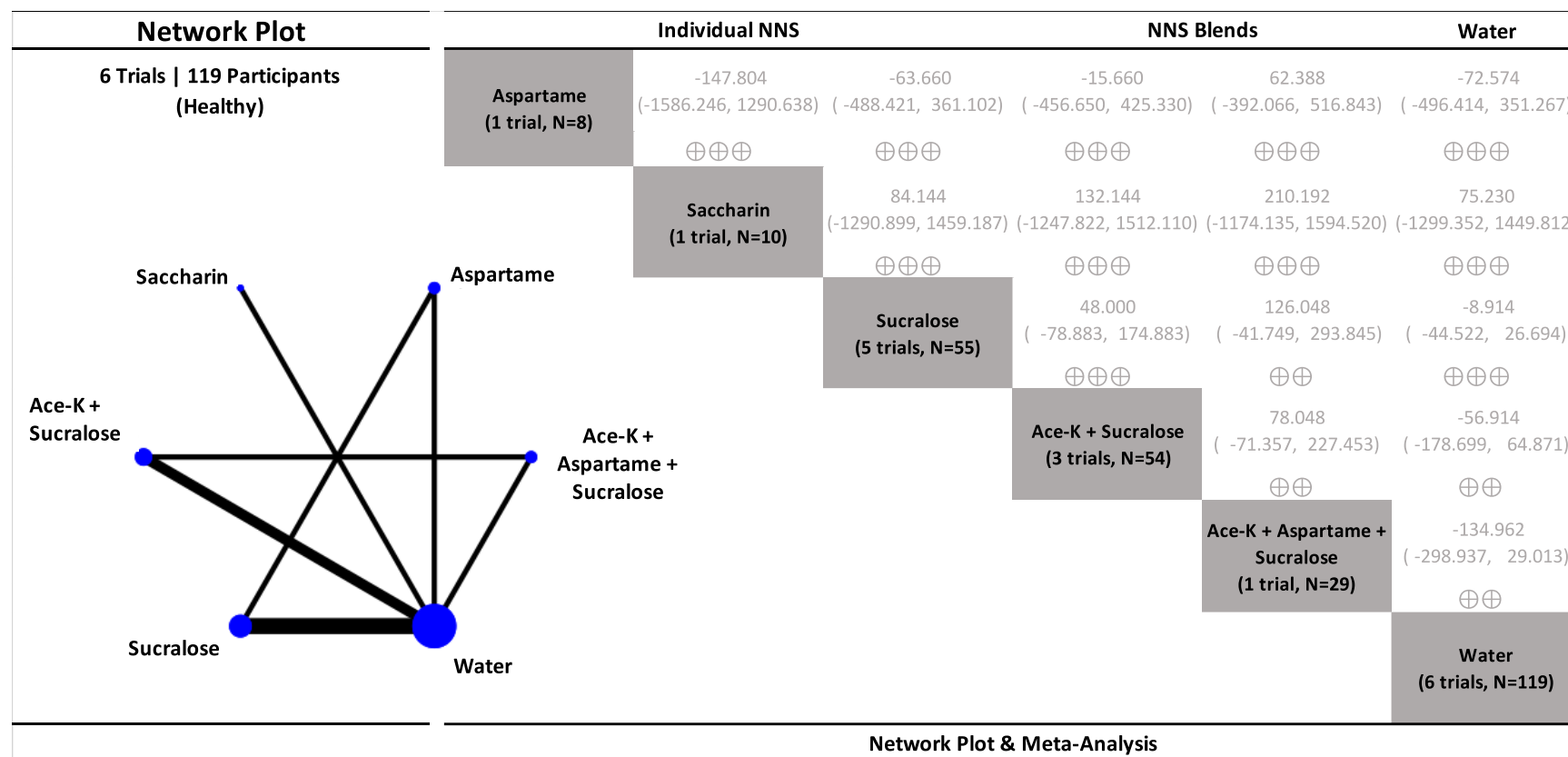
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 2250 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 20** and **Figure 48** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S48. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood INSULIN response in participants with TYPE 2 DIABETES



Green = no concerns; yellow = some concerns; red = major concerns

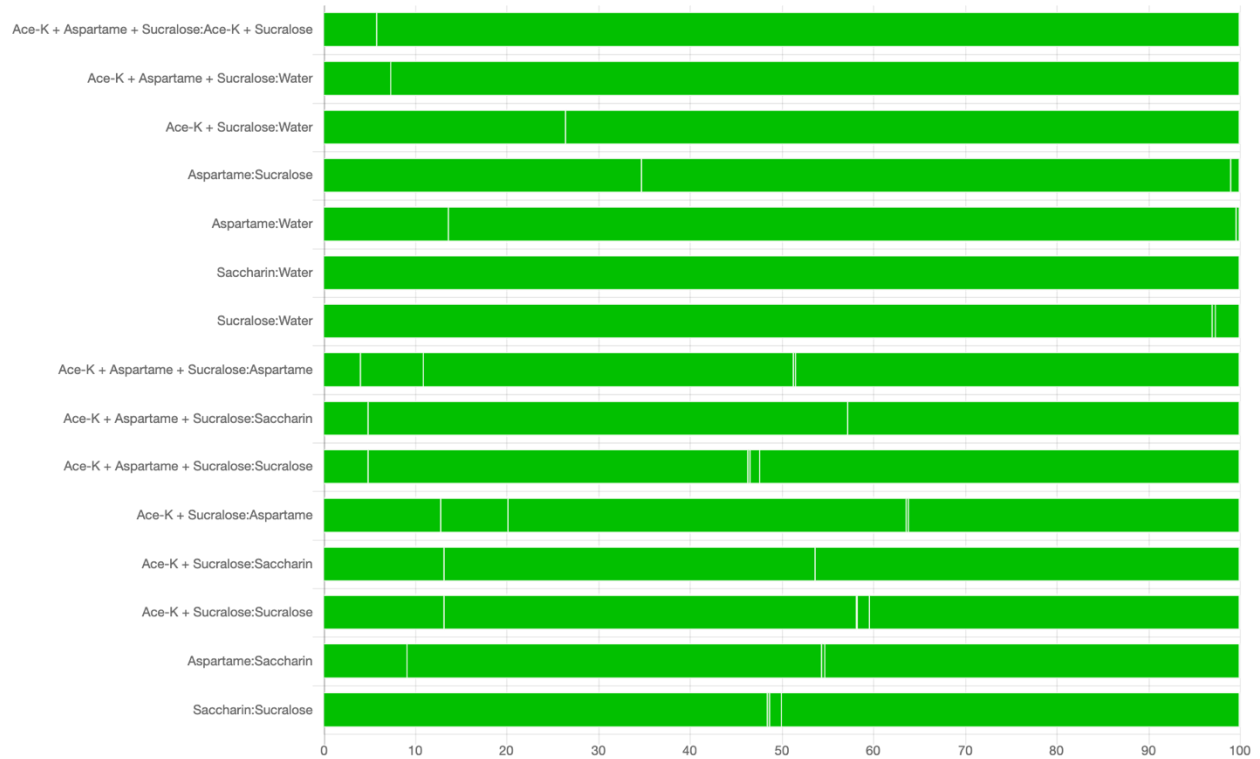
Figure S49. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants



Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are

grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 82 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 21 and Figures 50-53** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S50. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants



Green = no concerns; yellow = some concerns; red = major concerns

Figure S51. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants



Relative effect estimates below -82.0 and above 82.0 pmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CINeMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood GLP-1 incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per "Guideline Concerning the Safety and Physiological Effects of Novel Fibre

Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of GLP-1 iAUC by taking 20% of 412 pmol*mins/L which is the median of the difference in GLP-1 iAUC among healthy participants (~95 pmol*mins/L) and those with type 2 diabetes (~633 pmol*mins/L) after a glucose or meal tolerance test (30).

Figure S52. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants

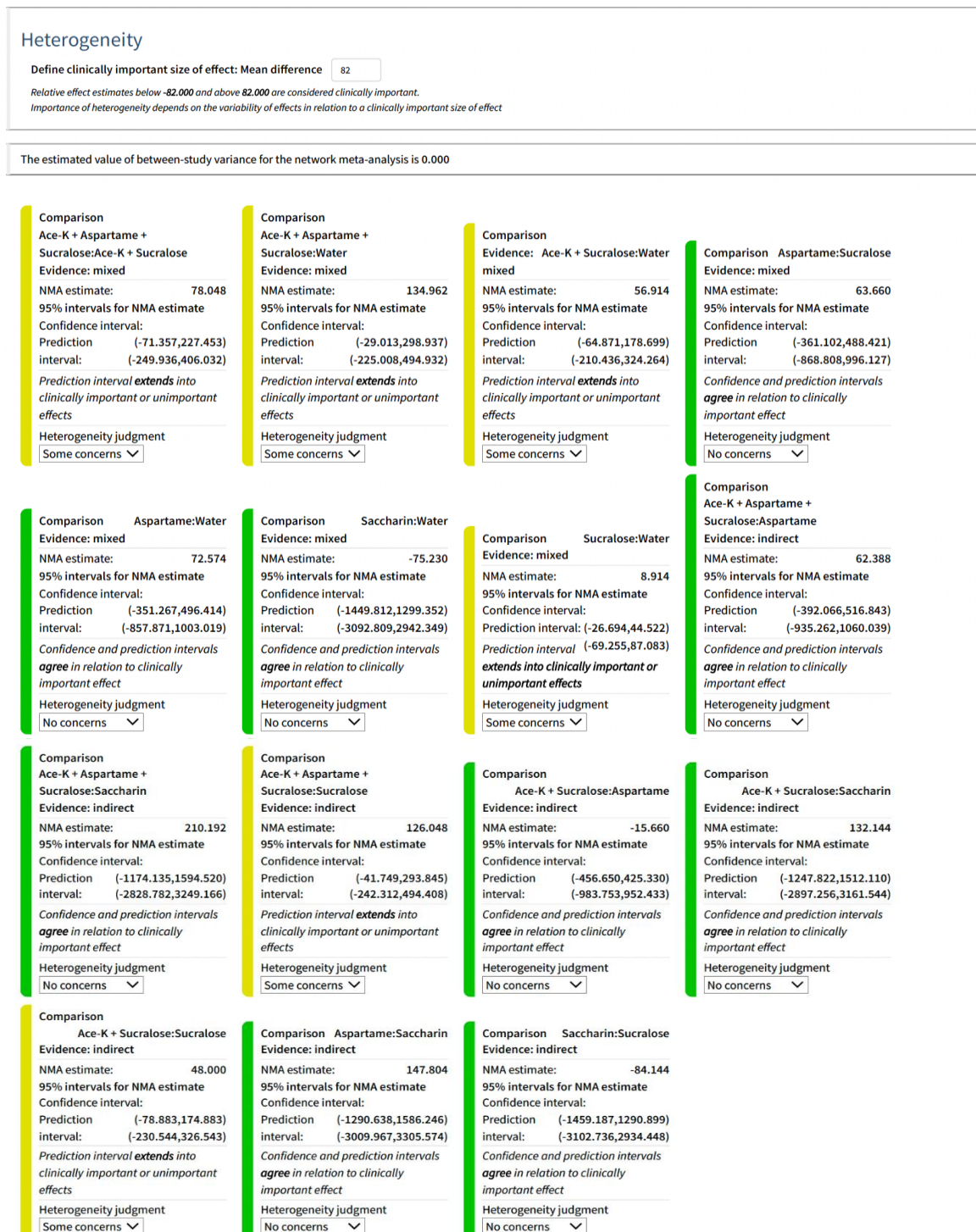


Figure S53. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in HEALTHY participants

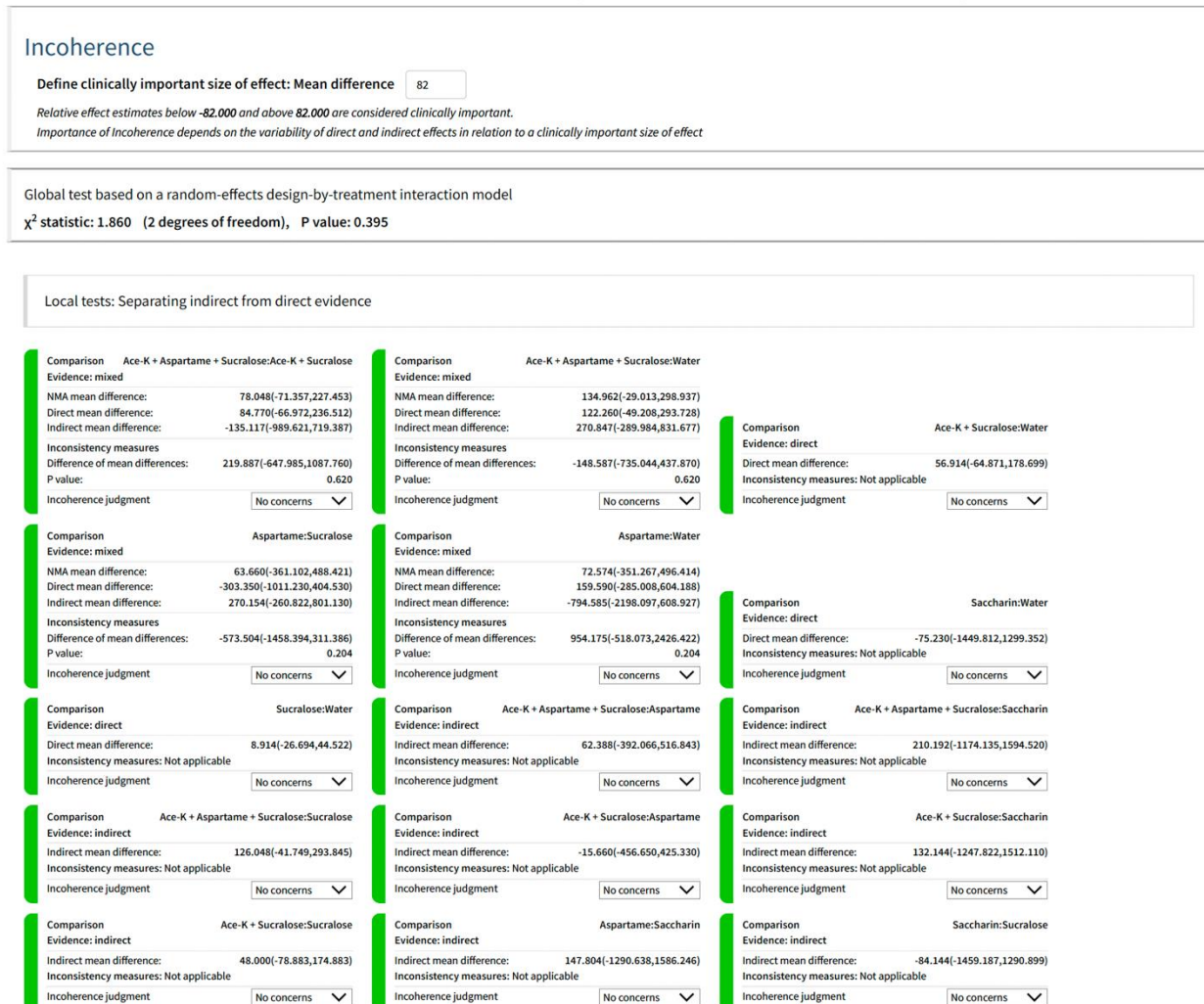
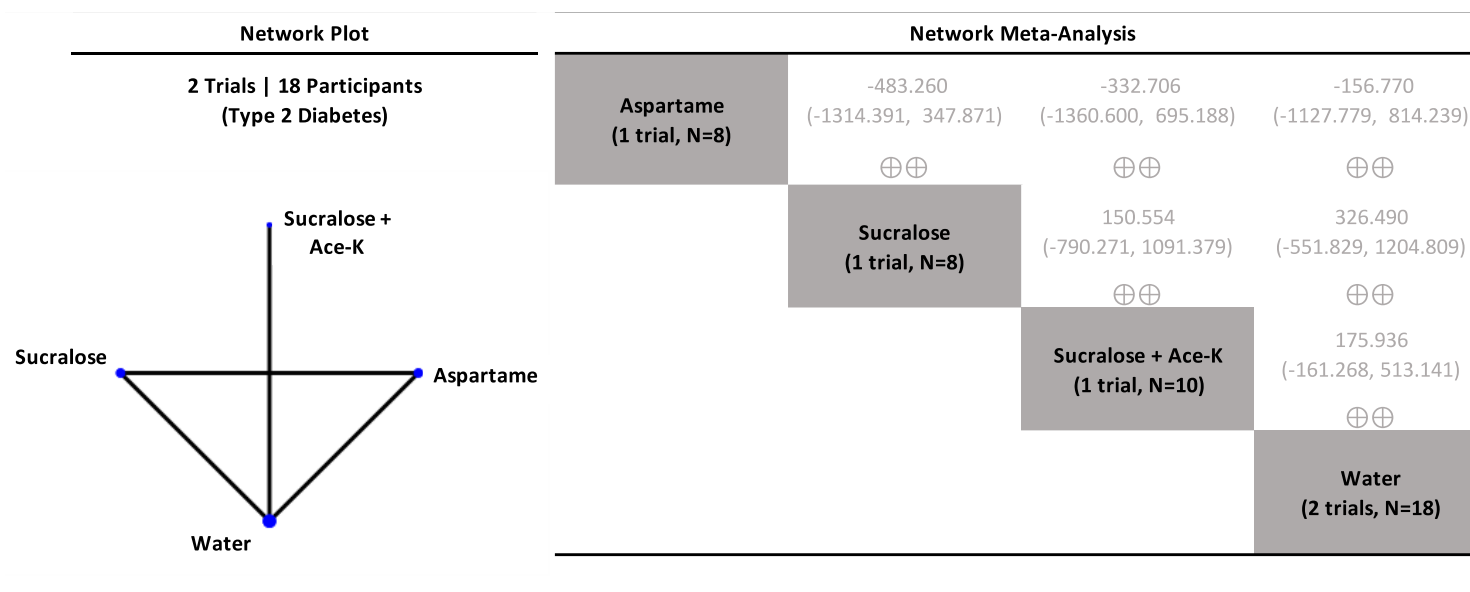
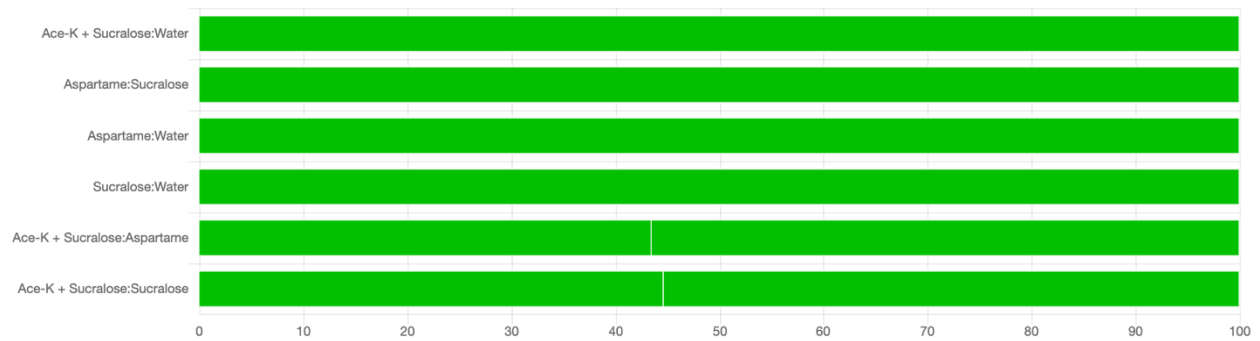


Figure S54. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in participants with TYPE 2 DIABETES



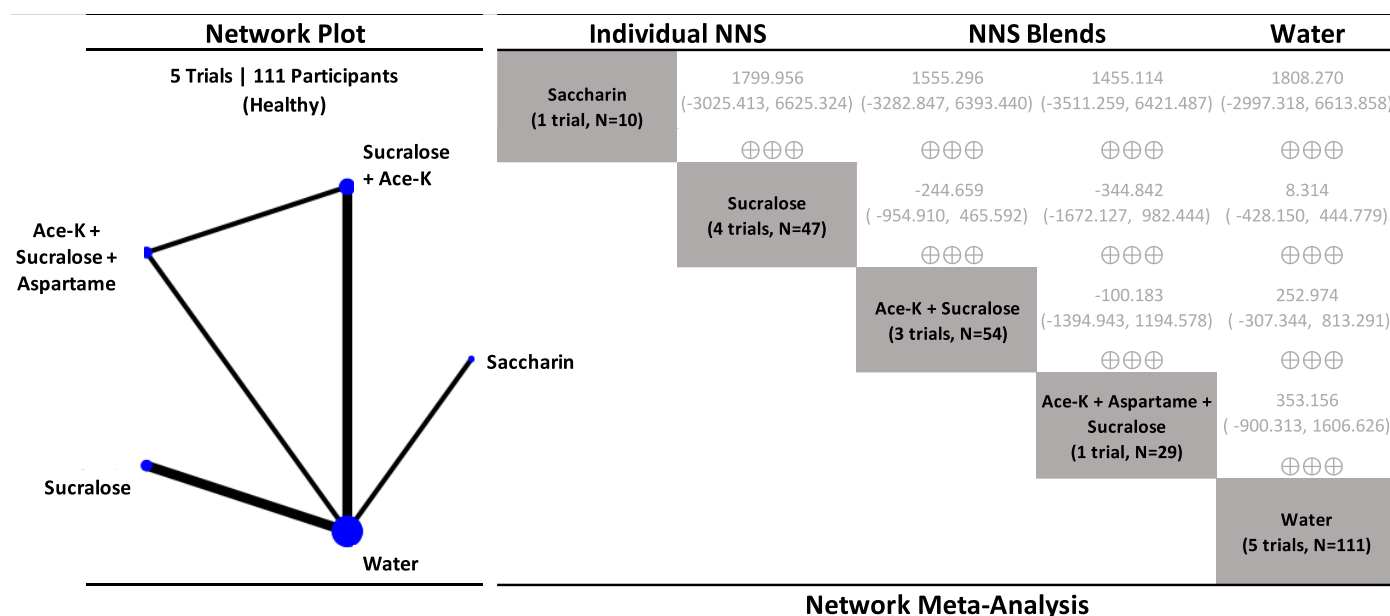
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 82 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 22 and Figure 55** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S55. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLP-1 response in participants with TYPE 2 DIABETES



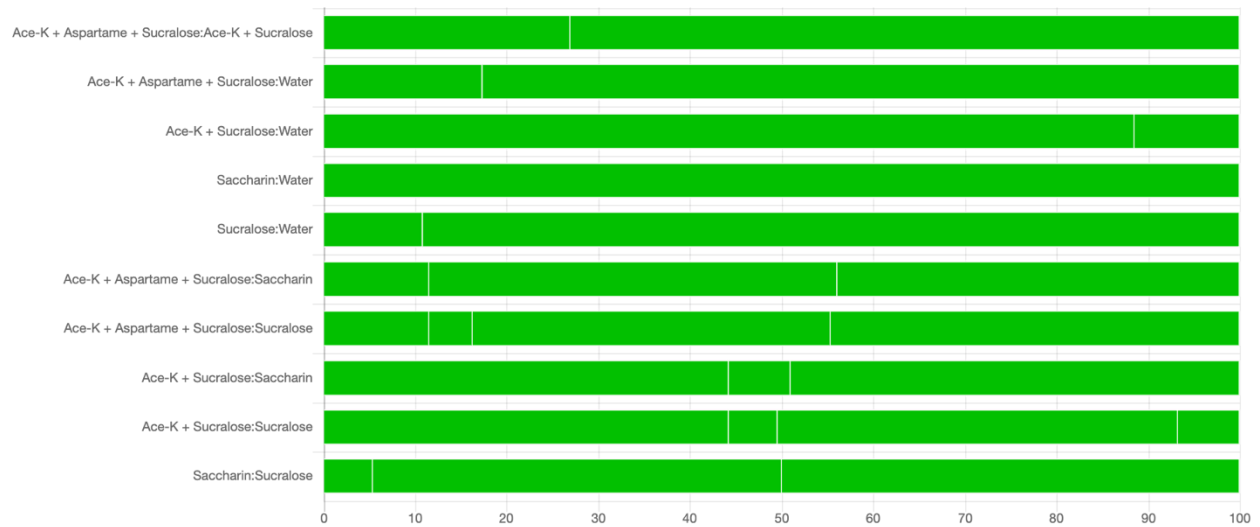
Green = no concerns; yellow = some concerns; red = major concerns

Figure S56. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants



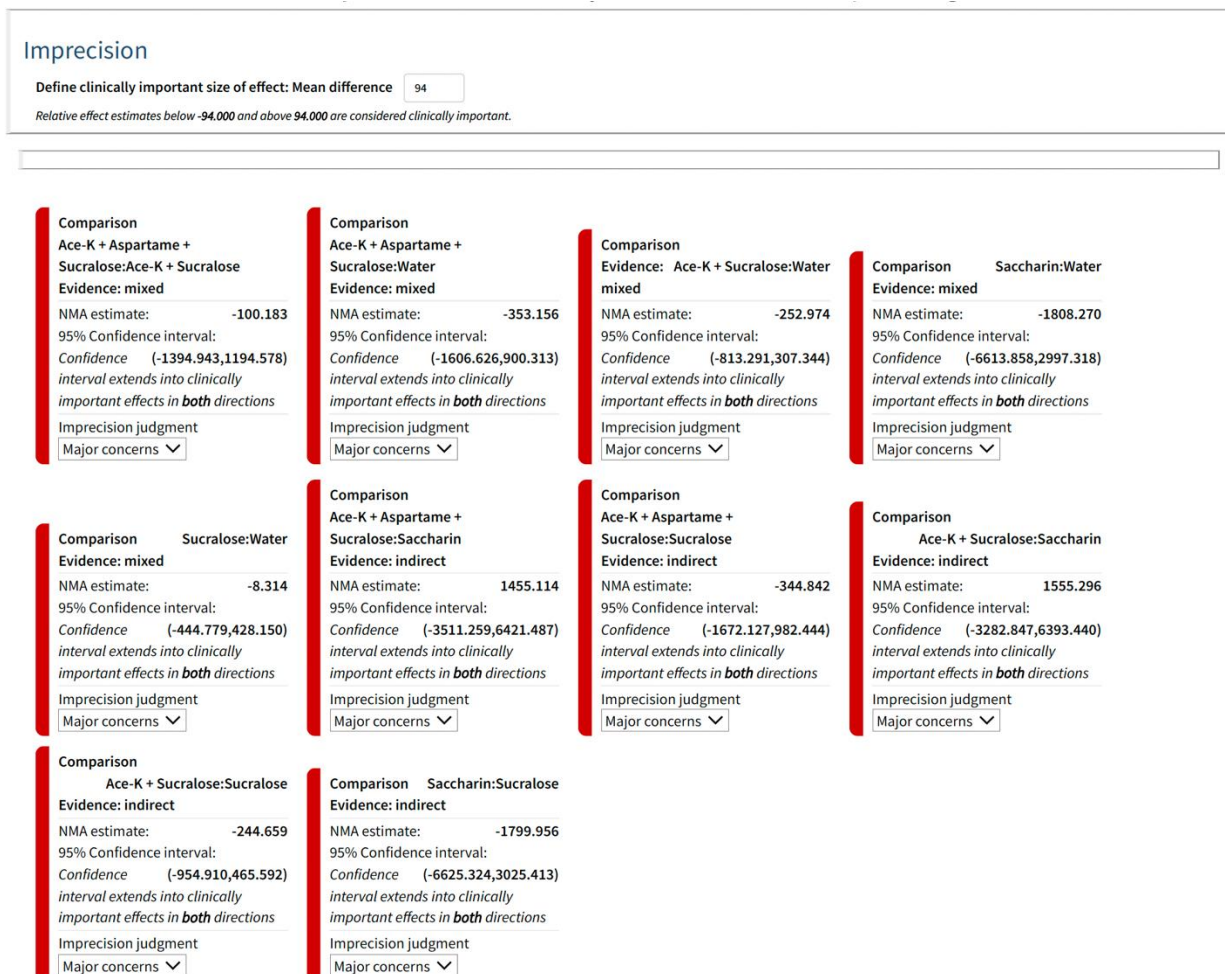
Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in black. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 94 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥1 MID) have a light blue background; moderate effects (≥2 MID) have a darker blue background; large effects (≥5 to <10 MID) have a purple background; very large effects (≥10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence ⊕⊕⊕⊕; moderate confidence ⊕⊕⊕; low confidence ⊕⊕; very low confidence ⊕. See **Supplementary Table 23 and Figures 57-60** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S57. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants



Green = no concerns; yellow = some concerns; red = major concerns

Figure S58. CINeMA output for the IMPRECISION domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants



Relative effect estimates below -94.0 and above 94.0 pmol*min/L (minimal important difference; MID) were considered clinically important. Judgements for IMPRECISION were assigned by the CiNEMA algorithm (27, 28). There is no general consensus on a clinically important size difference for 2-hour blood GIP incremental area under the curve (iAUC). Health Canada considers a 20% reduction in glucose iAUC to be the minimum physiologically relevant difference as per “Guideline Concerning the Safety and Physiological Effects of Novel Fibre Sources and Food Products Containing Them” (29). Extrapolating the 20% threshold in glucose iAUC, we calculated the MID of GIP iAUC by taking 20% of 468 pmol*mins/L which is the median of the difference in GIP iAUC among healthy participants (~168 pmol*mins/L) and those with type 2 diabetes (~768 pmol*mins/L) after a glucose or meal tolerance test (31).

Figure S59. CINeMA output for the HETEROGENEITY domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants

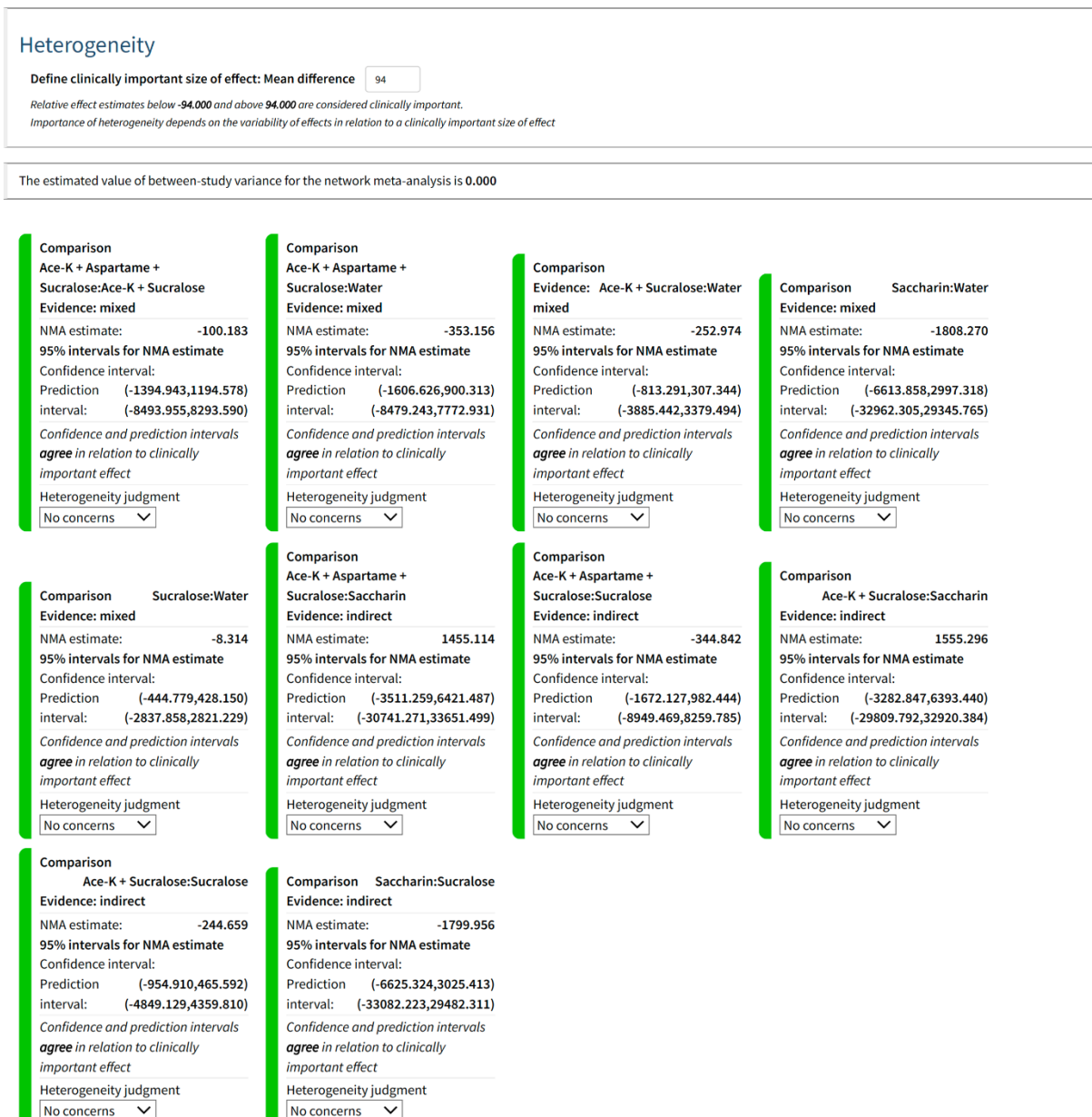


Figure S60. CINeMA output for the INCOHERENCE domain of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GIP response in HEALTHY participants

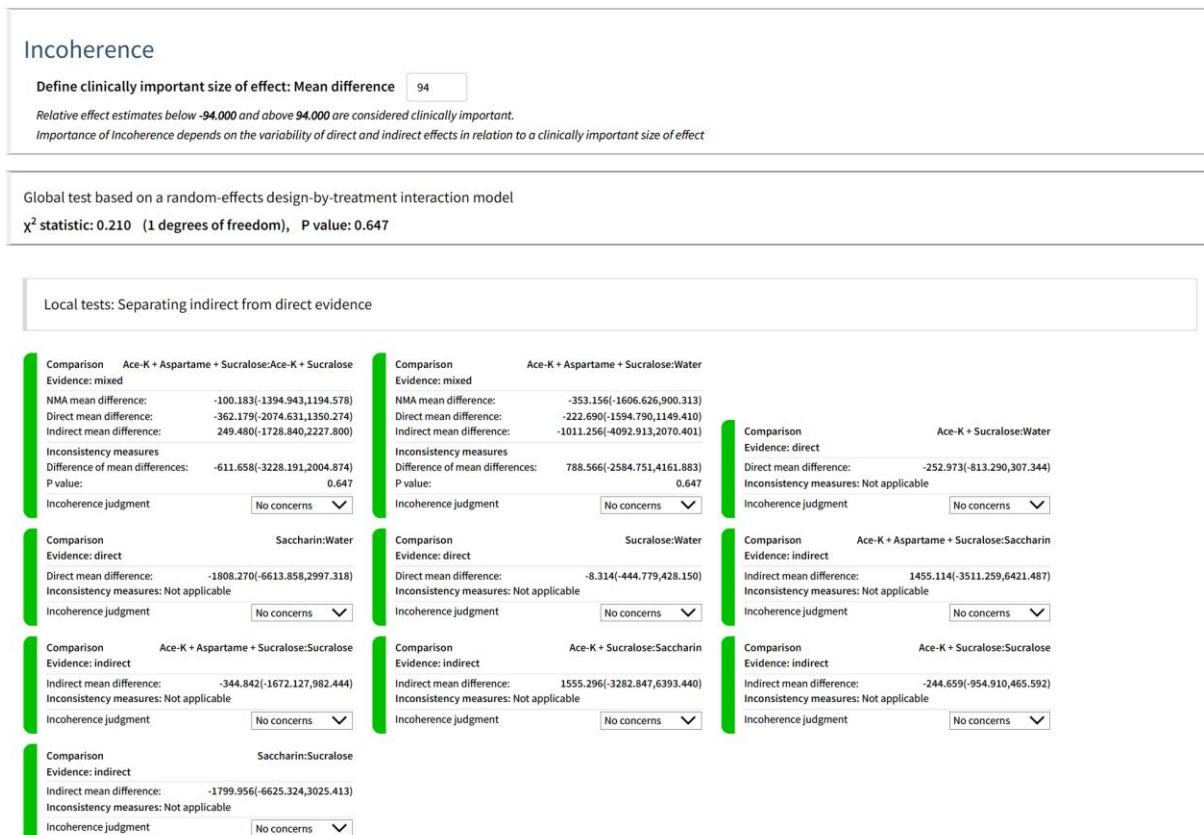
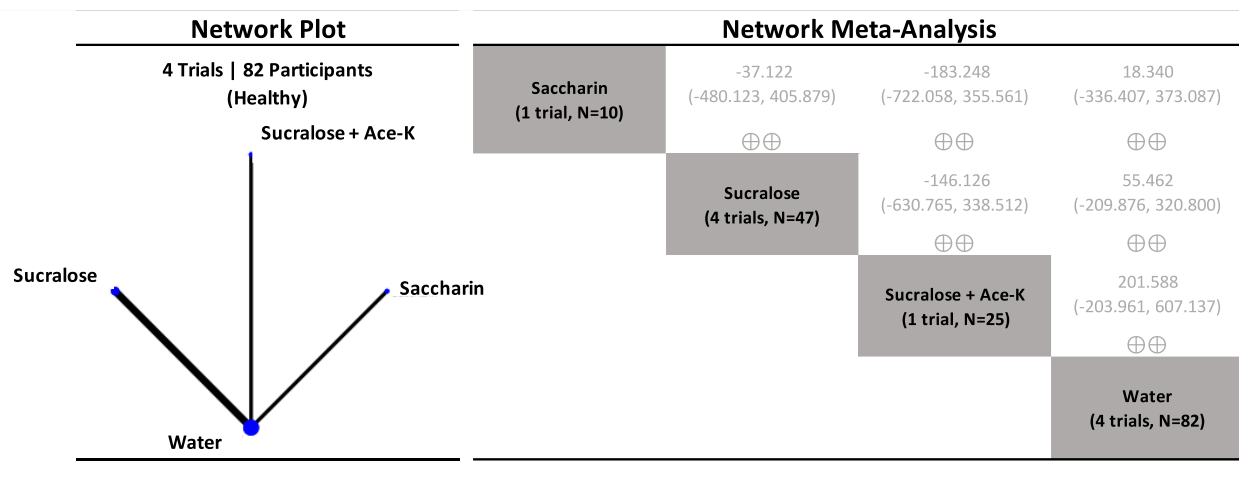
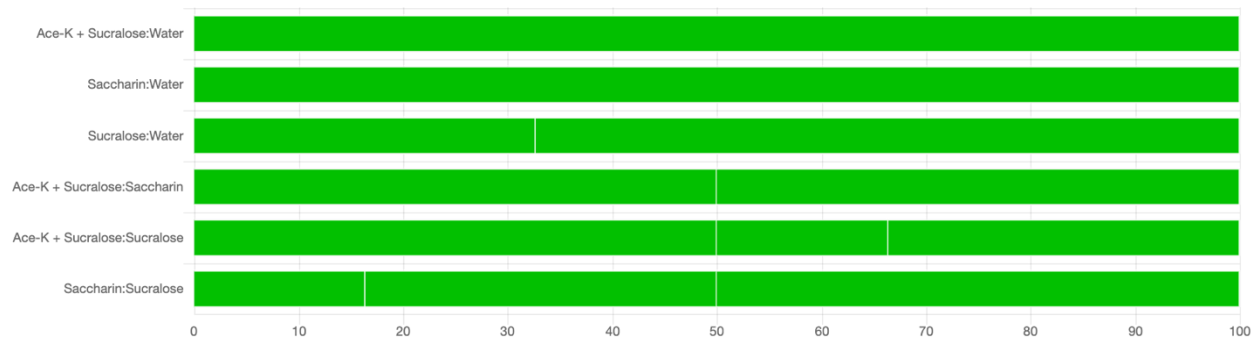


Figure S61. Network plot and meta-analysis of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants



Network plot: the size of the blue nodes is proportional to the number of participants and the line width is proportional to the number of studies. Network table: treatments are grouped by treatment type (i.e., individual non-nutritive sweeteners (NNS), NNS blends, water and caloric sweeteners) and are reported in alphabetical order. Treatment estimates (pmol*min/L) are MDs and 95% CIs of the column-defining treatment compared with the row-defining treatment. MDs less than 0 favor the column-defining treatment. MDs greater than 0 favor the row-defining treatment. Significant results are bolded in white. Non-significant results are grey and not bolded. The minimally important difference (MID) for postprandial glucose response is 205 pmol*min/L. Trivial (significant) effects (<1 MID) or no effects have a white background; small important effects (≥ 1 MID) have a light blue background; moderate effects (≥ 2 MID) have a darker blue background; large effects (≥ 5 to <10 MID) have a purple background; very large effects (≥ 10 MID) have a black background. Confidence in the effect estimate is shown for each treatment comparison: high confidence $\oplus\oplus\oplus\oplus$; moderate confidence $\oplus\oplus\oplus$; low confidence $\oplus\oplus$; very low confidence \oplus . See **Supplementary Table 24** and **Figure 62** for detailed assessments of the confidence in the effect estimate using the CINeMA framework.

Figure S62. Risk of bias assessment of DELAYED COUPLING INTERVENTIONS evaluating the effect of non-nutritive sweetened beverages (NNS beverages) sweetened single or blends of non-nutritive sweeteners (NNS), water, and sugar-sweetened beverages (SSBs) sweetened with caloric sweeteners on postprandial blood GLUCAGON response in HEALTHY participants



Green = no concerns; yellow = some concerns; red = major concerns

SUPPLEMENTARY REFERENCES

1. U.S. Food and Drug Administration. Additional Information about High-Intensity Sweeteners Permitted for Use in Food in the United States; 2018. Accessed at <https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states> on October 2, 2021. .
2. Shigeta H, Yoshida T, Nakai M, Mori H, Kano Y, Nishioka H, et al. Effects of aspartame on diabetic rats and diabetic patients. *J Nutr Sci Vitaminol (Tokyo)*. 1985;31(5):533-40.
3. Okuno G, Kawakami F, Tako H, Kashihara T, Shibamoto S, Yamazaki T, et al. Glucose tolerance, blood lipid, insulin and glucagon concentration after single or continuous administration of aspartame in diabetics. *Diabetes Res Clin Pract*. 1986;2(1):23-7.
4. Horwitz DL, McLane M, Kobe P. Response to single dose of aspartame or saccharin by NIDDM patients. *Diabetes Care*. 1988;11(3):230-4.
5. Møller SE. Effect of aspartame and protein, administered in phenylalanine-equivalent doses, on plasma neutral amino acids, aspartate, insulin and glucose in man. *Pharmacol Toxicol*. 1991;68(5):408-12.
6. Härtel B, Graubau H, Schneider B. The Influence of Sweetener Solutions on the Secretion of Insulin and the Blood Glucose Level. *Ernährungsumschau*. 1993;40(4):152-55.
7. Nguyen UN, Dumoulin G, Henriët MT, Regnard J. Aspartame ingestion increases urinary calcium, but not oxalate excretion, in healthy subjects. *J Clin Endocrinol Metab*. 1998;83(1):165-8.
8. Coppola L, Coppola A, Grassia A, Mastrolorenzo L, Lettieri B, De Lucia D, et al. Acute hyperglycemia alters von Willebrand factor but not the fibrinolytic system in elderly subjects with normal or impaired glucose tolerance. *Blood Coagul Fibrinolysis*. 2004;15(8):629-35.
9. Berlin I, Vorspan F, Warot D, Manéglia B, Spreux-Varoquaux O. Effect of glucose on tobacco craving. Is it mediated by tryptophan and serotonin? *Psychopharmacology (Berl)*. 2005;178(1):27-34.
10. Ford HE, Peters V, Martin NM, Sleeth ML, Ghatei MA, Frost GS, et al. Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy normal-weight subjects. *Eur J Clin Nutr*. 2011;65(4):508-13.
11. Maersk M, Belza A, Holst JJ, Fenger-Grøn M, Pedersen SB, Astrup A, et al. Satiety scores and satiety hormone response after sucrose-sweetened soft drink compared with isocaloric semi-skimmed milk and with non-caloric soft drink: a controlled trial. *Eur J Clin Nutr*. 2012;66(4):523-9.
12. Hazali N, Mohamed A, Ibrahim M, Masri M, Anuar K, Norazmir MN, et al. Effect of Acute Stevia Consumption on Blood Glucose Response in Healthy Malay Young Adults. *Sains Malaysiana*. 2014;43:649-54.
13. Bloomer R, Peel S, Moran R, MacDonnchadh J. Blood glucose and insulin response to artificially- and sugar-sweetened sodas in healthy men. *Integrative Food, Nutrition and Metabolism*. 2016;3.
14. González-Domínguez R, Mateos RM, Lechuga-Sancho AM, González-Cortés JJ, Corrales-Cuevas M, Rojas-Cots JA, et al. Synergic effects of sugar and caffeine on insulin-mediated

metabolomic alterations after an acute consumption of soft drinks. *Electrophoresis*. 2017;38(18):2313-22.

15. Goza R, Bunout D, Barrera G, de la Maza M, Hirsch S. Effect of Acute Consumption of Artificially Sweetened Beverages on Blood Glucose and Insulin in Healthy Subjects. *Journal of Nutrition & Food Sciences*. 2018;08.
16. Eckstein MLB, A. Haupt, S. Schierbauer, J. R. Zimmer, R. T. Wachsmuth, N. Zunner, B. Zimmermann, P. Obermayer-Pietsch, B. Moser, O. Acute Metabolic Responses to Glucose and Fructose Supplementation in Healthy Individuals: A Double-Blind Randomized Crossover Placebo-Controlled Trial. *Nutrients*. 2021;13(11):16.
17. Wolf-Novak LC, Stegink LD, Brummel MC, Persoon TJ, Filer LJ, Jr., Bell EF, et al. Aspartame ingestion with and without carbohydrate in phenylketonuric and normal subjects: effect on plasma concentrations of amino acids, glucose, and insulin. *Metabolism*. 1990;39(4):391-6.
18. Melchior JC, Rigaud D, Colas-Linhart N, Petiet A, Girard A, Apfelbaum M. Immunoreactive beta-endorphin increases after an aspartame chocolate drink in healthy human subjects. *Physiol Behav*. 1991;50(5):941-4.
19. Solomi L, Rees GA, Redfern KM. The acute effects of the non-nutritive sweeteners aspartame and acesulfame-K in UK diet cola on glycaemic response. *Int J Food Sci Nutr*. 2019;70(7):894-900.
20. Brown RJ, Walter M, Rother KI. Effects of diet soda on gut hormones in youths with diabetes. *Diabetes Care*. 2012;35(5):959-64.
21. Pepino MY, Tiemann CD, Patterson BW, Wice BM, Klein S. Sucralose affects glycemic and hormonal responses to an oral glucose load. *Diabetes Care*. 2013;36(9):2530-5.
22. Temizkan S, Deyneli O, Yasar M, Arpa M, Gunes M, Yazici D, et al. Sucralose enhances GLP-1 release and lowers blood glucose in the presence of carbohydrate in healthy subjects but not in patients with type 2 diabetes. *Eur J Clin Nutr*. 2015;69(2):162-6.
23. Sylvestsky AC, Brown RJ, Blau JE, Walter M, Rother KI. Hormonal responses to non-nutritive sweeteners in water and diet soda. *Nutrition & Metabolism*. 2016;13(1):71.
24. Karimian Azari E, Smith KR, Yi F, Osborne TF, Bizzotto R, Mari A, et al. Inhibition of sweet chemosensory receptors alters insulin responses during glucose ingestion in healthy adults: a randomized crossover interventional study. *Am J Clin Nutr*. 2017;105(4):1001-9.
25. Nichol AD, Salame C, Rother KI, Pepino MY. Effects of Sucralose Ingestion versus Sucralose Taste on Metabolic Responses to an Oral Glucose Tolerance Test in Participants with Normal Weight and Obesity: A Randomized Crossover Trial. *Nutrients*. 2019;12(1).
26. Solomi, L. (2020) 'Diet cola and glycaemia: The acute effects of a preload containing the non-nutritive sweeteners aspartame and acesulfame-K on the glycaemic response to a glucose load', *The Plymouth Student Scientist*, 13(1), p. 97-111.
27. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLOS Medicine*. 2020;17(4):e1003082.
28. Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Systematic Reviews*. 2020;16(1):e1080.

29. Bureau of Nutritional Sciences, Food Directorate, Health Products and Food Branch. Summary of Health Canada's Assessment of a Health Claim about a Polysaccharide Complex (Glucomannan, Xanthan Gum, Sodium Alginate) and a Reduction of Post-Prandial Blood Glucose Response. 2016. Accessed at https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/pdf/label-etiquet/claims-reclam/assess-evalu/glucose-complex-polysaccharides-complexe-glycemique-eng.pdf on June 20, 2021.
30. Calanna S, Christensen M, Holst JJ, Laferrère B, Gluud LL, Vilsbøll T, et al. Secretion of glucagon-like peptide-1 in patients with type 2 diabetes mellitus: systematic review and meta-analyses of clinical studies. *Diabetologia*. 2013;56(5):965-72.
31. Calanna S, Christensen M, Holst JJ, Laferrère B, Gluud LL, Vilsbøll T, et al. Secretion of glucose-dependent insulintropic polypeptide in patients with type 2 diabetes: systematic review and meta-analysis of clinical studies. *Diabetes Care*. 2013;36(10):3346-52.
32. Sievenpiper JL, Jenkins DJ, Josse RG, Vuksan V. Dilution of the 75-g oral glucose tolerance test increases postprandial glycemia: implications for diagnostic criteria. *Cmaj*. 2000;162(7):993-6.
33. Braunstein CR, Noronha JC, Glenn AJ, Viguiliouk E, Noseworthy R, Khan TA, et al. A Double-Blind, Randomized Controlled, Acute Feeding Equivalence Trial of Small, Catalytic Doses of Fructose and Allulose on Postprandial Blood Glucose Metabolism in Healthy Participants: The Fructose and Allulose Catalytic Effects (FACE) Trial. *Nutrients*. 2018;10(6).
34. Noronha JC, Braunstein CR, Glenn AJ, Khan TA, Viguiliouk E, Noseworthy R, et al. The effect of small doses of fructose and allulose on postprandial glucose metabolism in type 2 diabetes: A double-blind, randomized, controlled, acute feeding, equivalence trial. *Diabetes Obes Metab*. 2018;20(10):2361-70.
35. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. www.guidelinedevelopment.org/handbook.
36. Wolever TM, Jenkins DJ, Jenkins AL, Josse RG. The glycemic index: methodology and clinical implications. *Am J Clin Nutr*. 1991;54(5):846-54.
37. Chapter 2.5.5. Propagation of error considerations. NIST/SEMATECH e-Handbook of Statistical Methods. 2003. Accessed at <https://www.itl.nist.gov/div898/handbook/mpc/section5/mpc55.htm#exact> May on 13 Sep 2021. [