Supplementary file 1: Supplementary materials

Example of search strategy

„Artificial sweeteners" and "Natural non-caloric sweeteners" search strategy for Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

1 Aspartame/
2 aspartame*.mp.
3 acesulfame.mp.
4 ace K.mp.
5 Saccharin/
6 saccharin*.mp.
7 sucralose.mp.
8 neotame.mp.
9 advantame.mp.
10 Cyclamates/
11 cyclamate*.mp.
12 neohesperidin.mp.
13 alitame*.mp.
14 artificial sweetener*.mp.
15 Stevia/
16 stevia*.mp.
17 steviol*.mp.
18 stevioside*.mp.
19 rebaudioside*.mp.
20 rebiana*.mp.
21 thaumatin*.mp.
22 brazzein*.mp.
23 mogroside*.mp.
24 ((non-calori* or noncalori*) adj (sweetener* or sweetner*)).mp.
25 ((non-sugar or nonsugar) adj (sweetener* or sweetner*)).mp.
26 ((non-nutritive or nonnutritive) adj (sweetener* or sweetner*)).mp.
27 ((low-calori* or lowcalori*) adj (sweetener* or sweetner*)).mp.
28 ((intense or high intensity or high potency) adj (sweetener* or sweetner*)).mp.
29 natural sweetener*.mp.
30 Non-Nutritive Sweeteners/
31 natural sweetening agent*.mp.
32 sugar substitute*.mp.
33 ((non-caloric or noncaloric or zero caloric or diet) adj (beverage* or drink*)).mp.
34 sweetening agents/ or non-nutritive sweeteners/
35 or/1-34
36 exp animals/ not humans.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
37 35 not 36

Risk of Bias assessment of randomised controlled trials

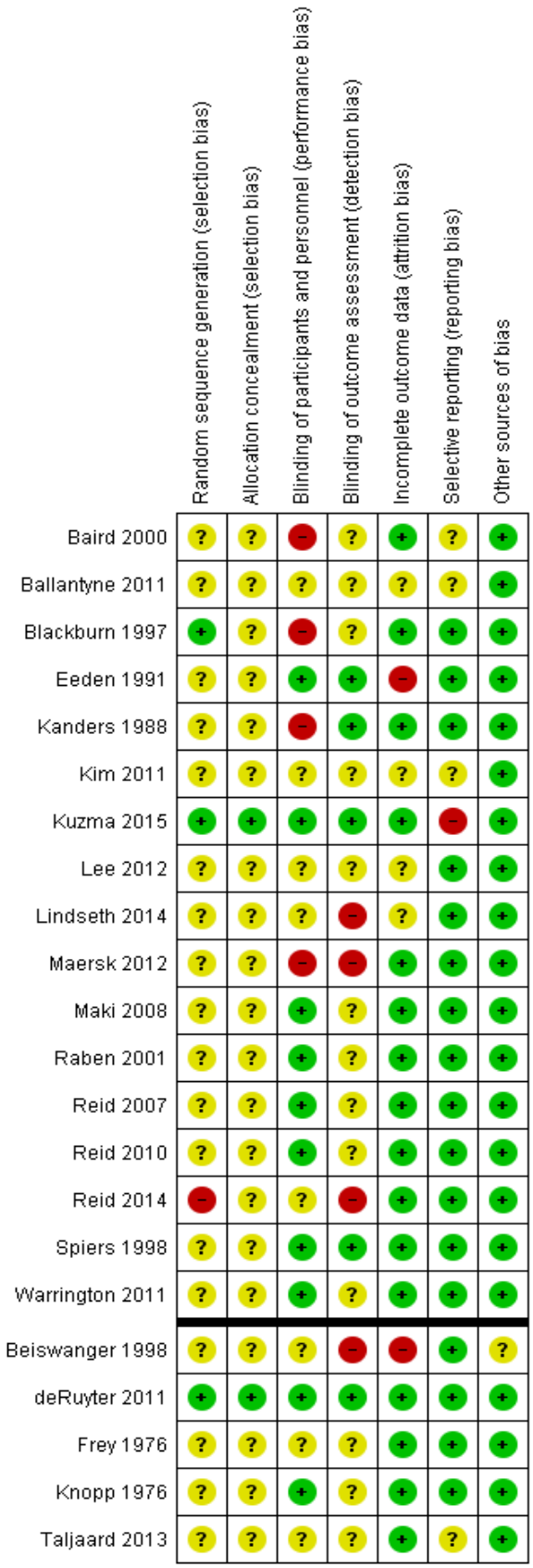

Figure 3: Risk of bias summary of RCTs including adults (top) and children (bottom)

Effects of interventions

Study ID	Effect of NSSs on body weight
RCTs	
Baird 2000	„No evidence of weight loss.“
Ballantyne 2011	„Weight is unaffected.“
Kim 2011	0.22 kg weight gain in intervention group 0.9 kg weight gain in control group
Controlled clinical trials and observational studies	
Naismith 1995	„No appreciable effect“
Naismith 1995	„No appreciable effect“
Parker 1997	„Significantly higher in intervention group“
Porikos 1982	„Significantly higher in control group“
Duran Aguero 2015	OR 0.2 [0.029 to 3.06]
Fernandes 2013	OR for larger waist circumference OR 1.01 [1.00 to 1.01] 1.00 [1.00 to 1.00]
Kuk 2016	MD in BMI 1.10 [0.39 to 1.81] MD in BMI 0.70 [-0.18 to 1.58]
Wulaningsih 2017	OR for abdominal obesity with aspartame 1.13 [1.01 to 1.26]

Table 1: Effect of NSSs on different outcome measures of overweight and obesity in healthy adults

Study ID	Outcome	MD [95% CI]
Warrington 2011	HbA1c (%)	-0.12 [-0.37 to 0.13]
Warrington 2011	C-peptide (ng/ml)	-0.06 [-0.60 to 0.48]
Raben 2001	HOMA ß (%)	-12.20 [-24.48 to 0.08]
Raben 2001	GIP (pmol/l)	-4.70 [-8.89 to -0.51]
Raben 2001	GLP-1 (pmol/l)	-4.40 [-6.34 to -2.46]
Raben 2001	Leptin (ng/ml)	-11.80 [-18.33 to -5.27]

Table 2: Effect of NSSs on intermediate markers for diabetes in healthy adults (end of study data only)

Study ID	Outcome	MD [95% CI]
Raben 2001, Reid, 2010, Reid 2014, Reid 2007	Carbohydrate intake	-89.49 g [-104.35 to -74.63]
Naismith 1995, Tordoff 1990	Carbohydrate intake	-7.15 kJ [-387.82 to 373.53]
Raben 2001, Reid, 2010, Reid 2014, Reid 2007	Fat intake	3.93 g [-2.51 to 10.37]
Raben 2001, Reid 2010, Reid 2014, Reid 2007	Protein intake	1.67 g [-1.21 to 4.54]
Naismith 1995, Tordoff 1990	Protein intake	6.07 g [-1.40 to 13.55]

Table 3: Effect of NSSs on macronutrient intake in healthy adults

Study ID	Type of cancer	OR [95% CI]
Cabaniols 2011	Brain	1.02 [0.57 to 1.85]
Gallus 2007	Breast	0.88 [0.70 to 1.10]
Gallus 2007	Colon	0.92 [0.75 to 1.13]
Bosetti 2009	Endometrial	0.71 [0.36 to 1.38]
Bosetti 2009	Gastric	0.65 [0.25 to 1.68]
Lim 2006	Gliomas	0.64 [0.37 to 1.10]
Gallus 2007	Larynx	1.59 [0.98 to 2.58]
Gallus 2007	Oesophagus	1.04 [0.52 to 2.09]

Gallus 2007	Oral cavity and pharynx	0.79 [0.45 to 1.39]
Gallus 2007	Ovary	0.61 [0.38 to 0.98]
Lim 2006	Overall hematopoietic cancer	0.89 [0.76 to 1.27]
Bosetti 2009	Pancreatic	0.19 [0.08 to 0.46]
Gallus 2007	Prostate	1.08 [0.81 to 1.45]
Gallus 2007	Rectum	0.79 [0.60 to 1.05]
Gallus 2007, Goodman 1986	Renal cell cancer	1.04 [0.81 to 1.34]
McCullough 2014	Hodgkin lymphoma	0.77 [0.44 to 1.32]
McCullough 2014	Multiple Myeloma	0.85 [0.62 to 1.17]
McCullough 2014	All non-Hodgkin lymphoma	1.29 [1.08 to 1.54]

Table 4: Effect of NSSs on the risk for different types of cancer

Study ID	Outcome	MD [95% CI]
Raben 2001, Warrington 2011	serum **triglyceride** concentration	-0.02 mmol/l [-0.21 to 0.16]
Raben 2001, Warrington 2011, Frey 1976*	**serum triglyceride**	0.27 mmol/l [-0.92 to 1.46]
Maersk 2012, Raben 2001, Warrington 2011	**serum cholesterol** concentrations	-0.14 mmol/l [-0.84 to 0.56]
Maersk 2012, Warrington 2011	**LDL cholesterol** concentration	-0.09 mmol/l [-1.04 to 0.86]
Maersk 2012, Raben 2001, Warrington 2011	serum **HDL cholesterol** concentration	-0.01 mmol/dl [-0.08 to 0.05]
Stanhope 2013, Stanhope 2015	serum triglyceride concentrations	”No difference between groups”

Table 5: Effect of NSSs on intermediate markers of cardiovascular disease in healthy adults, * sensitivity analysis

Dose	OR [95% CI]
Aspartame first consumed at age <3	1.0 [0.3 to 3.1]
Aspartame first consumed at age of 3-7 y	1.2 [0.4 to 3.6]
Aspartame consumption duration <2 y	1.2 [0.4 to 3.3]
Aspartame consumption duration ≥2 y	1.1 [0.3 to 3.4]
Aspartame consumption duration <1 times/week	1.6 [0.5 to 5.2]
Aspartame consumption duration ≥ 1 times/week	0.9 [0.3 to 2.4]

Table 6: Effect of different exposure categories of aspartame on risk for brain cancer in children

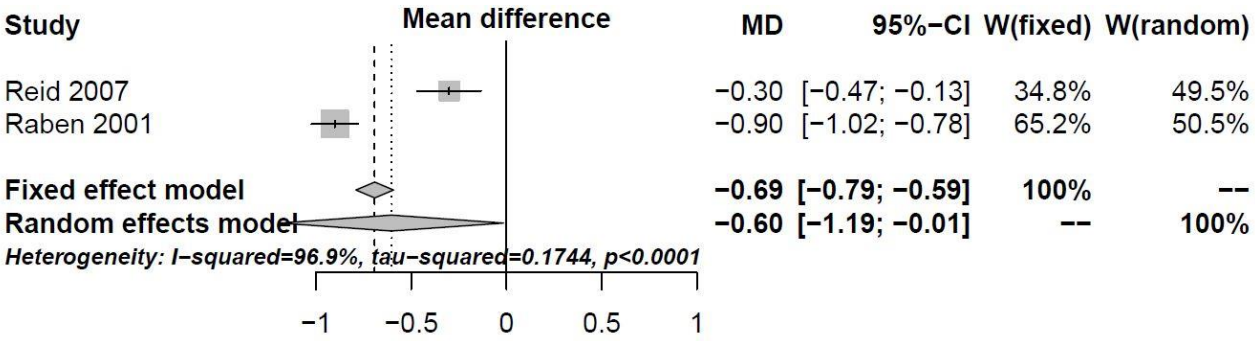

Figure 1: Effect of NSSs versus caloric sweetener on BMI in adults

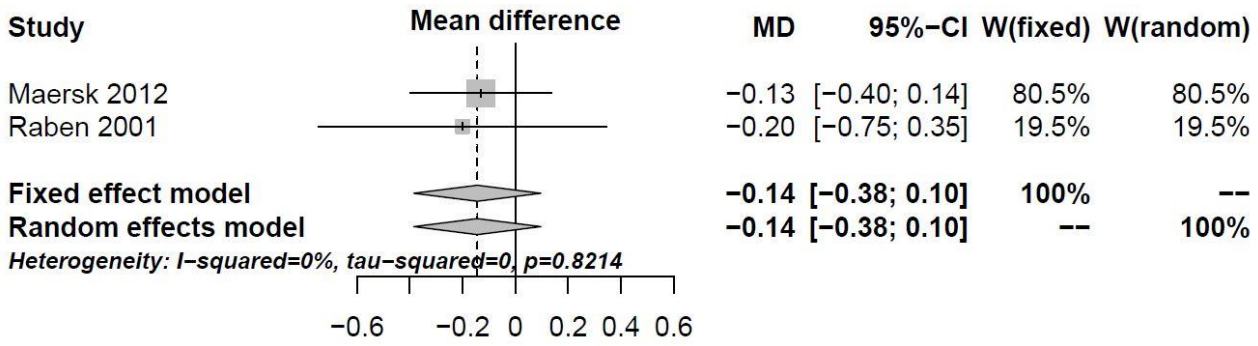

Figure 2: Effect of NSSs versus caloric sweetener on HOMA-IR in adults

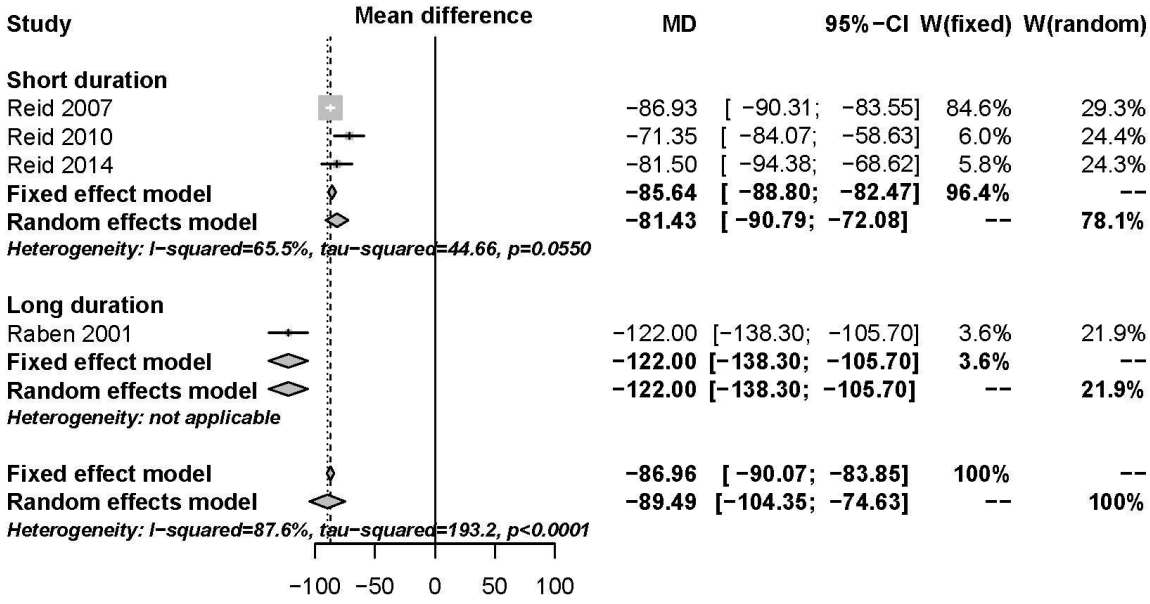

Figure 3: Effect of aspartame (Reid 1007, 2010 2014) or combination of NSSs (Raben2001) versus caloric sweetener on daily carbohydrate intake (g) by study duration in adults

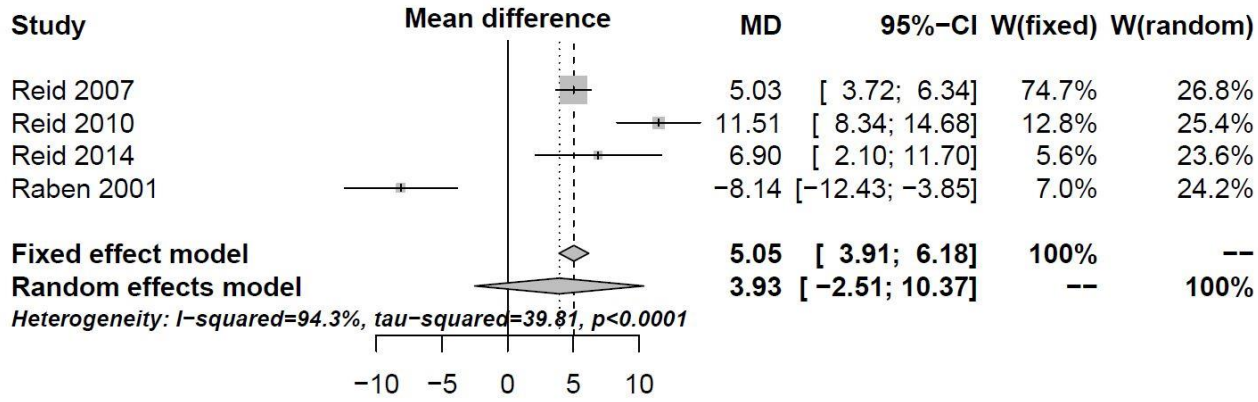

Figure 4: Effect of aspartame (Reid 1007, 2010 2014) or combination of NSSs (Raben2001) versus caloric sweetener on daily fat intake (g) in adults

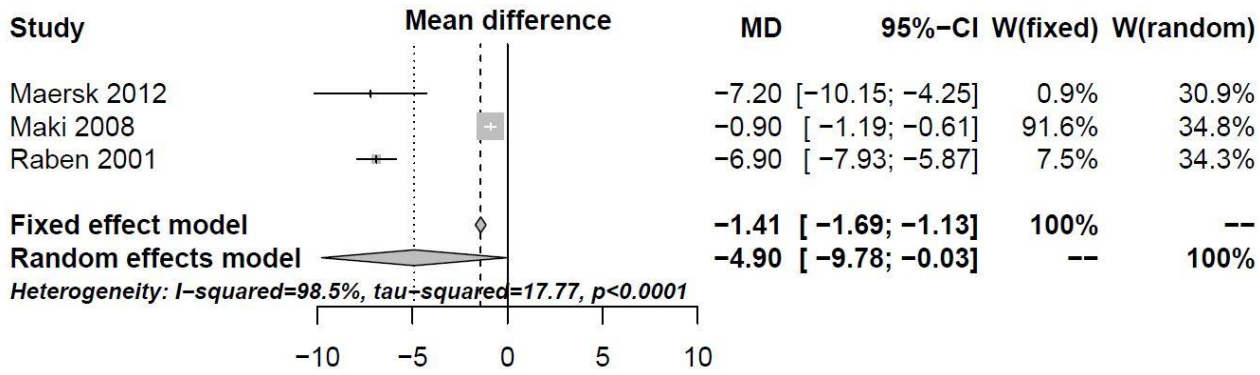

Figure 5: Effect of NSSs versus caloric sweeteners (Maersk 2012, Raben 2001) or placebo (Maki 2008) on systolic blood pressure in adults

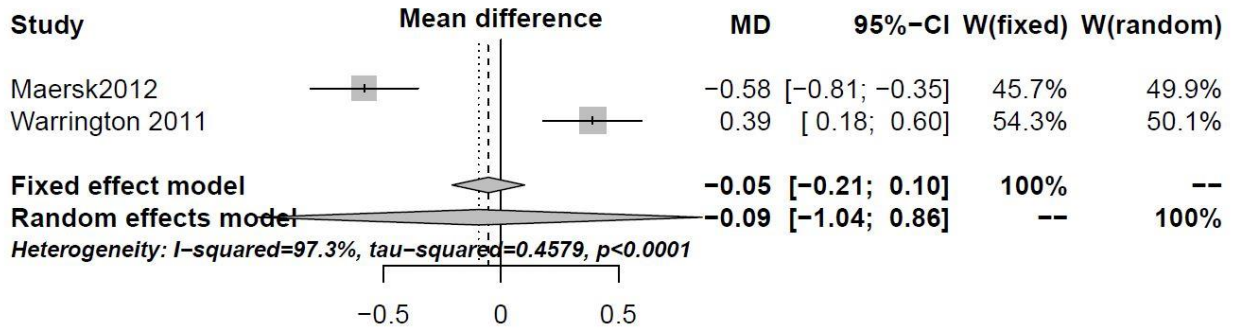

Figure 6: Effect of aspartame versus caloric sweetener (Maersk 2012) and advantame versus placebo (Warrington 2011) on LDL cholesterol in adults

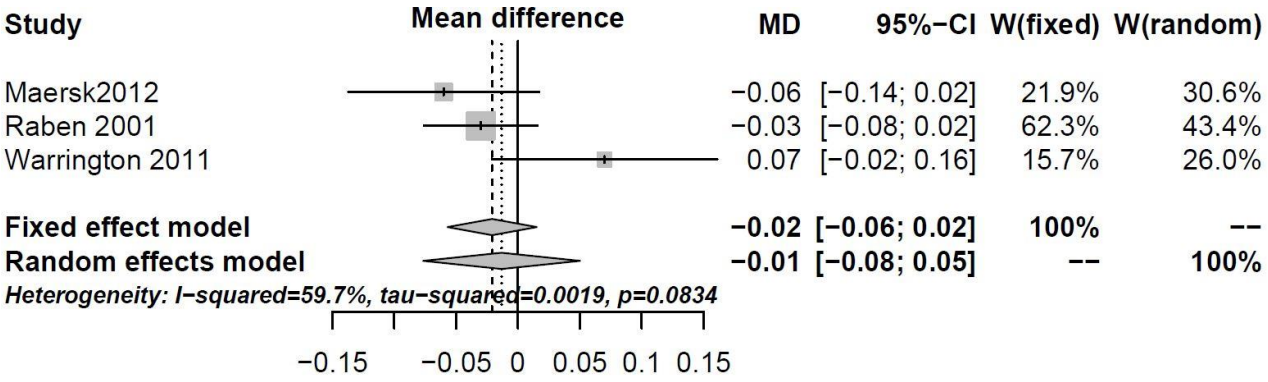

Figure 7: Effect of NSSs versus caloric sweetener (Maersk 2012, Raben 2001) or placebo (Warrington 2011) on HDL cholesterol in adults

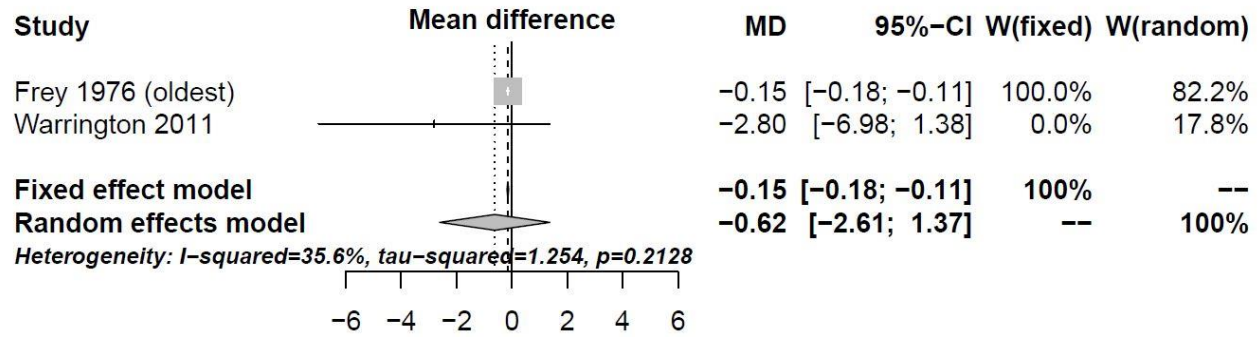

Figure 8: Effect of NSSs on change in creatinine (mg/dl) in adults

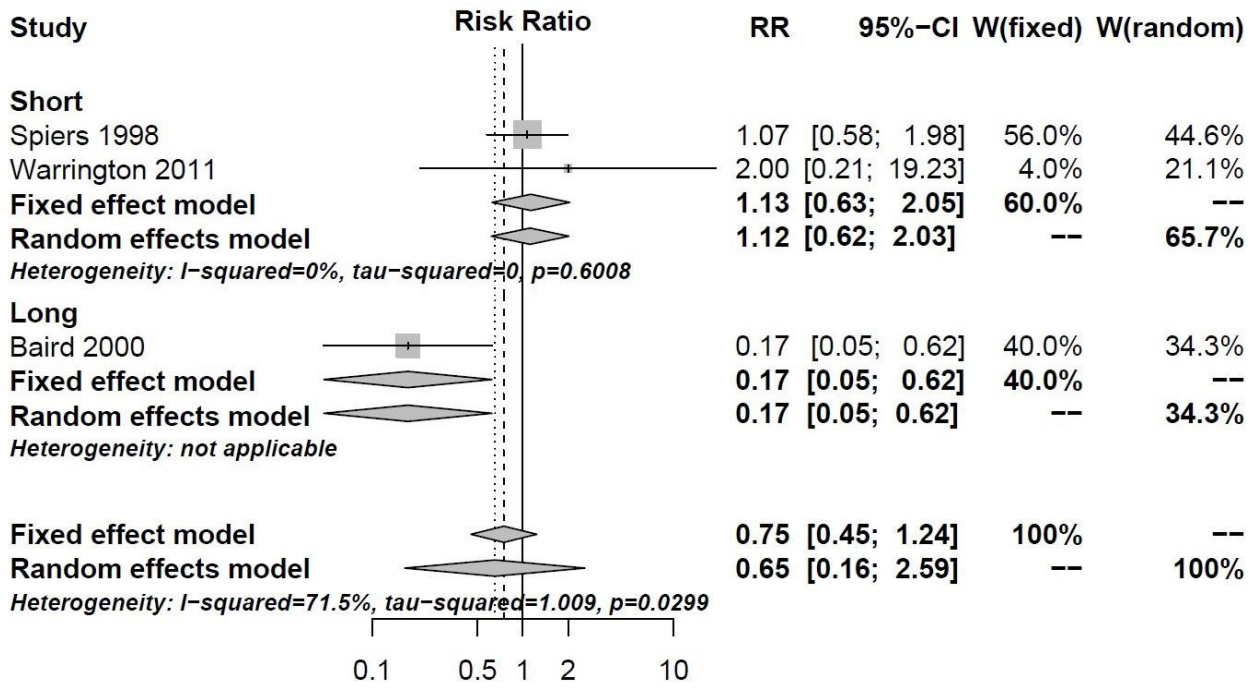

Figure 9: Effect of NSSs versus caloric sweetener (Baird 2000) or placebo (Spiers 1998, Warrington2011) on risk for adverse events in adults by duration

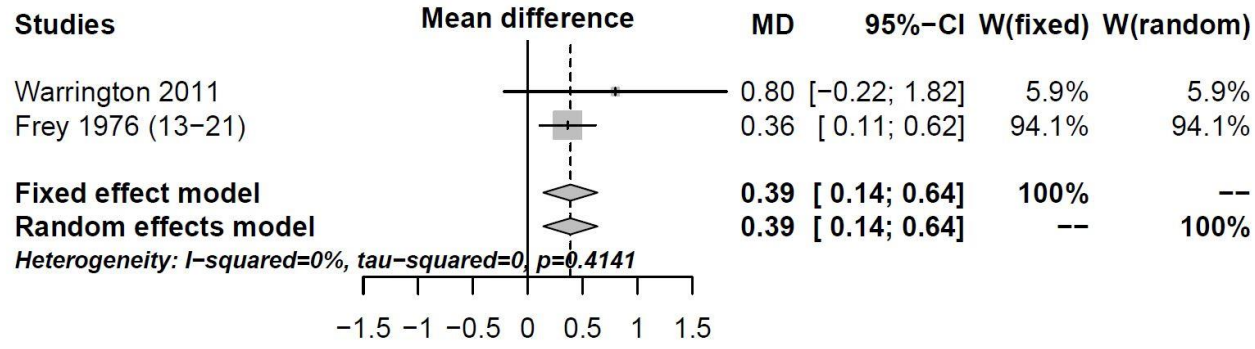

Figure 10: Effect of NSSs on change in haematocrit (%) in adults

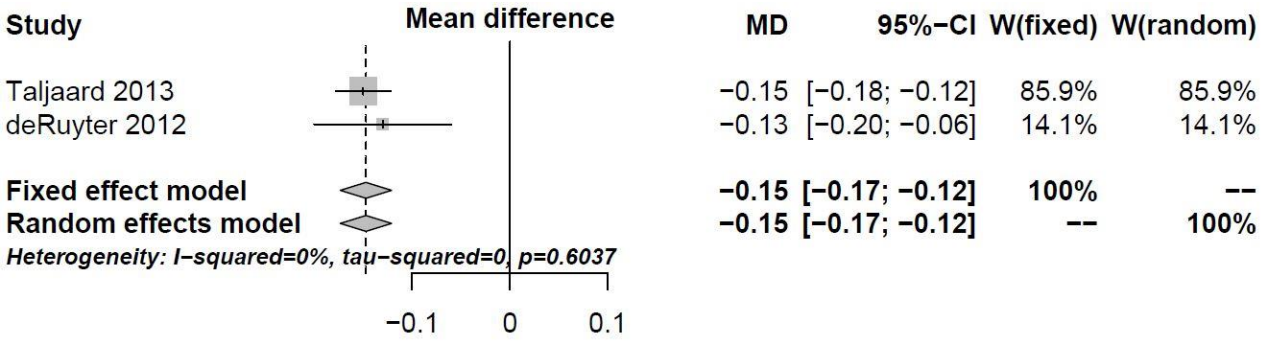

Figure 11: Effect of NSSs on change in BMI z-score in children

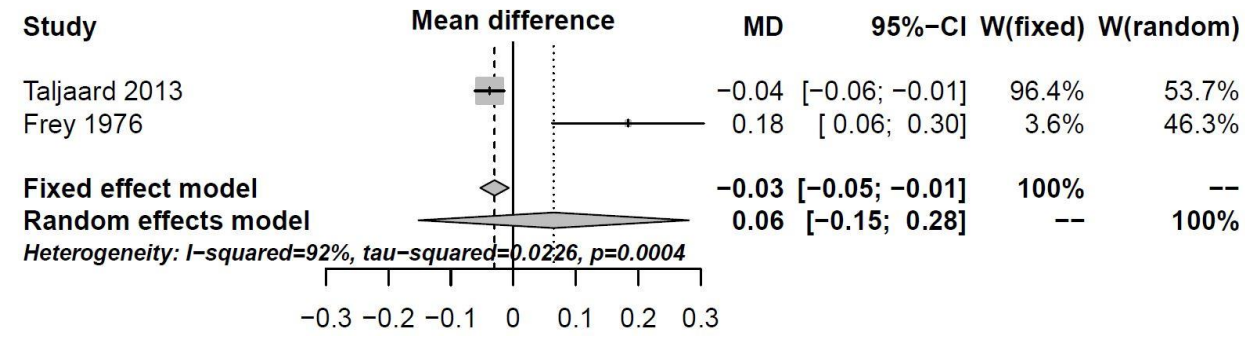

Figure 12: Effect of NSSs on blood Hb in children