Appendix G – Forest plots. Intervention studies on metabolic diseases

Figure G.1: Randomised controlled trials: effect of high vs. low sugar intake on measures of body fatness.

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Diet	Weeks	RoB
Source = Beverages							1							
Ruyter et al., 2014	238	0.97	0.28	[0.42; 1.52]	0	0	-	6	MF	GP	Mix	AL	72	1
Ebbeling et al., 2012	108	1.90	0.90	[0.14; 3.66]	0	0		17	MF	OW/OB	Mix	AL	56	1
Campos et al, 2015	13	2.30	3.27	[-4.11; 8.71]	0	2		18	MF	OW/OB	Mix	AL	12	2
Hollis et al, 2009	25	1.50	1.77	[-1.97; 4.97]	0	2		18	MF	OW	Mix	AL	12	1
Maersk et al, 2012*	14	1.00	2.70	[-4.29; 6.29]	0	0		18	MF	OW/OB	Mix	AL	24	2
Hernandez-Cordero et al, 2014	120	0.50	0.25	[0.00; 1.00]	1	0	100	20	F	OW/OB	Mix	AL	36	2
Random effects model (r = 0.82)		0.82		[0.36; 1.29]			◆							
Heterogeneity: $I^2 = 0\%$ [0%; 65%], $\tau^2 =$	0.0526, p	= 0.61												
Source = Mixed														
Markey et al, 2016	50	0.10	0.96	[-1.79; 1.99]	0	0		10	MF	Non-OB	Mix	AL	8	1
Smith et al, 1996	16	2.70	3.20	[-3.58; 8.98]	0	2		12	MF	H-TG	Mix	AL	24	2
Saris et al, 2000*	79	0.90	0.54	[-0.16; 1.96]	0	0	-	19	MF	OW/OB	Mix	AL	24	1
Raben et al, 2002*	20	2.60	0.57	[1.49; 3.71]	0	0		23	MF	OW	Mix	AL	10	1
Werner et al, 1984	12	1.40	3.03	[-4.54; 7.34]	0	2		24	MF	Gallstones	Mix	AL	6	2
Random effects model (r = 0.82)		1.39		[0.13; 2.65]										
Heterogeneity: $l^2 = 45\%$ [0%; 80%], $\tau^2 =$	= 0.8832, <i>j</i>	p = 0.12												
Random effects model (r = 0.82) Prediction interval Heterogeneity: $l^2 = 29\%$ [0%; 85%], $z^2 =$ Residual heterogeneity: $l^2 = 17\%$ [0%; 8				[0.53; 1.77] [-0.39; 2.69]			-4 -2 0 2 4 6 8 10							
Random effects model (r = 0.5): 1.13 [0 Random effects model (r = 0.99): 1.21			r 0.5 =	1 -> significant ef	ffect (0.82)		aok = Parallel Red = Cross-over on-significant (0.5); r 0.99 = 2 -> non sign	ificant effect (0.82) be	comes si	gnificant (0.99)				

Figure G.1a: Effect of high vs low sugar intake on body weight (kg)



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subject	Sugar	Diet	BW*	Weeks	RoB
Source = Beverages							1								
Ebbeling et al., 2012	108	0.57	0.28	[0.02; 1.12]	0	0		17	MF	OW/OB	Mix	AL	1.9	56	1
Campos et al, 2015	13	0.90	1.13	[-1.31; 3.11]	0	2		18	MF	OW/OB	Mix	AL	2.3	12	2
Hollis et al. 2009	25	0.40	0.31	[-0.22; 1.02]	0	2		18	ME	OW	Mix	AL	1.5	12	1
Hernandez-Cordero et al, 2014	120	0.20	0.08	[0.03; 0.37]	1	0	22	20	F	OW/OB	Mix	AL	0.5	36	2
Random effects model (r = 0.82)		0.29		[0.06; 0.51]			•								-
Heterogeneity: $I^2 = 0\% [0\%; 79\%], \tau^2$	= 0.0110			[]			-								
Hererogeneny. F one [one, rone], c	0.0110, p	0.00													
Source = Mixed															
Markey et al, 2016	50	0.00	0.28	[-0.56; 0.56]	0	0		10	MF	Non-OB	Mix	AL	0.1	8	1
Raben et al, 2002*	20	0.90	0.28	[0.35; 1.45]	ō	ő		23	MF	OW	Mix	AL	2.6	10	1
Random effects model (r = 0.82)	2.0	0.45	0.20	[-0.43; 1.33]							11112				
Heterogeneity: 1 ² = 80% [15%; 95%], -	2 - 0.3245			[0.00]			_								
Heterogeneity: 7 = 60% [10%, 50%], t	- 0.5240,	p = 0.02													
Random effects model (r = 0.82)		0.38		[0.10; 0.66]			•								
Prediction interval		0.00		[-0.35; 1.11]											
Heterogeneity: I ² = 39% [0%; 76%], τ ²	= 0.0497	= 0.15		[0.00, 1.11]											
Residual heterogeneity: 1 ² = 45% [0%; 1							-2 -1 0 1 2 3 4								
Random effects model (r = 0.5): 0.41 [_									
Random effects model (r = 0.99): 0.34 Random effects model (r = 0.99): 0.34			0.5				dk = Parallel Red = Cross-over	1		10					
Random effects model (r = 0.99): 0.34	1-0.02; 0.7	1	r 0.5 =	1 -> significant ef	tect (0.82)	becomes no	n-significant (0.5); r 0.99 = 2 -> non sign	incant effect (0.82) be	comes si	gnificant (0.99)				

Figure G.1b: Effect of high vs low sugar intake on BMI (kg/m2)

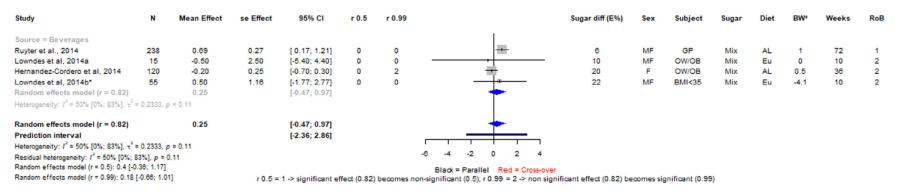


Figure G.1c: Effect of high vs low sugar intake on waist circumference (cm)

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subject	Sugar	Diet	BW*	Weeks	RoB
Source = Beverages Lowndes et al, 2014a Campos et al, 2015 Hernandez-Cordero et al, 2014 Lowndes et al, 2014b ⁻ Random effects model (r = 0.82) Heterogeneity: I^2 = 0% [0%; 74%], x^2 =	15 13 120 55	-0.80 2.00 0.20 0.90 0.22 2	1.68 1.85 0.14 1.00	[-4.09; 2.49] [-1.62; 5.62] [-0.08; 0.48] [-1.06; 2.86] [-0.06; 0.50]	0 0 0	2 2 0 2	·	10 18 20 22	MF F MF	OW/OB OW/OB OW/OB BMI<35	Mix Mix Mix Mix	Eu AL AL Eu	0 2.3 0.5 -4.1	10 12 36 10	2 1 2 2
Source = Mixed Raben et al, 2002* Random effects model (r = 0.82) Heterogeneity: not applicable	20	0.35 0.35	0.77	[-1.15; 1.85] [-1.15; 1.85]	0	0		23	MF	ow	Mix	AL	2.6	10	1
$\begin{array}{l} \textbf{Random effects model (r = 0.82)} \\ \textbf{Prediction interval} \\ \textbf{Heterogeneity: } \vec{r} = 0\% \left[0\%; 54\%\right], \tau^2 = 0\% \left[0\%; 7\%\right], \\ \textbf{Random effects model (r = 0.5): 0.28 [(r = 0.45): 0.28], \\ \textbf{Random effects model (r = 0.59): 0.0.5]}. \end{array}$	4%], p = 0. 0.03; 0.54]	62	r 0.5 =	[-0.05; 0.50] [-0.22; 0.67] 1 -> significant ef	fect (0.82)	becomes n	-4 -2 0 2 4 6 Black = Parallel Red = Cross-over on-significant (0.5); r 0.99 = 2 -> non signi	ficant effect (0.82) be	comes si	gnificant (0.99)				

Footnote to Figure G1. * differences in BW change between high and low sugar intake, AL = add libitum; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; Eu = eucaloric; F = females; GP = general population; H-TG = hyper-triglyceridemic; MF = males and females; Mix under Sugar = sugar mixtures; Mixed under Source = foods and beverages; N = average sample size per arm; OB = obese; OW = overweight; RoB = risk of bias (tier); r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement. Study duration is expressed in weeks.

Figure G.1d: Effect of high vs low sugar intake on body fat (%)

Figure G.2: Randomised controlled trials: effect of high vs. low sugar intake on measures of ectopic fat deposition

Study	N	SMD Effect	se Effect	95% CI	r 0.5	r 0.99						Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energ	y balan	ce							1										
Umpleby et al, 2017 (No NAFLD)	10	0.67	0.14	[0.40; 0.95]	0	0			-	+		20	м	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	7	0.67	0.20	[0.28; 1.05]	0	0			_			20	M	OW/NAFLD	Mix	Mix	2.1	12	2
Lowndes et al, 2014b*	11	0.31	0.12	[0.08; 0.55]	1	0			- 1			22	MF	BMI<35	Mix	в	-4.1	10	2
Random effects model (r = 0.82)		0.53		[0.28; 0.78]						-									
Heterogeneity: $I^2 = 57\%$ [0%; 88%], $\tau^2 = 0$	0.0280, j	p = 0.10																	
Diet = Ad libitum																			
Campos et al, 2015	13	0.74	0.11	[0.53; 0.95]	0	0				+		18	MF	OW/OB	Mix	в	2.3	12	1
Maersk et al, 2012*	11	0.90	0.13	[0.64; 1.15]	0	0						18	MF	OW/OB	Mix	в	1	24	2
Random effects model (r = 0.82)		0.80		[0.64; 0.96]						+									
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.35$																			
Random effects model (r = 0.82)		0.66		[0.45; 0.86]					1	•									
Prediction interval				[-0.02; 1.33]															
Heterogeneity: I ² = 67% [14%; 87%], τ ² =	0.0341,	p = 0.02																	
Residual heterogeneity: I ² = 46% [0%; 82	%]. p =	0.14					-2	-1	0	1	2								
Random effects model (r = 0.5): 0.47 [0.0	09; 0.85]						Blac	k = Paralle	Red	= Cross-	over								
Random effects model (r = 0.99): 0.77 [0	.45; 1.08	3]	r 0.5 =	1 -> significant ef	fect (0.82)	becomes r						icant effect (0.82) be	comes si	gnificant (0.99)					

Figure G.2a: Effect of high vs low sugar intake on liver fat (standardized mean difference)

Study	N	SMD Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral ener Umpleby et al, 2017 (No NAFLD) Umpleby et al, 2017 (NAFLD) Random effects model (r = 0.82) Heterogeneity: J ² = 75% [0%; 94%], z ²	10 7	0.29 -0.18 0.08	0.14 0.19	[0.03; 0.56] [-0.55; 0.19] [-0.38; 0.54]	0	0		20 20	M M	OW/No-NAFLD OW/NAFLD	Mix Mix	Mix Mix	2.2 2.1	12 12	2 2
Diet = Ad libitum Campos et al. 2015 Maersk et al. 2012* Random effects model (r = 0.82) Heterogeneity: J ² = 81% [21%; 96%], * ²	13 11 = 0.0587	0.27 0.65 0.46 , p = 0.02	0.10 0.13	[0.07; 0.47] [0.40; 0.90] [0.08; 0.83]	1 0	0	**	18 18	MF MF	OW/OB OW/OB	Mix Mix	B	2.3 1	12 24	1 2
Random effects model (r = 0.82) Prediction interval Heterogeneity: $l^2 = 78\%$ [42%; 92%], τ^2 Residual heterogeneity: $l^2 = 79\%$ [32%; Random effects model (r = 0.59): 0.4 [Random effects model (r = 0.99): 0.44	93%], p 0.12; 0.4]	< 0.01	r 0.5 =	[-0.03; 0.59] [-1.13; 1.69] 1 → significant ef	fect (0.82)	becomes n	-2 -1 0 1 2 Black = Parallel Red = Cross-over n-significant (0.5); r 0.99 = 2 -> non signi	ficant effect (0.82) be	comes s	ignificant (0.99)					

Footnote to Figure G2. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; M = males; MF = males and females; Mix under Sugar = sugar mixtures; Mix under Source = foods and beverages; N = average sample size per arm; NAFLD = non-alcoholic fatty liver disease; OB = obese; OW = overweight; RoB = risk of bias (tier); r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; SMD = standardized mean difference. Study duration is expressed in weeks.

Figure G.2b: Effect of high vs low sugar intake on visceral adipose tissue (standardized mean difference)

Figure G.3: Randomised controlled trials: effect of fructose vs. glucose on measures of ectopic fat deposition

Study	N	SMD Effect	se Effect	95% CI	r 0.5	r 0.99		Fru-Glu (E%)	Sex	Subjects	Source	BW*	Weeks	RoB
Diet = Isocaloric with neutral energy Johnston et al, 2013 (isocaloric) Random effects model Heterogeneity: not applicable	balance 16	0.15 0.15	0.09	[-0.02; 0.32] [-0.02; 0.32]	0	0	-	25	М	AO	в	-0.2	2	2
Diet = Isocaloric with positive energy Silbernagel et al, 2011 Johnston et al, 2013 (hypercaloric) Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$	/ balance 10 16	-0.07 -0.12 -0.11	0.14 0.09	[-0.33; 0.20] [-0.29; 0.05] [-0.25; 0.04]	0	0		22 25	MF M	BMI<35 AO	B	-1.5 0.4	4 2	1 2
Diet = Ad libitum Jin et al., 2014 Random effects model Heterogeneity: not applicable	10	-0.19 -0.19	0.13	[-0.44; 0.07] [-0.44; 0.07]	0	2		20	MF	NAFLD	в	0.2	4	1
Random effects model Prediction interval Heterogeneity: $I^2 = 58\%$ [0%; 88%], $\tau^2 = 0.$ Residual heterogeneity: $I^2 = 0\%$, $p = 0.72$ Random effects model ($r = 0.5$): -0.03 [-0.2 Random effects model ($r = 0.99$): -0.18 [-0.2	5; 0.2]		r 0.5	[-0.20; 0.12] [-0.67; 0.59]	effect (0.82) becomes n	-1 -0.5 0 0.5 Black = Parallel Red = Cro on-significant (0.5); r 0.99 = 2 ->	oss-over	becomes s	ignificant (0.99)				

Figure G.3a: Effect of fructose vs glucose on liver fat (standardized mean difference)

Study	N	SMD Effect	se Effect	95% CI	r 0.5	r 0.99		Fru-Glu (E%)	Sex	Subjects	Source	BW*	Weeks	RoB
Diet = Isocaloric with posi Silbernagel et al, 2011 Random effects model Heterogeneity: not applicable	itive en 9	ergy balance 0.00 0.00	0.15	[-0.30; 0.30] [-0.30; 0.30]	0	0	+	22	MF	BMI<35	в	-1.5	4	1
Diet = Ad libitum Stanhope et al, 2009* Random effects model Heterogeneity: not applicable	15	0.54 0.54	0.09	[0.36; 0.72] [0.36; 0.72]	0	0	-	25	MF	OW/OB	в	-0.2	8	2
Random effects model Heterogeneity: / ² = 90% [61%, Residual heterogeneity: / ² = N Random effects model (r = 0.1 Random effects model (r = 0.1	A%, p = 5): 0.28 [NA -3.16; 3.73]	r 0.5	[-0.25; 0.82] = 1 -> significant e	effect (0.82	?) becomes r	-1 -0.5 0 0.5 Black = Parallel Red = Cross-o on-significant (0.5); r 0.99 = 2 -> nor		becomes s	ignificant (0.99)				

Footnote to Figure G3. * differences in BW change between high and low sugar intake; AO = abdominal obesity; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; Fru = fructose; Glu = glucose; M = males; MF = males and females; N = average sample size per arm; NAFLD = non-alcoholic fatty liver disease; OB = obese; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier); SMD = standardized mean difference. Study duration is expressed in weeks.

Figure G.3b: Effect of fructose vs glucose on visceral adipose tissue (standardized mean difference)



Figure G.4: Randomised controlled trials: effect of high vs. low sugar intake on measures of glucose tolerance

Study	Ν	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral ene	rgy bala	nce					1								
Lewis et al, 2013	13	1.10	0.36	[0.38; 1.82]	1	0		10	MF	OW/OB	Mix	Mix	0.7	6	1
Hallfrisch et al, 1983a* (NI - HI)	24	8.40	3.15	[2.22; 14.58]	1	0		15	M	NI - HI	Fruct	F		5	2
Thompson et al, 1978	8	-1.00	4.63	[-10.08; 8.08]	0	0		20	M	GP	Mix	в		1	1
Despland et al, 2017	8	-0.24	0.28	[-0.79; 0.31]	0	2	iù i	25	M	GP	Mix	Mix		1	1
Israel et al, 1983*	24	19.70	2.99	[13.83; 25.57]	0	0		28	MF	H-I	Mix	F		6	1
Reiser et al, 1979a*	19	-7.60	2.57	[-12.64; -2.56]	1	0		30	MF	GP	Mix	F	0.5	6	2
Moser et al, 1986 (OC-users)	6	4.00	4.84	[-5.48; 13.48]	0	2		43	F	oc	Mix	F	-1	4	1
Moser et al, 1988 (No OC-users)	6	-5.00	5.52	[-15.81; 5.81]	0	2		43	F	Non-OC	Mix	F	1	4	1
Szanto et al, 1969	19	1.00	2.03	[-2.98; 4.98]	0	2		54	M	GP	Mix	Mix		2	2
Random effects model (r = 0.82)		2.36		[-2.89; 7.62]			-								
Heterogeneity: / ² = 88% [80%; 93%], τ	² = 54.47	10. <i>p</i> < 0.01													
Diet = Ad libitum															
Huttunen et al, 1976	40	-0.40	0.26	[-0.90; 0.10]	0	0	10 I	16	MF	GP	Mix	Mix		56	2
Maersk et al, 2012*	14	0.11	0.54	[-0.95; 1.17]	0	0		18	MF	OW/OB	Mix	в	1	24	2
Random effects model (r = 0.82)		-0.31		[-0.76; 0.15]			•								
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.3$	9														
Random effects model (r = 0.82)		1.82		[-2.30; 5.95]											
Prediction interval				[-13.40; 17.05]											
Heterogeneity: 12 = 86% [77%; 92%], -	² = 40.890	83, p < 0.01													
Residual heterogeneity: 12 = 87% [78%	92%], p	< 0.01					-20 -10 0 10 20								
Random effects model (r = 0.5): 0.32 [Black = Parallel Red = Cross-over								
Random effects model (r = 0.99): 1.88	[-2.98; 6.	7]	r 0.5	5 = 1 -> significant e	ffect (0.82) becomes n	n-significant (0.5); r 0.99 = 2 -> non signi	ficant effect (0.82) be	ecomes si	gnificant (0.99)					
				-			· · · · · · · · · · · · · · · · · · ·								

Figure G.4a: Effect of high vs low sugar intake on blood glucose at 120' during an OGTT (mg/dL)



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy balance	e						1								
Lewis et al, 2013	13	13.77	2.01	[9.83; 17.72]	0	0	E	10	MF	OW/OB	Mix	Mix	0.7	6	1
Hallfrisch et al, 1983a* (normoinsulinemic)	12	6.03	6.69	[-7.08; 19.14]	0	2		15	м	N-I	Fruct	F		5	2
Hallfrisch et al, 1983a* (hyperinsulinemic)	12	25.90	15.13	[-3.75; 55.55]	0	2		15	M	H-I	Fruct	F		5	2
Thompson et al, 1978	8	-3.00	6.17	[-15.09; 9.09]	0	2	+	20	M	GP	Mix	в		1	1
Despland et al, 2017	8	-8.50	9.05	[-28.24; 9.24]	0	2		25	M	GP	Mix	Mix		1	1
Israel et al, 1983*	24	27.00	6.14	[14.97; 39.03]	0	0	-	28	MF	H-I	Mix	F		6	1
Reiser et al, 1979a*	19	4.00	10.33	[-18.24; 24.24]	0	0		30	MF	GP	Mix	F	0.5	6	2
Moser et al, 1986 (OC-users)	6	-17.00	8.24	[-33.15; -0.85]	1	0		43	F	oc	Mix	F	-1	4	1
Moser et al, 1986 (No OC-users)	6	-23.00	5.91	[-34.58; -11.42]	0	0		43	F	Non-OC	Mix	F	1	4	1
Szanto et al, 1969	19	17.00	3.39	[10.36; 23.64]	0	0	100	54	M	GP	Mix	Mix		2	2
Random effects model (r = 0.82)		3.94		[-6.63; 14.51]			+								
Heterogeneity: $I^2 = 87\%$ [78%; 92%], $\tau^2 = 235.1578$, p < 0.0	01													
Diet = Ad libitum															
Maersk et al. 2012*	14	-34.00	33.27	[-99.21; 31.21]	0	0		18	MF	OW/OB	Mix	в	1	24	2
Random effects model (r = 0.82)		-34.00		[-99.21; 31.21]											
Heterogeneity: not applicable															
Random effects model (r = 0.82)		3.14		[-7.33; 13.60]			-								
Prediction interval				[-33.63; 39.91]											
Heterogeneity: 12 = 88% [76%; 91%], z2 = 235.6784	p < 0.0	01		•											
Residual heterogeneity: 1 ² = 87% [78%; 92%], p < 0							-100 -50 0 50 100								
Random effects model (r = 0.5): 4.03 [-7.61; 15.68]							Black = Parallel Red = Cross-over								
Random effects model (r = 0.99): 3.57 [-8.28; 15.4			r 0.6	5 = 1 -> significant ef	fect (0.82)	becomes n	on-significant (0.5); r 0.99 = 2 -> non sign	ificant effect (0.82) be	comes si	gnificant (0.99)					

Figure G.4b: Effect of high vs low sugar intake on insulin at 120' during an OGTT (pmol/L)



Figure G.4c: Effect of high vs low sugar intake on fasting glucose (mg/dL)

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral ener	rgy balan	ce					l l								
Lewis et al, 2013	13	7.20	2.16	[2.97; 11.43]	0	0		10.00	MF	OW/OB	Mix	Mix	0.7	6	1
Black et al, 2006	13	0.00	1.08	[-2.12; 2.12]	0	0	+	15.00	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al, 1983a* (NI - HI)	24	0.53	1.00	[-1.44; 2.50]	0	2	*	15.00	M	NI - HI	Fruct	F		5	
Swanson et al, 1992	14	0.00	1.71	[-3.35; 3.35]	0	0		16.60	MF	GP	Fruct	Mix		4	1
Lowndes et al, 2015	32	3.60	1.08	[1.48; 5.72]	0	0		18.00	MF	BMI<35	Mix	в		10	1
Umpleby et al, 2017 (No NAFLD)	14	-0.54	1.04	[-2.58; 1.50]	0	2		20.00	M	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	-0.72	0.97	[-2.63; 1.19]	0	2		20.00	M	OW/NAFLD	Mix	Mix	2.1	12	2
Lowndes et al, 2014b*	55	0.86	1.00	[-1.10; 2.82]	0	0	-	22.00	MF	BMI<35	Mix	в	-4.1	10	2
Israel et al. 1983*	24	11.10	1.24	[8.68; 13.52]	0	0		28.00	MF	H-I	Mix	F		6	1
Moser et al, 1986 (OC-users)	6	3.00	2.12	[-1.16; 7.16]	0	2	- <u>-</u>	43.00	F	OC	Mix	F	-1	4	1
Moser et al, 1986 (No OC-users)	6	14.00	4.18	[5.81; 22.19]	0	0		43.00	F	Non-OC	Mix	F	1	4	1
Random effects model (r = 0.82)		3.01		[0.41; 5.60]			-								
Heterogeneity: 12 = 89% [83%; 93%], t	² = 10.5569	, <i>p</i> < 0.01													
Diet = Ad libitum															
Majid et al. 2013	31	-4.68	1.08	[-6.75; -2.61]	0	0		8.00	м	GP	Mix	в		4	2
Markey et al, 2013 Markey et al, 2016	50	-0.90	0.64	[-2.16; 0.38]	0	2		10.00	ME	Non-OB	Mix	Mix	0.1	8	-
Campos et al, 2015	13	0.00	1.53	[-3.00; 3.00]	0	0		18.00	ME	OW/OB	Mix	B	2.3	12	
Hollis et al. 2009	25	4.32	2.18		0	0		18.00	ME	OW/OB		в	1.5	12	1
Maersk et al, 2003	14	3.06	2.10	[0.04; 8.60] [-1.66; 7.78]	0	2		18.00	ME	OW/OB	Mix	B	1.0	24	2
		2.16	1.44		0	0		19.00	ME	OW/OB		Mix	0.9		2
Saris et al, 2000* Hernandez-Cordero et al, 2014	79 120	0.40	0.30	[-0.65; 4.97]	0	2	T	20.00	F	OW/OB	Mix	B	0.5	24 38	2
Raben et al. 2002*	120	2.70	1.89	[-0.19; 0.99]	0	2	L and	23.00	ME	OW/OB	Mix	Mix	2.6	10	2
Random effects model (r = 0.82)	11	0.48	1.89	[-1.00; 6.40]	0	2	T==-	23.00	MF	OW	MIX	MIX	2.0	10	1
	2			[-1.48; 2.44]			T								
Heterogeneity: 1 ² = 79% [59%; 89%], τ	= 5.9111,	<i>p</i> < 0.01													
Random effects model (r = 0.82)		1.94		[0.23; 3.66]			-								
Prediction interval				[-5.61; 9.50]											
Heterogeneity: 1 ² = 87% [82%; 91%], τ	² = 12.0830	n < 0.01													
Residual heterogeneity: 1 ² = 86% [80%;							-5 0 5 10 15 20 25								
Random effects model (r = 0.5): 1.4 [-0						Black	Parallel Red = Cross-over								
Random effects model (r = 0.99): 2.38	[0.25; 4.46	1	r 0.5	= 1 -> significant el	ffect (0.82)		on-significant (0.5); r 0.99 = 2 -> non sign	nificant effect (0.82) b	ecomes si	gnificant (0.99)					

Figure G.4c1: Stratified by type of diet



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subject	Sugar	Diet	BW*	Weeks	RoB
Source = Beverages															
Majid et al, 2013	31	-4.68	1.06	[-6.75; -2.61]	0	0	-	8.00	M	GP	Mix	AL		4	2
Lowndes et al, 2015	32	3.60	1.08	[1.48; 5.72]	0	0		18.00	MF	BMI<35	Mix	Eu		10	1
Campos et al, 2015	13	0.00	1.53	[-3.00; 3.00]	0	0		18.00	MF	OW/OB	Mix	AL	2.3	12	1
Hollis et al, 2009	25	4.32	2.18	[0.04; 8.60]	1	0		18.00	MF	OW	Mix	AL	1.5	12	1
Maersk et al, 2012*	14	3.06	2.41	[-1.66; 7.78]	0	2		18.00	MF	OW/OB	Mix	AL	1	24	2
Hernandez-Cordero et al, 2014	120	0.40	0.30	[-0.19; 0.99]	0	2		20.00	F	OW/OB	Mix	AL	0.5	36	2
Lowndes et al, 2014b*	55	0.86	1.00	[-1.10; 2.82]	0	0	*	22.00	MF	BMI<35	Mix	Eu	-4.1	10	2
Random effects model (r = 0.82)		0.82		[-1.46; 3.10]			+								
Heterogeneity: $I^2 = 84\%$ [88%; 92%], τ^2	= 7.4990,	p < 0.01													
Source = Foods															
Hallfrisch et al, 1983a* (NI - HI)	24	0.53	1.00	[-1.44; 2.50]	0	2	÷ _	15.00	м	NI - HI	Fruct	Eu		5	
Israel et al, 1983*	24	11.10	1.24	[8.68; 13.52]	0	0		28.00	MF	H-I	Mix	Eu		6	1
Moser et al, 1986 (OC-users)	6	3.00	2.12	[-1.16; 7.16]	0	2		43.00	F	OC	Mix	Eu	-1	4	1
Moser et al, 1986 (No OC-users)	6	14.00	4.18	[5.81; 22.19]	0	0		43.00	F	Non-OC	Mix	Eu	1	4	1
Random effects model (r = 0.82)		6.63		[0.52; 12.75]											
Heterogeneity: 1 ² = 94% [88%; >97%], τ	² = 33.760	8. <i>p</i> < 0.01													
Source = Mixed							_								
Lewis et al, 2013	13	7.20	2.16	[2.97; 11.43]	0	0		10.00	MF	OW/OB	Mix	Eu	0.7	6	1
Markey et al, 2016	50	-0.90	0.64	[-2.16; 0.36]	0	2	<u>=</u>	10.00	MF	Non-OB	Mix	AL	0.1	8	1
Black et al, 2008	13	0.00	1.08	[-2.12; 2.12]	0	0	<u>+</u>	15.00	M	BMI<35	Mix	Eu	0.4	6	1
Swanson et al, 1992	14	0.00	1.71	[-3.35; 3.35]	0	0		16.60	MF	GP	Fruct	Eu		4	1
Saris et al, 2000*	79	2.16	1.44	[-0.65; 4.97]	0	0	_ <u>+</u> =-	19.00	MF	OW/OB	Mix	AL	0.9	24	1
Umpleby et al, 2017 (No NAFLD)	14	-0.54	1.04	[-2.58; 1.50]	0	2		20.00	M	OW/No-NAFLD	Mix	Eu	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	-0.72	0.97	[-2.63; 1.19]	0	2		20.00	M	OW/NAFLD	Mix	Eu	2.1	12	2
Raben et al, 2002*	11	2.70	1.89	[-1.00; 6.40]	0	2	<u>+</u>	23.00	MF	WO	Mix	AL	2.6	10	1
Random effects model (r = 0.82)		0.67		[-0.77; 2.12]			•								
Heterogeneity: $I^2 = 62\% [17\%; 82\%], \tau^2$	= 2.6027,	p = 0.01													
Random effects model (r = 0.82)		1.94		[0.23; 3.66]			•								
Prediction interval				[-5.61; 9.50]											
Heterogeneity: $I^2 = 87\%$ [82%; 91%], τ^2							-5 0 5 10 15 20 25								
Residual heterogeneity: 12 = 85% [77%;		0.01					-0 0 0 10 10 20 26								
Random effects model (r = 0.5): 1.4 [-0.							Parallel Red = Cross-over								
Random effects model (r = 0.99): 2.36 [0.25; 4.46	1	r 0.5	= 1 -> significant e	ffect (0.82)) becomes r	on-significant (0.5); r 0.99 = 2 -> non sign	ificant effect (0.82) b	ecomes si	ignificant (0.99)					

Figure G.4c2: Stratified by sugars source



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy balance	e.						1								
Lewis et al, 2013	13	28.02	1.52	[23.05; 29.00]	0	0		10	MF	OW/OB	Mix	Mix	0.7	0	1
Black et al, 2006	13	6.94	5.43	[-3.70; 17.58]	0	2	-	15	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al, 1983a* (normoinsulinemic)	12	-2.38	3.33	[-8.89; 4.17]	0	2		15	M	N-I	Fruct	F		5	2
Hallfrisch et al, 1983a* (hyperinsulinemic)	12	17.63	3.29	[11.18; 24.08]	0	0	22	15	M	H-I	Fruct	F		5	2
Lowndes et al, 2015	32	7.70	4.98	[-2.07; 17.47]	0	2		18	MF	BMI<35	Mix	в		10	1
Umpleby et al, 2017 (No NAFLD)	14	1.39	8.18	[-14.65; 17.42]	0	0		20	M	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	-1.39	8.20	[-17.48; 14.69]	0	0		20	M	OW/NAFLD	Mix	Mix	2.1	12	2
Israel et al, 1983*	12	113.82	18.31	[77.93; 149.70]	0	0		28	M	H-I	Mix	F	-3.8	8	1
Israel et al, 1983*	12	71.48	10.07	[51.74; 91.22]	0	0		28	F	H-I	Mix	F	0.2	6	1
Moser et al, 1986 (OC-users)	6	0.00	6.58	[-12.90; 12.90]	0	0	+	43	F	oc	Mix	F	-1	4	1
Moser et al, 1986 (No OC-users)	8	0.00	12.49	[-24.48; 24.48]	0	0		43	F	Non-OC	Mix	F	1	4	1
Random effects model (r = 0.82)		19.99		[0.67; 39.31]											
Heterogeneity: $I^2 = 93\%$ [90%; 95%], $\pi^2 = 998.795$	7, p < 0.0	01													
Diet = Ad libitum		2.40	1.77				1	10	MF	11 0.0					
Markey et al. 2016	48			[-1.07; 5.87]	0	2		10		Non-OB	Mix	Mix	0.1	8	1
Campos et al. 2015	13 14	15.27	12.63	[-9.48; 40.02]	0	2		18	MF	OW/OB OW/OB	Mix	B	2.3	12	1
Maersk et al, 2012*				[-7.53; 20.33]	-										2
Saris et al, 2000* Raben et al, 2002*	79 11	15.13 13.00	8.25 5.70	[-1.05; 31.31]	0	0	*	19 23	MF	OW/OB OW	Mix	Mix	0.9	24 10	1
Raben et al, 2002" Random effects model (r = 0.82)	11	7.58	5.70	[1.83; 24.17] [1.04; 14.12]	1	0		23	MP	OW	MIX	MIX	2.0	10	1
				[1.04; 14.12]			•								
Heterogeneity: $I^2 = 34\% [0\%; >75\%], \tau^2 = 21.4666$	p = 0.2	0													
Random effects model (r = 0.82)		16.21		[3.91; 28.50]			-								
Prediction interval				[-36.56; 68.97]											
Heterogeneity: 1 ² = 93% [90%; 95%], τ ² = 585.792	7. p < 0.0	01													
Residual heterogeneity: I ² = 91% [87%; 94%], p <							-50 0 50 100 150								
Random effects model (r = 0.5): 12.85 [1.89; 23.8						Blad	= Parallel Red = Cross-over								
Random effects model (r = 0.99): 18.04 [1.65; 34.4			r 0	.5 = 1 -> significant e	ffect (0.82)		on-significant (0.5); r 0.99 = 2 -> non signi	ficant effect (0.82) be	comes si	gnificant (0.99)					

Footnote to Figure G4. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F under Sex = females; F under Source = food; Fruct = fructose; GP = general population; H-I = hyperinsulinemia; M = males; MF = males and females; Mix under Sugar = sugar mixtures; Mix under Source = foods and beverages; N = average sample size per arm; N-I = normo-insulinemia; NAFLD = non-alcoholic fatty liver disease; OB = obese; OC = oral contraceptives; OW = overweight; r05 and r099 = change in the significance of the effect (0 = no change; 1 = change) when assuming a correlation coefficient of respectively 0.50 and 0.99 (instead of 0.82) when computing the SE of the effect measurement; RoB = risk of bias (tier). Study duration is expressed in weeks.

Figure G.4d: Effect of high vs low sugar intake on fasting insulin (pmol/L)

Figure G.5: Randomised controlled trials: effect of fructose vs. glucose on measures of glucose tolerance

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Fru-Glu (E%)	Sex	Subjects	Source	BW*	Weeks	RoB
Diet = Isocaloric with neutr	al energ	y balance					1							
Lowndes et al, 2015	32	1.80	1.97	[-2.06; 5.66]	0	0	- <u>+-</u> -	9.00	MF	BMI<35	в		10	1
Koh et al, 1988 (NGT)	9	-10.80	2.08	[-14.88; -6.72]	0	0		15.00	MF	NGT	Mix		4	2
Koh et al, 1988 (IGT)	9	-9.72	2.09	[-13.81; -5.63]	0	0		15.00	MF	IGT	Mix		4	2
Kelsay et al, 1974	8	-6.00	2.47	[-10.85; -1.15]	1	0		42.50	MF	GP	F		4	2
Random effects model		-6.15		[-11.85; -0.46]										
Heterogeneity: /2 = 88% [70%; 2	>95%], τ ²	= 29.0961, p < 0.01												
Diet = Isocaloric with posit														
Silbernagel et al, 2011	10	0.36	2.90	[-5.33; 6.05]	0	0		22.00	MF	BMI<35	в	-1.5	4	1
Random effects model		0.36		[-5.33; 6.05]										
Heterogeneity: not applicable														
Diet = Ad libitum	-													
				•			臣							1
						-					_		-	1
											_			1
	16		1.88	•	1	0		25.00	MF	OW/OB	в	-0.2	8	2
				[-0.13; 2.38]			•							
Heterogeneity: /* = 52% [0%; >	·84%], ±**	= < 0.0001, p = 0.10												
Random effects model		-2.67		1-6.46: 1.111										
		2.01												
	02%1 - ² -	27 9799 0 4 0 01		[10.00, 10.04]										
							-20 -10 0 10 20)						
	r 0.5 = 1 -> significant effect (0.82) becomes non-significant (0.57 : 0.59 = 2 -> non significant effect (0.82) becomes significant (0.99)													
Angelopoulos et al. 2015* Mark et al. 2014 Jin et al., 2014 Stanhope et al. 2009* Random effects model Heterogeneity: J ² = 52% [0%; > Random effects model Prediction interval Heterogeneity: J ² = 87% [78%; ' Random effects model (r = 0.5)	93%], τ ² =): -1.83 [-6	-2.67 27.9789, p < 0.01 8.05; 2.4]	0.77 1.53 5.16 1.88	[-0.71; 2.31] [-1.38; 4.62] [-19.47; 0.75] [0.01; 7.39] [-0.13; 2.38] [-6.46; 1.11] [-15.99; 10.64]	0 0 1	2 0 2 0	Black = Parallel Red = Cross-over		MF F MF MF	BMI<35 OW/OB NAFLD OW/OB	8 8 8	0.1 -0.4 0.2 -0.2	10 4 4 8	1 1 2

Figure G.5a: Effect of fructose vs glucose on fasting glucose (mg/dL)



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Fru-Glu (E%)	Sex	Subjects	Source	BW*	Weeks	RoB
Diet = Isocalorio with net Lowndes et al, 2015 Koh et al, 1988 (NGT) Koh et al, 1988 (IGT) Kelsay et al, 1974 Random effects model Heterogeneity: <i>i</i> ² = 84% [607	32 9 9 7	22.30 -80.04 -20.01 0.00 -12.48	10.38 18.18 26.38 10.62	[1.95; 42.65] [-91.76; -28.33] [-71.72; 31.69] [-20.81; 20.81] [-48.46; 23.60]	1 0 0	0 0 2 0	*	9.00 15.00 15.00 42.50	MF MF F	BMI<35 NGT IGT GP	B Mix Mix F	-	10 4 4 4	1 2 2 2
Diet = Isocaloric with por Silbernagel et al, 2011 Random effects model Heterogeneity: not applicable	10	ergy balance -5.00 -5.00	11.40	[-27.35; 17.35] [-27.35; 17.35]	0	0	Ŧ	22.00	MF	BMI<35	в	-1.5	4	1
Diet = Ad libitum Mark et al., 2014 Jin et al., 2014 Stanhope et al., 2009* Random effects model Heterogeneity: / ² = 62% [0%	35 10 16	7.38 149.21 6.25 8.14	5.73 61.65 11.70	[-3.86; 18.62] [28.38; 270.04] [-16.68; 29.17] [-1.91; 18.20]	0 1 0	2 0 0		16.00 20.00 25.00	F MF MF	OW/OB NAFLD OW/OB	B B B	-0.4 0.2 -0.2	4 4 8	1 1 2
Heterogenety: $I = 62\%$ [05 Random effects model Prediction interval Heterogeneity: $I^2 = 73\%$ [46] Residual heterogeneity: I^2 = Random effects model ($r = 0$ Random effects model ($r = 0$	6; 87%], - 79% [55%).5): 1.9 [-	-0.77 z ² = 524.0376, p < 0.0 ; 91%], p < 0.01 19.83; 23.63]	01	[-20.07; 18.53] [-61.75; 60.20] r 0.5 = 1 -> significant	effect (0.82	Blad	-100 0 100 200 300 = Parallel Red = Cross-over m-significant (0.5); r 0.99 = 2 -> non sign		becomes s	ignificant (0.99)	I			

Footnote to Figure G5. * differences in BW change between high and low sugar intake; B = beverages; BMI = body mass index; BW = body weight; CI = confidence interval; E% = energy percentage; F under Sex = females; F under Sex = females; F under Sex = females; Funder Sex = females; F under Sex = females; Funder Sex = females; Funder Sex = females; F under Sex = females; Funder Sex = females; Fu

Figure G.5b: Effect of fructose vs glucose on fasting insulin (pmol/L)

Figure G.6: Randomised controlled trials: effect of high vs. low sugar intake on blood lipids

Figure G.6a: Effect of high vs low sugar intake on total cholesterol (mg/dL)

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy balance	e						1								
Gostner et al, 2005	19	-10.00	6.61	[-22.96; 2.96]	0	2		6.00	MF	GP	Mix	F	0	4	1
Lewis et al, 2013	13	7.73	4.64	[-1.36; 16.83]	0	2		10.00	MF	OW/OB	Mix	Mix	0.7	6	1
Lowndes et al, 2014a	15	-14.30	8.14	[-30.26; 1.66]	0	2		10.00	MF	OW/OB	Mix	в	0	10	2
Black et al, 2006	13	23.59	18.56	[-12.79; 59.97]	0	2		15.00	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al. 1983a* (normoinsulinemic)	12	14.40	4.20	[6.17; 22.63]	0	0		15.00	M	N-I	Fruct	F		5	2
Hallfrisch et al, 1983a* (hyperinsulinemic)	12	11.40	8.40	[-5.06; 27.86]	0	2		15.00	M	H-I	Fruct	F		5	2
Swanson et al, 1992	14	14.31	3.95	[6.56; 22.05]	0	0		16.60	MF	GP	Fruct	Mix		4	1
Reiser et al, 1989a* (normoinsulinemic)	11	15.08	6.99	[1.38; 28.78]	1	0		20.00	M	N-I	Fruct	F		5	2
Reiser el al., 1989a* (hyperinsulinemic)	10	22.82	7.84	[7.44; 38.19]	1	0		20.00	M	H-I	Fruct	F		5	2
Umpleby et al, 2017 (No NAFLD)	14	10.83	5.92	[-0.77; 22.43]	0	2		20.00	M	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	13.53	7.32	[-0.81; 27.88]	0	2		20.00	M	OW/NAFLD	Mix	Mix	2.1	12	2
Lowndes et al. 2014b*	55	6.60	4.70	[-2.62; 15.82]	0	2		22.00	MF	BMI<35	Mix	в	-4.1	10	2
Israel et al. 1983*	12	52.00	8.11	[36.11; 67.89]	0	0		28.00	M	H-I	Mix	F	-3.8	6	1
Israel et al. 1983*	12	21.00	3.31	[14.51; 27.49]	0	0		28.00	F	H-I	Mix	F	0.2	6	1
Groen et al, 1966	15	27.00	8.16	[11.00; 43.00]	0	0		30.00	MF	GP	Mix	Mix	-0.6	5	2
Reiser et al, 1979a*	19	26.00	9.53	[7.31; 44.69]	1	0		30.00	MF	GP	Mix	F	0.5	6	2
Moser et al, 1986 (OC-users)	6	15.00	7.97	[-0.62; 30.62]	0	2		43.00	F	OC	Mix	F	-1	4	1
Moser et al, 1986 (No OC-users)	6	-14.00	12.33	[-38.17; 10.17]	0	2		43.00	F	Non-OC	Mix	F	1	4	1
Random effects model (r = 0.82) Heterogeneity: I ² = 75% [80%; 84%], t ² = 158.7958	8, p < 0.01	13.39		[6.63; 20.16]			*								
Diet = Ad libitum															
Majid et al, 2013	31	-26.68	4.44	[-35.39; -17.98]	0	0		8.00	M	GP	Mix	в		4	2
Markey et al, 2016	50	0.39	2.17	[-3.86; 4.63]	0	0	-	10.00	MF	Non-OB	Mix	Mix	0.1	8	1
Smith et al, 1996	16	19.34	9.13	[1.44; 37.23]	1	0		12.00	MF	H-TG	Mix	Mix	2.7	24	2
Huttunen et al, 1976	40	-7.73	11.32	[-29.93; 14.46]	0	0		16.00	MF	GP	Mix	Mix		72	2
Campos et al, 2015	13	0.00	6.86	[-13.45; 13.45]	0	0		18.00	MF	OW/OB	Mix	в	2.3	12	1
Hollis et al, 2009	25	0.39	5.39	[-10.17; 10.95]	0	0	- <u></u>	18.00	MF	OW	Mix	в	1.5	12	1
Maersk et al, 2012*	14	35.19	7.78	[19.94; 50.44]	0	0	- <u>x</u> -	18.00	MF	OW/OB	Mix	в	1	24	2
Saris et al, 2000*	79	-0.77	3.90	[-8.42; 6.88]	0	0	*	19.00	MF	OW/OB	Mix	Mix	0.9	24	1
Hernandez-Cordero et al, 2014	120	-1.00	1.07	[-3.10; 1.10]	0	2		20.00	F	OW/OB	Mix	в	0.5	36	2
Raben et al, 2002*	11	-4.25	10.50	[-24.83; 16.33]	0	0		23.00	MF	ow	Mix	Mix	2.6	10	1
Werner et al, 1984	12	5.80	8.37	[-10.60; 22.20]	0	2		24.00	MF	Gallstones	Mix	Mix	1.4	6	2
Random effects model (r = 0.82)		1.34		[-7.71; 10.38]			+								
Heterogeneity: $I^2 = 84\%$ [72%; 90%], $\pi^2 = 189.0115$	5, p < 0.01														
Random effects model (r = 0.82)		8.71		[2.86; 14.56]			-								
Prediction interval				[-21.33; 38.76]											
Heterogeneity: I ² = 87% [82%; 90%], τ ² = 205.4915	5. p < 0.01	i i													
Residual heterogeneity: 12 = 79% [70%; 85%], p < 0							-40 -20 0 20 40 60								
Random effects model (r = 0.5): 7.27 [1.43; 13.11]															
Random effects model (r = 0.99): 9.38 [3.14; 15.61			r 0.	5 = 1 -> significant ef	fect (0.82)		on-significant (0.5); r 0.99 = 2 -> non sign	nificant effect (0.82) be	ecomes si	gnificant (0.99)					

Figure G.6a1: Stratified by type of diet



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subject	Sugar	Diet	BW*	Weeks	RoB
Source = Beverages															
Majid et al, 2013	31	-26.68	4.44	[-35.39; -17.98]	0	0		8.00	M	GP	Mix	AL		4	2
Lowndes et al, 2014a	15	-14.30	8.14	[-30.26; 1.66]	0	2		10.00	MF	OW/OB	Mix	Eu	0	10	2
Campos et al, 2015	13	0.00	6.86	[-13.45; 13.45]	0	0		18.00	MF	OW/OB	Mix	AL	2.3	12	1
Hollis et al, 2009	25	0.39	5.39	[-10.17; 10.95]	0	0		18.00	MF	ow	Mix	AL	1.5	12	1
Maersk et al, 2012*	14	35.19	7.78	[19.94; 50.44]	0	0		18.00	MF	OW/OB	Mix	AL	1	24	2
Hernandez-Cordero et al, 2014	120	-1.00	1.07	[-3.10; 1.10]	0	2		20.00	F	OW/OB	Mix	AL	0.5	38	2
Lowndes et al, 2014b*	55	6.60	4.70	[-2.62; 15.82]	0	2	+=-	22.00	MF	BMI<35	Mix	Eu	-4.1	10	2
Random effects model (r = 0.82)		-0.30		[-14.02; 13.41]											
Heterogeneity: $I^2 = 90\%$ [82%; 94%], $\tau^2 = 309.1118$, p < 0.01														
Source = Foods							_								
Gostner et al, 2005	19	-10.00	6.61	[-22.96; 2.96]	0	2	- <u></u> -	6.00	MF	GP	Mix	Eu	0	4	1
Hallfrisch et al, 1983a* (normoinsulinemic)	12	14.40	4.20	[6.17; 22.63]	0	0		15.00	M	N-I	Fruct	Eu		5	2
Hallfrisch et al, 1983a* (hyperinsulinemic)	12	11.40	8.40	[-5.06; 27.86]	0	2		15.00	M	H-I	Fruct	Eu		5	2
Reiser et al, 1989a* (normoinsulinemic)	11	15.08	6.99	[1.38; 28.78]	1	0		20.00	M	N-I	Fruct	Eu		5	2
Reiser el al., 1989a* (hyperinsulinemic)	10	22.82	7.84	[7.44; 38.19]	1	0		20.00	M	H-I	Fruct	Eu		5	2
Israel et al, 1983*	12	52.00	8.11	[36.11; 67.89]	0	0		28.00	M	H-I	Mix	Eu	-3.8	6	1
Israel et al, 1983*	12	21.00	3.31	[14.51; 27.49]	0	0	-	28.00	F	H-I	Mix	Eu	0.2	6	1
Reiser et al, 1979a*	19	26.00	9.53	[7.31; 44.69]	1	0		30.00	MF	GP	Mix	Eu	0.5	6	2
Moser et al, 1986 (OC-users)	6	15.00	7.97	[-0.62; 30.62]	0	2	-	43.00	F	OC	Mix	Eu	-1	4	1
Moser et al, 1986 (No OC-users)	6	-14.00	12.33	[-38.17; 10.17]	0	2		43.00	F	Non-OC	Mix	Eu	1	4	1
Random effects model (r = 0.82)		15.85		[5.12; 26.57]											
Heterogeneity: I ² = 80% [84%; 89%], τ ² = 241.0777	. p < 0.01														
Source = Mixed							_								
Lewis et al, 2013	13	7.73	4.64	[-1.36; 16.83]	0	2	<u>+</u>	10.00	MF	OW/OB	Mix	Eu	0.7	6	1
Markey et al. 2016	50	0.39	2.17	[-3.86; 4.63]	0	0	÷	10.00	MF	Non-OB	Mix	AL	0.1	8	1
Smith et al, 1996	16	19.34	9.13	[1.44; 37.23]	1	0		12.00	MF	H-TG	Mix	AL	2.7	24	2
Black et al, 2006	13	23.59	18.56	[-12.79; 59.97]	0	2	-	15.00	М	BMI<35	Mix	Eu	0.4	6	1
Huttunen et al, 1976	40	-7.73	11.32	[-29.93; 14.46]	0	0		16.00	MF	GP	Mix	AL	-	72	2
Swanson et al, 1992	14	14.31	3.95	[8.58; 22.05]	0	0	1-	16.60	MF	GP	Fruct	Eu		4	1
Saris et al, 2000*	79	-0.77	3.90	[-8.42; 6.88]	0	0		19.00	MF	OW/OB	Mix	AL	0.9	24	1
Umpleby et al, 2017 (No NAFLD)	14	10.83	5.92	[-0.77; 22.43]	0	2		20.00	м	OW/No-NAFLD	Mix	Eu	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	13.53	7.32	[-0.81; 27.88]	0	2		20.00	м	OW/NAFLD	Mix	Eu	2.1	12	2
Raben et al, 2002*	11	-4.25	10.50	[-24.83; 16.33]	0	0		23.00	MF	ow	Mix	AL	2.6	10	1
Werner et al, 1984	12	5.80	8.37	[-10.60; 22.20]	0	2		24.00	MF	Gallstones	Mix	AL	1.4	6	2
Groen et al, 1968	15	27.00	8.16	[11.00; 43.00]	0	0		30.00	MF	GP	Mix	Eu	-0.6	5	2
Random effects model (r = 0.82) Heterogeneity: l^2 = 60% [25%; 79%], τ^2 = 41.9199,	p < 0.01	7.98		[2.67; 13.28]			•								
Random effects model (r = 0.82)		8.71		[2.86; 14.56]			•								
Prediction interval				[-21.33; 38.76]											
Heterogeneity: I ² = 87% [82%; 90%], τ ² = 205.4915.	p < 0.01														
Residual heterogeneity: 1 ² = 81% [72%; 86%], p < 0							-40 -20 0 20 40 60								
Random effects model (r = 0.5): 7.27 [1.43; 13.11]							Black = Parallel Red = Cross-over								
Random effects model (r = 0.99): 9.38 [3.14; 15.61]			r 0.	5 = 1 -> significant ef	fect (0.82)		on-significant (0.5); r 0.99 = 2 -> non sign	ificant effect (0.82) be	ecomes si	gnificant (0.99)					

Figure G.6a2: Stratified by sugars source



Figure G.6b: Effect of high vs low sugar intake on LDL-cholesterol (mg/dL)

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy bala	nce														
Gostner et al, 2005	19	-13.30	6.12	[-25.30; -1.30]	1	0		6.00	MF	GP	Mix	F	0	4	1
Lewis et al, 2013	13	3.87	3.67	[-3.32; 11.06]	0	2		10.00	MF	OW/OB	Mix	Mix	0.7	6	1
Lowndes et al, 2014a	15	-11.80	6.85	[-25.22; 1.62]	0	2		10.00	MF	OW/OB	Mix	в	0	10	2
Black et al, 2006	13	20.50	6.41	[7.94; 33.05]	1	0		15.00	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al, 1983a* (NI - HI)	24	6.90	4.58	[-2.08; 15.88]	0	2		15.00	M	NI - HI	Fruct	F		5	2
Swanson et al, 1992	14	10.44	3.26	[4.08; 18.82]	1	0		16.60	MF	GP	Fruct	Mix		4	1
Reiser et al, 1989a* (normoinsulinemic)	11	12.76	4.90	[3.15; 22.37]	1	0		20.00	M	N-I	Fruct	F		5	2
Reiser el al., 1989a* (hyperinsulinemic)	10	8.12	5.64	[-2.94; 19.18]	0	2		20.00	M	H-I	Fruct	F		5	2
Umpleby et al, 2017 (No NAFLD)	14	5.41	4.65	[-3.69; 14.52]	0	2		20.00	M	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	6.57	6.27	[-5.71; 18.86]	0	2		20.00	M	OW/NAFLD	Mix	Mix	2.1	12	2
Lowndes et al, 2014b*	55	3.60	4.00	[-4.24; 11.44]	0	2		22.00	MF	BMI<35	Mix	в	-4.1	10	2
Israel et al, 1983*	12	35.00	6.60	[22.08; 47.94]	0	0		28.00	M	H-I	Mix	F	-3.8	6	1
Israel et al, 1983*	12	14.00	3.31	[7.51; 20.49]	0	0		28.00	F	H-I	Mix	F	0.2	6	1
Random effects model (r = 0.82)		7.88		[1.82; 13.94]			-								
Heterogeneity: $I^2 = 75\%$ [58%; 88%], $\tau^2 = 97.9159$, $p < 0.01$															
Diet = Ad libitum															
Majid et al, 2013	31	-20.11	3.31	[-26.60; -13.62]	0	0		8.00	м	GP	Mix	в		4	2
Markey et al, 2016	50	0.39	1.82	[-3.18; 3.96]	0	0	- <u>+</u>	10.00	ME	Non-OB	Mix	Mix	0.1	8	1
Hollis et al. 2009	25	1.55	5.39	[-9.02; 12.12]	0	0	<u> </u>	18.00	MF	ow	Mix	в	1.5	12	1
Maersk et al. 2012*	14	22.43	7.77	[7.21; 37.65]	1	0	□	18.00	ME	OW/OB	Mix	в	1	24	2
Saris et al. 2000*	79	-2.71	3.35	[-9.28; 3.86]	0	0		19.00	MF	OW/OB	Mix	Mix	0.9	24	1
Hernandez-Cordero et al. 2014	120	-6.00	0.75	[-7.47; -4.53]	0	0	I	20.00	F	OW/OB	Mix	в	0.5	36	2
Werner et al, 1984	12	1.18	7.35	[-13.25; 15.57]	0	0		24.00	MF	Gallstones	Mix	Mix	1.4	6	2
Random effects model (r = 0.82)		-1.66		[-10.17; 6.84]											-
Heterogeneity: /2 = 87% [76%; 93%], x2 = 111.0	518, p <	0.01													
Random effects model (r = 0.82)		4.49		[-0.88; 9.87]			-								
Prediction interval				[-19.76; 28.75]											
Heterogeneity: I ² = 90% [85%; 93%], τ ² = 125.7		0.01					20 0 00 10								
Residual heterogeneity: I ² = 81% [71%; 87%], p							-20 0 20 40								
Random effects model (r = 0.5): 3.38 [-2.03; 8.7						E	Black = Parallel Red = Cross-over								
Random effects model (r = 0.99): 4.91 [-0.88; 1	0.71]		r 0.	5 = 1 -> significant et	ffect (0.82) becomes n	on-significant (0.5); r 0.99 = 2 -> non sign	ificant effect (0.82) be	comes si	gnificant (0.99)					

Figure G.6b1: Stratified by type of diet



Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subject	Sugar	Diet	BW*	Weeks	RoB
Source = Beverages															
Majid et al, 2013	31	-20.11	3.31	[-28.60; -13.62]	0	0		8.00	M	GP	Mix	AL		4	2
Lowndes et al, 2014a	15	-11.80	6.85	[-25.22; 1.62]	0	2		10.00	MF	OW/OB	Mix	Eu	0	10	2
Hollis et al, 2009	25	1.55	5.39	[-9.02; 12.12]	0	0		18.00	MF	ow	Mix	AL	1.5	12	1
Maersk et al, 2012*	14	22.43	7.77	[7.21; 37.65]	1	0		18.00	MF	OW/OB	Mix	AL	1	24	2
Hernandez-Cordero et al, 2014	120	-6.00	0.75	[-7.47; -4.53]	0	0		20.00	F	OW/OB	Mix	AL	0.5	36	2
Lowndes et al, 2014b*	55	3.60	4.00	[-4.24; 11.44]	0	2		22.00	MF	BMI<35	Mix	Eu	-4.1	10	2
Random effects model (r = 0.82)		-2.50		[-13.52; 8.52]											
Heterogeneity: $I^2 = 87\%$ [75%; 94%], $\tau^2 = 184.0$	8678, p < (0.01													
Source = Foods															
Gostner et al, 2005	19	-13.30	6.12	[-25.30; -1.30]	1	0		6.00	MF	GP	Mix	Eu	0	4	1
Hallfrisch et al, 1983a* (NI - HI)	24	6.90	4.58	[-2.08; 15.88]	0	2		15.00	M	NI - HI	Fruct	Eu		5	2
Reiser et al, 1989a* (normoinsulinemic)	11	12.76	4.90	[3.15; 22.37]	1	0		20.00	M	N-I	Fruct	Eu		5	2
Reiser el al., 1989a* (hyperinsulinemic)	10	8.12	5.64	[-2.94; 19.18]	0	2		20.00	м	H-I	Fruct	Eu		5	2
Israel et al, 1983*	12	35.00	6.60	[22.06; 47.94]	0	0		28.00	M	H-I	Mix	Eu	-3.8	6	1
Israel et al, 1983*	12	14.00	3.31	[7.51; 20.49]	0	0		28.00	F	H-I	Mix	Eu	0.2	6	1
Random effects model (r = 0.82)		10.52		[-1.23; 22.26]											
Heterogeneity: $I^2 = 84\%$ [88%; 92%], $\tau^2 = 187.5$	9384, p < (0.01													
Source = Mixed															
Lewis et al, 2013	13	3.87	3.67	[-3.32; 11.06]	0	2		10.00	MF	OW/OB	Mix	Eu	0.7	6	1
Markey et al, 2016	50	0.39	1.82	[-3.18; 3.96]	0	0	÷	10.00	MF	Non-OB	Mix	AL	0.1	8	1
Black et al, 2006	13	20.50	6.41	[7.94; 33.05]	1	0		15.00	M	BMI<35	Mix	Eu	0.4	6	1
Swanson et al, 1992	14	10.44	3.26	[4.06; 16.82]	1	0		16.60	MF	GP	Fruct	Eu		4	1
Saris et al, 2000*	79	-2.71	3.35	[-9.28; 3.86]	0	0		19.00	MF	OW/OB	Mix	AL	0.9	24	1
Umpleby et al, 2017 (No NAFLD)	14	5.41	4.65	[-3.69; 14.52]	0	2		20.00	M	OW/No-NAFLD	Mix	Eu	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	6.57	6.27	[-5.71; 18.86]	0	2	<u> </u>	20.00	M	OW/NAFLD	Mix	Eu	2.1	12	2
Werner et al, 1984	12	1.16	7.35	[-13.25; 15.57]	0	0		24.00	MF	Gallstones	Mix	AL	1.4	6	2
Random effects model (r = 0.82)		4.79		[0.27; 9.32]			-								
Heterogeneity: J ² = 62% [18%; 82%], τ ² = 23.84	411, p = 0.	01													
Random effects model (r = 0.82)		4.49		[-0.88; 9.87]			-								
Prediction interval				[-19.76; 28.75]											
Heterogeneity: 1 ² = 90% [85%; 93%], τ ² = 125.7		0.01					-20 0 20 40								
Residual heterogeneity: /2 = 81% [71%; 88%], /							-20 0 20 40								
Random effects model (r = 0.5): 3.38 [-2.03; 8.							Black = Parallel Red = Cross-over								
Random effects model (r = 0.99): 4.91 [-0.88; 1	10.71]		r 0.	5 = 1 -> significant e	fect (0.82)) becomes n	on-significant (0.5); r 0.99 = 2 -> non sign	ificant effect (0.82) be	ecomes si	gnificant (0.99)					

Figure G.6b2: Stratified by sugars source



Figure G.6c: Effect of high vs low sugar intake on HDL-cholesterol (mg/dL)

Study	N	Mean Effect	se Effect	95% CI	r 0.5	r 0.99		Sugar diff (E%)	Sex	Subjects	Sugar	Source	BW*	Duration	RoB
Diet = Isocaloric with neutral energy bala	ance														
Gostner et al, 2005	19	1.30	1.92	[-2.48; 5.08]	0	2		6.00	MF	GP	Mix	F	0	4	1
Lewis et al, 2013	13	3.87	1.83	[0.27; 7.48]	1	0		10.00	MF	OW/OB	Mix	Mix	0.7	6	1
Lowndes et al, 2014a	15	-3.30	3.44	[-10.04; 3.44]	0	2		10.00	MF	OW/OB	Mix	в	0	10	2
Black et al, 2006	13	0.00	1.39	[-2.73; 2.73]	0	0		15.00	M	BMI<35	Mix	Mix	0.4	6	1
Hallfrisch et al, 1983a* (NI - HI)	24	2.10	1.03	[0.08; 4.12]	1	0		15.00	M	NI - HI	Fruct	F		5	2
Swanson et al, 1992	14	3.09	1.62	[-0.09; 6.28]	0	2		16.60	MF	GP	Fruct	Mix		4	1
Reiser et al, 1989a* (normoinsulinemic)	11	1.93	1.70	[-1.40; 5.27]	0	2		20.00	M	N-I	Fruct	F		5	2
Reiser el al., 1989a* (hyperinsulinemic)	10	0.39	1.61	[-2.77; 3.55]	0	0		20.00	M	H-I	Fruct	F		5	2
Umpleby et al, 2017 (No NAFLD)	14	1.16	1.74	[-2.28; 4.58]	0	2		20.00	M	OW/No-NAFLD	Mix	Mix	2.2	12	2
Umpleby et al, 2017 (NAFLD)	11	2.32	1.87	[-1.35; 5.99]	0	2		20.00	M	OW/NAFLD	Mix	Mix	2.1	12	2
Lowndes et al, 2014b*	55	-0.20	1.59	[-3.32; 2.92]	0	0		22.00	MF	BMI<35	Mix	в	-4.1	10	2
Israel et al, 1983*	12	3.00	1.20	[0.65; 5.35]	1	0		28.00	M	H-I	Mix	F	-3.8	6	1
Israel et al, 1983*	12	7.00	1.80	[3.47; 10.53]	0	0		28.00	F	H-I	Mix	F	0.2	6	1
Random effects model (r = 0.82)		1.97		[0.96; 2.99]			-								
Heterogeneity: $I^2 = 32\%$ [0%; 65%], $z^2 = 0.8370$, $p = 0.13$															
Diet = Ad libitum							_								
Majid et al, 2013	31	2.32	0.84	[0.67; 3.97]	1	0	1	8.00	M	GP	Mix	в		4	2
Markey et al, 2016	50	0.00	1.18	[-2.32; 2.32]	0	0		10.00	MF	Non-OB	Mix	Mix	0.1	8	1
Smith et al, 1996	16	-3.87	2.63	[-9.02; 1.29]	0	2		12.00	MF	H-TG	Mix	Mix	2.7	24	2
Campos et al, 2015	13	0.00	3.62	[-7.10; 7.10]	0	0		18.00	MF	OW/OB	Mix	в	2.3	12	1
Hollis et al, 2009	25	1.55	2.21	[-2.78; 5.88]	0	2		18.00	MF	OW	Mix	в	1.5	12	1
Maersk et al, 2012*	14	2.32	2.64	[-2.86; 7.50]	0	0		18.00	MF	OW/OB	Mix	в	1	24	2
Saris et al, 2000*	79	-1.93	1.24	[-4.36; 0.50]	0	0		19.00	MF	OW/OB	Mix	Mix	0.9	24	1
Hernandez-Cordero et al, 2014	120	-1.90	0.30	[-2.49; -1.31]	0	0	FF	20.00	F	OW/OB	Mix	в	0.5	36	2
Raben et al, 2002*	11	1.16	3.23	[-5.17; 7.49]	0	0		23.00	MF	ow	Mix	Mix	2.6	10	1
Werner et al, 1984	12	-4.25	1.41	[-7.02; -1.49]	1	0		24.00	MF	Gallstones	Mix	Mix	1.4	6	2
Random effects model (r = 0.82)		-0.66		[-2.25; 0.94]			-								
Heterogeneity: $I^2 = 73\%$ [49%; 88%], $\tau^2 = 3.635$	i9, p < 0.0	01													
Random effects model (r = 0.82)		0.83		[-0.25; 1.91]			-								
Prediction interval				[-3.51; 5.17]											
Heterogeneity: $I^2 = 77\%$ [66%; 85%], $\tau^2 = 4.050$	5 p < 0.0	01													
	$\begin{array}{cccccccccccccccccccccccccccccccccccc$														
Random effects model (r = 0.5): 0.54 [-0.52; 1.							Black = Parallel Red = Cross-over								
	andom effects model (= 0.3), 0.34 [vs.02, 1.01] Black = Parallel Red = Cross-over Black = Parallel Red = Cross-over														
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Figure G.6c1: Stratified by type of diet