Table S1. Search strategy for studies assessing the effect of fructose and its epimers (allulose, tagatose and sorbose) on markers of long-term glycemic control

Database	Search Period	Search Terms
MEDLINE	1946 to April 18, 2018	 exp Fructose/ psicose.mp. allulose.mp. tagatose.mp. sorbose.mp. 1 or 2 or 3 or 4 or 5 exp Glucose/ glycaemic.mp. glycaemia.mp. glycaemia.mp. glycaemia.mp. glycaemia.mp. exp Glucose Tolerance Test/ OGTT.mp. exp Hemoglobin A, Glycosylated/ HbA1c.mp. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 6 and 17 limit 18 to animals 18 not 19 clinical trial.mp. clinical trial.pt. random:.mp. tu.xs. 21 or 22 or 23 or 24 20 and 25
EMBASE	1946 to April 18, 2018	 exp fructose/ psicose.mp. allulose.mp. tagatose.mp. tagatose.mp. 1 or 2 or 3 or 4 or 5 exp glucose/ glycaemic.mp. glycaemic.mp. glycaemia.mp. glycemia.mp. glycemia.mp. exp insulin/ exp oral glucose tolerance test/ OGTT.mp. exp hemoglobin A1c/ HbA1c.mp. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 6 and 17 limit 18 to animals 18 not 19 random:.tw. clinical trial:.mp. exp health care quality/

		24. 21 or 22 or 23 25. 20 and 24
Cochrane Central	1946 to April 18, 2018	1. Fructose/
Register of		2. psicose.mp.
Controlled Trials		3. tagatose.mp.
		4. 1 or 2 or 3
		5. Glucose/
		6. glycaemic.mp.
		7. glycemic.mp.
		8. glycaemia.mp.
		9. glycemia.mp.
		10. Insulin/
		11. exp Glucose Tolerance Test/
		12. OGTT.mp.
		13. exp Hemoglobin A, Glycosylated/
		14. HbA1c.mp.
		15. 5 or 6 or $\overline{7}$ or 8 or 9 or 10 or 11 or 12 or 13 or 14
		16. 4 and 15

Table S2. Select sensitivity analyses in which the systematic removal of an individual trial altered the effect estimate or the evidence for heterogeneity

Outcome	Removal of	MD [95% Cl], P-value I ² , P-value
	ALLULOSE	
Fasting glucose, mmol/l	Hayashi et al.	-0.28 [-0.52, -0.04], p=0.02 l ² =0%, P _Q =0.57
	TAGATOSE	
Fasting glucose, mmol/l	Ensor et al.	-0.12 [-0.61, 0.37], p=0.63 I ² =NA P _Q =NA

Table S3. Sensitivity analyses using correlation coefficients of 0.25 and 0.75 for crossover trials

Outcome	_	CI], P-value value
(No. crossover trials/total trials)	Correlation coefficient of 0.25	Correlation coefficient of 0.75
	FRUCTOSE	
HbA _{1c} , % (3/7)	-0.40 [-0.67, -0.13], p=0.003 I ² = 0%, P _Q =0.57	-0.34 [-0.62, -0.06], p=0.02 I ² = 33%, P _Q =0.18
Fasting glucose, mmol/L (7/12)	-0.14 [-0.25, -0.03], p=0.01 $I^2 = 30\%$, P _Q =0.16	-0.12 [-0.27, 0.02], p=0.10 I ² = 48%, P _Q =0.04
Fasting insulin, pmol/L (6/10)	3.78 [-3.46, 11.02], p=0.31 I ² = 0%, P _Q =0.64	-1.50 [-8.83, 5.82], p=0.69 I ² = 13%, P _Q =0.33
	TAGATOSE	
Fasting glucose, mmol/L (1/2)	-0.33 [-0.60, -0.05], p=0.02 I ² = 0%, P _Q =0.46	-0.27 [-0.50, -0.03], p=0.03 I ² = 14%, P _Q =0.28
Fasting insulin, pmol/L (2/3)	-1.12 [-6.86, 4.63], p=0.70 $I^2 = 36\%$, P _Q =0.21	-2.42 [-7.00, 2.15], p=0.30 I ² = 70%, P _Q =0.04

Table S4. GRADE assessment

	Grading o	of Recommendation	ns, Assessment, De	evelopment and Evalua	ation (GRADE)		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
HbA _{1c} in	FRUCTOSE trials				·		
7	randomized trials	not serious	not serious	serious ¹	serious ²	none ¹⁵	⊕⊕⊖⊖LOW
Fasting	glucose in FRUCTOSE trials	L	l				
12	randomized trials	not serious	not serious	serious ³	serious ⁴	none	⊕⊕⊖⊖LOW
Fasting	insulin in FRUCTOSE trials	ļ	<u>I</u>	l	1		
10	randomized trials	not serious	not serious	serious⁵	serious ⁶	none	⊕⊕⊖⊖LOW
HbA _{1c} in	ALLULOSE_trials	I	I		1		
2	randomized trials	not serious	not serious	serious ⁷	serious ⁸	none ¹⁵	⊕⊕⊖⊖LOW
Fasting	glucose in ALLULOSE trials		•				
2	randomized trials	not serious	not serious	serious ⁷	serious ⁹	none ¹⁵	⊕⊕⊖⊜LOW
Fasting	insulin in ALLULOSE trials		•		•	•	
2	randomized trials	not serious	not serious	serious ⁷	serious ¹⁰	none ¹⁵	⊕⊕⊖⊖ LOW
HbA _{1c} in	TAGATOSE trial		I				
1	randomized trials	not serious	not serious	not serious ¹¹	serious ¹²	none ¹⁵	⊕⊕⊕⊖ MODERATE
Fasting	glucose in TAGATOSE trials	ļ.	ł	<u>I</u>	<u>.</u>	•	
2	randomized and non- randomized trials	not serious	not serious	not serious ¹¹	serious ¹³	none ¹⁵	⊕⊕⊕⊖ MODERATE
Fasting	insulin in <u>TAGATOSE</u> trials			·			
3	randomized and non- randomized trials	not serious	serious	not serious ¹¹	serious ¹⁴	none ¹⁵	⊕⊕⊕⊖ MODERATE

¹ Serious indirectness for the effect of small doses of fructose on HbA_{1c}, as the median follow-up duration was relatively short (2.5 weeks) Only 3/7 trials had a follow-up duration of \geq 8-weeks.

²Serious imprecision for the effect of small doses of fructose on HbA_{1c}, as the 95% CIs (-0.64% to -0.13%) overlap the minimally important difference for clinical benefit (0.3%)

³Serious indirectness for the effect of small doses of fructose on fasting glucose, as the median follow-up duration was relatively short (2 weeks).

⁴Serious imprecision for the effect of small doses of fructose on fasting glucose, as the 95% CIs (-0.24 mmol/l to -0.03 mmol/l) overlap the minimally important difference for clinical benefit (0.5 mmol/l)

⁵Serious indirectness for the effect of small doses of fructose on fasting insulin, as the median follow-up duration was relatively short (2 weeks).

⁶Serious imprecision for the effect of small doses of fructose on fasting insulin, as the 95% CIs (-4.19 pmol/l to 9.62 pmol/l) overlap the minimally important difference for clinical benefit (5 pmol/l)

⁷Serious indirectness for the effect of small doses of allulose on HbA_{1c} , fasting glucose and fasting insulin, as the study setting was limited to Asia (Japan and Korea) which may affect the generalizability of the results

⁸Serious imprecision for the effect of small doses of allulose on HbA_{1c}, as the 95% CIs (-0.03% to 0.07%) overlap the minimally important difference for clinical benefit (0.3%)

⁹Serious imprecision for the effect of small doses of allulose on fasting glucose, as the 95% CIs (-0.35 mmol/l to 0.00 mmol/l) overlap the minimally important difference for clinical benefit (0.5 mmol/l)

¹⁰Serious imprecision for the effect of small doses of allulose on fasting insulin, as the 95% CIs (-2.17 pmol/l to 0.79 pmol/l) overlap the minimally important difference for clinical benefit (5 pmol/l)

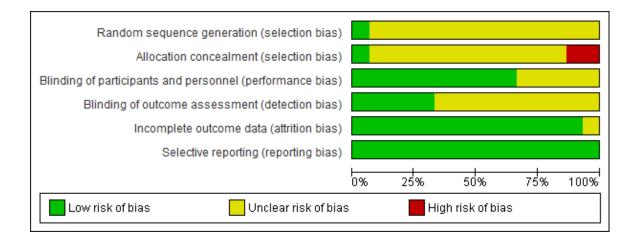
¹¹No serious indirectness of the effect of small doses of tagatose on HbA_{1c}, fasting glucose, and fasting insulin, as 356 - 378 participants were included in the analysis even though 1 - 3 trials were available. Trials were of sufficient length and assessed the effect of small doses of tagatose in a large population of interest (i.e. type 2 diabetes). The one multi-center trial (USA & India) studying 356 participants with type 2 diabetes had a follow-up duration of 40 weeks.

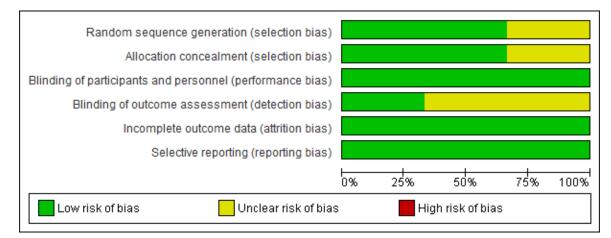
¹²Serious imprecision for the effect of small doses of tagatose on HbA_{1c}, as the 95% CIs (-0.34% to -0.06%) overlap the minimally important difference for clinical benefit (0.3%)

¹³Serious imprecision for the effect of small doses of tagatose on fasting glucose, as the 95% CIs (-0.57 mmol/l to 0.04 mmol/l) overlap the minimally important difference for clinical benefit (0.5 mmol/l)

¹⁴Serious imprecision for the effect of small doses of tagatose on fasting insulin, as the 95% CIs (-6.95 pmol/l to 3.77 pmol/l) overlap the minimally important difference for clinical benefit (5 pmol/l)

¹⁵Not able to assess publication bias as <10 trials were available





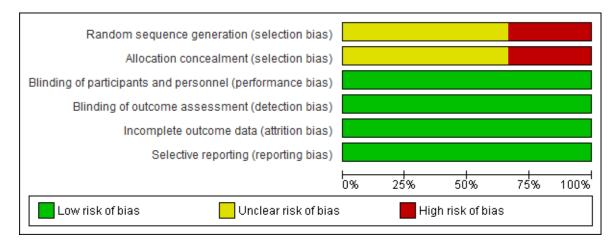


Figure S1. Risk of bias summary of controlled feeding trials assessing the effect of small doses of fructose (top), allulose (middle) and tagatose (bottom) on markers of glycemic control. Colored bars represent the proportion of studies assessed as low (green), unclear (yellow) and high (red) risk of bias for the 6 domains of bias above according to criteria set by the Cochrane Risk of Bias tool.

tudy or Subgroup	Year	Intervention, N	Control, N	Weight		Mean Difference [95% CI] in HbA _{1c} , %
Overweight/Obese						
tizkalla et al. (Expt 1) [43,44]	1986	8	8	13.7%	-0.50 [-1.19, 0.19]	
izkalla et al. (Expt 2) [43,44]	1986	6	6	13.0%	-0.60 [-1.31, 0.11]	
ubtotal					-0.55 [-1.04, -0.06]	
leterogeneity: Tau ² = 0.00; Chi ² = 0.04, df = 1 (P = 0.84); l ² = 0%						
est for overall effect: Z = 2.19 (P = 0.03)						
ype 1 Diabetes						
aganus et al. (control) [45]	1987	8	8	17.5%	-0.30 [-0.91, 0.31]	
'aganus et al. (guar) [45]	1987	22	22	11.6%	-0.50 [-1.24, 0.24]	
ubtotal					-0.38 [-0.85, 0.09]	
leterogeneity: Tau ² = 0.00; Chi ² = 0.17, df = 1 (P = 0.68); I ² = 0%						
est for overall effect: Z = 1.58 (P = 0.11)						
ype 2 Diabetes						
rigoresco et al. [46]	1988	8	8	7.0%	0.50 [-0.46, 1.46]	
aisman et al. [49]	2006	12	13	24.9%	-0.22 [-0.73, 0.29]	
ubtotal					0.02 [-0.65, 0.69]	
leterogeneity: Tau ² = 0.11; Chi ² = 1.68, df = 1 (P = 0.19); I ² = 41%						
est for overall effect: Z = 0.06 (P = 0.95)						
lixed (T1D and T2D)						
layo et al. [47]	1990	6	8	12.3%	-0.85 [-1.58, -0.12]	
ubtotal					-0.85 [-1.58, -0.12]	
eterogeneity: Not applicable						
est for overall effect: Z = 2.30 (P = 0.02)						
otal					-0.38 [-0.64, -0.13]	◆
eterogeneity: Tau ² = 0.00; Chi ² = 5.87, df = 6 (P = 0.44); I ² = 0%						
est for overall effect: Z = 2.94 (P = 0.003)						-2 -1 U 1
st for subgroup differences: Chi ² = 3.31, df = 3 (P = 0.35), I ² = 9.5%						
						Favours Favours
						fructose comparator

Figure S2. Forest plot of the effect of small doses (\leq 50g/day) of fructose on HbA_{1c}. Pooled effect estimates for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with random effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for six of the seven trials (Rizkalla *et al.* (Expt 1) [43], Paganus *et al.* (control) [45], Paganus *et al.* (guar) [45], Grigoresco *et al.* [46], Vaisman *et al.* [49], Blayo *et al.* [47]), as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity.

Study or Subgroup	Year	Intervention, N	Control, N	Weight		Mean Difference [95% CI] in fasting glucose, mmol/I
lealthy				_		
unehag et al. [48]	2002	24	12	11.6%	-0.30 [-0.54, -0.06]	
eberli et al. [50]	2011	29	29	20.8%	-0.11 [-0.23, 0.01]	-
ubtotal					-0.18 [-0.35, 0.00]	•
eterogeneity: Tau ² = 0.01; Chi ² = 2.01, df = 1 (P = 0.16); I ² = 50%						
est for overall effect: Z = 1.95 (P = 0.05)						
fixed (Lean and Overweight/Obese)						
eden et al. [51]	2014	40	40	14.2%	-0.11 [-0.31, 0.09]	- +
owndes et al. [52]	2015	30	34	11.6%	-0.10 [-0.34, 0.14]	— <u> </u>
ibtotal					-0.11 [-0.26, 0.04]	•
eterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.95); I ² = 0%						
est for overall effect: Z = 1.38 (P = 0.17)						
verweight/obese						
zkalla et al. (Expt 1) [43,44]	1986	8	8	12.8%	-0.11 [-0.33, 0.11]	
zkalla et al. (Expt 2) [43,44]	1986	6	6	5.7%	0.06 [-0.33, 0.45]	
eden et al. (- exercise) [53]	2015	7	7	4.9%	-0.05 [-0.48, 0.38]	
eden et al. (+ exercise) [53]	2015	7	7	4.9%	0.15 [-0.28, 0.58]	
btotal					-0.04 [-0.20, 0.12]	
eterogeneity: Tau ² = 0.00; Chi ² = 1.40, df = 3 (P = 0.71); l ² = 0%						
st for overall effect: Z = 0.45 (P = 0.65)						
ypertriglyceridemia						
rner et al. [42]	1979	4	4	6.7%	-0.18 [-0.53, 0.17]	
btotal					-0.18 [-0.53, 0.17]	
eterogeneity: Not applicable						-
est for overall effect: Z = 1.00 (P = 0.32)						
/pe 2 Diabetes						
urner et al. (DM2) [42]	1979	2	2	1.7%	0.57 [-0.21, 1.35]	
igoresco et al. [46]	1988	8	8	0.3%	-0.40 [-2.26, 1.46]	
btotal					0.42 [-0.30, 1.15]	
eterogeneity: Tau ² = 0.00; Chi ² = 0.89, df = 1 (P = 0.35); l ² = 0%						
st for overall effect: Z = 1.15 (P = 0.25)						
ixed (T1D and T2D)						
ayo et al. [47]	1990	6	8	4.9%	-0.78 [-1.21, -0.35]	
btotal					-0.78 [-1.21, -0.35]	~
terogeneity: Not applicable						-
st for overall effect: Z = 3.55 (P = 0.0004)						
tal					-0.13 [-0.24, -0.03]	•
eterogeneity: Tau ² = 0.01; Chi ² = 16.86, df = 11 (P = 0.11); I ² = 35%						
st for overall effect: Z = 2.48 (P = 0.01)						-2 -1 0 1 2
st for subgroup differences: Chi ² = 12.71, df = 5 (P = 0.03), l ² = 60.7%						Favours Favours
						fructose comparator

Figure S3. Forest plot of the effect of small doses (\leq 50g/day) of fructose on fasting glucose. Pooled effect estimates for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with random effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for all trials, as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity.

Study or Subgroup	Year	Intervention, N	Control, N	Weight		Mean Difference [95% CI] in fasting insulin, pmol/l
Healthy						
Sunehag et al. [48]	2002	24	12	33.9%	2.08 [-9.78, 13.94]	_ _
Subtotal					2.08 [-9.78, 13.94]	★
Heterogeneity: Not applicable						Ē
Test for overall effect: Z = 0.34 (P = 0.73)						
Mixed (Lean and Overweight/Obese)						
Heden et al. [51]	2014	40	40	18.5%	-5.00 [-21.05, 11.05]	— —
Lowndes et al. [52]	2015	30	34	9.8%	22.30 [0.21, 44.39]	
Subtotal					7.55 [-19.11, 34.22]	
Heterogeneity: Tau ² = 275.60; Chi ² = 3.84, df = 1 (P = 0.05); I ² = 74%						-
Test for overall effect: Z = 0.56 (P = 0.58)						
Overweight/obese						
Rizkalla et al. (Expt 1) [43,44]	1986	8	8	11.0%	6.95 [-13.85, 27.75]	
Rizkalla et al. (Expt 2) [43,44]	1986	6	6	17.0%	7.64 [-9.12, 24.40]	
Heden et al. (- exercise) [53]	2015	7	7	2.5%	-24.45 [-68.06, 19.16]	· · · · · · · · · · · · · · · · · · ·
Heden et al. (+ exercise) [53]	2015	7	7	2.5%	14.85 [-28.76, 58.46]	
Subtotal					5.52 [-6.50, 17.54]	←
Heterogeneity: Tau ² = 0.00; Chi ² = 2.07, df = 3 (P = 0.56); I ² = 0%						-
Test for overall effect: Z = 0.90 (P = 0.37)						
Hypertriglyceridemia						
Turner et al. [42]	1979	4	4	3.5%	-24.70 [-61.49, 12.09]	
Subtotal					-24.70 [-61.49, 12.09]	
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
Type 2 Diabetes						
Turner et al. (DM2) [42]	1979	2	2	0.7%	-24.61 [-105.26, 56.04]	· · · · ·
Grigoresco et al.	1988	8	8	0.6%	-2.08 [-91.53, 87.37]	
Subtotal					-14.51 [-74.41, 45.39]	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.13, df = 1 (P = 0.71); I ² = 0%					-	
Test for overall effect: Z = 0.47 (P = 0.64)						
Total					2.72 [-4.19, 9.62]	+
Heterogeneity: Tau ² = 0.00; Chi ² = 8.78, df = 9 (P = 0.46); I ² = 0%						-100 -50 0 50 100
Test for overall effect: Z = 0.77 (P = 0.44)						
Test for subgroup differences: Chi ² = 2.80, df = 4 (P = 0.59), I ² = 0%						Favours Favours
						fructose comparator

Figure S4. Forest plot of the effect of small doses (\leq 50g/day) fructose on fasting insulin. Pooled effect estimates for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with random effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for all trials, as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity.

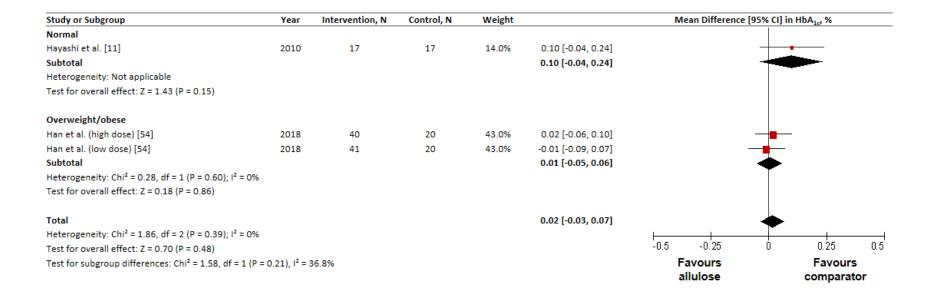


Figure S5. Forest plot of the effect of small doses (\leq 50g/day) of allulose on HbA_{1c}. Pooled effect estimate for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with fixed effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for Hayashi *et al.* [11], as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity

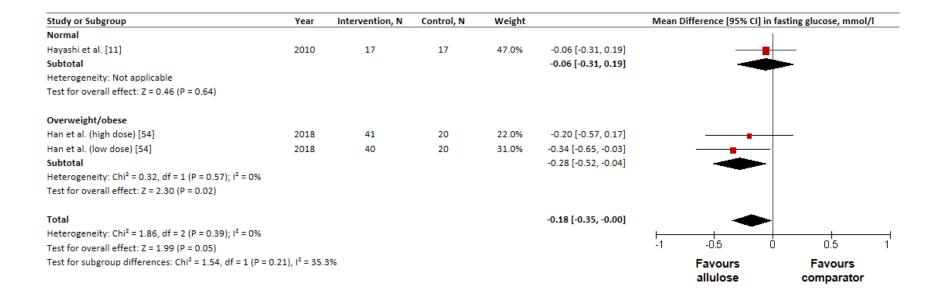


Figure S6. Forest plot of the effect of small doses (\leq 50g/day) of allulose on fasting glucose. Pooled effect estimate for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with fixed effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for Hayashi *et al.* [11], as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity

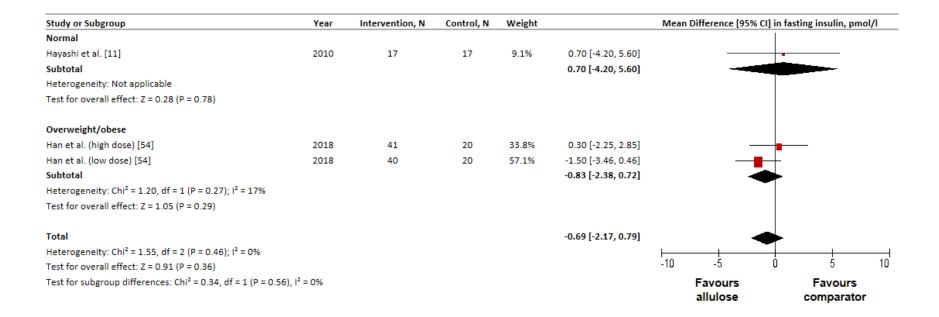


Figure S7. Forest plot of the effect of small doses (\leq 50g/day) of allulose on fasting insulin. Pooled effect estimate for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with fixed effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for Hayashi *et al.* [11], as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity

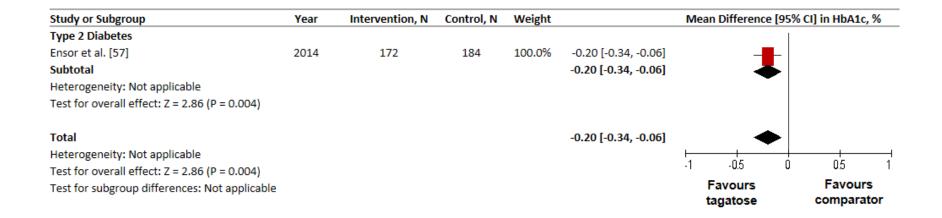


Figure S8. Forest plot of the effect of small doses (\leq 50g/day) of tagatose on HbA_{1c}. Pooled effect estimate for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with fixed effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences, as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity

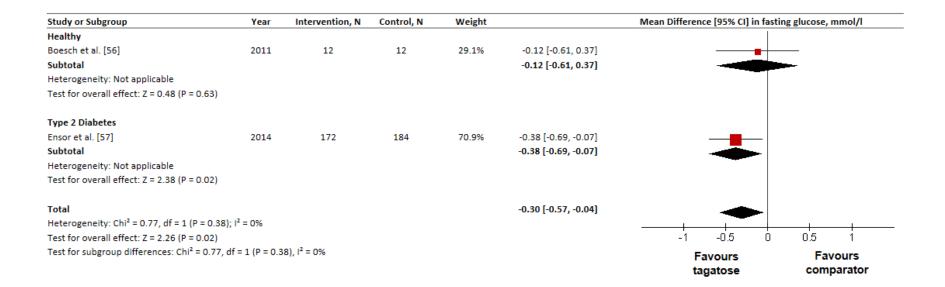


Figure S9. Forest plot of the effect of small doses (\leq 50g/day) of tagatose on fasting glucose. Pooled effect estimate for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with fixed effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences, as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity

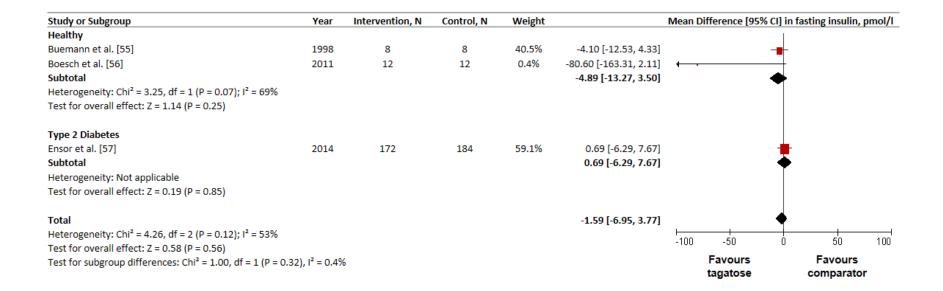


Figure S10. Forest plot of the effect of small doses (\leq 50g/day) of tagatose on fasting insulin. Pooled effect estimate for the overall effect is represented by the diamond. Data are expressed as mean differences (MDs) with 95% confidence intervals (CIs), using the generic inverse variance method with fixed effects models. Paired analyses were applied to all crossover trials. Values are between-treatment end differences for two of the three trials (Buemann *et al.* [55], Boesch *et al.* [56]), as change-from-baseline data were not available. Inter-study heterogeneity was tested by the Cochran Q-statistic at a significance level of p<0.10 and quantified by I², levels \leq 50% represent moderate heterogeneity, \geq 50% representing substantial heterogeneity, and \geq 75% representing considerable heterogeneity

				_	M	ean difference (9	5% CI) in fa	sting glucose (mr	nol/L)		_	
Subgroup	Level	Trials	N	Within subgroups						Between subgroups	Residual I ² P-	value
ſotal		12	239	-0.13 [-0.24, -0.03]		-						
lge	24 years	6	118	-0.10 [-0.29, 0.10]		_	-			-0.07 [-0.36, 0.22]	40%	0.59
	> 24 years	6	121	-0.17 [-0.39, 0.04]			•					
omparator	Glucose (1)	7	175	-0.09 [-0.18, 0.00]			-			1 vs 2: 0.32 [0.06, 0.57]	0%	0.05
	Starch (2)	3	58	-0.41 [-0.65, -0.17]			-			1 vs 3: -0.04 [-0.42, 0.35]		
	Dextromaltose (3)	2	6	-0.05 [-0.43. 0.32]			•			2 vs 3: -0.36 [-0.80, 0.08]		
Dose	≤ 36 g/day	5	86	-0.24 [-0.45, -0.03]		•				0.16 [-0.10, 0.43]	30%	0.20
	> 36 g/day	7	153	-0.08 [-0.23, 0.08]			-•					
ructose form	Liquid	10	189	-0.09 [-0.18, 0.00]			-			-0.32 [-0.57, -0.07]	0%	0.02
	Mixed	2	50	-0.41 [-0.64, -0.18]			-					
Design	Parallel	5	142	-0.20 [-0.40, -0.01]			•			0.14 [-0.13, 0.40]	34%	0.28
	Crossover	7	97	-0.07 [-0.25, 0.11]		-	-+					
Juration	≤ 2 weeks	8	124	-0.09 [-0.26, 0.09]		-	_			-0.12 [-0.42, 0.17]	40%	0.37
	> 2 weeks	4	115	-0.21 [-0.45, 0.02]			•					
inergy Balance	Positive	4	83	-0.07 [-0.30, 0.17]		_	_ •			1 vs 2: 0.10 [-0.26, 0.45]	42%	0.72
	Negative	6	56	-0.16 [-0.43, 0.10]			•			1 vs 3: 0.13 [-0.26, 0.53]		
	Neutral	2	100	-0.20 [-0.52, 0.12]			•			2 vs 3: 0.04 [-0.38, 0.45]		
					-1.00	-0.50	0.00	0.50	1.00			
						Favours		Favours				
						fructose		comparato	r			

Figure S11. Forest plot of subgroup analyses investigating the effect of small doses of fructose on fasting glucose. Subgroups include age, comparator, dose, fructose form, design, duration and energy balance. Data are represented as MD with 95% CIs. Differences between subgroups were tested using meta-regression and the significance level was reported as a p-value, where p<0.05 is considered significant. The residual I² value indicates heterogeneity unexplained by the subgroup.

Subgroup												
• ·	Level	Trials	N	Within subgroups						Between subgroups	Residual I ²	P-value
Total		12	239	-0.13 [-0.24, -0.03]								
Random Sequence Generation	Unclear ROB (1)	11	175	-0.14 [-0.29, 0.02]		-				0.04 [-0.41, 0.49]	41%	0.86
	Low ROB (2)	1	64	-0.10 [-0.52, 0.32]			•					
	High ROB (3)	0	-	-								
Allocation Concealment	Unclear ROB (1)	9	169	-0.15 [-0.33, 0.03]		_	_			1 vs 2: 0.05 [-0.44, 0.54]	46%	0.84
	Low ROB (2)	1	64	-0.10 [-0.56, 0.36]			•			1 vs 3: -0.08 [-0.77, 0.60]		
	High ROB (3)	2	6	-0.02 [-0.53, 0.49]						2 vs 3: -0.13 [-0.67, 0.41]		
Blinding of Participants and Personnel	Unclear ROB (1)	5	72	-0.26 [-0.51, -0.02]			•			0.17 [-0.11, 0.46]	10%	0.07
	Low ROB (2)	7	167	-0.09 [-0.23, 0.05]								
	High ROB (3)	0	-	-								
Blinding of Outcome Assessment	Unclear ROB (1)	8	118	-0.20 [-0.39, -0.01]			•			0.11 [-0.15, 0.38]	28%	0.20
	Low ROB (2)	4	121	-0.09 [-0.27, 0.09]			+					
	High ROB (3)	0	-	-			1					
incomplete Outcome Data	Unclear ROB (1)	1	29	-0.11 [-0.47, 0.25]			•	_		-0.03 [-0.42, 0.37]	36%	0.83
	Low ROB (2)	11	210	-0.14 [-0.30, 0.03]		-						
	High ROB (3)	0	-	-								
Selective Outcome Reporting	Unclear ROB (1)	0	-	-						-	-	-
	Low ROB (2)	12	239	-0.13 [-0.24, -0.03]			_					
	High ROB (3)	0	-	-								
					-1.0	-0.5	0.0	0.5	1.0			
						Favours		Favours				
						fructose		comparato	-			

Figure S12. Forest plot of subgroup analyses investigating the effect of small doses of fructose on fasting glucose. Subgroups include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selecting outcome reporting. Data are represented as MD with 95% CIs. Differences between subgroups were tested using meta-regression and the significance level was reported as a p-value, where p<0.05 is considered significant. The residual I^2 value indicates heterogeneity unexplained by the subgroup.

					Mean difference (95% CI) in fasting insulin (pmol/L)		_	
Subgroup	Level	Trials	Ν	Within subgroups		Between subgroups	Residual I ²	P-value
Total		10	196	2.72 [-4.19, 9.62]	- 			
Age	≤ 24 years	6	118	1.87 [-7.58, 11.32]	_ _	5.35 [-18.50, 29.20]	5%	0.62
	> 24 years	4	78	7.22 [-14.68, 29.12]				
omparator	Glucose (1)	6	146	5.02 [-5.62, 15.66]	- - -	1 vs 2: 3.01 [-14.72, 20.74]	0%	0.30
	Starch (2)	2	44	2.01 [-12.17, 16.19]	_	1 vs 3: 29.70 [-12.06, 71.46]		
	Dextromaltose (3)	2	6	-24.68 [-65.07, 15.70]		2 vs 3: 26.69 [-16.11, 69.49]		
Dose	≤ 36 g/day	4	72	4.54 [-6.52, 15.59]	_ _	-4.66 [-22.32, 13.00]	5%	0.56
	> 36 g/day	6	124	-0.13 [-13.90, 13.65]	_ _			
ructose form	Liquid	9	160	2.92 [-7.95, 13.80]	_ _	-0.84 [-21.05, 19.37]	9%	0.93
	Mixed	1	36	2.08 [-14.95, 19.11]	+			
)esign	Parallel	4	128	6.90 [-2.69, 16.50]	- - -	-14.76 [-32.78, 3.26]	0%	0.10
	Crossover	6	68	-7.86 [-23.11, 7.40]				
Duration	≤2 weeks	8	124	0.62 [-7.96, 9.19]	—	20.28 [-6.37, 46.93]	0%	0.12
	> 2 weeks	2	72	20.90 [-4.33, 46.13]				
nergy Balance	Positive	3	54	-4.96 [-22.52, 12.61]	_ _	1 vs 2: -7.87 [-30.85, 15.11]	2%	0.48
	Negative	5	42	2.91 [-11.90, 17.73]	\$	1 vs 3: -11.81 [-33.74, 10.13]		
	Neutral	2	100	6.85 [-6.28, 19.98]		2 vs 3: -3.94 [-23.73, 15.86]		
					-100 -75 -50 -25 0 25 50 75 100			
					Favours Favours			
					fructose comparator			

Figure S13. Forest plot of subgroup analyses investigating the effect of small doses of fructose on fasting insulin. Subgroups include age, comparator, dose, fructose form, design, duration and energy balance. Data are represented as MD with 95% CIs. Differences between subgroups were tested using meta-regression and the significance level was reported as a p-value, where p<0.05 is considered significant. The residual I² value indicates heterogeneity unexplained by the subgroup.

					Mean difference (95% CI) in fasting insulin (pmol/L)		_	
Subgroup	Level	Trials	N	Within subgroups		Between subgroups	Residual I ²	P-value
Total		10	196	2.72 [-4.19, 9.62]	-			
Random Sequence Generation	Unclear ROB (1)	9	132	0.60 [-7.95, 9.15]		21.70 [-5.66, 49.06]	0%	0.11
Random Sequence Generation						21.70 [-5.66, 49.06]	0%	0.11
	Low ROB (2)	1	64	22.30 [-3.69, 48.29]				
	High ROB (3)	0	-	-				
Allocation Concealment	Unclear ROB (1)	1	64	1.85 [-7.13, 10.83]	_ _	1 vs 2: 20.45 [-7.67, 48.57]	096	0.13
	Low ROB (2)	7	126	22.30 [-4.35, 48.95]		1 vs 3: 46.98 [-1.40, 95.37]		
	High ROB (3)	2	6	-24.68 [-65.07, 15.70]		2 vs 3: 26.53 [-14.83, 67.90]		
Blinding of Participants and Personnel	Unclear ROB (1)	4	58	0.87 [-14.00, 15.75]		2.86 [-14.75, 19.15]	8%	0.73
	Low ROB (2)	6	138	3.73 [-7.52, 14.99]				
	High ROB (3)	ō	-	-	, The second sec			
Blinding of Outcome Assessment	Unclear ROB (1)	6	104	-2.45 [-12.74, 7.85]		13.68 [-3.08, 30.43]	0%	0.10
	Low ROB (2)	4	92	11.23 [-1.99, 24.45]				
	High ROB (3)	0	22	-	▼			
	High KOB (5)	0	-	-				
Incomplete Outcome Data	Unclear ROB (1)	0	-	-		-	-	-
	Low ROB (2)	10	196	2.72 [-4.19, 9.62]	- -			
	High ROB (3)	0	-	-				
Selective Outcome Reporting	Unclear ROB (1)	0		-				-
	Low ROB (2)	10	196	2.72 [-4.19, 9.62]	_ _ _			
	High ROB (3)	0			ľ			
	11911100(0)							
					-100 -75 -50 -25 0 25 50 75 100			
					Favours Favours			
					fructose comparator			

Figure S14. Forest plot of subgroup analyses investigating the effect of small doses of fructose on fasting insulin. Subgroups include age, comparator, dose, fructose form, design, duration and energy balance. Data are represented as MD with 95% CIs. Differences between subgroups were tested using meta-regression and the significance level was reported as a p-value, where p<0.05 is considered significant. The residual I² value indicates heterogeneity unexplained by the subgroup.

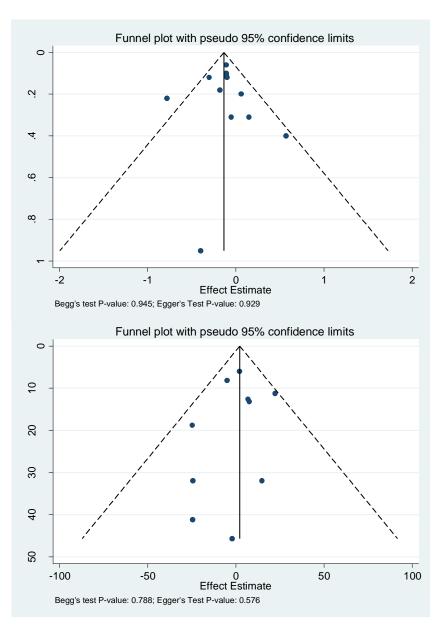


Figure S15. Publication bias funnel plots for the effect of small doses (\leq 50g/d) of fructose on fasting glucose (top) and fasting insulin (bottom). The solid line represents the pooled effect estimate expressed as the mean difference (MD). The dashed line represents pseudo-95% confidence intervals and the circles represent effect estimates for each included study. P-values were derived from quantitative assessment of publication bias by Egger's and Begg's test set at a significance level of p<0.05