World Cancer Research Fund International

Literature Review

Diet, nutrition and physical activity: Energy balance and body fatness

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Analysing research on cancer prevention and survival

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Table 1 List of abbreviated terms used in the literature review

Abbreviated term	Term in full
+VE	Positive association, or positive effect
ΔWC_{BMI}	Waist circumference for a given BMI
%E	Percentage energy
BMI	Body mass index
BF	Breastfeeding
Ca	Calcium
$CaCO_3$	Calcium carbonate
CHO	Carbohydrate(s)
CI	Confidence interval (95% unless stated otherwise)
d_+	Overall effect size (as reported in Garcia et al. 2016)
ED	Energy density
EBF	Exclusive breastfeeding
FMI	Fat mass index
HFCS	High fructose corn syrup
HR	Hazard ratio
INV	Inverse association, or inverse effect
kg	Kilogram
MD	Mean difference
kJ	Kilojoules
m	Metre
Med diet	Mediterranean diet
MET	Metabolic equivalent
MUFA	Monounsaturated fatty acid
n	Number of participants
NNS	Non-nutritively sweetened [drinks]
NR	Not reported
NS	Not significant
NIL	No association, or no effect
OR	Odds ratio
r	Correlation coefficient
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SE or SEM	Standard error (of the mean)
SFA	Saturated fatty acid

SFT	Skin fold thickness
SMD	Standardised mean difference
SSB(s)	Sugar sweetened beverage(s)
Vit D	Vitamin D
WC	Waist circumference
WHR	Waist-hip ratio
WMD	Weighted mean difference

Table 2 List of abbreviated study or report names used in the literature review

Abbreviated name	Name in full
ALSPAC	Avon Longitudinal Study of Parents and Children
ARIC	Atherscleros*i*s Risk in Communities
AusDiab	Australian Diabetes Obesity and Lifestyle Study
CARDIA	The Coronary Artery Risk Development in Young Adults Study
ECHO cohort	Etiology of Childhood Obesity cohort
EPIC	European Prospective Investigation into Cancer and Nutrition
EPIC-DiOGenes	EPIC-Diet, Obesity and Genes project
EPIC-PANACEA	EPIC-Physical Activity, Nutrition, Alcohol, Cessation of smoking, and Eating out of home in relation to Anthropometry
HEAPS	Health, Eating and Play Study
IDEA cohort	Identifying Determinants of Eating and Activity cohort
MONICA1	*MONI*toring of trends and determinants in *CA*rdiovascular disease
MRC NSHD	Medical Research Council National Survey of Health and Development
NICE	National Institute for Health and Care Excellence
NLSAH	National Longitudinal Study of Adolescent Health
PAGAC	Physical Activity Guidelines Advisory Committee
Project EAT	Project Eating Among Teens study
SUN	Seguimiento University of Navarra
USDA DGAC	The United States Department of Agriculture Dietary Guidelines Advisory Committee

Background

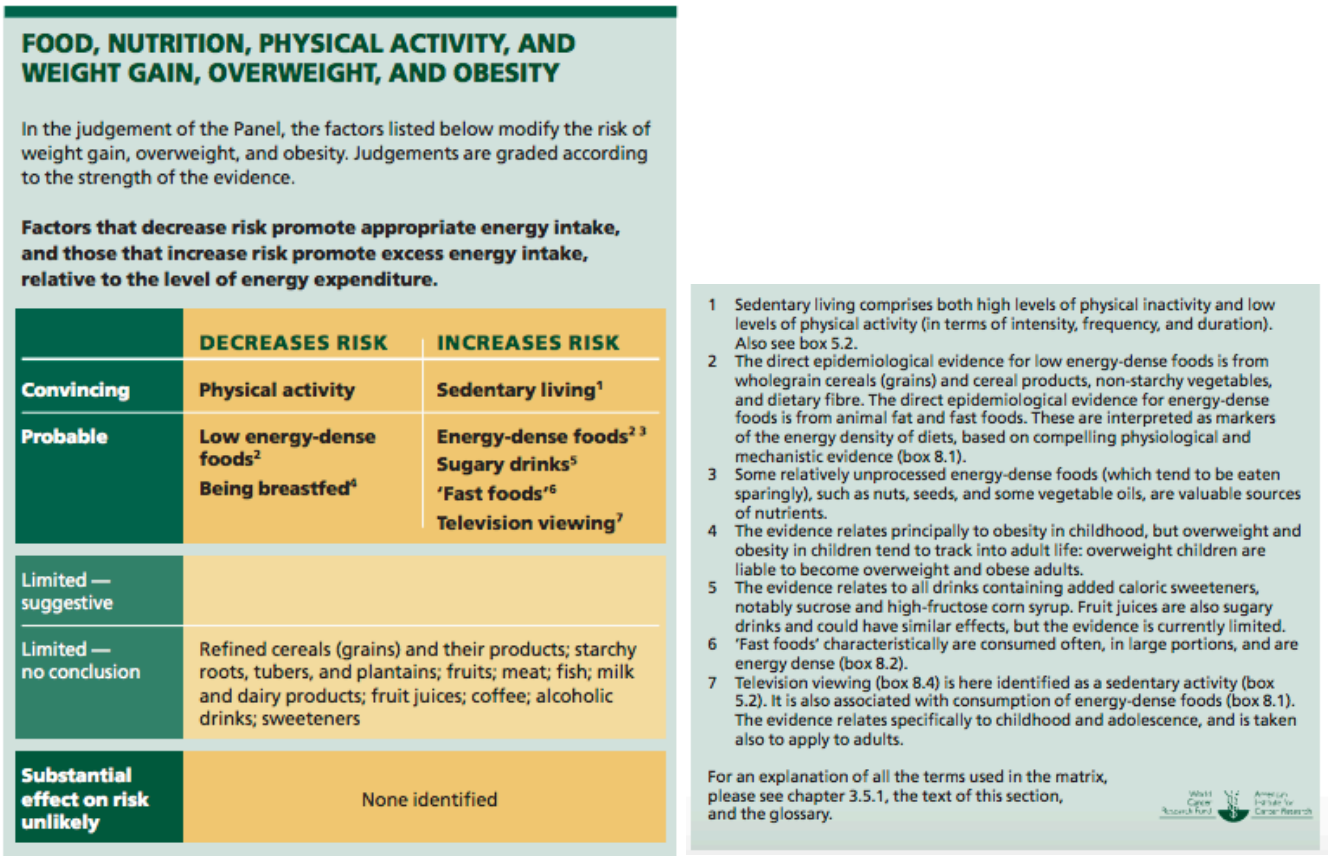
The objective of this literature review is to address the research question “What are the diet, nutrition, and physical activity related determinants of weight gain, overweight, and obesity in humans?”. The underlying mechanisms relating to these causes will also be briefly included.

This literature review will be used to update the WCRF/AICR 2007 Expert Report World Cancer Research Fund / American Institute for Cancer Research 2007 chapter 8 on the determinants of weight gain, overweight and obesity. This update is for the upcoming WCRF/AICR report, *Diet, Nutrition, Physical Activity and Cancer: A Global Perspective*, our Third Expert Report, to be published in 2018.

This literature review does not present conclusions or judgements on the strength of the evidence. The WCRF/AICR Continuous Update Project (CUP) Panel will discuss and judge the evidence presented in this literature review. These updated judgements will be included in the Third Expert Report.

For reference, below are the 2007 Expert Report conclusions from the evidence for weight gain, overweight and obesity based on the 2005 WCRF/AICR systematic literature review (SLR) (see: Summerbell et al. 2009) and Expert Panel discussion.

Figure 1 Conclusions from the WCRF/AICR 2007 Expert Report on the determinants of weight gain, overweight and obesity



FOOD, NUTRITION, PHYSICAL ACTIVITY, AND WEIGHT GAIN, OVERWEIGHT, AND OBESITY

In the judgement of the Panel, the factors listed below modify the risk of weight gain, overweight, and obesity. Judgements are graded according to the strength of the evidence.

Factors that decrease risk promote appropriate energy intake, and those that increase risk promote excess energy intake, relative to the level of energy expenditure.

	DECREASES RISK	INCREASES RISK
Convincing	**Physical activity**	**Sedentary living[1]**
Probable	**Low energy-dense foods[2]** **Being breastfed[4]**	**Energy-dense foods[2 3]** **Sugary drinks[5]** **'Fast foods'[6]** **Television viewing[7]**
Limited — suggestive		
Limited — no conclusion	Refined cereals (grains) and their products; starchy roots, tubers, and plantains; fruits; meat; fish; milk and dairy products; fruit juices; coffee; alcoholic drinks; sweeteners	
Substantial effect on risk unlikely	None identified	

1 Sedentary living comprises both high levels of physical inactivity and low levels of physical activity (in terms of intensity, frequency, and duration). Also see box 5.2.
2 The direct epidemiological evidence for low energy-dense foods is from wholegrain cereals (grains) and cereal products, non-starchy vegetables, and dietary fibre. The direct epidemiological evidence for energy-dense foods is from animal fat and fast foods. These are interpreted as markers of the energy density of diets, based on compelling physiological and mechanistic evidence (box 8.1).
3 Some relatively unprocessed energy-dense foods (which tend to be eaten sparingly), such as nuts, seeds, and some vegetable oils, are valuable sources of nutrients.
4 The evidence relates principally to obesity in childhood, but overweight and obesity in children tend to track into adult life: overweight children are liable to become overweight and obese adults.
5 The evidence relates to all drinks containing added caloric sweeteners, notably sucrose and high-fructose corn syrup. Fruit juices are also sugary drinks and could have similar effects, but the evidence is currently limited.
6 'Fast foods' characteristically are consumed often, in large portions, and are energy dense (box 8.2).
7 Television viewing (box 8.4) is here identified as a sedentary activity (box 5.2). It is also associated with consumption of energy-dense foods (box 8.1). The evidence relates specifically to childhood and adolescence, and is taken also to apply to adults.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Methodology overview

The full protocol is in the **Appendix**.

In brief, this literature review is a 'review of published reviews'. The main data source is an evidence review published in 2014 by the National Institute of Health and Care Excellence (NICE), entitled *'Maintaining a healthy weight and preventing excess weight gain in children and adults: An evidence review of modifiable diet and physical activity components, and associated behaviours'* (available at https://www.nice.org.uk/guidance/ng7/evidence). This is based on the 2005 SLR undertaken by WCRF/AICR for the 2007 Expert Report. This evidence review is referred to as the ***NICE (2014) report*** throughout this literature review

The evidence in the NICE (2014) report was updated for this literature review with evidence from three other sources:

- Relevant studies reviewed in the USDA DGAC (2015) scientific report (U.S Department of Agriculture Nutrition Evidence Library 2015).
- A preliminary literature search for exposures not covered by the NICE (2014) report ('lactation' and 'having been breastfed') conducted in August 2015.
- A full supplementary literature search conducted by the team at Imperial College London in August 2016 for relevant published reviews which conducted meta-analyses after the NICE (2014) report cut-off (October 2013).

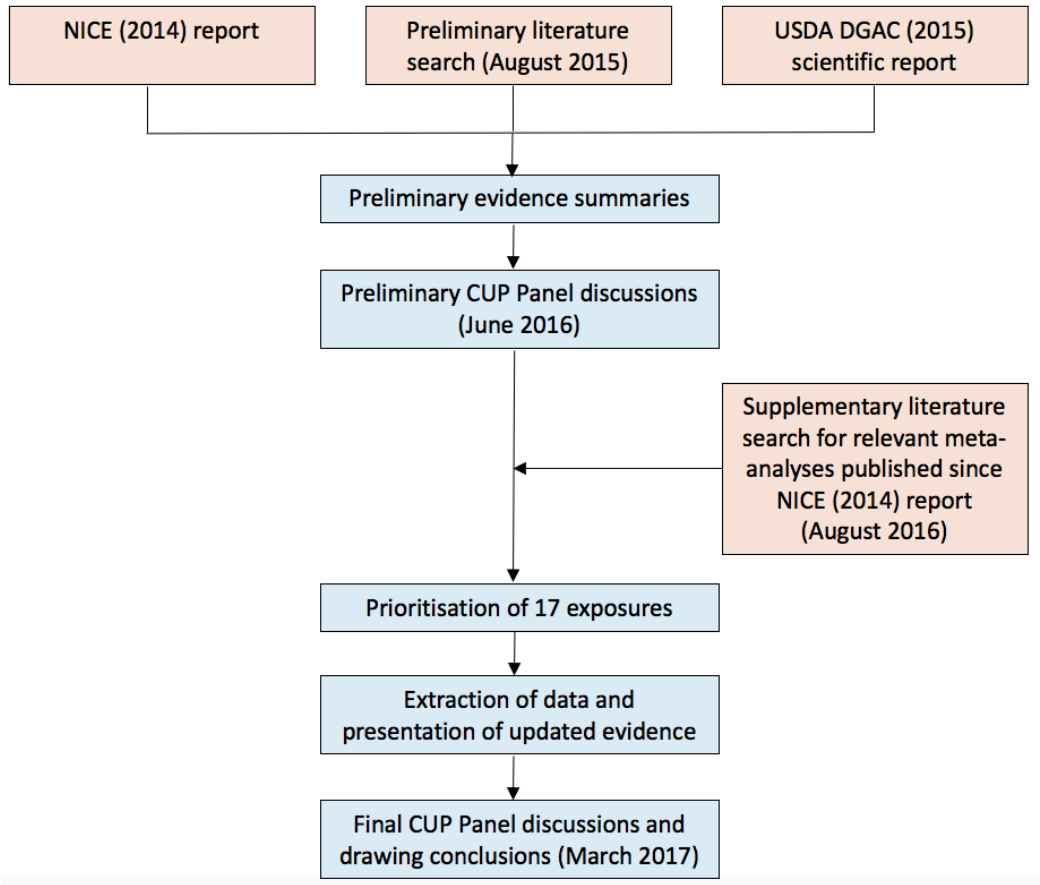
Seventeen prioritised exposures were agreed prior to full data extraction: Mediterranean diet; lactation; having been breastfed; wholegrains; refined grains; fruits and vegetables; meat; milk and dairy products; fast foods; sugar sweetened beverages; foods containing dietary fibre; sugars; dietary fat; physical activity;

sedentary time; screen time; and energy density of the diet. Please see the protocol in the **Appendix** for the process of prioritisation.

Published reviews were quality assessed using the criteria from the NICE (2014) report (see **Appendix** in this literature review and Appendix D in NICE (2014) report).

The figure below briefly summarises the process for updating the evidence for the determinants of weight gain, overweight and obesity. Orange boxes indicate sources of evidence and blue boxes indicate an action or set of actions within the process.

Figure 2 Process for updating the evidence for the determinants of weight gain, overweight and obesity



Results of literature search

The date range of the supplementary literature search was 1st October 2013 to 21st August 2016.

Figure 3 Flow chart for the supplementary literature search (conducted August 2016)

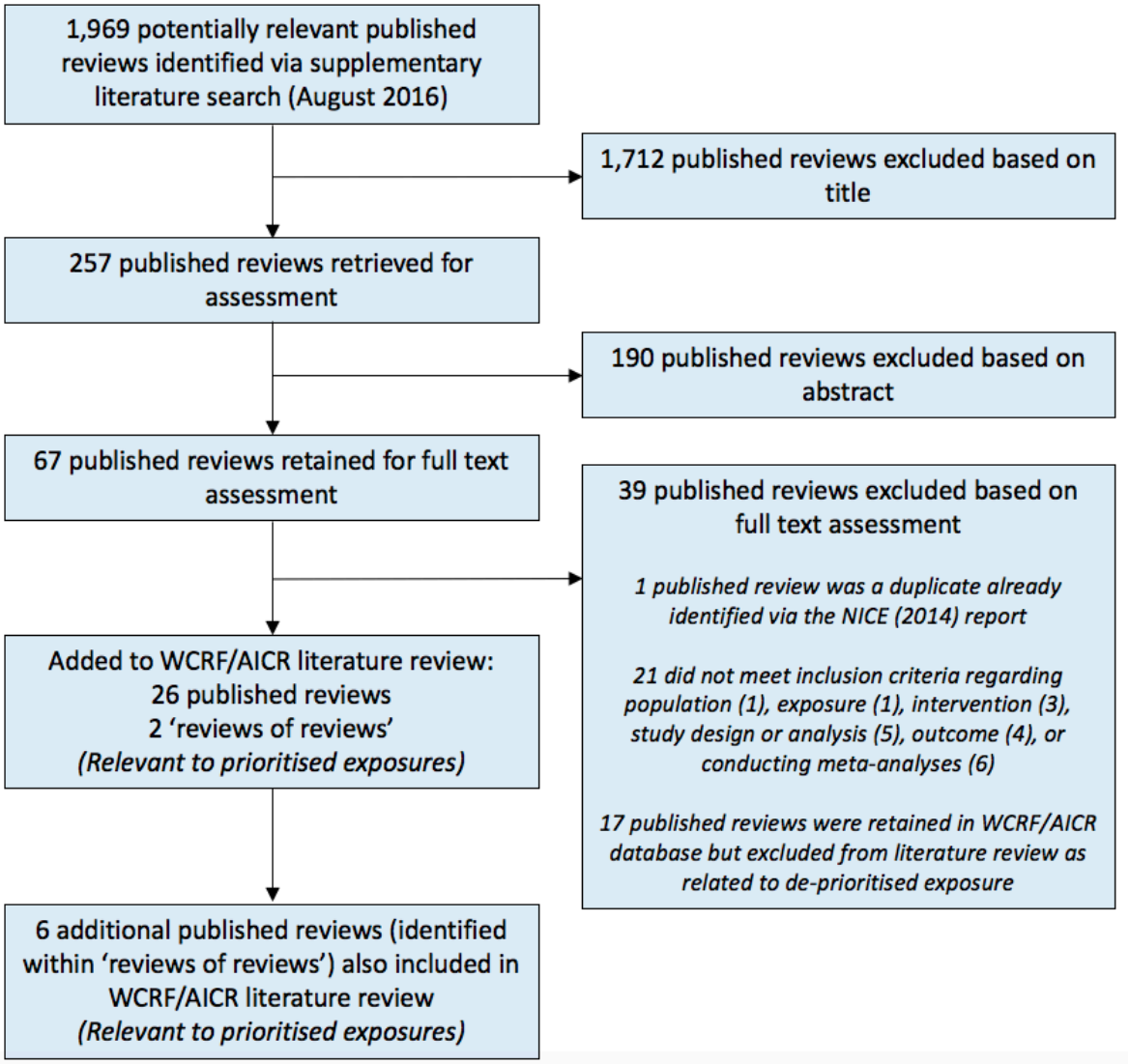


Table 3 Total number of published reviews included in WCRF/AICR literature review

Source of evidence	No. of published reviews identified	No. of 'reviews of reviews' identified	No. of additional unique published reviews identified via 'reviews of reviews'
NICE (2014) report	33	Nil*	3
Preliminary literature search (August 2015)	5	1	4
Supplementary literature search (August 2016)	26	2	6
USDA DGAC (2015) scientific report	1		
Total number of reports and published reviews from four sources of evidence listed above	**81**		

*Two published reviews also identified and reported results from other published reviews but were not formal 'reviews of reviews'.

Evidence by exposure: Part 1 – Prioritised exposures

Part 1 contains the evidence for the prioritised exposures (please see the protocol in **Appendix** for further explanation). The prioritised exposures are: Mediterranean diet, lactation, having been breastfed, wholegrains, refined grains, fruits and vegetables, meat, dairy, fast foods, sugar sweetened beverages, dietary fibre, sugars, dietary fat, physical activity, sedentary time, screen time, and energy density.

Presentation format of the evidence

The structure for each exposure section follows this approximate outline:

1. Evidence identified for the 2017 update
2. Evidence in children *(as available)*
   - **2.1** Meta-analyses of RCTs *(purple tables)*
   - **3.2** Meta-analyses of prospective cohort studies *(purple tables)*
   - **3.3** Individual RCTs, not included in meta-analyses *(orange tables)*
   - **3.4** Individual prospective cohort studies, not included in meta-analyses *(orange tables)*
3. Evidence in adults
   - **2.1** Meta-analyses of RCTs *(purple tables)*
   - **3.2** Meta-analyses of prospective cohort studies *(purple tables)*
   - **3.3** Individual RCTs, not included in meta-analyses *(orange tables)*
   - **3.4** Individual prospective cohort studies, not included in meta-analyses *(orange tables)*
4. Possible mechanisms
5. Summary of evidence

In each 'evidence identified' table, a 'Y' ('yes') in the row regarding the USDA DGAC (2015) scientific report (third row down) denotes that this exposure is included in the USDA DGAC (2015) scientific report. The relevant evidence on the exposure from the USDA DGAC (2015) scientific report has been extracted and presented in this literature review. Conversely, a 'N' ('no') in this row denotes the exposure is not included in the USDA DGAC (2015) scientific report. The example below shows an exposure which *is* included in the USDA DGAC (2015) scientific report, indicated next to the red arrow.

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Fogelholm et al (2012) [+]; Kastorini et al (2011) [+]
USDA DGAC (2015) scientific report [++]	Y	
Supplementary literature search August 2016	1	Garcia et al (2016) [++]

The quality rating of published reviews is also reported in the 'evidence identified' tables. The symbol corresponds to the criteria as applied in the NICE (2014) report (see protocol in the **Appendix** of this literature review and Appendix D of the NICE (2014) report):

[-] Low quality
[+] Moderate quality
[++] High quality

In each results table, the direction of relationship is indicated with **+VE** (positive effect or association), **INV** (inverse effect or association), or **NIL** (no effect or association, e.g. RR=1.00).

Where available, forest plots corresponding to meta-analysis results are presented. These are copies directly from the original paper, with permission. For full citation of the studies included in meta-analyses, please consult the original published review.

1. Patterns of Diet

1.1 Mediterranean diet

1. Evidence identified for 2017 update

Table 4 Published reviews identified for the 2017 update – Mediterranean diet

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Fogelholm et al. 2012 [+]; Kastorini et al. 2011 [+]
USDA DGAC (2015) scientific report [++]	Y	
Supplementary literature search August 2016	1	Garcia et al. 2016 [++]

Notes on the evidence:

- No evidence was identified with respect to children.
- There are multiple definitions of a Mediterranean diet. A Mediterranean type dietary pattern generally describes a diet rich in fruits and vegetables, with modest amounts of meat and dairy, some fish and wine, and rich in unrefined olive oil. In addition, it is traditionally associated with high levels of physical activity. There are recognised scores for quantifying adherence to a Mediterranean type dietary pattern but exactly what each dietary pattern comprises varies.

2.1 Children

2.1 Meta-analysis of RCTs in children

Nil

2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Nil

3. Adults

3.1 Meta-analysis of RCTs in adults

Table 5 Meta-analyses of RCTs in adults – Mediterranean diet

Adults					
Meta-analyses of RCTs					
Med diet=Mediterranean diet; MD=mean difference; d_+=overall effect size. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Waist circumference	Garcia et al. 2016	Adherence to Med diet vs. control 4 weeks–4 years	d_+	**-0.54 (-0.77, -0.31)** **INV**	Studies=29; n=4,133 I^2=96%
	Kastorini et al. 2011	Adherence to Med diet vs. control 6 weeks–4 years	MD	**-0.42 (-0.82, -0.02) cm** **INV**	Studies=11; n=1,646 I^2= ~0%

Two reviews each conducted a meta-analysis of RCTs in adults investigating the effect of adherence to the Mediterranean diet, relative to control, on adiposity. Both meta-analyses reported statistically significant, inverse effects, with adherence to the Mediterranean diet reducing waist circumference. Garcia et al (2016) reported the effect size using ***d*$_+$**, defined as 'overall effect size', and did not indicate any clinical units.

There was overlap of five RCTs between the two meta-analyses.

The interventions used in each of the included RCTs varied in detail of recommendations given to participants and macronutrient composition. The control also varied and included a low fat/high carbohydrate diet, 'prudent' diet, the participants' habitual diet, the American Diabetes Association recommended diet, and being given general healthy eating advice.

Kastorini et al (2011) noted that their meta-analysis result was mainly attributed to one study (McManus et al. 2001).

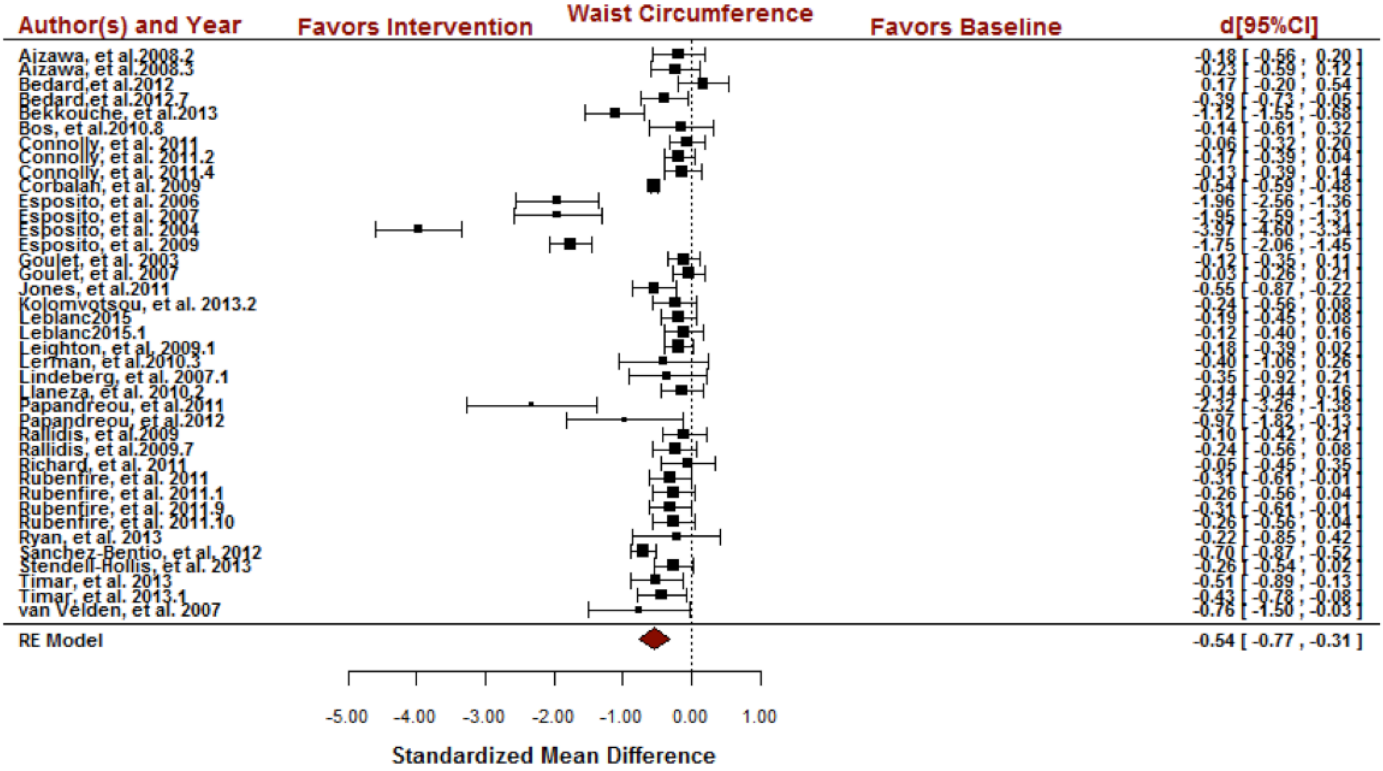
Garcia et al (2016) included some intervention studies where it was not clear if the participants were randomised. They conducted a moderator analysis based on study design, which did not alter the direction or significance of the effect. The effect direction was also unchanged by moderator analyses of region, 'impact per paper' metric, study duration, proportion of female participants, using a behavioural technique, or level of supervision.

The forest plot corresponding to the Garcia et al (2016) meta-analysis is presented below. A forest plot was not available for the Kastorini et al (2011) meta-analysis.

Adults | RCTs | Waist circumference | Garcia et al (2016) | Mediterranean diet

Forest Plot for waist circumference. Note: Squares represent point estimates for each individual study; extended line shows 95% confidence intervals (CIs); dotted line represents the null value of zero; diamond represents the weighted mean effect size for the outcome (Garcia et al 2016).

Figure 4 Meta-analysis of RCTs in adults – Mediterranean type dietary pattern – Garcia et al 2016 – Waist circumference



3.2 Meta-analyses of prospective cohort studies in adults

Nil

3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 6 Results of individual prospective cohort studies in adults – Mediterranean diet

Adults					
Prospective cohort studies					
Med diet=Mediterranean diet; MD=mean difference; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Beunza et al. 2010 *Fogelholm et al. 2012* and *U.S Department of Agriculture Nutrition Evidence Library 2015*	Med diet score ≥6 vs. ≤3 at baseline (adherence measure) 5.7 years	MD	**-0.059 (-0.111, -0.008) kg per year** **INV**	10,376
	Romaguera et al. 2010 Fogelholm et al. 2012 and *U.S Department of Agriculture Nutrition Evidence Library 2015*	Per two point increase in Med diet score (adherence measure) 2–11 years	MD	**-0.05 (-0.07, -0.02) kg over 5 years** **INV**	373,803
	Sanchez-Villegas et al. 2006 *Fogelholm et al. 2012*	Quartiles of Med diet score at baseline (adherence measure; Q1 = lowest) 28 months	Q1: **0.73 (0.53, 0.93) kg** Q2: **0.87 (0.68, 0.86) kg** Q3: **0.66 (0.61, 0.80) kg** Q4: **0.65 (0.59, 0.80) kg** p for trend=0.291 **INV**		6,319
BMI change		Quartiles of Med diet score at baseline (adherence measure; Q1 = lowest) 28 months	Q1: **0.26 (0.19, 0.33) kg/m^2** Q2: **0.30 (0.21, 0.39) kg/m^2** Q3: **0.24 (0.14, 0.33) kg/m^2** Q4: **0.23(0.12, 0.33) kg/m^2** p for trend=0.279 **INV**		6,319
Waist circumference	Tortosa et al. 2007 *Kastorini et al. 2011* and *U.S Department of Agriculture Nutrition Evidence Library 2015*	Highest vs. lowest Med diet score (adherence measure) 6 years	MD	**-0.50 (-1.96, 0.96) cm** **INV**	2,563
	Rumawas et al. 2009 *Kastorini et al. 2011* and *U.S Department of Agriculture Nutrition Evidence Library 2015*	Quintiles of Med diet pattern score (adherence measure; Q1 = lowest) 7 years	Q1: **98.9 (98.4, 99.4) cm** Q2: **98.2 (97.7, 98.6) cm** Q3: **98.6 (98.1, 99.0) cm** Q4: **98.2 (97.8, 98.6) cm** Q5: **97.1 (96.7, 97.6) cm** p for trend <0.001 **INV**		2,730
Odds of obesity	Mendez et al. 2006 *U.S Department of Agriculture Nutrition Evidence Library 2015*	High Med diet adherence score (6–8/8) at baseline *(female)* 3 years	OR	**0.69 (0.54, 0.89)** **INV**	17,238
		High Med diet adherence score (6–8/8) at baseline *(male)* 3 years	OR	**0.68 (0.53, 0.89)** **INV**	10,589

Four prospective cohort studies (six publications) investigating the Mediterranean diet and adiposity in adults were identified in three reviews. These provided eight results across four outcomes: weight change; BMI change; waist circumference; and odds of obesity. All eight results reported inverse associations (with higher adherence to a Mediterranean dietary pattern reducing adiposity), of which five were statistically significant.

Four studies were conducted in Spanish cohorts: one with the EPIC-Spain cohort (Mendez et al 2006) and three with the SUN cohort (Beunza et al 2010; Sanchez-Villegas et al 2006; and Tortosa et al 2007). Romaguera et al (2010) conducted their study with the EPIC-Panacea cohort and Rumawas et al (2009) conducted theirs with the Framington Heart Study Offspring cohort.

Each of the studies applied a slightly different scoring system for measuring the Mediterranean diet but all considered 'positive' constituents and 'negative' constituents. Positive items: vegetables, fruits, nuts, legumes, fish, moderate alcohol, MUFA:SFA, cereals and grains. Negative items: meat and poultry, dairy products.

In a sensitivity analysis, Beunza et al (2010) applied five additional different scoring systems, including those used by Sanchez-Villegas et al (2006) and Rumawas et al (2009). The observed inverse association was unchanged by the particular scoring system applied; three of the five were statistically significant.

4. Possible mechanisms

Summarised from the 2007 Expert Report and Schroder 2007:

Dietary Fibre – The Mediterranean diet is a dietary pattern rich in plant foods, which provide a high amount and wide variety of both soluble and insoluble dietary fibres.

- Fibre consumption may increase satiation by increasing chewing, slowing gastric emptying and elevating stomach distension, and stimulation of cholecystokinin. Fibre-rich foods tend to contain a larger volume of water, which also elevates stomach distension.
- The increased viscosity of soluble fibre can reduce the overall rate and extent of digestion, which may also result in reduced energy from protein and fat and a blunted post-prandial glycaemic and insulinaemic response to carbohydrates.
- Fibre-induced delayed absorption and the resultant presence of macronutrients in the distal small intestine, known as the ileal brake, mediate the release of several gut hormones.

Dietary Fat – Increased consumption of vegetable oils, such as olive oil, and fish and reduced intake of saturated fats are key components of the Mediterranean diet and alter the MUFA:SFA.

- Olive oil consumption is less likely to promote weight gain than consumption of other fats. This may be explained physiologically by the degree to which fats are oxidised or stored as adipose tissue. Human studies have shown that polyunsaturated fats, such as olive oil, are better oxidised than saturated fats.
- In addition, human studies have shown administration of olive oil promotes diet-induced thermogenesis (increased energy production from metabolism of food).
- Equally, high consumption of olive oil is also closely associated with intake of vegetables and pulses/legumes. Therefore, a higher consumption of olive oil may be a marker of a healthier dietary pattern.

Energy Density – The average energy density of a Mediterranean diet is lower than a "Western type" diet.

- Several human clinical studies have shown that high energy dense diets can undermine normal appetite regulation, termed 'passive overconsumption'. Higher energy density diets tend to lead to greater energy intake. The lower energy density of the Mediterranean diet tends to lead to the opposite, lower energy intake. Also see dietary fibre, above.
- Studies have shown that consumption of low energy dense foods, such as first-course salads, increase satiety and reduce total meal energy intake.

5. Summary of evidence

5.1 Children

N/A

5.2 Adults

Two meta-analyses of RCTs reported modest but statistically significant inverse effects, with adherence to a Mediterranean diet reducing adiposity. Four prospective cohort studies (six publications) provided eight results, all of which also reported inverse associations (five were statistically significant). Authors from one study applied five additional Mediterranean diet scoring systems to their data and found the direction of association unchanged, although significance was lost with two.

1.2 Lactation (mother)

1. Evidence identified for the 2017 update

Table 7 Published reviews identified for the 2017 update – Lactation

Source	No. of reviews	Authors [quality]
NICE (2014) report	Nil	*NICE (2014) report did not review lactation as an exposure*
Preliminary literature search August 2015	2	Neville et al. 2014 [++];Ip et al. 2007 [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	1	He et al. 2015 [++]

Notes on the evidence:

- This exposure was not included in the NICE (2014) report; for details on the WCRF/AICR literature search, please see the protocol in the **Appendix**.
- This exposure specifically looks at the association between lactation and adiposity in the mother; for evidence relating to the association between breastfeeding and adiposity in the infant, please see **Section 1.3**.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=500, so only studies with more than 500 participants are reported in detail here.

2. Mothers

2.1 Meta-analyses of RCTs

Table 8 Meta-analyses of RCTs in mothers – Lactation

Mothers					
Meta-analyses of RCTs					
SMD=standardised mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Post-partum weight retention (weight loss)	He et al. 2015	Exclusive breastfeeding or mixed feeding vs. formula feeding Unclear follow up period	SMD	**0.57 (0.19, 0.94) kg** INV	Studies=3; n=not reported I^2=not reported

One review conducted a meta-analysis of RCTs and reported a significant inverse effect: women who breastfed their infants retained less weight postpartum (lost more weight) than those who formula fed their infants. The review did not comment on the individual interventions or the degree of adherence from participants.

The review also reported results for different durations of breastfeeding; this was done when combining the results of both RCTs and prospective cohort studies (results for meta-analyses of prospective cohort studies *not* in combination with RCTs are presented in **Section 2.2** of this exposure). In total, 11 studies (RCTs, n=3; prospective cohort studies, n=8) were meta-analysed and the results reported different associations dependent on duration of breastfeeding:

- Breastfeeding duration 1 to ≤3 months: No significant association (**SMD -0.09 [-0.76, 0.58] kg**)
- Breastfeeding duration 3-6 months: Significant inverse association (**SMD 0.87 [0.57, 1.17] kg**)
- Breastfeeding duration 6 to ≤9 months: No significant association (**SMD 0.21 [-0.42, 0.83] kg**)
- Breastfeeding duration 9 to ≤12 months: Significant inverse association (**SMD 0.37 [0.14, 0.61] kg**)

The authors also noted that although the individual studies tended to show inverse associations between breastfeeding and postpartum weight retention, the associations were often confounded by other factors such as gestational weight gain, physical activity level, and pre-pregnancy weight. It is not possible to rule out residual confounding.

There was no forest plot of the meta-analysis of RCTs.

2.2 Meta-analyses of prospective cohort studies

Table 9 Meta-analyses of prospective cohort studies in mothers – Lactation

Mothers					
Meta-analyses of prospective cohort studies					
SMD=standardised mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Post-partum weight retention (weight loss)	He et al (2015)	Exclusive breastfeeding or mixed feeding vs. formula feeding Unclear follow up period	SMD	**1.18 (0.74, 1.62) kg** **INV**	Studies=8; n=not reported I^2=not reported

One review conducted a meta-analysis of prospective cohort studies and reported a significant inverse association: women who breastfed their infants retained less weight postpartum than those who formula fed their infants. The assessment of exposure to breastfeeding differed between studies. The authors noted that most studies compared women who breastfed with women who formula fed, while a few compared women who "have lactation with women who have non-lactation" – this terminology was not clarified in the review. One cohort study included in the meta-analysis had a retrospective study design.

Please see **Section 2.1** of this exposure for results stratified by duration of breastfeeding.

There was no forest plot of the meta-analysis of prospective cohort studies.

2.3 Individual RCTs, not in meta-analyses

Nil

2.4 Individual prospective cohort studies, not in meta-analyses

Table 10 Results of individual prospective cohort studies in mothers – Lactation

Mothers				
Prospective cohort studies				
SFT=skinfold thickness. Significant results are highlighted in **red**.				
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***	***n***
Weight change	Baker et al. 2008 *Neville et al. 2014*	Exclusive breastfeeding for 6 months Up to 18 months	**Inverse association at 6 months postpartum** p< 0.0001 **INV** **Inverse association at 18 months postpartum** p<0.05 **INV**	36,030
	Gunderson et al. 2008 *Neville et al. 2014*	Duration of exclusive breastfeeding 12 months	**Shorter duration of breastfeeding associated with being >5 kg above pre-pregnancy weight at follow up** p=0.009 **INV**	940
	Linne et al. 2003 *Ip et al. 2007*	Ohlin's lactation score at baseline of study period 15 years	Became overweight: **Lower score** Maintained normal weight: **Higher score p<0.05** **INV**	Baseline=1,423 Follow up=563
	Ohlin et al. 1990 **Update: Ohlin et al. 1996** *Neville et al. 2014; Ip et al. 2007*	Ohlin's lactation score, summed monthly Up to 12 months	2.5–6 months: **Women with higher lactation score lost significantly more weight than women with lower scores** **INV** 2.5–12 months: **No difference in weight loss between higher and lower scores** **NIL**	1,423
	Oken et al. 2007 *Neville et al. 2014*	Exclusive breastfeeding vs. other feeding categories (formula, mixed) Up to 12 months	**No significant difference between groups** p=0.38 **NIL**	902
	Olson et al. 2003 *Neville et al. 2014; Ip et al. 2007*	Lactation score, summed weekly 12 months	**Higher score significantly associated with decreased weight retention, p=0.04** **INV**	540
	Sichieri et al. 2003 *Ip et al. 2007*	Women who breastfed vs. women who did not 3 years	**1 kg higher weight gain in women who breastfed** (both nulli- and primiparous) **+VE**	4,348
	Schauberger et al. 1992 *Neville et al. 2014*	Women who breastfed vs. women who did not Up to 6 months	**No association at 2 weeks, 6 weeks, or 6 months** **NIL**	795
Skinfold thickness	Sidebottom et al. 2001 *Neville et al. 2014*	Exclusive breastfeeding vs. formula or combined feeding 6 weeks	**No significant association** **NIL**	557
			Mean SFT at all sites lower among women who breastfed vs. those who did not p<0.05 **INV**	

Nine prospective cohort studies in two reviews reported 12 results across two outcomes: weight change and skinfold thickness. Seven results reported inverse associations between breastfeeding and postpartum weight change; all were statistically significant. One result reported a non-significant positive association and four results reported no association.

The level of adjustment applied in each study varied. The most highly adjusted studies were Baker et al (2008) and Olson et al (2003) which both adjusted for seven potential confounding factors, including

gestational weight gain. Gunderson et al (2008), Oken et al (2007), Schauberger et al (1992), and Sidebottom et al (2001) did not adjust for any potentially confounding factors.

There were 26 prospective cohort studies with fewer than 500 participants. Twenty three of the studies measured weight change, with eight reporting significant inverse associations. Eleven studies measured change in body composition and one reported a significant inverse association. Body composition was measured by a variety of methods, including DXA scans, skinfold thickness measurements, underwater weighing, whole-body potassium (for lean body mass), and bioelectrical impedance (for percentage body fat).

Studies n<500: Janney et al. 1997, Walker et al. 2004, Haiek et al. 2001, Bradshaw et al. 1988, Butte et al. 2003, Chou et al. 1999, Dugdale et al. 1989, Gould Rothberg et al. 2011, Kramer et al. 1993, Laskey et al. 1998, Lyu et al. 2009, Manning-Dalton et al. 1983, Martin et al. 2014, Motil et al. 1998, Nuss et al. 2006, Ostbye et al. 2012, Potter et al. 1991, Scholl et al. 1995, Sheikh 1971, To et al. 2009, Walker 1996, Walker et al. 2006, Butte et al. 1997, Moller et al. 2012, Ota et al. 2008, and van Raaij et al. 1991.

[3. Null section]

*Please note that this exposure is only applicable to mothers and is not stratified by adults and children. Therefore there is a single evidence section (**Section 2**).*

4. Possible mechanisms

As per preliminary discussions (June 2016):

- Lactation increases energy expenditure, which may result in a negative energy balance.
- Women who breastfeed may be more likely to engage in other healthy behaviours.
- Reverse causation is possible – women living with overweight or obesity are less likely to initiate breastfeeding and lactate for shorter durations than normal-BMI women.

5. Summary of evidence

5.1 Mothers

One review conducted meta-analyses, one with RCTs and one with prospective cohort studies. Both results reported significant inverse relationships. The significance of the results was attenuated when stratified by duration of breastfeeding. The authors noted some issues with study quality. Nine prospective cohort studies from two reviews reported mainly inverse associations. Measurement of feeding status varied between studies.

1.3 Having been breastfed (infant)

1. Evidence identified for 2017 update

Table 11 Published reviews identified for the 2017 update – Having been breastfed

Source	No. of reviews	Authors [quality]
NICE (2014) report	Nil	*NICE (2014) did not review breastfeeding as an exposure*
Preliminary literature search August 2015	8	Weng et al. 2012 [++]; Beyerlein et al. 2011 [-]; Ryan 2007 [-]; Pearce et al. 2013 [++]; Arenz et al. 2004 [++]; Owen et al. 2005a [+]; Owen et al. 2005b [++]; Harder et al. 2005 [+]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	4	Victora et al. 2016 [++]; Giugliani et al. 2015 [++]; Horta et al. 2015 [++]; Yan et al. 2014 [++]

Notes on the evidence:

- The published reviews by Harder et al (2005), Arenz et al (2004) (part of 2007 Expert Report evidence base), Owen et al (2005a) (part of 2007 Expert Report evidence base), and Owen et al (2005b) were identified in Beyerlein and von Kries (2011). Beyerlein and von Kries (2011) was identified via the preliminary literature search and is a review of reviews in itself. The published reviews in Beyerlein and von Kries (2011), such as those mentioned above, are reported in the relevant exposure section of this literature review.
- The published reviews by Giugliani et al (2015) and Horta et al (2015) were identified in Victora et al (2016). Victora et al (2016) was identified via the supplementary literature search and is a review of reviews in itself. The published reviews in Victora et al (2016), such as those mentioned above, are reported in the relevant exposure section of this literature review.
- The three cohort studies identified for the 2007 Expert Report evidence base, Burke et al (2003), Reilly et al (2005), and Kvaavik et al (2005), are reviewed within subsequent meta-analyses: Yan et al (2014), Weng et al (2012), and Horta et al (2015), respectively.
- There was considerable but incomplete overlap of included studies between meta-analyses of prospective cohort studies; the number of overlapping studies between meta-analyses is indicated in the table below. Please note that where three or more reviews have the same number of overlapping studies, it does not necessarily indicate that it is the same studies that overlap, e.g. 10 studies overlap between Horta et al (2015) and Yan et al (2015), and 10 studies overlap between Horta et al (2015) and Owen et al (2005b); however, these are not the same 10 studies.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=1000, so only studies with more than 1000 participants are reported in detail here.

Table 12 Overlapping studies between meta-analyses of prospective cohort studies in infants – Having been breastfed

Overlapping studies between meta-analyses of prospective cohort studies								
Please note that Harder et al (2005) conducted two meta-analyses (same publication), listed in this table as (1) and (2); these meta-analyses appear in the results table later in this document in the same order; (1) total duration of breastfeeding, (2) per month of breastfeeding. Owen et al 2005a and Owen et al 2005b are separate reviews in different publications.								
	Horta et al 2015	Yan et al 2014	Weng et al 2014	Harder et al 2005 (1)	Harder et al 2005 (2)	Arenz et al 2004	Owen et al 2005a	Owen et al 2005b
Horta et al 2015	-	10	6	11	7	2	8	10
Yan et al 2014		-	6	7	5	2	2	2
Weng et al 2014			-	1	0	1	1	1
Harder et al 2005 (1)				-	11	1	6	7
Harder et al 2005 (2)					-	1	4	4
Arenz et al 2004						-	2	2
Owen et al 2005a							-	6
Owen et al 2005b								-

2. Infants

2.1 Meta-analyses of RCTs

Please note – the time period noted on the right hand side of the intervention description cell is the *duration of follow-up* not the *duration of breastfeeding*.

Table 13 Meta-analyses of RCTs in infants – Having been breastfed

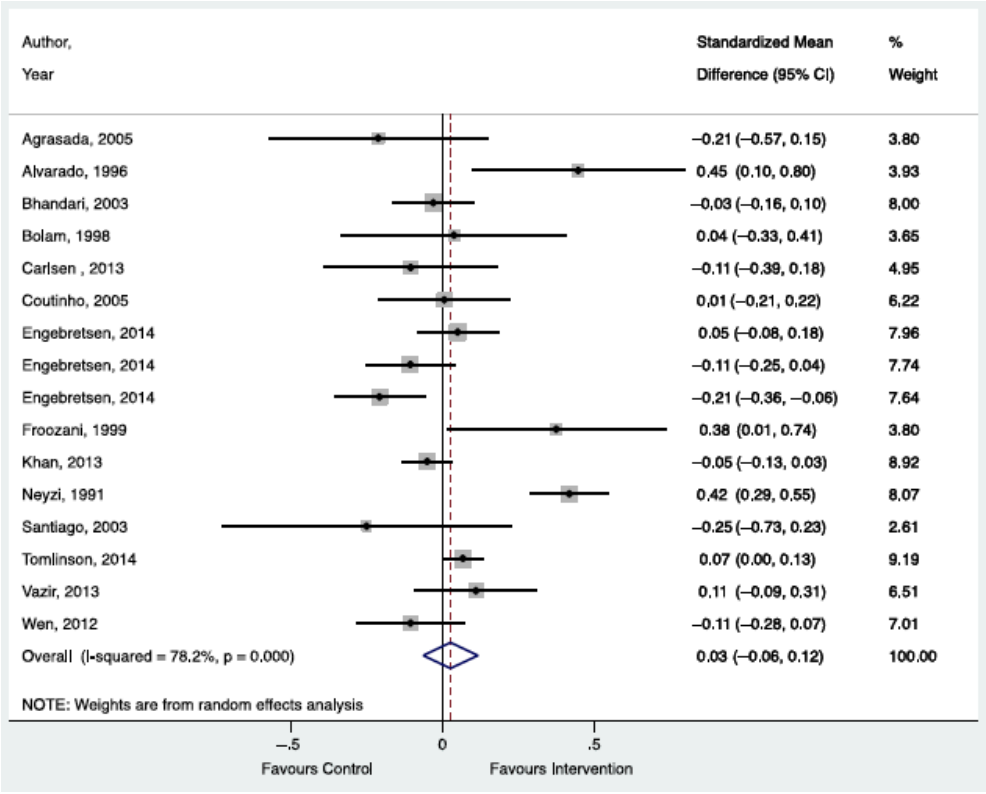
Infants					
RCTs					
BF=breastfeeding; SMD=standardised mean difference. Significant results are highlighted in **red**.					
Outcome	*Publication*	*Intervention description*	*Results*		
Weight z score	Giugliani et al (2015)	Increased BF duration (varied interventions) vs. usual care/no intervention 3mo–8 years	SMD	**0.03 (-0.06, 0.12)** **+VE**	Studies=16; n=14,736 I^2=78%
BMI or weight-for-height z score		Increased BF duration (varied interventions) vs. usual care/no intervention 3mo–8 years	SMD	**-0.06 (-0.12, 0.00)** **INV** ***Borderline signif***	Studies=12; n=29,063 I^2=61%

One review (Giugliani et al 2015) conducted two meta-analyses of RCTs, with outcomes of childhood weight z score and BMI or weight-for-height z score. These meta-analyses encompassed 19 unique studies and overlapped five studies. Increased breastfeeding duration had no significant effect on change in weight z score and had a borderline significant effect on change in BMI or weight-for-height z score. Increased breastfeeding duration was achieved through a variety of interventions: lactation counselling, health education, group sessions, and health promotion. It was unclear what the level of compliance to the intervention in each study was. The meta-analyses included studies from 11 countries: Belarus, Australia, Denmark, Bangladesh, Finland, Dominican Republic, India, Burkina Faso, Uganda, South Africa, and Brazil.

The corresponding forest plots are presented below.

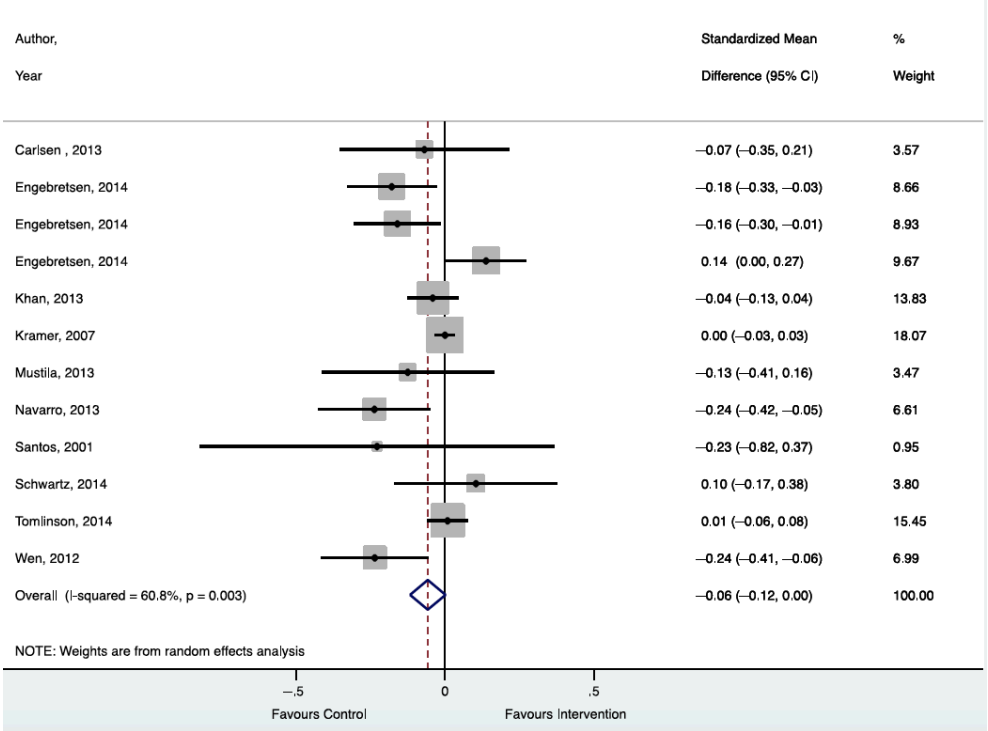
Infants | RCTs | Weight z score | Giugliani et al 2015 | Increased breastfeeding duration

Standardised mean differences in weight in different studies, comparing intervention vs. control groups (Giugliani et al 2015).
Please note – the Engebretsen (2014) trial was conducted in three countries (Burkina Faso, Uganda, and South Africa) and so provided three estimates.
Figure 5 Meta-analysis of RCTs in infants – Having been breastfed – Giugliani et al 2015– Weight z score



Infants | RCTs | BMI or weight-for-height z score | Giugliani et al 2015 | Increased breastfeeding duration

Standardised mean differences in BMI or weight/length or height in different studies, comparing intervention vs. control groups (Giugliani et al 2015).
Please note – the Engebretsen (2014) trial was conducted in three countries (Burkina Faso, Uganda, and South Africa) and so provided three estimates.
Figure 6 Meta-analysis of RCTs in infants – Having been breastfed – Giugliani et al 2015 – BMI or weight-for-height z score



2.2 Meta-analyses of prospective cohort studies

Please note – the time period noted on the right hand side of the exposure description cell is the *duration of follow-up* not the *duration of breastfeeding*.

Table 14 Meta-analyses of prospective cohort studies in infants – Having been breastfed

Infants					
Prospective cohorts					
BF=breastfeeding; OR=odds ratio; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	*Publication*	*Exposure description*	*Results*		
BMI	Owen et al (2005a)	BF vs. formula fed (varied definitions) 1–70 years	MD	**-0.04 (-0.05, -0.02) kg/m²** INV	Studies=36; n=355,301 I^2=not reported
Odds of overweight / obesity	Horta et al (2015)	BF vs. not-BF (varied definitions)* 2–62 years	OR	**0.79 (0.73, 0.85)** INV	Studies=54; n=not reported I^2=12%
	Yan et al (2014)	BF vs. not-BF (varied definitions)* 1–16 years	OR	**0.78 (0.73, 0.82)** INV	Studies=15; n=141,247 I^2=not reported
	Weng et al (2012)	Ever BF vs. never BF (varied definitions) 2–16 years	OR	**0.85 (0.74, 0.99)** INV	Studies=10; n=not reported I^2=73%
	Arenz et al (2004)	BF vs. not-BF (varied definitions)* 4–6 years	OR	**0.73 (0.64, 0.85)** INV	Studies=2; n=4389 (Study inclusion not clear) I^2=not reported
	Owen et al (2005b)	BF vs. formula fed <1–33 years	OR	**0.87 (0.85, 0.89)** INV	Studies=29; n=298,900 X^2_{28}=111, p<0.001
	Harder et al (2005)	Total duration of BF (up to 12 months) <1–33 years	Regression coefficient	**0.94 (0.89, 0.98)** INV	Studies=17; n=121,072 I^2=not reported
		Per month of BF <1–33 years	OR	**0.96 (0.94, 0.98)** INV	Studies=11; n=74,102 I^2=not reported
*Includes infants not breastfed at a certain time point and those who were never breastfed; in general, "more" vs. "less" breastfed.					

Eight meta-analyses, across seven reviews, were conducted using prospective cohort studies, with one reporting on BMI, six reporting odds of overweight or obesity, and one reporting a regression coefficient relating to the odds of overweight or obesity. All meta-analyses reported significant, protective associations for breastfeeding over adiposity. Definitions of infant feeding categories varied between the included studies, based on duration of breastfeeding and degree of exclusivity. Additionally, different thresholds were used to define overweight or obesity.

The meta-analysis reporting on BMI (Owen et al 2005a) included 36 studies but did not stratify between study types and the result encompasses 17 cross-sectional studies. This meta-analysis also has the widest follow-up range of 1–70 years. Three further meta-analyses included studies not of a prospective cohort design: in Yan et al (2014), Owen et al (2005b), and Harder et al (2005). Yan et al (2014) included 15 studies, of which five are listed as historical cohort studies; the result reported was calculated using a fixed effects model. Owen et al (2005b) included 10 cross sectional studies, two case control studies, and four historical cohorts. Harder et al (2005) conducted two meta-analyses investigating the duration of breastfeeding and risk of adiposity, one regarding total duration and one regarding per additional month of breastfeeding; both meta-analyses included a single study listed as case-control design.

The meta-analysis by Horta et al (2015) has the highest number of included studies (54, all prospective cohort design) and the highest number of unique studies not in any other meta-analysis (42).

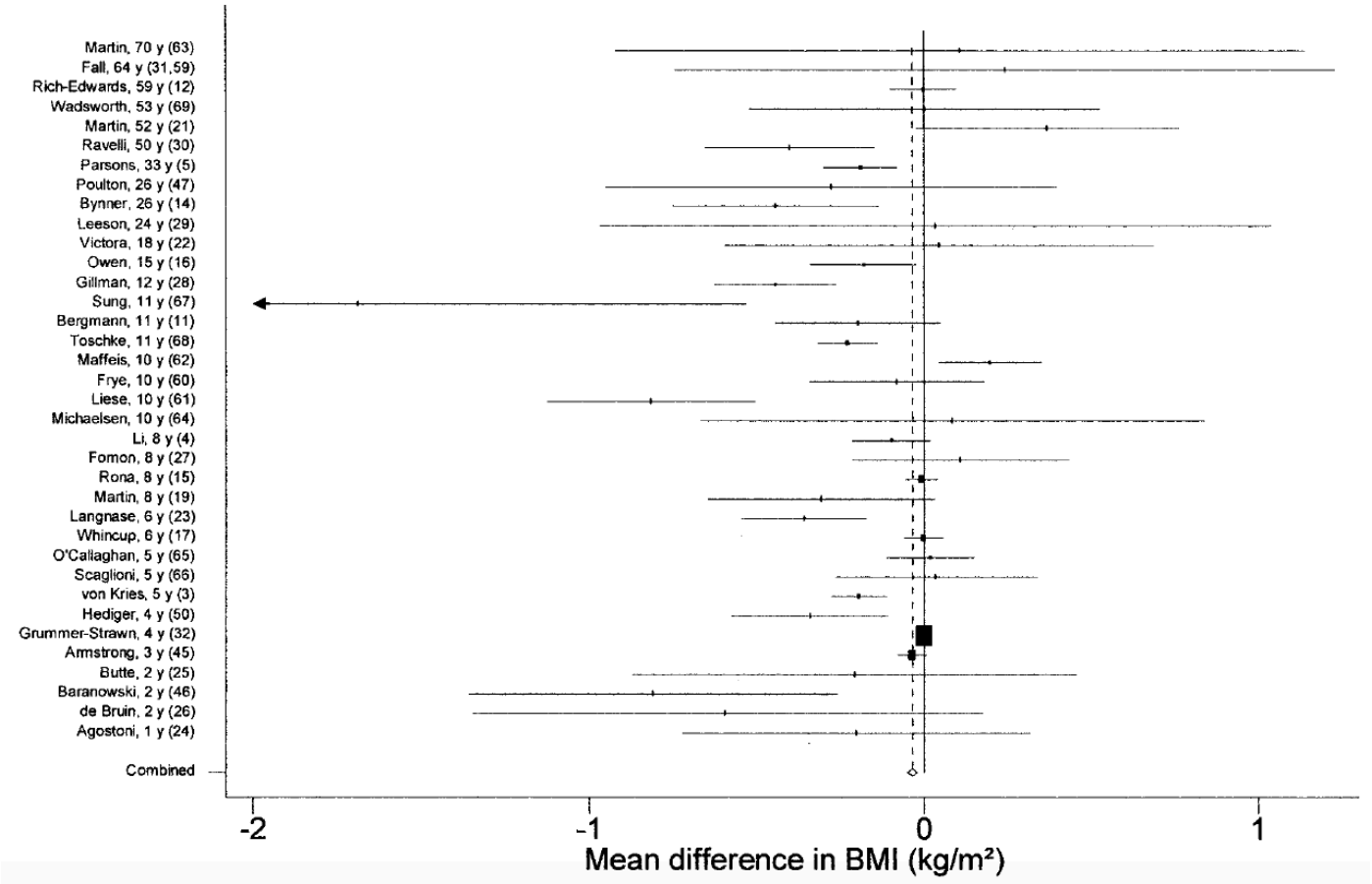
The corresponding forest plots for Owen et al (2005a), Weng et al (2012), Owen et al (2005b), and Harder et al (2005) are presented below; forest plots were not available for Horta et al (2015), Yan et al (2014), and Arenz et al (2004).

Infants | Prospective cohorts | BMI | Owen et al 2005a | Breastfed vs. bottle fed

Mean (95% CI) difference in BMI between breastfed and bottle-fed participants in 36 studies (4 crude estimates, 32 adjusted for age). Box area of each study is proportional to the inverse of the variance, and horizontal lines show the 95% CI. The first author of each study is indicated on the y-axis, the mean age of that study's subjects (in y) is shown in ascending order, and the review's reference number is shown in parentheses. The pooled estimate, which is based on a fixed-effects model, is shown by a dashed vertical line; the diamond indicates the 95% CI (Owen et al 2005a).

Please note the 19 prospective cohort studies used in this meta-analysis are as follows (listed in the order they appear on the left hand side of the plot): Martin et al (2002); Rich-Edwards et al (2004)*; Wadsworth et al (1999); Martin et al (2005)*; Parsons et al (2003); Poulton et al (2001); Bynner et al (2003)*; Victora et al (2003); Bergmann et al (2003); Frye et al (2003)*; Michaelsen et al (1997)*; Fomon et al (1984); Martin et al (2004); Langnase et al (2003); O'Callaghan et al (1997); Scaglioni et al (2000); Butte et al (2000)*; de Bruin et al (1998)*; and Agostoni et al (2000)*. An asterisk (*) denotes a study which is only included in this meta-analysis.*

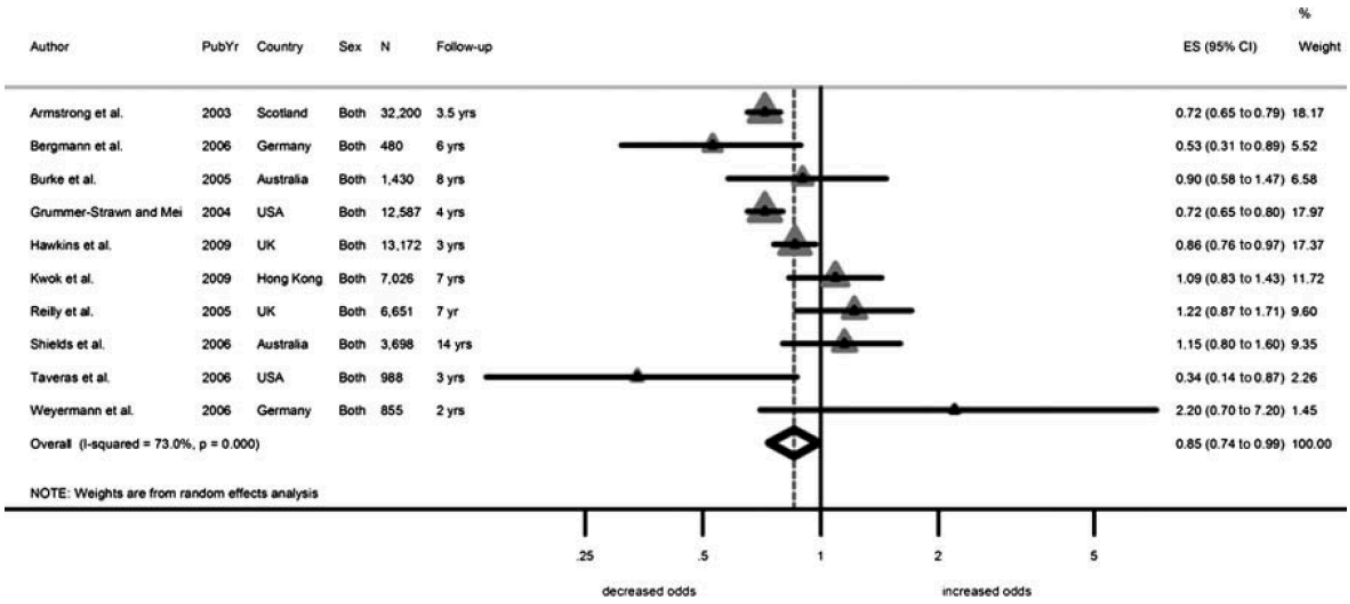
Figure 7 Meta-analysis of prospective cohort studies in infants – Having been breastfed – Owen et al 2005a – BMI



Infants | Prospective cohorts | Odds of overweight or obesity | Weng et al 2012 | 'Ever' breastfed vs. 'never' breastfed

Pooled adjusted OR for childhood overweight from random effects meta-analysis of 10 studies: ever breastfed compared with never breastfed. ES = effect size (Weng et al 2012).

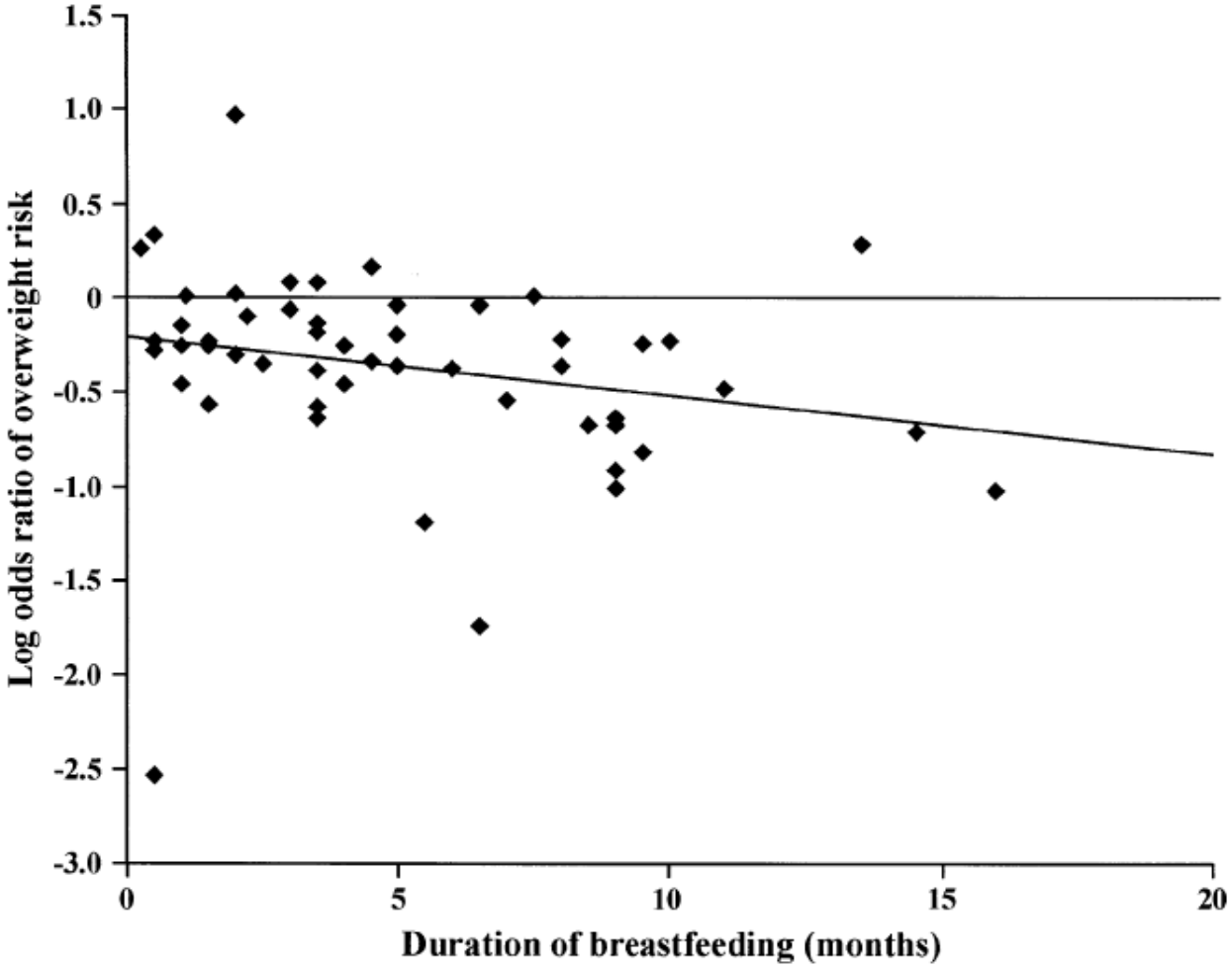
Figure 8 Meta-analysis of prospective cohort studies in infants – Having been breastfed – Weng et al 2012 – Odds of overweight or obesity



Infants | Prospective cohorts | Odds of overweight or obesity | Harder et al 2005 | Duration of breastfeeding

Scatterplot and meta-regression line of log odds ratio of risk of overweight/obesity associated with breastfeeding, according to duration of breastfeeding. A total of 17 studies provided 52 estimates of duration of breastfeeding and overweight. Weighted meta-regression revealed a significant inverse linear relation between the duration of breastfeeding and the risk of overweight (regression coefficient: 0.94; 95% confidence interval: 0.89, 0.98) (Harder et al 2005).

Figure 9 Meta-regression of prospective cohort studies in infants – Having been breastfed – Harder et al 2005 – Odds of overweight or obesity

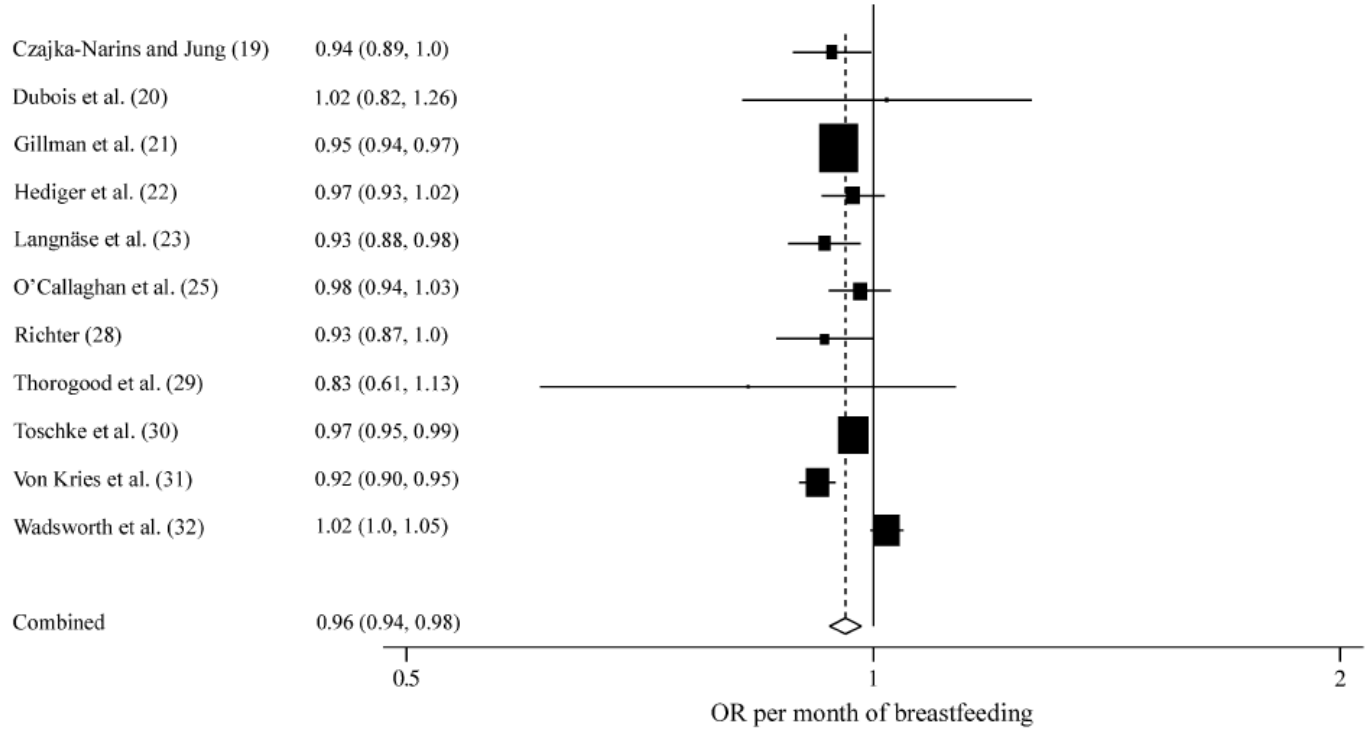


Infants | Prospective cohorts | Odds of overweight or obesity | Harder et al 2005 | Duration of breastfeeding

Odds ratios (with corresponding 95% confidence intervals in parentheses) for overweight, per month of breastfeeding. Studies are ordered alphabetically by first author. The pooled or ''combined'' odds ratio (OR) was calculated by a random-effects model (Harder et al 2005).

Please note that the single study listed by the review as case-control design is Dubois et al (1979).

Figure 10 Meta-analysis of prospective cohort studies in infants – Having been breastfed – Harder et al 2005 – Odds of overweight or obesity



2.3 Individual RCTs, not in meta-analyses

Please note – the time period noted on the right hand side of the exposure description cell is the *duration of follow-up* not the *duration of breastfeeding*.

Table 15 Results of individual RCTs in infants – Having been breastfed

Infants				
RCTs				
EBF=exclusive breastfeeding. Significant results are highlighted in **red**.				
Outcome	*Publication* *Review*	*Intervention description*	*Results*	*n*
Weight	Jakobsen et al. 2008 Giugliani et al (2015)	EBF promotion intervention vs. usual care 151-180 days	**Intervention: 7.5 kg** **Control 7.8 kg** p=0.04 **INV**	1,721
Weight-for-age z score		EBF promotion intervention vs. usual care 151-180 days	**Intervention: -0.16** **Control: 0.08** p=0.05 **INV**	1,721

Ten relevant RCTs were identified by Giugliani et al (2015) but not included in the meta-analyses due to the format of data presentation. Of these, one study included more than 1,000 participants and the results are presented in the table above, as per agreed criteria for reporting individual studies.

The study by Jakobsen et al (2008) was conducted in Guinea Bissau and reported significantly lower weights for intervention infants relative to control infants at 26 weeks. The sample size was reported as 1,721 participants; however, data on weight were only available for 699 infants.

The process indicator for intervention used by the authors was 'time to introduction of water and weaning food'. More than 70% of children received water during the first month of life and at four months only 1.2% had not started receiving water. Overall, water was introduced significantly later in the intervention group compared with control, p=0.003. Overall, weaning food was significantly delayed in the intervention group compared with control, HR 0.79 (0.70, 0.91).

The remaining nine studies with fewer than 1,000 participants provided 15 results across five outcomes: weight; weight-for-age z score; BMI z score; weight velocity at 6–10 months; and overweight/obesity. Of these results, nine reported increased adiposity with intervention relative to control, three reported an inverse effect with intervention, and two reported no association without indication of direction. None were statistically significant. The sample size ranged from 54 to 735 participants and the follow up period ranged from five months to 11 years.
Studies n<1000: Alvarado et al. 1999, Barros et al. 1995, Gagnon et al. 2002, Ghosh et al. 2002, Guldan et al. 2000, Haider et al. 2000, Karanja et al. 2010, Louzada et al. 2012, and Thakur et al. 2012

2.4 Individual prospective cohort studies, not included in meta-analyses

Please note – the time period noted on the right hand side of the exposure description cell is the *duration of follow-up* not the *duration of breastfeeding*.

Table 16 Results of individual prospective cohort studies in infants – Having been breastfed

Infants					
Prospective cohort studies					
BF=breastfeeding; EBF=exclusive breastfeeding; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	*Publication* *Review*	*Exposure description*	*Results*		*n*
Weight-for-age z scores	Kramer et al. 2002 *Owen et al (2005b)*	Weaned at 1 month vs. BF >6 months 12 months	**Lower attained weight-for-age z score at follow up in BF group** Full data not provided **INV**		1,378
% overweight	Salsberry et al. 2005 *Ryan (2007)*	'Ever' BF vs. 'never' BF 6-7 years	**Ever BF: 0.11 %** **Never BF: 0.14 %** Significant difference p=0.05 **INV**		3,022
Odds of "elevated weight gain"	Kalies et al. 2005 *Ryan (2007)*	EBF <6 months vs. >6 months 2 years	OR	**1.65 (1.17, 2.30)** **INV**	2,624
Odds of overweight or obesity	Nelson et al. 2005 *Ryan (2007)*	BF for ≥9 months vs. no BF *(girls)* 12-21 years	OR	**0.78 (0.64, 0.96)** **INV**	6,069
		BF for ≥9 months vs. no BF *(boys)* 12-21 years	OR	**0.83 (0.67, 1.04)** **INV**	5,929

Seventeen relevant prospective cohort studies that were not included in any meta-analyses were identified; of these, four had more than 1,000 participants and the results are presented in the table above. All five results reported a protective association of breastfeeding over adiposity, three of which were statistically significant. The four studies represent three countries: USA (Salsberry et al 2005; Nelson et al 2005); Germany (Kalies et al 2005); and Belarus (Kramer et al 2002).

In Kramer et al (2002), infants who were weaned in the first month were used to approximate a formula-fed cohort. It was not clear how many received any breast milk after one month of age. The other group was exclusively breastfed for more than six months with continued breastfeeding (to some degree) for more than 12 months.

Of the remaining 13 studies (14 publications) investigating breastfeeding and measures of adiposity with fewer than 1,000 participants, 14 results were provided. Ten results reported no significant association, three reported a positive association, and one reported an inverse association; none were significant.
Studies n<1000: Agras et al. 1987, Agras et al. 1990 (same cohort as Agras 1987), Kuperberg et al. 2006, Birkbeck et al. 1985, Dine et al. 1979, Fawzi et al. 1997, Harrison et al. 1987, Jooste et al. 1991, Marmot et al. 1980, Oakley 1977, Ong et al. 2002, Persson 1985, Saarinen et al. 1979, and Vobecky et al. 1983

[3. Null section]
*Please note that this exposure is, understandably, not stratified by adults and children. Therefore there is a single evidence section (**Section 2**).*

4. Possible mechanisms

4.1 Explained by confounding factors

The association between breastfeeding and reduced risk of adiposity could be explained by confounding factors, such as maternal weight, education, socioeconomic status, and age, indirectly influencing offspring weight gain independently of infant feeding practice. Controlling for these factors in cohort studies weakens, but does not eliminate, the association. Studies of infant feeding practices in sibling pairs, aiming to control for complex lifestyle factors, has produced mixed results. RCTs may introduce other biases, such as additional instructions on baby-led feeding. (Summarised by Bartok et al. 2009)

4.2 Explained by behavioural factors

In formula fed infants visual information on milk volume consumed is available to the caregiver and it is hypothesised that caregiver feeding behaviours can override infant self-regulation leading to excess caloric intake. Bartok and Ventura suggest there is evidence that the trust breastfeeding mothers learn from early feeding experience may translate into less controlling feeding practices in the infant's later life, ultimately leading to better self-regulation and lower adiposity. (Summarised by Bartok et al 2009)

4.3 Explained by breast milk composition

- **Energy**: Increased milk volumes consumed, and a higher energy density of formula, lead to a 15–23% higher total energy intake in 3–18 month old formula fed infants. A higher energy intake also endures in formula fed infants when complementary foods are added to the diet. (Summarised in Mameli et al. 2016)
- **Protein**: Formula milks typically contains 50–80% more protein than breast milk, and according to the "early protein hypothesis", a higher protein intake during infancy significantly influences the infant's growth pattern, increasing the likelihood of obesity development. (Summarised in Mameli et al 2016 and Bartok et al 2009)
- **Fats**: Fat content is higher in breast milk relative to formula milk, particularly long-chain polyunsaturated fatty acids. Higher levels of breast-milk fatty acids are associated with lower glucose levels in skeletal muscle of breast-fed infants (summarised in Mameli et al 2016). The omega-6/omega-3 ratio in formula milk may stimulate adipocyte growth and differentiation, and may also promote inflammation (summarised in Bartok et al 2009).
- **Other bioactive components**: Breast milk contains many bioactive components such as immunoglobulins, enzymes, hormones, cytokines, growth factors, and gut-brain peptides, which are postulated to modulate the infant's energy metabolism. Leptin may influence the infant's satiety; however, the fat content of breast milk may artificially elevate radioimmunoassay-measured leptin levels. (Summarised in Bartok et al 2009)
- **Modulation of the infant microbiome**: After delivery mode (vaginal vs. caesarean), feeding mode (breast vs. formula) is the major determinant of initial microbiome colonisers in the infant. Initially determined differences in gut microbiome between breast- and formula fed infants are maintained by the presence of specific oligosaccharides in human milk acting as prebiotics supporting growth of specific bacteria. Crucial imprinting events in infancy are mediated via the infant's gut microbiome. (Summarised in Victora et al 2016)
- **(Epi)genetic programming**: Breast milk fat globules contain many secreted micro-RNAs, the expression of which is modulated by the maternal diet, which are predicted to target several genes

within the infant (summarised in Victora et al 2016). Breast milk may also mitigate the usual adverse effect of peroxisome proliferating-activated receptor-ϒ polymorphisms on adiposity and metabolism by containing peroxisomes proliferator-activated receptor-modulating constituents such as long-chain polyunsaturated fatty acids and prostaglandin-J (summarised in Victora et al 2016).

5. Summary of evidence

5.1 Infants

Ten relevant reviews were identified, containing 159 unique studies. Within those, ten meta-analyses were identified across eight reviews, reporting on four outcomes: weight z score, BMI or weight-for-height z score, odds of overweight/obesity at follow up, and BMI. The two meta-analyses of RCTs reported one borderline significant protective effect and one non-significant positive effect. All interventions were education-based and level of compliance was not always reported. Of the eight meta-analyses of prospective cohort studies investigating being breastfed and adiposity, all reported significant, protective associations. Although these eight meta-analyses were primarily conducted with prospective cohort studies, four also contained other study designs. The studies not included in meta-analyses with more than 1,000 participants all reported inverse relationships; studies with fewer than 1,000 participants provided mixed results, none were significant.

2. Foods and drinks

2.1 Wholegrains

1. Evidence identified for 2017 update

Table 17 Published reviews identified for the 2017 update – Wholegrains

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Bautista-Castano et al. 2012 [++]; Pol et al. 2013 [++]; WCRF (2006) [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	2	Fardet et al. 2014 [+]; Ye et al. 2012 [+]

Notes on the evidence:

- The published review by Ye et al (2012) was identified in Fardet and Boirie (2014). Fardet and Boirie (2014) was identified via the supplementary literature search and is a review of reviews in itself. The published reviews in Fardet and Boirie (2014), such as that mentioned above, are reported in the relevant exposure section of this literature review.
- The review identified by NICE (2014) report 'WCRF (2006)' is the WCRF/AICR 2005 SLR for the determinants of weight gain, overweight and obesity. This is now available as an open access published article (reference = Summerbell et al 2009). All the relevant information can be found in the published article.
- As there is no unanimously accepted definition of wholegrains, the definition as used in each review, or individual study, is reported in the text.
- For reference, The Wholegrains Council (2004) define wholegrains as: "Whole grains or foods made from them contain all the essential parts and naturally-occurring nutrients of the entire grain seed in their original proportions. If the grain has been processed (e.g., cracked, crushed, rolled, extruded, and/or cooked), the food product should deliver the same rich balance of nutrients that are found in the original grain seed."

2. Children

2.1 Meta-analyses of RCTs in children
Nil

2.2 Meta-analyses of prospective cohort studies in children
Nil

2.3 Individual RCTs in children, not in meta-analyses
Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses
Nil

3. Adults

3.1 Meta-analyses of RCTs in adults

Table 18 Meta-analyses of RCTs in adults – Wholegrains

Adults – Wholegrains					
Meta-analyses of RCTs					
WMD=weight mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Pol et al (2013)	Increased wholegrain intake (18.2–150g per day) 3–16 weeks	WMD	**0.06 (-0.09, 0.20) kg** +VE	Studies=26; n=2,060 I^2=0%
		Wholegrain intake g per day Unclear follow up period	Beta-coefficient	**-0.0013 (-0.011, 0.009) kg** INV	Studies=not reported; n=not reported I^2=not reported
	Ye et al (2012)	Wholegrain intervention vs. control 2–16 weeks	WMD	**-0.18 (-0.54, 0.18) kg** INV	Studies=9; n=629 I^2=82%
% body fat change	Pol et al (2013)	Increased wholegrain intake (48–105 g per day) 3–16 weeks	WMD	**-0.48 (-0.95, -0.01) %** INV	Studies=7; n=1,087 I^2=0%
Waist circumference change	Pol et al (2013)	Increased wholegrain intake (48 – 105 g per day) 3–16 weeks	WMD	**-0.15 (-0.51, 0.22) cm** INV	Studies=9; n=1,317 I^2=67%

Two reviews conducted five meta-analyses across three outcomes: weight; percentage body fat; and waist circumference. Four results reported inverse relationships between wholegrain intake and adiposity, of which one was statistically significant (percentage body fat). The analysis for percentage body fat was strongly influenced by one study (Kim et al 2008) and its removal from analysis led to a loss of statistical significance.

Pol et al (2013)

- The meta-analyses of weight and wholegrain intake reported a non-significant effect. Stratifying for background diet (energy restriction or not) did not affect the results. The authors also stratified between types of wholegrain: interventions with oats, rye, barley, and rice resulted in greater decreases in weight than controls, with rice being statistically significant. Results for mixed wholegrains and wheat showed the opposite. (See forest plot below.)
- The high heterogeneity observed in the waist circumference meta-analysis is attributable to one study (Maki et al. 2010).
- All food was provided to both intervention and control groups in the majority of studies (21/26); in the other five, food was provided to the intervention group only. The increased intake of wholegrain (additional 18.2–150g per day) was achieved via a variety of products: bread, crisp breads, ready-to-eat breakfast cereals, noodles, pasta, snack/cereal bars, muffins, ready meals, and the entire grain (e.g. rice, barley).
- Pol et al (2013) referenced the HEALTHGRAIN definition of wholegrain ("Whole grains shall consist of the intact, ground, cracked, or flaked kernel after the removal of inedible parts such as the hull and husk. The principal anatomical components – the starchy endosperm, germ and bar – are present in the same relative proportions as they exist in the intact kernel") but did not specify a definition of wholegrain as part of their inclusion criteria. The review did exclude studies that were based on individual grain components (for example, bran or germ).

Ye et al (2012)

- Details on dosages and format of the individual interventions were not reported. The interventions varied in type of wholegrain: rye bread; oats; oat cereal; “wholegrains” (general); rye wholegrain and bran; wholegrain wheat; and oat bran.
- There was overlap of studies with the Pol et al (2013) meta-analysis (seven of nine studies).
- High heterogeneity was observed.

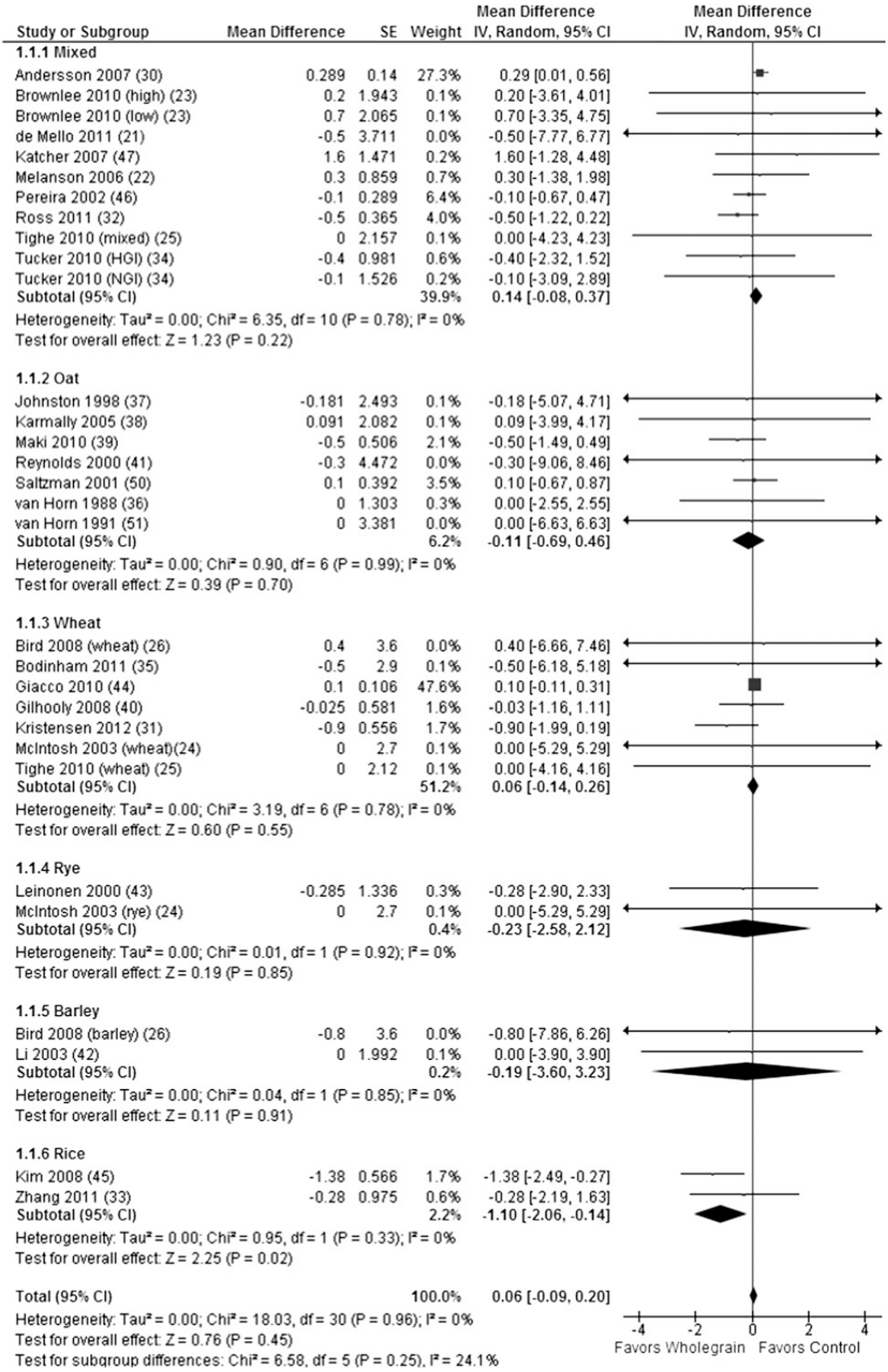
All meta-analyses contained one study that included hyperglycaemic participants as part of the sample (Tucker et al 2010).

The forest plots corresponding to the above meta-analyses are presented below.

Adults | RCTs | Weight | Pol et al 2013 | Wholegrain intake

Forest plot of the results of the fixed-effects meta-analysis of change in body weight according to grain type shown as pooled mean differences with 95% CIs. For each study, the square represents the point estimate of the intervention effect. Horizontal lines join lower and upper limits of the 95% CI of this effect. The area of shaded squares reflects the relative weight of the study in the meta-analysis. Diamonds represent the subgroup mean difference and pooled mean differences. HGI, hyperglycemic/ insulinemic; high, high whole-grain dose (115 g/d); IV, inverse variance; low, low whole-grain dose (74 g/d); NGI, normoglycemic/insulinemic (Pol et al 2013).

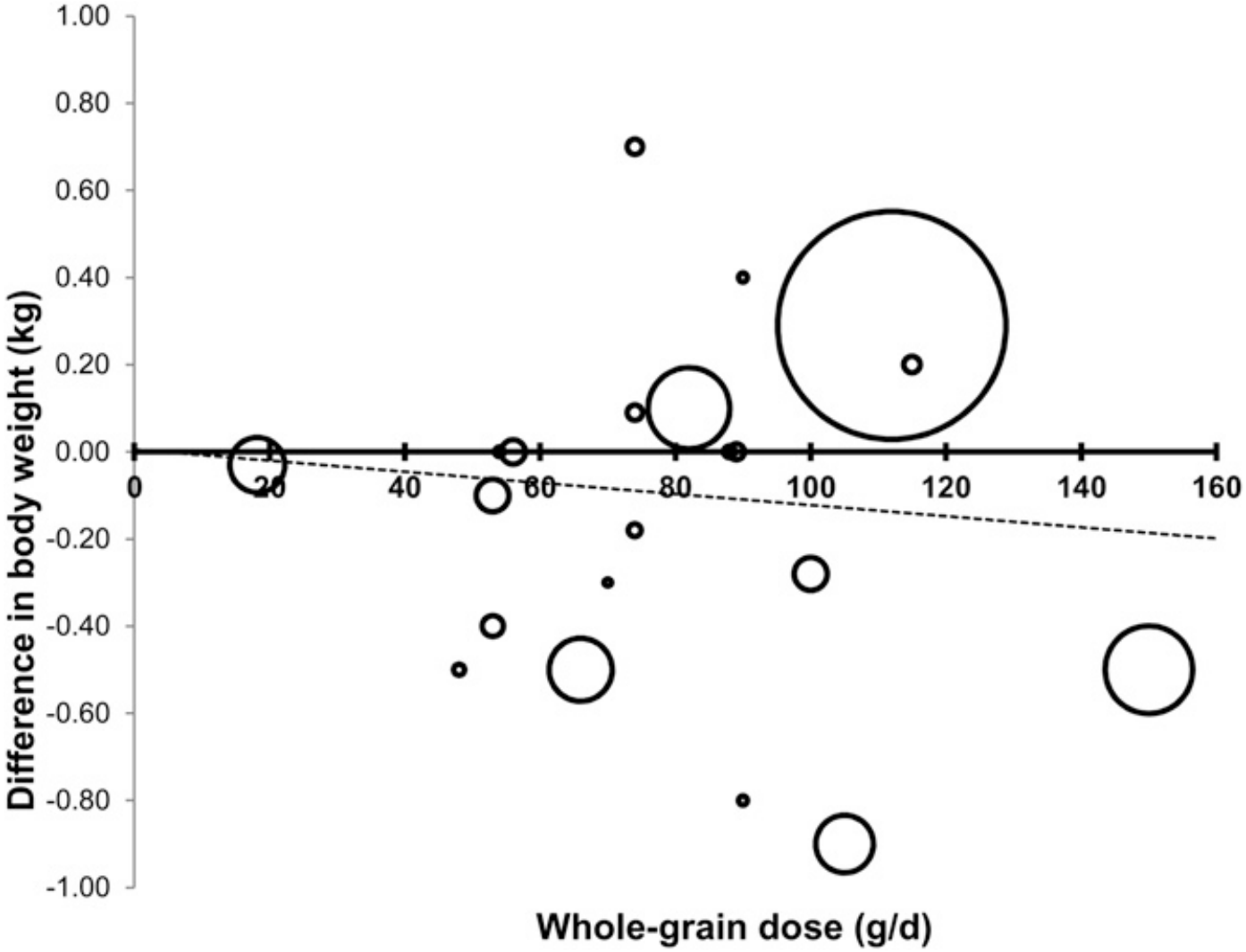
Figure 11 Meta-analysis of RCTs in adults – Wholegrains – Pol et al 2013 – Weight



Adults | RCTs | Weight | Pol et al 2013 | Per gram of wholegrain per day

Mean differences in body weight change by whole-grain dose. In the metaregression analysis, the size of the circles is proportional to the precision of the estimate used in the metaregression. The line indicates the predicted effects (regression line). There was no significant association [b = -0.0013 0013 kg x g/d (95% CI: -0.011, 0.009 kg x g/d); z = 0.245, P = 0.81] (Pol et al 2013).

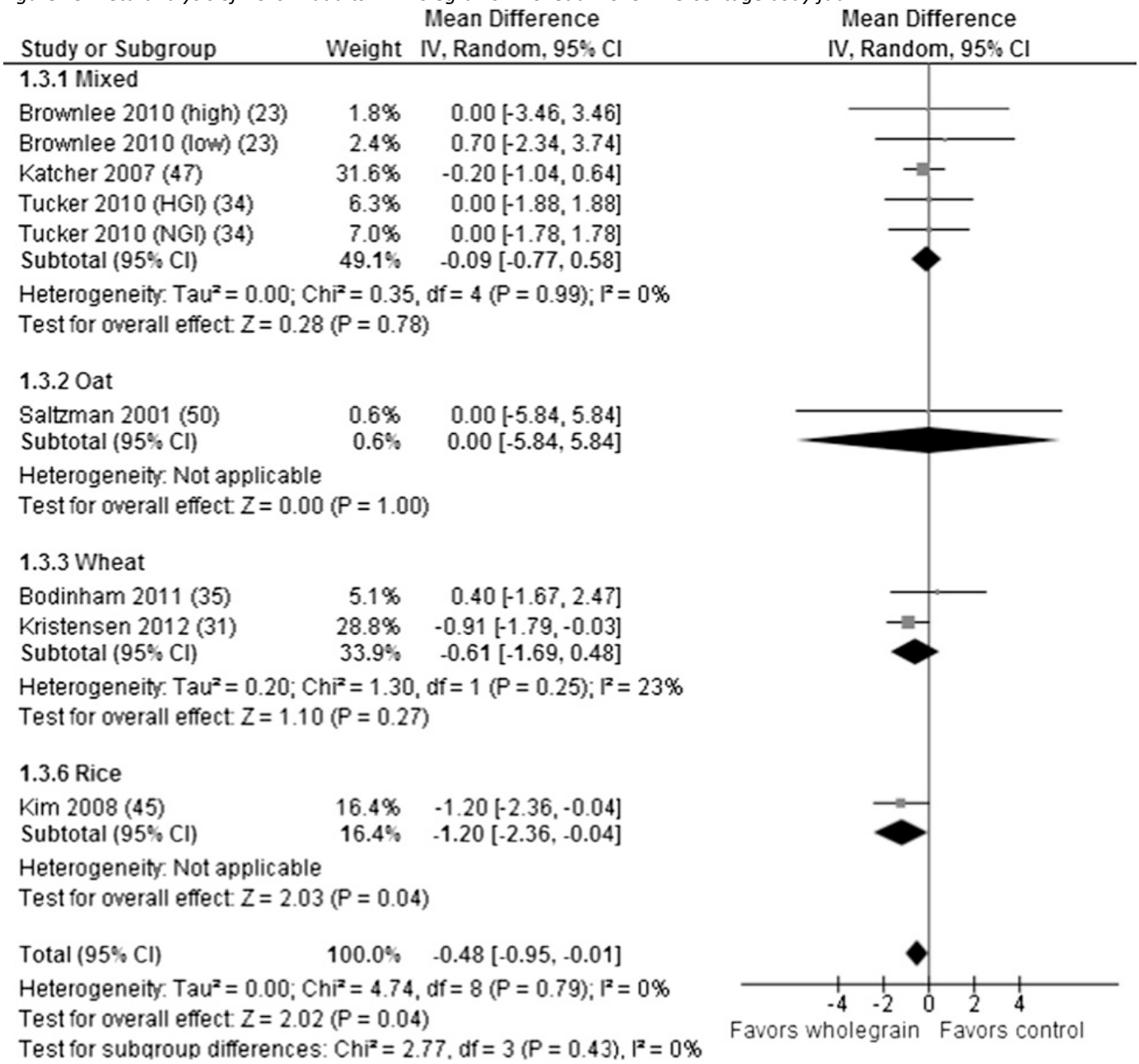
Figure 12 Meta-regression of RCTs in adults – Wholegrains – Pol et al 2013 – Weight



Adults | RCTs | Percentage body fat | Pol et al 2013 | Wholegrain intake

Forest plot of the results of the fixed effects meta-analysis of change in the percentage of body fat according to grain type shown as pooled mean differences with 95% CIs. For each study, the square represents the point estimate of the intervention effect. Horizontal lines join the lower and upper limits of the 95% CI of this effect. The area of the shaded squares reflects the relative weight of the study in the meta-analysis. Diamonds represent the subgroup mean difference and pooled mean differences. HGI, hyperglycemic/insulinemic; high, high whole-grain dose (115 g/d); IV, inverse variance; low, low whole-grain dose (74 g/d); NGI, normoglycemic/insulinemic (Pol et al 2013).

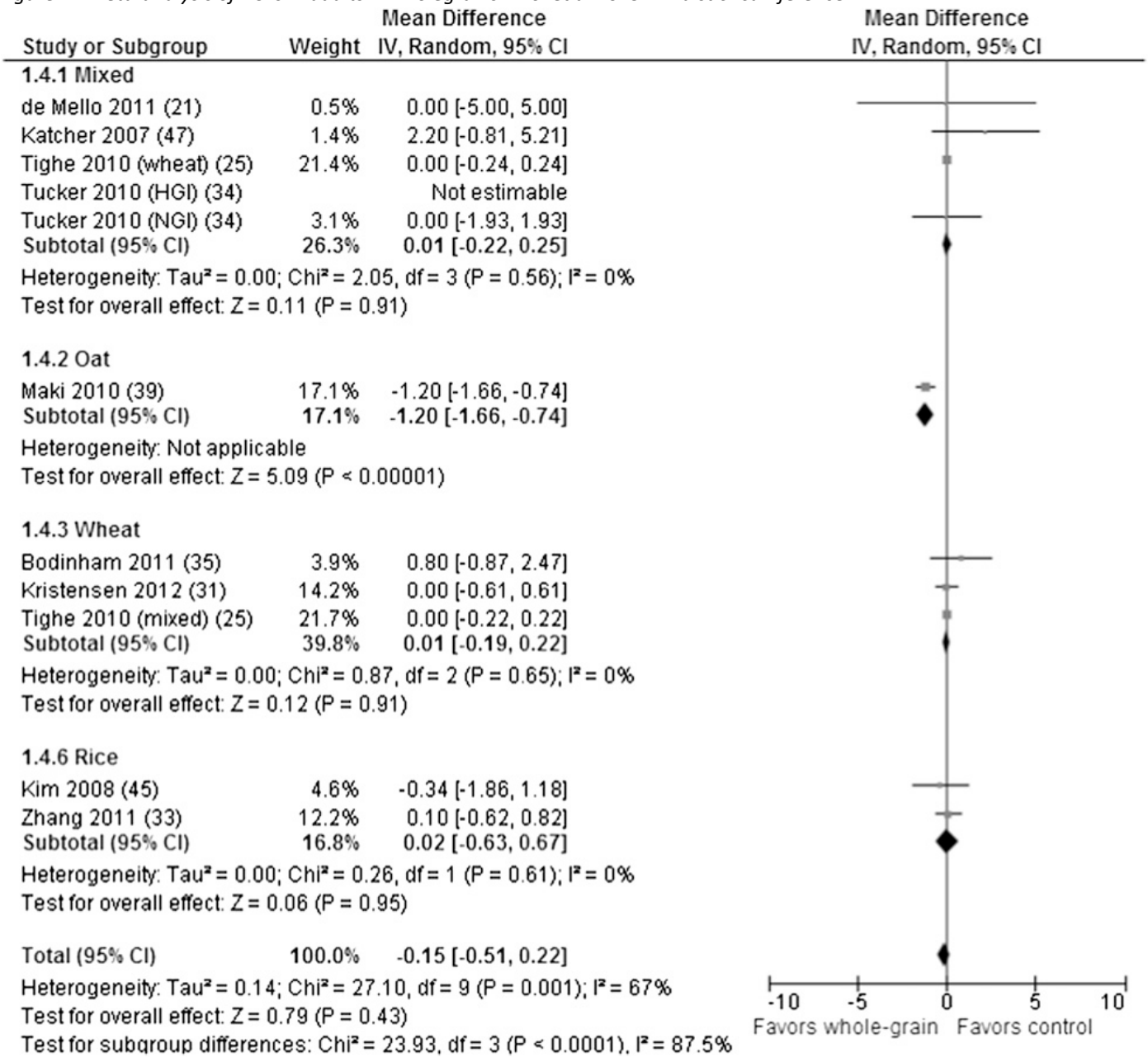
Figure 13 Meta-analysis of RCTs in adults – Wholegrains – Pol et al 2013 – Percentage body fat



Adults | RCTs | Waist circumference | Pol et al 2013 | Wholegrain intake

Forest plot of the results of the fixed effects meta-analysis of change in waist circumference according to grain type shown as pooled mean differences with 95% CIs. For each study, the square represents the point estimate of the intervention effect. Horizontal lines join the lower and upper limits of the 95% CI of this effect. The area of the shaded squares reflects the relative weight of the study in the meta-analysis. Diamonds represent the subgroup mean difference and pooled mean differences. HGI, hyperglycemic/insulinemic; IV, inverse variance; NGI, normoglycemic/insulinemic (Pol et al 2013).

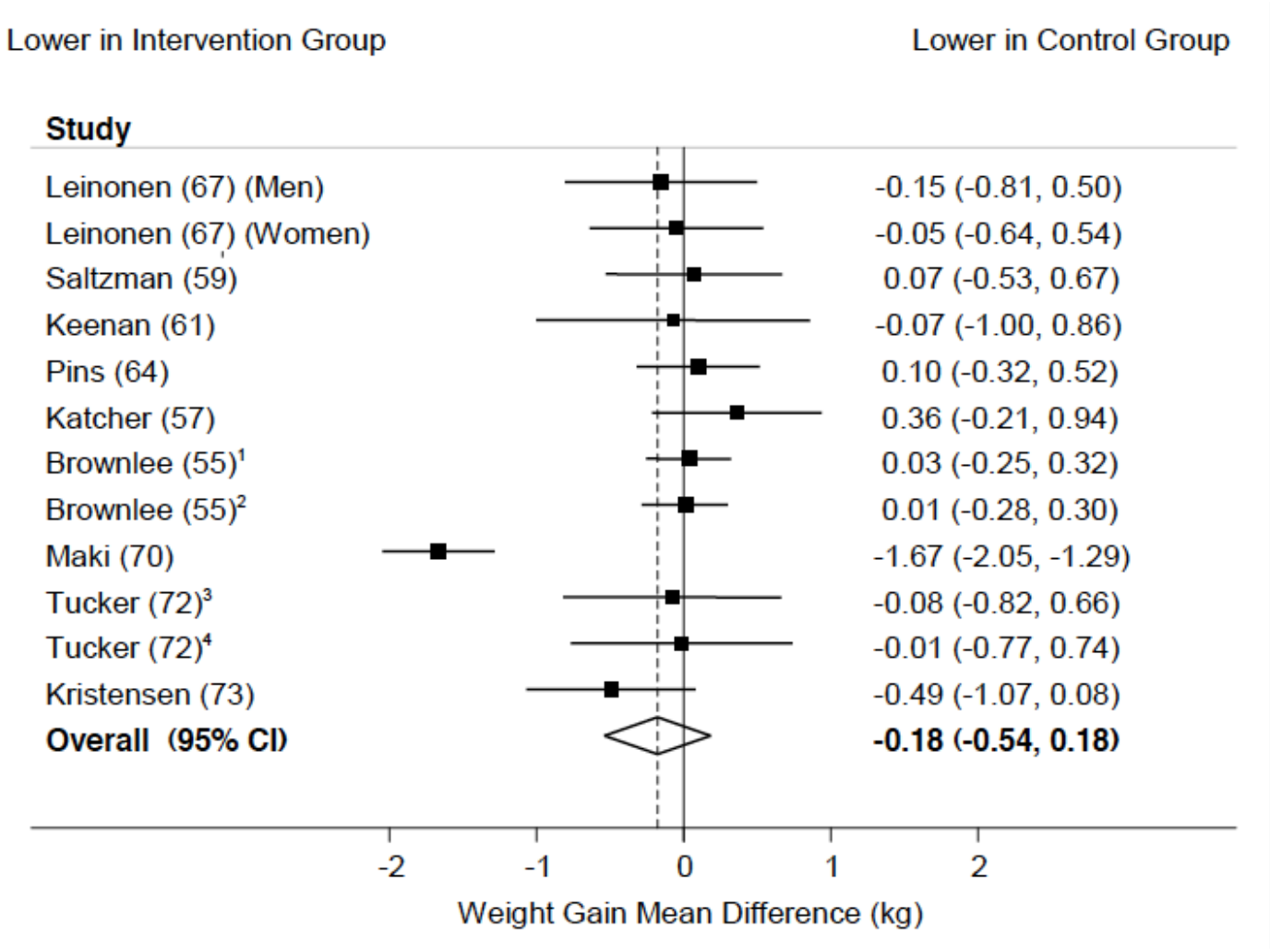
Figure 14 Meta-analysis of RCTs in adults – Wholegrains – Pol et al 2013 – Waist circumference



Adults | RCTs | Weight | Ye et al 2012 | Wholegrain intervention vs. control

Weighted mean differences (95% CI) of weight gain (kg) after whole grain intervention vs. control in randomized controlled trials. [1]Dosage: 60 g/day; [2]Dosage: 60-120 g/day; [3]Healthy participants; [4]Hyperglycemic participants. Squares indicate the mean difference in each study. The size of the square is proportional to the weight of each study in the overall random-effects estimate. The horizontal line represents the 95% CI. The weighted mean difference and its 95% CI are indicated by the open diamond. I2=82.2%, P <.0001. (Ye et al 2012)

Figure 15 Meta-analysis of RCTs in adults – Wholegrains – Ye et al 2012 – Weight



3.2 Meta-analyses of prospective cohort studies in adults

Nil

3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 19 Results of individual prospective cohort studies in adults – Wholegrains

Adults – Wholegrains					
Prospective cohort studies					
OR=odds ratio; RR=relative risk. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight	Koh-Banerjee et al. 2004 *Bautista-Castano et al (2012); WCRF (2006);* and *Ye et al (2012)*	Highest vs. lowest quintile of wholegrain intake 8 years	Highest intake quintile: **0.75 kg** Lowest intake quintile: **1.24 kg** p for trend < 0.0001 **INV**		27,082
Waist circumference	Halkjaer et al. 2006 *Bautista-Castano et al (2012)*	Per MJ per day of wholegrain products at baseline *(female)* 5.3 years	Beta-coefficient	**0.15 (-0.06, 0.36) cm** **+VE**	22,570
		Per MJ per day of wholegrain products at baseline *(male)* 5.3 years	Beta-coefficient	**0.08 (-0.06, 0.22) cm** **+VE**	20,126
	Halkjær et al. 2004 *Bautista-Castano et al (2012)* and *WCRF (2006)*	Per quintile intake of wholegrain bread at baseline *(female)* 6 years	Beta-coefficient	**-0.20 (-0.49, 0.09) cm** **INV**	1,092
		Per quintile intake of wholegrain bread at baseline *(male)* 6 years	Beta-coefficient	**-0.07 (-0.30, 0.17) cm** **INV**	1,135
Odds of weight gain >25kg	Liu et al (2003) *Bautista-Castano et al (2012); WCRF (2006);* and *Ye et al (2012)*	Highest vs. lowest quintile of wholegrain intake 12 years	Risk estimate	**0.77 (0.59, 1.01)** p for trend=0.03 **INV**	657
Odds of obesity		Highest vs. lowest quintile of wholegrain intake 12 years	OR	**0.81 (0.73, 0.91)** p for trend=0.0002 **INV**	6,400
Relative risk of overweight	Bazzano et al (2005) *WCRF (2006)* and *Ye et al (2012)*	Intake of >1 serving wholegrain breakfast cereal per day vs. rarely/never eat 13 years	RR	**0.91 (0.79, 1.05)** p for trend=0.13 **INV**	17,881

Four prospective cohort studies (five publications) provided eight results across five outcomes: weight; waist circumference; odds of weight gain of more than 25kg; odds of obesity; and relative risk of overweight. Six results reported an inverse association between wholegrain intake and adiposity, of which two were statistically significant. Two results reported positive associations; neither were significant.

The study by Liu et al (2003) used the Nurses' Health Study I cohort. Bazzano et al (2005) and Koh-Banerjee et al (2004) both used the Health Professionals Follow up Study cohort. The population used by Halkjaer et al (2004) includes men and women and forms part of the larger MONICA1 Study cohort. Halkjaer et al (2006) used data from the Danish Diet, Cancer and Health study.

Liu et al (2003) used the Jacobs definition of wholegrain foods, where foods containing more than 25% wholegrain by weight. Koh-Banerjee et al (2004) considered wholegrains in their intact and pulverized forms, with each ingredient required to satisfy the content of an individual type of grain (bran, endosperm, and

germ in proper proportions); wholegrain content by gram was calculated for individual foods. Halkjaer et al (2006), Halkjaer et al (2004), and Bazzano et al (2005) all used food frequency questionnaires to ascertain wholegrain intake, with specific foods and products categorised as wholegrain, although it was unclear how this categorisation was done.

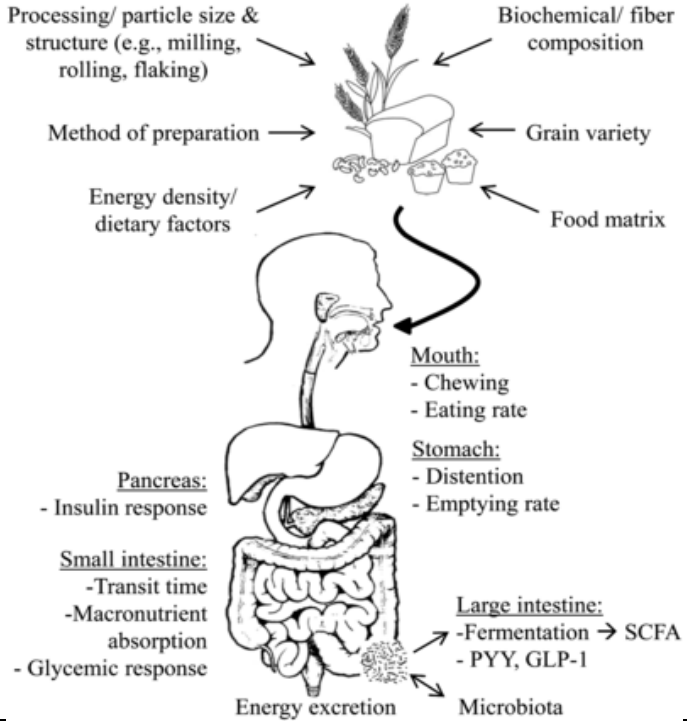
4. Possible mechanisms

Karl et al. 2012 summarised the possible mechanisms for wholegrain intake influencing weight gain (also see corresponding diagram below the text):

- **Chewing**: The fibre content, particle size, and structural integrity of wholegrains alter the amount of chewing required. Increased chewing may promote satiation by enhancing gastric distention, augmenting gut hormone responses, prolonging orosensory stimulation, or slowing eating rate.
- **Low energy density**: Wholegrain foods generally have a low energy density. This effect derives from the low digestible energy per unit mass and water-holding capacities of dietary fibres intrinsic to many wholegrains. Short-term studies have demonstrated that humans have a tendency to eat a consistent weight of food irrespective of energy content, indicating that appetite is influenced more by the mass of food than the amount of energy. Consequently, decreasing dietary energy density results in a reduction in energy intake without a concomitant increase in hunger.
- **Reduced post-prandial glycaemic response**: The glycaemic response associated with consuming wholegrain foods is not solely dependent on fibre content; factors such as the structural integrity, grain particle size after processing, and the food matrix determine glycaemic responses to wholegrain foods. Wholegrain-rich meals have also been shown to favourably affect glucose metabolism following the subsequent meal. For example, relative to refined grain wheat bread, consuming an equivalent amount of available carbohydrate from barley kernels prepared using various methods at evening meals depressed the glycaemic response following a standardised breakfast the next morning.
- **Gut microbiota**: Short chain fatty acids produced during the fermentation of certain fibres within wholegrains contribute to the regulation of body weight and composition by serving as metabolizable energy sources. These can mediate hepatic and peripheral glucose and lipid oxidation and stimulate secretion of the gut hormones peptide-YY and GLP-1. These act to suppress appetite, slow gastrointestinal transit, and modulate glucose metabolism.

Figure 16 Wholegrains - Mechanisms of action - From Karl et al 2012

Structural and physicochemical properties of wholegrain foods mediate the effect of wholegrain on physiologic factors influencing body weight and composition.
From: Karl et al (2012).
WG = wholegrain; SCFA = short chain fatty acids; PYY = peptide-YY; GLP = glucagons-like peptide-1.



5. Summary of evidence

5.1 Children

N/A

5.2 Adults

Three reviews investigating wholegrain intake and adiposity were identified from the NICE (2015) report and one via the supplementary literature search. None of the included studies investigated children. One review conducted four meta-analyses of RCTs: three results reported an inverse relationship (one statistically significant), and one reported a non-significant positive relationship. Some differences were noted between grain types. Another review conducted a meta-analysis of RCTs and reported non-significant inverse effect. Five individual prospective cohort studies provided eight results: six reported inverse associations (two were statistically significant) and two reported non-significant positive associations. Four of the five prospective cohort studies had substantially larger sample sizes than the studies within the meta-analyses combined.

2.2 Refined grains

1. Evidence identified for the 2017 update

Table 20 Published reviews identified for the 2017 update – Refined grains

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Bautista-Castano et al. 2012 [++];Fogelholm et al. 2012 [+];Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	Nil	-

Notes on the evidence:

- The supplementary literature search yielded no meta-analyses, so all the evidence presented here is derived from the NICE (2014) report.

2. Children

2.1 Meta-analysis of RCTs in children
Nil

2.2 Meta-analyses of prospective cohort studies in children
Nil

2.3 Individual RCTs in children, not in meta-analyses
Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses
Nil

3. Adults

3.1 Meta-analysis of RCTs in adults

Nil

3.2 Meta-analyses of prospective cohort studies in adults

Nil

3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.2.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 21 Results of individual prospective cohort studies in adults – Refined grains

Adults					
Prospective cohort studies					
ΔWC_{BMI}=waist circumference for a given BMI; OR=odds ratio; RR=relative risk. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Koh-Banerjee et al. 2004 *Bautista-Castano et al (2012)*	Servings per day of refined grain cereal *(males)* 8 years	**Positive association with weight gain** p for trend <0.001 Specific data points not provided **+VE**		27,082
		Categories of refined grain intake *(males)* 8 years	**"No associations were observed between changes in refined-grain … consumption and body weight"** Specific data points not provided **NIL**		27,082
	Mozaffarian et al. 2011 *Fogelholm et al (2012)*	Increased servings per day of refined grains over a four year period 20 years	MD	**0.39 (0.21, 0.58) lb** p<0.001 **+VE**	120,887
BMI change	Newby et al. 2003a *Summerbell et al (2009)* and *Bautista-Castano et al (2012)*	'White bread'-defined dietary pattern vs. 'healthy' dietary pattern at baseline 1 year	Beta-coefficient	**0.05 (-0.10, 0.23) kg/m^2** **+VE**	459
Waist circumference	Halkjær et al. 2004 *Bautista-Castano et al (2012), Summerbell et al (2009)* and *Fogelholm et al (2012)*	Per quintile intake of refined bread *(females)* 6 years	Beta-coefficient	**0.29 (0.07, 0.51) cm** **+VE**	1,073
		Per quintile intake of refined bread *(males)* 6 years	Beta-coefficient	**-0.06 (-0.22, 0.09) cm** **INV**	1,127
	Halkjaer et al. 2006 *Bautista-Castano et al (2012)*	Per MJ per day of refined grain products and potatoes *(females)* 5.3 years	Beta-coefficient	**0.48 (0.18, 0.78) cm** **+VE**	22,570
		Per MJ per day of refined grain products and potatoes *(males)* 5.3 years	Beta-coefficient	**0.06 (-0.12, 0.25) cm** **+VE**	20,126
	Newby et al. 2003a *Summerbell et al (2009)*	'White bread'-defined dietary pattern vs. 'healthy' dietary pattern at baseline 1 year	Beta-coefficient	**0.90 (0.12, 1.68) cm** **+VE**	449
ΔWC_{BMI}	Romaguera et al. 2011 *Fogelholm et al (2012)*	100kcal increments of white bread consumption over one year 5.5 years	Beta-coefficient	**0.01 (0.01, 0.02) cm** **+VE**	48,631

Odds of weight gain	Liu et al. 2003 *Bautista-Castano et al (2012), Summerbell et al (2009)* and *Fogelholm et al (2012)*	Highest vs. lowest quintile intake of refined grains 12 years	OR	**1.26 (0.97, 1.64)** p for trend=0.04 **+VE**	74,091
Risk of overweight	Bazzano et al. 2005 *Summerbell et al (2009)*	Intake of >1 serving refined grain breakfast cereal per day vs. rarely/never eat 13 years	RR	**0.81 (0.65, 1.01)** p for trend=0.08 **INV**	17,881
Odds of obesity	Liu et al. 2003 *Bautista-Castano et al (2012), Summerbell et al (2009)* and *Fogelholm et al (2012)*	Highest vs. lowest quintile intake of refined grains 12 years	OR	**1.18 (1.08, 1.28)** p for trend <0.0001 **+VE**	74,091

Seven prospective cohort studies (eight publications) in adults were identified from three reviews. These provided 13 results across eight outcomes: weight; weight change; BMI change; waist circumference; ΔWC_{BMI}; odds of weight gain; risk of being overweight; and odds of being obese.

Ten results reported a positive association between refined grain intake and adiposity, of which seven were statistically significant. Two results reported inverse, non-significant associations, and one result reported no association.

Koh-Banerjee et al (2004) and Bazzano et al (2005) used data from the Health Professionals Follow up Study cohort (all male); Liu et al (2003) used data from the Nurses' Health Study I cohort (all female). Mozzafarian et al (2011) pooled data from the Nurses' Health Study I, the Nurses' Health Study II, and the Health Professionals Follow up Study cohorts. Romaguera et al (2011) pooled data from the EPIC cohort across five centres. Halkjaer et al (2004) used data from the MONICA1 Danish cohort and Halkjaer et al (2006) used data from the Danish Diet, Cancer and Health Study.

Three studies investigated specific refined grain products: white/refined grain bread (Halkjaer et al 2004; Romaguera et al 2001) and refined grain breakfast cereal (Bazzano et al 2005). Koh-Banerjee et al (2004) reported results for refined grains and refined grain cereals separately, although it was unclear if the refined grain cereals result was specifically referring to breakfast cereals. Koh-Banerjee et al (2004) defined their refined grain category as grain products with <25% wholegrain content, and included breakfast cereals, bread, English muffins, bagels, rolls, pancakes, waffles, white rice, pasta, cookies, doughnuts, brownies, sweet rolls, coffee cake, and pizza.

Newby et al (2003) compared two dietary patterns, one of which was defined by high intake of white bread but represents a wider, less healthy dietary pattern than its comparator. In the 'white bread' pattern the greatest source of energy was white bread; the 'healthy' pattern contained relatively greater contributions from fruit, high-fibre cereal, and reduced fat dairy, and relatively lower contributions from fast food, non-diet soda, and salty snacks.

4. Possible mechanisms

As summarised by Fogelholm et al (2012):

- **High glycaemic index**: refined grain products often have a high glycaemic index, provoking high insulin responses and a fast glucose decline. These properties could increase hunger and enhance lipogenesis (see next point), thereby promoting obesity. (As summarised in Fogelholm et al 2012)
- **Lipogenesis**: experimental data indicate that refined grain products, unlike wholegrain products, can induce an increase in fat synthesis in animal feeding trials even when the total energy intake is unchanged and body weight remains constant. (As summarised in Liu et al 2003)

5. Summary of evidence

5.1 Children

N/A

5.2 Adults

No meta-analyses of RCTs or prospective cohort studies in adults were identified. Seven individual studies (eight publications), all prospective cohort design, were identified within three published reviews. Thirteen results were reported: 10 indicated a positive association (seven statistically significant), two reported an inverse association (both non-significant, and both in males), and one reported no association. Several studies overlapped in their use of cohort data. Three studies reported results with respect to a specific refined grain product, five reported with respect to overall refined grain intake.

2.3 Fruit and (non-starchy) vegetables

1. Evidence identified for 2017 update

Table 22 Published reviews identified for the 2017 update – Fruit and vegetables

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Summerbell et al. 2009 [++]; U.S Department of Agriculture Nutrition Evidence Library 2010c [+]; U.S Department of Agriculture Nutrition Evidence Library 2010a [+]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	7	Bertoia et al. 2015 [+]; Bertoia et al. 2016 [+]; Kaiser et al. 2016 [++]; Mytton et al. 2014 [++]; Schwingshackl et al. 2015 [++]; Fardet et al. 2014 [+]; Tohill et al. 2004 [+]

Notes on the evidence:

- The published review by Tohill et al (2004) was identified in Fardet and Boirie (2014). Fardet and Boirie (2014) was identified via the supplementary literature search and is a review of reviews in itself. The reviews in Fardet and Boirie (2014), such as Tohill et al (2004), are reported in the relevant exposure section of this literature review.
- USDA (2010a) investigated studies of fruit and vegetable intake in adults. All included studies were either included as part of a meta-analysis from another published review or did not meet inclusion criteria (see protocol in **Appendix**). Therefore, USDA (2010a) is not referred to in the results section of this exposure.
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.
- Bertoia et al (2016) investigated dietary flavonoid intake and adiposity. This published review is included in this literature review as flavonoids can be viewed as a marker for fruit and vegetable intake. The related mechanisms between dietary flavonoid intake and adiposity are summarised in **Section 4** of this exposure.
- The exposure varied between studies: fruits alone, vegetables alone, or all fruits and vegetables combined; this is reflected in the way the results are set out in this literature review.

Amendment August 2017
An erratum was issued for Mytton et al (2014) in BMC Public Health (2017) 17:662 (Mytton et al. 2017). The results have been updated in this literature review.

The table below indicates the available evidence type against each exposure.

Table 23 Types of available evidence – Fruit and vegetables

Type of available evidence			
Exposure	**Type of available evidence**	**Children**	**Adults**
Fruits	Meta-analyses of RCTs	N	N
	Meta-analyses of prospective cohort studies	N	Y
	Single RCTs	N	N
	Single prospective cohort studies	Y	Y
Vegetables	Meta-analyses of RCTs	N	N
	Meta-analyses of prospective cohort studies	N	Y
	Single RCTs	N	N

	Single prospective cohort studies	Y	Y
Fruit and veg combined	Meta-analyses of RCTs	N	Y
	Meta-analyses of prospective cohort studies	N	Y
	Single RCTs	N	Y
	Single prospective cohort studies	Y	Y
Dietary flavonoids	Meta-analysis of prospective cohort studies	N	Y

2. Children

The evidence relating to intake of (i) fruits, (ii) vegetables, and (iii) fruits and vegetables combined and adiposity in children is presented below.

2.1 Fruits

2.1.1 Meta-analyses of RCTs in children

Nil

2.1.2 Meta-analyses of prospective cohort studies in children

Nil

2.1.3 RCTs in children, not included in meta-analyses

Nil

2.1.4 Prospective cohort studies in children, not included in meta-analyses

Table 24 Results of individual prospective cohort studies in children – Fruit

Children – Fruits					
Prospective cohort studies					
SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI z score change	Field et al. 2003 Summerbell et al (2009) *and* USDA (2010c)	Per serving intake of fruit *(girls)* 3 years	Beta coefficient	**0.001 (-0.001, 0.003)** Additionally adjusted for energy: **0.005 (0.003, 0.007)** **+VE**	8,203
		Per serving intake of fruit *(boys)* 3 years	Beta coefficient	**-0.001 (-0.004, 0.001)** Additionally adjusted for energy: **0.001 (-0.001, 0.004)** **INV**	6,715
	Faith et al. 2006 USDA (2010c)	Fruit intake, servings per day 2 years	Beta coefficient	**0.01 SE±0.002** p=0.76 **+VE**	825
Weight change	Newby et al. 2003b USDA (2010c)	Per serving of fruit per day One year	Beta coefficient	**0.03 SE±0.03 kg per year** p=0.32 Additionally adjusted for energy **0.04 SE±0.03** p=0.17 **+VE**	1,379

Three prospective cohort studies investigated the association between fruit intake and adiposity in children, reporting four results across two outcomes: BMI z score change and weight change. None of the studies reported significant results. However, Field et al (2003) reported a significant positive association between fruit intake and BMI z score in girls when using the model which adjusted for energy intake. The ages of the children varied between studies: 9–14 years (Field et al 2003); 1–5 years (Faith et al 2006); and 2–5 years (Newby et al 2003).

2.2 Vegetables

2.2.1 Meta-analyses of RCTs in children

Nil

2.2.2 Meta-analyses of prospective cohort studies in children

Nil

2.2.3 RCTs in children, not included in meta-analyses

Nil

2.2.4 Prospective cohort studies in children, not included in meta-analyses

Table 25 Results of individual prospective cohort studies in children – Vegetables

Children – Vegetables					
Prospective cohort studies					
SE=standard error; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI z score change	Field et al. 2003 Summerbell et al (2009) *and* USDA (2010c)	Per serving intake of veg *(girls)* 3 years	Beta coefficient	**0.000 (-0.001, 0.001)** NIL Additionally adjusted for energy: **0.003 (0.001, 0.004)** +VE	8,203
		Per serving intake of veg *(boys)* 3 years	Beta coefficient	**-0.003 (-0.004, -0.001)** INV Additionally adjusted for energy: **-0.000 (-0.002, 0.001)** NIL	6,715
	Faith et al. 2006 USDA (2010c)	Veg intake, servings per day 2 years	Beta coefficient	**-0.002 SE±0.002** p=0.52 INV	825
Weight change	Newby et al. 2003b USDA (2010c)	Per additional serving of veg One year	MD	**0.06 SE±0.03 kg per year** p=0.06 +VE Additionally adjusted for energy: **0.09 SE±0.04** p=0.02 +VE	1,379

Three prospective cohort studies across two reviews investigated the association between vegetable intake and adiposity in children, reporting four results across two outcomes: BMI z score change and weight change. One result (Field et al 2003) reported a significant inverse association between vegetable intake and BMI z score change in boys; the significance was lost when using the model which additionally adjusted for energy intake. The positive association for girls observed by Field et al (2003) was only significant after adjusting for energy intake; this was the same for the result from Newby et al (2003). Faith et al (2006) reported a non-significant inverse association, with lower BMI z scores with increased servings of vegetables.

2.3 Fruits and vegetables combined

2.3.1 Meta-analyses of RCTs in children

Nil

2.3.2 Meta-analyses of prospective cohort studies in children

Nil

2.3.3 RCTs in children, not included in meta-analyses

Nil

2.3.4 Prospective cohort studies in children, not included in meta-analyses

Table 26 Results of individual prospective cohort studies in children – Fruit and vegetables combined

Children – Fruits and vegetables combined					
Prospective cohort studies					
r=correlation coefficient. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI z score change	Field et al. 2003 Summerbell et al (2009) *and* USDA (2010c)	Per serving intake of fruits and veg *(girls)* 3 years	Beta coefficient	**-0.000 (-0.001, 0.001)** **NIL** Additionally adjusted for energy: **0.002 (0.001, 0.003)** **+VE**	8,203
		Per serving intake of fruits and veg *(boys)* 3 years	Beta coefficient	**-0.001 (-0.002, 0.000)** **INV** Additionally adjusted for energy: **0.000 (-0.000, 0.001)** **NIL**	6,715
Weight change	Kaikkonen et al. 2015 Schwingshakl et al (2015)	Monthly portions of fruits and veg *(girls)* 21 years	**r = -0.01 over 6 years** Significance level not reported **INV**		875
		Monthly portions of fruits and veg *(boys)* 21 years	**r = -0.03 over 6 years** Significance level not reported **INV**		761

Two prospective cohort studies investigated the association between fruit and vegetable intake combined and adiposity in children, reporting four results across two outcomes: BMI z score change and weight change. Neither study reported significant results; however, one (Field et al 2003) reported a significant, positive association in boys when additionally adjusting for energy intake. The study by Kaikkonen et al (2015) recruited participants aged 3, 6, 9, 12, 15, and 18 years and followed them all into adulthood over 21 subsequent years.

3. Adults

The evidence relating to intake of (i) fruits, (ii) vegetables, and (iii) fruits and vegetables and adiposity in adults is presented below.

3.1 Fruit

3.1.1 Meta-analyses of RCTs in adults

Nil

3.1.2 Meta-analyses of prospective cohort studies in adults

Table 27 Meta-analyses of prospective cohort studies in adults – Fruit

Adults – Fruits					
Meta-analyses of prospective cohort studies					
MD=mean difference; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Weight change	Bertoia et al (2015)	Per daily serving of fruits over a four year period 24 years	MD	**-0.53 (-0.61, -0.44) lb** **INV**	Studies=3; n=117,918 I^2=not reported
	Schwingshakl et al (2015)	Per additional 100g intake of fruits per day over one year period 5–20 years	Beta coefficient	**-13.68 (-22.97, -4.40) g** **INV**	Studies=5; n=354,880 I^2=96%
Waist circumference	Schwingshakl et al (2015)	Increased fruit consumption (per whole fruit or per 100kcal higher intake) over one year period 5.5–5.9 years	Beta coefficient	**-0.04 (-0.05, -0.02) cm** **INV**	Studies=2; n=48,879 I^2=29%
Odds of weight gain or overweight	Schwingshakl et al (2015)	Highest intake categories of fruits 3 – 17 years	OR	**0.83 (0.71, 0.99)** **INV**	Studies=4; n=93,266 I^2=28%

Two reviews conducted four meta-analyses of prospective cohort studies in adults investigating fruit intake and adiposity; all reported significant inverse associations.

Bertoia et al 2015 conducted a meta-analysis investigating the effect of each daily serving of fruit on weight over a four year period and reported a significant association. This meta-analysis used the Nurse's Health Study I, the Nurse's Healthy Study II, and the Health Professions Follow up Study, plus one additional cohort also conducted in North America.

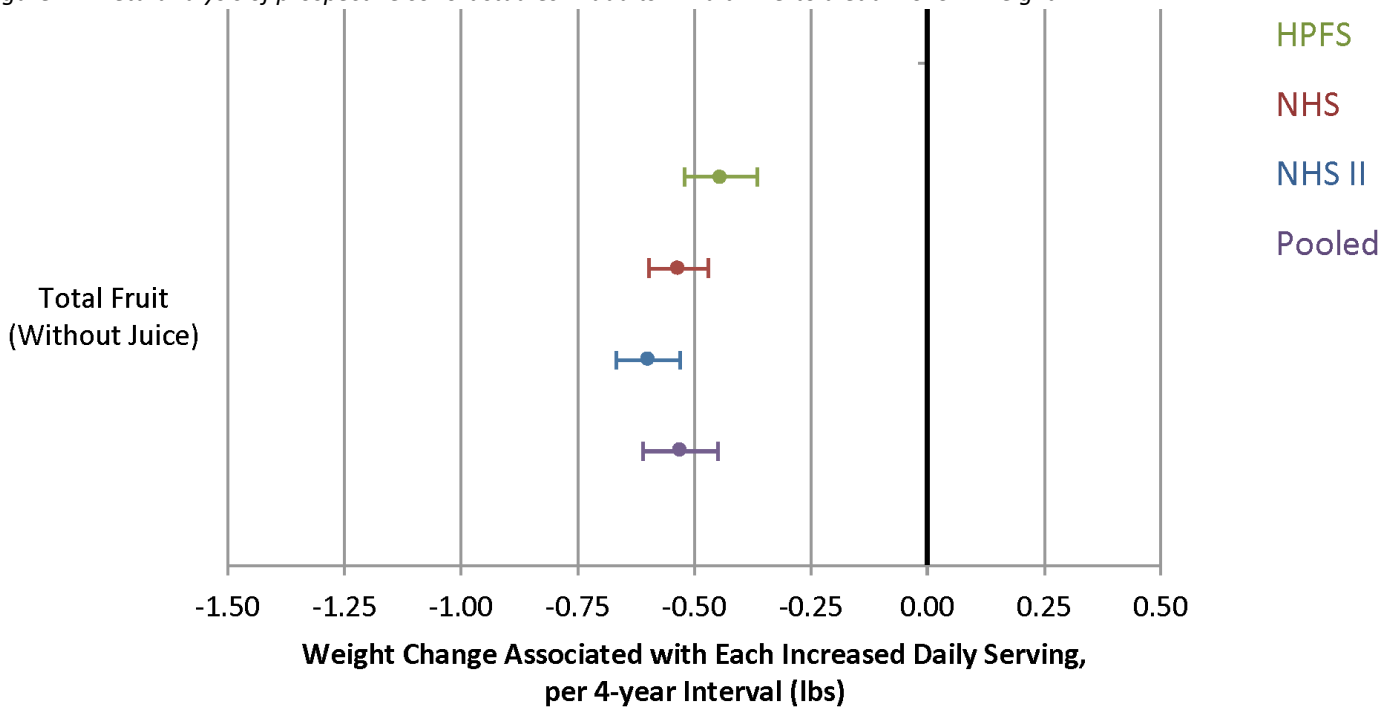
Another review (Schwingshakl et al 2015) conducted three meta-analyses investigating the effect of fruit intake on adiposity in adults with respect to weight, waist circumference, and odds of weight gain or overweight; all reported significant, protective associations.

The corresponding forest plots are presented below.

Adults | Prospective cohort studies | Weight | Bertoia et al 2015 | Per daily serving of fruit

Relationships between changes in total vegetable and total fruit intake and weight change over 4 y in three cohorts. Total fruit (without juice): raisins, grapes, avocados, bananas, cantaloupe, watermelon, apples, pears, peaches (fresh or canned), apricots (fresh or canned), plums (fresh or canned), strawberries, blueberries, prunes, oranges, grapefruit (fresh or juice). Adjusted for baseline age and BMI and change in the following lifestyle variables: smoking status, physical activity, hours of sitting or watching TV, hours of sleep, fried potatoes, juice, whole grains, refined grains, fried foods, nuts, whole-fat dairy, low-fat dairy, sugar-sweetened beverages, sweets, processed meats, non-processed meats, trans fat, alcohol, and seafood (Bertoia et al 2015).

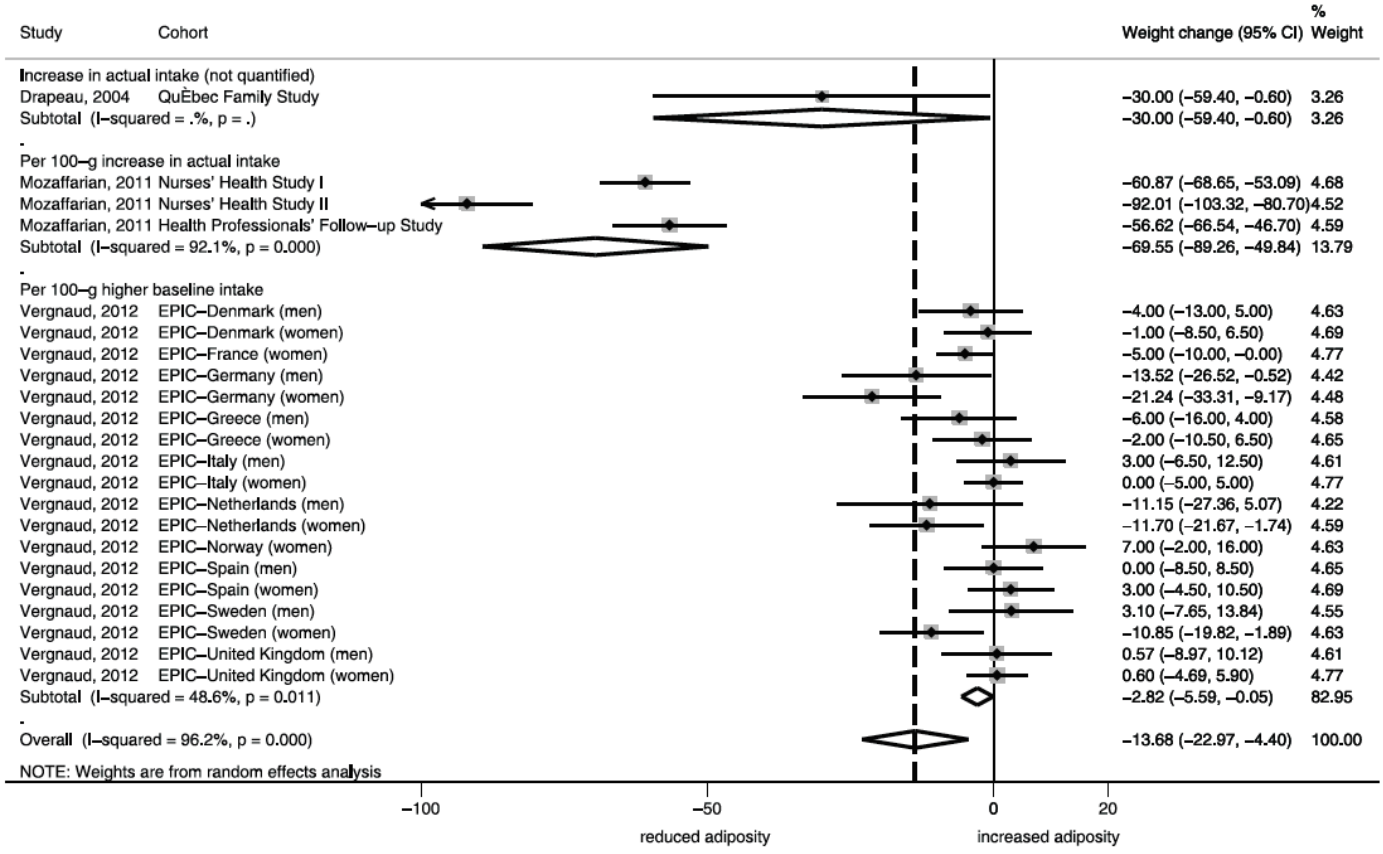
Figure 17 Meta-analysis of prospective cohort studies in adults – Fruit – Bertoia et al 2015 – Weight



Adults | Prospective cohort studies | Weight | Schwingshakl et al 2015 | Per additional 100g intake of fruit

Forest plot of associations between changes in body weight (g/year) and fruit consumption in cohort studies of adults (Schwingshakl et al 2015).

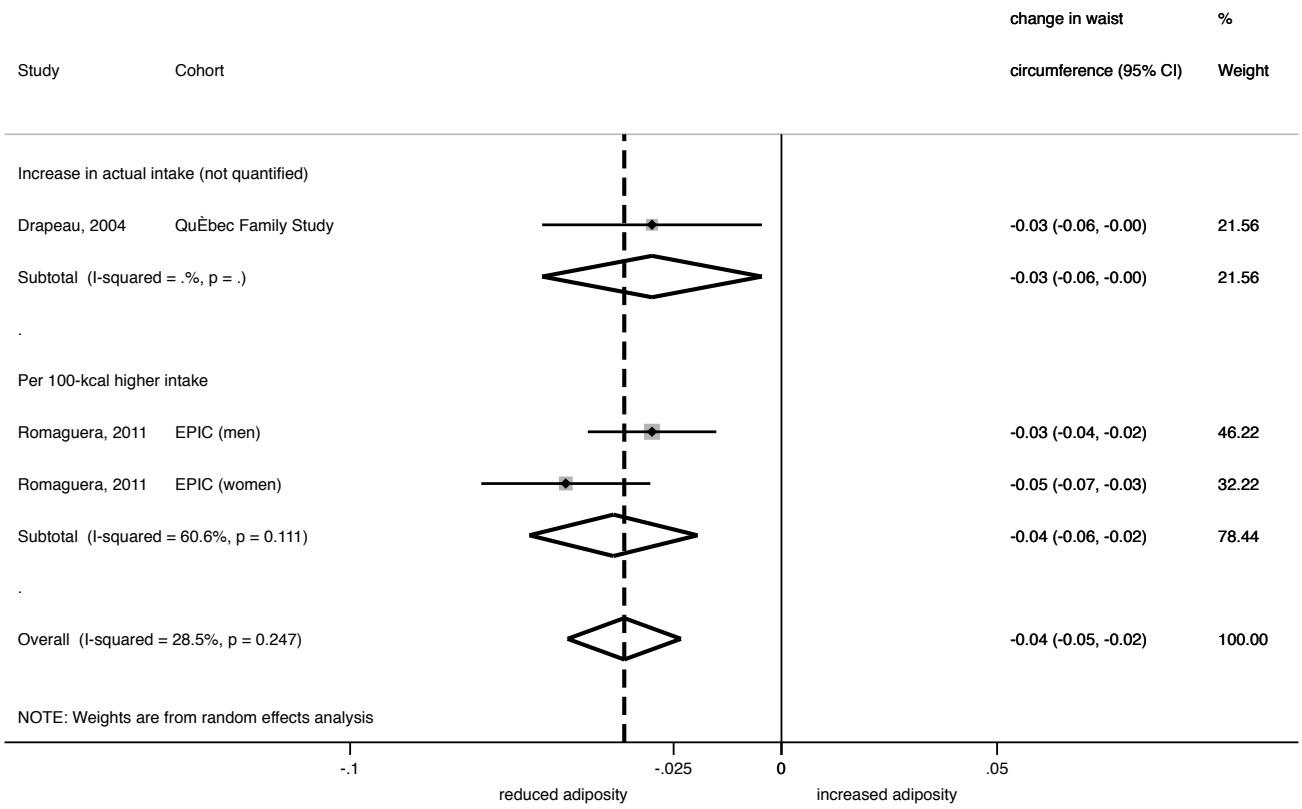
Figure 18 Meta-analysis of prospective cohort studies in adults – Fruit – Schwingshakl et al 2015 – Weight



Adults | Prospective cohort studies | Waist circumference | Schwingshakl et al 2015 | Increased fruit consumption

Forest plot of association between changes in waist circumference (cm/year) and fruit consumption in cohort studies of adults (Schwingshakl et al 2015).

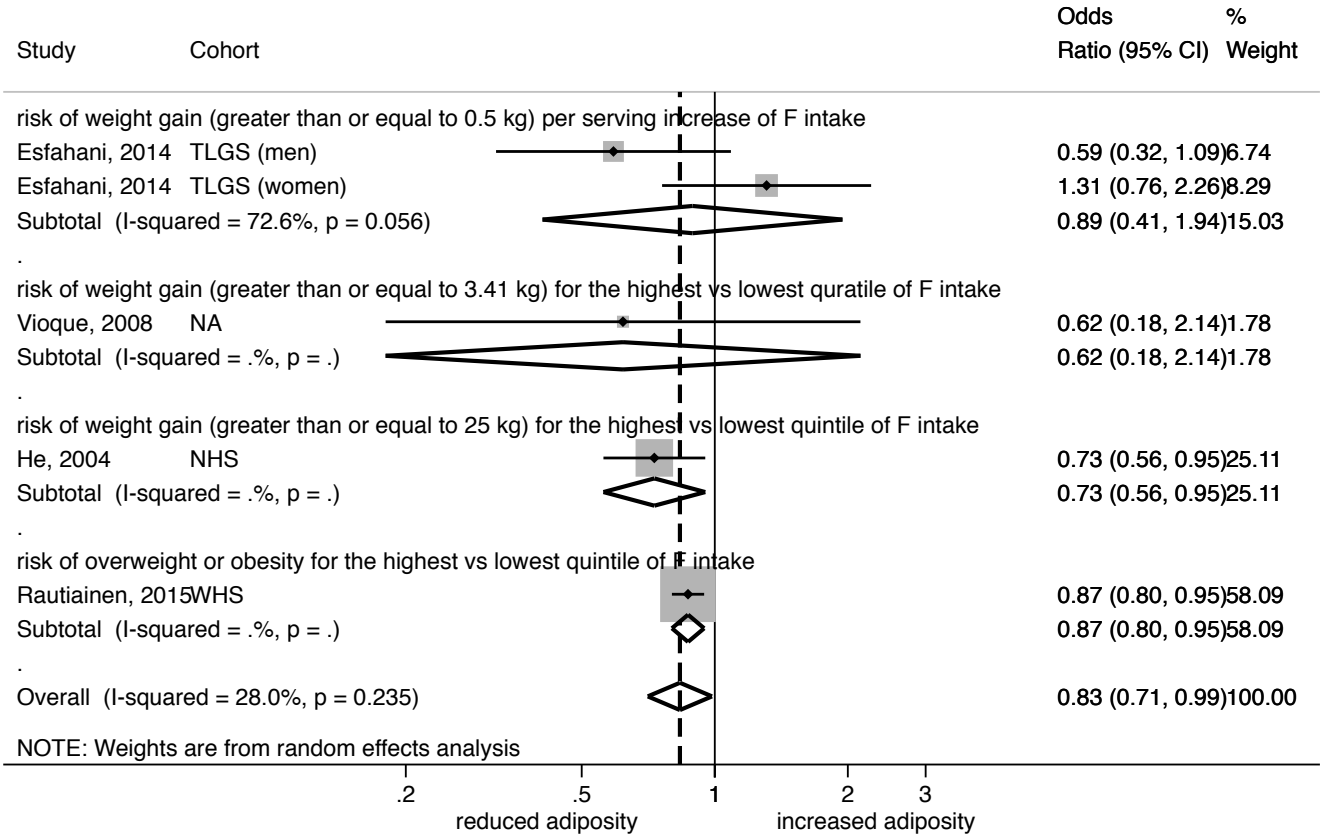
Figure 19 Meta-analysis of prospective cohort studies in adults – Fruit – Schwingshakl et al 2015 – Waist circumference



Adults | Prospective cohort studies | Odds of weight gain or overweight | Schwingshakl et al 2015 | Highest intake categories of fruit

Forest plot showing pooled odds ratio with 95% confidence intervals for weight gain / overweight, (abdominal) obesity comparing categories of fruit intakes (Schwingshakl et al 2015).

Figure 20 Meta-analysis of prospective cohort studies in adults – Fruit – Schwingshakl et al 2015 – Odds of weight gain or overweight



3.1.3 RCTs in adults, not included in meta-analyses

Nil

3.1.4 Prospective cohort studies in adults, not included in meta-analyses

Table 28 Results of individual prospective cohort studies in adults – Fruit

Adults – Fruits					
Prospective cohort studies					
OR = odds ratio; SE = standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Parker et al. 1997 Summerbell et al (2009)	Servings of fruit per week 4 years	Regression coefficient	**0.4001 SE±0.2973** p=0.17 **+VE**	465
	Sanchez-Villegas et al. 2006 Schwingshakl et al (2015) *and* Summerbell et al (2009)	Tertiles of fruit intake g per day (Lowest <189.2; Middle 189.2-355; Highest >355) 28 months	Lowest tertile: **0.77 (0.61, 0.93) kg** Middle tertile: **0.76 (0.53, 0.99) kg** Highest tertile: **0.68 (0.44, 0.93) kg** p for trend=0.46 **INV**		6,319
BMI change	de Munter et al. 2015 Schwingshakl et al (2015)	Increased intake fruit from less than daily (<1) to daily (≥1 serving) *(females)* 8 years	Beta coefficient	**0.02 (-0.08, 0.12)** **+VE**	9,461
		Increased intake fruit from less than daily (<1) to daily (≥1 serving) *(males)* 8 years	Beta coefficient	**-0.07 (-0.16, 0.02)** **INV**	7,249
Weight gain (>2kg/year)	Schulz et al. 2002 Summerbell et al (2009)	Per additional 100g intake of fruit per day *(female)* 2.2 years	OR	**0.94 (0.86, 1.02)** **INV**	11,005
		Per additional 100g intake of fruit per day *(male)* 2.2 years	OR	**0.94 (0.83, 1.05)** **INV**	6,364
Weight gain (<2kg/year)		Per additional 100g intake of fruit per day *(female)* 2.2 years	OR	**0.94 (0.88, 1.00)** **INV**	11,005
		Per additional 100g intake of fruit per day *(male)* 2.2 years	OR	**1.04 (0.96, 1.13)** **+VE**	6,364
Weight loss (<2kg/year)		Per additional 100g intake of fruit per day *(female)* 2.2 years	OR	**1.01 (0.95, 1.07)** **INV**	11,005
		Per additional 100g intake of fruit per day *(male)* 2.2 years	OR	**1.05 (0.97, 1.13)** **INV**	6,364
Weight loss (>2kg/year)		Per additional 100g intake of fruit per day *(female)* 2.2 years	OR	**1.03 (0.97, 1.11)** **INV**	11,005
		Per additional 100g intake of fruit per day *(male)* 2.2 years	OR	**1.03 (0.93, 1.14)** **INV**	6,364

Four prospective cohort studies investigated fruit intake and adiposity in adults, reporting 12 results across four outcomes: BMI change; weight change; odds of weight gain (>2kg/year and <2kg/year); and odds of weight loss (>2kg/year and <2kg/year). Nine results reported an inverse association and three reported a positive association. None of the results were statistically significant; however one result from Schulz et al (2002) reported a borderline significant 6% reduced risk of a small weight gain per 100g of fruit per day for women.

3.2 Vegetables

3.2.1 Meta-analyses of RCTs in adults

Nil

3.2.2 Meta-analyses of prospective cohort studies in adults

Table 29 Meta-analyses of prospective cohort studies in adults – Vegetables

Adults – Vegetables					
Meta-analyses of prospective cohorts					
MD=mean difference; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Weight change	Bertoia et al (2015)	Per daily serving of veg over a four year period 24 years	MD	**-0.25 (-0.35, -0.14) lb** **INV**	Studies=3; n=117,918 I^2=not reported
	Schwingshakl et al (2015)	Per additional 100g intake of veg per day over one year period 5–20 years	Regression coefficient	**1.69 (-10.37, 13.74) g** **+VE**	Studies=4; n=354,632 I^2=97%
Odds of weight gain or overweight	Schwingshakl et al (2015)	Highest vs. lowest intakes of veg (varied category thresholds) 3–17 years	OR	**0.83 (0.70, 0.99)** **INV**	Studies=5; n=172,502 I^2=75%

Three meta-analyses, from two reviews (Bertoia et al 2015 and Schwingshakl et al 2015), investigated the effect of vegetable intake on weight change and odds of weight gain or overweight. Two results reported significant inverse associations; one reported a non-significant positive association.

Bertoia et al (2015) and Schwingshakl et al (2015) both use the Nurses' Health Study I, the Nurses' Health Study II, and the Health Professionals' Follow-up Study in their meta-analyses reporting on weight change; however, Schwingshakl et al (2015) also include data from the EPIC cohort, as reported by Vergnaud et al. 2012. Schwingshakl et al (2015)'s meta-analysis reporting the odds of weight gain or overweight had no study overlap with the other two meta-analyses. Bertoia et al (2015) included fresh potatoes in their categorisation of vegetable intake.

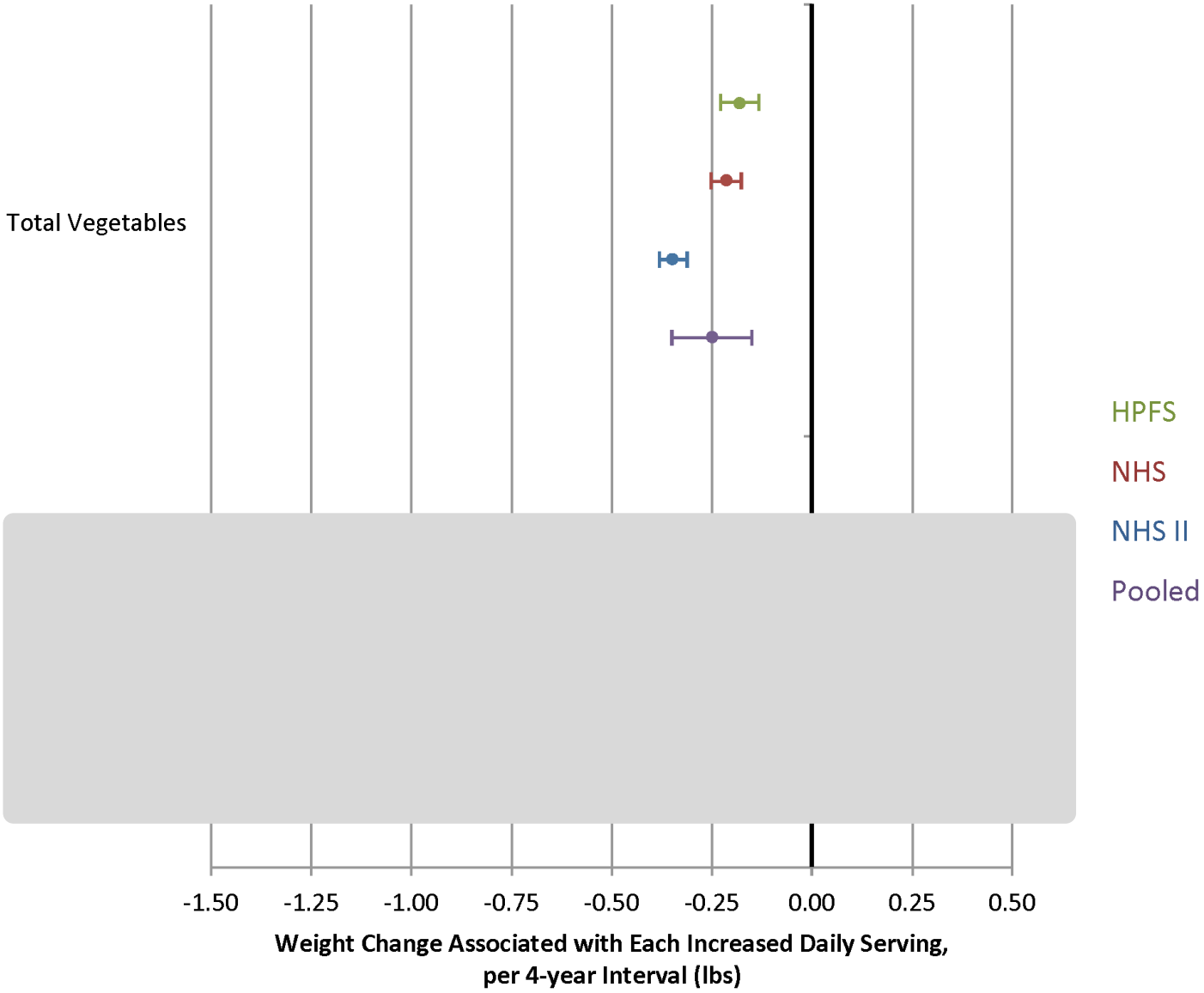
The corresponding forest plots are presented below.

Adults | Prospective cohort studies | Weight | Bertoia et al 2015 | Per daily serving of vegetables

Relationships between changes in total vegetable and total fruit intake and weight change over 4 y in three cohorts. Total vegetables: string beans, broccoli, cabbage/coleslaw, cauliflower, Brussels sprouts, carrots (raw, cooked, or juice), corn, peas, lima beans, mixed vegetables or vegetable soup, beans, lentils, celery, squash, eggplant, zucchini, yams, sweet potatoes, baked/boiled/mashed potatoes, spinach, kale, mustard or chard greens, iceberg or head lettuce, romaine or leaf lettuce, peppers, tomatoes, onions, tofu and soy (soy burger, soybeans, miso, or other soy protein) (Bertoia et al 2015).

Please note – rectangular grey box is placed to obscure the pooled results for fruit (presented in Section 3.2.1.2)

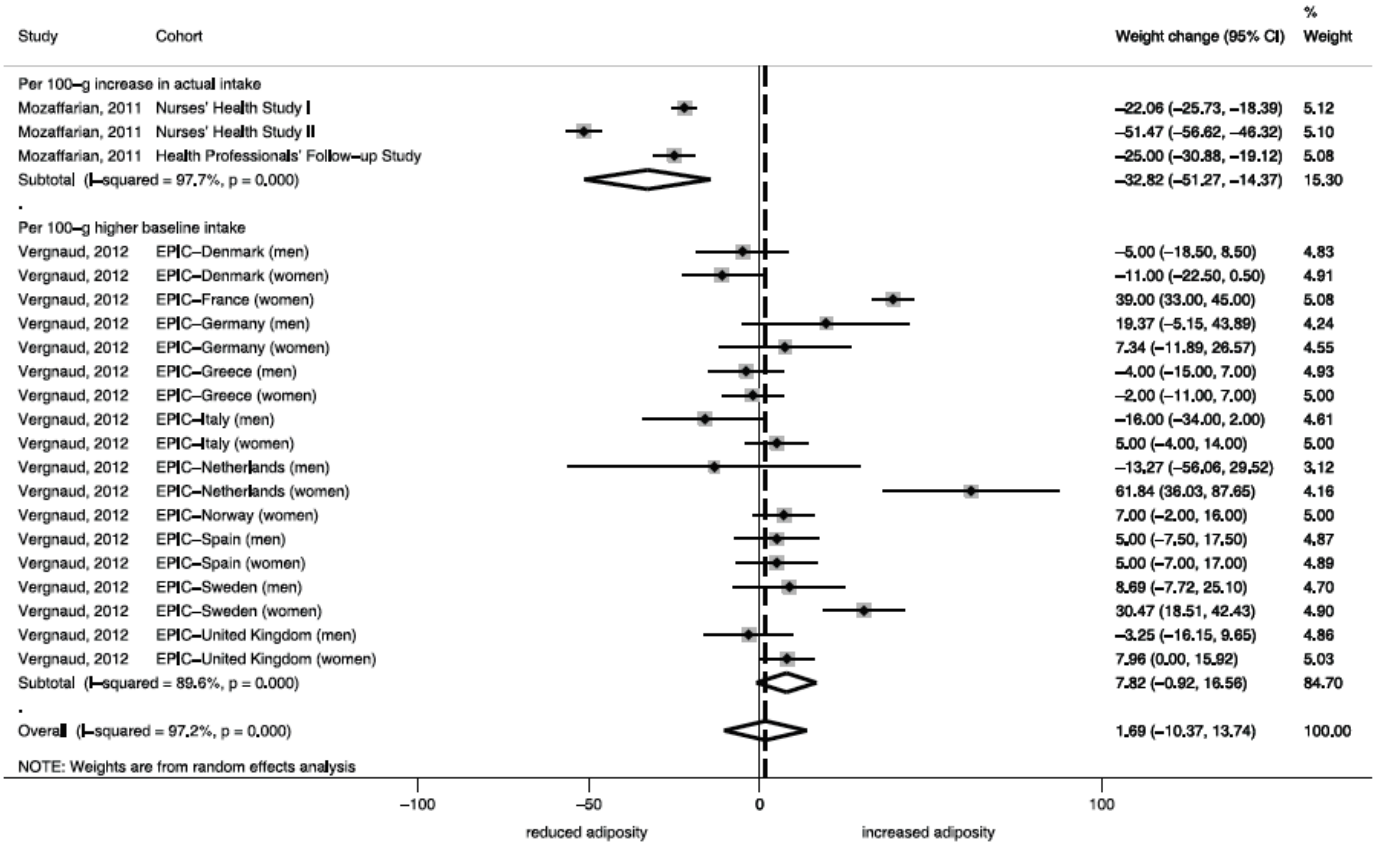
Figure 21 Meta-analysis of prospective cohort studies in adults – Vegetables – Bertoia et al 2015 – Weight



Adults | Prospective cohort studies | Weight | Schwingshakl et al 2015 | Per additional 100g intake of vegetables

Forest plot of associations between changes in body weight (g/year) and vegetable consumption in cohort studies of adults (Schwingshakl et al 2015).

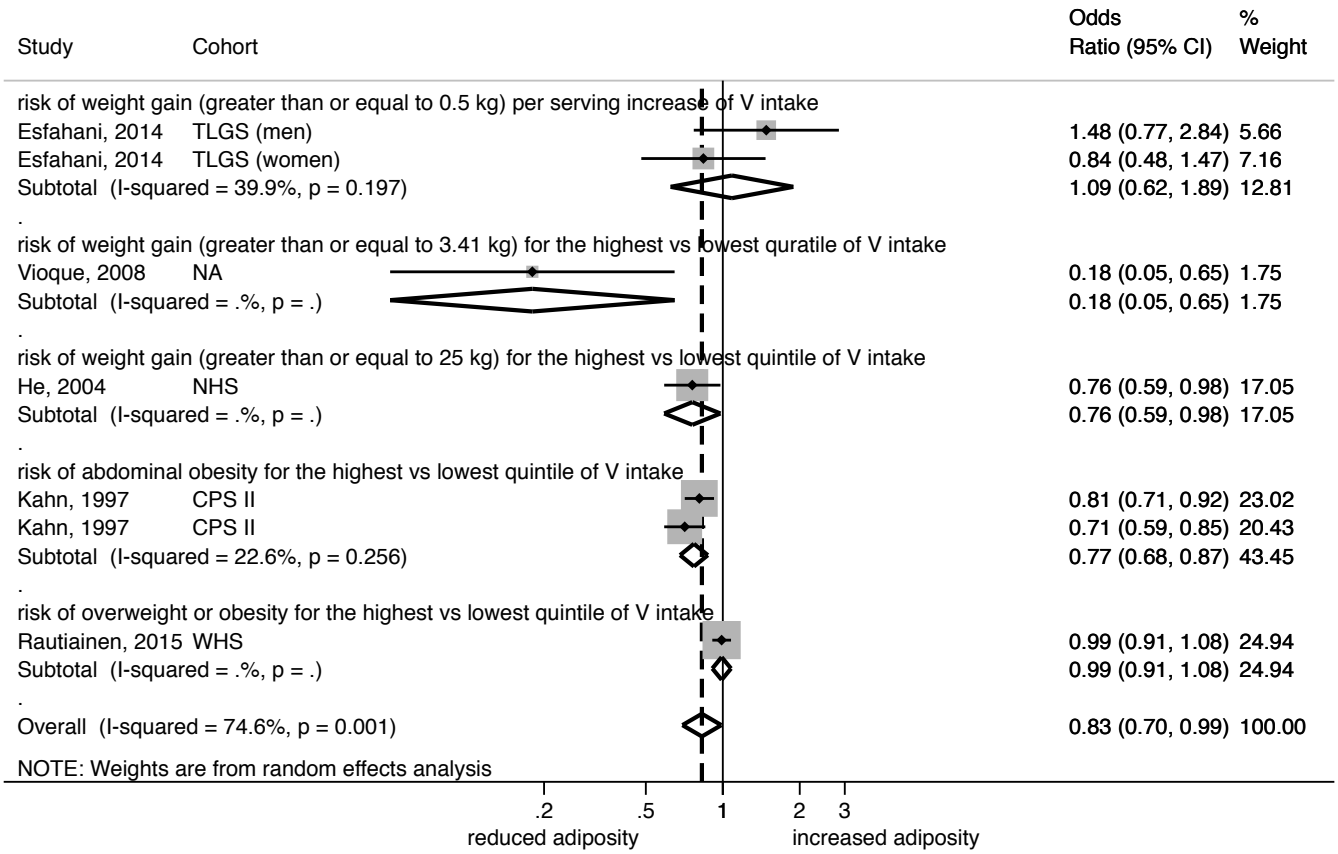
Figure 22 Meta-analysis of prospective cohort studies in adults – Vegetables – Schwingshakl et al 2015 – Weight



Adults | Prospective cohort studies | Odds of weight gain or overweight | Schwingshakl et al 2015 | Highest vs. lowest intakes of vegetables

Forest plot showing pooled odds ration with 95% confidence intervals for weight gain/overweight, (abdominal) obesity comparing categories of vegetable intakes (Schwingshakl et al 2015).

Figure 23 Meta-analysis of prospective cohort studies in adults – Vegetables – Schwingshakl et al 2015 – Odds of weight gain or overweight



3.2.3 RCTs in adults, not included in meta-analyses

Nil

3.2.4 Prospective cohort studies in adults, not included in meta-analyses

Table 30 Results of individual prospective cohort studies in adults – Vegetables

Adults – Vegetables					
Prospective cohort studies					
MD=mean difference; OR=odds ratio; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** *Review*	***Exposure description***	***Results***		***n***
BMI change	Kahn et al. 1997 Tohill et al 2004	Highest vs. lowest quintile of vegetable intake *(female)* 10 years	MD	**-0.12 SE± 0.05** p=0.009 **INV**	44,080
		Highest vs. lowest quintile of vegetable intake *(male)* 10 years	MD	**-0.12 SE± 0.05** p=0.012 **INV**	35,156
Weight change	Parker et al. 1997 Summerbell et al (2009)	Servings of veg per week 4 years	Beta coefficient	**-0.0502 SE± 0.3487** p=0.89 **INV**	465
	Sanchez-Villegas et al. 2006 Schwingshakl et al (2015) *and* Summerbell et al (2009)	Tertiles of veg intake g per day (Lowest <356.8; Middle 356.8-567.4; Highest >567.4) 5 years	Lowest tertile: **0.73 (0.57, 0.89) kg** Middle tertile: **0.61 (0.38, 0.84) kg** Highest tertile: **0.69 (0.45. 0.94) kg** p for trend=0.88 **INV**		6,319
Weight gain (>2kg/year)	Schulz et al. 2002 Summerbell et al (2009)	Per additional 100g intake of veg per day *(female)* 2.2 years	OR	**0.99 (0.88, 1.10)** **INV**	11,005
		Per additional 100g intake of veg per day *(male)* 2.2 years	OR	**0.98 (0.85, 1.14)** **INV**	6,364
Weight gain (<2kg/year)		Per additional 100g intake of veg per day *(female)* 2.2 years	OR	**0.90 (0.82, 0.98)** **INV**	11,005
		Per additional 100g intake of veg per day *(male)* 2.2 years	OR	**1.05 (0.94, 1.17)** **+VE**	6,364
Weight loss (<2kg/year)		Per additional 100g intake of veg per day *(female)* 2.2 years	OR	**1.02 (0.94, 1.11)** **INV**	11,005
		Per additional 100g intake of veg per day *(male)* 2.2 years	OR	**1.00 (0.89, 1.11)** **NIL**	6,364
Weight loss (>2kg/year)		Per additional 100g intake of veg per day *(female)* 2.2 years	OR	**1.01 (0.92, 1.11)** **INV**	11,005
		Per additional 100g intake of veg per day *(male)* 2.2 years	OR	**0.99 (0.87, 1.13)** **+VE**	6,364
Odds of "weight gain at the waist"	Kahn et al. 1997 Tohill et al 2004	Highest vs. lowest quintile of vegetable intake *(female)* 10 years	OR	**0.71 (0.59, 0.86)** **INV**	44,080
		Highest vs. lowest quintile of vegetable intake *(male)* 10 years	OR	**0.81 (0.71, 0.93)** **INV**	35,156
Likelihood of eating cruciferous veg	Adams et al. 2007 Summerbell et al (2009)	Women in the BMI-gain group One year	OR	**0.15 (0.05, 0.52)** **INV**	116

Five prospective cohort studies investigated vegetable intake and adiposity in adults, reporting 15 results across six outcomes: BMI change; weight change; odds of weight gain (>2kg/year and <2kg/year); odds of weight loss (>2kg/year and <2kg/year); odds of "weight gain at the waist"; and odds of eating cruciferous vegetables (with respect to adiposity category). Twelve results reported an inverse association, six of which were statistically significant. Two results reported a positive association (neither statistically significant) and one reported no association.

The result from Adams (2007) reported that women categorised in the 'BMI-gain' group at follow up were significantly less likely to eat cruciferous vegetables over the preceding year.

3.3 Fruit and vegetables combined

3.3.1 Meta-analyses of RCTs in adults

Table 31 Meta-analyses of RCTs in adults – Fruit and vegetables combined

Adults – Fruits and vegetables combined					
Meta-analyses of RCTs					
SMD=standardised mean difference; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Kaiser et al (2016)	Increased fruit and veg intake (varied interventions) vs. control 8–10 weeks	SMD	**-0.16 (-0.78, 0.46)** **INV**	Studies=2; n=135 I^2=49%
		Increased fruit and veg intake (varied interventions) vs. control 8 weeks–6 months	SMD	**0.04 (-0.10, 0.17)** **+VE**	Studies=7; n=1,149 I^2=5%
	Mytton et al (2014)*	Increased fruit and veg intake (50–465g/day; varied interventions) vs. control 4–52 weeks	MD	**-0.54 (-1.05, -0.04) kg** **INV**	Studies=7; n=1,026 I^2=73%
*Please note that an erratum was issued for Mytton et al (2014) in BMC Public Health (2017) 17:662 (Mytton et al. 2017). The results have been updated in this literature review.					

Two published reviews (Kaiser et al 2016 and Mytton et al 2014) conducted three meta-analyses investigating the effect of increased fruit and vegetable intake on changes in body weight. Two results reported inverse effects (one was significant) and one result reported a non-significant positive effect.

- Kaiser et al (2016) conducted their first meta-analysis with two studies which met all their inclusion criteria; they then conducted a second meta-analysis with five additional studies which met all but one of their inclusion criteria. With two studies, the result indicated an inverse association between fruit and vegetable intake and adiposity; with seven studies, the result indicated a positive association between fruit and vegetable intake and adiposity. Neither result was statistically significant.
- Mytton et al (2014) conducted a meta-analysis with seven studies, one of which was also included in both the Kaiser et al (2016) meta-analyses. A significant inverse effect was reported.
- It appears that discrepancy in inclusion stems from differing inclusion criteria, for example, minimum number of participants and minimum follow up period.

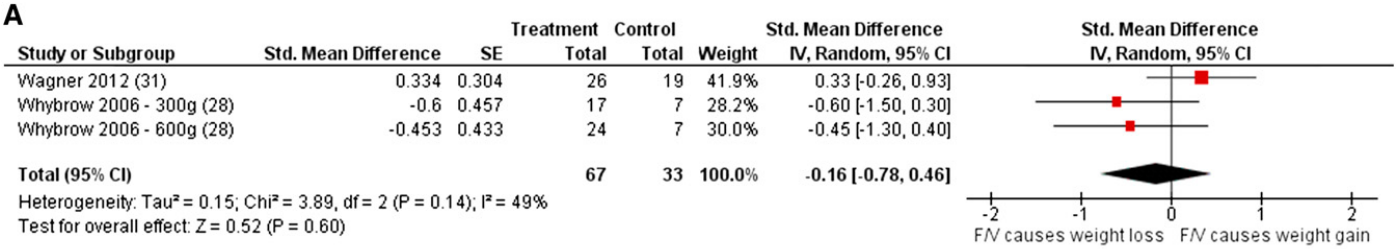
Increased fruit and vegetable intake was achieved through a variety of interventions across all the studies: dietary advice to increase intake; direct provision of whole fruits and vegetables; provision of a store card to buy fruits and vegetables; behavioural interventions. The interventions for four of the seven studies included in the Mytton et al (2014) meta-analysis were focused on fruit intake.

The corresponding forest plots are presented below.

Adults | RCTs | Weight | Kaiser et al 2016 | Increased fruit and vegetable intake (studies=2)

Forest plot of F/V randomized trials that met all inclusion criteria by using Std. mean differences. Overall r^2 = 0.0056. Squares indicate the mean treatment effect expressed as the standardized mean difference between treatment and control (the width of the line extending to each side represents the 95% confidence interval of the standardized mean difference). Diamonds indicate the summary statistic (standardized mean difference) of all studies combined and the width represents the 95% confidence interval of the summary statistic. F/V, fruit and vegetable; IV, inverse variance; Std., standardized (Kaiser et al 2016).

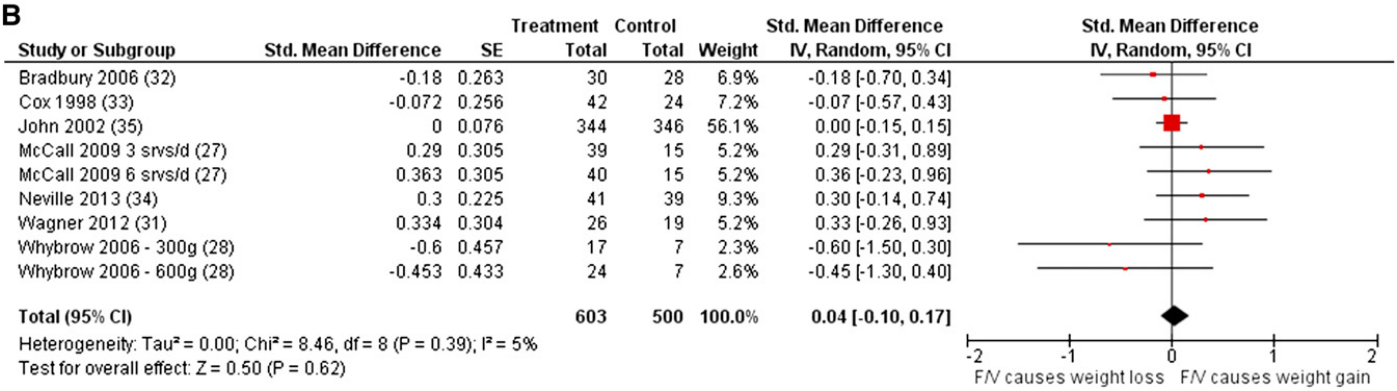
Figure 24 Meta-analysis of RCTs (n=2) in adults – Fruit and vegetables – Kaiser et al 2016 – Weight



Adults | RCTs | Weight | Kaiser et al 2016 | Increased fruit and vegetable intake (studies=7)

Forest plot of F/V randomized trials that met all inclusion criteria by using Std. mean differences plus additional studies that met all criteria except for not explicitly stating weight as an outcome of interest. Overall **r**2 = 0.0004. Squares indicate the mean treatment effect expressed as the standardized mean difference between treatment and control (the width of the line extending to each side represents the 95% confidence interval of the standardized mean difference). Diamonds indicate the summary statistic (standardized mean difference) of all studies combined and the width represents the 95% confidence interval of the summary statistic. F/V, fruit and vegetable; IV, inverse variance; Std., standardized (Kaiser et al 2016).

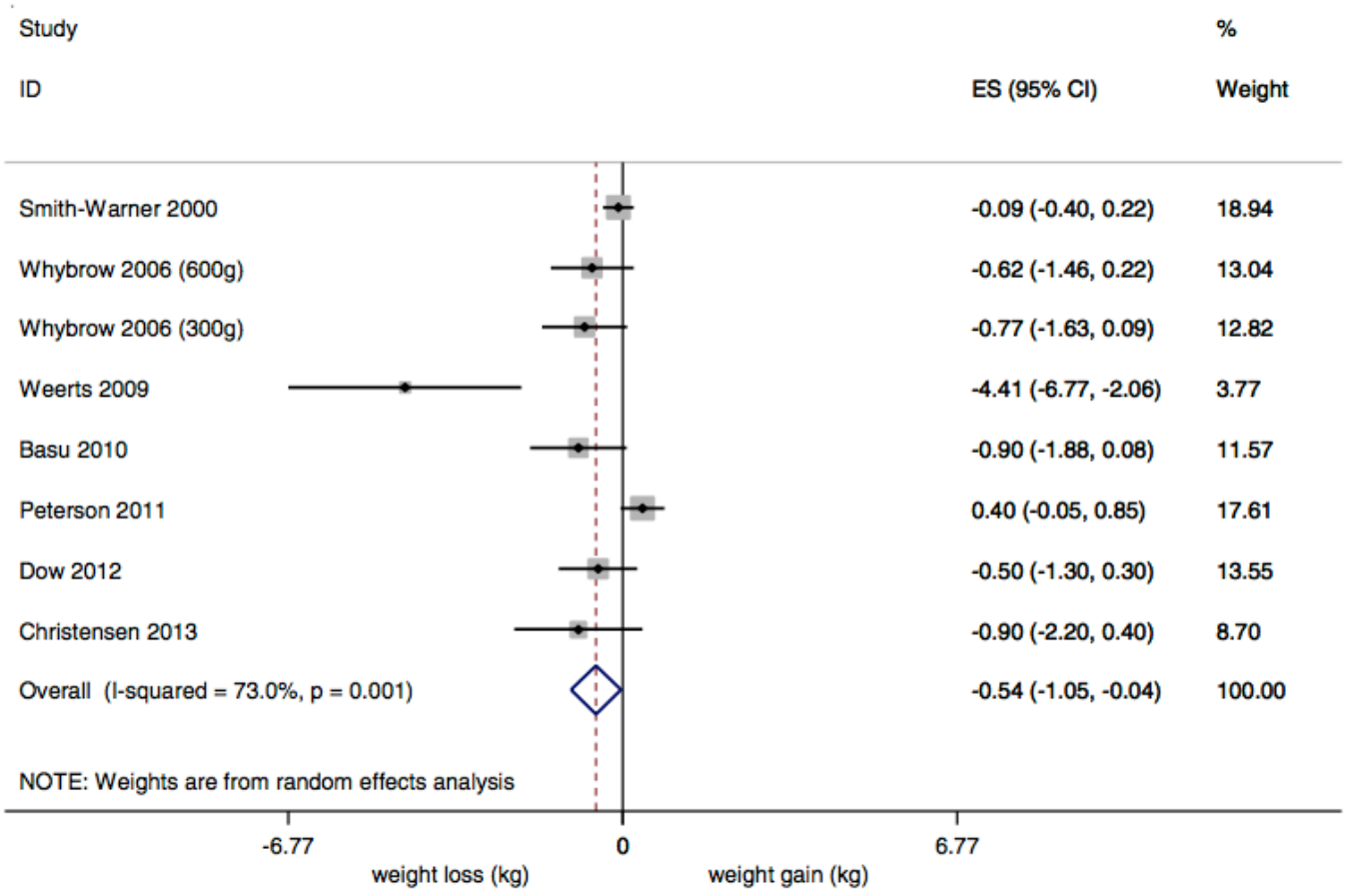
Figure 25 Meta-analysis of RCTs (n=7) in adults – Fruit and vegetables – Kaiser et al 2016 – Weight



Adults | RCTs | Weight | Mytton et al 2014 | Increased fruit and vegetable intake

Revised figure (2a) Meta-analyses of the effect of high vegetable and fruit intake compared to low vegetable and fruit intake on body weight (Amended) (Mytton et al 2017).

Figure 26 Meta-analysis of RCTs in adults – Fruit and vegetables – Mytton et al 2014 – Weight



3.3.2 Meta-analyses of prospective cohort studies in adults

Table 32 Meta-analyses of prospective cohort studies in adults – Fruit and vegetables combined

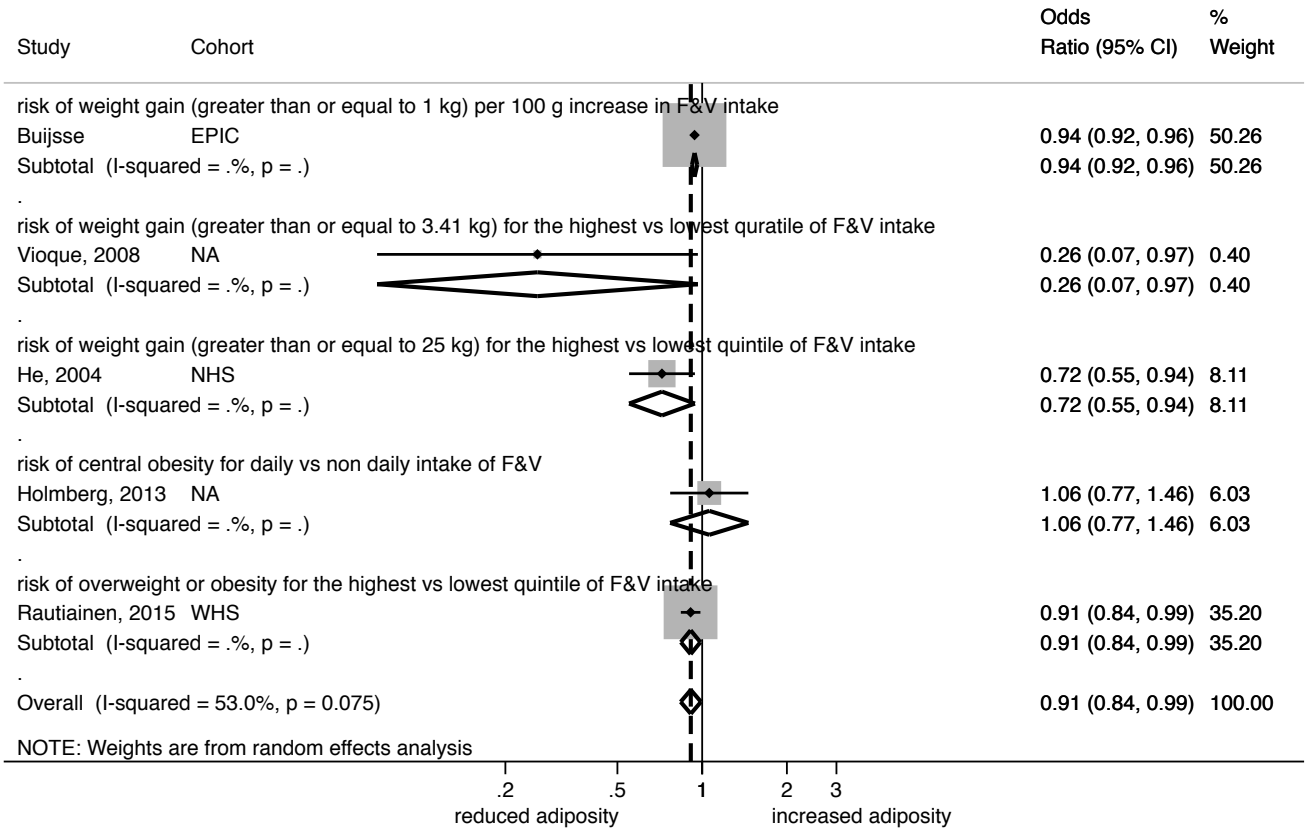
Adults – Fruits and vegetables combined					
Prospective cohort studies					
OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Odds of weight gain or overweight	Schwingshakl et al (2015)	Highest intake categories of fruit and veg 5–17 years	OR	**0.91 (0.84, 0.99)** INV	Studies=5; n=327,492 I^2=53%

One published review conducted a meta-analysis investigating fruit and vegetable intake and odds of weight gain or overweight and reported a significant inverse result. One of five included cohorts was from EPIC, as reported by Buijisse et al (2009). The exposure definition varied between studies: per 100g increase in fruit and vegetable intake; highest vs. lowest quintile intake of fruit and vegetables; quartiles of fruit and vegetable intake; and daily vs. non-daily intake of fruit and vegetables. The threshold for weight gain varied between studies: >1kg; >3.41kg; >25kg; and unspecified. The corresponding forest plot is presented below.

Adults | Prospective cohort studies | Odds of weight gain or overweight | Schwingshakl et al 2015 | Highest intake categories of fruit and vegetable

Forest plot showing pooled odds ration with 95% confidence intervals for weight gain / overweight, (abdominal) obesity comparing categories of fruit and vegetable consumption (Schwingshakl et al 2015).

Figure 27 Meta-analysis of prospective cohort studies in adults – Fruit and vegetables – Schwingshakl et al 2015 – Odds of weight gain or overweight



3.3.3 RCTs in adults, not included in meta-analyses

Table 33 Results of individual RCTs in adults – Fruit and vegetables combined

Adults – Fruits and vegetables combined				
RCTs				
Significant results are highlighted in **red**.				
Outcome	***Publication*** ***Review***	***Intervention description***	***Results***	***n***
BMI	Zino et al. 1997 Kaiser et al (2016)	Eight servings of fruit and veg per day vs. habitual diet 8 weeks	**No significant difference** Specific data on BMI not reported	87
Weight change	Djuric et al. 2006 Kaiser et al (2016)	Low fat diet vs. high fruit and veg diet vs. low fat diet + high fruit and veg diet vs. control One year	Low fat diet: **-5.3 lb** High fruit and veg diet: **5.36 lb** Low fat + high fruit and veg diet: **-2.3 lb** Control: **0.4 lb** Level of significance not reported	122
	Maskarinec et al. 1999 Kaiser et al (2016)	Increased fruit and veg intake to 9 servings per day (dietary counselling and group activities) vs. no intervention 6 months	Intervention: **1 lb** No intervention: **0 lb** Level of significance not reported	29
Unclear	Singh et al. 1992 Mytton et al (2014)	Increased fruit and veg intake (average 294g/day) via dietary advice vs. no intervention 4 weeks	*Results not reported in review; unable to access full text article via PubMed, Imperial College Library, or Google Scholar*	463

Three RCTs investigated combined fruit and vegetable intake and adiposity in adults, providing three results. One result reported no significant effect without reference to direction (Zino et al 1997). Maskarinec et al (1999) reported a significantly higher fruit and vegetable intake in the intervention arm relative to control; however, there were no significant differences in weight within or between groups at baseline or at follow up. The study by Djuric et al (2006) reported a positive effect of a high fruit and vegetable diet but an inverse effect when this was combined with a low fat diet intervention.

One further study was identified in the Mytton et al (2014) review; the review did not provide details of the results and it was not possible to obtain a full text version of the original article, so the results are not reported here.

3.2.3.4 Prospective cohort studies in adults, not included in meta-analyses

Table 34 Results of individual prospective cohort studies in adults – Fruit and vegetables combined

Adults – Fruits and vegetables combined					
Prospective cohort studies					
SD=standard deviation. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI change	Deforche et al. 2015 Schwingshakl et al (2015)	Per increase of one consumption per week of fruit and veg 1.5 years	Beta coefficient	**0.11 (-0.37, 0.60) kg/m²** p=0.65 **+VE**	291
Weight change	Aljadani et al. 2013 Schwingshakl et al (2015)	Highest tertile of intake vs. lowest tertile of intake 6 years	Beta coefficient	**-0.72 (-1.42, -0.03) kg** p=0.041 **INV**	1,356
	Nikolaou et al. 2014 Schwingshakl et al (2015)	Meeting '5-a-day' goal vs. not meeting goal <1 year	Beta coefficient	**0.21 (-0.08, 0.50)** **+VE**	1,275
	Sammel et al. 2003 Summerbell et al (2009)	The sum of servings of fruits, juices, veg, and green salads 4 years	Weight gain >10lb: **3.4 SD±3.3 servings per day** Did not gain >10lb: **4.3 SD±3.7 servings per day** p=0.055 **INV**		336
Waist circumference	Halkjær et al. 2004 Schwingshakl et al (2015) *and* Summerbell et al (2009)	Per quintile increase intake of fruit and vegetables *(female)* 6 years	Beta coefficient	**-0.03 (-0.25, 0.20) cm** **INV**	1,115
		Per quintile increase intake of fruit and vegetables *(male)* 6 years	Beta coefficient	**-0.01 (-0.17, 0.15) cm** **INV**	1,152

Five prospective cohort studies in adults investigating combined fruit and vegetable intake and adiposity were identified across two reviews, providing six results across three outcomes: BMI change; weight change; and waist circumference. Two results reported non-significant positive associations. Four results reported inverse associations, of which one was statistically significant. In this study, fruit and vegetable intake was measured at baseline through a 'Fruit and Vegetable Index' (FAVI) which measured both frequency and diversity of intake, with a maximum score of 333; the lowest tertile mean score was 34.6 SD±28.0 and the highest tertile mean score was 117.2 SD±18.9. Two results reported non-significant positive associations.

3.5 Dietary flavonoids

Table 35 Meta-analyses of prospective cohort studies in adults – Dietary flavonoids

Adults					
Meta-analyses of prospective cohort studies					
SD=standard deviation; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Bertoia et al (2016)	Total flavenoid intake (SD per day [194mg]) per four year period 24 years	MD	**-0.20 (-0.31, -0.09) lb** **INV**	Studies=3; n=124,086 I^2=not reported

One review conducted a meta-analysis of dietary flavonoid intake and adiposity using the Nurse's Health Study I, the Nurse's Health Study II, and the Health Professions Follow-up Study cohorts. The result reported a protective association between flavonoid intake and weight change over a four year period. The authors calculated flavonoid intake as "the frequency of consumption of specified portions of flavonoid containing foods multiplied by the flavonoid content (aglycone equivalents) per serving of that food, summed across all foods and beverages". The milligram equivalent of the standard deviation was 194mg. After adjustment for fibre intake, associations remained significant for three flavonoid subclasses: anthocyanins, proanthocyanidins, and total flavonoid polymers. A corresponding forest plot was not available.

4. Possible mechanisms

Summarised from WCRF/AICR 2007 Expert Report:

- Increased consumption of non-starchy vegetables, which are generally low in energy density, may results in a compensatory decrease in consumption of more energy-dense foods.
- Most non-starchy vegetables tend to have a low glycaemic index and contain soluble dietary fibre, which may result in slowed gastric emptying and increased satiety.
- Fruit and vegetables contain high concentrations of a range of important micronutrients such as antioxidants and phytoestrogens that may also have a beneficial influence on the energy homeostatic pathways.

Summarised from Ledoux et al. 2011:

- **Energy intake**: In experimental studies of adults reporting the expected relationship, weight loss occurred when energy intake was reduced in conjunction with increased fruit and veg consumption and decreased energy-dense food consumption. When fruit and veg consumption increased without change in energy intake, weight loss did not occur.
- **Displacement**: Increased in fruit and veg intake without intentional energy intake or energy-dense food restraint may have a weak displacement effect on energy-dense foods.
- **Fibre**: Increases in fibre intake (without instruction to do so) co-occurs with increases in fruit and vegetable consumption and losses in weight.
- **Part of a wider dietary pattern**: Fruit and veg consumption may lead to a weight loss or lower weight gain as part of a larger dietary change pattern that includes increases in fibre content and/or lowers energy density of the diet.

With respect to dietary flavonoids (as summarised by Bertoia et al 2016):

- The particular fruits and vegetables associated with less weight gain are rich sources of several flavonoid subclasses, particularly flavonols, anthocyanins, and flavones.
- Several flavonoid subclasses have been shown to decrease energy intake, increase glucose uptake in muscle in vivo, and decrease glucose uptake in adipose tissue in vitro (animal models and short term human studies).
- Studies focusing on flavonoids via green tea intake provide evidence to suggest flavonoids may decrease fat absorption, increase energy expenditure, and inhibit adipogenesis.

5. Summary of evidence

5.1 Children

- **Fruits**: Three prospective cohorts provided four results, of which three reported positive associations and one reported an inverse association. One result reporting a positive association was statistically significant after further adjusting for energy intake. Follow up ranged from one to three years and the smallest cohort had 825 participants.
- **Vegetables**: Three prospective cohort studies provided four results, of which one reported a positive association, two reported inverse associations, and one reported no association. Significance varied depending on whether the study adjusted for total energy intake. These studies were the same ones that provided evidence on fruit intake.
- **Fruits and vegetables combined**: Two prospective cohort studies provided four results: three reported inverse associations and one reported no association. One result reported a significant positive association after further adjusting for energy intake. Follow up ranged from three to 21 years. Both studies stratified results by gender and marginally larger effects were reported for boys.

5.2 Adults

- **Fruits**: Four meta-analyses of prospective cohort studies all reported significant inverse associations. There were four individual prospective cohort studies, which provided 12 mixed results: 9 reported inverse associations, three reported positive associations. None were statistically significant.
- **Vegetables**: Three meta-analyses of prospective cohort studies reported two significant, inverse associations, and one non-significant positive association. Five individual prospective cohort studies provided 15 additional results: 12 reported inverse associations, of which six were statistically significant, two reported non-significant positive associations, and one reported no association.
- **Fruits and vegetables combined**: Two published reviews conducted meta-analyses of RCTs; of three results, one reported a non-significant positive effect and two reported inverse effects, of which one was significant. One meta-analysis of prospective cohort studies reported a significant inverse association. Three individual RCTs reported mixed results depending on which arm of the multiple arm interventions are considered. Five prospective cohort studies provided six results, of which four reported an inverse association (one statistically significant) and two non-significant positive associations.
- **Dietary flavonoids**: One meta-analysis of prospective cohort studies reported a statistically significant inverse association.

2.4 Meat

1. Evidence identified for 2017 update

Table 36 Published reviews identified for the 2017 update – Meat

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Fogelholm et al. 2012 [+]; U.S Department of Agriculture Nutrition Evidence Library 2010a [+];Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	Nil	-

Notes on the evidence:

- The supplementary literature search yielded no meta-analyses, so all the evidence presented here is derived from the NICE (2014) report.
- The three relevant reviews provided 12 unique studies, all of which were prospective cohort studies in adults. The results of those have been categorised based on exposure: total meat intake; red meat intake; processed meat intake; and poultry intake.
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Children

2.1 Meta-analysis of RCTs in children
Nil

2.2 Meta-analyses of prospective cohort studies in children
Nil

2.3 Individual RCTs in children, not in meta-analyses
Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses
Nil

3.2 Adults

3.2.1 Meta-analysis of RCTs in adults

Nil

3.2.2 Meta-analyses of prospective cohort studies in adults

Nil

3.2.3 Individual RCTs in adults, not in meta-analyses

Nil

3.2.4 Individual prospective cohort studies in adults, not in meta-analyses

The three relevant reviews provided 12 unique studies, all of which were prospective cohort studies in adults. The evidence in this section is divided into four subsections:

- Total meat intake
- Red meat intake
- Processed meat intake
- Poultry intake

Total meat

Table 37 Results of individual prospective cohort studies in adults – Total meat

Adults					
Prospective cohort studies					
ΔWC_{BMI}=waist circumference for a given BMI; OR=odds ratio; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Vergnaud et al. 2010 *Fogelholm et al (2012)*	Per 100kcal increase in total meat consumption 5 years	Beta-coefficient	**65 (39, 90) g/y** p<0.00001 **+VE**	373,803
	Sanchez-Villegas et al. 2006 *Summerbell et al (2009)* and *Fogelhom et al (2012)*	Tertiles of meat intake 28 months	Low: **0.41 (0.26, 0.56) kg** Mid: **0.62 (0.40, 0.84) kg** High: **0.79 (0.56, 1.02) kg** p for trend=0.001 **+VE**		6,319
	Rosell et al. 2006 *Fogelholm et al (2012)*	'Meat-eater' dietary pattern vs. 'fish-eater' dietary pattern over one year *(female)* 5.3 years	Meat-eater: **423 (403, 443) g** Fish-eater: **338 (300, 376) g** p<0.05 **+VE**		16,593
		'Meat-eater' dietary pattern vs. 'fish-eater' dietary pattern over one year *(male)* 5.3 years	Meat-eater: **406 (373, 439) g** Fish-eater: **377 (298, 456) g** p>0.05 **+VE**		5,373
		'Meat-eater' dietary pattern vs. 'vegetarian' dietary pattern over one year *(female)* 5.3 years	Meat-eater: **423 (403, 443) g** Vegetarian: **392 (364, 420) g** p>0.05 **+VE**		16,593
		'Meat-eater' dietary pattern vs. 'vegetarian' dietary pattern over one year *(male)* 5.3 years	Meat-eater: **406 (373, 439) g** Vegetarian: **386 (339, 433) g** p>0.05 **+VE**		5,373
		'Meat-eater' dietary pattern vs. 'vegan' dietary pattern over one year *(female)* 5.3 years	Meat-eater: **423 (403, 443) g** Vegan: **303 (211, 396) g** p<0.05 **+VE**		16,593
		'Meat-eater' dietary pattern vs. 'vegan' dietary pattern over one year *(male)* 5.3 years	Meat-eater: **406 (373, 439) g** Vegan: **284 (178, 390) g** p<0.05 **+VE**		5,373
Weight gain >2kg	Schulz et al. 2002 *Summerbell et al (2009)*	Per 100g of meat intake *(female)* 2.2 years	OR	**1.36 (1.04, 1.79)** **+VE**	11,005
		Per 100g of meat intake *(male)* 2.2 years	OR	**1.06 (0.85, 1.32)** **+VE**	6,364
Weight gain <2kg		Per 100g of meat intake *(female)* 2.2 years	OR	**1.21 (0.98, 1.50)** **+VE**	11,005
		Per 100g of meat intake *(male)* 2.2 years	OR	**1.00 (0.83, 1.20)** **NIL**	6,364
Weight loss <2kg		Per 100g of meat intake *(female)* 2.2 years	OR	**0.79 (0.64, 0.97)** **+VE**	11,005
		Per 100g of meat intake *(male)* 2.2 years	OR	**1.01 (0.85, 1.21)** **INV**	6,364
Weight loss >2kg		Per 100g of meat intake *(female)* 2.2 years	OR	**0.81 (0.64, 1.03)** **+VE**	11,005
		Per 100g of meat intake *(male)* 2.2 years	OR	**0.79 (0.63, 1.00)** p<0.05 **+VE**	6,364
BMI change	Kahn et al. 1997 *Summerbell et al (2009)*	Highest vs. lowest quintile of meat intake *(female)* 10 years	MD	**0.19 kg/m^2 SE ±0.05** p<0.001 **+VE**	44,080

		Highest vs. lowest quintile of meat intake *(male)* 10 years	MD	**0.34 kg/m² SE ±0.05** p<0.001 **+VE**	35,156
	Wagemakers et al. 2009 *USDA (2010)*	Per 10g increase in total meat intake at baseline *(female)* 10 years	Beta-coefficient	**0.013 SE±0.005 kg/m²** p=0.008 **+VE**	635
		Per 10g increase in total meat intake at baseline *(male)* 10 years	Beta-coefficient	**0.013 SE±0.003 kg/m²** p<0.001 **+VE**	517
Waist circumference	Halkjær et al. 2004 *Summerbell et al (2009)* and *Fogelhom et al (2012)*	Per quintile increase of meat product intake *(female)* 6 years	Beta-coefficient	**0.20 (-0.05, 0.44) cm** **+VE**	1,120
		Per quintile increase of meat product intake *(male)* 6 years	Beta-coefficient	**0.11 (-0.06, 0.28) cm** **+VE**	1,166
	Wagemakers et al. 2009 *USDA (2010)*	Per 10g increase in total meat intake at baseline *(female)* 10 years	Beta-coefficient	**0.035 SE±0.012 cm** p=0.003 **+VE**	635
		Per 10g increase in total meat intake at baseline *(male)* 10 years	Beta-coefficient	**0.034 SE±0.009 cm** p<0.001 **+VE**	517
ΔWC_{BMI}	Romaguera et al. 2011 *Fogelholm et al (2012)*	100kcal increments of meat product intake over one year 5.5 years	Beta-coefficient	**0.02 (0.00, 0.03) cm** p=0.036 **+VE**	48,631
Odds of "gaining weight at the waist"	Kahn et al. 1997 *Summerbell et al (2009)*	Highest vs. lowest quintile of meat intake *(female)* 10 years	OR	**1.50 (1.20, 1.87)** **+VE**	44,080
		Highest vs. lowest quintile of meat intake *(male)* 10 years	OR	**1.46 (1.25, 1.71)** **+VE**	35,156

Eight publications from three reviews provided 27 results across seven outcomes: weight change; odds of weight gain (small <2kg, or large >2kg); odds of weight loss (small <2kg, or large >2kg); BMI change; waist circumference; waist circumference for a given BMI; and odds of 'gaining weight at the waist'. Twenty five results reported a positive association between total meat intake and adiposity (17 were statistically significant), one result reported an inverse association, and one result reported no association.

Vergnaud et al (2010) used a multivariate adjusted model, of which one factor was 'total energy intake'.

Rosell et al (2006) investigated the EPIC-Oxford cohort, which differs from the other EPIC cohorts as it involves subjects who are more health conscious than the general population. The authors investigated adiposity change by comparing dietary patterns characterised by source of protein (meat, fish, vegetarian, vegan).

Three other studies also used data from EPIC cohorts: Schulz et al (2002) investigated the EPIC-Potsdam cohort, Romaguera et al (2011) investigated EPIC-DiOGenes, and Vergnaud et al (2010) investigated 16 EPIC cohorts.
Sanchez-Villegas et al (2006) = the SUN Cohort; Kahn et al (1997) = Cancer Prevention Study II; Wagemakers et al = MRC NSHD 1964 birth cohort; and Halkjaer et al (2004) = MONICA1.

Red meat

Table 38 Results of individual prospective cohort studies in adults – Red meat

Adults					
Prospective cohort studies					
ΔWC_{BMI}=waist circumference for a given BMI; MD=mean difference; OR=odds ratio; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Vergnaud et al. 2010 *Fogelholm et al (2012)*	Per 100kcal increase in red meat intake 5 years	Beta-coefficient	**15 (1, 28) g/y** p=0.03 **+VE**	373,803
	Parker et al. 1997 *Summerbell et al (2009)*	"Red meat intake" 4 years	Beta-coefficient	**0.245 (-1.42, 1.91) kg** p=0.77 **+VE**	465
	Mozaffarian et al. 2011 *Fogelholm et al (2012)*	Per serving per day of unprocessed red meat in a four year period 20 years	MD	**0.95 (0.55, 1.34) lb** p<0.001 **+VE**	120,877
BMI	Wagemakers et al. 2009 *USDA (2010)*	Per 10g increased intake of red meat at baseline *(female)* 10 years	Beta-coefficient	**0.009 SE±0.006 kg/m^2** p>0.05 **+VE**	635
		Per 10g increased intake of red meat at baseline *(male)* 10 years	Beta-coefficient	**0.008 SE±0.005 kg/m^2** p>0.05 **+VE**	517
Waist circumference	Halkjaer et al. 2009 *Fogelholm et al (2009)*	Per 60kcal per day intake of red meat *(female)* 5 years	Regression coefficient	**-0.13 (-0.24, -0.03) cm** **INV**	22,570
		Per 60kcal per day intake of red meat *(male)* 5 years	Regression coefficient	**-0.06 (-0.11, -0.003) cm** **INV**	20,126
	Wagemakers et al. 2009 *USDA (2010)*	Per 10g increased intake of red meat at baseline *(female)* 10 years	Beta-coefficient	**0.033 SE±0.015 cm** p=0.033 **+VE**	635
		Per 10g increased intake of red meat at baseline *(male)* 10 years	Beta-coefficient	**0.027 SE±0.015 cm** p=0.045 **+VE**	517
ΔWC_{BMI}	Romaguera et al. 2011 *Fogelholm et al (2012)*	100kcal increments of red meat intake over one year 5.5 years	Beta-coefficient	**0.01 (-0.01, 0.04) cm** p=0.207 **+VE**	48,631
Odds of weight gain	Bes-Rastrollo et al. 2006 *Summerbell et al (2009)* and *Fogelholm et al (2012)*	Intake of red meat ≥128.7g per day 28.5 months	OR	**1.16 (1.00, 1.36)** **+VE** ***Borderline signif***	7,194

Seven prospective cohort studies from three reviews provided 11 results across five outcomes: weight change; BMI; waist circumference; waist circumference for a given BMI; and odds of weight gain. Nine results reported a positive association between red meat intake and adiposity (four were statistically significant and one was borderline) and two results from the same study (Halkjaer et al 2009) reported significant inverse associations.

Vergnaud et al (2010) used a multivariate adjusted model, of which one factor was 'total energy intake'. The result from Bes-Rastrollo et al (2006) reported a significant, positive association between red meat intake and adiposity; after adjustment with a multivariate model significance was lost but the p-trend remained significant.

Vergnaud et al (2010) used data from EPIC-PANACEA and Romaguera et al (2011) used data from EPIC-DiOGenes. Mozzafarian et al (2011) used data from the Nurses' Health Study I, the Nurses' Health Study II, and the Health Professionals Follow up Study cohorts.

Processed meat

Table 39 Results of individual prospective cohort studies in adults – Processed meat

Adults					
Prospective cohort studies					
ΔWC_{BMI}=waist circumference for a given BMI; MD=mean difference; OR=odds ratio; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight	Vergnaud et al. 2010 *Fogelholm et al (2012)*	Per 100kcal increase in processed meat intake 5 years	Beta-coefficient	**25 (15, 34) g/y** p<0.00001 **+VE**	373,803
	Mozaffarian et al. 2011 *Fogelholm et al (2012)*	Per serving per day of processed meat in a four year period 20 years	MD	**0.93 (0.79, 1.08) lb** p<0.001 **+VE**	120,877
Weight gain >2kg	Schulz et al. 2002 *Summerbell et al (2009)*	Per 100g of processed meat intake *(female)* 2.2 years	OR	**1.20 (0.96, 1.52)** **+VE**	11,005
		Per 100g of processed meat intake *(male)* 2.2 years	OR	**1.17 (0.97, 1.41)** **+VE**	6,364
Weight gain <2kg		Per 100g of processed meat intake *(female)* 2.2 years	OR	**1.10 (0.91, 1.31)** **+VE**	11,005
		Per 100g of processed meat intake *(male)* 2.2 years	OR	**1.09 (0.94, 1.27)** **+VE**	6,364
Weight loss <2kg		Per 100g of processed meat intake *(female)* 2.2 years	OR	**0.75 (0.63, 0.91)** **+VE**	11,005
		Per 100g of processed meat intake *(male)* 2.2 years	OR	**1.17 (1.01, 1.36)** **INV**	6,364
Weight loss >2kg		Per 100g of processed meat intake *(female)* 2.2 years	OR	**0.75 (0.61, 0.93)** **+VE**	11,005
		Per 100g of processed meat intake *(male)* 2.2 years	OR	**1.08 (0.90, 1.29)** **INV**	6,364
BMI	Wagemakers et al. 2009 *USDA (2010)*	Per 10g increased intake of processed meat at baseline *(female)* 10 years	Beta-coefficient	**0.004 SE±0.008 kg/m²** p>0.05 **+VE**	635
		Per 10g increased intake of processed meat at baseline *(male)* 10 years	Beta-coefficient	**0.015 SE±0.006 kg/m²** p=0.009 **+VE**	517
Waist circumference	Halkjaer et al. 2009 *Fogelholm et al (2009)*	Per 60kcal per day intake of processed meat *(female)* 5 years	Regression coefficient	**0.20 (0.04, 0.36) cm** **+VE**	22,570
		Per 60kcal per day intake of processed meat *(male)* 5 years	Regression coefficient	**0.01 (-0.06, 0.08) cm** **+VE**	20,126
	Wagemakers et al. 2009 *USDA (2010)*	Per 10g increased intake of processed meat at baseline *(female)* 10 years	Beta-coefficient	**0.042 SE±0.02 cm** p=0.047 **+VE**	635

		Per 10g increased intake of processed meat at baseline *(male)* 10 years	Beta-coefficient	**0.031 SE±0.016 cm** p=0.037 **+VE**	517
ΔWC_{BMI}	Romaguera et al. 2011 *Fogelholm et al (2012)*	100kcal increments of processed meat intake over one year 5.5 years	Beta-coefficient	**0.04 (0.02, 0.06) cm** p=0.001 **+VE**	48,631

Six studies, from three reviews, provided 17 results across six outcomes: weight; odds of weight gain (>2kg or <2kg); odds of weight loss (>2kg or <2kg); BMI; waist circumference; and waist circumference for a given BMI. Fifteen results reported a positive association between processed meat intake and increased adiposity, of which nine were statistically significant. Two results reported an inverse association, of which one was statistically significant. Both of these results were in males from the Schulz et al (2002) cohort and reported increased odds of weight loss (<2kg and >2kg) with increasing intake of processed meat.

Vergnaud et al (2010) used a multivariate adjusted model, of which one factor was 'total energy intake'. Three studies used data from the EPIC cohort: Vergnaud et al (2010) used data from EPIC-PANACEA, Schulz et al (2002) used data from one centre (Potsdam), and Romaguera et al (2011) used data from EPIC-DiOGenes.

Poultry

Table 40 Results of individual prospective cohort studies in adults – Poultry

Adults					
Prospective cohort studies					
ΔWC_{BMI}=waist circumference for a given BMI. Significant results are highlighted in **red.**					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight	Vergnaud et al. 2010 *Fogelholm et al (2012)*	Per 100kcal increase in poultry intake 5 years	Beta-coefficient	**45 (29, 62) g/y** p<0.00001 **+VE**	373,803
Waist circumference	Halkjaer et al. 2009 *Fogelholm et al (2009)*	Per 60kcal per day intake of poultry *(female)* 5 years	Regression coefficient	**0.19 (0.01, 0.37) cm** **+VE**	22,570
		Per 60kcal per day intake of poultry *(male)* 5 years	Regression coefficient	**0.05 (-0.08, 0.17) cm** **+VE**	20,126
ΔWC_{BMI}	Romaguera et al. 2011 *Fogelholm et al (2012)*	100kcal increments of poultry intake over one year 5.5 years	Beta-coefficient	**-0.02 (-0.05, 0.02) cm** p=0.373 **INV**	48,631

Three studies from the same review provided four results related to consumption of poultry and measures of adiposity. Three results reported a positive association, of which two were statistically significant. The other result reported a non significant, inverse association. All studies used highly adjusted models, including adjustments for total energy intake and baseline adiposity.

Vergnaud et al (2010) used a multivariate adjusted model, of which one factor was 'total energy intake'. Vergnaud et al (2010) and Romaguera et al (2011) both used data from the EPIC cohorts; Vergnaud et al (2010) used EPIC-PANACEA, Romaguera et al (2011) used EPIC-DiOGenes.

4. Possible mechanisms

As summarised by Fogelholm et al (2012):

- **Energy density**: Meat is energy dense and thereby may increase total energy intake. In addition, meat may also have a high fat content.
- **Acting as a marker**: Meat intake may only reflect some undetected dietary or lifestyle pattern(s) that contribute to weight gain, rather than be a risk factor in itself.
- **Outcomes masking the process**: Meat may increase fat-free mass and so BMI as an outcome may be misleading.

5. Summary of evidence

5.1 Children

N/A

5.2 Adults

In total, 12 unique studies provided 59 results investigating the exposures of total meat intake, red meat intake, processed meat intake, and poultry intake. Fifty two results reported a positive association between intake of meat and adiposity, of which 32 were statistically significant and one was borderline significant. Six results reported an inverse association, of which three were statistically significant. One result reported no association.

Four studies used data from the EPIC cohorts and one study used data from the Nurses' Health Study I, the Nurses' Health Study II, and the Health Professionals Follow up Study cohorts.

2.5 Milk and dairy products

1. Evidence identified for 2017 update

Table 41 Published reviews identified for the 2017 update – Milk and dairy products

Source	No. of reviews	Authors [quality]
NICE (2014) report	5	Abargouei et al. 2012 [++]; Louie et al. 2011 [++]; U.S Department of Agriculture Nutrition Evidence Library 2010a [+]; Barr 2003 [+]; Lanou et al. 2008 [-]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	3	Benatar et al. 2013 [++];Booth et al. 2015 [++]; Schwingshackl et al. 2016 [++]

Notes on the evidence:

- The USDA (2010) published review identified three systematic reviews as part of its review process: Barr (2003); Lanou and Barnard (2008); and Winzenberg et al. 2007. None of these conducted meta-analyses.
    - Relevant individual studies not included in the other meta-analyses identified were extracted from Barr (2003) (quality assessment: [+]) and Lanou et al (2008) (quality assessment: [-]) and are reported in the results section.
    - Winzenberg et al (2007) was excluded as it focused on calcium supplementation only.
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that consistent assessment grades are given.
- The NICE (2014) report refers to the exposure as 'milk and dairy [products]'. In this literature review, the term 'dairy' is applied throughout to mean all dairy products, including milk. Where possible the specific product is noted.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=1,000 for prospective cohort studies in children and adults, so only studies with more than 1,000 participants are reported in detail here.
- There was considerable but incomplete overlap of included studies between meta-analyses of RCTs of adults; the number of overlapping studies is indicated in the table below.

Table 42 Overlapping studies between meta-analyses of RCTs in adults – Milk and dairy products

Overlapping studies between meta-analyses of RCTs									
Please note that some reviews conducted more than one meta-analysis; these have been separated by outcome.									
		Weight			**Waist circumference**		**Body fat**	**Fat mass**	**Lean mass**
		Benatar 2013	Booth 2015	Abargouei 2012	Benatar 2013	Abargouei 2012	Booth 2015	Abargouei 2012	Abargouei 2012
Weight	Benatar 2013	-	10	5	6	1	8	4	3
	Booth 2015		-	12	4	5	20	9	5
	Abargouei 2012			-	1	7	9	11	6
Waist circum-ference	Benatar 2013				-	0	3	1	0
	Abargouei 2012					-	4	5	4
Body fat	Booth 2015						-	8	4
Fat mass	Abargouei 2012							-	5
Lean mass	Abargouei 2012								-

2. Children

2.1 Meta-analysis of RCTs in children

Nil

2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Table 43 Results of individual RCTs in children – Milk and dairy products

Children				
RCTs				
Ca=calcium; vit D=vitamin D; SE=standard error. Significant results are highlighted in **red**.				
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***	***n***
Weight	Lappe et al. 2004 USDA (2010)	Ca rich diet (1,500mg per day) via increased dairy **vs.** habitual diet 2 years	**No significant difference** **NIL**	59
	Chan et al. 1995 Barr (2003) *and* Lanou et al (2008)	Dairy product supplementation (up to 1,200mg Ca per day) **vs.** habitual diet 1 year	Intervention**: +6.4 kg** Control**: +7.2 kg** p>0.05 **+VE**	48
	Cadogan et al. 1997 Barr (2003) *and* Lanou et al (2008)	Addition of 568ml milk per day **vs.** habitual diet 18 months	Intervention: **+8.0 kg** Control: **+7.2 kg** p>0.05 **INV**	82
	Merrilees et al. 2000 Barr (2003) *and* Lanou et al (2008)	Addition of dairy foods (equivalent to 1000mg Ca per day) **vs.** habitual diet 2 years	Intervention: **+4.6 kg** Control: **+4 kg** p>0.05 **+VE**	91
	Du et al. 2004 Lanou et al (2008)	144 ml milk per day (Ca fortified) **vs.** 144ml milk per day (Ca and vit D fortified) **vs.** habitual diet 2 years	**Percentage weight change across study:** Ca fortified milk: **34.6 %** Ca and vit D fortified milk: **35.9 %** Habitual diet: **30.8 %** **Both intervention groups significantly higher than no intervention p<0.05** **+VE**	698
	Lau et al. 2004 Lanou et al (2008)	40g high Ca milk powder per day **vs.** 80g high Ca milk powder per day **vs.** control 18 months	**Mean rate of change per year:** 40g: **5.53 (SE 0.33) kg** 80g: **5.43 (SE 0.35) kg** Control: **5.05 (SE 0.32) kg** p>0.05 **+VE**	344
	Volek et al. 2003 Lanou et al (2008)	3 servings 1% milk per day **vs.** 3 servings juice (not Ca fortified) per day 12 weeks	**No significant difference between groups** **NIL**	28
BMI	Lappe et al. 2004 USDA (2010)	Ca rich diet (1500mg per day) via increased dairy **vs.** habitual diet 2 years	**No significant difference between groups** **NIL**	59
Fat mass	Lau et al. 2004 Lanou et al (2008)	40g high Ca milk powder per day **vs.** 80g high Ca milk powder per day **vs.** control 18 months	**Mean rate of change per year:** 40g: **1.35 (SE 0.39) kg** 80g: **1.38 (SE 0.39) kg** Control: **0.85 (SE 0.36) kg** **No significant differences between groups** **+VE**	344

	Volek et al. 2003 Lanou et al (2008)	3 servings 1% milk per day **vs.** 3 servings juice (not Ca fortified) per day 12 weeks	**No significant difference between groups** **NIL**	28
% body fat	Volek et al. 2003 Lanou et al (2008)	3 servings 1% milk per day **vs.** 3 servings juice (not Ca fortified) per day 12 weeks	**No significant difference between groups** **NIL**	28
Lean body mass	Lau et al. 2004 Lanou et al (2008)	40g high Ca milk powder per day **vs.** 80g high Ca milk powder per day **vs.** control 18 months	**Mean rate of change per year:** 40g: **3.41 (SE 0.14) kg** 80g: **3.36 (SE 0.14) kg** Control: **3.19 (SE 0.13) kg** **No significant differences between groups** **+VE**	344
	Volek et al. 2003 Lanou et al (2008)	3 servings 1% milk per day **vs.** 3 servings juice (not Ca fortified) per day 12 weeks	**No significant difference between groups** **NIL**	28

Seven RCTs were identified investigating dairy intake and adiposity in children. One study was reviewed directly by USDA (2010) (Lappe et al 2004), three studies were in a systematic review (Lanou and Barnard 2008) identified by USDA (2010), and three other studies were in two systematic reviews (Lanou and Barnard 2008 and Barr 2003) identified by USDA (2010).

Thirteen results were reported across five outcomes: weight; BMI; fat mass; percentage body fat; and lean body mass. One statistically significant result was reported by Du et al (2004) who found that percentage weight change was higher in both intervention groups relative to the control group; this was the largest identified study. Of the six other results where the review reported on direction, five showed higher weight gain with intervention and one showed higher weight gain with no intervention; none were statistically significant.

Five RCTs were conducted in girls (Lappe et al 2004; Chan et al 1995; Cadogan et al 1997; Merrilees et al 2000; and Du et al 2004) and one was conducted in boys (Volek et al 2003). Compensation in energy intake when dairy products were added was observed in Chan et al (1995) (complete compensation), Merrilees et al (2000) (complete compensation), and Cadogan et al (1997) (partial compensation). This information was not reported for the remaining studies. The RCT by Volek et al (2003) included a resistance training programme for all participants.

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 44 Results of individual prospective cohort studies in children – Milk and dairy products

Children					
Prospective cohort studies					
SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight	Newby et al. 2004 Louie et al (2011) *and* USDA (2010)	Milk intake, ounces per day 8 months	Beta-coefficient	**0.00 SE± 0.01 lb per year** p=0.84 **NIL**	1,345
BMI	Newby et al. 2004 Louie et al (2011) *and* USDA (2010)	Milk intake, ounces per day 8 months	Beta-coefficient	**0.00 ±0.00 kg/m² per year** p=0.96 **NIL**	
	Berkey et al. 2004 USDA (2010)	Milk consumption over 1 year *(girls)* 2 years	Beta-coefficient	**0.017 SE± 0.012 kg/m²** p=0.153 **+VE**	6,688
		Milk consumption over 1 year *(boys)* 2 years	Beta-coefficient	**0.013 SE± 0.013 kg/m²** p=0.320 **+VE**	5,067
	Berkey et al. 2005 Louie et al (2011) *and* USDA (2010)	Intake of >3 servings of milk per day vs. intake of 1–2 servings per day *(girls)* 3 years	Beta-coefficient	**0.093 (±0.034) kg/m²** p=0.007 **+VE**	7,279
		Intake of >3 servings of milk per day vs. intake of 1–2 servings per day *(boys)* 3 years	Beta-coefficient	**0.076 (±0.038) kg/m²** p=0.04 **+VE**	5,550
	Striegel-Moore et al. 2006 Louie et al (2011)	Per 100g increase in total milk intake per day 10 years	Predicted change in parameter	**-0.002 SE± 0.006** p>0.05 **INV**	2,371

Eleven prospective cohort studies in children investigated dairy intake and adiposity. Of those, four studies had more than 1,000 participants and are presented in the table above. These provided seven results across two outcomes: weight and BMI. Four results reported positive associations, of which two were statistically significant, one result reported a non-significant inverse association, and two results reported no association. All the studies reported results with respect to milk intake only.

The remaining seven studies (n<1,000) provided 13 additional results across six outcomes: weight; BMI; BMI z score; fat mass; body fat; percentage body fat; and risk of overweight. It was unclear to what extent fat mass and body fat were the same. Eight results reported no association and five results reported inverse associations, of which four were statistically significant. None reported a positive association. The sample size ranged from 53 to 852 participants and follow up duration ranged from one to 10 years. Seven results related to milk as the exposure, the other six results related to total dairy intake, with varied definitions.
Studies n<1000: Tam et al. 2006, Johnson et al. 2007, Huh et al. 2010, Carruth et al. 2001, Moore et al. 2006, Phillips et al. 2003, and Fiorito et al. 2009.

3. Adults

3.1 Meta-analysis of RCTs in adults

Table 45 Meta-analyses of RCTs in adults – Milk and dairy products

Adults					
Meta-analyses of RCTs					
MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight	Benatar et al (2013)	Increased dairy intake (all types) vs. no intervention 4–156 weeks	MD	**0.60 (0.30, 0.90) kg** +VE	Studies=18; n=1,629 I^2=32%
	Booth et al (2015)	Dairy food supplements vs. no intervention 12 weeks–12 months	MD	**-0.06 (-0.54, 0.43) cm** INV	Studies=31; n=2,091 I^2=57%
	Abargouei et al (2012)	High dairy intake vs. low dairy intake 21–48 weeks	MD	**-0.61 (-1.29, 0.07) kg** INV	Studies=14; n=833 I^2=not reported
Waist circumference	Benatar et al (2013)	Increased dairy intake (all types) vs. no intervention 4–52 weeks	MD	**-0.07 (-1.24, 1.10) cm** INV	Studies=6; n=440 I^2=74%
	Abargouei et al (2012)	High dairy intake vs. low dairy intake 21–48 weeks	MD	**-2.19 (-3.42, -0.96) cm** INV	Studies=8; n=441 I^2=not reported
Body fat	Booth et al (2015)	Dairy food supplements vs. no intervention 12 weeks–12 months	MD	**-0.36 (-0.80, 0.09) kg** INV	Studies=21; n=1,289 I^2=61%
Fat mass	Abargouei et al (2012)	High dairy intake vs. low dairy intake 21–48 weeks	MD	**-0.72 (-1.29, -0.14) kg** INV	Studies=12; n=638 I^2=not reported
Lean mass	Abargouei et al (2012)	High dairy intake vs. low dairy intake 21–48 weeks	MD	**0.58 (0.18, 0.99) kg** +VE	Studies=6; n=258 I^2=not reported

Three reviews conducted eight meta-analyses of RCTs across five outcomes: weight; waist circumference; body fat; fat mass; and lean mass. It was unclear if 'body fat' and 'fat mass' had the same definition between reviews. Six of the eight results reported an inverse effect of dairy intake on measures of adiposity, of which two were statistically significant. Two results reported a positive effect, both of which were significant. One of the results reporting a positive effect related to [total] weight change, and the other related to lean mass change.

Abargouei et al (2012) did not report I^2 values but did report p values for presence of significant heterogeneity: weight meta-analysis, p=0.04; waist circumference meta-analysis, p=0.03; fat mass meta-analysis, p=0.007; and lean mass meta-analysis, p=0.07.

Benatar et al (2013) was the only review to solely select studies of interventions without energy restriction for inclusion; the other reviews included interventions with energy restriction alongside those with ad libitum diets. This review reported a statistically significant positive relationship between dairy intake and total weight change, and a non-significant inverse relationship between dairy intake and waist circumference.

Abargouei et al (2012) stratified their meta-analyses for studies with, and without, energy restriction (see forest plots below). For the outcomes of waist circumference and fat mass, the direction of effect was maintained for both stratification categories, but was no longer significant for studies without energy restriction. For the outcomes of weight and lean mass, the direction and significance was maintained for

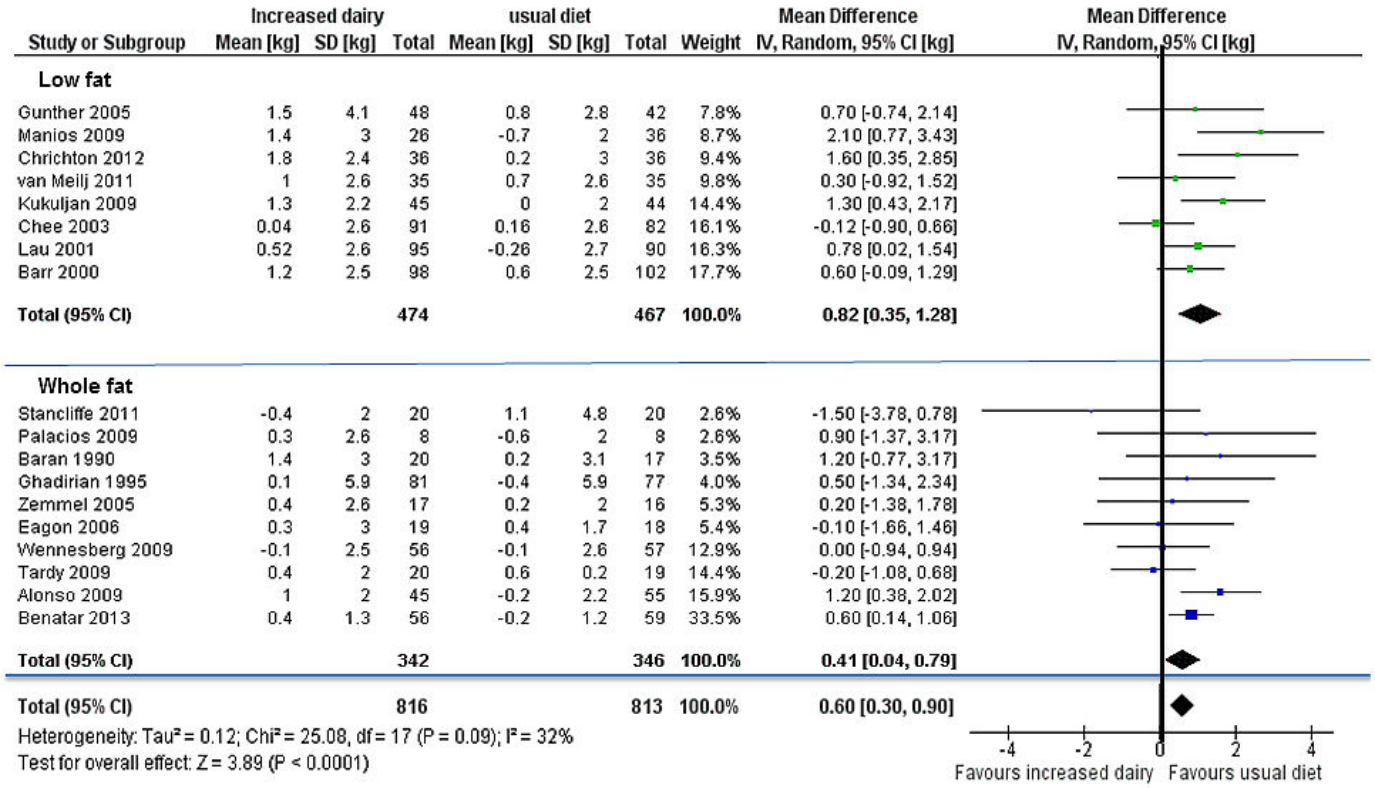
studies with energy restriction, but a non-significant, positive effect was reported for studies without energy restriction.

The forest plots corresponding to the above meta-analyses are presented below.

Adults | RCT | Weight | Benatar et al 2013 | Increased dairy intake

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: van Meilj 2011; Baran 1990; Ghadirian 1995; Eagon 2006; Alonso 2009.

Figure 28 Meta-analysis of RCTs in adults – Dairy – Benatar et al 2013 – Weight



* Total number =1629, 82% female, mean baseline weight 77.7 (SD 16.2) kg, median study duration 26 (IQR10-39)weeks

Adults | RCT | Weight | Booth et al 2015 | Dairy food supplements

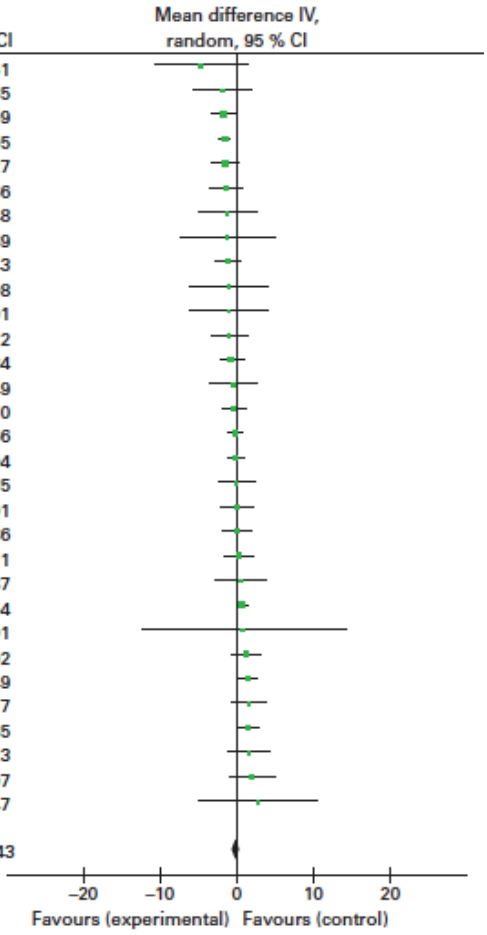
Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: Angeles-Agdeppa 2010; Torres 2010; Rosado 2011; Bowen 2004; Tanaka 2014; Wagner 2007.

Figure 29 Meta-analysis of RCTs in adults – Dairy – Booth et al 2015 – Weight

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference	95 % CI
Zemel *et al.* (2004)[37]	–11·07	5·41	11	–6·6	8·16	10	0·6	–4·47	–10·45,1·51
Thompson *et al.* (2005)[2]	–11·8	6·1	22	–10	6·8	26	1·4	–1·80	–5·45, 1·85
Zemel *et al.* (2005)[68]	–6·63	2·6	18	–4·99	2	16	4·3	–1·64	–3·19, –0·09
Stancliffe *et al.* (2011)[43]	–0·4	0·4	20	1·1	1·2	20	7·0	–1·50	–2·05, –0·95
Zemel *et al.* (2009)[40]	–4·61	3·02	23	–3·15	3·16	26	3·9	–1·46	–3·19, 0·27
Torres *et al.* (2010)[65]	–5·1	3·49	19	–3·8	2·68	20	3·4	–1·30	–3·26, 0·66
Harvey-Berino *et al.* (2005)[8]	–10·8	5·9	23	–9·6	6·5	21	1·4	–1·20	–4·88, 2·48
Smilowitz *et al.* (2011)[39]	–4·3	10·2	22	–3·2	10·3	23	0·6	–1·10	–7·09, 4·89
Jones *et al.* (2013)[61]	–3·3	2·68	20	–2·2	2·12	18	4·3	–1·10	–2·63, 0·43
Witbracht *et al.* (2013)[44]	–6·5	8·9	24	–5·5	9·6	27	0·8	–1·00	–6·08, 4·08
Angeles-Agdeppa *et al.* (2010)[19]	0·8	8·7	30	1·7	10·6	30	0·9	–0·90	–5·81, 4·01
Torres *et al.* (2013)[66]	–5·3	3·82	18	–4·4	2·47	17	3·1	–0·90	–3·02, 1·22
Frestedt *et al.* (2008)[59]	–3·82	3·06	31	–3·24	2·49	28	4·6	–0·58	–2·00, 0·84
Rosado *et al.* (2011)[63]	–3·6	6·8	43	–3·2	6·7	41	2·1	–0·40	–3·29, 2·49
Van Loan *et al.* (2011)[67]	–6·3	2·9	35	–6	3·1	36	4·7	–0·30	–1 ·70, 1·10
Chee *et al.* (2003)[69]	0·04	2·58	91	0·16	2·63	82	6·4	–0·12	–0·90, 0·66
Wennersberg *et al.* (2009)[73]	–0·1	2·5	57	–0·1	2·6	56	5·9	0·00	–0·94, 0·94
Gunther *et al.* (2005)[29]	0·9	2·5	9	0·8	2·5	10	2·9	0·10	–2·15, 2·35
Haub *et al.* (2005)[5]	0·1	3	17	0	2·9	20	3·5	0·10	–1 ·81, 2·01
Josse *et al.* (2011)[62]	–4·26	3·37	30	–4·36	3·57	30	3·8	0·10	–1·66,1·86
Bowen *et al.* (2004)[58]	–9	3	25	–9·3	3·5	25	3·7	0·30	–1·51, 2·11
Barr *et al.* (2000)[33]	1·2	12·1	98	0·6	11·5	102	1·7	0·60	–2·67, 3·87
Lau *et al.* (2001)[72]	0·52	2·63	95	–0·26	2·66	90	6·4	0·78	0·02, 1·54
Palacios *et al.* (2011)[38]	0·3	15·1	8	–0·6	11·4	8	0·1	0·90	–12·21, 14·01
Kukuljan *et al.* (2009)[71]	1·3	4·33	45	0	3·95	44	3·9	1·30	–0·42, 3·02
Tanaka *et al.* (2014)[45]	–1·1	3·3	102	–2·6	3·8	98	5·8	1·50	0·51, 2·49
Wagner *et al.* (2007C)[41]	–4·2	3·3	17	–5·8	2·77	13	3·0	1·60	–0·57, 3·77
Crichton *et al.* (2012)[70]	1·8	2·4	36	0·2	3	36	5·1	1·60	0·35, 2·85
Thomas *et al.* (2010)[64]	–1·1	2·5	14	–2·7	4·5	15	2·4	1·60	–1·03, 4·23
Manios *et al.* (2009)[30]	1·4	2·02	39	–0·7	8·57	36	2·1	2·10	–0·77, 4·97
Gilbert *et al.* (2011)[60]	–2·9	11·8	13	–5·8	7·1	12	0·4	2·90	–4·67, 10·47
Total (95 % CI)			1055			1036	100·0	–0·06	–0·54, 0·43

Heterogeneity: τ^2=0·80; χ^2=70·10, df=30 (P<0·0001); I^2=57 %

Test for overall effect: Z=0·23 (P=0·81)

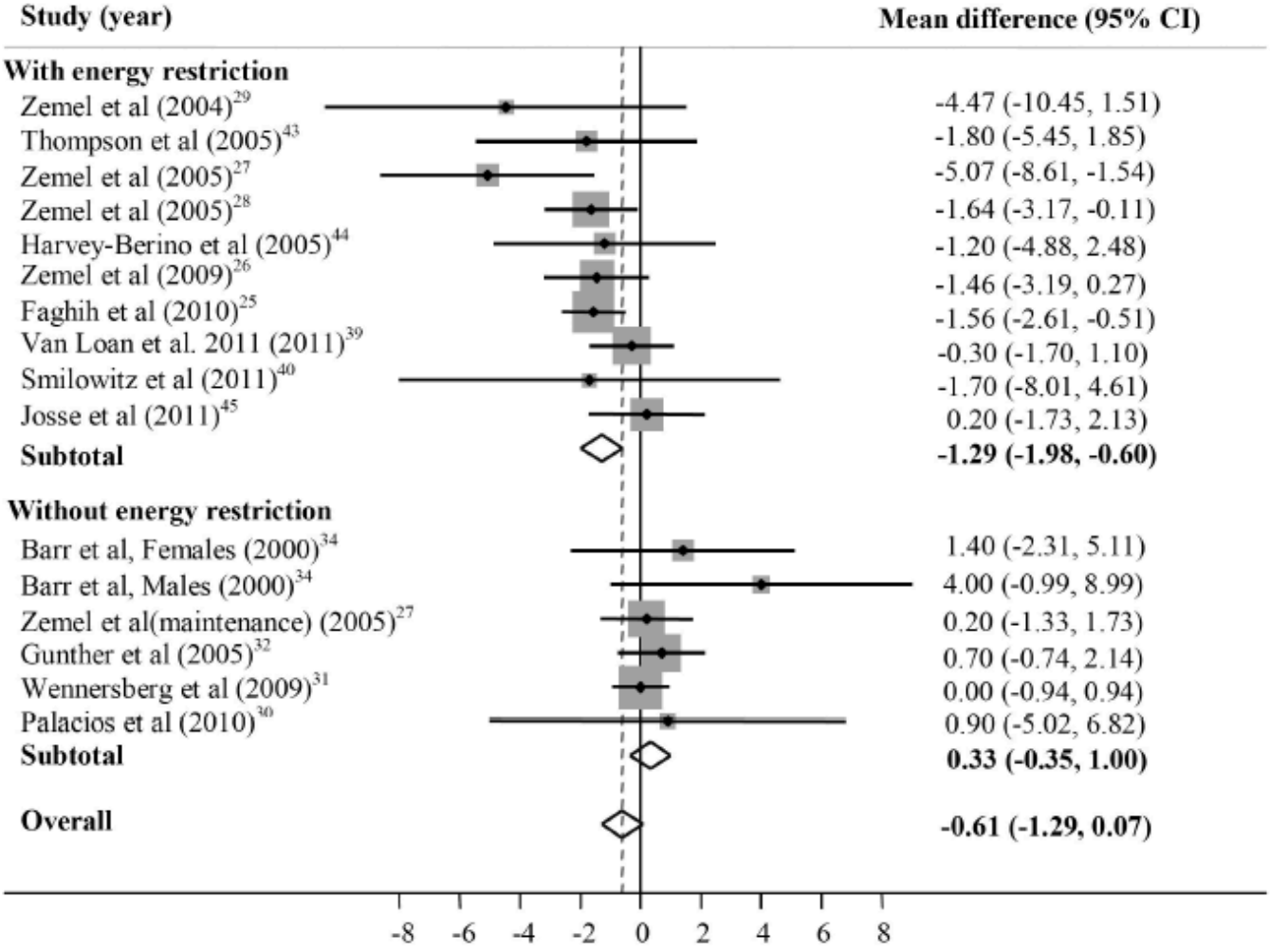


Adults | RCT | Weight | Abargouei et al 2012 | High vs. low dairy intake

Forest plot of randomized controlled trials illustrating weighted mean difference in weight change between dairy-supplemented and control groups for all eligible studies as well as for subgroup analysis based on energy restriction. For all studies combined, slightly greater weight loss was seen among those with high dairy intake compared with those with low dairy intake (P for heterogeneity= 0.04, Q test, I-square=41.2% and Tau-square=0.64). Meta-analysis of studies that administered high dairy intake without energy-restriction showed no significant effect of dairy intake on weight change (P for heterogeneity= 0.67, Q test, I-square=0.0% and Tau-square=0.0). For studies that administered energy-restriction, we found the significant effect of dairy intake on weight loss (P for heterogeneity= 0.32, Q test, I- square=12.5% and Tau-square=0.15) (Abargouei et al 2012).

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: nil. However, Faghih 2010 is unique to all meta-analyses by Abargouei et al (2012).

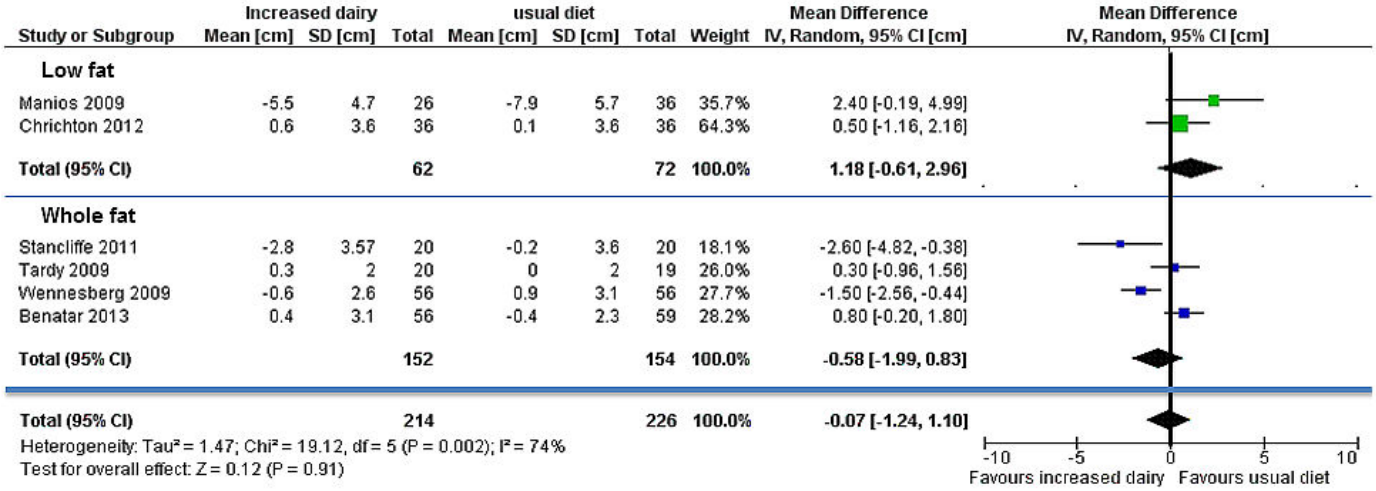
Figure 30 Meta-analysis of RCTs in adults – Dairy – Abargouei et al 2012 – Weight



Adults | RCT | Waist circumference | Benatar et al 2013 | Increased dairy intake

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: nil. However, Benatar 2013 and Tardy 2009 are unique to both meta-analyses by Benatar et al (2013).

Figure 31 Meta-analysis of RCTs in adults – Dairy – Benatar et al 2013 – Waist circumference



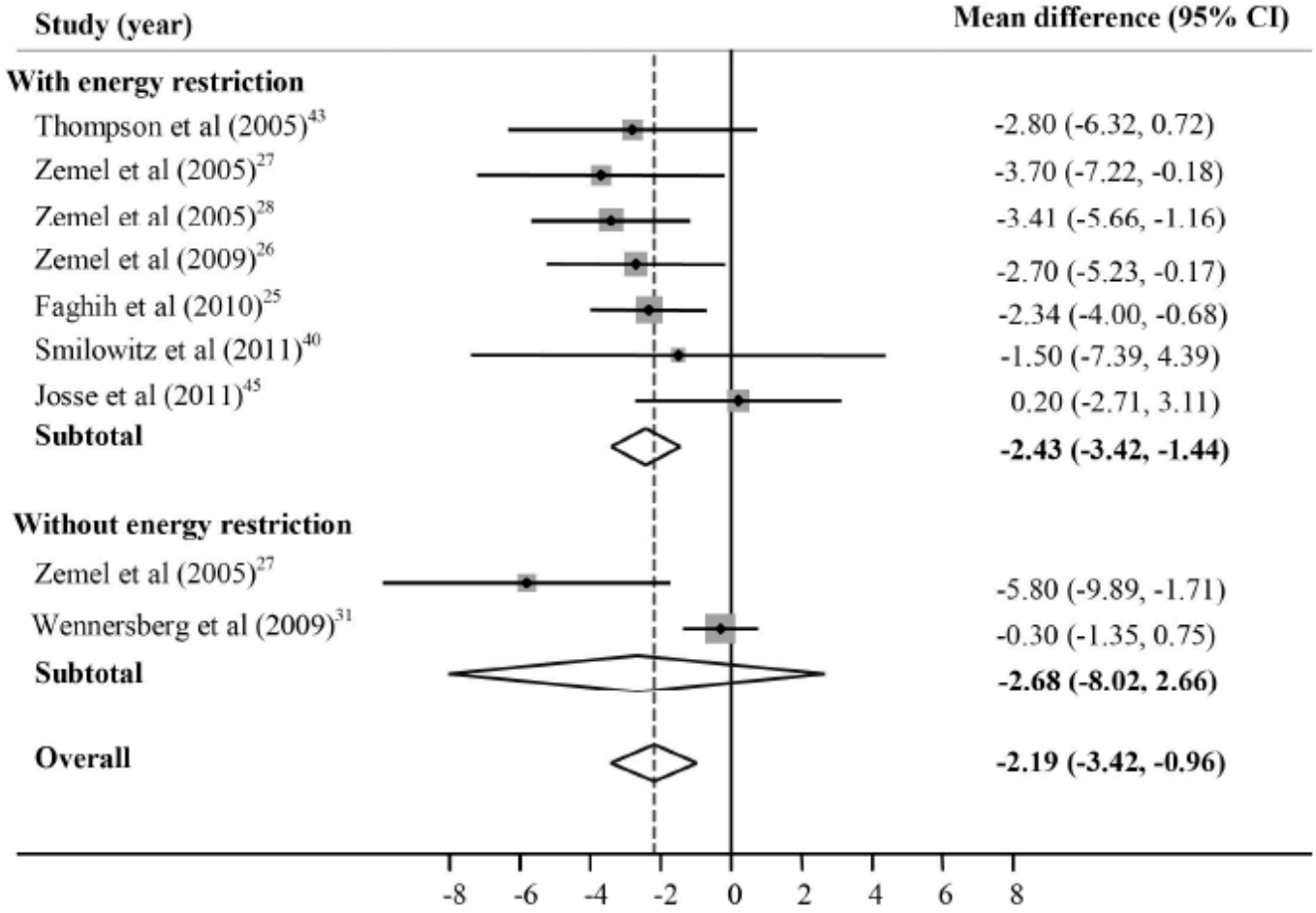
*Total number =440, 73% female, mean baseline waist circumference 96.5 (SD 7.5) cm, median study duration 10 (IQR 4-16) weeks

Adults | RCT | Waist circumference | Abargouei et al 2012 | High vs. low dairy intake

Forest plot of randomized controlled trials illustrating weighted mean difference in waist circumference (WC) between dairy-supplemented and control groups for all eligible studies as well as for subgroup analysis based on energy restriction. For all studies combined, the significant effect of dairy consumption on WC was seen (P for heterogeneity= 0.03, Q test, I-square=53.4% and Tau-square=1.63). For 6 RCTs that administered energy restriction, high dairy intake has been resulted in a greater reduction in WC compared with that in control group (P for heterogeneity= 0.60, Q test, I-square=0.0% and Tau-square=0.0). Such finding was not obtained for 2 RCTs that had not administered energy restriction (P for heterogeneity= 0.01, Q test, I-square=84.7% and Tau-square=12.8) (Abargouei et al 2012).

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: nil. However, Faghih 2010 is unique to all meta-analyses by Abargouei et al (2012).

Figure 32 Meta-analysis of RCTs in adults – Dairy – Abargouei et al 2012 – Waist circumference



Adults | RCT | Body fat | Booth et al 2015 | Dairy food supplementation

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: nil. However, the following are only found in the other Booth et al (2015) meta-analysis: Frestedt 2008; Gilbert 2011; Torres 2013; Witbracht 2013; Haub 2005; Jones 2013; Thomas 2010.

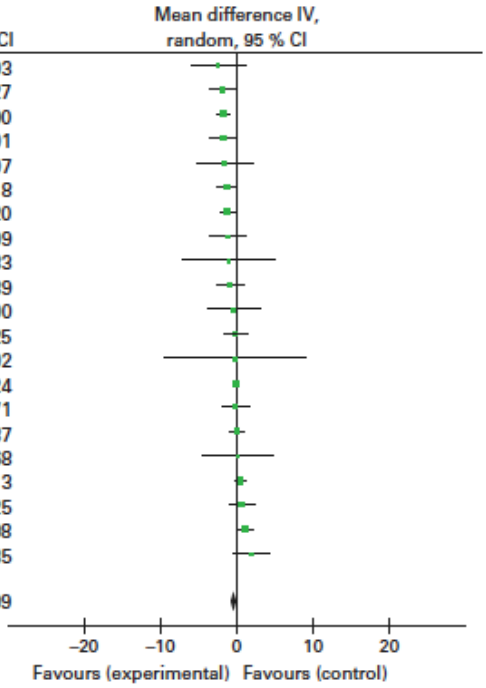
Figure 33 Meta-analysis of RCTs in adults – Dairy – Booth et al 2015 – Body fat

(C)

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference	95 % CI
Zemel *et al.* (2004)[37]	–7·16	4·05	11	–4·81	3·86	10	1·5	–2·35	–5·73, 1·03
Zemel *et al.* (2009)[40]	–4·43	2·54	23	–2·69	2·7	26	5·1	–1·74	–3·21, –0·27
Stancliffe *et al.* (2011)[43]	–1·3	0·9	20	0·4	1·6	20	8·5	–1·70	–2·50, –0·90
Zemel *et al.* (2005)[68]	–4·43	1·99	18	–2·75	2·9	16	4·3	–1·68	–3·37, 0·01
Thompson *et al.* (2005)[2]	–9	6	22	–7·5	6·6	26	1·4	–1·50	–5·07, 2·07
Josse *et al.* (2011)[62]	–4·84	2·73	30	–3·64	2·74	30	5·5	–1·20	–2·58, 0·18
Frestedt *et al.* (2008)[59]	–2·81	2·12	31	–1·62	1·75	28	7·5	–1·19	–2·18, –0·20
Harvey-Berino *et al.* (2005)[8]	–10·1	3·6	23	–9	3·8	21	3·0	–1·10	–3·29, 1·09
Gilbert *et al.* (2011)[60]	–6	8·8	13	–5	5·9	12	0·5	–1·00	–6·83, 4·83
Torres *et al.* (2013)[66]	–4·5	2·97	18	–3·7	2·06	17	4·4	–0·80	–2·49, 0·89
Witbracht *et al.* (2013)[44]	–5	5·2	24	–4·7	6·8	27	1·6	–0·30	–3·60, 3·00
Van Loan *et al.* (2011)[67]	–5·2	2·8	35	–5·1	3	36	5·6	–0·10	–1·45,1·25
Palacios *et al.* (2011)[38]	–0·52	11	8	–0·43	7·2	8	0·2	–0·09	–9·20, 9·02
Chee *et al.* (2003)[69]	–0·04	1·14	91	–0·04	0·18	82	11·5	0·00	–0·24, 0·24
Haub *et al.* (2005)[5]	1·3	2·6	17	1·3	2·7	20	4·3	0·00	–1·71, 1·71
Wennersberg *et al.* (2009)[73]	–0·3	2·2	57	–0·4	2	56	8·7	0·10	–0·67, 0·87
Jones *et al.* (2013)[61]	–1·6	6·6	20	–1·8	7·4	18	0·9	0·20	–4·28, 4·68
Lau *et al.* (2001)[72]	0·42	1·95	95	–0·14	1·99	90	9·9	0·56	–0·01, 1·13
Kukuljan *et al.* (2009)[71]	0·7	3·66	45	–0·1	3·29	44	5·2	0·80	–0·65, 2·25
Crichton *et al.* (2012)[70]	1·3	2·4	36	0·2	1·8	36	7·5	1·10	0·12, 2·08
Thomas *et al.* (2010)[64]	–1·8	2·1	14	–3·8	4·1	15	2·7	2·00	–0·35, 4·35
Total (95 % CI)			651			638	100·0	–0·36	–0·80, 0·09

Heterogeneity: τ^2=0·43; χ^2=50·76, df=20 (P=0·0002); I^2=61 %

Test for overall effect: Z=1·58 (P=0·11)

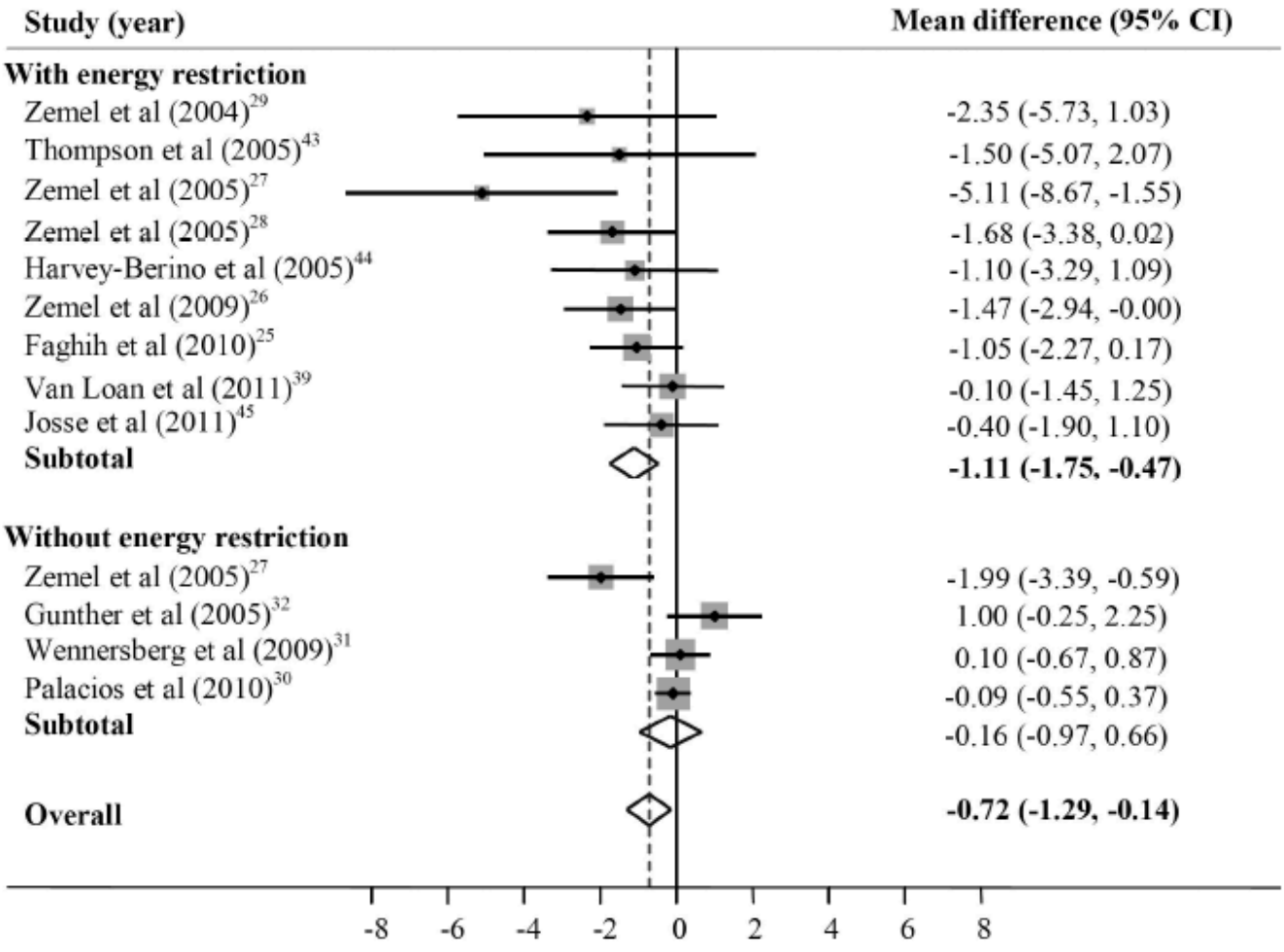


Adults | RCT | Fat mass | Abargouei et al 2012 | High vs. low dairy intake

Forest plot of randomized controlled trials illustrating weighted mean difference in fat mass between dairy-supplemented and control groups for all eligible studies as well as for subgroup analysis based on energy restriction. For all eligible studies combined, the significant effect of dairy intake on reducing fat mass was observed (P for heterogeneity< 0.01, Q test, I-square=56.1% and Tau-square=0.51). For 7 RCTs with energy restriction, the effect was also significant (P for heterogeneity= 0.33, Q test, I-square=12.0% and Tau square=0.11). However, data from 4 RCTs, that did not administered energy restriction, indicated no significant effect of dairy intake on body fat mass (P for heterogeneity= 0.02, Q test, I-square=70.7% and Tau-square=0.46) (Abargouei et al 2012).

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: nil. However, Faghih 2010 is unique to all meta-analyses by Abargouei et al (2012).

Figure 34 Meta-analysis of RCTs in adults – Dairy – Abargouei et al 2012 – Fat mass

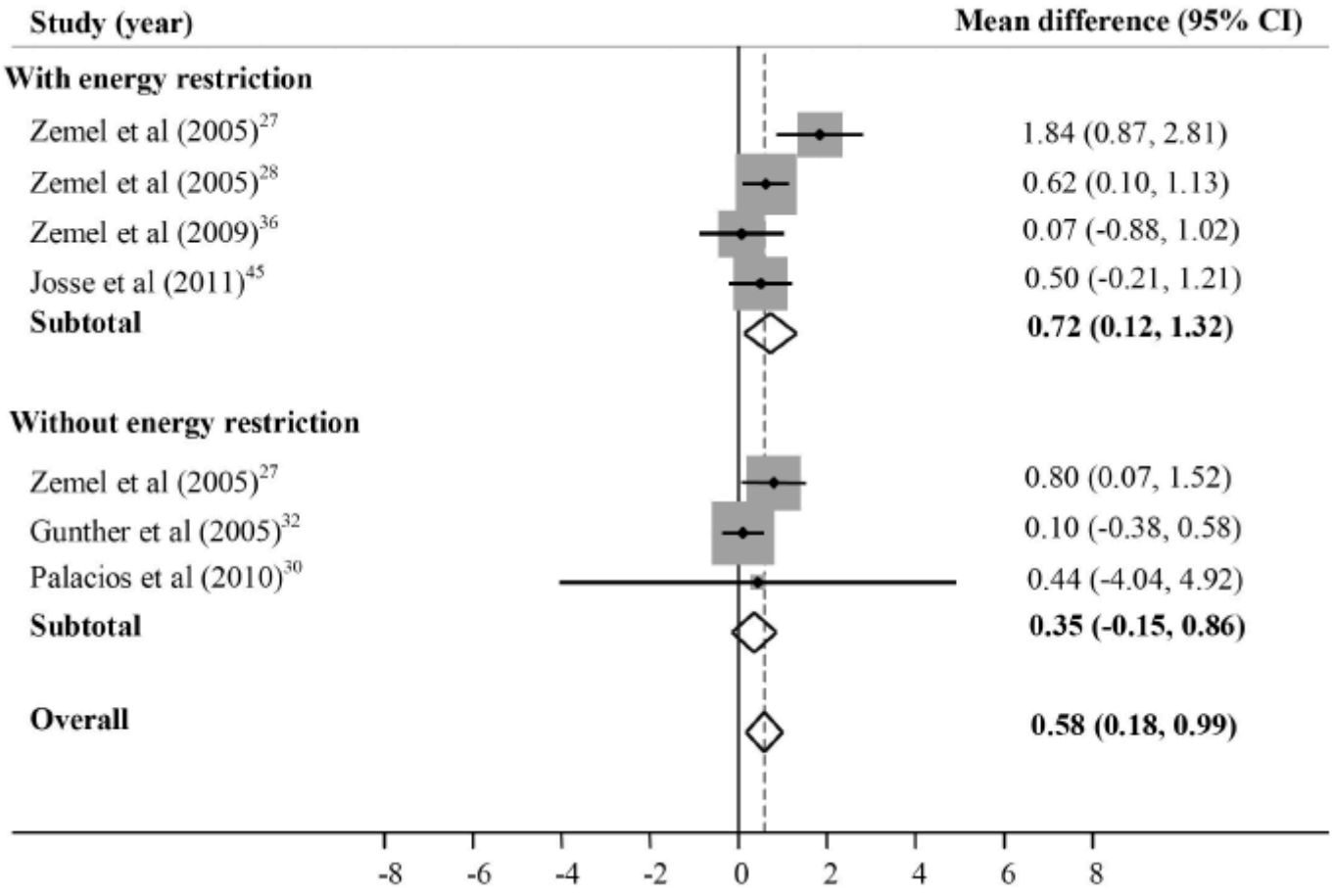


Adults | RCT | Lean mass | Abargouei et al 2012 | High vs. low dairy intake

Forest plot of randomized controlled trials illustrating weighted mean difference in Lean body mass between dairy-supplemented and control groups for all eligible studies as well as for subgroup analysis based on energy restriction. For all studies combined, the significant effect of dairy consumption on WC was seen (P for heterogeneity= 0.07, Q test, I-7 square=48.9% and Tau-square=0.13). For 4 RCTs that administered energy restriction, high dairy intake has been resulted in a greater reduction in WC compared with that in control group (P for heterogeneity= 0.06, Q test, I-square=59.7% and Tau-square=0.21). Such finding was not obtained for 3 RCTs that had not administered energy restriction (P for heterogeneity= 0.29, Q test, I-square=19.5% and Tau-square=0.05) (Abargouei et al 2012).

Please note – there is overlap of included studies between this meta-analysis and the others (see table on page 227). Studies unique to this meta-analysis are: nil. However, Faghih 2010 is unique to all meta-analyses by Abargouei et al (2012).

Figure 35 Meta-analysis of RCTs in adults – Dairy – Abargouei et al 2012 – Lean mass



3.2 Meta-analyses of prospective cohort studies in adults

Table 46 Meta-analyses of prospective cohort studies in adults – Milk and dairy products

Adults					
Meta-analyses of prospective cohort studies					
MD=mean difference; OR=odds ratio; RR=relative risk; HR=hazard ratio. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Weight	Schwingshakl et al (2016)	Highest vs. lowest total dairy intakes over 1 year 1–12.9 years	MD	**-16.66 (-75.57, 39.24) g** **INV**	Studies=5; n=43,836 I^2=82%
Waist circumference		Highest vs. lowest total dairy intakes over 1 year 1–12.9 years	MD	**-0.07 (-0.21, 0.08) cm** **INV**	Studies=4, n=9,200 I^2=74%
Risk estimate for overweight		Dairy consumption (undefined) 6.6–11.2 years	OR/RR/HR	**0.87 (0.76, 1.00)** **INV** ***Borderline signif***	Studies=3; n=30,111 I^2=0%
Risk estimate for abdominal obesity		Dairy consumption (undefined) 3.2–20 years	OR/RR/HR	**0.85 (0.76, 0.95)** **INV**	Studies=6; n=26,167 I^2=81%

One review conducted four meta-analyses across four outcomes: weight; waist circumference; risk estimate for overweight; and risk estimate for abdominal obesity. All results reported an inverse association between intake of dairy and measure of adiposity; one result was statistically significant and one was borderline significant.

In the meta-analysis for weight, the sample size per study ranged from 76 to 19,615 participants; the smallest study also had the shortest follow up (one year). One of the studies was conducted only in men. For the waist circumference meta-analysis, the sample size per study ranged from 76 to 3,440 participants.

In the risk of overweight meta-analysis, one study was conducted with subjects overweight at baseline (Pereira et al 2002) and for another study, the exposure was specifically defined as yoghurt intake (Martinez-Gonzalez et al 2014).

The meta-analysis of risk of abdominal obesity used studies of exposures across a variety of dairy products (milk, yoghurt, butter, cream), with one study (Shin et al 2013) investigating total dairy intake.

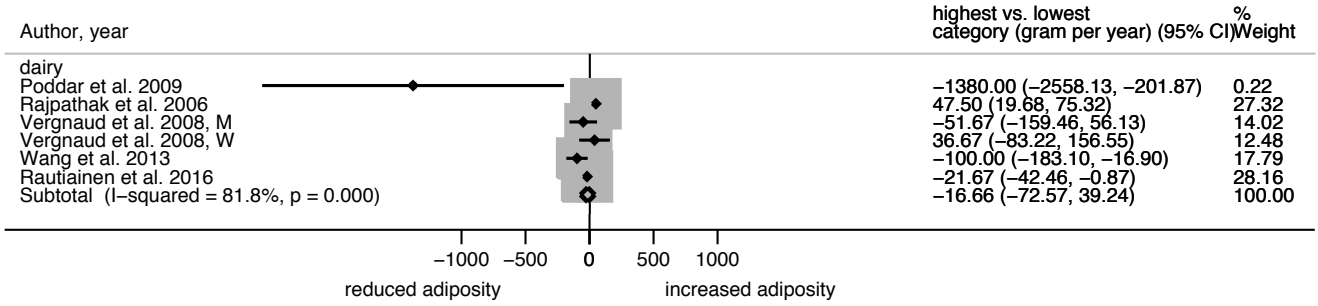
Schwingshakl et al (2016) have also conducted 12 further meta-analyses within this review, stratifying between low fat- and high fat dairy products, and between different dairy products (milk, cheese, and yoghurt). One was a statistically significant result: risk estimate for “adiposity” with the exposure of ‘whole fat dairy’, **OR/RR/HR 0.88 (0.80, 0.97)**. This risk estimate pools a variety of outcomes including changes in waist circumference, waist circumference thresholds, waist-to-hip ratio >1, risk of obesity, risk of abdominal obesity, and weight gain of >1kg. For two of the studies, the data used by the review are with respect to intake of butter (Holmberg et al 2013; Rosell et al 2006).

The forest plots corresponding to the above meta-analyses are presented below.

Adults | Prospective cohort studies | Weight | Schwingshakl et al 2016 | Highest vs. lowest total dairy intakes over one year

Forest plot of mean changes in body weight (gram/year) comparing highest vs. lowest dairy consumption category (Schwingshakl et al 2016).

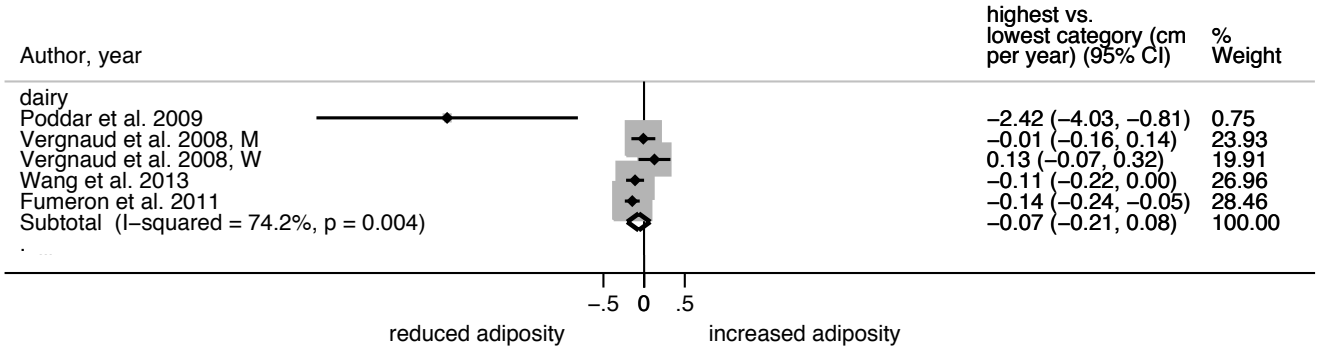
Figure 36 Meta-analysis of prospective cohort studies in adults – Dairy – Schwingshakl et al 2016 – Weight



Adults | Prospective cohort studies | Waist circumference | Schwingshakl et al 2016 | Highest vs. lowest total dairy intakes over one year

Forest plot of mean changes in waist circumference (cm/year) comparing highest vs. lowest dairy consumption category (Schwingshakl et al 2016).

Figure 37 Meta-analysis of prospective cohort studies in adults – Dairy – Schwingshakl et al 2016 – Waist circumference

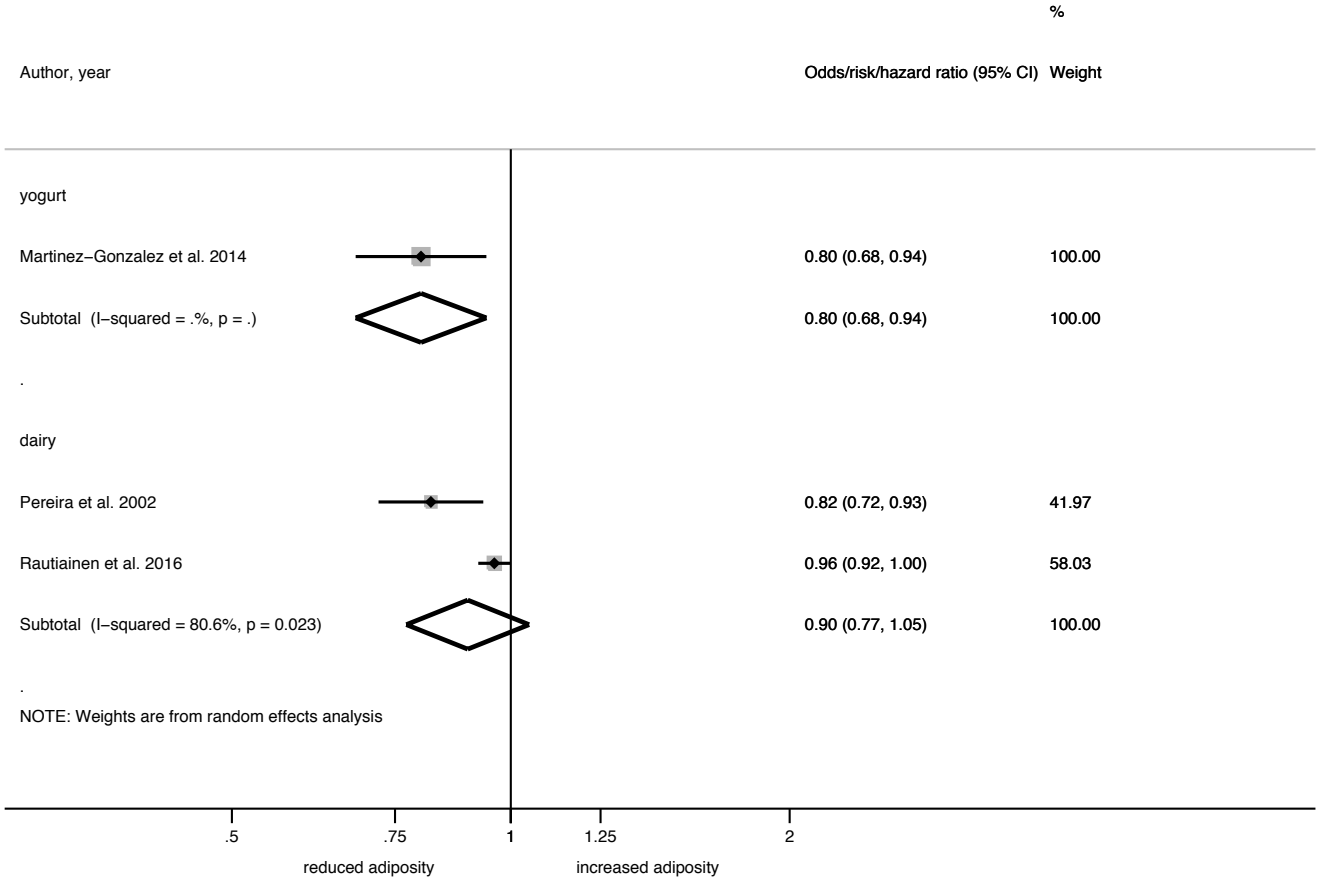


Adults | Prospective cohort studies | Risk estimate for overweight | Schwingshakl et al 2016 | Dairy consumption

Forest plot showing pooled results of OR/RR/HR with 95% CI for overweight comparing categories of dairy intakes (Schwingshakl et al 2016).

*Please note – the total pooled result [**0.87 (0.76, 1.00)**] is reported in the review's text but is not on the figure here.*

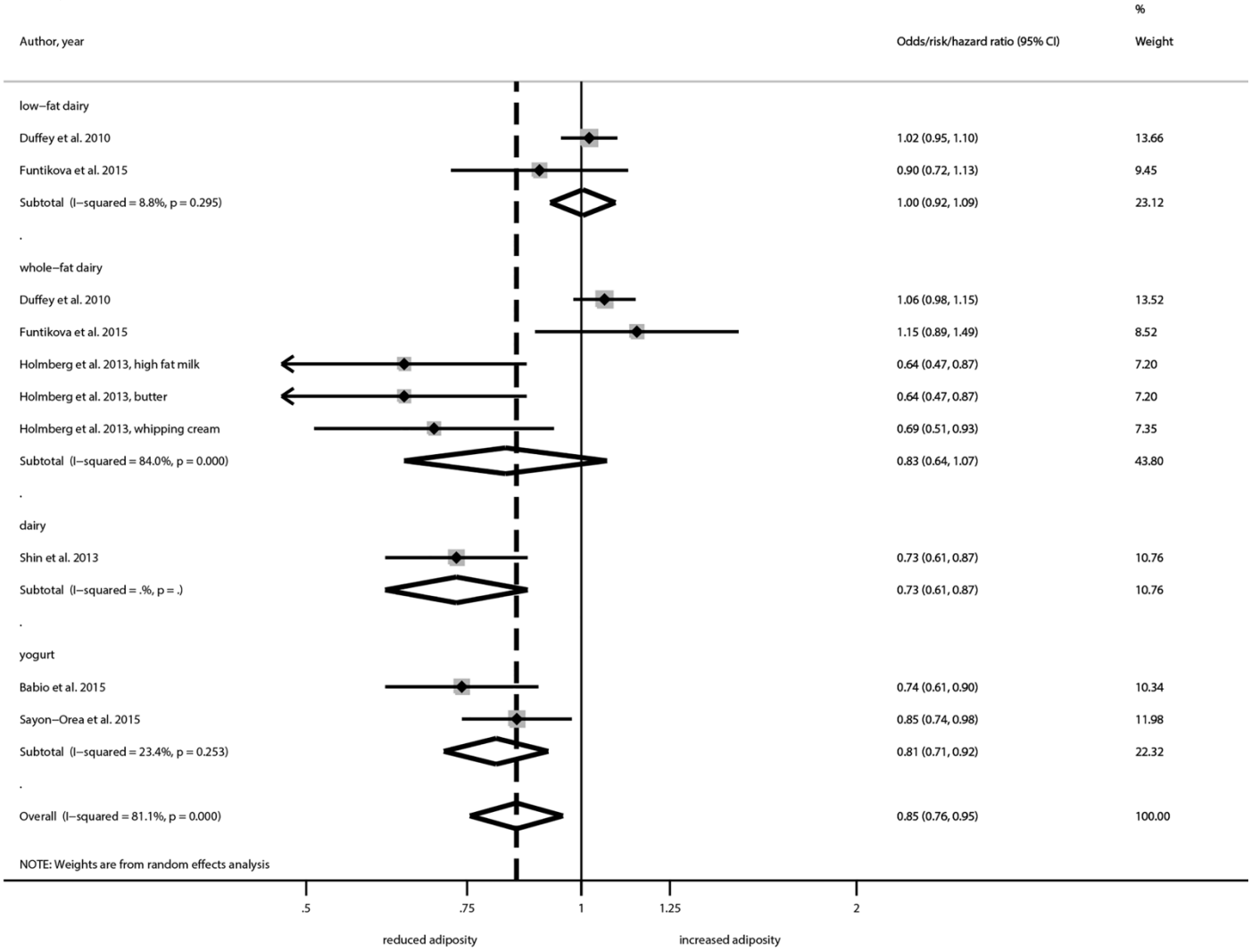
Figure 38 Meta-analysis of prospective cohort studies in adults – Dairy – Schwingshakl et al 2016 – Risk estimates for overweight



Adults | Prospective cohort studies | Risk estimate for abdominal obesity | Schwingshakl et al 2016 | Dairy consumption

Forest plot showing pooled OR/RR/HR with 95% confidence intervals for abdominal obesity comparing categories of dairy intakes (Schwingshakl et al 2016).

Figure 39 Meta-analysis of prospective cohort studies in adults – Dairy – Schwingshakl et al 2016 – Risk estimates for abdominal obesity



3.3 Individual RCTs in adults, not in meta-analyses

Table 47 Results of individual RCTs in adults – Milk and dairy products

Adults				
RCTs				
Ca = calcium; $CaCO_3$ = calcium carbonate. Significant results are highlighted in **red**.				
Outcome	***Publication*** ***Review***	***Intervention description***	***Results***	***n***
BMI	Prince et al. 1995 / Devine et al. 1996 Barr (2003) *and* Lanou et al (2008)	(1) Placebo vs. (2) milk powder [1g Ca per day] vs. (3) Ca tablets [1g per day] vs. (4) Ca tablets + exercise 2 years	(1) **Data not reported** (2) **No significant difference start vs. finish** (3) **No significant difference start vs. finish** (4) **Data not reported**	168
Weight change	Storm et al. 1998 Barr (2003)	~250ml milk per day vs. 1g per day $CaCO_3$ or placebo 2 years	"**No significant differences in change in weight or body composition among treatment groups** [personal communication between study and review authors]"	60
	Cleghorn et al. 2001 Barr (2003) *and* Lanou et al (2008)	3L per week Ca fortified milk vs. no intervention 2 years	**0.06kg (-0.71, 0.83) kg**	115

Four RCTs were identified examining dairy intake and adiposity in adults, none of which included more than 1,000 participants. Two publications were reported together (Prince et al 1995 and Devine et al 1996) in the corresponding reviews (Barr 2003, and Lanou and Barnard 2008) as they relate to the same trial. All studies came from systematic reviews identified by the USDA (2010) review. Three results were reported across two outcomes (BMI and weight), none of which were statistically significant. The direction of association was reported for one result (Cleghorn et al 2001), indicating a positive relationship between dairy intake and weight. This result was obtained through personal communication between the review and study authors.

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 48 Results of individual prospective cohort studies in adults – Milk and dairy products

Adults					
Prospective cohort studies					
ΔWC_{BMI} = waist circumference for a given BMI; MD = mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Snijder et al. 2008 Schwingshakl et al (2016) *and* Louie et al (2011)	Per serving increase of dairy 6.4 years	MD	**11.56 (-13.55, 36.67) g** **+VE**	1,124
	Nikolaou et al. 2014 Schwingshakl et al (2016)	Intake of dairy products (2-3 servings per day) 9 months	Beta-coefficient	**-0.001** p=0.02 Units=unclear **INV**	1,275
BMI	Zong et al. 2014 Schwingshakl et al (2016)	Intake of >1 serving of dairy foods per day vs. non-consumers 6 years	**-0.30 (-0.54, -0.05) kg/m^2** p for trend=0.001 **INV**		1,903
Waist circumference	Halkjaer et al. 2009 Schwingshakl et al (2016) *and* Louie et al (2011)	Per 60kcal increased whole fat dairy intake per day *(female)* 5 years	Beta-coefficient	**-0.09 (-0.15, -0.03) cm** **INV**	22,570
		Per 60kcal increased whole fat dairy intake per day *(male)* 5 years	Beta-coefficient	**-0.01 (-0.05, 0.03) cm** **INV**	20,126
		Per 60kcal increased low fat dairy intake per day *(female)* 5 years	Beta-coefficient	**-0.04 (-0.08, 0.01) cm** **INV**	22,570
		Per 60kcal increased low fat dairy intake per day *(male)* 5 years	Beta-coefficient	**-0.001 (-0.04, 0.03) cm** **INV**	20,126
	Zong et al. 2014 Schwingshakl et al (2016)	Intake of >1 serving of dairy foods per day vs. non-consumers 6 years	**-0.93 (-1.79, -0.07) cm** p for trend=0.045 **INV**		1,903
ΔWC_{BMI}	Romaguera et al. 2011 Schwingshakl et al (2016)	Per 100kcal increased intake of dairy products over 1 year 5.5 years	Beta-coefficient	**-0.01 (-0.02, -0.01) cm** p<0.001 **INV**	48, 631

Eight prospective cohort studies in adults investigated dairy intake and adiposity, of which five included more than 1,000 participants. These five studies provided nine results across four outcomes: weight change; BMI; waist circumference; and waist circumference for a given BMI. One result reported a non-significant positive association. Eight results reported inverse associations, of which five were statistically significant. All the studies examined increasing dairy intake; however, Halkjaer et al (2009) distinguished between low fat and whole fat dairy.

Romaguera et al (2011) used data from eight centres in the EPIC cohort, the study by Zong et al (2013) was conducted in China with middle age and old subjects, Halkjaer et al (2009) was conducted with Danish adults, Nikolaou et al (2014) investigated first year undergraduate students, and the study by Snijder et al (2008) was conducted in Holland.

Snijder et al (2008), Halkjaer et al (2009), and Romaguera et al (2011) adjusted for energy intake.

The remaining three studies provided eight results across four outcomes: weight; waist circumference; odds of weight gain; and odds of weight loss. Four results reported non-significant positive associations and four results reported inverse associations (of which one was statistically significant).
Studies n<1000: Drapeau et al. 2004, Hosseini Esfahani et al. 2014, and Kaikkonen et al. 2015.

4. Possible mechanisms

As summarised by Schwingshackl et al (2016):

- **The role of calcium**:
  - Modulation of adipocyte lipid metabolism and fatty acid absorption from gastrointestinal tract by the effects of dietary calcium on intracellular calcium.
  - High calcium intake may reduce lipogenesis and increase lipolysis by hormone regulation.
- **Other constituents of dairy products**:
  - Whey protein – effects on muscle sparing and lipid metabolism
  - Conjugated linoleic acid – regulation of adipogenesis, inflammation, and lipid metabolism
  - Milk proteins – positive influence on satiety; insulinotropic effect.
- **Specific dairy products**:
  - Yoghurts
    - Nutrients therein have a higher bioavailability compared to other forms of dairy.
    - Gut microbiota plays a decisive role in weight control – probiotic yoghurts may enhance growth of beneficial intestinal microbiota and modulate gut function through regulation of the immune system.

5. Summary of evidence

5.1 Children

No meta-analyses examining dairy intake in children and adiposity were identified. Four published reviews identified a total of 18 unique studies (RCTs and prospective cohort studies), providing 33 results. The results were mixed: 16 results reported no association and did not indicate a direction; 10 reported positive associations (three statistically significant); and seven reported inverse associations (four statistically significant). The majority of RCTs did not comment on the extent of compensation in energy intake when dairy was added as the intervention. Of the prospective cohort studies, the majority (14/20 results) examined milk as the exposure.

5.2 Adults

Eight meta-analyses of RCTs across three reviews reported results for five outcomes. Six of the eight results reported an inverse relationship between dairy intake and adiposity (two statistically significant); two reported a positive relationship (both significant), one with [total] weight change, and one with lean mass change. Four meta-analyses of prospective cohort studies from one review reported results for four outcomes. All results reported an inverse association, one of which was significant. The exposure definition varied between the included studies. Twelve publications reported 20 results: six reported positive associations (none significant), 12 reported inverse associations (six statistically significant), and two reported no association.

2.6 Fast foods

1. Evidence identified for 2017 update

Table 49 Published reviews identified for the 2017 update – Fast foods

Source	No. of reviews	Authors [quality]
NICE (2014) report	5	Bezerra et al. 2012 [++]; Mesas et al. 2012 [+]; U.S Department of Agriculture Nutrition Evidence Library 2010a [+]; Summerbell et al. 2009 [++]; Rosenheck 2008 [+]
USDA DGAC (2015) scientific report [++]	Y	
Supplementary literature search August 2016	Nil	-

Notes on the evidence:

- No additional meta-analyses were identified via the supplementary literature search, so all the evidence presented here is derived from the NICE (2014) report and the USDA DGAC (2015) report (included as per protocol, see **Appendix**).
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.
- The relevant studies identified across the included published reviews tended to define the exposure in two broad categories: (i) intake of fast food and (ii) eating out at restaurants. The results are grouped together under these headings; where possible potential overlap is noted.

2. Children

2.1 Meta-analysis of RCTs in children

Nil

2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 50 Results of individual prospective cohort studies in children – Fast foods

Children					
Prospective cohort studies					
OR=odds ratio; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI change	Taveras et al. 2005 *USDA (2010)* and *USDA DGAC (2015)*	Increased consumption of fried food away from home from baseline to follow up 3 years	Beta coefficient	**0.21 (0.03, 0.39) kg/m²** **+VE**	14,355
		Decreased consumption of fried food away from home from baseline to follow up 3 years	Beta coefficient	**-0.03 (-0.25, 0.19) kg/m²** **+VE**	
	Laska et al. 2012 *USDA DGAC (2015)*	Frequency of fast food purchases over one month 2 years	Girls: **Not significant** Boys: **Not significant** **NIL**		693
BMI z score change	Niemeier et al. 2006 *USDA (2010), Summerbell et al (2009)* and *USDA DGAC (2015)*	Frequency of fast food consumption at baseline 5 years	Beta coefficient	**0.02 SE ±0.01** p<0.05 **+VE**	9,919
	Fraser et al. 2012 *USDA DGAC (2015)*	Frequency of fast food consumption at baseline 2 years	Beta coefficient	**0.0822 SE ±0.028** p<0.05 **+VE**	4,022
	Thompson et al. 2004 *Mesas et al (2012), USDA (2010), Summerbell et al (2009), Rosenheck et al (2008)* and *USDA DGAC (2015)*	Frequency of 'quick service' foods at baseline (never; once per week; ≥2 times per week) 4–7 years	Never: **0.28 SE ±0.07** Once per week: **0.20 SE ±0.10** ≥2 times per week: **0.82 SE ±0.15** F=6.49, p=0.0023 **+VE**		101
	MacFarlane et al. 2009 *USDA DGAC (2015)*	Frequency of fast food consumption 3 years	**Not significant** **NIL**		293
% body fat	Fraser et al. 2012 *USDA DGAC (2015)*	Frequency of fast food consumption at baseline 2 years	Beta coefficient	**2.063 SE ±0.3713 %** p<0.05 **+VE**	4,022
	Laska et al. 2012 *USDA DGAC (2015)*	Frequency of fast food purchases over one month 2 years	Girls: **Not significant** Boys: **Not significant** **NIL**		693
	MacFarlane et al. 2009 *USDA DGAC (2015)*	Frequency of fast food consumption 3 years	**Not significant** **NIL**		293

Risk of overweight	Haines et al. 2007 *USDA (2010)* and *USDA DGAC (2015)*	Fast food consumption in days per week at baseline *(girls)* 5 years	OR	**0.88 (0.79, 0.98)** **INV**	1,380
		Fast food consumption in days per week at baseline *(boys)* 5 years	OR	**1.03 (0.90, 1.17)** **+VE**	1,119
Risk of obesity	Fraser et al. 2012 *USDA DGAC (2015)*	Frequency of fast food consumption at baseline 2 years	OR	**1.23 (1.02, 1.49)** **+VE**	4,022

Seven individual prospective cohort studies investigating fast food intake and adiposity in children provided 13 results across five outcomes: BMI change; BMI z score change; percentage body fat; risk of overweight; and risk of obesity. Eight results reported positive associations, of which six were statistically significant. One study reported a statistically significant inverse association in an all female cohort. Four results reported no association. Baseline age range was five to 15.9 years.

The studies varied in their definitions of 'fast foods'. For example, Taveras et al (2007) defined the exposure as 'fried food consumed away from home', Thompson et al (2004) referred to 'quick service' foods, and Laska et al (2012) asked participants "in past month how many times did you buy food at a restaurant where food is ordered at a counter or drive through window (no waiters/waitresses)?".

Neimeier et al (2006) investigated a cohort of adolescents as they transitioned to young adulthood, with mean age at recruitment of 15.9 years and mean age at follow up of 21.3 years.

Thompson et al (2004) investigated an all-female cohort, all the other studies had mixed gender cohorts. The USDA DGAC (2015) review authors noted that of the studies included in that review, findings seemed to indicate possible gender differences, which may be related to reverse causality.

The studies varied in adjustment for potentially confounding factors. Niemeier et al (2006) was the most highly adjusted (for ethnicity, month of interview, parental education, physical activity, sedentary behaviour, and change in sedentary behaviour).

Taveras et al (2005) = Growing Up Today study; Laska et al (2012) = IDEA and ECHO cohorts; Niemeier et al (2006) = NLSAH; Fraser et al (2012) = ALSPAC; MacFarlane et al (2009) = HEAPS; Haines et al (2007) = Project EAT study; Thompson et al (2004) = a cohort examined via the Massachusetts Institute of Technology.

3. Adults

3.2.1 Meta-analysis of RCTs in adults

Nil

3.2 Meta-analyses of prospective cohort studies in adults

Nil

3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Intake of fast food

Table 51 Results of individual prospective cohort studies in adults – Fast foods

Adults					
Prospective cohort studies					
SE=standard error; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	French et al. 2000 *Bezerra et al (2012), Mesas et al (2012), USDA (2010), Summerbell et al (2009), Rosenheck et al (2008)* and *USDA DGAC (2015)*	Per increase of one fast food meal per week 3 years	Beta coefficient	**0.72 SE ±0.20 kg** p=0.01 **+VE**	891
	Duffey et al. 2009 *Bezerra et al (2012)* and *USDA DGAC (2015)*	Frequency of meals at fast food restaurants per week at baseline 13 years	Beta coefficient	**0.15 SE ±0.05 kg** p<0.001 **+VE**	3,643
	Pereira et al. 2005 *Bezerra et al (2012), Mesas et al (2012), USDA (2010), Summerbell et al (2009), Rosenheck et al (2008)* and *USDA DGAC (2015)*	Frequency of fast food consumption at baseline *(black people)* 15 years	Beta coefficient	**2.22 SE ±0.72 kg** p=0.0014 **+VE**	1,444
		Frequency of fast food consumption at baseline *(white people)* 15 years	Beta coefficient	**1.56 SE ±0.55 kg** p=0.0064 **+VE**	1,587
		Change in frequency of fast food consumption over study duration *(black people)* 15 years	Beta coefficient	**0.74 SE ±0.45 kg** p=0.1053 **+VE**	1,444
		Change in frequency of fast food consumption over study duration *(white people)* 15 years	Beta coefficient	**1.84 SE ±0.44 kg** p<0.0001 **+VE**	1,587
	Li et al. 2009 *USDA (2010)* and *USDA DGAC (2015)*	More than 1–2 meals at fast food restaurants per week vs. no consumption 1 year	Beta coefficient	**0.65 SE ±0.32 kg** p<0.05 **+VE**	1,145
BMI change	Jeffery et al. 1998 *Bezerra et al (2012)* and *Summerbell et al (2009)*	Frequency per week of eating at fast food restaurants *(high income female)* 1 year	Beta coefficient	**0.02 (-0.05, 0.09) kg/m^2** **+VE**	529
		Frequency per week of eating at fast food restaurants *(low income female)*	Beta coefficient	**-0.06 (-0.20, 0.08) kg/m^2** **INV**	332

		1 year			
		Frequency per week of eating at fast food restaurants *(male)* 1 year	Beta coefficient	**-0.23 (-0.56, 0.11) kg/m²** **INV**	198
	Duffey et al. 2007 *Bezerra et al (2012), Mesas et al (2012), USDA (2010), Rosenheck et al (2008)* and *USDA DGAC (2015)*	Increase in frequency of fast food consumption across study period 3 years	Beta coefficient	**0.20 (0.005, 0.393) kg/m²** p=0.044 **+VE**	3,394
		Increase in frequency of fast food and restaurant food consumption across study period 3 years	Beta coefficient	**0.29 (0.060, 0.509) kg/m²** p=0.013 **+VE**	3,394
Waist circumference	Duffey et al. 2009 *Bezerra et al (2012)* and *USDA DGAC (2015)*	Frequency of meals at fast food restaurants per week at baseline 13 years	Beta coefficient	**0.12 SE ±0.04 cm** p>0.05 **+VE**	3,643
	Li et al. 2009 *USDA (2010)* and *USDA DGAC (2015)*	More than 1–2 meals at fast food restaurants per week vs. no consumption 1 year	Beta coefficient	**1.06 SE ±0.41 cm** p<0.05 **+VE**	1,145
Odds of weight maintenance	Ball et al. 2002 *Bezerra et al (2012)* and *Summerbell et al (2009)*	Occasional consumption of fast food relative to never/rarely 4 years	OR	**0.85 (0.75, 0.96)** **+VE**	8,726
		Frequent consumption of fast food relative to never/rarely 4 years	OR	**0.88 (0.76, 1.02)** **+VE**	
Odds of weight gain	Bes-Rastrollo et al. 2006 *Mesas et al (2012)* and *Rosenheck et al (2008)*	Highest vs. lowest quintile of fast food consumption 28.5 months	OR	**1.2 (1.02, 1.41)** **+VE**	7,194
Risk of obesity	Boggs et al. 2013 *USDA DGAC (2015)*	Frequency of item specific fast food consumption (more than once per week vs. fewer than five times per year): Hamburgers 14 years	HR	**1.27 (1.14, 1.41)** p for trend<0.001 **+VE**	19,479
		Frequency of item specific fast food consumption (more than once per week vs. fewer than five times per year): Fried chicken 14 years	HR	**1.08 (0.96, 1.21)** p for trend=0.02 **+VE**	19,479
		Frequency of item specific fast food consumption (more than once per week vs. fewer than five times per year): Pizza 14 years	HR	**1.08 (0.92, 1.27)** p for trend=0.04 **+VE**	19,479
		Frequency of item specific fast food consumption (more than once per week vs. fewer than five times per year): Chinese food 14 years	HR	**1.20 (1.05, 1.37)** p for trend=0.05 **+VE**	19,479
		Frequency of item specific fast food consumption (more than once per week vs. fewer than five times per year): Mexican food 14 years	HR	**0.92 (0.74, 1.14)** p for trend=0.78 **INV**	19,479

		Frequency of item specific fast food consumption (more than once per week vs. fewer than five times per year): Fried fish 14 years	HR	**0.92 (0.75, 1.12)** p for trend=0.78 **INV**	19,479

Seven prospective cohort studies (nine publications) investigating intake of fast food and adiposity in adults provided 23 results across six outcomes: weight change; BMI change; waist circumference; odds of weight maintenance; odds of weight gain; and risk of obesity. Nineteen results reported positive associations, of which 15 were statistically significant. Four results reported inverse associations; none were statistically significant.

Three studies were conducted in all female cohorts: French et al (2000), Ball et al (2002), and Boggs et al (2013).

Ball et al (2002) reported the odds of maintaining weight within 5% of baseline and found those who consumed fast food occasionally had 15% lower odds of maintaining their weight relative to those who consumed fast food never or rarely; the odds of weight maintenance were 12% lower for those who consumed fast food frequently compared to those who consumed never or rarely.

Boggs et al (2013) reported results in relation to specific foods items; these can be regarded as foods typically available from fast food establishments, although the study did not distinguish between food providers (fast food or restaurant food). The hazard ratio was significant for two out of six food items (hamburgers and Chinese food); however, the p for trend was significant for fried chicken and pizza intakes as well.

All the studies specifically asked participants regarding fast food intake or visits to fast food establishments; however, it was not clear the extent to which the definitions used overlapped.

French et al (2000) = Pound of Prevention Study; Duffey et al (2007), Duffey et al (2009), and Pereira et al (2005) = CARDIA study; Li et al (2009) = Portland Neighborhood Environment and Health Study; Jeffery et al 1998) = Supplemental Nutrition Program for Women, Infants and Children; Ball et al (2002) = Australian Longitudinal Study on Women's Health; Bes-Rastrollo et al (2006) = SUN cohort; Boggs et al (2013) = Black Women's Health Study.

Eating at restaurants and cafeterias

Table 52 Results of individual prospective cohort studies in adults – Eating in restaurants and cafeterias

Adults					
Prospective cohort studies					
OR=odds ratio; HR=hazard ratio; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Bes-Rastrollo et al. 2010 *Bezerra et al (2012), Mesas et al (2012)* and *USDA DGAC (2015)*	≥2 times per week eating out relative to never/rarely 4.4 years	Beta coefficient	**129 (62, 197) g per year** p<0.001 **+VE**	9,182
	Duffey et al. 2009 *Bezerra et al (2012)* and *USDA DGAC (2015)*	Increase of one meal at a restaurant per week at baseline 13 years	Beta coefficient	**0.09 SE ±0.04 kg** p>0.05 **+VE**	3,643
BMI change	Chung et al. 2007 *Bezerra et al (2012)*	Decreased individual spending on eating out per $1 10 years	Beta coefficient	**-0.0003 kg/m^2** p<0.05 **+VE**	6,012
	Duffey et al. 2007 *Bezerra et al (2012), Mesas et al (2012), USDA (2010), Rosenheck et al (2008)* and *USDA DGAC (2015)*	Increase in frequency of restaurant food consumption across study period 3 years	Beta coefficient	**-0.01 (-0.212, 0.187) kg/m^2** p=0.903 **INV**	3,394
	Bes-Rastrollo et al. 2010 *Bezerra et al (2012), Mesas et al (2012)* and *USDA DGAC (2015)*	≥2 times per week eating out relative to never/rarely 4.4 years	Beta coefficient	**0.07 (0.04, 0.10) kg/m^2** p<0.001 **+VE**	9,182
Waist circumference	Duffey et al. 2009 *Bezerra et al (2012)* and *USDA DGAC (2015)*	Increase of one meal at a restaurant per week at baseline 13 years	Beta coefficient	**0.08 SE ±0.03 cm** p>0.05 **+VE**	3,643
Odds of weight gain	Bes-Rastrollo et al. 2010 *Bezerra et al (2012), Mesas et al (2012)* and *USDA DGAC (2015)*	≥2 times per week eating out relative to never/rarely 4.4 years	OR	**1.36 (1.13, 1.63)** **+VE**	9,182
Risk of overweight/ obesity		≥2 times per week eating out relative to never/rarely 4.4 years	HR	**1.33 (1.13, 1.57)** **+VE**	

Three prospective cohort studies (four publications) in adults investigating eating out and adiposity provided eight results across five outcomes: weight change; BMI change; waist circumference; odds of weight gain; and risk of overweight. Seven results reported positive associations, of which five were statistically significant. One result reported a non-significant inverse association.

Duffey et al 2009 and 2007 both used data from the CARDIA study of young adults. The mean age of participants in Bes-Rastrollo et al (2010) was 36.7 years, and Chung et al (2007) included adults over the age of 50 years.

Duffey et al 2009 and 2007 both distinguished via their food frequencies questionnaires between intake of foods from fast food establishments and intake of food from restaurants and cafeterias. However, it was unclear if this was clearly distinguished in the other studies: Bes-Rastrollo et al (2010) asked participants about 'meals eaten away from home' and Chung et al (2007) asked participants about total spending ($) on eating out.

Duffey et al (2009), Duffey et al (2007), and Bes-Rastrollo et al (2010) all used highly adjusted multivariate models to calculate results; Chung et al (2007) did not report on adjustment for potential confounders

4. Possible mechanisms

As per 2007 Expert Report:

- Most fast foods or takeaway food are energy-dense, and may also be eaten in large portions.
- Most fast foods are very different from those cooked at home. Lack of knowledge of the exact ingredients and cooking methods used to produce the finished product may remove health-related barriers to consumption.

5. Summary of evidence

5.1 Children

There were no relevant meta-analyses or individual RCTs investigating eating outside of the home intake and adiposity in children. Seven prospective cohort studies provided thirteen results: eight results reported positive associations (six were significant), one result reported a statistically significant inverse association, and four reported no association. The definition of the exposure varied between studies. The majority of studies (4/7) had more than 1,000 participants.

5.2 Adults

There were no relevant meta-analyses or individual RCTs investigating eating outside of the home intake and adiposity in adults. In total eleven publications were identified which examined either fast food intake or eating out. The definition of exposure varied between studies.

Seven studies (nine publications) investigated fast food intake specifically and provided 23 results: 19 reported positive associations (15 were statistically significant) and four reported non-significant inverse associations. Three of the studies were conducted in all female cohorts. Three publications used data from the CARDIA study cohort.

Four studies investigated eating out (restaurants, cafeterias) providing eight results: seven reported positive associations (five were statistically significant) and one reported a non-significant inverse association.

2.7 Sugar sweetened beverages

1. Evidence identified for 2017 update

Table 53 Published reviews identified for the 2017 update – SSBs

Source	No. of reviews	Authors [quality]
NICE (2014) report	5	Malik et al. 2013 [++]; Kaiser et al. 2013 [++]; Mattes et al. 2011 [++]; Te Morenga et al. 2013 [++]; U.S Department of Agriculture Nutrition Evidence Library 2010a [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	7	Pan et al. 2013 [+]; Fardet et al. 2014 [+]; Olsen et al. 2009 [++]; Malik et al. 2006 [+]; Perez-Morales et al. 2013 [+]; Gibson 2008 [+]; Vartanian et al. 2007 [+]

Notes on the evidence:

- Throughout this section the term sugar sweetened beverage(s) has been abbreviated to 'SSB(s)'.
- The review by Mattes et al (2011) was updated by Kaiser et al (2013), therefore Mattes et al (2011) is not referred to in the results section of this literature review.
- The published reviews by Olsen et al (2009), Malik et al (2006), Perez-Morales et al (2013), Gibson (2008), and Vartanian et al (2007) were identified in Fardet and Boirie (2014). Fardet and Boirie (2014) was identified via the supplementary literature search and is a review of reviews in itself. The published reviews in Fardet and Boirie (2014), such as those mentioned above, are reported in the relevant exposure section of this literature review.
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.
- There is moderate overlap of included studies between meta-analyses and this is commented on within the text of each section.
- The definition of SSBs varies between included reviews and individual studies. Where possible the type of beverage being investigated is reported. In general, SSB is taken to mean beverages that are sweetened with sugars (usually sucrose or high fructose corn syrup) and include fizzy drinks/sodas, cordials, and cocoa drinks.
- Several studies report on fruit juice as an exposure in addition to SSBs; in this section only data with respect to SSBs are presented.
- NICE (2014) noted that the review by Kaiser et al (2013), which concluded that the relationship between reducing SSB intake and reducing obesity was equivocal, was primarily funded by NIH but that several authors received fees from food and beverage companies.

2. Children

2.1 Meta-analysis of RCTs in children

Table 54 Meta-analyses of RCTs in children – SSBs

Children					
Meta-analyses of RCTs					
WMD=weighted mean difference; SMD=standardised mean difference; SSB=sugar-sweetened beverage. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
BMI change	Malik et al (2013)	Reduced SSB intake vs. control 25 weeks–18 months	WMD	**-0.17 (-0.39, 0.05) kg/m²** **+VE**	Studies=5; n=2,772 I^2=75%
Adiposity change	Kaiser et al (2013)	Reduced SSB intake vs. control 4 weeks–18 months	SMD	**-0.06 (-0.13, 0.01)** **+VE**	Studies=8; n=3,205 I^2=59%

Two meta-analyses of RCTs investigating SSB intake and adiposity in children were identified from two reviews. Malik et al (2013) reported a non-significant difference in change in BMI from reducing SSB intake using a random effects model, indicating an effect in the predicted direction. Kaiser et al (2013) standardised a range of adiposity measures (percentage weight change, BMI, BMI z score) and reported a non-significant positive effect (reduced SSB intake reduced adiposity). Age at recruitment ranged from 8.2 to 16 years (Malik et al 2013); it was unclear for the Kaiser et al (2013) meta-analysis.

In summarising the studies that investigated reduced intake of SSBs, Kaiser et al (2013) included two studies in adult populations. The other six studies are all in child populations, of which five are also included in the Malik et al (2013) meta-analysis. There was discrepancy in the number of participants in the five overlapping studies between the reviews; the reason for this was unclear.

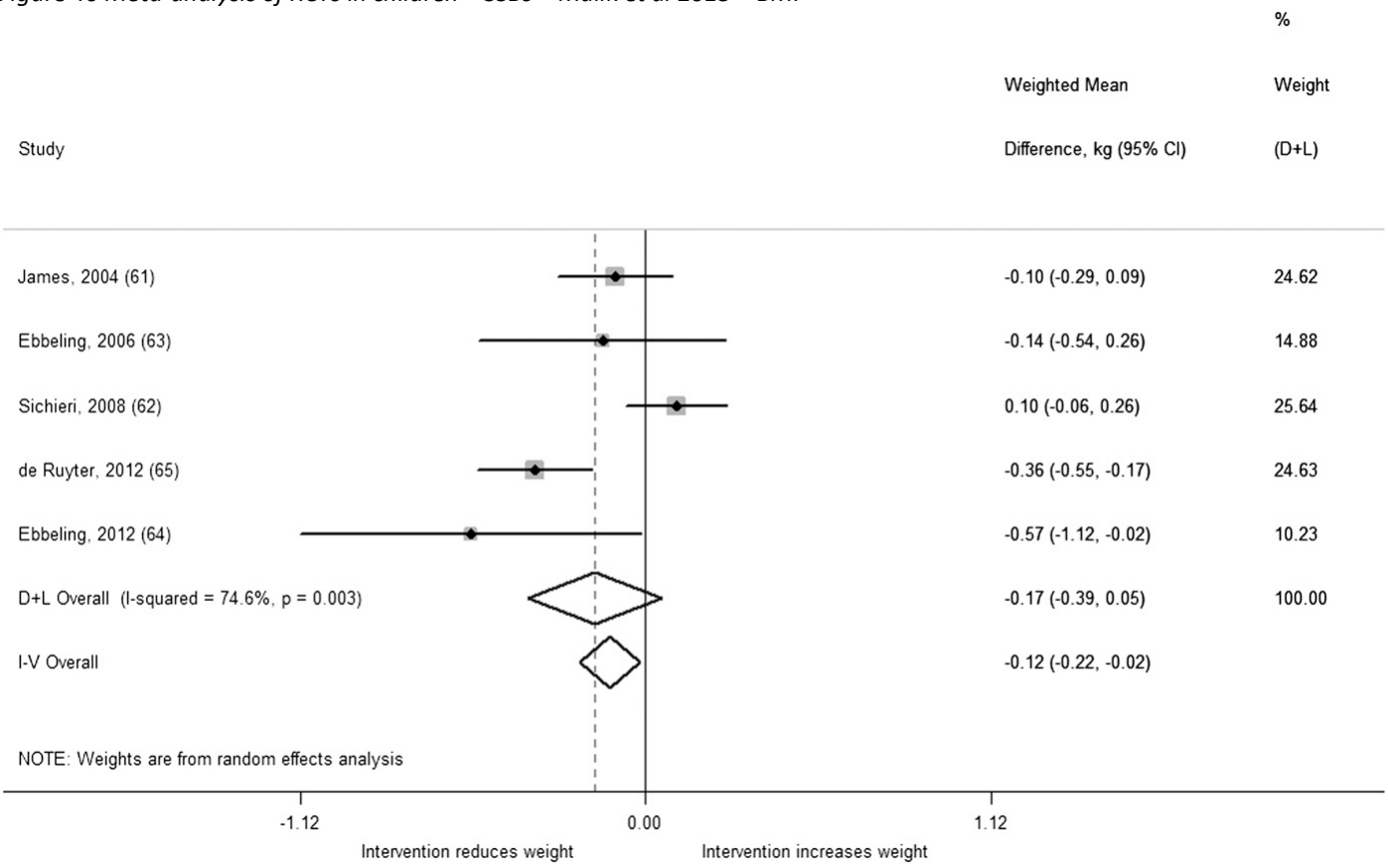
Both meta-analyses included studies of school based programmes to reduce SSB intake; the degree of success in reducing SSB intake was not clear. Both reviews noted that the non-significant effects may reflect the difficulty in achieving SSB reduction, particularly with interventions not providing substitute beverages. Whether or not individual studies used an intention-to-treat analysis was not reported.

The forest plots corresponding to the above meta-analyses are presented below.

Children | RCTs | BMI | Malik et al (2013) | Reduced SSB intake

Weighted mean differences in BMI change (95% CI) between the intervention and control regimens from randomized controlled trials in children. Interventions evaluated the effect of reducing sugar-sweetened beverages. Horizontal lines denote 95% CIs; solid diamonds represent the point estimate of each study. Open diamonds represent pooled estimates of the intervention effect, and the dashed line denotes the point estimate of the pooled result from the random-effects model (D+L). Weights are from the random-effects analysis (D+L). Pooled estimates from the random-effects analysis (D+L) and the fixed-effects analysis (I-V) are shown based on 5 randomized controlled trials (n = 2772). The I^2 and P values for heterogeneity are shown. D+L, DerSimonian and Laird; I-V, inverse variance (Malik et al 2013).

Figure 40 Meta-analysis of RCTs in children – SSBs – Malik et al 2013 – BMI

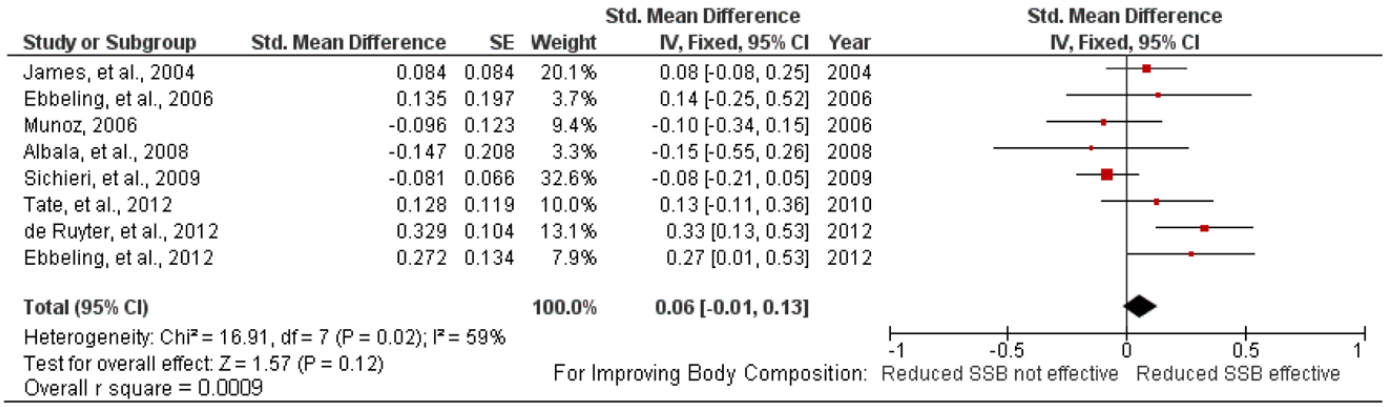


Children | RCTs | Adiposity | Kaiser et al (2013) | Reduced SSB intake

Forest plot comparing studies of reduced sugar-sweetened beverage (SSB) consumption; subjects in all weight categories included. Note: R square values were calculated from the overall standardized mean difference estimate (d) per the method found in Hedges et al (1985) (Kaiser et al 2013).

Please note – the authors have inverted the sign (negative to positive) of the effect in the forest plot, compared to the text. The interpretation of the result remains the same.

Figure 41 Meta-analysis of RCTs in children – SSBs – Kaiser et al 2013 – Adiposity measures



2.2 Meta-analyses of prospective cohort studies in children

Table 55 Meta-analyses of prospective cohort studies in children – SSBs

Children					
Meta-analyses of prospective cohort studies					
WMD=weighted mean difference; OR=odds ratio; SSB=sugar-sweetened beverage. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
BMI change	Malik et al (2013)	Per 12oz serving of SSB per day across study period 6 months–14 years	WMD	**0.07 (0.01, 0.12) kg/m^2** **+VE**	Studies=15; n=25,745 I^2=92%
		Per 12oz serving of SSB per day over 1 year 6 months–14 years	WMD	**0.06 (0.02, 0.1) kg/m^2** **+VE**	Studies=7; n=15,736 I^2=64%
Odds of overweight or obesity	Te Morenga et al (2013)	Intake of more than one serving of SSB per day vs. little/nil intake 1–8 years	OR	**1.55 (1.32, 1.82)** **+VE**	Studies=5; n=12,317 I^2=0%

Three meta-analyses of prospective cohort studies from two reviews investigated SSB intake and adiposity in children; all reported significant positive associations.

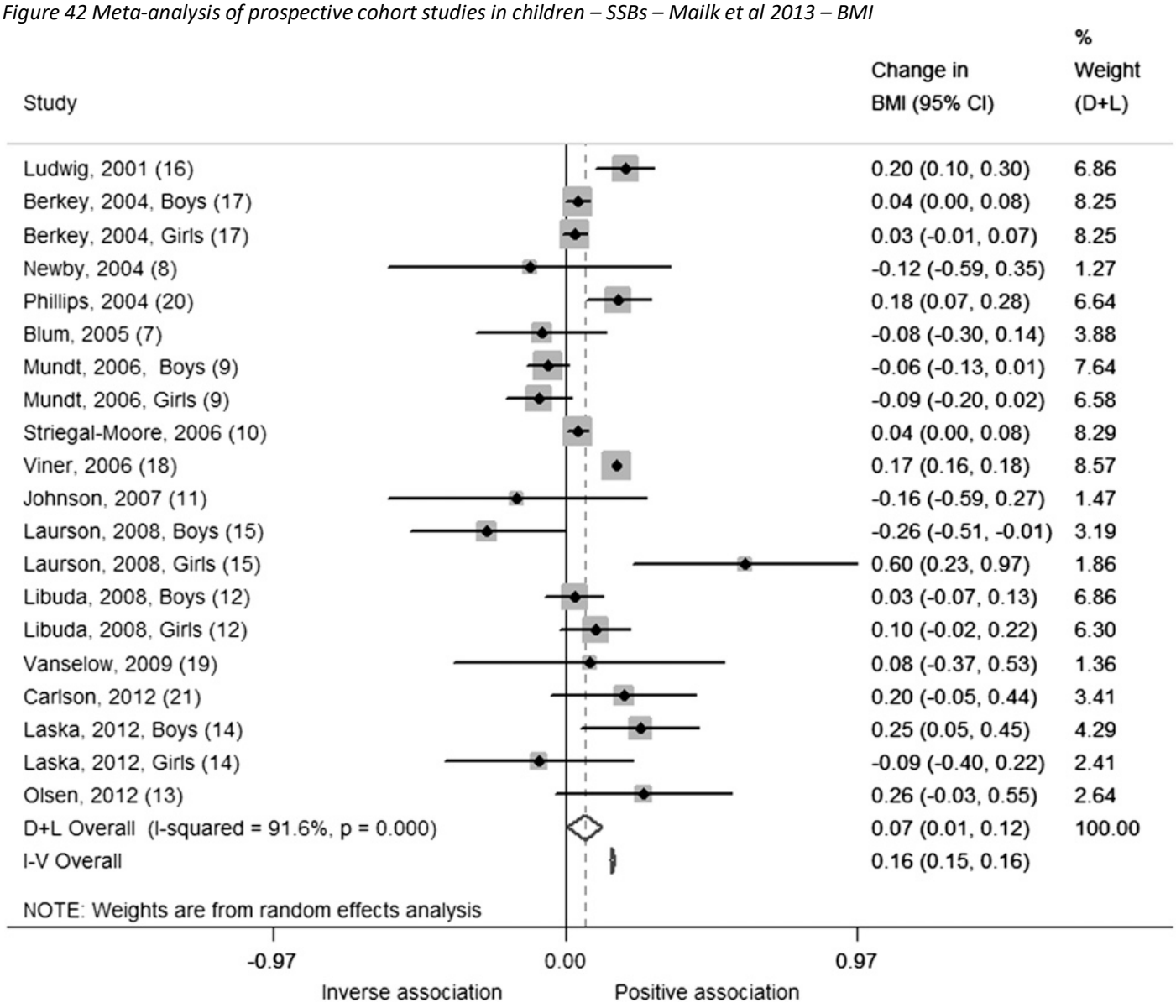
In the meta-analyses from Malik et al (2013), ten of included studies were based in the USA, four in Europe, and one in Canada. Baseline ages ranged from 2 to 16 years. The authors noted that when the analysis was stratified for studies that were adjusted for total energy and those that were not, the estimate was greater in studies that did not make the adjustment (adjusted studies WMD 0.04 (0.00, 0.07) kg/m^2, I^2=0%, comparisons=3; unadjusted studies WMD 0.08 (0.02, 0.14) kg/m^2, I^2=91%, comparisons=17).

The age at recruitment in the meta-analysis by Te Morenga et al (2013) ranged from 2 to 13 years. Three of the studies were conducted in the USA, one in Holland, and one in Canada. The focus of this systematic review was free sugars intake, rather than specifically SSBs, which was reflected in the inclusion criteria; however, all the studies included in this meta-analysis have SSB intake as the exposure. The exposure measurement varied between studies (see relevant forest plot below for description).

Children | Prospective cohort studies | BMI | Malik et al (2013) | Increased SSB intake across study period

Changes in BMI (95% CI) per 1-serving/d increase in sugar-sweetened beverages during the time period specified in each study from prospective cohort studies in children. Horizontal lines denote 95% CIs; solid diamonds represent the point estimate of each study. Open diamonds represent pooled estimates, and the dashed line denotes the point estimate of the pooled results from the random-effects model (D+L). Study weights are from the random-effects analysis (D+L). Pooled estimates from the random-effects analysis (D + L) and the fixed-effects analysis (I-V) are shown based on 15 cohort studies (n = 25,745). The I^2 and P values for heterogeneity are shown. D+L, DerSimonian and Laird; I-V, inverse variance (Malik et al 2013).

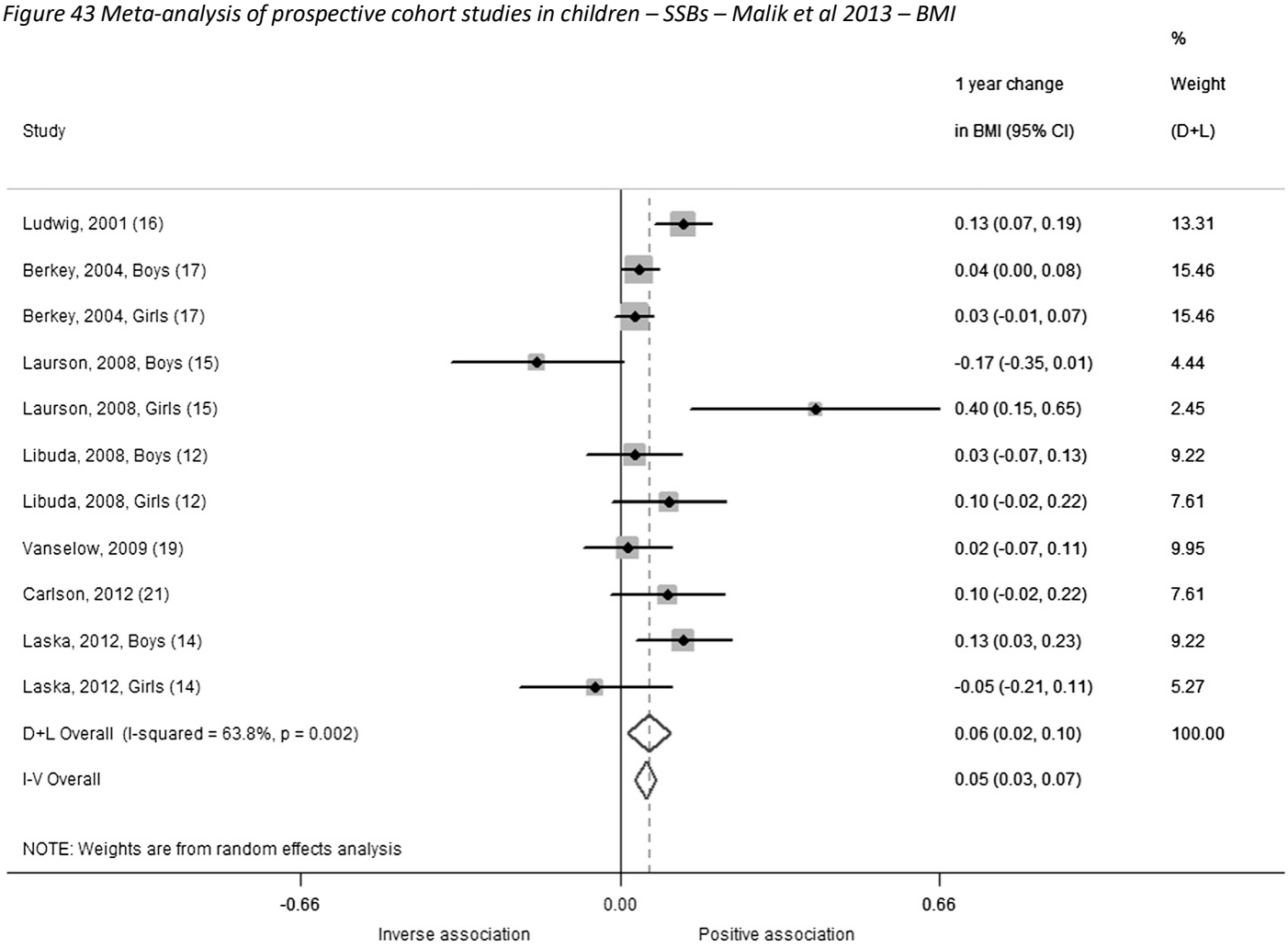
Figure 42 Meta-analysis of prospective cohort studies in children – SSBs – Mailk et al 2013 – BMI



Children | Prospective cohort studies | BMI | Malik et al (2013) | Increased SSB intake over one year

One-year changes in BMI (95% CI) per 1-serving/d increase in sugar-sweetened beverages from prospective cohort studies in children using a change versus change analysis strategy. Horizontal lines denote 95% Cis; solid diamonds represent the point estimate of each study. Open diamonds represent pooled estimates, and the dashed line denotes the point estimate of the pooled result from the random-effects model (D+L). Weights are from the random-effects analysis (D+L). Pooled estimates from the random-effects analysis (D+L) and the fixed-effects analysis (I-V) are shown based on 7 cohort studies (n = 16,004). The I^2 and P values for heterogeneity are shown. D+L, DerSimonian and Laird; I-V, inverse variance (Malik et al 2013).

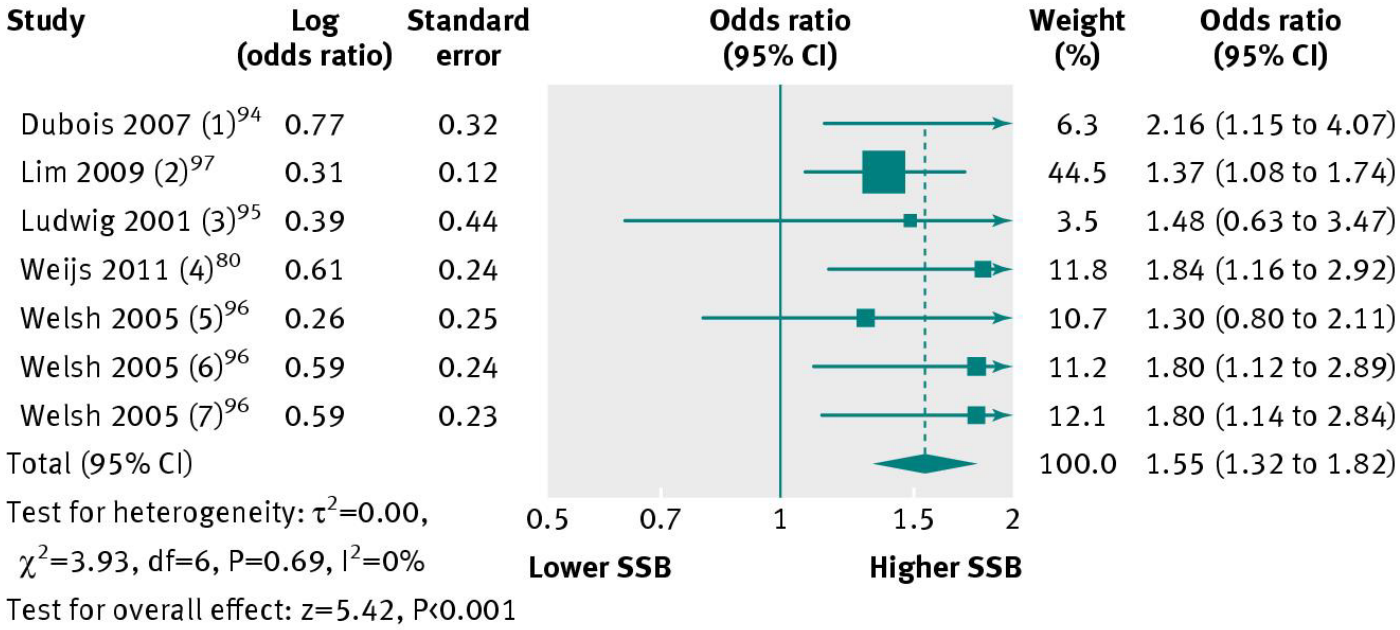
Figure 43 Meta-analysis of prospective cohort studies in children – SSBs – Malik et al 2013 – BMI



Children | Prospective cohort studies | Odds of overweight | Te Morenga et al (2013) | Increased SSB intake across study period

Association between free sugars intakes (primarily SSB intake) and measures of body fatness in children. Pooled estimates for odd ratios for incident overweight or obesity in children consuming one or more servings of sugar sweetened beverages per day at baseline compared with children who consumed none or very little at baseline. Overall estimate shows higher odds of overweight or obesity at follow-up in those who consumed one or more servings of sugar sweetened beverages at baseline. Data are expressed as odds ratio (95% confidence interval), using generic inverse variance models with random effects (Te Morenga et al 2013).

Figure 44 Meta-analysis of prospective cohort studies in children – SSBs – Te Morenga et al 2013 – Odds of overweight



(1) OR for incident obesity in frequent versus infrequent consumers of SSB between meals

(2) OR for incident overweight per daily serve SSB (8 oz)

(3) OR for incident obesity per daily serve SSB

(4) OR for incident overweight per approximate daily serve SSB (5% energy from beverage sugar)

(5) OR for incident overweight in normal weight children who consumed ›1 serve/d SSB versus ‹1 serve SSB/d

(6) OR for remaining overweight in overweight children who consumed ›1 serve/d SSB versus ‹1 serve SSB/d

(7) OR for incident overweight in children at risk of overweight who consumed ›1 serve/d SSB versus ‹1 serve SSB/d

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 56 Results of individual prospective cohort studies in children – SSBs

Children					
Prospective cohort studies					
SSB=sugar-sweetened beverage; SE=standard error; CI=confidence interval; CHO=carbohydrate; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Mrdjenovic et al. 2003 *USDA (2010); Olsen and Heitmann (2009); Gibson (2008); Vartanian et al (2007)*	Higher (>12oz SSB per day) vs. lower (6–12oz SSB per day) intake categories 4–8 weeks	Higher: **1.12 ±0.7 kg** Lower: **0.32–0.48 ±0.4 kg** p=0.40 **+VE**		21
BMI change	Nissinen et al. 2009 *Te Morenga et al (2013)*	Per 10 unit per month intake of SSB at baseline *(girls)* 21 years	Beta coefficient	**-0.16 SE ±0.14** p=0.24 **INV**	1,172
		Per 10 unit per month intake of SSB at baseline *(boys)* 21 years	Beta coefficient	**0.01 SE ±0.01** p=0.51 **+VE**	967
		Per 10 unit per month increase in SSB intake *(girls)* 21 years	Beta coefficient	**0.45 SE ±0.12** p<0.001 **+VE**	1,172
		Per 10 unit per month increase in SSB intake *(boys)* 21 years	Beta coefficient	**-0.04 SE ±0.11** p=0.71 **INV**	967
	Stoof et al. 2013 *USDA (2010)*	Per additional serving of SSB at baseline *(girls)* 24–30 years	Beta coefficient	**0.43 (-0.39, 1.25) kg/m^2** p=0.30 **+VE**	124
		Per additional serving of SSB at baseline *(boys)* 24–30 years	Beta coefficient	**0.24 (-0.33, 0.82) kg/m^2** p=0.41 **+VE**	114
BMI z score change	Haerens et al. 2010 *Te Morenga et al (2013)*	Additional serving of SSB per day at baseline 3 years	Beta coefficient	**-0.016 SE ±0.009** p>0.05 **INV**	585
		Per increase in frequency of serving of SSB per day across study period 3 years	Beta coefficient	**-0.009 SE ±0.011** p>0.05 **INV**	585
	Tam et al. 2006 *USDA (2010); Olsen and Heitmann (2009)*	Median intake of CHO (g per day) from soft drinks and cordials *(healthy weight at baseline)* 5 years	BMI maintenance: **20 (0, 70) g CHO in SSB per day** BMI gain: **29 (0, 92) g CHO in SSB per day** p=0.002 **+VE**		281
		Median intake of CHO (g per day) from soft drinks and cordials *(overweight at baseline)* 5 years	BMI maintenance: **30 (0, 108) g CHO in SSB per day** BMI loss: **6.5 (0, 170) g CHO in SSB per day** p=0.019 **+VE**		281
BMI z score	Feeley et al. 2013 *Malik et al (2013)*	Frequency of SSB intake per week *(boys)* 4 years	Beta coefficient	**0.044 (0.022, 0.067)** p<0.01 **+VE**	607
Fat mass		Frequency of SSB intake per week *(boys)* 4 years	Beta coefficient	**0.018 (0.002, 0.036) kg** p<0.05 **+VE**	607

Percentage body fat	Fiorito et al. 2009 *Te Morenga et al (2013)* and *USDA (2010)*	Per 8oz serving of SSB per day at baseline *(girls)* 10 years	Regression coefficient	**0.18 (CI=not reported)** p<0.05 **+VE**	166
	Stoof et al. 2013 *USDA (2010)*	Per additional serving of SSB at baseline *(girls)* 24–30 years	Beta coefficient	**-0.72 (-2.44, 1.01) %** p=0.41 **INV**	124
		Per additional serving of SSB at baseline *(boys)* 24–30 years	Beta coefficient	**1.14 (0.04, 2.23) %** p=0.04 **+VE**	114
Percentage trunk fat		Per additional serving of SSB at baseline *(girls)* 24–30 years	Beta coefficient	**-0.85 (-3.02, 1.31) %** p=0.44 **INV**	124
		Per additional serving of SSB at baseline *(boys)* 24–30 years	Beta coefficient	**1.62 (0.14, 3.10) %** p=0.03 **+VE**	114
Waist circumference	Kral et al. 2008 *Perez-Morales et al (2013)*	Change in intake of soda over study period 3 years	Beta coefficient	**0.04 SE ±0.009** p=0.0001 **+VE**	42
Odds of overweight	Nissinen et al. 2009 *Te Morenga et al (2013)*	Per 10 unit per month increase in SSB intake vs. low, stable intake *(girls)* 21 years	OR	**1.90 (1.38, 2.61)** **+VE**	1,172
		Per 10 unit per month increase in SSB intake vs. low, stable intake *(boys)* 21 years	OR	**1.07 (0.74, 1.57)** **+VE**	967
	Wijga et al. 2010 *Malik et al (2013)*	Intake of SSB vs. no intake 1–4 years	OR	**0.91 (0.44, 1.88)** **INV**	3,963

Nine prospective cohort studies investigating SSB intake and adiposity in children provided 22 results across nine outcomes: weight change; BMI; attained BMI z score; BMI z score change; fat mass; percentage body fat; percentage trunk fat; waist circumference; and odds of overweight. Of these 15 reported positive associations (of which ten were statistically significant) and seven reported non-significant inverse associations.

Age at recruitment varied between the studies, ranging from three to 18 years. One study, Nissinen et al (2009) recruited participants whose baseline ages spanned three to 18 years and Mrdjenovic et al (2003) recruited participants whose baseline ages spanned six to 13 years. The remaining studies all recruited participants at a specific year of age.

The number of participants in Kral et al (2008) was not clear: the published review (Perez-Morales et al 2013) reported n=135, however via inspection of the original paper it appears n=42.

3. Adults

3.1 Meta-analysis of RCTs in adults

Table 57 Meta-analyses of RCTs in adults – SSBs

Adults					
Meta-analyses of RCTs					
WMD=weighted mean difference; SMD=standardised mean difference; SSB=sugar-sweetened beverage. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Malik et al (2013)	Increased SSB intake (600–1135ml per day) vs. control 3 weeks–6 months	WMD	**0.85 (0.50, 1.20) kg** **+VE**	Studies=5; n=292 I^2=0%
	Kaiser et al (2013)	Increased SSB intake vs. control 3 weeks–6 months	SMD	**0.28 (0.12, 0.44)** **+VE**	Studies=7; n=665 I^2=48%

Two meta-analyses of RCTs in adults investigated SSB intake and weight change; both reported a significant positive association. There is overlap of two studies between the meta-analyses.

Malik et al (2013) noted that when the analysis was stratified for baseline weight status there was greater, although non-significant, weight gain in the three studies conducted in non-overweight populations. The sample sizes of the five included studies ranged from 29 to 133 participants; one was an all-male sample, and two were all-female samples.

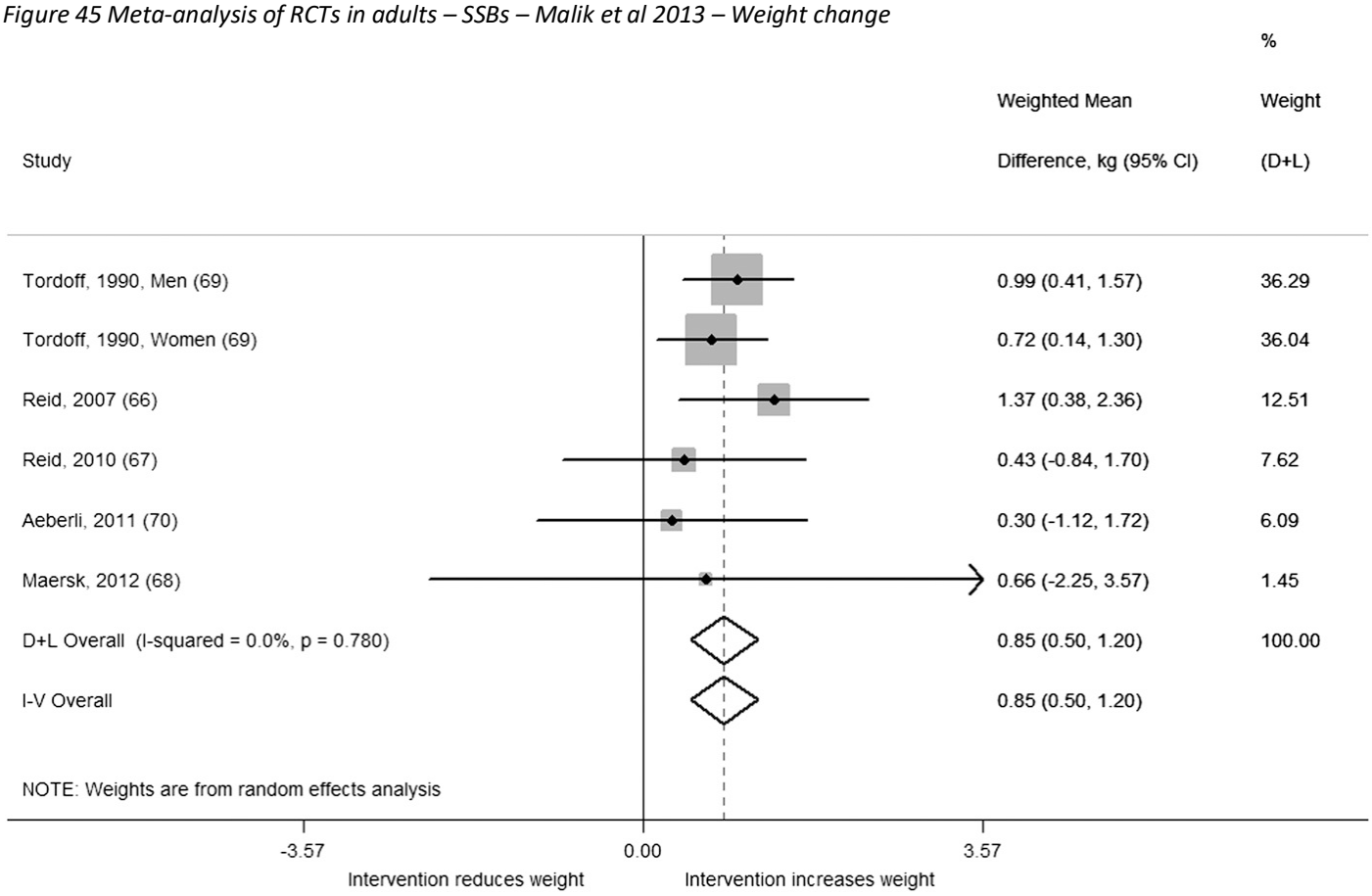
The interventions of the studies included by Kaiser et al (2013) varied with respect to volume, energy content, and type of SSB provided. Sample size ranged from 30 to 300 participants. One study was conducted in an overweight population. In order to summarise all the studies they identified, Kaiser et al (2013) included one study in children in the meta-analysis, which also had the most participants (Vaz et al. 2011).

The forest plots corresponding to the above meta-analyses are presented below.

Adults | RCTs | Weight change | Malik et al (2013) | Increased SSB intake

Weighted mean differences (95% CI) in weight change (kg) between the intervention and control regimens from randomized controlled trials in adults. Interventions evaluated the effect of adding sugar-sweetened beverages. Horizontal lines denote 95% CIs; solid diamonds represent the point estimate of each study. Open diamonds represent pooled estimates of the intervention effect, and the dashed line denotes the point estimate of the pooled result from the random-effects model (D+L). Weights are from the random-effects analysis (D+L). Pooled estimates from the random-effects analysis (D+L) and the fixed effects analysis (I-V) are shown based on 5 randomized controlled trials (n = 292). The I2 and P values for heterogeneity are shown. D+L, DerSimonian and Laird; I-V, inverse variance (Malik et al 2013).

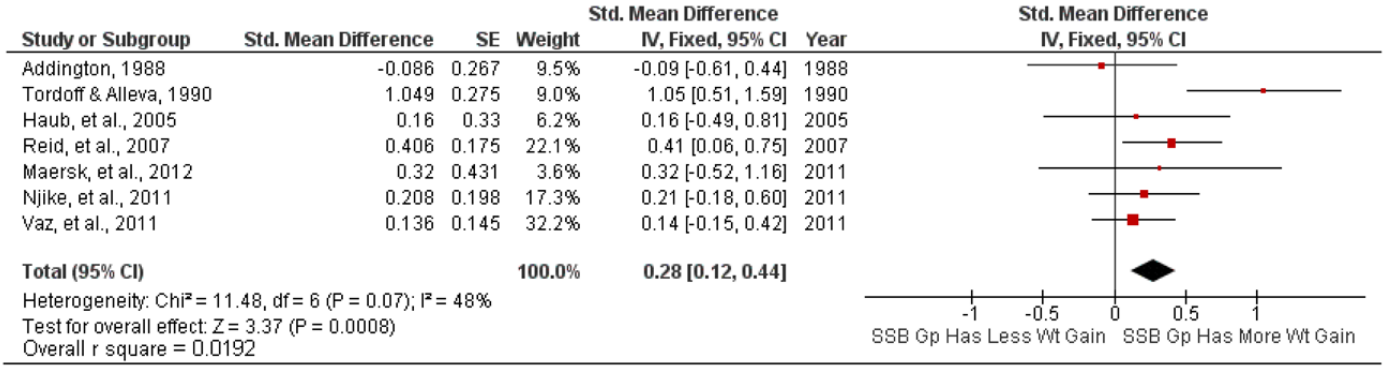
Figure 45 Meta-analysis of RCTs in adults – SSBs – Malik et al 2013 – Weight change



Adults | RCTs | Weight change | Kaiser et al (2013) | Increased SSB intake

Forest plot comparing studies of added sugar-sweetened beverage (SSB) consumption. Note: R square values were calculated from the overall standardized mean difference estimate (d) per the method found in Hedges et al (1985) (Kaiser et al 2013).

Figure 46 Meta-analysis of RCTs in adults – SSBs – Kaiser et al 2013 – Weight change



3.2 Meta-analyses of prospective cohort studies in adults

Table 58 Meta-analyses of prospective cohort studies in adults – SSBs

Adults					
Meta-analyses of prospective cohort studies					
WMD=weighted mean difference; MD=mean difference; SSB=sugar-sweetened beverage. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Weight change	Malik et al (2013)	Per 12oz serving of SSB per day over 1 year 1–20 years	WMD	**0.22 (0.09, 0.34) kg** +VE	Studies=7; n=170,141 I^2=70%
	Pan et al (2013)	Per standard serving of SSB per day over 4 year period 20 years	MD	**0.36 (0.24, 0.48) kg** +VE	Studies=3; n=124,988 I^2= not reported

Two meta-analyses of prospective cohort studies investigating SSB intake and weight change in adults were identified across two reviews; they both reported significant, positive results.

Malik et al (2013) noted that when stratified for baseline weight status, greater, although non-significant, weight gain in the two studies conducted in overweight populations was observed. Three included studies were in all-female cohorts, of which one was in women living with overweight or obesity; one study was in an all-male cohort. One mixed gender study was with participants with pre-hypertension or stage 1 hypertension.

The meta-analysis by Pan et al (2013) pooled data from the Nurses' Health Study I, the Nurses' Health Study II, and the Health Professionals' Follow up Study. A study included by Malik et al (2013) (Mozaffarian et al. 2011) also used data from these cohorts. Exclusion of Mozaffarian et al (2011) from the Malik et al (2013) meta-analysis increased the summary estimate (WMD 0.31 [0.11, 0.50] kg) but did not affect heterogeneity (I^2=71%).

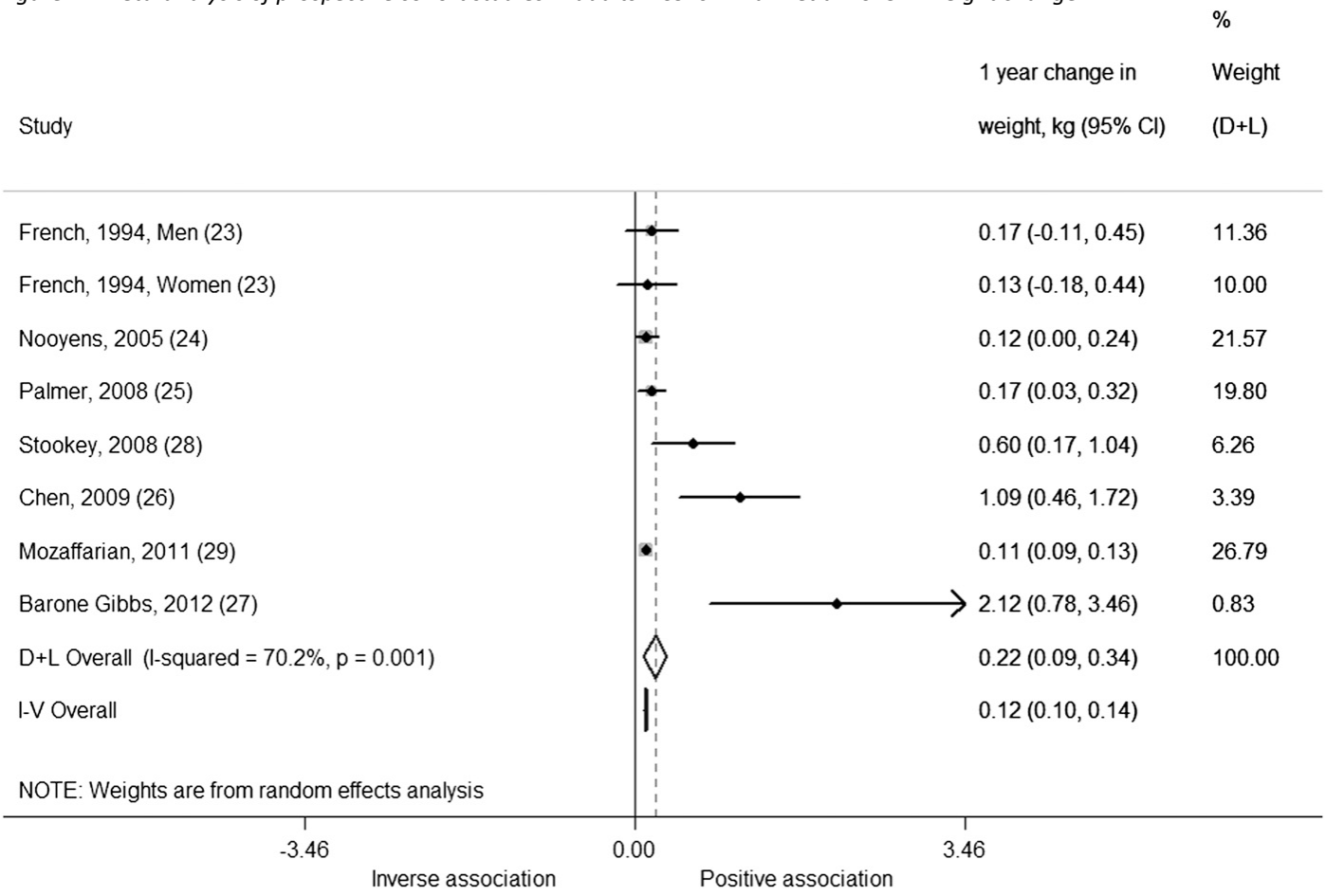
An I^2 value was not reported by Pan et al (2013) but the authors did note the p for heterogeneity <0.001.

A forest plot was only available for the Malik et al (2013) meta-analysis.

Adults | Prospective cohort studies | Weight change | Malik et al (2013) | Increased SSB intake over one year

One-year changes (95% CI) in weight (kg) per 1-serving/d increase in sugar-sweetened beverages from prospective cohort studies in adults using a change versus change analysis strategy. Horizontal lines denote 95% CIs; solid diamonds represent the point estimate of each study. Open diamonds represent pooled estimates, and the dashed line denotes the point estimate of the pooled result from the random-effects model (D+L). Weights are from the random-effects analysis (D+L). Pooled estimates from the random-effects analysis (D+L) and the fixed-effects analysis (I-V) are shown based on 7 cohort studies (n = 174,252). The I^2 and P values for heterogeneity are shown. D+L, DerSimonian and Laird; I-V, inverse variance (Malik et al 2013).

Figure 47 Meta-analysis of prospective cohort studies in adults – SSBs – Malik et al 2013 – Weight change



3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 59 Results of individual prospective cohort studies in adults – SSBs

Adults					
Prospective cohort studies					
OR=odds ratio; SSB=sugar sweetened beverage; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Schulze et al. 2004 *Malik et al 2006; Gibson 2008; Vartanian et al 2007; Olsen and Heitmann 2009*	**Intake change across study:** ≤1 drink/week (low-low) ≥1 drink/day (high-high) ≥1 drink/day to ≤1/week (high-low) ≤1 drink/week to ≥1/day (low-high) 4 years	**Mean weight change** Low-low: **3.22 SE± 0.03 kg** High-high: **3.11 SE± 0.13 kg** High-low: **1.56 SE± 0.19 kg** Low-high: **4.49 SE± 0.19 kg *** *All means significantly different from low-high, p<0.01 **+VE**		51,603
BMI change			**Mean BMI change** Low-low: **1.18 SE± 0.01 kg/m²** High-high: **1.15 SE± 0.05 kg/m²** High-low: **0.57 SE± 0.07 kg/m²** Low-high: **1.65 SE± 0.07 kg/m² *** *All means significantly different from low-high, p<0.01 **+VE**		51,603
	Inoue et al. 2010 *Malik et al (2013)*	Intake of soft drinks and soda every day vs. rarely *(female)* 4 years	Regression coefficient	**0.0083 SE ±0.0235** p=0.0002 **+VE**	18,137
	Fowler et al. 2008 *Malik et al (2013)*	Quartiles of SSB intake relative to non-consumers 7–8 years	Non-consumers: **1.48 (1.30, 1.66) kg/m²** Q1: **1.18 (0.90, 1.45) kg/m²** Q2: **1.17 (0.93, 1.41) kg/m²** p=0.04 Q3: **1.05 (0.83, 1.26) kg/m²** p=0.003 Q4: **1.15 (0.95, 1.34) kg/m²** p=0.02 p for trend=0.009 **INV**		3,682
Odds of weight gain	Bes-Rastrollo et al. 2006 *Malik et al (2013); Olsen and Heitman (2009); Malik et al (2006); Gibson (2008)*	Highest vs. lowest quintile of SSB intake *(participants who maintained weight prior to recruitment)* 28.5 months	OR	**1.08 (0.89, 1.32)** **+VE**	2,320
		Highest vs. lowest quintile of SSB intake *(participants who gained weight prior to recruitment)* 28.5 months	OR	**1.55 (1.16, 2.07)** **+VE**	4,874
Odds of overweight	Kvaavik et al. 2007 *USDA (2010); Malik et al (2006); Olsen and Heitmann (2009); Gibson (2008)*	Long term high consumers vs. long term low consumers *(female)* 8 years	OR	**1.57 (0.46, 5.33)** **+VE**	196
		Long term high consumers vs. long term low consumers *(male)* 8 years	OR	**1.05 (0.46, 2.40)** **+VE**	192
Odds of obesity		Long term high consumers vs. long term low consumers *(female)* 8 years	OR	**0.80 (0.09, 6.85)** **INV**	196

		Long term high consumers vs. long term low consumers *(male)* 8 years	OR	**2.29 (0.48, 10.96)** **+VE**	192
	Dhingra et al. 2007 *Malik et al (2013)*	Intake of ≥1 serving of SSB per day vs. no intake 4 years	OR	**1.31 (1.02, 1.68)** **+VE**	6,039
Odds of unhealthy waist circumference		Intake of ≥1 serving of SSB per day vs. no intake 4 years	OR	**1.30 (1.09, 1.56)** **+VE**	6,039

Six prospective cohort studies investigating SSB intake and adiposity in adults were identified in six reviews, providing 12 results across six outcomes: weight change; BMI change; odds of weight gain; odds of overweight; odds of obesity; and odds of an unhealthy waist circumference. Ten results reported positive associations, of which six were statistically significant, and two results reported inverse associations, of which one was statistically significant.

Schulze et al (2004) used the Nurses' Health Study cohort. They reported that women who increased their intake of SSBs over the four year study period (indicated as 'low-high' in the results table) had significantly larger increases in both weight and BMI compared to women with a consistent intake (either at 'high' or 'low' levels) or decreased intakes (indicated as 'high-low') across the study period, $p<0.001$.

The study by Inoue et al (2010) was conducted in a mixed sample but the result for men with respect to SSBs was not reported. This was the only study in an all-Asian population. The study by Kvaavik et al (2005) recruited participants as children (aged 15 years); however, the data used in this analysis was for intakes of SSB over 8 years between the ages of 25 and 33 years.

Fowler et al (2008) reported results for BMI change four quartiles of intake relative to non-consumers; non-consumers vs. Q2, vs. Q3, and vs. Q4 was significantly different, and the p for trend of an inverse association was significant at $p=0.009$. The main factor of investigation in this study was artificially sweetened beverages.

Quintiles of SSB consumption in the Bes-Rastrollo et al (2006) study ranged from <4 ml per day (quintile 1) to ≥80 ml per day (quintile 5). Long term high consumers in the Kvaavik et al (2005) study consumed a mean of 470 SD ±271 g per day of SSB, and long term low consumers consumed a mean of 43 SD ±60 g per day. Dhingra et al (2007) defined an unhealthy waist circumference as >102cm for men, and >88cm for women.

4. Possible mechanisms

As per 2007 Expert Report:

- Energy from sugars may not be compensated for in the same way when consumed in a soft drink as when consumed as part of a solid meal.
- In adults, short term intake of sugar-sweetened foods and drinks (80% drinks) promoted weight gain, while consumption of artificially sweetened foods resulted in weight loss.

5. Summary of evidence

5.1 Children

The two meta-analyses of RCTs both reported non-significant positive effects. The non-significant effects may reflect the difficulty in achieving SSB reduction in the intervention. The three meta-analyses of prospective cohort studies reported significant, positive effects. There were nine prospective cohort studies not included in meta-analyses, which provided 22 results. Fifteen reported positive associations, of which ten were significant; seven reported non-significant inverse associations.

5.2 Adults

Two meta-analyses of RCTs both reported significant, positive effects. Two meta-analyses of prospective cohort studies also reported significant, positive associations. Six prospective cohort studies were identified but not included in any meta-analyses, providing 12 results. Ten results reported positive associations (of which six were statistically significant) and two reported inverse associations (of which one was statistically significant).

3. Dietary constituents

3.1 Non-starch polysaccharide (dietary fibre)

1. Evidence Identified for 2017 update

Table 60 Published reviews identified for the 2017 update – Dietary fibre

Source	No. of reviews	Authors [quality]
NICE (2014) report	4	Summerbell et al. 2009 [++];Wanders et al. 2011 [+]; Ye et al (2012) [+]; U.S Department of Agriculture Nutrition Evidence Library 2010a [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	Nil	-

Notes on the evidence:

- The supplementary literature search identified no meta-analyses; all the studies presented in this literature review have been identified via the NICE (2014) report.
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.
- Ishihara et al. 2003 is an individual prospective cohort study not included in a meta-analysis identified in Summerbell et al (2009). The full text article is in Japanese. Summerbell et al (2009) provided a detailed results summary in English and so the result is included in this literature review.

2. Children

2.1 Meta-analysis of RCTs in children

Nil

2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 61 Results of individual prospective cohort studies in children – Dietary fibre

Children					
Prospective cohort studies					
OR=odds ratio; SD=standard deviation; SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI z score	Cheng et al. 2009 USDA (2010)	Per 1 SD increase in fibre intake (equivalent to 5.3-7g) 4 years	Beta-coefficient	**-0.007 SE±0.012** p=0.5 **INV**	215
Weight	Berkey et al. 2000 Summerbell et al (2009) *and* USDA (2010)	Fibre intake (g per day) *(girls)* 1 year	Regression coefficient	**0.0011 (-0.00733, 0.00952)** p=0.799 **+VE**	6,149
		Fibre intake (g per day) *(boys)* 1 year	Regression coefficient	**-0.0046 (-0.01381, 0.00461)** p=0.320 **INV**	4,620
	Newby et al. 2003b USDA (2010)	Total intake of dietary fibre 6-12 months	Beta-coefficient	**0.01 SE±0.02 kg per year** p=0.53 **+VE**	1,379
% body fat	Cheng et al. 2009 USDA (2010)	Per 1 SD increase in fibre intake (equivalent to 5.3-7g) 4 years	Beta-coefficient	**0.016 SE±0.137 %** p=0.9 **+VE**	215
Odds of overweight or obesity	Ishihara et al. 2003 Summerbell et al (2009)	"Those who consumed a large amount of fibre products" at age 1.5-3 years 10-11 years	OR	**0.78 (0.60, 1.02)** **INV**	737

Four prospective cohort studies were identified across two reviews, providing six results across four outcomes: BMI z score; weight; percentage body fat; and odds of overweight or obesity.

Three results reported positive associations between fibre intake and adiposity, and three results reported inverse associations; none were significant.

The largest cohort (Berkey et al 2000) reported a non-significant positive association for girls (n=6,149) and a non-significant inverse association in boys (n=4,620).

Cheng et al (2009) calculated dietary fibre intake from weighed three day dietary records using the LEBTAB database; Berkey et al (2000) used the Association of Analytical Chemists dietary fibre definition to calculate intake; in the other studies it was not clear how they defined and calculated dietary fibre intake.

3. Adults

3.1 Meta-analysis of RCTs in adults

Table 62 Meta-analyses of RCTs in adults – Dietary fibre

Adults					
RCTs					
WMD=weighted mean difference; CI=confidence interval. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Wanders et al (2011)	Increased fibre intake (mean dose 11.1g per day) vs. no intervention 11.1 weeks	WMD	**-1.3 %** (CI not reported) Lower -18.5%; upper 2.9% **INV**	Studies=61; n=2,486 I^2=not reported
			WMD	**-0.7 kg** (CI not reported) **INV**	Studies=61; n=2,486 I^2=not reported
		Per gram increase in fibre intake per day Over four weeks	Regression coefficient	**-0.014 %** (CI not reported) **INV**	Studies=61 ; n=2,486 I^2=not reported

Wanders et al (2011) conducted a meta-analysis of 61 RCTs in adults investigating fibre intake and weight change across the intervention periods (percentage and absolute change) and over four weeks (dose response). All results reported an inverse association; the authors did not report standard deviations, confidence intervals, or indicate significance level.

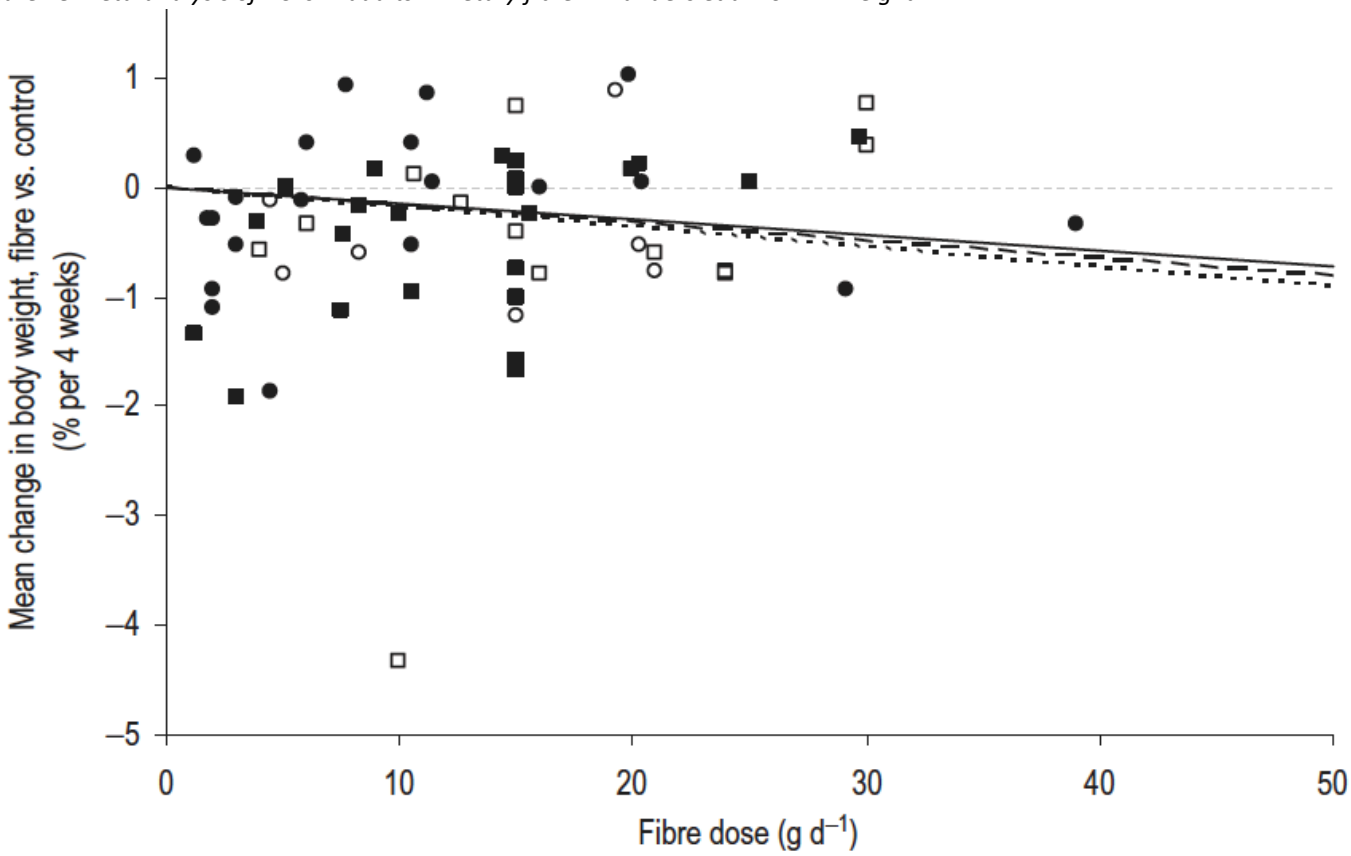
The included RCTs encompassed 11 fibre types: dextrin; marine polysaccharide; chitosan; fructan; arabinoxylan; mannan; arabinoxylan-rich (wheat bran and psyllium gum); beta-glucan-rich; glucan; resistant starch; and pectin. The format of the increased fibre intake varied between intervention (food vs. supplement; solid vs. liquid) and the majority of the studies appeared to be in population living with overweight or obesity (exact numbers not reported).

The corresponding dose response figure is presented below.

Adults | RCTs | Weight | Wanders et al 2011 | Per gram increase in fibre per day over four weeks

Mean changes in body weight by fibre dose, viscosity and fermentability. Black symbols, more viscous fibres; white symbols, less viscous fibres. Squares, more fermentable fibres; circles, less fermentable fibres. Regression lines: —, overall; - - - -, more viscous fibres; ·····, more fermentable fibres. Regression lines were forced through the origin because a zero change in diet should produce a zero change in appetite or body weight. Regression lines were weighted for number of subjects per study. Mean change in body weight per 4 weeks for all comparisons (n = 66). The slope of the overall regression line is -0.014X; the slope of the more viscous fibres regression line is -0.016X; the slope of the more fermentable fibres regression line is -0.018X (Wanders et al 2011).

Figure 48 Meta-analysis of RCTs in adults – Dietary fibre – Wanders et al 2011 – Weight



3.2.2 Meta-analyses of prospective cohort studies in adults

Nil

3.2.3 Individual RCTs in adults, not in meta-analyses

Nil

3.2.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 63 Results of individual prospective cohort studies in adults – Dietary fibre

Adults					
Prospective cohorts					
OR=odds ratio; SD=standard deviation. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Colditz et al. 1990 Summerbell et al (2009)	Crude fibre intake (g per day) 4 years	Beta coefficient	**0.029 *t*=1.7** +VE	31,940
		Dietary fibre intake (g per day) 4 years	Beta coefficient	**0.0055 *t*=1.4** +VE	31,940
	Koh-Banerjee et al. 2004 Ye et al (2012)	Quintiles of change in fibre intake (g per day) 8 years	Highest quintile: **0.39 SD±0.2 kg** Lowest quintile: **1.4 SD±0.2 kg** p for trend<0.0001 INV		27,082
Weight (attained)	Ludwig et al. 1999 Summerbell et al (2009)	Highest vs. lowest quintile intake of dietary fibre content at base line *(white females and males)* 10 years	Highest quintile: **166.7 lb** Lowest quintile: **174.8 lb** p for trend<0.001 INV		1,602
		Highest vs. lowest quintile intake of dietary fibre content at base line *(black females and males)* 10 years	Highest quintile: **177.6 lb** Lowest quintile: **185.6 lb** p for trend=0.001 INV		1,307
Waist-hip ratio	Ludwig et al. 1999 Summerbell et al (2009)	Highest vs. lowest quintile intake of dietary fibre content at base line *(white females and males)* 10 years	Highest quintile: **0.801** Lowest quintile: **0.813** p for trend=0.004 INV		1,598
		Highest vs. lowest quintile intake of dietary fibre content at base line *(black females and males)* 10 years	Highest quintile: **0.799** Lowest quintile: **0.809** p for trend=0.05 INV		1,302
Odds of BMI>25	Liu et al. 2003 Summerbell et al (2009) *and* Ye et al (2012)	Highest vs. lowest quintile intake of dietary fibre intake 12 years	OR	**0.51 (0.39, 0.67)** p for trend<0.0001 INV	16,587
Odds of BMI>30		Highest vs. lowest quintile intake of dietary fibre intake 12 years	OR	**0.66 (0.58, 0.74)** p for trend<0.0001 INV	16,587

Four publications from two reviews provided nine results across four outcome categories: weight (change and attained); waist-hip ratio; odds of BMI >25 kg/m^2; and odds of BMI >30 kg/m^2. Two results from the same study (Colditz et al 1990) reported significant positive associations between fibre intake and adiposity. The seven other results reported an inverse association, of which six were statistically significant.

Two studies used the all female Nurses' Health Study I cohort but data were extracted 13 years apart and included a different number of participants (Colditz et al 1990, n=31,940; Liu et al 2003, n=16,587). The study by Koh-Banerjee et al (2004) is in the all-male Health Professionals' Follow up Study cohort.

4. Possible mechanisms

Summarised from 2007 Expert Report:

- Fibre from food has a low energy density, as it is not digested in the small bowel and can only undergo partial fermentation in the large bowel.
- Fibre consumption may increase satiation by increasing chewing, slowing gastric emptying and elevating stomach distension, and stimulation of cholecystokinin.
- The increased viscosity of soluble fibre can reduce the overall rate and extent of digestion, which may also result in reduced energy from protein and fat and a blunted post-prandial glycaemic and insulinaemic response to carbohydrates.
- Fibre-induced delayed absorption and the resultant presence of macronutrients in the distal small intestine, known as the ileal brake, mediate the release of several gut hormones.

5. Summary of evidence

5.1 Children

There were no meta-analyses or individual RCTs identified that investigated dietary fibre intake and adiposity in children. Four prospective cohort studies were identified across two reviews reported six results: three reported positive associations and three reported inverse associations; none were significant.

5.2 Adults

One review (Wanders et al 2011) conducted a meta-analysis of RCTs in adults, reporting three results with the outcome of weight. The authors reported inverse effects but did not state any levels of significance. The majority of studies in the meta-analysis were in participants living with overweight or obesity. There were no meta-analyses of prospective cohort studies, or any individual RCTs. Four individual prospective cohort studies were identified providing nine results. Two results from the same study reported significant positive associations; the remaining seven results reported inverse associations, of which six were statistically significant.

3.2 Sugars

1. Evidence identified for 2017 update

Table 64 Published reviews identified for the 2017 update – Sugars

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Te Morenga et al. 2013 [++]; Sievenpiper et al. 2012 [++]; Wiebe et al. 2011 [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	1	Ma et al. 2016 [++]

Notes on the evidence:

- The dietary constituent considered by the NICE (2014) report is 'dietary sugars' defined as "glucose, fructose, sucrose, honey, and syrups refined from cane, beet, corn, and other sources, either added to foods or intrinsically found in foods, particularly fruits". However, none of the identified RCTs within the above reviews used whole fruit intake to modify dietary sugar intake; furthermore, none of the identified prospective cohort studies included fruit intake in their exposure descriptions of sugars intake.
- Taking this into account, it would be possible to make conclusions with the evidence presented here regarding 'free sugars', as defined by the WHO/FAO (2003) report. This defines free sugars as "monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates".
- The Wiebe et al (2011) published review identified by the NICE (2014) report investigated the effects of nutritive- and non-nutritive sweeteners on blood glucose, blood lipids, and weight management. A meta-analysis for adiposity outcomes was not conducted, therefore the relevant individual studies within the Wiebe et al review are presented in **Section 3.3** of this exposure.
- There appears to be minimal overlap of included studies between meta-analyses; any overlap is highlighted in the commentary below. It appears that the discrepancy in inclusion relates to the specific criteria laid out by each review, particularly with respect to subject health status and the format of the free sugars (saccharide type; whole foods vs. fluids).

2. Children

2.1 Meta-analyses of RCTs in children

Table 65 Meta-analyses of RCTs in children – Sugars

Children					
Meta-analyses of RCTs					
SMD = standardised mean difference; SSB = sugar-sweetened beverage. Significant results are highlighted in **red**.					
Outcome	***Review***	***Intervention description***	***Results***		
BMI or BMI z score	Te Morenga et al (2013)	Habitual diet vs. reduced free sugars intake (nutrition education; provision of non-caloric SSBs) 16–52 weeks	SMD	**0.09 (-0.14, 0.32)** **+VE**	Studies=5; n=2,968 I^2= 82%

One review (Te Morenga et al 2013) conducted a meta-analysis of RCTs in children investigating the effect of reduced intake of dietary sugars on BMI or BMI z score change and reported a non-significant effect of reduced free sugars intake reducing adiposity. The method to reduce free sugars intake varied between studies: three nutrition education interventions; one behavioural intervention; and one home delivery of non-caloric beverages intervention. Three out of five studies focused on reduction in SSB consumption. Furthermore, compliance was reported as 'poor' in three of the studies. Age at recruitment ranged from seven to 18 years.

Below is the corresponding forest plot.

Children | RCTs | BMI or BMI z score | Te Morenga et al 2013 | Reduced sugars intake

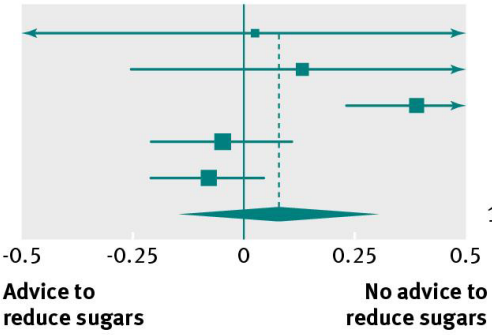
Effect of reducing free sugars on measures of body fatness in children. Pooled effects for standardised mean difference in body mass index for studies comparing advice to reduce intake of free sugars with no advice regarding free sugars. Data are expressed as weighted, standardised mean difference (95% confidence interval), using generic inverse variance models with random effects (Te Morenga et al 2013).

Figure 49 Meta-analysis of RCTs in children – Sugars – Te Morenga et al 2013 – BMI or BMI z score

	No advice			Advice					
Study	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Standard mean difference (95% CI)**	**Weight (%)**	**Standard mean difference (95% CI)**
Davis 2009[46]	0.20	11.88	16	-0.10	8.56	21		8.5	0.03 (-0.62 to 0.68)
Ebbeling 2006[27]	0.21	1.06	50	0.07	1.02	53		15.6	0.13 (-0.25 to 0.52)
James 2004[29]	0.80	0.30	279	0.70	0.20	295		24.8	0.39 (0.23 to 0.56)
Paineau 2008[33]	0.05	0.96	297	0.10	1.14	298		25.0	-0.05 (-0.21 to 0.11)
Sichieri 2009[40]	0.22	0.95	434	0.32	1.47	495		26.1	-0.08 (-0.21 to 0.05)
Total (95% CI)			1076			1162		100.0	0.09 (-0.14 to 0.32)

Test for heterogeneity: τ^2=0.05, χ^2=22.03, df=4, P<0.001, I^2=82%

Test for overall effect: z=0.75, P=0.45



2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 66 Results of individual prospective cohort studies in children – Sugars

Children					
Prospective cohort studies					
OR = odds ratio; CI = confidence interval. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight	Butte et al. 2007 *Te Morenga et al (2013)*	Per % energy intake from fructose 1 year	Beta coefficient	**-3.54 (-10.44, 3.36) kg** **INV**	798
		Per % energy intake from sucrose 1 year	Beta coefficient	**-1.53 (-5.87, 2.81) kg** **INV**	
		Per % energy intake from added sugars 1 year	Beta coefficient	**-1.52 (-3.72, 0.68) kg** **INV**	
BMI z score	Haerens et al. 2010 *Te Morenga et al (2013)*	Additional daily serving of sweets at baseline 4 years	Beta coefficient	**-0.009 (-0.03, 0.01)** **INV**	585
		Per increase in frequency of daily servings of sweets 4 years	Beta coefficient	**0.00 (-0.03, 0.03)** **NIL**	
	Herbst et al. 2011 *Te Morenga et al (2013)*	Per % energy from total added sugars at 1 year into study 6 years	Beta coefficient	**-0.116 (-0.228, -0.004)** **INV**	216
	Phillips et al. 2004 *Te Morenga et al (2013)*	Highest vs. lowest quartiles of % energy from sweets at baseline *(females)* Approx. 7 years	Beta coefficient	**0.082 (CI not reported)** p=0.066 p for trend=0.088 **+VE**	132
BMI	Williams et al. 2008 *Te Morenga et al (2013)*	Intake of sucrose (g per day) at baseline 4 years	Beta coefficient	**-0.10 (-0.2, 0.0)** p=0.046 **INV**	519
	Nissinen et al. 2009 *Te Morenga et al (2013)*	Per 10 units per month intake of sweets at baseline *(males)* 21 years	Beta coefficient	**<0.01 (-12.71, 12.73)** **NIL**	<967 (not clear in text)
		Per 10 units per month intake of sweets at baseline *(females)* 21 years	Beta coefficient	**0.03 (-12.69, 12.75)** **+VE**	<1172 (not clear in text)
		Per 10 units per month increase intake of sweets *(males)* 21 years	Beta coefficient	**-0.13 (-10.13, 9.87)** **INV**	<967 (not clear in text)
		Per 10 units per month increase intake of sweets *(females)* 21 years	Beta coefficient	**-0.12 (-10.12, 9.88)** **INV**	<1172 (not clear in text)
% body fat	Herbst et al. 2011 *Te Morenga et al (2013)*	Per % energy intake from total added sugars at 1 year into study 6 years	Beta coefficient	**-0.014 (-0.043, 0.015) %** **INV**	216
		Per 5% energy intake increase in added sugars 6 year	Beta coefficient	**0.010 (-0.11, 0.13) %** **+VE**	

Odds of overweight	Nissinen et al. 2009 *Te Morenga et al (2013)*	Per 10 units per month increase intake of sweets *(males)* 21 years	OR	**1.02 (0.71, 1.46)** **+VE**	939
		Per 10 units per month increase intake of sweets *(females)* 21 years	OR	**0.87 (0.62, 1.22)** **INV**	1,144

Six prospective cohort studies in children reported 16 results across five outcomes: weight; BMI z score; BMI; percentage body fat; and odds of overweight. Ten results reported inverse associations, of which two were significant. Two results reported non-significant positive associations and two reported no association. Age at baseline ranged from one year to 18 years.

Of the six prospective cohort studies in children, one reported on weight as an outcome (Butte et al 2007) with respect to three exposures: percentage energy intakes from fructose, sucrose, and added sugars. All reported non-significant, inverse associations.

Three studies reported on BMI z score but varied in their definition of the exposure: serving frequency of sweets (Haerens et al 2010); percentage energy from added sugars (Herbst et al 2011); and highest vs. lowest quintiles of percentage energy intake from sweets (Phillips et al 2004). One study (Herbst et al 2011) reported a significant, association of higher intake of total sugars at one year into the study being related to lower BMI z score at seven years. The other studies reported non-significant associations

Two studies reported on BMI (Williams et al 2008; Nissinen et al 2009), with one study stratifying for females and males (Nissinen et al 2009). Williams et al (2008) reported a significant inverse association; Nissinen et al (2009) reported non-significant associations. The studies reporting on percentage body fat and the odds of being overweight at follow-up also reported non-significant results (Herbst et al 2011; Nissinen et al 2009).

3 Adults

3.1 Meta-analyses of RCTs in adults

Table 67 Meta-analyses of RCTs in adults – Sugars

Adults					
Meta-analyses of RCTs					
SMD = standardised mean difference; WMD = weighted mean difference; CHO = carbohydrate; HFCS = high fructose corn syrup; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Review***	***Intervention description***	***Results***		
Weight	Te Morenga et al (2013) See: Plots A and B	Ad libitum diet with reduced sugars intake vs. habitual diet (difference sugars intake: 1–14% total energy) 10–32 weeks	WMD	**-0.80 (-1.21, -0.39) kg** +VE	Studies=5; n=1,286 I^2=17%
		Isocaloric exchange of sugars (40-300g/day) vs. complex CHO 2–26 weeks	WMD	**0.04 (-0.04, 0.13) kg** +VE	Studies=11; n=144 I^2=32%
	Sievenpiper et al (2012) See: Plot C	Isocaloric exchange of fructose (median dose 69.1g/day) vs. other dietary CHO (starch, sucrose, glucose, HFCS) 1–26 weeks	MD	**-0.13 (-0.37, 0.10) kg** INV	Studies=13; n=417 I^2=8%
	Te Morenga et al (2013) See: Plot D	Hypercaloric addition of free sugars (amount not prescribed in all trials) vs. habitual diet 2–26 weeks	WMD	**0.75 (0.30, 1.19) kg** +VE	Studies=10; n=382 I^2=82%
	Sievenpiper et al (2012) See: Plot E	Hypercaloric addition of fructose (median dose 182g/day) vs. habitual diet 1–10 weeks	MD	**0.37 (0.15, 0.58) kg** +VE	Studies=8; n=176 I^2= 0%
Accumulated ectopic liver fat	Ma et al (2016) See: Plots F and G	Hypercaloric addition of free sugars (~20–43% total energy) vs. habitual diet 1– 26 weeks	SMD	**0.93 (0.64, 1.21)** +VE	Studies=8; n=104 I^2=0%
Accumulated ectopic lower extremity muscle fat		Hypercaloric addition of free sugars (~20–43% total energy) vs. habitual diet 1– 26 weeks	SMD	**0.63 (0.23, 1.04)** +VE	Studies=5; n=80 I^2=42%

Three reviews conducted seven meta-analyses of RCTs across three outcomes: weight; accumulated ectopic liver fat; and accumulated ectopic lower extremity muscle fat. Six of the seven results reported positive effects, of which five were significant. One result reported a non-significant inverse effect.

Meta-analyses differed on how sugars were manipulated in the control groups: one meta-analysis investigated reduced intake of sugars; two meta-analyses investigated isocaloric exchange of sugars; and four meta-analyses investigated hypercaloric increased intake of sugars.

Reduced intake of sugars

One meta-analysis (Te Morenga et al 2013) investigated reduced intake of dietary sugars and reported a significant reduction in weight; two of the five included studies were based on patient groups: one in overweight subjects (Saris et al. 2000) and one in overweight subjects with hypertriglyceridaemia (Smith et al. 1996).

Isocaloric exchange of sugars

The two meta-analyses investigating isocaloric exchange of free sugars with other dietary carbohydrates (Te Morenga et al 2013; Sievenpiper et al 2011) both reported non-significant associations. (Please note that 11 trials are included in the Te Morenga meta-analysis (counting from the forest plot and the results table) but the text states 12 trials are included.) Of the 11 studies meta-analysed by Te Morenga et al, eight were in diabetic patient groups (types 1 and 2). The trials within the Sievenpiper meta-analysis were all based on normal weight subjects; two trials (three estimates) included participants with hypertriglyceridaemia and one trial included participants with chronic kidney disease. There was overlap of one included study (Swanson et al. 1992) between the two meta-analyses of isocaloric exchange.

Hypercaloric increased sugars intake

Two meta-analyses investigated hypercaloric addition of free sugars with both reporting a significant increase in weight. In one meta-analysis (Te Morenga et al 2013) four of the 10 included studies used SSB as the exposure of interest. In the same meta-analysis, when stratified for length of intervention, the effect size was higher for studies lasting more than eight weeks (n=2). The other hypercaloric meta-analysis (Sievenpiper et al 2012) focused solely on increased intake of fructose, provided in fluid format.

Two meta-analyses were conducted based on RCTs in adults investigating the effect of hypercaloric addition of free sugars on accumulated ectopic fat (liver and lower extremity muscle) (Ma et al 2015); both reported a significant increase in ectopic fat deposition. The meta-analysis of studies reporting on ectopic liver fat accumulation stratified via type of free sugar (sucrose and fructose) and both indicated a significant, positive association. Both of the Ma et al meta-analyses had two studies that overlapped with the meta-analysis of hypercaloric trials by Sievenpiper et al (2012): Ngo Sock et al. 2010 and Le et al. 2009.

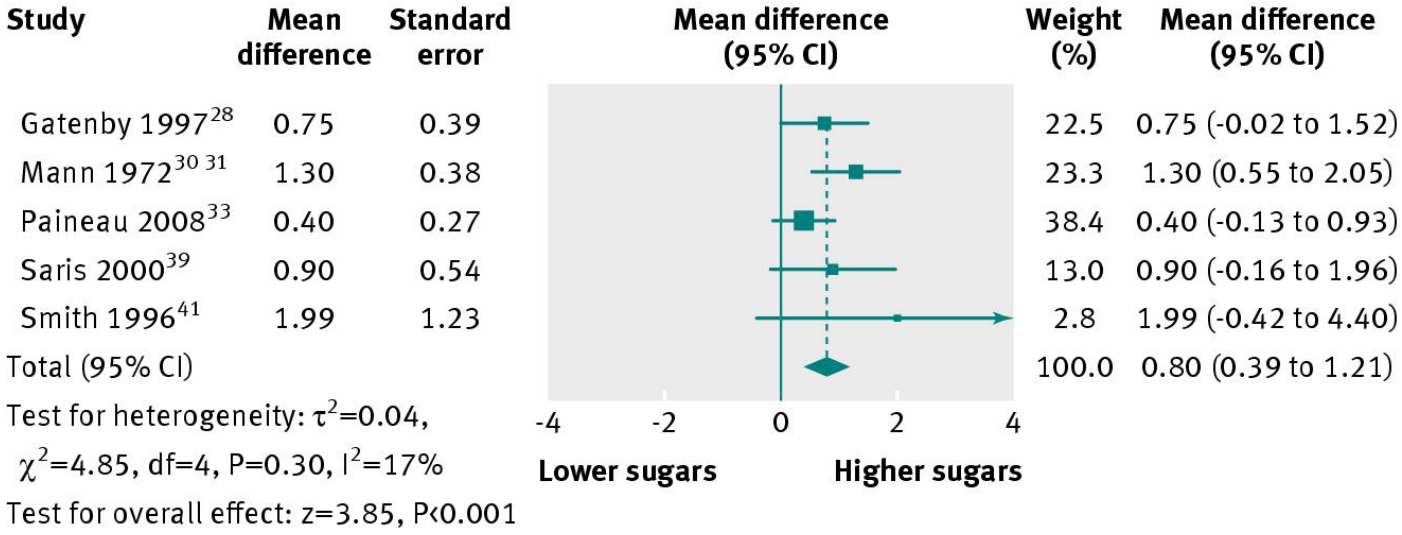
The forest plots corresponding to the above seven meta-analyses are presented below.

Adults | RCTs | Weight | Te Morenga et al 2013 | Reduced sugars intake (Plot A, see Table 67)

Effect of reducing intake of free sugars on measures of body fatness in adults. Pooled effects for difference in body weight (kg) shown for studies comparing reduced intakes (lower sugars) with usual or increased intakes (higher sugars). Overall effect shows increased body weight after intervention in the higher sugars groups. Data are expressed as weighted mean difference (95% confidence interval), using generic inverse variance models with random effects (Te Morenga et al 2013).

Please note that authors have inverted the results to present them in the forest plot; in the text results = -0.80 (-1.21, -0.39) kg, whereas in the forest plot results = +0.80 (+0.39, +1.21) kg.

Figure 50 Meta-analysis of RCTs in adults – Sugars (reduced intake) – Te Morenga et al 2013 – Weight

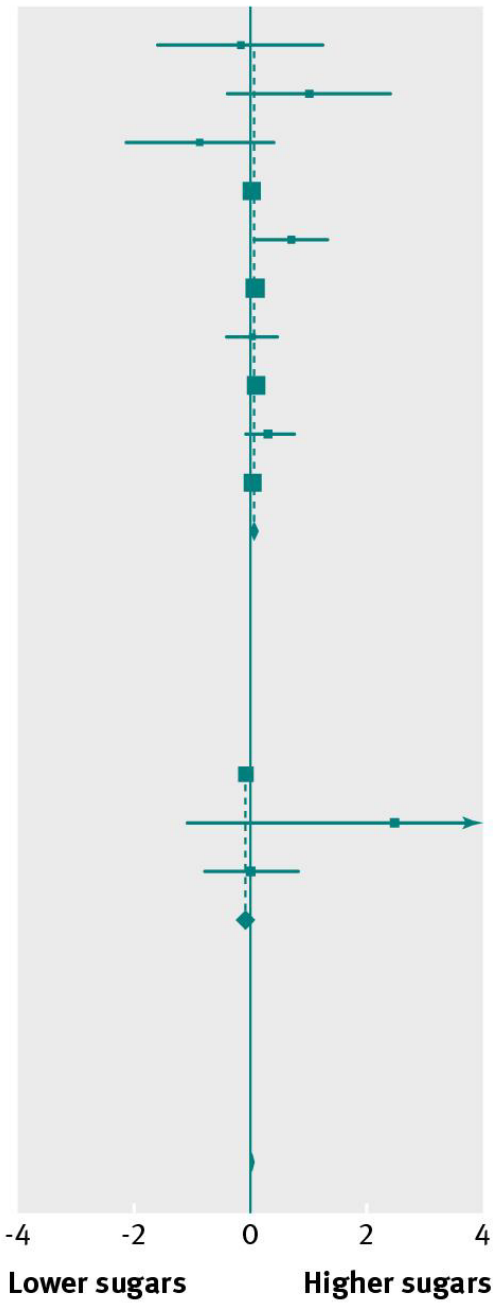


Adults | RCTs | Weight | Te Morenga et al 2013 | Isocaloric exchange of sugars for complex CHO (Plot B, see Table 67)

Isocaloric exchanges of free sugars with other carbohydrates or other macronutrient sources. Pooled effects for difference in body weight (kg) for studies comparing isoenergetic exchange of free sugars (higher sugars) with other carbohydrates (lower sugars). Data are expressed as weighted mean difference (95% confidence interval), using generic inverse variance models with random effects (Te Morenga et al 2013).

Please note that authors reported 12 studies in the text, but there are 11 studies (13 comparisons) listed in the forest plot.

Figure 51 Meta-analysis of RCTs in adults – Sugars (isocaloric) – Te Morenga et al 2013 – Weight



Study	Mean difference	Standard error	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
Treatments <8 weeks duration					
Bantle 1992[48]	-0.20	0.73		0.3	-0.20 (-1.63 to 1.23)
Bantle 1993[49]	1.00	0.73		0.3	1.00 (-0.43 to 2.43)
Koivisto 1993[51]	-0.90	0.65		0.4	-0.90 (-2.17 to 0.37)
Malerbi 1996 (1)[52]	0.01	0.06		19.4	0.01 (-0.11 to 0.13)
Malerbi 1996 (2)[53]	0.70	0.31		1.7	0.70 (0.09 to 1.31)
Mann 1972b[53]	0.10	0.07		17.0	0.10 (-0.04 to 0.24)
Mann 1973[54]	0.11	0.23		3.1	0.01 (-0.43 to 0.46)
Peterson 1986 (3)[56]	0.10	0.07		17.0	0.10 (-0.04 to 0.24)
Peterson 1986 (4)[58]	0.30	0.22		3.3	0.30 (-0.13 to 0.73)
Swanson 1992[58]	0.01	0.06		19.4	0.01 (-0.11 to 0.13)
Subtotal (95% CI)				81.9	0.07 (-0.01 to 0.15)
Test for heterogeneity: τ^2=0.00, χ^2=11.50, df=9, P=0.24, I^2=22%					
Test for overall effect: z=1.64, P=0.10					
Treatments ≥8 weeks duration					
Grigoresco 1988[50]	-0.10	0.07		17.0	-0.10 (-0.24 to 0.04)
Osei 1989[55]	2.50	1.84		0.1	2.50 (-1.11 to 6.11)
Santacroce 1990[57]	0	0.40		1.1	0.00 (-0.78 to 0.78)
Subtotal (95% CI)				18.1	-0.09 (-0.27 to 0.09)
Test for heterogeneity: τ^2=0.00, χ^2=2.05, df=2, P=0.36, I^2=2%					
Test for overall effect: z=0.97, P=033					
Total (95% CI)				100.0	0.04 (-0.04 to 0.13)
Test for heterogeneity: τ^2=0.01, χ^2=17.57, df=12, P=0.13, I^2=32%					
Test for overall effect: z=1.03, P=0.30					
Test for subgroup differences: χ^2=2.42, df=1, P=0.12, I^2=58.6%					

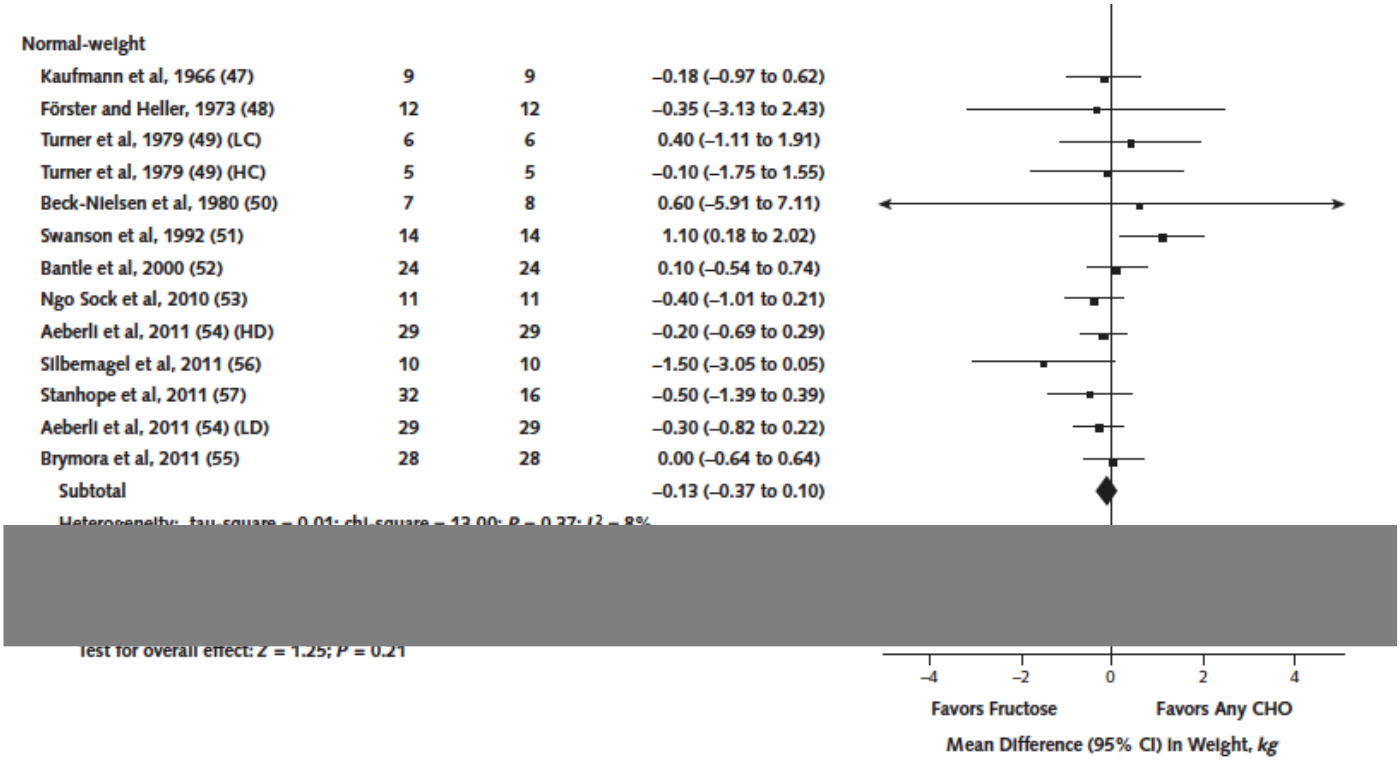
(1) Fructose *v* starch, (2) Sucrose *v* starch, (3) Patients with type 1 diabetes, (4) Patients with type 2 diabetes

Adults | RCTs | Weight | Sievenpiper et al 2012 | Isocaloric exchange of fructose for other CHO (Plot C, see Table 67)

Forest plots of isocaloric feeding trials investigating the effect of isocaloric exchange of fructose for carbohydrate on body weight (kg) in normal-weight people (Sievenpiper et al 2012).

Please note – rectangular grey box is placed to obscure the pooled results for "normal weight" + "obese subjects" + "diabetic subjects" (category titles as per published review).

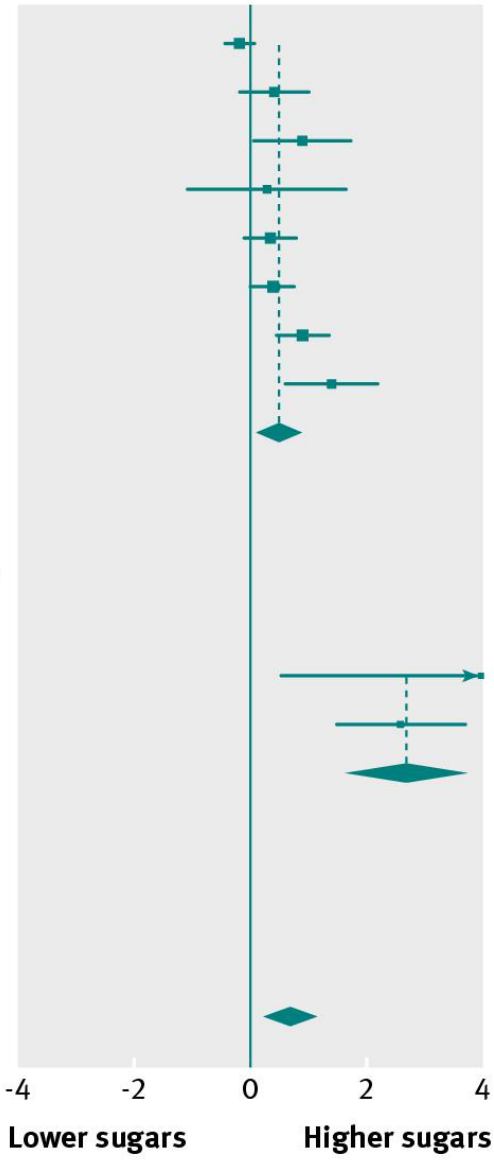
Figure 52 Meta-analysis of RCTs in adults – Sugars (isocaloric) – Sievenpiper et al 2012 – Weight



Adults | RCTs | Weight | Te Morenga et al 2013 | Hypercaloric addition of sugars (Plot D, see Table 67)

Effect of increasing free sugars on measures of body fatness in adults. Pooled effects for difference in body weight (kg) shown for studies comparing increased intake (higher sugars) with usual intake (lower sugars). Overall effect shows increased body weight after intervention in the higher sugars groups. Data are expressed as weighted mean difference (95% confidence interval), using generic inverse variance models with random effects (Te Morenga et al 2013).

Figure 53Meta-analysis of RCTs in adults – Sugars (hypercaloric) – Te Morenga et al 2013 – Weight



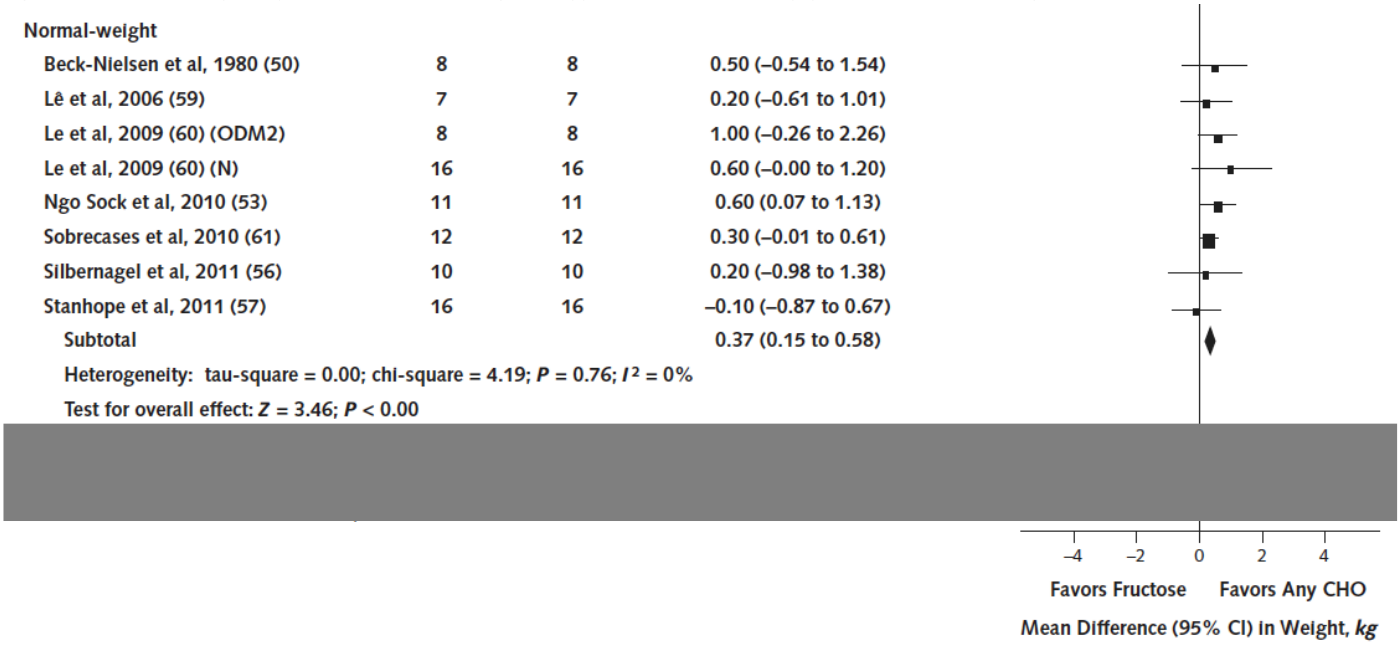
Study	Mean difference	Standard error	Mean difference (95% CI)	Weight (%)	Mean difference (95% CI)
Studies <8 weeks					
Aeberil 2011[47]	-0.17	0.13		14.1	-0.17 (-0.42 to 0.08)
Brynes 2003[26]	0.41	0.30		11.7	0.41 (-0.18 to 1.00)
Marckmann 2000[32]	0.90	0.43		9.6	0.90 (0.06 to 1.74)
Reid 2007[38]	0.30	0.70		6.1	0.30 (-1.07 to 1.67)
Reid 2010[37]	0.36	0.22		12.9	0.36 (-0.07 to 0.79)
Szanto 1969[43]	0.40	0.19		13.4	0.40 (0.03 to 0.77)
Tordoff 1990[44]	0.91	0.22		12.9	0.91 (0.47 to 1.35)
Werner 1984[45]	1.40	0.40		10.1	1.40 (0.62 to 2.18)
Subtotal (95% CI)				90.8	0.52 (0.14 to 0.89)
Test for heterogeneity: τ^2=0.20, χ^2=30.39, df=7, P<0.001, I^2=77%					
Test for overall effect: z=2.70, P=0.007					
Studies >8 weeks					
Poppitt 2002[34]	3.97	1.75		1.5	3.97 (0.55 to 7.39)
Raben 2002[35]	2.60	0.57		7.7	2.60 (1.49 to 3.71)
Subtotal (95% CI)				9.2	2.73 (1.68 to 3.78)
Test for heterogeneity: τ^2=0.00, χ^2=0.56, df=1, P=0.46, I^2=0%					
Test for overall effect: z=5.07, P<0.001					
Total (95% CI)				100.0	0.75 (0.30 to 1.19)
Test for heterogeneity: τ^2=0.35, χ^2=50.93, df=9, P<0.001, I^2=82%					
Test for overall effect: z=3.30, P=0.001					
Test for subgroup differences: χ^2=14.98, df=1, P<0.001, I^2=93.3%					

Adults | RCTs | Weight | Sievenpiper et al 2012 | Hypercaloric addition of fructose (Plot E, see Table 67)

Forest plots of hypercaloric feeding trials investigating the effect of a control diet supplemented with 18% to 97% (104 to 250 g per day) excess energy from fructose on body weight (kg) in normal-weight people (Sievenpiper et al 2012).

Please note – rectangular grey box is placed to obscure the pooled results for "normal weight" + "obese subjects" + "diabetic subjects" (category titles as per published review).

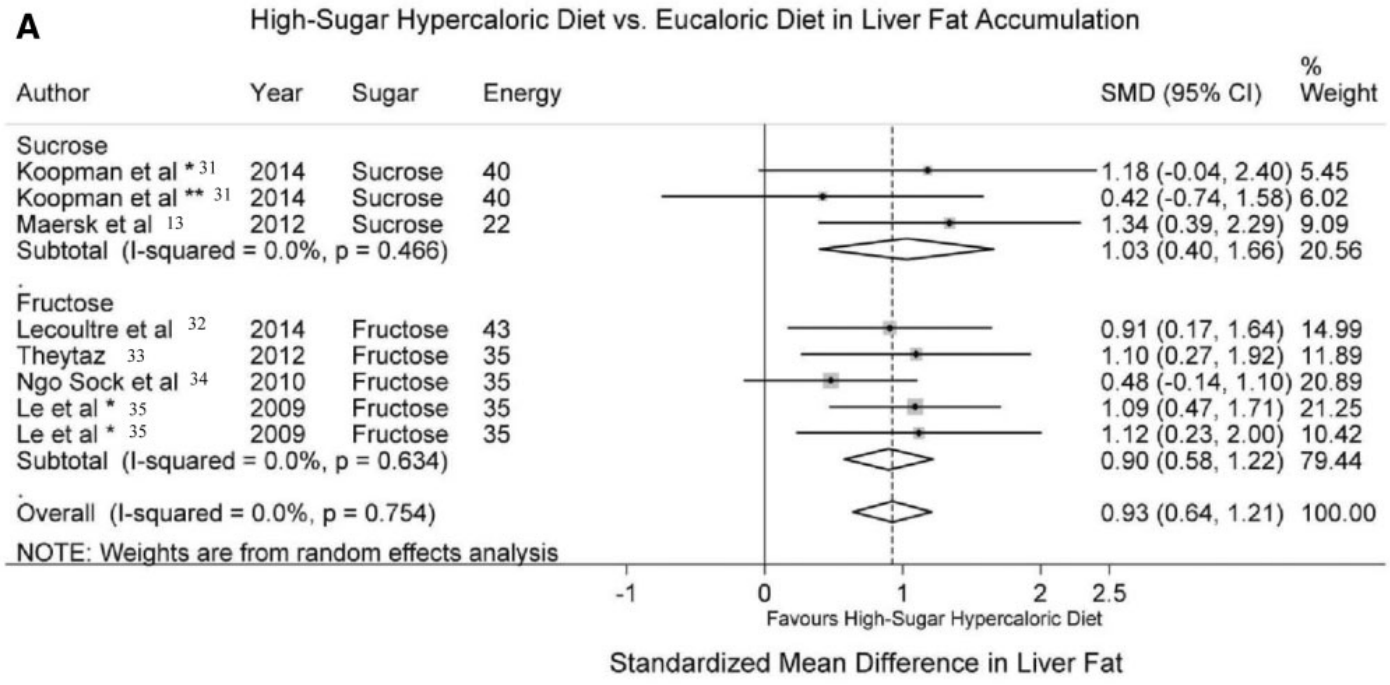
Figure 54 Meta-analysis of RCTs in adults – Sugars (hypercaloric) – Sievenpiper et al 2012 – Weight



Adults | RCTs | Accumulated ectopic liver fat | Ma et al 2016 | Hypercaloric addition of sugars (Plot F, Table 67)

Effects of high-sugar (sucrose and fructose) hypercaloric diets vs eucaloric diets with no excess added sugars on fat accumulation in liver. Data were presented as standardized mean differences (SMD) with 95% confidence intervals (95%CI). Meta-analyses were conducted using Der Simonian and Laird's random-effects models. Overall effect, z=6.37; P < 0.001 (Ma et al 2016).

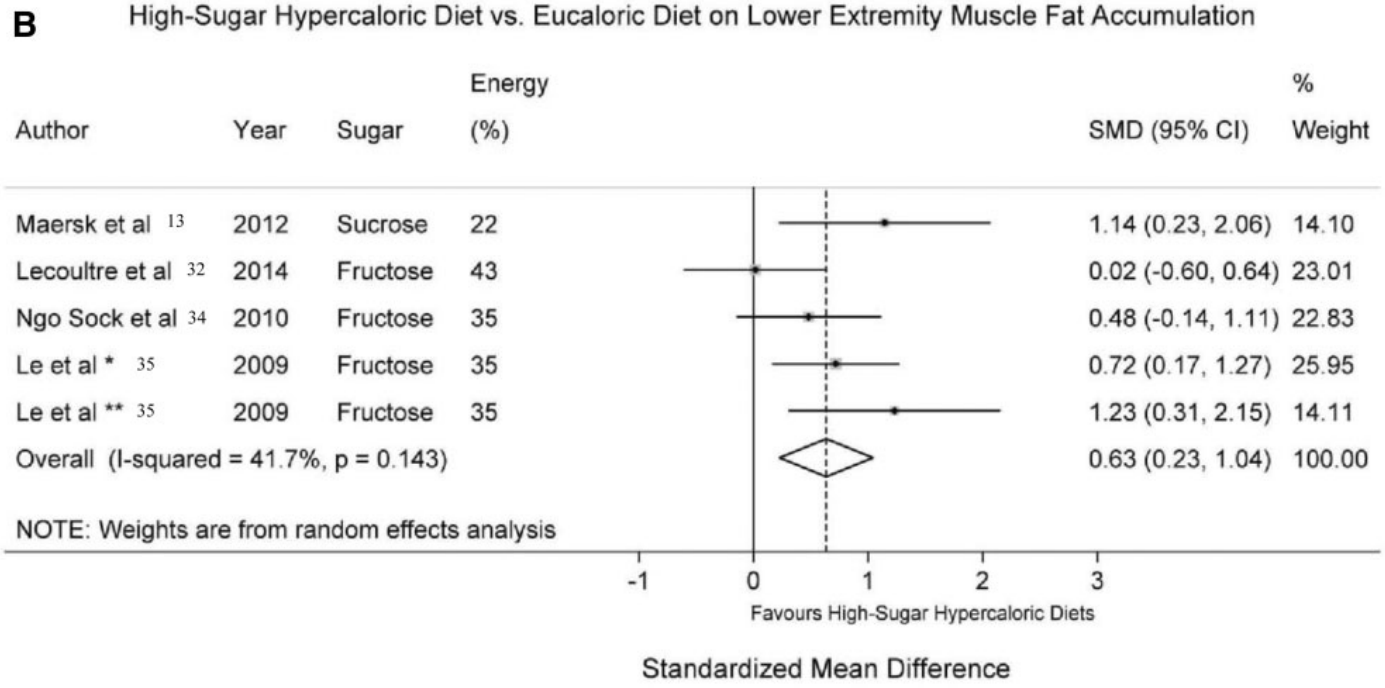
Figure 55 Meta-analysis of RCTs in adults – Sugars – Ma et al 2016 – Ectopic liver fat



Adults | RCTs | Accumulated ectopic lower extremity muscle fat | Ma et al 2016 | Hypercaloric addition of sugars (Plot G, see Table 67)

Effects of high-sugar hypercaloric diets vs eucaloric diets with no excess added sugars on fat accumulation in lower-extremity muscle. Data were presented as standardized mean differences (SMD) with 95% confidence intervals (95%CI). Meta-analyses were conducted using DerSimonian and Laird's random-effects models. Overall effect, z=3.04; P=0.002 (Ma et al 2016).

Figure 56 Meta-analysis of RCTs in adults – Sugars – Ma et al 2016 – Ectopic lower extremity muscle fat



3.2 Meta-analyses of prospective cohort studies in adults

Table 68 Meta-analyses of prospective cohort studies in adults – Sugars

Adults					
Meta-analyses of prospective cohorts					
Significant results are highlighted in **red**.					
Outcome	***Review***	***Exposure description***	***Results***		
Weight	Te Morenga et al (2013)	Additional daily serving of sweets at baseline 2–9.9 years	Regression coefficient	**0.00 (-0.02, 0.03)** **NIL**	Studies=4; n=47,068 I^2=74%
		Additional daily serving of sweets increase from baseline 4–5.9 years	Regression coefficient	**0.02 (-0.02, 0.07)** **+VE**	Studies=2; n=50,670 I^2=91%

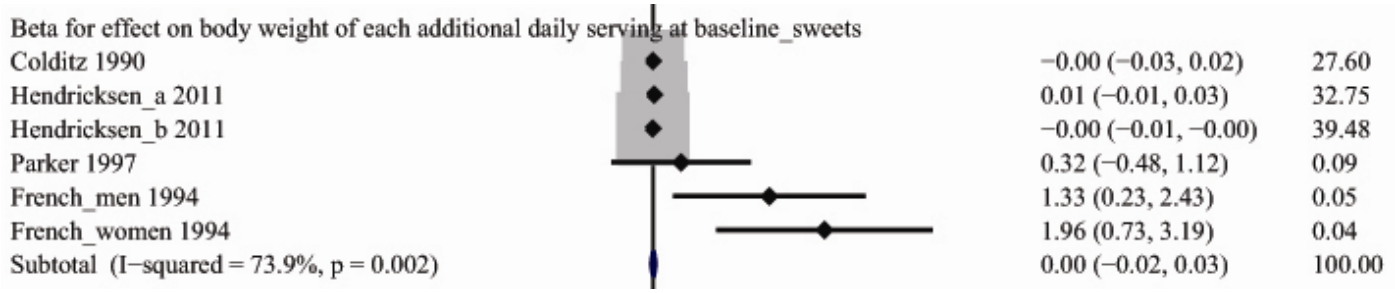
One review conducted two meta-analyses of prospective cohort studies in adults reporting on weight change (Te Morenga et al 2013). One meta-analysis investigated baseline intake of sweets and change in weight, reporting no association. The second investigated increases in daily servings of sweets and reported a non-significant positive association.

The exposure was defined differently between studies in both meta-analyses: grams of sucrose per day (two studies); kJ sweets and cakes per day (one study); sweet food serving frequency (two studies); and self-perceived change in sweet foods intake (one study). The corresponding forest plots are presented below.

Adults | Prospective cohorts | Weight | Te Morenga et al 2013 | Additional daily serving of sweets at baseline

Forest plot of associations between body weight and measures of sugars in cohort studies in adults. Far right column = % weight of study; column second in from right = effect size with 95% confidence interval (Te Morenga et al 2013).

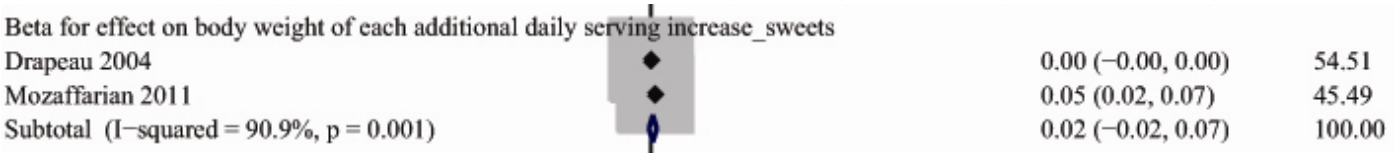
Figure 57 Meta-analysis of prospective cohort studies in adults – Sugars (baseline) – Te Morenga et al 2013 – Weight



Adults | Prospective cohorts | Weight | Te Morenga et al 2013 | Additional daily serving increase of sweets

Forest plot of associations between body weight and measures of sugars in cohort studies in adults. Far right column = % weight of study; column second in from right = effect size with 95% confidence interval (Te Morenga et al 2013).

Figure 58 Meta-analysis of prospective cohort studies in adults – Sugars (change) – Te Morenga et al 2013 – Weight



3.3 Individual RCTs in adults, not in meta-analyses

Table 69 Results of individual RCTs in adults – Sugars

Adults					
RCTs					
MD=mean difference; FOS=fructooligosaccharide. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Intervention description***	***Results***		***n***
BMI	Okuno et al. 2010 *Wiebe et al (2011)*	Addition of 40g isomaltulose + sucrose per day vs. addition of 40g sucrose per day 12 weeks	MD	**-0.04 (-0.4, 0.3) kg/m²** **INV**	50
Weight			MD	**-0.06 (-0.9, 0.8) kg** **INV**	
Weight	MacDonald et al. 1973 *Wiebe et al (2011)*	Addition of 6.5g/kg sucrose per day vs. addition of 6.5g/kg glucose per day 2 x 11 day periods (crossover)	MD	**0.2 (-0.07, 0.4) kg** **+VE**	10
Weight	Luo et al (1996) *Wiebe et al (2011)*	Addition of 20g FOS per day vs. addition of 20g sucrose per day 2 x 4 weeks (crossover)	MD	**1.0 (-2.4, 4.4) kg** **+VE**	24

Three RCTs not included in any meta-analyses with adiposity as an outcome were identified. All three compared addition of different types of sugars added to a background diet: ad libitum diet (Okuno et al 2010); restriction to 1g/kg of calcium caseinate (MacDonald et al 1973); and recommended low fibre diet (Luo et al 1996). None compared addition of a sugar compared to no addition of a sugar. Trial length was generally short.

One trial (Okuno et al 2010) reported no difference in change in BMI or weight when comparing addition of isomaltulose + sucrose to sucrose alone over 12 weeks. Two crossover trials reported non-significant positive effects when comparing sucrose with glucose (MacDonald and Taylor 1973) and when comparing fructooligosaccharide with sucrose (Luo et al 1996).

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 70 Results of individual prospective cohort studies in adults – Sugars

Adults					
Prospective cohort studies					
OR=odds ratio; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight gain (>2kg/year)	Schulz et al. 2002 *Te Morenga et al (2013)*	Per additional 100g intake of sweets per day *(female)* 2.2 years	OR	**1.31 (0.98, 1.73)** +VE	11,005
		Per additional 100g intake of sweets per day *(male)* 2.2 years	OR	**1.48 (1.03, 2.13)** +VE	6,364
Weight gain (<2kg/year)		Per additional 100g intake of sweets per day *(female)* 2.2 years	OR	**0.93 (0.72, 1.20)** INV	11,005
		Per additional 100g intake of sweets per day *(male)* 2.2 years	OR	**1.10 (0.81, 1.51)** +VE	6,364
Weight loss (<2kg/year)		Per additional 100g intake of sweets per day *(female)* 2.2 years	OR	**0.81 (0.63, 1.04)** +VE	11,005
		Per additional 100g intake of sweets per day *(male)* 2.2 years	OR	**1.43 (1.07, 1.90)** INV	6,364
Weight loss (>2kg/year)		Per additional 100g intake of sweets per day *(female)* 2.2 years	OR	**0.67 (0.49, 0.92)** +VE	11,005
		Per additional 100g intake of sweets per day *(male)* 2.2 years	OR	**0.70 (0.45, 1.08)** +VE	6,364
Waist circumference	Halkjaer et al. 2006 * *Te Morenga et al (2013)*	Per MJ per day of sweet foods at baseline *(female)* 5.3 years	MD	**0.39 (0.18, 0.60) cm** +VE	22,570
		Per MJ per day of sweet foods at baseline *(male)* 5.3 years	MD	**0.09 (-0.06, 0.23) cm** +VE	20,126
	Halkjaer et al. 2009 * *Te Morenga et al (2013)*	Per 60kcal per day of jams, syrups, and sugars *(female)* 5.3 years	MD	**0.05 (-0.03, 0.13) cm** +VE	22,570
		Per 60kcal per day of jams, syrups, and sugars *(male)* 5.3 years	MD	**-0.0004 (-0.06, 0.06) cm** INV	20,126
	Halkjær et al. 2004 *Te Morenga et al (2013)*	Per quintile increase intake of sweet foods at baseline *(female)* 6 years	MD	**-0.08 (-0.30, 0.13) cm** INV	1,119
		Per quintile increase intake of sweet foods at baseline *(male)* 6 years	MD	**0.04 (-0.10, 0.19) cm** +VE	1,156
*These publications use data from the same study population (Danish Diet, Cancer and Healthy Study)					

Three study populations (four publications) reported 14 results across three outcomes: odds of weight gain; odds of weight loss; and waist circumference. Ten results reported positive associations (three were statistically significant) and four results reported inverse associations (one was statistically significant).

One study (Schulz et al 2002) reported the odds ratios for different levels of weight gain and loss at follow-up: large weight gain (>2kg per year); small weight gain (<2kg per year); small weight loss (<2kg per year);

and large weight loss (>2kg per year). This was stratified for females and males. Significant results were reported for large weight gain in males (increased odds), small weight loss in males (increased odds), and large weight loss in females (decreased odds).

Three studies reported on waist circumference with varied definitions of the exposure: per MJ per day of sweet foods (Halkjaer et al 2006); per 60kcal per day of jams, sugars, and syrups (Halkjaer et al 2009); per quintile increase of sweet foods (Halkjaer et al 2004). One significant association was identified for increased waist circumference per MJ per day of sweet foods at baseline in females; the other five results reported were non-significant. Halkjaer et al 2006 and Halkjaer et al 2009 used the same population (Danish Diet, Cancer and Health Study) to calculate results but reported with different exposure definitions.

4. Possible mechanisms

As summarised by Te Morenga et al (2013):

- The hypercaloric results in combination with the isocaloric results strongly suggest that energy imbalance is a major mediating factor with respect to increased free sugars intake leading to increased adiposity.
- Foods containing free sugars are typically (although not invariably) energy dense; frequent and substantial consumption of energy dense foods is associated with weight gain and excess adiposity.
- Sugars increase fructose levels, which may increase levels of uric acid and hyperinsulinaemia, identified as potentially important and independent predictors of obesity.
- SSBs and dietary fructose may promote the deposition of liver, skeletal, and visceral fat and an increase in serum lipids independently of an effect on body weight.

5. Summary of evidence

5.1 Children

The single available meta-analysis investigating RCTs of free sugars intake and adiposity in children reported a non-significant positive effect; this may be related to poor compliance to the intervention. The six individual prospective cohort studies not in meta-analyses reported inconsistent effects (both positive and inverse associations); two inverse associations were statistically significant.

5.2 Adults

Seven meta-analyses of RCTs from three reviews investigating free sugars intake and adiposity in adults generally showed consistent effects of increased adiposity with increased intake, decreased adiposity with decreased intake, or minimal adiposity change with isocaloric intake. Five of the meta-analyses of RCTs results reported significant effects. Two meta-analyses of prospective cohort studies from one review reported no significant associations.

Three RCTs not included in any meta-analyses were identified; all compared one type of sugar to another and reported no significant effects.

Four prospective cohort study publications provided 14 results: ten reported positive associations (of which three were statistically significant) and four results reported inverse associations (of which one was statistically significant).

3.3 Dietary fat

1. Evidence identified for 2017 update

Table 71 Published reviews identified for the 2017 update – Dietary fat

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Hooper et al. 2012 [++]; U.S Department of Agriculture Nutrition Evidence Library 2010a [++]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	1	Hooper et al. 2015 [++]

Notes on the evidence:

- The Cochrane Review by Hooper et al (2012) was superseded by the review by Hooper et al (2015). In the evidence sections here, only Hooper et al (2015) is reported.
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.
- The USDA (2010) published review only investigated studies in children.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=1,000, so only studies with more than 1,000 participants are reported in detail here.

2. Children

2.1 Meta-analysis of RCTs in children

Nil

2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Table 72 Results of individual RCTs in children – Dietary fat

Children					
RCTs not in meta-analyses					
MD=mean difference; CI=confidence interval. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Intervention description***	***Results***		***n***
BMI	Mihas et al. 2010 *Hooper et al (2015)*	Health education to reduce fat intake vs. habitual diet 17 months	MD	**-1.20 kg/m²** (CI=not reported) **+VE**	191
	Caballero et al. 2003 *USDA (2010)*	Health education to reduce fat intake vs. habitual diet 3 years	MD	**-0.2 (-0.50, 0.15) kg/m²** p=0.298 **+VE**	1,704
	Niinikoski et al. 2007 *USDA (2010)*	Dietary counselling to reduce fat intake to 30% total energy vs. habitual diet 13.4 years	**No significant difference between groups** p=0.28 Data for means not provided **NIL**		1,062
% body fat	Caballero et al. 2003 *USDA (2010)*	Health education to reduce fat intake vs. habitual diet 3 years	MD	**0.2 (-0.84, 1.31) %** p=0.664 **INV**	1,704

Three RCTs were identified in two reviews, reporting four results across two outcomes: BMI and percentage body fat. All studies investigated the effect of advice to reduce intake of fat on measures of adiposity. One result reported no significant association and did not report direction of effect. Two results reported non-significant positive associations (advice to reduce fat intake leading to reduced adiposity) and one result reported a non-significant, inverse association.

Age at recruitment ranged from seven months to 13 years.

All interventions were health education or dietary counselling based interventions designed to reduce intake of dietary fat. Caballero et al (2003) and Niinikoski et al (2007) reported the percentage energy intake from fat at follow up for intervention and control groups, both noting a significantly lower intake of fat as a percentage of total energy in the intervention groups. The success of the intervention was unclear in Mihas et al (2010). Caballero et al (2003) reported using an intention-to-treat analysis; it was not clear if Niinikoski et al (2007) and Mihas et al (2010) also used this approach.

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 73 Results of individual prospective cohort studies in children – Dietary fat

Children					
Prospective cohort studies not in meta-analyses					
SE=standard error. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Newby et al. 2003b *USDA (2010)*	Each additional serving of 'fat foods' 6–12 months	Beta coefficient	**0.05 SE± 0.02 kg per year** p=0.01 **+VE**	1,379
		% energy from fat 6–12 months	Beta coefficient	**-0.02 SE± 0.01 kg per year** p=0.07 **INV**	1,379
BMI change	Lee et al. 2012 *Hooper et al (2015)*	Per 1% energy from fat 2 years	Regression coefficient	**0.021 (-0.004, 0.046) kg/m^2** p=0.104 **+VE**	1,504
	Berkey et al. 2000 *USDA (2010)*	Fat intake grams per day *(girls)* 1 year	Beta coefficient	**0.0008 SE± 0.0016 kg/m^2** p=0.632 **+VE**	6,149
		Fat intake grams per day *(boys)* 1 year	Beta coefficient	**-0.0015 SE± 0.0017 kg/m^2** p=0.375 **INV**	4,620

Three prospective cohort studies investigating total fat intake and adiposity in children with more than 1,000 participants were identified in two reviews. These provided five results across two outcomes: weight change and BMI change. Three results reported positive associations between fat intake and adiposity, of which one was statistically significant. Two results reported non-significant inverse associations. Age range at baseline ranged from two to 19 years.

The 'fat foods' group in Newby et al (2003) was defined specifically for that study but is similar to categorisation of scheme used in the USDA Food Guide Pyramid. The model used adjusted for age, sex, and sociodemographic variables (ethnicity, residence, level of poverty, maternal education, and birth weight). Energy was omitted from the model. When energy was included in the model the beta coefficient was 0.07 kg per year for each additional serving of 'fat foods' (SE± 0.02, p=0.003).

The remaining 26 studies with fewer than 1,000 participants provided 35 results across 7 outcomes: weight; BMI; BMI z score; BMI percentile; percentage body fat; fat mass; and skinfold thickness measures. Eighteen results reported no association without comment on direction, 15 results reported a positive association (13 of which were statistically significant), and two results reported inverse associations (both of which were statistically significant). The sample sizes ranged from 48 to 879 participants, with all but two studies having fewer than 500 participants.

Studies n<1000: Butte et al. 2007, Magarey et al. 2001, Twisk et al. 1998, Bogaert et al. 2003, Carruth et al. 2001, Davison et al. 2001, Rolland-Cachera et al. 2013, Brixval et al. 2009, Klesges et al. 1995, Cohen et al. 2014, Alexy et al. 1999, Alexy et al. 2004, Boulton et al. 1995, Francis et al. 2003, Gazzaniga et al. 1993, Johnson et al. 2008a, Karaolis-Danckert et al. 2007, Lee et al. 2001, Maffeis et al. 1998, Robertson et al. 1999, Rolland-Cachera et al. 1995, Scaglioni et al. 2000, Shea et al. 1993, Skinner et al. 2003, Skinner et al. 2004, and Boreham et al. 1999.

3. Adults

3.1 Meta-analysis of RCTs in adults

Table 74 Meta-analyses of RCTs in adults – Dietary fat

Adults					
Meta-analyses of RCTs					
MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Hooper et al (2015)	Reduced proportion of energy as fat vs. habitual diet 6 months–8 years	MD	**-1.54 (-1.97, -1.12) kg** **+VE**	Studies=24; n=53,647 I^2=77%
BMI change			MD	**-0.5 (-0.7, -0.3) kg/m²** **+VE**	Studies=10; n=45,703 I^2=74%

One review conducted two meta-analyses of RCTs in adults investigating the effect of advice to reduce fat intake on weight change and BMI change. Both results reported a significant effect of reduced adiposity with lower proportion of energy as fat.

A high degree of heterogeneity between trials was observed in both meta-analyses, which the authors attributed to type and number of participants, the duration and nature of the interventions, control methods, and follow up. The majority of studies included in the review were in patient group populations and 17 studies were in single sex populations (13 in females, 4 in males).

Hooper et al (2015): Inclusion criteria *(quoted from the published review)*

- Included: All randomised controlled trials (RCTs) of interventions stating an intention to reduce dietary fat, when compared with a usual or modified fat intake. A low fat intake was considered to be ≤30% energy from fat, and at least partially replace the energy lost with carbohydrates (simple or complex), protein or fruit and vegetables. A modified fat diet was considered to be >30% energy from total fats, and included higher levels of mono-unsaturated or poly-unsaturated fats than a 'usual' diet.
- Excluded:
    - Studies aiming to reduce the weight of some or all participants, those that included only participants who had recently lost weight, or recruited participants according to a raised body weight or BMI.
    - Multifactorial interventions other than diet or supplementation.
    - Atkins-type diets aiming to increase protein and fat intake, studies where fat was reduced by means of a fat substitute (like Olestra), enteral and parenteral feeds, and formula weight-reducing diets.

Hooper et al (2015): Sensitivity analysis and heterogeneity *(quoted from the published review)*

- Sensitivity analyses did not lose the statistically significant relative weight reduction in the low fat arm for:
    - Removing studies without clear allocation concealment
    - Running fixed-effect (rather than random-effects) meta-analysis
    - Removing studies with attention bias favouring those in the low fat arm
    - Removing studies with other interventions alongside the fat reduction
- The direction of effect was consistent – participants eating lower total fat intakes were lower in weight (on average) at the study end than participants eating a higher percentage of total fat. This was observed in a variety of population groups and over varied time periods (six months to several years).
- The only inconsistency was in the size of effect. The heterogeneity was partly explained by:

- Degree of reduction of fat intake
- Level of control group fat intake

The forest plots corresponding to the above meta-analyses are presented below.

In addition, a table with details of the included studies follows each forest plot.

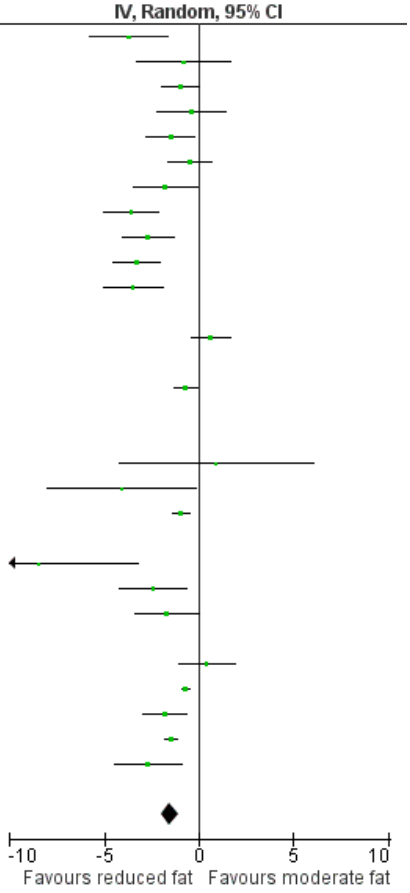
Adults | RCT | Weight | Hooper et al 2015 | Reduced fat intake

Forest plot of comparison of fat reduction versus usual fat diet in adult RCTs, outcome = weight, kg (Hooper et al 2015).

Figure 59 Meta-analysis of RCTs in adults – Dietary fat – Hooper et al 2015 – Weight

	Reduced fat			Usual or modified fat				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Auckland reduced fat 1999	-1.6	5.4	48	2.13	5	51	2.8%	-3.73 [-5.78, -1.68]
BDIT Pilot Studies 1996	59.6	7.3	76	60.4	8.4	78	2.1%	-0.80 [-3.28, 1.68]
Bloemberg 1991	-0.94	2.68	39	0.06	1.86	40	5.5%	-1.00 [-2.02, 0.02]
BRIDGES 2001	0.1	4.85	48	0.5	4.07	46	3.3%	-0.40 [-2.21, 1.41]
Canadian DBCP 1997	62	9.1	388	63.5	9.4	401	4.6%	-1.50 [-2.79, -0.21]
de Bont 1981 non-obese	-0.4	2.8	36	0.1	2	29	5.0%	-0.50 [-1.67, 0.67]
de Bont 1981 obese	-2.7	3.6	34	-0.9	3.5	35	3.5%	-1.80 [-3.48, -0.12]
DEER 1998 exercise men	-4.2	4.2	48	-0.6	3.1	47	4.0%	-3.60 [-5.08, -2.12]
DEER 1998 exercise women	-3.1	3.7	43	-0.4	2.5	43	4.5%	-2.70 [-4.03, -1.37]
DEER 1998 no exercise men	-2.8	3.5	49	0.5	2.7	46	4.7%	-3.30 [-4.55, -2.05]
DEER 1998 no exercise wom	-2.7	3.5	46	0.8	4.2	45	3.8%	-3.50 [-5.09, -1.91]
Diet and Hormone Study 2003	-0.68	0	81	-0.14	0	96		Not estimable
Kentucky Low Fat 1990	1.06	2.49	47	0.44	2.68	51	5.4%	0.62 [-0.40, 1.64]
MeDiet 2006	-1.3	0	51	-0.6	0	55		Not estimable
MSFAT 1995	0.4	2.36	117	1.12	2.36	103	6.8%	-0.72 [-1.34, -0.10]
NDHS Open 1st L&M 1968	-2.45	0	332	-1.91	0	348		Not estimable
NDHS Open 2nd L&M 1968	-1.8	0	179	-1.2	0	215		Not estimable
Nutrition & Breast Health	67.3	13.8	47	66.4	12	50	0.6%	0.90 [-4.26, 6.06]
Pilkington 1960	66.7	5.9	12	70.8	5.2	23	1.0%	-4.10 [-8.06, -0.14]
Polyp Prevention 1996	-0.65	5.22	943	0.31	5.22	943	7.3%	-0.96 [-1.43, -0.49]
Rivellese 1994	-1.8	0	27	-1.6	0	17		Not estimable
Simon Low Fat Breast CA	63.4	11.1	34	71.9	11.7	38	0.6%	-8.50 [-13.77, -3.23]
Strychar 2009	-0.83	3	15	1.6	1.8	15	3.3%	-2.43 [-4.20, -0.66]
Swedish Breast CA 1990	-0.4	5.5	63	1.3	5.5	106	3.5%	-1.70 [-3.41, 0.01]
Veterans Dermatology 1994	-2	0	38	0.5	0	58		Not estimable
WHEL 2007	74.1	19.53	1308	73.7	19.2	1313	4.0%	0.40 [-1.08, 1.88]
WHI 2006	-0.8	10.1	16297	-0.1	10.1	25056	7.9%	-0.70 [-0.90, -0.50]
WHT Feasibility 1990	-1.91	4.9	159	-0.08	4.3	102	5.1%	-1.83 [-2.96, -0.70]
WHT:FSMP 2003	-1.8	4	1325	-0.3	4.2	883	7.6%	-1.50 [-1.85, -1.15]
WINS 1993	-2.7	15.3	386	0	15.3	998	3.3%	-2.70 [-4.50, -0.90]
Total (95% CI)			**22316**			**31331**	**100.0%**	**-1.54 [-1.97, -1.12]**

Heterogeneity: Tau² = 0.58; Chi² = 99.49, df = 23 (P < 0.00001); I² = 77%
Test for overall effect: Z = 7.14 (P < 0.00001)



Adults | RCT | Weight | Hooper et al 2015 | Reduced fat intake

For references to studies within Table 75, please see Hooper et al (2015).

Table 75 Details of RCTs included in meta-analysis (weight) - Dietary fat

Study/ Subgroup	Participants	No. randomised to each arm	Intervention	Control	Total fat/energy reduction OR % fat reduction (isocaloric)	Result of study/effect on weight (+ve or inverse)	Dietary Outcome – changes in %E from total fat (and SFA)
Auckland reduced fat 1999	Impaired glucose intolerance/high blood glucose	Unclear how many randomised 176 between both groups Intervention: 48 Analysed Control: 51 Analysed	Reduced fat diet (No specific goal) Aimed to reduce total fat in diet	Usual diet intake	Solely aimed to reduce total amount of fat in diet – *ad libitum diet*	+VE	Intervention: 26.1%E from total fat at 1 yr 10.0%E from SFA at 1 yr Control: 33.6%E from total fat at 1yr 13.4%E from SFA at 1 yr
BDIT Pilot Studies 1996	100% Women with mammographic dysplasia	Intervention: 148 randomised (76 analysed) Control: 147 randomised (78 analysed)	Total fat 15%E (replace fat by complex CHO), maintain isocaloric diet with aim to maintain weight	Healthy diet advice, no alteration in dietary fat advised, aim to maintain weight	Isocaloric	+VE	Intervention at 9.2yrs: 31.7%E from fat 10.6%E from SFA Control at 9.2yrs: 35.3%E from fat 12.3%E from SFA
Bloemberg 1991	100% Men with untreated raised total cholesterol	Intervention: randomised 39 (analysed 39) Control: randomised 41 (analysed 40)	30%E from fat, PUFA/SFA 1.0, dietary cholesterol 20mg	Usual diet (no advice)	Isocaloric	+VE	Intervention group: 5% reduction in %E from total fat (33.5%E overall) in 6 months 4.3% reduction in SFA %E Control Group: 1.5% reduction in %E (36.8%E overall) in 6 months 0.7% reduction in SFA %E

BRIDGES 2001	100% Women diagnosed with Stage I or II breast cancer over last 2 years	Intervention: randomised unclear – at least 50 (analysed 48) Control: Randomised unclear- at least 56 (analysed 46)	Total fat 20%E, high fibre, plant-based micronutrients (additional [separate] arm of intervention – stress reduction)	Usual Diet (No formal intervention)	Isocaloric	+VE	Intervention (at 12 months): 29.9%E from fat Control (at 12 months): 33.6 %E from fat
Canadian DBCP 1997	100% Women with mammographic densities >50% breast area	Intervention: randomised 448+ (analysed 388) Control: randomised 448+ (analysed 401)	Total fat 15%E, protein 20%E, CHO 65%E, isocaloric diet	Usual Diet (encouraged to continue usual diet, interviewed by dietician)	Isocaloric (replaced with CHO)	+VE	Intervention (at 2 years): 21.3%E from fat Control (at 2 years): 31.8%E from fat
De Bont 1981 non-obese	100% Women with type 2 diabetes	Intervention: randomised unclear (analysed 71 for obese & non-obese) Control: randomised unclear (analysed 65 for obese & non-obese)	30%E from fat, focus on reducing meat fat, dairy foods and substituting margarines to improve SFA/PUFA ratio. CHO increased to maintain energy intake	Usual diet but with CHO <40%E	Isocaloric	+VE	**for obese and non-obese** Intervention: 10.1% reduction in %E from fat in 6 months (31.1%E from fat overall) Control: 1% reduction in %E from fat in 6 months (41.8 %E from fat overall)
De Bont 1981 obese	100% Women with type 2 diabetes	Intervention: randomised unclear (analysed 71 for obese & non-obese) Control: randomised unclear (analysed 65 for obese & non-obese)	30%E from fat, focus on reducing meat fat, dairy foods and substituting margarines to improve SFA/PUFA ratio. CHO increased to maintain energy intake	Usual diet but with CHO <40%E	Isocaloric	+VE	**for obese and non-obese** Intervention: 10.1% reduction in %E from fat in 6 months (31.1%E from fat overall) Control: 1% reduction in %E from fat in 6 months (41.8 %E from fat overall

DEER 1998 exercise men	100% Men with raised LDL and low HDL Cholesterol	Intervention: randomised 51 (analysed 48) Control: randomised 50 (analysed 47)	NCEP step 2 diet: <30%E from fat, <7%E from SFA, 200mg/d cholesterol (and exercise intervention)	Usual diet (and exercise intervention) no advice provided	Isocaloric	+VE	Intervention: 8.2% reduction in %E from total fat (22.2%E from fat overall) and 3.9%E reduction from SFA in 12 months Control: 0.5% reduction in %E from fat (29.9%E from fat overall) and 0.1%E reduction from SFA in 12 months
DEER 1998 exercise women	100% postmenopausal women with raised LDL and low HDL cholesterol	Intervention: randomised 43 (analysed 43) Control: randomised 44 (analysed 43)	NCEP step 2 diet: <30%E from fat, <7%E from SFA, 200mg/d cholesterol (and exercise intervention)	Usual diet (and exercise intervention) no advice given	Isocaloric	+VE	Intervention: 8.0% reduction in %E from total fat (20.4%E from fat overall) and 3.0%E reduction from SFA in 12 months Control: 0.3% reduction in %E from fat (28.7%E from fat overall) and 0.2%E increase from SFA in 12 months
DEER 1998 no exercise men	100% men with raised LDL and low HDL cholesterol	Intervention: randomised 49 (analysed 49) Control: randomised 47 (analysed 46)	NCEP step 2 diet: <30%E from fat, <7%E from SFA, 200mg/d cholesterol (and usual exercise)	Usual diet (and usual exercise)	Isocaloric	+VE	Intervention: 8.0% reduction in %E from total fat (22.4%E from fat overall) and 3.4%E reduction from SFA in 12 months Control: 0.7% reduction in %E from fat (29.7%E from fat overall) and 0.0%E change from SFA in 12 months
Deer 1998 no exercise women	100% postmenopausal women with raised LDL and low HDL cholesterol	Intervention: randomised 46 (analysed 45) Control: randomised 47 (analysed 46)	NCEP step 2 diet: <30%E from fat, <7%E from SFA, 200mg/d cholesterol (and usual exercise)	Usual diet (and usual exercise)	Isocaloric	+VE	Intervention: 5.7% reduction in %E from total fat (22.7%E from fat overall) and 2.4%E reduction from SFA in 12 months Control: 0.2% reduction in %E

							from fat (28.2%E from fat overall) and 0.2%E increase from SFA in 12 months
Diet and Hormone Study 2003	100% healthy premenopausal women aged 20-40 years	Intervention: randomised 106 (analysed 81) Control: randomised 107 (analysed 96)	<20%E from fat, 25-30g/d fibre, >8 Servings/d fruit and vegetables, CHO 60-65%E. protein 15-20%E	Usual diet (minimal intervention)	Isocaloric	*Not reported/ able to estimate*	Intervention: Total fat intake 22.2%E at 12 months(cycles) SFA intake 14.9%E at 12 months (cycles) Control: Total fat intake 30.7%E at 12 months (cycles) SFA intake 23.9%E at 12 months (cycles)
Kentucky Low Fat 1990	Moderately hyper-cholesterolaemic, non-obese Caucasian men and women aged 30 to 50	Intervention: randomised 56 (analysed 47) Control: randomised 62 (analysed 51)	25%E from fats, 20%E from protein, 55%E from CHO, <200mg/d cholesterol	No diet intervention	Isocaloric	INV	Intervention: 30%E from total fat after 1 year 9%E SFA after 1 year Control: 31%E total fat after 1 year 10%E SFA after 1 year
MeDiet 2006	100% healthy postmenopausal women with above median serum testosterone	Intervention: randomised 58 (analysed at 6 months, 51) Control: randomised 57 (analysed at 6 months, 55)	Reduced/modified fat – taught Sicilian diet (by professional chefs) including reduced total, saturated and omega-6 fats, increased blue fish (high in omega-3) increased whole cereals, legumes, seeds, fruit and vegetables	Usual diet – with advice to increase fruit/veg intake	Change in diet style – to med diet	*Not reported/ able to estimate*	Intervention: 30.9%E from total fat 8.4%E from SFA Control: 34.0%E from total fat 11.2%E from SFA

MSFAT 1995	Healthy people aged 20-55years	Intervention: randomised 120? (analysed 117) Control: randomised 120? (analysed 103)	Usual diet – participants advised to use products from trial shop at least once a week (low fat products provided)	Usual diet – participants advised to use products from trial shop at least once a week (usual fat products provided)	Reduced total fat intake	+VE	Intervention: 34.7%E from total fat 14.2%E from SFA Control: 42.7%E from total fat 18.2%E from SFA
NDHS Open 1st L&M 1968	100% 'free-living' men	Intervention B: randomised 385 (analysed 332) Intervention X: randomised 54 (analysed 46) Control: randomised 382 (analysed 348)	Intervention B: Dietary advice to reduce SFA and cholesterol, purchase of reduced or modified fat items from trial shop: Total fat 30%E, SFA<9%E, dietary cholesterol 350-450mg/d, PUFA 15%E, P/S 1.5 Intervention X: dietary advice but no trial shop: Total fat 30%E, SFA<9%E, dietary cholesterol 350-450mg/d, PUFA 15%E, P/S 1.5	Dietary advice to reduce SFA and cholesterol, purchase of usual fat items from trial shop: Total fat 40%E, SFA 16-18%E, dietary cholesterol 650-750mg/d, P/S 1.5	*Not reported/ able to estimate*	*Not reported/ able to estimate*	Intervention B: 29.7%E from total fat through study 7.1%E from SFA through study Intervention X: 31.7%E from total fat through study 8.9%E from SFA through study Control: 34.9%E from total fat through study 11.6%E from SFA through study
NDHS Open 2nd L&M 1968	100% Free-living men who had participated in NDHS 1st studies	Intervention BC: randomised 194 (analysed 179) Control: randomised 304 (analysed 215)	Advice to reduce SFA and cholesterol and purchase of reduced/modified items from trial shop: Total fat 30-40%E, SFA reduced, dietary cholesterol	Advice to continue to usual diet and purchase usual fat items from a trial shop: 40%E, SFA 16-18%E, dietary cholesterol 650-750mg/d, P/S 1.5	*Not reported/ able to estimate*	*Not reported/ able to estimate*	Intervention: 32.5%E from total fat through study 7.4%E from SFA through study Control: 35.5%E from total fat through study 12.0%E from SFA through study

		NB – there were multiple interventions, only BC relevant for SLR	350-450mg/d, increased PUFA, P/S 1.5-2.0				
Nutrition and Breast Health	100% Pre-menopausal women at increased risk of breast cancer	<u>Intervention:</u> randomised 69 (analysed 47) <u>Control:</u> randomised 53 (analysed 50)	Total fat 15%E (half of group randomised to 9 portions/d of fruit & veg) – met with dietician until compliant	Follow usual diet, given daily food guide pyramid (half of group randomised to 9 portions/d of fruit & veg)	Isocaloric	INV	<u>Intervention:</u> 15.7%E from total fat at 12 months 7.2%E from SFA at 12 months <u>Control:</u> 32.7%E from total fat at 12 months 11.6%E from SFA at 12 months
Pilkington 1960	100% Men with angina or who have had an MI	<u>Intervention reduced fat:</u> randomised unclear (analysed 12) <u>Intervention modified fat:</u> randomised unclear (analysed 23)	Reduced fat: total fat 20g/d, advice to avoid dairy fats except skimmed milk plus 1 egg or 21g cheese/d, lean meat and fish each allowed once/d, other non-fatty foods unlimited	Modified fat: fat aims not stated, dairy produce avoided except skimmed milk, 90 ml/d soya oil provided, lean meat after 6 months along with 113 g/wk 'relatively unsaturated' margarine, fish/veg allowed freely	*Reduced fat: no calorie control but significant changes to diet type* *Modified fat: changes to types of fat but no aims, other foods not restricted*	+VE	<u>Reduced fat:</u> 15.8%E from total fat during treatment <u>Modified Fat:</u> 36.0%E from total fat during treatment
Polyp Prevention 1996	People with at least one adenomatous polyp of the large bowel removed	<u>Intervention:</u> randomised 1037 (analysed 943) <u>Control:</u> randomised 1042 (analysed 943)	Low fat – total fat 20%E from total fat, 18g fibre/1000kcal, 5-8 servings of fruit and veg daily	Usual diet – limited advice	Isocaloric (replace with fruit, veg, grains)	+VE	<u>Intervention:</u> 23.8%E from total fat at 4 years <u>Control:</u> 33.9%E from total fat at 4 years

Rivellese 1994	Adults with primary hyperlipoproteinaemia	Intervention reduced fat: randomised 33 (analysed 27) Intervention modified fat: randomised 30 (analysed 17)	Reduced fat: total fat 25%E, SFA 8%E, MUFA 15%E, PUFA 2%E, dietary cholesterol <300 mg/d, CHO 58%E, protein 17%E, soluble fibre 41 g/d Seen by dietitian and doctors regularly	Modified fat: 38%E, SFA <10%E, MUFA 20%E, PUFA 2%E, dietary cholesterol <300 mg/d, CHO 47%E, protein 15%E, soluble fibre 19 g/d Seen by dietician and doctors regularly	*Energy intake goals not available - % fat changes rather than calorie intake changes?*	*Not reported/ able to estimate*	Reduced fat: 27%E from total fat at 5/6months 6%E from SFA at 5/6months Modified fat: 36%E from total fats at 5/6 months 7%E from SFA at 5/6 months
Simon Low Fat Breast CA	100% women with a high risk of breast cancer	Intervention: randomised 98 (analysed 34) Control: randomised 96 (analysed 38)	Total fat 15%E	Usual diet – no further advice	Isocaloric *(minimal impact on calorie intake)*	+VE	Intervention: 18.0%E from total fat at 12 months 6.0%E from SFA at 12 months Control: 33.8%E from total fat at 12 months 11.3%E from SFA at 12 months
Strychar 2009	People with well-controlled type I diabetes mellitus	Intervention reduced fat: randomised 18 (analysed 15) Intervention modified fat: randomised 17 (analysed 15)	Reduced fat: total fat 27-30%E, SFA<10%E, MUFA 10%E, CHO 54-57%E	Modified fat: total fat 37-40%E, SFA< 10%E, MUFA 20%E, CHO 43-57%E	Isocaloric	+VE	*Not reported/able to estimate* Baseline levels (mean for both groups): 36.9%E from total fat 11.7%E from SFA

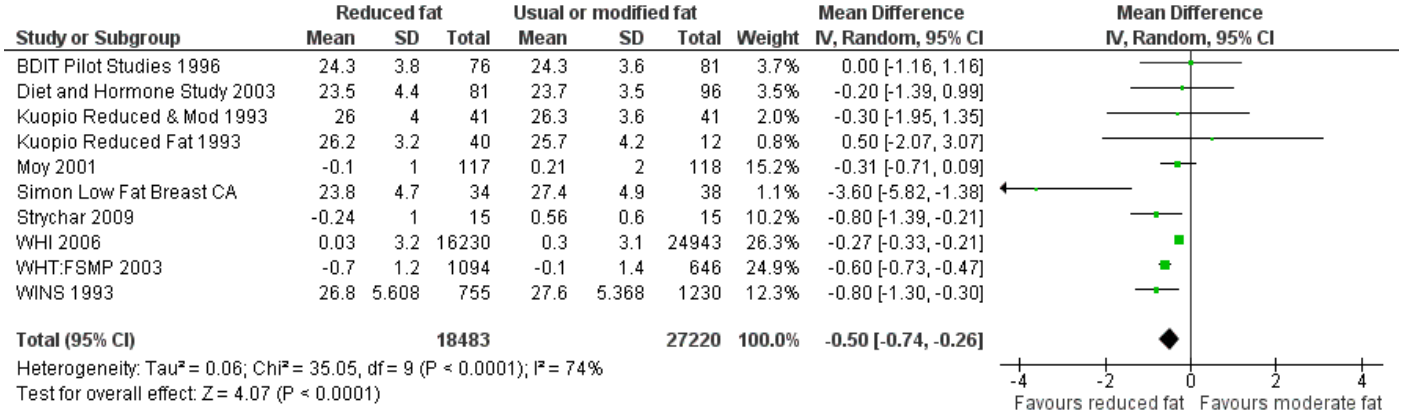
Swedish Breast CA 1990	100% Women who've had surgery for breast cancer	Intervention: randomised 119 (analysed 106) Control: randomised 121 (analysed 63)	20-25%E from fat, increase from energy from CHO to replace lost energy	Usual diet – no advice	Isocaloric	+VE	Intervention: 12.9% reduction in %E from total fat (24%E overall) at 2 years 6.8% reduction in %E from SFA at 2 years Control : 3.1% reduction in %E from total fat (34.1%E overall) 1.9% reduction in %E from SFA
Veterans Dermatology 1994	People with non-melanoma skin cancer	Intervention: randomised 66 (analysed 58) Control: randomised 67 (analysed 58)	Total fat 20%E, protein 15%E, CHO 65%E	Usual diet – no advice	Isocaloric	*Not reported/ able to estimate*	Intervention: 20.7%E from total fat during study (4-24months) 6.6%E from SFA during study Control: 37.8%E from total fat during study 12.8%E from SFA during study
WHEL 2007	100% Women with previously treated early breast cancer	Intervention: randomised 1546 (analysed 1308) Control: randomised 1561 (analysed 1313)	15-20%E from fat, 5 vegetables/d, 3 fruit/d, 16o vegetable juice and 30 g/d of fibre	Usual diet – 30%E from fat	Isocaloric	INV	Intervention: 28.9%E from total fat at 72 months 7.2%E from SFA at 72 months Control: 32.4%E from total fat at 72 months 8.9%E from SFA at 72 months
WHI 2006	100% Post-menopausal women aged 50-79 years	Intervention: Randomised 19,541 (analysed 16,297) Control: randomised 29,294 (analysed 25,056)	Low fat (20%E from fat) with increased fruit and veg	Usual diet – with educational materials	Isocaloric	+VE	Intervention: 28.8%E from total fat at 6 years 9.5%E from SFA at 6 years Control: 37.0%E from total fat at 6 years 12.4%E from SFA at 6 years

WHT Feasibility 1990	100% women at increased risk of breast cancer	Intervention: randomised119 (analysed 102) Control: randomised 184 (analysed 159)	20%E from fat – flexible style diet plans	Maintain usual diet	*Not reported*	+VE	Intervention: 22.6%E from total fat at 2 years 7.2%E from SFA at 2 years Control: 36.8%E from total fat at 2 years 12.3%E from SFA at 2 years
WHT:FSMP 2003	100% postmenopausal women from diverse ethnic and socioeconomic backgrounds	Intervention: randomised 1325 (analysed 1071 at 6mo, 698 at 12mo, 285 at 18mo) Control: randomised 883 (analysed 649 at 6mo, 443 at 12mo, 194 at 18mo)	Up to 20%E from fat, reduced SFA and dietary cholesterol, increased fruit, veg and whole grains	Maintain usual diet	*Not reported*	+VE	Intervention: 25.4%E from total fat at 12mo 8.7%E from SFA at 12 mo Control: 36.0%E from total fat at 12mo 12.1%E from SFA at 12 mo
WINS 1993	100% Women with localised resected breast cancer	Intervention: randomised 975 (analysed 386) Control: randomised 1462 (analysed 998)	Total fat 15-20%E	Usual diet, minimal nutritional counselling on nutritional adequacy	Isocaloric	+VE	Intervention: 20.3%E from total fat at 1 yr 10.4%E from SFA at 1yr Control: 29.2%E from total fat at 1 yr 16.6%E SFA at 1 yr

Adults | RCT | BMI | Hooper et al 2015 | Reduced fat intake

Forest plot of comparison of fat reduction versus usual fat diet in adult RCTs, outcome = BMI, kg/m^2 (Hooper et al 2015).

Figure 60 Meta-analysis of RCTs in adults – Dietary fat – Hooper et al 2015 – BMI



Adults | RCT | BMI | Hooper et al 2015 | Reduced fat intake

For references to studies within Table 76, please see Hooper et al (2015).

Table 76 Details of RCTs included in meta-analysis (BMI) - Dietary fat

Study/ Subgroup	Participants	No. randomised to each arm	Intervention	Control	Total fat/energy reduction OR % fat reduction (isocaloric)	Result of study/effect on BMI (+ve or inverse)	Dietary Outcome – changes in %E from total fat/SFA
BDIT Pilot Studies 1996	100% Women with mammographic dysplasia	Intervention: 148 randomised (76 analysed) Control: 147 randomised (78 analysed)	Total fat 15%E (replace fat by complex CHO), maintain isocaloric diet with aim to maintain weight	Healthy diet advice, no alteration in dietary fat advised, aim to maintain weight	Isocaloric	NIL	Intervention at 9.2yrs: 31.7%E from fat 10.6%E from SFA Control at 9.2yrs: 35.3%E from fat 12.3%E from SFA
Diet and Hormone Study 2003	100% healthy premenopausal women aged 20-40 years	Intervention: randomised 106 (analysed 81) Control: randomised 107 (analysed 96)	<20%E from fat, 25-30g/d fibre, >8 Servings/d fruit and vegetables, CHO 60-65%E. protein 15-20%E	Usual diet (minimal intervention)	Isocaloric	+VE	Intervention: Total fat intake 22.2%E at 12 months(cycles) SFA intake 14.9%E at 12 months (cycles) Control: Total fat intake 30.7%E at 12 months (cycles) SFA intake 23.9%E at 12 months (cycles)

Kuopio Reduced and Mod 1993	Free-living people aged 30 to 60 with serum total cholesterol levels 6.5 to 8.0mmol/L	Intervention AHA: Randomised 41 (analysed 41) Control: randomised 41 (analysed 41)	Total fat 30%E, SFA<10%E, MUFA 10%E, PUFA 10%E, sunflower oil, sunflower spread and skimmed milk provided	Total fat 38%E , SFA <14%E, MUFA 18%E, PUFA <6%, rapeseed oil, rapeseed spread and skimmed milk provided	Isocaloric *Diet plan developed for different groups based on estimated energy requirement*	+VE	Intervention: total fat intake 34%E at 14-28 weeks SFA intake 11%E at 14-24 weeks Control: total fat intake 35%E at 14-24 weeks SFA intake 11%E at 14-24weeks
Kuopio Reduced Fat 1993	Free-living people aged 30 to 60 with serum total cholesterol levels 6.5-8.00 mmol/L	Intervention: randomised 40 (analysed 40) Control: randomised 37 (analysed 12)	Low Fat Diet: total fat 28-30%E, SFA <14%E, MUFA 10%E, PUFA 4%E. butter, rapeseed spread and skimmed milk provided	High Saturated Fat Diet: advised 38% total fat, SFA<18%E, MUFA 15%E, PUFA <5%E, rapeseed oil, butter and semi-skimmed milk provided	Isocaloric *Diet plan developed for different groups based on estimated energy requirement*	INV	Intervention: total fat intake 31%E at 14-24 weeks SFA intake 12%E at 14-24 weeks Control (High saturated fat diet): Total fat intake 36%E at 14-24weeks SFA intake 15%E at 14-24weeks
Moy 2001	Middle-aged sibling of people with early CHD, with at least 1 CVD risk factor	Intervention: randomised 135 (analysed 117) Control: Randomised 132 (analysed 118)	Reduced fat – aim <40g/d fat with nurse management	Usual diet, with physician management	Reduced total fat intake (<40g/d)	+VE	Intervention: total fat 34.1%E at 2yrs SFA intake 11.5%E at 2 yrs Control: total fat 38.0%E at 2 yrs SFA 14.4%E at 2 yrs
Simon Low Fat Breast CA	100% women with a high risk of breast cancer	Intervention: randomised 98 (analysed 34) Control: randomised 96 (analysed 38)	Total fat 15%E	Usual diet – no further advice	Isocaloric *Study reported minimal impact on calorie intake*	+VE	Intervention: 18.0%E from total fat at 12 months 6.0%E from SFA at 12 months Control: 33.8%E from total fat at 12 months 11.3%E from SFA at 12 months

Strychar 2009	People with well-controlled type I diabetes mellitus	Intervention reduced fat: randomised 18 (analysed 15) Intervention modified fat: randomised 17 (analysed 15)	Modified fat: total fat 37-40%E, SFA< 10%E, MUFA 20%E, CHO 43-57%E	Reduced fat: total fat 27-30%E, SFA<10%E, MUFA 10%E, CHO 54-57%E	Isocaloric	+VE	*Not reported/able to estimate*
WHI 2006	100% Post-menopausal women aged 50-79 years	Intervention: Randomised 19,541 (analysed 16,297) Control: randomised 29,294 (analysed 25,056)	Low fat (20%E from fat) with increased fruit and veg	Usual diet – with educational materials	Isocaloric	+VE	Intervention: 28.8%E from total fat at 6 years 9.5%E from SFA at 6 years Control: 37.0%E from total fat at 6 years 12.4%E from SFA at 6 years
WHT:FSMP 2003	100% postmenopausal women from diverse ethnic and socioeconomic backgrounds	Intervention: randomised 1325 (analysed 1071 at 6mo, 698 at 12mo, 285 at 18mo) Control: randomised 883 (analysed 649 at 6mo, 443 at 12mo, 194 at 18mo)	Up to 20%E from fat, reduced SFA and dietary cholesterol, increased fruit, veg and whole grains	Maintain usual diet	*Not reported/ able to estimate*	+VE	Intervention: 25.5%E from total fat at 12mo 8.7%E from SFA at 12 mo Control: 36.0%E from total fat at 12mo 12.1%E from SFA at 12 mo
WINS 1993	100% Women with localised resected breast cancer	Intervention: randomised 975 (analysed 386) Control: randomised 1462 (analysed 998)	Total fat 15-20%E	Usual diet, minimal nutritional counselling on nutritional adequacy	Isocaloric	+VE	Intervention: 20.3%E from total fat at 1 yr 10.4%E from SFA at 1yr Control: 29.2%E from total fat at 1 yr 16.6%E SFA at 1 yr

3.2 Meta-analyses of prospective cohort studies in adults

Table 77 Meta-analyses of prospective cohort studies in adults – Dietary fat

Adults					
Meta-analyses of prospective cohort studies					
Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Weight change	Summerbell et al (2009)	Fat as % of total energy intake Unclear follow up period	Regression coefficient	**0.07 (-0.03, 0.16)** Units=unclear **+VE**	Studies=4; n=9,753 I^2=not reported

One review conducted a meta-analysis with prospective cohort studies in adults investigating the association between intake of fat as a percentage of total energy intake and weight change. The result reported a non-significant positive association.

The authors conducted meta-regression to test for length of follow up and gender as causes of heterogeneity: follow up was a significant cause of heterogeneity ($p<0.001$) but gender was not ($p=0.05$). The I^2 value for the meta-analysis was reported separately for men and women: men, $I^2=58\%$, $p=0.09$; women, $I^2=78\%$, $p=0.04$.

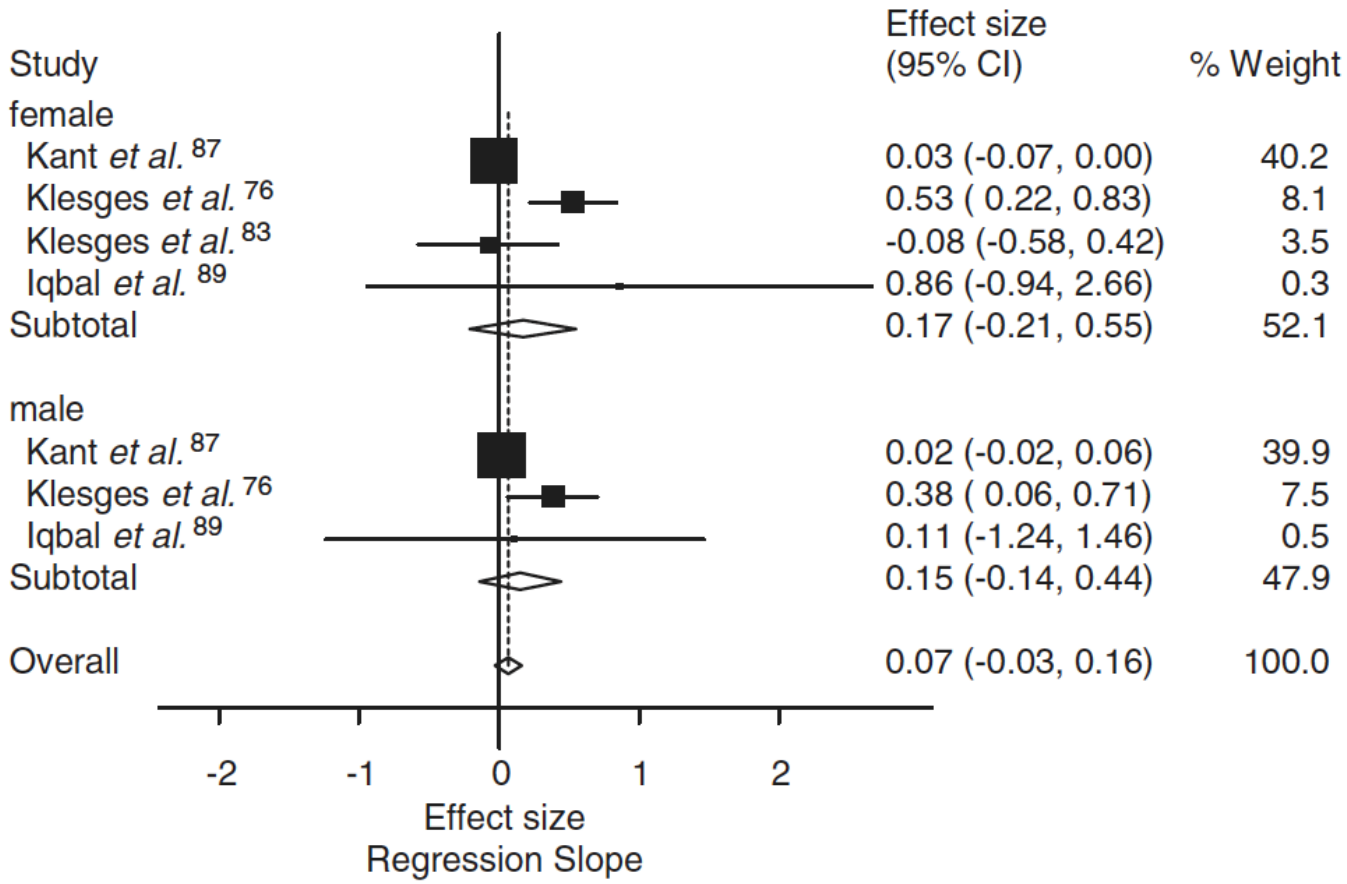
Each of the studies had a different level of adjustment for potential confounders, from six to 13 factors. All models adjusted for a measure of physical activity.

The forest plot corresponding to the above meta-analysis is presented below.

Adults | Prospective cohort studies | Weight change | Summerbell et al 2009 | Total fat intake

The forest plot is presented below with the overall summary. The exposure is fat intake as percentage of energy. The outcome is weight change expressed as regression coefficient (Summerbell et al 2009).

Figure 61 Meta-analysis of prospective cohort studies in adults – Dietary fat – Summerbell et al 2009 – Weight change



3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 78 Results of individual prospective cohort studies in adults – Dietary fat

Adults					
Prospective cohort studies not in meta-analyses					
CHO=carbohydrate; MD=mean difference; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight (attained)	Ludwig et al. 1999 *Hooper et al (2015)* and *Summerbell et al (2009)*	Highest vs. lowest quintiles of total fat intake *(white females and males)* 10 years	Highest quintile: **169.4 lb** Lowest quintile: **168.6 lb** p for trend=0.32	+VE	1,602
		Highest vs. lowest quintiles of total fat intake *(black females and males)* 10 years	Highest quintile: **185.7 lb** Lowest quintile: **182.1 lb** p for trend=0.03	+VE	1,307
Weight change	MacInnis et al. 2013 *Hooper et al (2015)*	Per 10% energy from fat at baseline 11.7 years	Beta coefficient	**0.26 kg** p=0.03 +VE	5,879
	Vergnaud et al. 2013 *Hooper et al (2015)*	Substitution of 5% energy from protein for fat *(female)* 5 years	Beta coefficient	**-772 (-1064, -480) g** p<0.0001 INV	270,348
		Substitution of 5% energy from protein for fat *(male)* 5 years	Beta coefficient	**-283 (-473, -93) g** p=0.003 INV	103,455
		Substitution of 5% energy from CHO for fat *(female)* 5 years	Beta coefficient	**-105 (-331, 120) g** p=0.36 INV	270,348
		Substitution of 5% energy from CHO for fat *(male)* 5 years	Beta coefficient	**-17 (-110, 77) g** p=0.73 INV	103,455
	Coakley et al. 1998 *Hooper et al (2015)* and *Summerbell et al (2009)*	Per 10g per day increase in fat intake *(45–54 year old males)* 4 years	Regression coefficient	**0.10 (0.094, 0.106) g** p<0.001 +VE	10,272
		Per 10g per day increase in fat intake *(55–64 year old males)* 4 years	Regression coefficient	**0.10 (0.092, 0.108) g** p<0.001 +VE	5,729
		Per 10g per day increase in fat intake *(>65 years old males)* 4 years	Regression coefficient	**0.10 (0.090, 0.110) g** p>0.05 +VE	3,477
	Colditz et al. 1990 *Hooper et al (2015)* and *Summerbell et al (2009)*	Total fat intake (g) per day *(female)* 4 years	Beta coefficient	**-0.0007** *t*=-0.4 Units unclear INV	31,940
Weight gain >2kg	Schulz et al. 2002 *Summerbell et al (2009)*	Per 100g intake of fats *(female)* 2.2 years	OR	**1.75 (1.01, 3.06)** +VE	11,005
		Per 100g intake of fats *(male)* 2.2 years	OR	**1.49 (0.86, 2.59)** +VE	6,364
Weight gain <2kg		Per 100g intake of fats *(female)*	OR	**1.24 (0.81, 1.91)** +VE	11,005

		2.2 years			
		Per 100g intake of fats *(male)* 2.2 years	OR	**1.24 (0.80, 1.93)** **+VE**	6,364
Weight loss <2kg		Per 100g intake of fats *(female)* 2.2 years	OR	**0.73 (0.48, 1.11)** **+VE**	11,005
		Per 100g intake of fats *(male)* 2.2 years	OR	**1.55 (1.02, 2.36)** **INV**	6,364
Weight loss >2kg		Per 100g intake of fats *(female)* 2.2 years	OR	**0.52 (0.32, 0.86)** **+VE**	11,005
		Per 100g intake of fats *(male)* 2.2 years	OR	**0.57 (0.32, 1.01)** **+VE**	6,364
Waist circumference	Halkjaer et al. 2006 *Hooper et al (2015)* and *Summerbell et al (2009)*	Per MJ per day of fat intake 5 years	MD	**0.04 (-0.06, 0.13) cm** **+VE**	42,696
	MacInnis et al. 2013 *Hooper et al (2015)*	Per 10% energy from fat at baseline 11.7 years	Beta coefficient	**0.85 cm** p<0.001 **+VE**	5,879
Waist-hip ratio	Ludwig et al. 1999 *Hooper et al (2015)* and *Summerbell et al (2009)*	Highest vs. lowest quintiles of total fat intake *(white females and males)* 10 years	Highest quintile: **0.803** Lowest quintile: **0.802** p for trend=0.50 **+VE**		1,602
		Highest vs. lowest quintiles of total fat intake *(black females and males)* 10 years	Highest quintile: **0.811** Lowest quintile: **0.806** p for trend=0.22 **+VE**		1,307

Seven prospective cohort studies investigating total fat intake and adiposity in adults with more than 1,000 participants were identified in two reviews (see **Section 2**). These provided 23 results across five outcomes: weight (change and attained); odds of weight gain; odds of weight loss; waist circumference; and waist-hip ratio. Seventeen results reported positive associations between fat intake and adiposity, with seven being statistically significant. Six results reported inverse associations, of which three were statistically significant: Vergnaud et al (2013) reported a higher proportion of fat at the expense of protein was associated with weight decreases in both men and women, and Schulz et al (2002) reported increased odds of a small weight loss (<2kg) with increasing intake of fat in men. Five of the studies adjusted for total energy intake (Ludwig et al 1999; Vergnaud et al 2013; Coakley et al 1998; MacInnis et al 2013; and Colditz et al 1990).

Two studies were in single sex populations: Coakley et al (1998) used data from the Health Professionals Follow up Study cohort (all male) and Colditz et al (1990) used data from the Nurse's Health Study I cohort (all female).

Two studies used data from the EPIC cohort: Schulz et al (2002) used data from the EPIC-Potsdam cohort and Vergnaud et al (2013) used data from EPIC-PANACEA.

In the study by Ludwig et al (1999), the lowest quintile of fat intake was 30% of total energy and the highest quintile was 41.7% of total energy (both medians). This was the only study to stratify results by ethnicity.

In Schulz et al (2002), the 'fats' food group included intake of butter, margarine, and oil. Other potential sources of dietary fats, such as meat, nuts, seeds, desserts, and cakes were included in groups separate to 'fats'.

In the six remaining studies with fewer than 1,000 participants, there were seven results across four outcomes: weight; weight gain; BMI; and waist circumference. Four results reported no association, two results reported positive associations (one was statistically significant), and one result reported a significant inverse association. The sample sizes ranged from 230 to 782 participants.

Studies n<1000: Parker et al. 1997, Mosca et al. 2004, Ma et al. 2005, Lissner et al. 1997, Sammel et al. 2003 and Eck et al. 1995.

4. Possible mechanisms

As summarised in from preliminary discussions (June 2016):

- **Energy per gram**: Fat contains more energy per gram than carbohydrate or protein, which may contribute to passive overconsumption of calories.
- **Nutrient storage**: When fat is being stored during positive energy balance, the metabolic process only requires a small degree of oxidation (approximately 3% of the energy stored).
- **Appetite controls**:
    - Prolonged consumption of a high-fat diet may desensitise the individual to a number of appetite controls.
    - The palatability of fat may induce voluntary overconsumption.
    - Increased intake of high-sugar and high-fat foods has been associated with great reward response/decreased inhibitory response to such foods.

5. Summary of evidence

5.1 Children

Four results from three RCTs showed no association (one result), non-significant positive associations (two results), and a non-significant inverse association (one result).

In three prospective cohorts (where n>1,000) in children, three results reported positive associations (one significant) and two result reported inverse associations. The remaining 26 prospective cohort studies (where n<1,000, and n<500 in 24/26 studies) had mixed results: 18 reported no association, 15 reported a positive association (13 significant), and two reported an inverse association (both significant).

5.2 Adults

One review conducted two meta-analyses of RCTs and reported statistically significant positive effects. A separate review conducted one meta-analysis of prospective cohort studies, which included fewer studies, reported a non-significant positive association.

Seven prospective cohort studies (where n>1,000) in adults provided 23 results; of which 17 reported positive associations (seven statistically significant) and six reported inverse associations (three statistically significant). The remaining six studies (where n<1,000) had mixed results: four results reported no association, one result reported a significant inverse association, and two results reported positive associations (one was statistically significant).

4. Physical Activity

1. Evidence identified for 2017 update

Table 79 Published reviews identified for the 2017 update – Physical activity

Source	No. of reviews	Authors [quality]
NICE (2014) report	8	Ismail et al. 2012 [++]; te Velde et al. 2012 [+]; Laframboise et al. 2011 [+]; Kelley et al. 2006 [++]; Summerbell et al. 2009 [++]; Murphy et al. 2007 [++]; Benson et al. 2008 [+]; Oja et al. 2011 [+]
USDA DGAC (2015) scientific report [++]	Y	
Supplementary literature search August 2016	8	Costigan et al. 2015 [++]; Hespanhol Junior et al. 2015 [++]; Oja et al. 2015 [++]; van 't Riet et al. 2014 [++]; Bochner et al. 2015 [++]; Gao et al. 2016 [++]; Hanson et al. 2015 [++]; Murtagh et al. 2015 [++]

Notes on the evidence:

- NICE (2014) distinguished between 10 separate sub-categories of physical activity:
  - Evidence for five sub-categories was regarded as inconclusive and is not presented here: sport participation; active travel; activities of daily living; incidental physical activity; and physical activity intensity, frequency, and duration.
  - The other five sub-categories are: recreational physical activity; walking; cycling; aerobic activity; and strength (resistance) training.
  - NICE (2014) does not report evidence with respect to total physical activity. Studies that reported on total physical activity were extracted and presented in **Section 2.1** (children) and **3.1** (adults).
    - USDA DGAC (2015) uses evidence from the Physical Activity Guidelines Committee Report, published in 2008 (Physical Activity Guidelines Advisory Committee 2008) with respect to total physical activity. This is noted within the relevant sections of this literature review.
- In this literature review, recreational physical activity is considered in two broader categories: (i) aerobic recreational physical activity, and (ii) strength training recreational physical activity.
  - Within the first category, the relevant evidence from NICE (2014) for recreational physical activity (aerobic), walking, cycling, and aerobic activity is presented together.
  - Within the second category, evidence from NICE (2014) for strength training is presented.
- The majority of the evidence pertains to aerobic recreational activity; evidence in children is in **Section 2.2** and evidence in adults is **Section 3.2** within this exposure.
  - There were four published reviews (with meta-analyses) which specifically investigated walking and adiposity (in adults only); the evidence for this is presented within **Section 3.2.5** of this exposure and can be considered as a distinct sub-category of aerobic recreational physical activity.
- Fewer studies report on strength training and the evidence for this is presented for both children and adults in **Sections 2.3** and **3.3** respectively.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=500 participants, so only studies with more than 500 participants are reported in detail here.
- There was overlap between the meta-analyses; this is presented in **Table 81**.
- Laframboise et al (2011) investigated studies of aerobic physical activity in children. All studies which met the inclusion criteria (see protocol in the **Appendix**) had fewer than 500 participants.

Therefore the Laframboise et al (2011) published review is not referred to explicitly in the results section of this exposure.

- Ishihara et al (2003) is an individual prospective cohort study not included in a meta-analysis identified in Summerbell et al (2009). The full text article is in Japanese. Summerbell et al (2009) provided a detailed results summary in English and so the result is included in this literature review.

The table below indicates the available evidence against each exposure:

Table 80 Types of available evidence – Physical activity

Type of available evidence			
Exposure	**Type of available evidence**	**Children**	**Adults**
Total physical activity	Meta-analyses of RCTs	X	X
	Meta-analyses of prospective cohort studies	X	X
	Single RCTs	X	X
	Single prospective cohort studies	Y	Y
Aerobic recreational physical activity	Meta-analyses of RCTs	Y	Y
	Meta-analyses of prospective cohort studies	Y	X
	Single RCTs*	Y	X
	Single prospective cohort studies	Y	Y
Walking (sub category of aerobic recreational physical activity)	Meta-analyses of RCTs	Y	X
Strength training	Meta-analyses of RCTs	X	Y
	Meta-analyses of prospective cohort studies	X	Y
	Single RCTs	X	Y
	Single prospective cohort studies	Y	Y

Table 81 Overlapping studies between meta-analyses of RCTs in adults – Walking

Overlap between meta-analyses

The meta-analyses have been grouped by review. Each review has several meta-analyses with the outcome used as an identifier. A code using the lead author (e.g. Gao 1) has been used to identify each individual meta-analysis down the right hand side for cross referencing.

	Gao et al (2016)			Hanson and Jones (2015)			Murtagh et al (2015)					Murphy et al (2007)		
	Gao 1	Gao 2	Gao 3	Han 1	Han 2	Han 3	Murt 1	Murt 2	Murt 3	Murt 4	Murt 5	Murp 1	Murp 2	Murp 3
	BMI	*Weight*	*%BF*	*%BF*	*BMI*	*WC*	*BMI*	*WC*	*WHR*	*Weight*	*%BF*	*Weight*	*BMI*	*%BF*
Gao 1	-	6	3	0	0	0	3	1	1	3	2	3	3	2
Gao 2		-	3	0	0	0	3	1	1	3	2	3	3	2
Gao 3			-	0	0	0	2	0	0	2	2	0	2	2
Han 1				-	5	0	3	0	1	3	3	1	1	2
Han 2					-	2	1	0	1	1	1	0	0	0
Han 3						-	0	0	0	0	0	0	0	0
Murt 1							-	9	12	21	13	9	10	8
Murt 2								-	10	10	4	1	1	0
Murt 3									-	14	7	3	3	2
Murt 4										-	14	11	10	8
Murt 5											-	7	7	8
Murp 1												-	14	11
Murp 2													-	10
Murp 3														-

2. Children

2.1 Total Physical Activity

2.1.1 Meta-analysis of RCTs in children

Nil

2.1.2 Meta-analyses of prospective cohort studies in children

Nil

2.1.3 Individual RCTs in children, not in meta-analyses

Nil

2.1.4 Individual prospective cohort studies in children, not in meta-analyses

Table 82 Results of individual prospective cohort studies in children – Total physical activity

Children					
Prospective cohort studies					
SE=standard error; MET=metabolic equivalent; OR=odds ratio; CI=confidence interval. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI change	Berkey et al. 2000 *Summerbell et al (2009)*	Total physical activity (excl gym) at baseline, hours per day *(girls)* 1 year	Beta coefficient	**-0.0284 SE± 0.0142 kg/m²** p=0.046 **INV**	6,149
		Total physical activity (excl gym) at baseline, hours per day *(boys)* 1 year	Beta coefficient	**-0.0261 SE± 0.0156 kg/m²** p=0.094 **INV**	4,620
	Berkey et al. 2003 *PAGAC (2008)* in *USDA DGAC (2015)*	One year increase in total activity, hours per day *(girls)* 1 year	Beta coefficient	**-0.033 (-0.077, 0.011)** **INV**	6,767
		One year increase in total activity, hours per day *(boys)* 1 year	Beta coefficient	**0.059 (0.007, 0.112)** **+VE**	5,120
		One year increase in MET hours per day *(girls)* 1 year	Beta coefficient	**-0.006 (-0.014, 0.003)** **INV**	6,767
		One year increase in MET hours per day *(boys)* 1 year	Beta coefficient	**0.009 (0.001, 0.019)** **+VE**	5,120
	Crocker et al. 2003 *PAGAC (2008)* in *USDA DGAC (2015)*	Total physical activity at baseline 1 year	Pearson product moment correlation	**= -0.02** Not significant **INV**	631
	Gidding et al. 2006 *PAGAC (2008)* in *USDA DGAC (2015)*	Per 100 unit increase in MET score 3 years	**No association** Data not available to access **NIL**		585
BMI change (log transformed)	Mo-suwan et al. 2000 *Summerbell et al (2009)*	Exercising "less than others", as reported by parents at baseline 5 years	Coefficient	**0.113 SE± 0.028** p=0.000 **INV**	1,290
		Exercising "more than others", as reported by parents at baseline 5 years	Coefficient	**0.068 SE± 0.037** p=0.068 **+VE**	1,290
Maintaining healthy weight	O'Brien et al. 2007 *Summerbell et al (2009)*	Higher activity in the three years prior to follow up 10 years	OR	**1.07** (CI=not reported) **INV**	960

Risk of overweight	Yang et al. 2006 *PAGAC (2008)* in *USDA DGAC (2015)*	Change in total physical activity from baseline: increasingly active *(girls)* 21 years	OR	**1.25 (0.61, 2.53)** **+VE**	693
		Change in total physical activity from baseline: increasingly active *(boys)* 21 years	OR	**0.76 (0.42, 1.38)** **INV**	626
		Change in total physical activity from baseline: decreasingly active *(girls)* 21 years	OR	**2.35 (1.16, 4.78)** **INV**	693
		Change in total physical activity from baseline: decreasingly active *(boys)* 21 years	OR	**1.20 (0.67, 2.18)** **INV**	626
		Change in total physical activity from baseline: persistently inactive *(girls)* 21 years	OR	**2.18 (1.05, 7.57)** **INV**	693
		Change in total physical activity from baseline: persistently inactive *(boys)* 21 years	OR	**0.52 (0.22, 1.23)** **+VE**	626
Risk of obesity	Yang et al. 2006 *PAGAC (2008)* in *USDA DGAC (2015)*	Change in total physical activity from baseline: increasingly active *(girls)* 21 years	OR	**0.80 (0.29, 2.19)** **INV**	693
		Change in total physical activity from baseline: increasingly active *(boys)* 21 years	OR	**0.79 (0.32, 1.98)** **INV**	626
		Change in total physical activity from baseline: decreasingly active *(girls)* 21 years	OR	**2.72 (1.04, 7.09)** **INV**	693
		Change in total physical activity from baseline: decreasingly active *(boys)* 21 years	OR	**1.04 (0.41, 2.63)** **INV**	626
		Change in total physical activity from baseline: persistently inactive *(girls)* 21 years	OR	**1.51 (0.32, 6.99)** **INV**	693
		Change in total physical activity from baseline: persistently inactive *(boys)* 21 years	OR	**0.87 (0.27, 2.85)** **+VE**	626
	Ishihara et al. 2003 *Summerbell et al (2009)*	At aged 3 years, those who "moved around a lot" vs. those who "moved around a little" 10 years 11 months	OR	**0.81 (0.36, 1.83)** **INV**	737

Eight prospective cohort studies with more than 500 participants were identified. These provided 24 results across five outcomes: BMI change; BMI change (log transformed); odds of maintaining a healthy weight; risk of overweight; and risk of obesity. Seventeen results reported inverse associations, of which five were statistically significant. Six results reported positive associations, of which two (both from the same study and in boys) were statistically significant. One result reported no significant association.

The study by Crocker et al (2003) was conducted in an all-girl cohort.

O'Brien et al (2007) used accelerometers to measure total physical activity; the other studies used questionnaires or observed reports from parents.

Berkey et al (2003) reported inverse associations for girls and positive associations for boys (all in normal weight range at baseline). When the analysis was conducted only in children with a BMI above the 85th percentile at baseline, all the associations were inverse and statistically significant.

Gidding et al (2006) reported no association but the authors noted a trend for a lower BMI when increased time was spent in intense activity.

There were 19 prospective cohorts (23 publications) in children with fewer than 500 participants. Three studies reported significant inverse associations, two further studies reported significant inverse associations but only in boys, and one other study reported a significant inverse association for change in fat mass only (other outcomes within the study were BMI percentage change and waist circumference percentage change). The remaining studies reported non-significant associations.
Studies n<500: Jago et al. 2005, Janz et al. 2009, Metcalf et al. 2008, Janz et al. 2005, Moore et al. 1995, Moore et al. 2003, Stevens et al. 2004, Twisk et al. 1998, Twisk et al. 2000, Twisk et al. 2002, Davison et al. 2001, Maffeis et al. 1998, Horn et al. 2001, Ku et al. 1981, Berkowitz et al. 1985, Figueroa-Colon et al. 2000, Ara et al. 2006, Bogaert et al. 2003, Elgar et al. 2005, Kettaneh et al. 2005, Mundt et al. 2006, Ekelund et al. 2007, and Li et al. 2007.

The USDA DGAC (2015) produced a summary statement regarding the evidence from PAGAC (2008). The research questions and conclusion are copied below:

Question 1: What is the relationship between physical activity, body weight, and health outcomes in children and adolescents?
Source of Evidence: Physical Activity Guidelines Advisory Committee Report, 2008
Conclusion: The DGAC concurs with the 2008 PAGAC, which found that strong evidence demonstrates that the physical fitness and health status of children and adolescents is substantially enhanced by frequent physical activity. Compared to inactive young people, physically active children and adolescents have higher levels of cardiorespiratory endurance and muscular strength, and well documented health benefits include lower body fatness, more favorable cardiovascular and metabolic disease risk profiles, enhanced bone health, and reduced symptoms of anxiety and depression. These conclusions are based on the results of prospective observational studies in which higher levels of physical activity were found to be associated with favorable health parameters as well as intervention studies in which exercise treatments caused improvements in 170 physical fitness and various health-related factors.
DGAC Grade: Strong

2.2 Aerobic recreational physical activity

2.2.1 Meta-analyses of RCTs in children

Table 83 Meta-analyses of RCTs in children – Aerobic recreational activity

Children – Aerobic recreational activity					
Meta-analyses of RCTs					
SMD=standardised mean difference; MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Bochner et al (2015)	Active video gaming vs. no intervention 10–24 weeks	SMD	**-0.08 (-0.25, 0.08) kg** **INV**	Studies=7; n=588 I^2=not reported
BMI change	van't Riet et al (2014)	Active video gaming vs. no intervention 10–36 weeks	SMD	**0.20 (-0.08, 0.48)** **+VE**	Studies=5; n=561 I^2=46%
	Costigan et al (2015)	High intensity interval training programme vs. control 4–26 weeks	MD	**-0.6 (-0.9, -0.4) kg/m^2** **INV**	Studies=8; n=870 I^2=0%
% body fat change		High intensity interval training programme vs. control 4–26 weeks	MD	**-1.6 (-2.9, -0.5) %** **INV**	Studies=7; n=786 I^2=63%
Waist circumference		High intensity interval training programme vs. control 4–26 weeks	MD	**-1.5 (-4.1, -1.1) cm** **INV**	Studies=6; n=unclear I^2=68%

Three reviews conducted meta-analyses of RCTs in children investigating adiposity and aerobic activity. These provided five results across four outcomes: weight change; BMI change; percentage body fat change; and waist circumference. Four results reported inverse effects of the aerobic activity intervention reducing adiposity measures, of which three were statistically significant. One result reported a non-significant positive effect.

Bochner et al (2015) and van't Riet et al (2014) both investigated active video gaming as the form of aerobic exercise, which generally included participation in an aerobic activity led by an on-screen video three to seven times per week. There was overlap of five studies between the meta-analyses, with four of those being in overweight children. Sample size ranged from 20 to 322 participants. Age at recruitment ranged from seven to 19 years in Bochner et al (2015); not reported in van't Riet et al (2014). The I^2 value was not reported in Bochner et al (2015) but they reported a test for heterogeneity: χ^2=0.69, df=6, P=1.0. Both reviews reported that the studies included were of low quality.

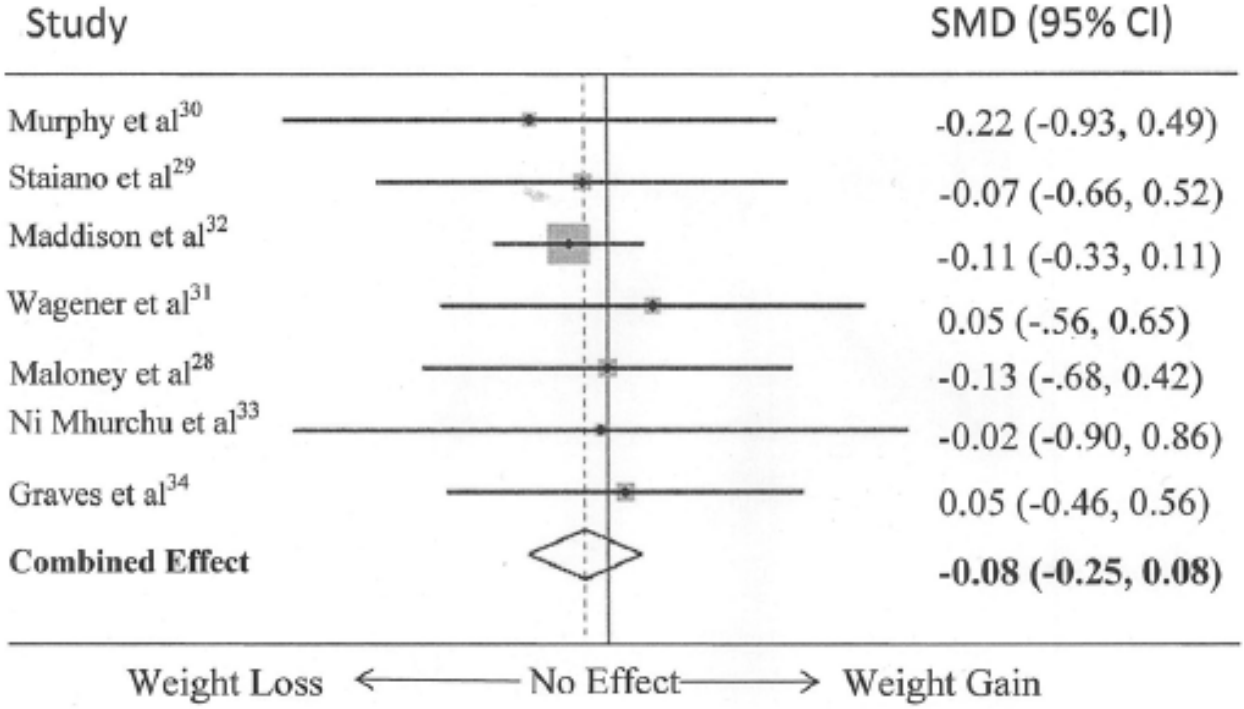
Costigan et al (2015) investigated high intensity interval training in adolescents across several sports (sprints, walking, swimming, and cycling), with two to six sessions per week. Three of the included studies were in adolescents living with obesity and one was with adolescents with learning disabilities. Age at recruitment ranged from 11 to 18 years. Results were reported for BMI change, percentage body fat change, and waist circumference; all reported significant inverse associations. In the result reported for waist circumference, the authors did not clearly state which studies were included in this meta-analysis.

The forest plots corresponding to the above meta-analyses are presented below; a forest plot was not available for the Costigan et al (2015) meta-analysis with waist circumference as the outcome.

Children | RCTs | BMI change | Bochner et al (2015) | Active video gaming

Forest plot of the combined effect of exergaming on weight (SMD, standardized mean difference; CI, confidence interval) (Bochner et al 2015).

Figure 62 Meta-analysis of RCTs in children – Active video gaming – Bochner et al 2015 – BMI change

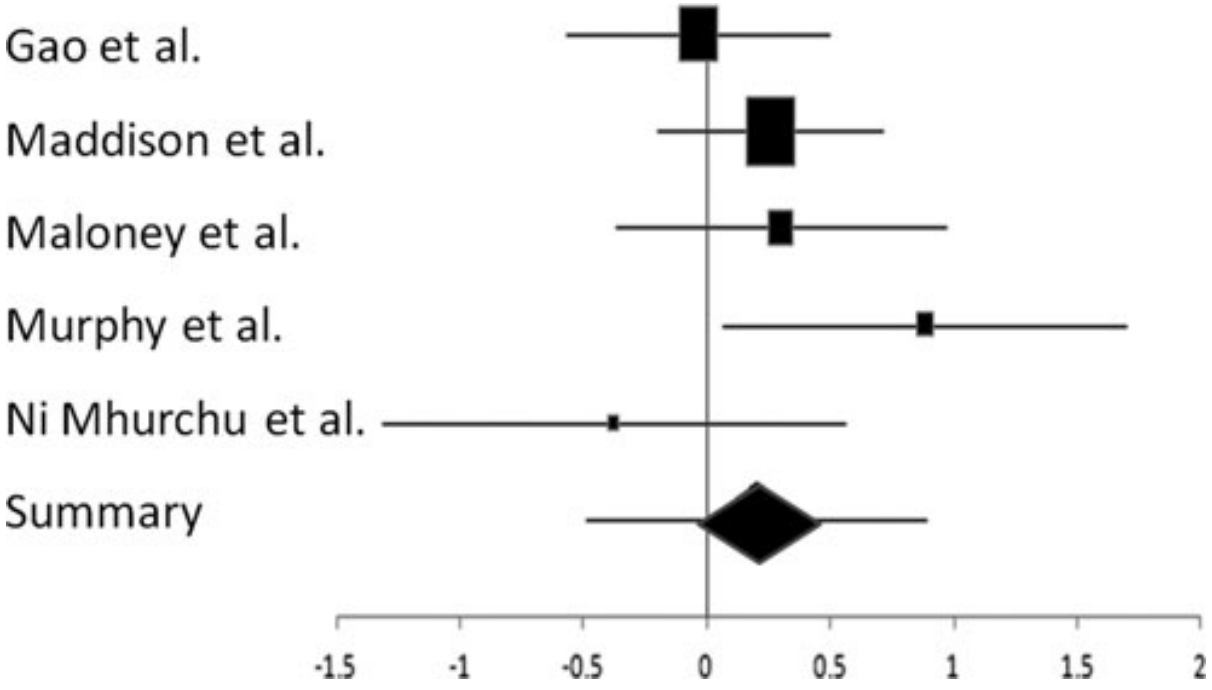


Children | RCTs | BMI change | van't Riet et al (2014) | Active video gaming

Please note

- *There was no legend to this plot in the original study.*
- *The summary diamond represents the effect estimate and the 95% confidence interval calculated from this meta-analysis. The arms extending from the diamond represent the 'prediction interval' calculated by the authors showing the 95% range of 'true effects' expected to be shown in future individual studies investigating this exposure.*

Figure 63 Meta-analysis of RCTs in children – Active video gaming – van't Riet et al (2014) – BMI change

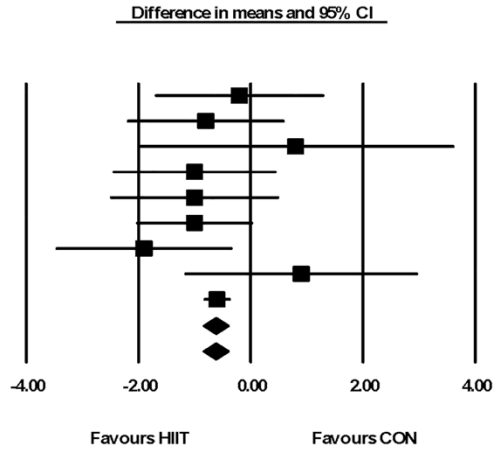


Children | RCTs | BMI change | Costigan et al (2015) | High intensity interval training

Forest plot of high-intensity interval training (HIIT) effect on body mass index (Costigan et al 2015).

Figure 64 Meta-analysis of RCTs in children – HIIT – Costigan et al 2015 – BMI change

Model	Studyname	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Banquet (2001) Boys	-0.200	0.768	0.590	-1.705	1.305	-0.260	0.795
	Banquet (2001) Girls	-0.800	0.717	0.514	-2.205	0.605	-1.116	0.264
	Boer (2014)	0.800	1.442	2.079	-2.026	3.626	0.555	0.579
	Buchan (2011)	-1.000	0.743	0.552	-2.456	0.456	-1.346	0.178
	Buchan (2012)	-1.000	0.767	0.588	-2.504	0.504	-1.304	0.192
	Buchan (2013)	-1.000	0.529	0.280	-2.036	0.036	-1.891	0.059
	Farah (2014)	-1.900	0.803	0.645	-3.474	-0.326	-2.366	0.018
	Koubaa (2013)	0.900	1.060	1.123	-1.177	2.977	0.849	0.396
	Tjonna (2009)	-0.600	0.124	0.015	-0.842	-0.358	-4.855	0.000
Fixed		-0.632	0.112	0.013	-0.853	-0.412	-5.624	0.000
Random		-0.632	0.112	0.013	-0.853	-0.412	-5.624	0.000

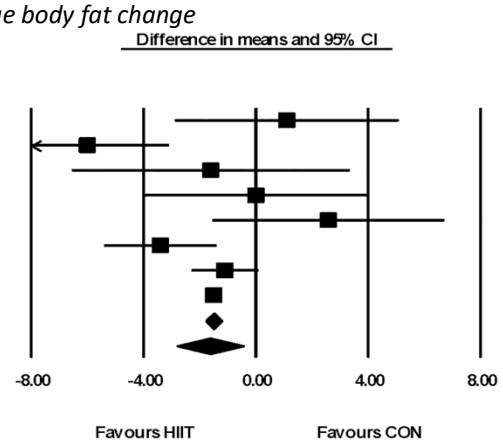


Children | RCTs | % body fat change | Costigan et al (2015) | High intensity interval training

Forest plot of high-intensity interval training (HIIT) effect on percentage body fat (Costigan et al 2015).

Figure 65 Meta-analysis of RCTs in children – HIIT – Costigan et al 2015 – Percentage body fat change

Model	Studyname	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Banquet (2001) Boys	1.100	2.036	4.145	-2.890	5.090	0.540	0.589
	Banquet (2001) Girls	-6.000	1.486	2.208	-8.912	-3.088	-4.038	0.000
	Boer (2014)	-1.600	2.526	6.382	-6.552	3.352	-0.633	0.527
	Buchan (2012)	0.000	2.012	4.048	-3.943	3.943	0.000	1.000
	Buchan (2011)	2.580	2.112	4.459	-1.559	6.719	1.222	0.222
	Farah (2014)	-3.400	1.021	1.043	-5.401	-1.399	-3.330	0.001
	Racil (2013)	-1.100	0.609	0.371	-2.294	0.094	-1.805	0.071
	Tjonna (2009)	-1.500	0.154	0.024	-1.803	-1.197	-9.710	0.000
Fixed		-1.519	0.146	0.021	-1.805	-1.233	-10.400	0.000
Random		-1.647	0.603	0.364	-2.829	-0.464	-2.729	0.006



2.2.2 Meta-analyses of prospective cohort studies in children

Nil

2.2.3 Individual RCTs in children, not in meta-analyses

Nil

2.2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 84 Results of individual prospective cohort studies in children – Aerobic recreational activity

Children – Aerobic recreational activity					
Prospective cohort studies					
RR=relative risk; OR=odds ratio. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Risk of overweight	Cleland et al. 2008 *Te Velde et al (2012)*	Aged 5-6 years: >2 hours outdoor play per day vs. <1 hour per day *(girls)* 3 years	RR	**0.99 (0.40, 2.46)** **INV**	188
		Aged 5-6 years: >2 hours outdoor play per day vs. <1 hour per day *(boys)* 3 years	RR	**0.61 (0.18, 2.05)** **INV**	
		Aged 10-12 years: >2 hours outdoor play per day vs. <1 hour per day *(girls)* 3 years	RR	**0.69 (0.55, 0.87)** **INV**	360
		Aged 10-12 years: >2 hours outdoor play per day vs. <1 hour per day *(boys)* 3 years	RR	**0.73 (0.73, 0.73)** **INV**	
Odds of overweight	Gable et al. 2007 *Te Velde et al (2012)*	Frequency of aerobic activity (days per week) at baseline 3 years	OR	**1.02 (0.98, 1.06)** **+VE**	8,000
Odds of obesity	Bak et al. 2004 *Summerbell et al (2009)*	High leisure time physical activity level at baseline vs. inactive 10–11 years	OR	**1.10 (0.28, 4.34)** **+VE**	1,278
Odds of 'excess weight gain'	O'Loughlin et al. 2000 *Summerbell et al (2009)*	Lowest frequency category of participation in aerobic activities and sports vs. highest *(boys)* 2 years	OR	**2.18 (1.01, 4.71)** **INV**	319
		No sport participation outside of school vs. participation *(boys)* 2 years	OR	**2.14 (0.96, 4.77)** **INV**	319
		No sport participation outside of school vs. participation *(girls)* 1 year	OR	**1.90 (1.18, 3.06)** **INV**	857

Four prospective cohort studies in children not included in meta-analyses that had more than 500 participants in total were identified. These provided nine results across four outcomes: risk of overweight; odds of overweight; odds of obesity; and odds of excess weight gain. Seven results reported inverse associations (increased physical activity decreased adiposity, or decreased physical activity increased adiposity), of which four were statistically significant. Two results reported non-significant positive associations.

O'Loughlin et al (2000) defined excess weight gain as "a change in BMI equal to or greater than 90th percentile change in BMI for same-age, same-gender students in the study population".

Ages at baseline were as follows: Cleland et al (2008) 5-6 years (younger children) and 10-12 years (older children), Gable et al (2007) 5 years, O'Loughlin et al (2000) 9-12 years, and Bak et al (2004) 19 years (median).

Nine prospective cohort studies with fewer than 500 participants were identified, providing 22 results. Fourteen results reported no association; five results reported inverse associations (four were statistically

significant), and three results reported positive associations (all three statistically significant). Age at baseline range from five to 16 years old.

Studies n<500: Salbe et al. 2002, Davison et al. 2001, Elgar et al. 2005, Bogaert et al. 2003, Horn et al. 2001, Kettaneh et al. 2005, Lefevre et al. 2002, Barnekow-Bergkvist et al. 2001, and Klesges et al. 1995.

2.2.5 Walking (as a sub category of recreational activity)

Nil

2.3 Strength training

2.3.1 Children

There were no meta-analyses of RCTs or prospective cohort studies in children investigating strength training and adiposity. One RCT (Weltman et al. 1987) identified in a group of 29 boys investigating strength training and adiposity was identified in the review by Benson et al (2008). This reported a significant positive effect of higher weight gain in the circuit training intervention group relative to control ($p<0.05$).

3. Adults

3.1 Total Physical Activity

3.1.1 Meta-analysis of RCTs in adults

Nil

3.1.2 Meta-analyses of prospective cohort studies in adults

Nil

3.1.3 Individual RCTs in adults, not in meta-analyses

Nil

3.1.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 85 Results of individual prospective cohort studies in adults – Total physical activity

Adults					
Prospective cohort studies					
SE=standard error; SD=standard deviation; CI=confidence interval; MD=mean difference; MET=metabolic equivalent. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Macdonald et al. 2003 *Summerbell et al (2009)*	Per 1 unit increase in physical activity level from baseline to follow up 5-7 years	Unstandard -ised beta coefficient	**-0.771 (-1.007, -0.534) %** **INV**	1,064
	Di Pietro et al. 2004 *Summerbell et al (2009)*	Change in physical activity level of 0.10 METs compared to stable physical activity level 5 years	MD	**-0.12 (-0.16, -0.07) kg** **INV**	2,501
	Heitmann et al. 1997 *Sumerbell et al (2009)*	Tertiles of physical activity at baseline 6 years	**No significant association** p>0.24 **NIL**		4,600
	Sternfeld et al. 2004 *Summerbell et al (2009)*	Per 1 unit increase in physical activity (1-5 scale): sports/ exercise 3 years	Beta coefficient	**-0.32 SE± 0.08 kg** p<0.0001 **INV**	3,064
		Per 1 unit increase in physical activity (1-5 scale): daily routine activity 3 years	Beta coefficient	**-0.21 SE± 0.10 kg** p=0.03 **INV**	3,064
		Per 1 unit increase in physical activity (1-5 scale): household/ care giving activity 3 years	Beta coefficient	**-0.15 SE± 0.09 kg** p=0.10 **INV**	3,064
Weight gain attenuated	Schmitz et al. 2000 *Summerbell et al (2009)*	Per 200 exercise units increase *(black women)* 10 years	Beta coefficient	**-1.16 SE± 0.17 kg** p=0.0001 **INV**	648
		Per 200 exercise units increase *(black men)* 10 years	Beta coefficient	**-0.38 SE± 0.11 kg** p=0.0007 **INV**	601
		Per 200 exercise units increase *(white women)* 10 years	Beta coefficient	**-0.70 SE± 0.14 kg** p=0.0001 **INV**	675
		Per 200 exercise units increase *(white men)* 10 years	Beta coefficient	**-0.49 SE± 0.10** p=0.0001 **INV**	846

BMI	Taylor et al. 1994 *Summerbell et al (2009)*	(1) Those who maintained or reduced physical activity relative to (2) those who became more active *(female, smokers)* 7 years	Mean BMI slope	**(1) 0.26 SD± 0.38** **(2) 0.12 SD± 0.25** p=not reported **INV**	668
		(1) Those who maintained or reduced physical activity relative to (2) those who became more active *(male, smokers)* 7 years	Mean BMI slope	**(1) 0.13 SD± 0.25** **(2) 0.10 SD± 0.34** p=not reported **INV**	568
		(1) Those who maintained or reduced physical activity relative to (2) those who became more active *(female, non-smokers)* 7 years	Mean BMI slope	**(1) 0.17 SD± 0.35** **(2) 0.11 SD± 0.32** p=not reported **INV**	668
		(1) Those who maintained or reduced physical activity relative to (2) those who became more active *(male, non-smokers)* 7 years	Mean BMI slope	**(1) 0.13 SD± 0.32** **(2) 0.08 SD± 0.24** p=not reported **INV**	568
BMI change	Ma et al. 2005 *Summerbell et al (2009)*	Per 5 unit increase in MET hours per day 1 year	Coefficient	**-0.03 (-0.06, -0.001) kg/m^2** p=0.049 **INV**	572
	Sundquist et al. 1998 *Summerbell et al (2009)*	Becoming more active over duration of study *(female)* 8 years	Beta coefficient	**-0.17** (CI=not reported) **INV**	1,972
		Becoming more active over duration of study *(male)* 8 years	Beta coefficient	**-0.12** (CI=not reported) **INV**	1,871
		Becoming inactive over duration of study *(female)* 8 years	Beta coefficient	**0.20** (CI=not reported) **INV**	1,972
		Becoming inactive over duration of study *(male)* 8 years	Beta coefficient	**0.28** (CI=not reported) p<0.05 **INV**	1,871
Waist circumference	Sternfeld et al. 2004 *Summerbell et al (2009)*	Per 1 unit increase in physical activity (1-5 scale): sports/ exercise 3 years	Beta coefficient	**-0.10 SE± 0.07 cm** p=0.18 **INV**	3,064
		Per 1 unit increase in physical activity (1-5 scale): daily routine activity 3 years	Beta coefficient	**-0.14 SE± 0.09 cm** p=0.14 **INV**	3,064
		Per 1 unit increase in physical activity (1-5 scale): household/ care giving activity 3 years	Beta coefficient	**0.01 SE± 0.08 cm** p=0.88 **+VE**	3,064

Eight prospective cohort studies in adults with more than 500 participants were identified. These reported 22 results across five outcomes: weight change; weight gain attenuated; BMI; BMI change; and waist circumference. Twenty results reported inverse associations, of which ten were statistically significant. One result reported a non-significant positive association and one result reported no significant association.

Three studies were in single gender cohorts: two in all-female cohorts (MacDonald 2003 and Sternfeld 2004) and one in an all-male cohort (Di Pietro 2004).

All studies measured total physical activity through self report, either via questionnaires or interviews.

There were eight prospective cohort studies in adults with fewer than 500 participants. These provided 14 results: eight reported inverse associations (of which five were significant); and six reported no associations. **Studies n<500**: Schoeller et al. 1997, Wier et al. 2001, Hughes et al. 2002, Tataranni et al. 2003, Sammel et al. 2003, Kyle et al. 2006, Raguso et al. 2006, and Murray et al. 1996.

The USDA DGAC (2015) produced a summary statement regarding the evidence from PAGAC (2008). The research questions and conclusion are copied below:

Question 2: What is the relationship between physical activity and body weight?
Source of Evidence: Physical Activity Guidelines Advisory Committee Report, 2008
Conclusion: The DGAC concurs with the 2008 PAGAC, which found that compared to less active people, physically active adults and older adults exhibit a higher level of cardiorespiratory and muscular fitness, healthier body weight and body composition, and a biomarker profile that is more favorable for preventing cardiovascular disease (CVD) and type 2 diabetes and enhancing bone health. In addition, there is an association between higher levels of physically activity in adults and older adults and lower rates of all-cause mortality, coronary heart disease, high blood pressure, stroke, type 2 diabetes, metabolic syndrome, colon cancer, breast cancer, and depression. High-intensity muscle-strengthening activity enhances skeletal muscle mass, strength, power, and intrinsic neuromuscular activation. Physically active adults who are overweight or obese experience a variety of health benefits that are generally similar to those observed in physically active people of ideal body weight. Physical activity reduces risk of depression and is associated with lower risk of cognitive decline in adults and older adults. Physical activity is associated with higher levels of functional health and a lower risk of falling in older adults.
DGAC Grade: Strong

3.2 Aerobic recreational physical activity

3.2.1 Meta-analysis of RCTs in adults

Table 86 Meta-analyses of RCTs in adults – Aerobic recreational activity

Adults – Aerobic recreational activity					
Meta-analyses of RCTs					
WMD=weighted mean difference; MD=mean difference; SMD=standardised mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight change	Hespanhol et al (2016)	Running programme vs. no intervention 12–52+ weeks	WMD	**-2.74 (-3.43, -2.06) kg** **INV**	Studies=21; n=979 I^2=0%
	Kelley and Kelley (2006)	Varied aerobic exercise vs. control 8 weeks–6 years (max)	MD	**-3.4 (-5.3, -1.5) kg** **INV**	Studies=3; n=not reported I^2=not reported
BMI change	van't Riet et al (2014)	Active video gaming vs. no intervention 3–20 weeks	SMD	**0.68 (0.13, 1.24)** **+VE**	Studies=6; n=142 I^2=68%
	Hespanhol et al (2016)	Running programme vs. no intervention 12–52+ weeks	WMD	**-0.23 (-0.61, 0.15) kg/m²** **INV**	Studies=10; n=256 I^2=0%
Lean body mass change		Running programme vs. no intervention 12–52+ weeks	WMD	**-0.24 (-0.60, 0.12) kg** **INV**	Studies=6; n=462 I^2=39%
% body fat change		Running programme vs. no intervention 12–52+ weeks	WMD	**-1.63 (-2.15, -1.12) %** **INV**	Studies=11; n=657 I^2=0%
	Kelley (2006)	Varied aerobic exercise vs. control 8 weeks–6 years (max)	MD	**-1.4 (-2.3, -0.6) %** **INV**	Studies=3; n=not reported I^2=not reported
Fat mass change	Oja et al (2015)	Interventions to participate in football (soccer) vs. no intervention Follow up not reported	MD	**-2.64 (-6.06, 0.78) kg** **INV**	Studies=5; n=not reported I^2=16%
Visceral adipose tissue change	Ismail et al (2012)	Varied aerobic exercise interventions vs. control 4 weeks–16 months	SMD	**-0.23 (-0.35, -0.12)** **INV**	Studies=27; n=1,409 I^2=71%

Five reviews conducting meta-analyses of RCTs in adults investigating aerobic activity and adiposity were identified. These provided nine results across six outcomes: weight change; BMI change; lean body mass change; percentage body fat change; fat mass change; and visceral adipose tissue change. Eight results reported inverse effects (with increased physical activity reducing adiposity measures), of which five were statistically significant. One result reported a significant positive effect.

One published review (Hespanhol et al 2016) reported a result with the outcome of 'lean body mass change' (non-significant inverse effect) which may not directly apply to the remit of this review.

Kelley (2006) did not report I^2 values but did report Q statistics as follows: for weight change meta-analysis, Q=2.8, p=0.25; for percentage body fat meta-analysis, Q= 1.7, p=0.43.

Kelley and Kelley (2006) and Ismail et al (2012) both investigated a variety of aerobic activities, with the most prevalent being cycling and jogging/running. Ismail et al (2012) has an overlap of one study with Hespanhol et al (2016).

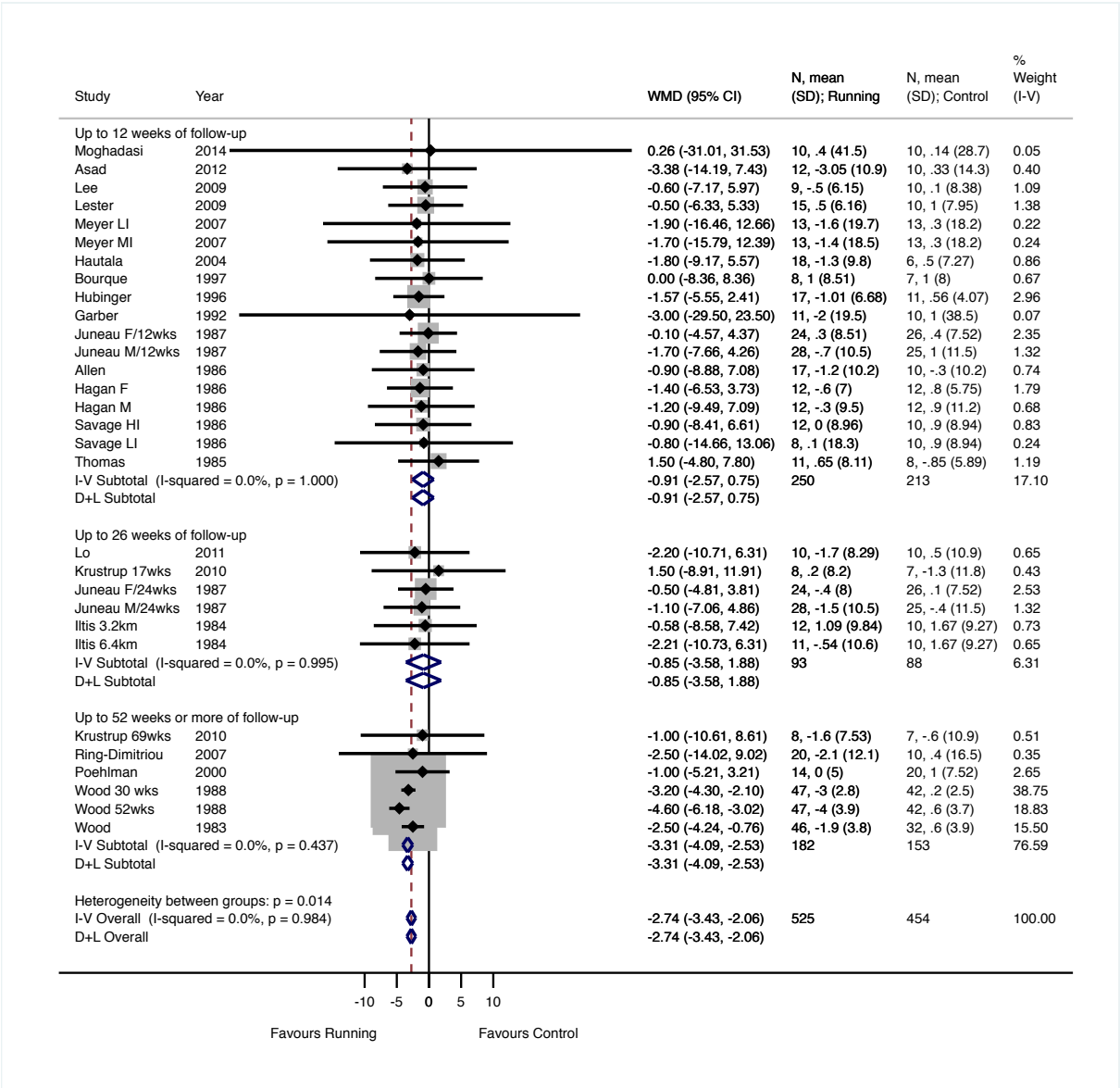
Van't Riet et al (2014) investigated active video gaming interventions in an elderly population. Sample size ranged from 15 to 34 participants and it was unclear if the result was adjusted for any potential confounding factors.

The available forest plots corresponding to the above meta-analyses are presented below.

Adults | RCTs | Weight change | Hespanol et al (2016) | Running

Overall and length of training subgroups meta-analyses for body weight (kg). "I-V Overall" represents the overall fixed-effect model weighted by the inverse-variance. "I-V Subtotal" represents the fixed-effect model weighted by the inverse-variance by length of training. "D+L Overall" represents the overall random-effects model weighted by the inverse of the variance within and between (tau-squared) studies. "D+L Subtotal" represents the random-effects model weighted by the inverse of the variance within and between (tau-squared) studies by length of training. WMD: weighted mean difference. N: number of participants. SD: standard deviation. I-V: inverse-variance. D+L: DerSimonian and Laird method with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. HI: high intensity. MI: moderate intensity. LI: low intensity. M: males. F: females. Wks: weeks (Hespanol et al 2016).

Figure 66 Meta-analysis of RCTs in adults – Running – Hespanhol et al 2016 – Weight change

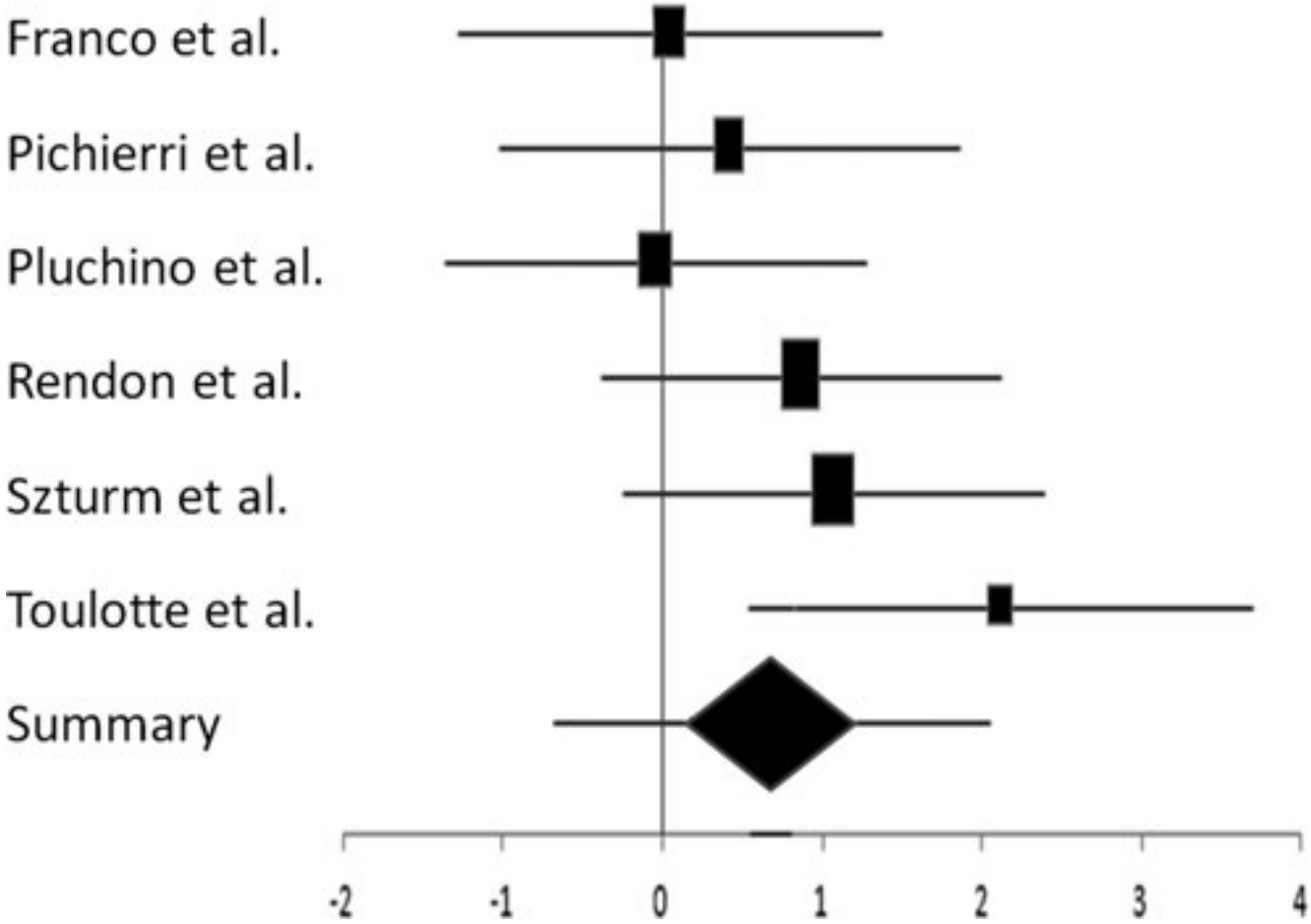


Adults | RCTs | BMI change | van't Riet et al (2014) | Active video gaming

Please note

- *There was no legend to this plot in the original study.*
- *The summary diamond represents the effect estimate and the 95% confidence interval calculated from this meta-analysis. The arms extending from the diamond represent the 'prediction interval' calculated by the authors showing the 95% range of 'true effects' expected to be shown in future individual studies investigating this exposure.*

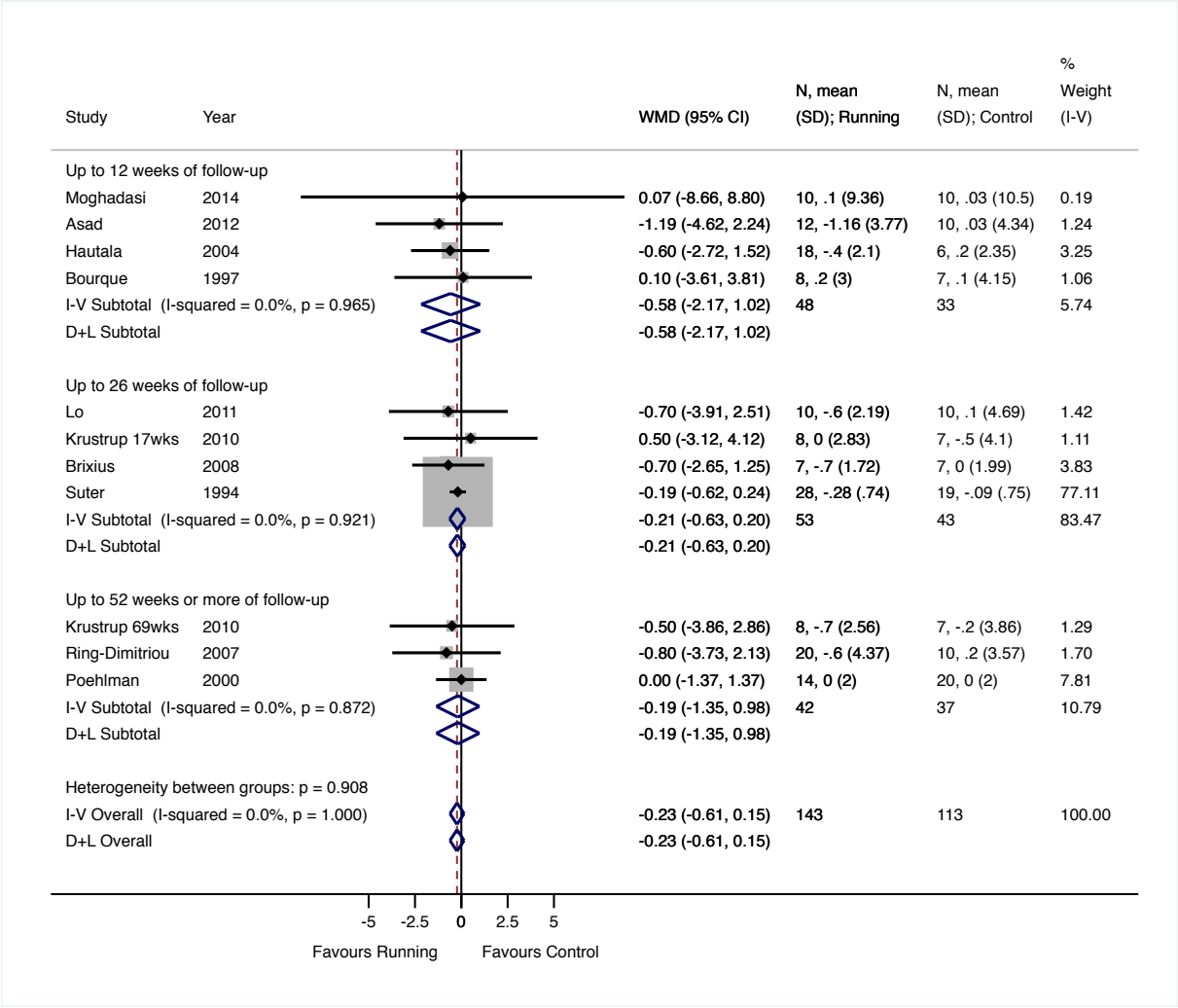
Figure 67 Meta-analysis of RCTs in adults – Active video gaming – van't Riet et al 2014 – BMI change



Adults | RCTs | BMI change | Hespanhol et al (2016) | Running

Overall and length of training subgroups meta-analyses for body mass index (kg/m^2). "I-V Overall" represents the overall fixed-effect model weighted by the inverse-variance. "I-V Subtotal" represents the fixed-effect model weighted by the inverse-variance by length of training. "D+L Overall" represents the overall random-effects model weighted by the inverse of the variance within and between (tau-squared) studies. "D+L Subtotal" represents the random-effects model weighted by the inverse of the variance within and between (tau-squared) studies by length of training. WMD: weighted mean difference. N: number of participants. SD: standard deviation. I-V: inverse-variance. D+L: DerSimonian and Laird method with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. Wks: weeks (Hespanol et al 2016).

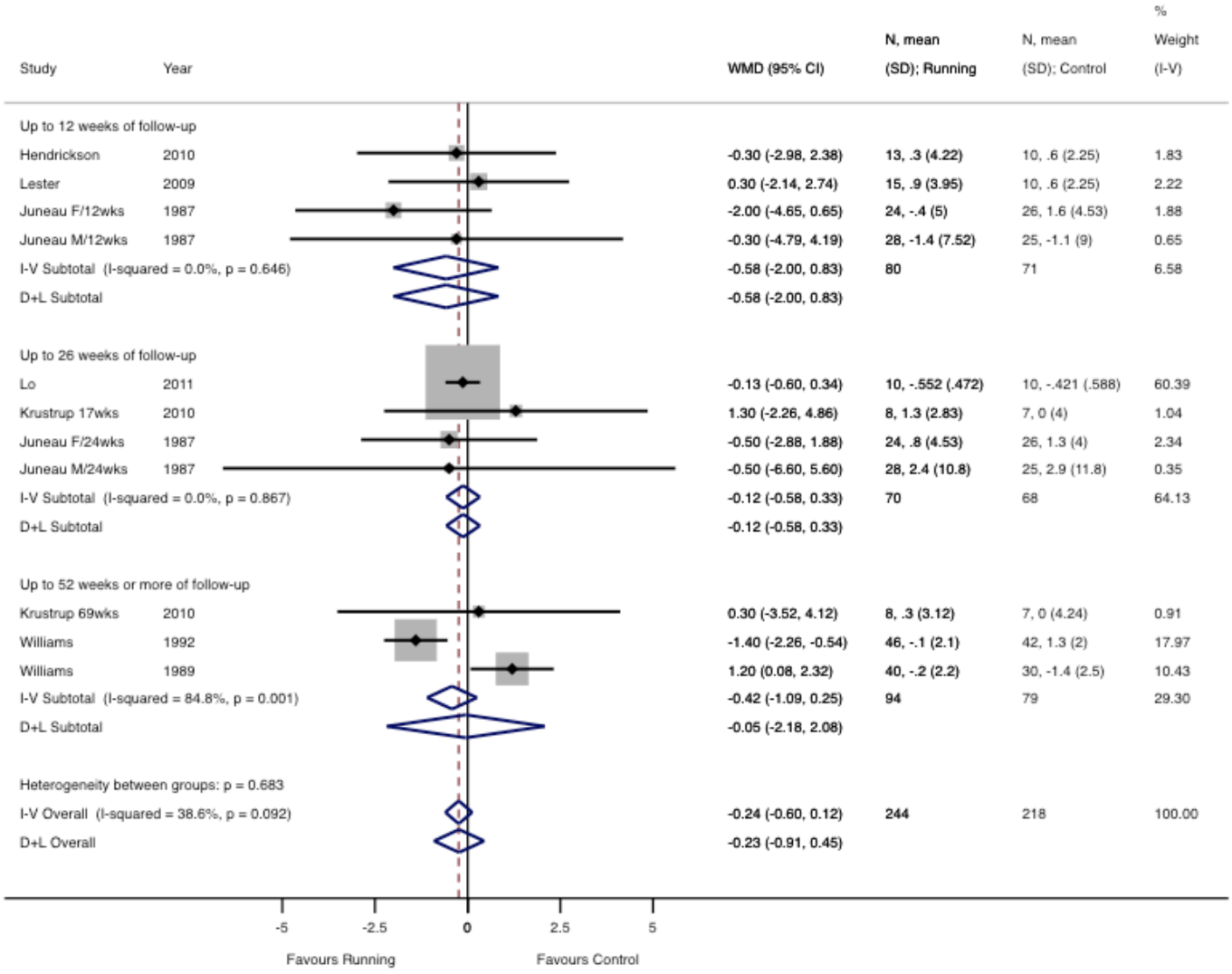
Figure 68 Meta-analysis of RCTs in adults – Running – Hespanhol et al 2016 – BMI change



Adults | RCTs | Lean body mass change | Hespanhol et al (2016) | Running

Overall and length of training subgroups meta-analyses for lean body mass (kg). "I-V Overall" represents the overall fixed-effect model weighted by the inverse-variance. "I-V Subtotal" represents the fixed-effect model weighted by the inverse-variance by length of training. "D+L Overall" represents the overall random-effects model weighted by the inverse of the variance within and between (tau-squared) studies. "D+L Subtotal" represents the random-effects model weighted by the inverse of the variance within and between (tau-squared) studies by length of training. WMD: weighted mean difference. N: number of participants. SD: standard deviation. I-V: inverse-variance. D+L: DerSimonian and Laird method with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. M: males. F: females. Wks: weeks (Hespanol et al 2016).

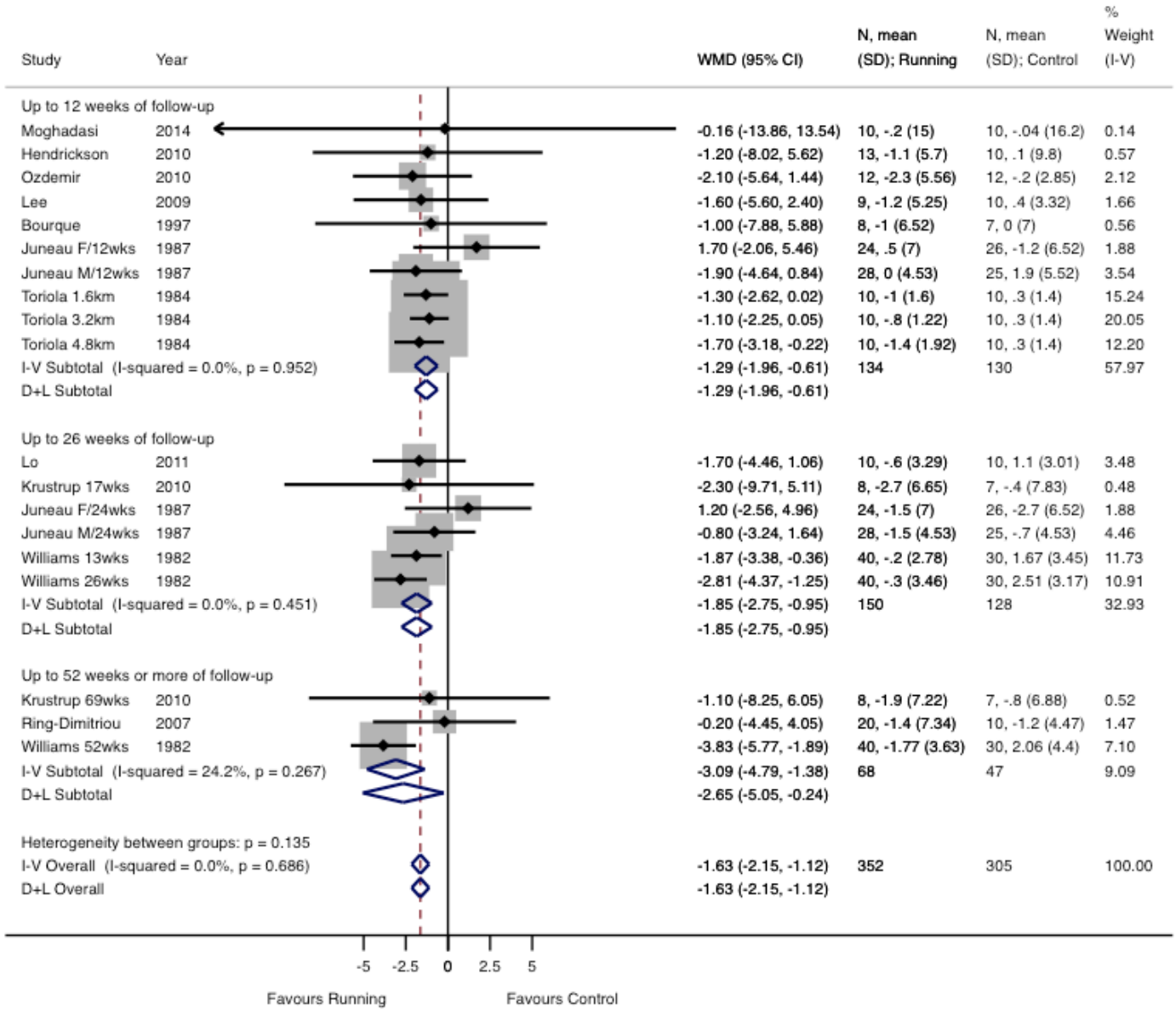
Figure 69 Meta-analysis of RCTs in adults – Running – Hespanhol et al 2016 – Lean body mass change



Adults | RCTs | % body fat change | Hespanhol et al (2016) | Running

Overall and length of training subgroups meta-analyses for percentage body fat. "I-V Overall" represents the overall fixed-effect model weighted by the inverse-variance. "I-V Subtotal" represents the fixed-effect model weighted by the inverse-variance by length of training. "D+L Overall" represents the overall random-effects model weighted by the inverse of the variance within and between (tau-squared) studies. "D+L Subtotal" represents the random-effects model weighted by the inverse of the variance within and between (tau-squared) studies by length of training. WMD: weighted mean difference. N: number of participants. SD: standard deviation. I-V: inverse-variance. D+L: DerSimonian and Laird method with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model. M: males. F: females. Wks: weeks (Hespanol et al 2016).

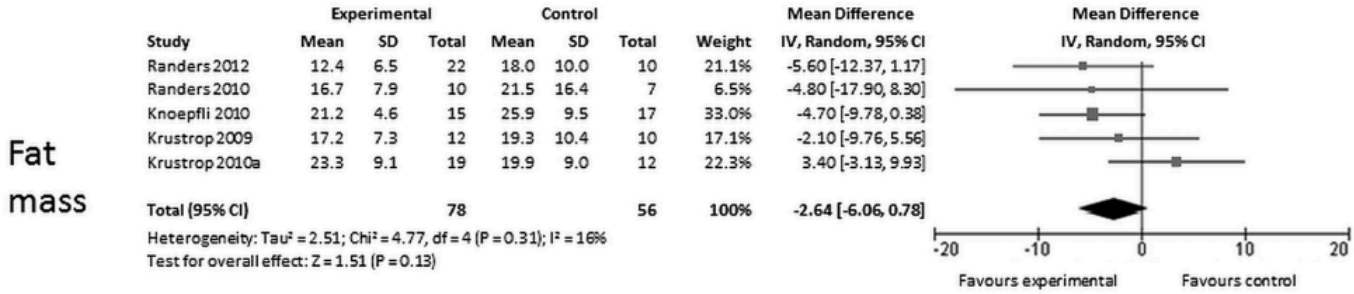
Figure 70 Meta-analysis of RCTs in adults – Running – Hespanhol et al 2016 – Percentage body fat change



Adults | RCTs | Fat mass change | Oja et al (2015) | Participation in football

Meta-analysis of the effects of recreational football on fat mass (kg) (Oja et al 2015).

Figure 71 Meta-analysis of RCTs in adults – Participation in football – Oja et al 2015 – Fat mass change

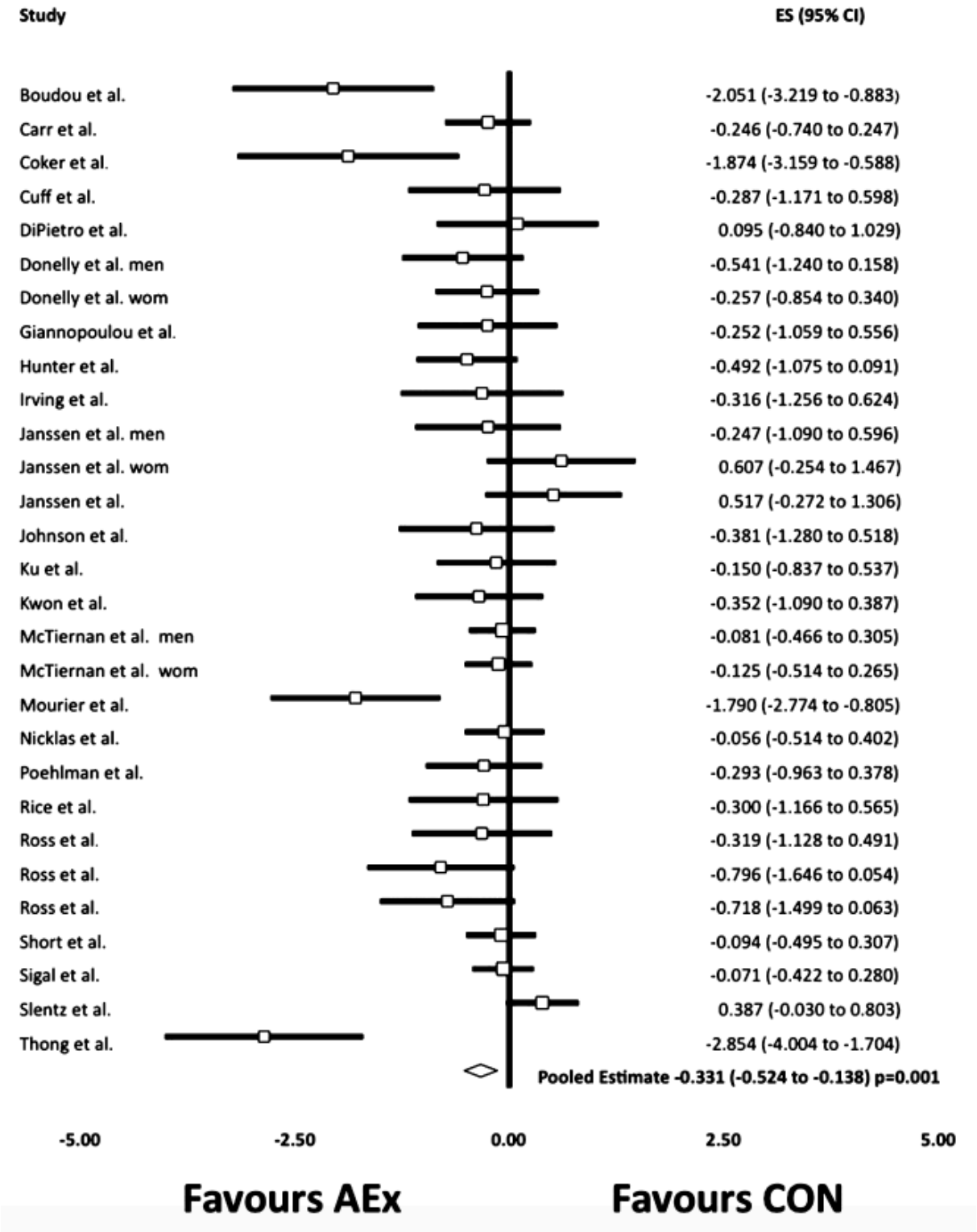


Adults | RCTs | Visceral adipose tissue change | Ismail et al (2012) | Varied aerobic exercise

Forest plot for aerobic exercise studies (n=29). Graph depicts effect size and 95% confidence interval for individual studies and the pooled estimate (Ismail et al 2012).

Please note – this figure shows the pooled estimate using a random effects model with one outlier study removed; effect direction and significance remains the same as that reported in the text and table above. No forest plot was available for the meta-analysis with all studies included. Appears that some studies are counted more than once (e.g. Ross et al) however Table 2 in Ismail et al (2012) suggests these are separate studies.

Figure 72 Meta-analysis of RCTs in adults – Varied aerobic exercise – Ismail et al 2012 – Visceral adipose tissue change



3.2.2 Meta-analyses of prospective cohort studies in adults

Nil

3.2.3 Individual RCTs in adults, not in meta-analyses

There were no RCTs in adults investigating aerobic activity and adiposity with more than 500 participants.

Eight RCTs with fewer than 500 participants were identified. These provided 11 results: eight reported inverse effects (four of which were significant), one reported a non-significant positive effect, and two reported no association.

Studies n<500: Nindl et al. 2010, Suter et al. 1992, Thomas et al. 1984, Williams et al. 1983, Wilmore et al. 1980, Carrasco et al. 2012, Meyers 2006 and Park et al. 2003.

3.2.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 87 Results of individual prospective cohort studies in adults – Aerobic recreational activity

Adults – Aerobic recreational activity					
Prospective cohort studies					
MD = mean difference; OR = odds ratio; RR = relative risk; MET = metabolic equivalent. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Littman et al. 2005 *Oja et al (2015)*	Per 5 MET hours per week *(female, BMI<25kg/m² at baseline)* 10 years	Beta coefficient	**-0.90 (-1.1, -0.7) lb** INV	7,944
		Per 5 MET hours per week *(male, BMI<25kg/m² at baseline)* 10 years	Beta coefficient	**-0.38 (-0.5, -0.2) lb** INV	7,556
		Per exercise session per week *(female, BMI<25kg/m² at baseline)* 10 years	Beta coefficient	**-0.76 (-0.9, -0.6) lb** INV	7,944
		Per exercise session per week *(male, BMI<25kg/m² at baseline)* 10 years	Beta coefficient	**-0.31 (-0.4, -0.2) lb** INV	7,556
	Fogelholm et al. 2000 *Summerbell et al (2009)*	Increase in physical activity index across study period 10 years	Beta coefficient	**-1.12 SE ±0.54 kg** p=0.04 INV	1,030
	Haapanen et al. 1997 *Summerbell et al (2009)*	Physically inactive all the time at baseline vs. physically active all the time *(female)* 10 years	MD	**0.3 SE ±0.3 kg** p=0.35 INV	2,695
		Physically inactive all the time at baseline vs. physically active all the time *(male)* 10 years	MD	**1.2 SE ±0.4 kg** p=0.001 INV	2,564
	Lusk et al. 2010 *Oja et al (2011)*	Per 30 minutes per day increase in cycling 16 years	MD	**-1.59 (-2.0, -1.08) kg/m²** INV	18,414
BMI change	Droyvold et al. 2004b *Summerbell et al (2009)*	Leisure time physical activity >8 times per week vs. never or less than once per week at baseline *(female)* 11 years	MD	**-0.18 (-0.32, -0.05) kg/m²** INV	9,357

	Droyvold et al. 2004a *Summerbell et al (2009)*	Leisure time physical activity >8 times per week vs. never or less than once per week at baseline *(male)* 11 years	Beta coefficient	**-0.075 (-0.191, 0.041) kg/m²** **INV**	6,749
	Wagner et al. 2001 *Summerbell et al (2009)*	>9 MET hours per week vs. <3 MET hours per week in leisure time physical activity 5 years	Regression coefficient	**-0.0186 SE ±0.0478 kg/m²** p=0.50 **INV**	8,069
		Walking or cycling to work (MET hours per week) 5 years	Regression coefficient	**-0.0059 SE ±0.0029 kg/m²** p=0.04 **INV**	8,069
Waist circumference	Berentzen et al. 2008 *Oja et al (2015)*	<2 hours per week of leisure time physical activity vs. moderate/high physical activity* *(female)* 10 years	Beta coefficient	**-0.04 (-1.54, 1.47) cm** **+VE**	2782
		<2 hours per week of leisure time physical activity vs. moderate/high physical activity* *(male)* 10 years	Beta coefficient	**0.20 (-1.12, 1.53) cm** **INV**	2026
Odds of weight gain	Mekary et al. 2009 *Oja et al (2015)*	Maintained >30 minutes aerobic activity per day across study period vs. those who maintained <30 minutes 8 years	OR	**0.68 (0.64, 0.73)** **INV**	46,754
		Increased to >30 minutes aerobic activity per day across study period vs. those who maintained <30 minutes 8 years	OR	**0.64 (0.60, 0.68)** **INV**	46,754
Odds of moderate weight gain	Blanck et al. 2007 *Summerbell et al (2009)*	0 MET hours per week of aerobic physical activity **vs.** >0 to 4 MET hours per week 7 years	OR	**1.14 (0.93, 1.40)** **INV**	18,583
		>18 MET hours per week of aerobic physical activity **vs.** >0 to 4 MET hours per week 7 years	OR	**1.04 (0.92, 1.17)** **+VE**	18,583
Odds of large weight gain		0 MET hours per week of aerobic physical activity **vs.** >0 to 4 MET hours per week 7 years	OR	**1.01 (0.82, 1.25)** **INV**	18,583
		>18 MET hours per week of aerobic physical activity **vs.** >0 to 4 MET hours per week 7 years	OR	**0.88 (0.77, 0.99)** **INV**	18,583
Risk of weight gain	Rissanen et al. 1991 *Summerbell et al (2009)*	Rarely participate in recreational aerobic activity vs. frequently *(females)* 5.7 years	RR	**1.6 (1.2, 2.2)** **INV**	12,669
		Rarely participate in recreational aerobic activity vs. frequently *(males)* 5.7 years	RR	**1.9 (1.5, 2.3)** **INV**	
Odds of obesity	Petersen et al. 2004 *Summerbell et al (2009)*	High leisure time physical activity vs. low at 2nd survey (outcome measured at 3rd survey) *(female)* 10 years	OR	**1.35 (0.83, 2.18)** **+VE**	3,653

		High leisure time physical activity vs. low at at 2nd survey (outcome measured at 3rd survey) *(male)* 10 years	OR	**1.93 (1.03, 3.60)** **+VE**	2,626
*Definitions as per Berentzen et al (2008): Moderate physical activity: more than 4 h/week of light physical activity or 2–4 h/week of more vigorous physical activity; High physical activity: more than 4 h/week of moderate physical activity or regular heavy exercise or competitive sports several times per week.					

Twelve publications (11 different study populations) in adults investigating aerobic activity and adiposity with more than 500 participants were identified. These provided 24 results across eight outcomes: weight change; BMI change; waist circumference; odds of weight gain; odds of moderate weight gain; odds of large weight gain; risk of weight gain; and odds of obesity. Twenty results reported inverse associations (with increased activity decreasing adiposity, and decreased activity increasing adiposity), of which 14 were statistically significant. Four results reported positive associations, of which one was statistically significant.

All studies assessed activity level through self reported questionnaires, surveys, or interviews and adjusted for a variety of potential confounders.

Berentzen et al (2008) identified a non-significant positive association between less than two hours of leisure time physical activity per week (relative to more than four hours) and waist circumference change in females, and a non-significant inverse association in males. The authors suggest that sports activities specifically may be a more important predictor of adiposity change than overall leisure time activity.

Peterson et al (2004) reported a 35% increased risk of obesity at the 3rd survey for females and 93% increased risk for males for participants reporting the highest levels of leisure time physical activity at the 2nd survey (relative to the lowest). The authors reported that cross sectional analysis of the cohort data showed significant inverse associations for both genders (for levels of leisure time physical activity at follow up and risk of obesity). The authors noted that the majority of participants changed their level of leisure time physical activity across the course of the study.

Two further prospective cohort studies in adults with more than 500 participants were identified (Williamson et al 1993 and Fortier et al 2002); however it was not possible to access these. The results, as per the review, reported no significant associations.

Six prospective cohort studies with fewer than 500 participants were identified. These provided 10 additional results: four reported inverse associations (one of which was statistically significant) and six reported no association.
Studies n<500: Sammel et al. 2003, Klesges et al. 1992a, Klesges et al. 1992b, Eck et al. 1995, Chakravarty et al. 2008 and Delvaux et al. 1999.

3.2.5 Walking as a sub-category of recreational aerobic activity

Walking – Meta-analyses

As described in **Section 2**, there were four reviews (with meta-analyses) related specifically to walking as an aerobic activity. The evidence for walking is presented below and may be thought of as a distinct sub-category of aerobic recreational physical activity in general.

Table 88 Meta-analyses of RCTs in adults – Walking

Adults – Walking (as a sub category of aerobic recreational activity)					
Meta-analyses of RCTs					
WMD = weighted mean difference; MD = mean difference; SD = standard deviation. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Weight *	Murphy et al (2007)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-0.95 SD ±0.61 kg** p<0.001 **INV**	Studies=18; n=738 I^2=not reported
Weight change	Gao et al (2016)	Walking intervention vs. habitual lifestyle 12–48 weeks	WMD	**-1.14 (-1.86, -0.42) kg** **INV**	Studies=8; n=853 I^2=20%
	Murtagh et al (2015)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-1.37 (-1.75, -1.00) kg** **INV**	Studies=25; n=1,275 I^2=66%
BMI *	Murphy et al (2007)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-0.28 SD ±0.20 kg/m²** p=0.015 **INV**	Studies=16; n=838 I^2=not reported
BMI change	Gao et al (2016)	Walking intervention vs. habitual lifestyle 12–48 weeks	WMD	**-0.33 (-0.62, -0.04) kg/m²** **INV**	Studies=6; n=701 I^2=11%
	Hanson et al (2015)	Walking intervention vs. habitual lifestyle 12–26 weeks	MD	**-0.71 (-1.19, -0.23) kg/m²** **INV**	Studies=12; n=451 I^2=0%
	Murtagh et al (2015)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-0.53 (-0.72, -0.35) kg/m²** **INV**	Studies=23; n=1,201 I^2=70%
% body fat change	Gao et al (2016)	Walking intervention vs. habitual lifestyle 12–48 weeks	WMD	**-2.36 (-3.21, -1.52) %** **INV**	Studies=3; n=444 I^2=0%
	Hanson et al (2015)	Walking intervention vs. habitual lifestyle 12–26 weeks	MD	**-1.31 (-2.10, -0.52) %** **INV**	Studies=7; n=328 I^2=0%
	Murtagh et al (2015)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-1.22 (-1.70, -0.73) %** **INV**	Studies=14; n=719 I^2=68%
% body fat *	Murphy et al (2007)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-0.63 SD ±0.66 %** p=0.035 **INV**	Studies=12; n=604 I^2=not reported
Waist circumference	Hanson et al (2015)	Walking intervention vs. habitual lifestyle 12–26 weeks	MD	**-3.55 (-8.08, 0.98) cm** **INV**	Studies=2; n=35 I^2=0%
	Murtagh et al (2015)	Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-1.51 (-2.34, -0.68) cm** **INV**	Studies=11; n=574 I^2=38%
Waist-hip ratio		Walking intervention vs. habitual lifestyle 8–52 weeks	WMD	**-0.01 (-0.02, 0.00)** **INV**	Studies=14; n=706 I^2=60%
*Unclear if result is difference in change between groups, or difference in attained measure between groups.					

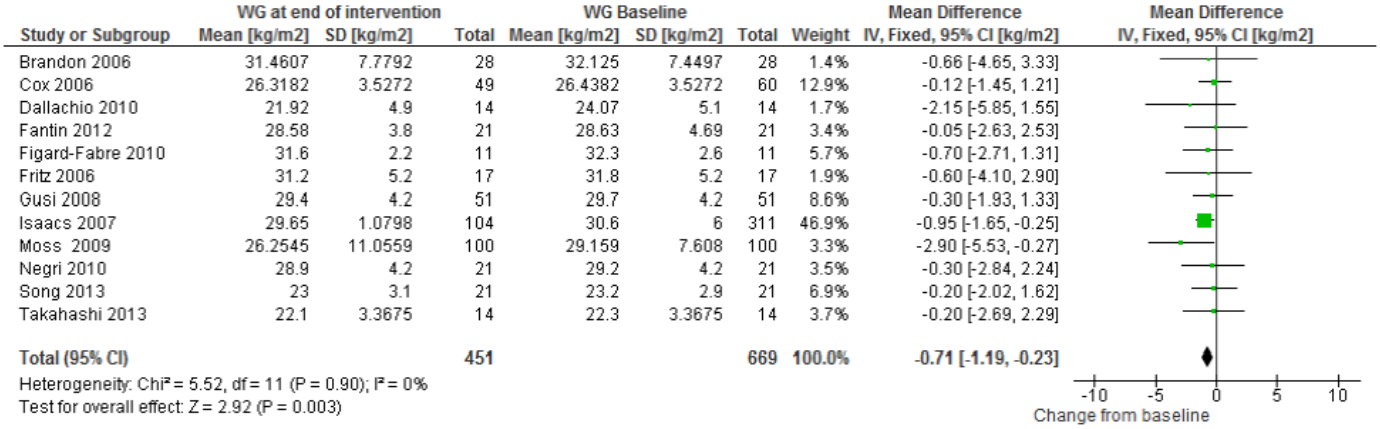
Four reviews conducted meta-analyses of RCTs in adults investigating walking interventions and adiposity. These provided 14 results across five outcomes: weight change; BMI change; percentage body fat change; waist circumference; and waist-hip ratio. It was unclear if the outcomes from the Murphy et al (2007) review were difference in attained measures between groups or difference in change between groups. All fourteen results reported inverse effects, with the walking intervention reducing adiposity, of which 12 were statistically significant. The waist-hip ratio result from Murtagh et al (2015) appears borderline significant but is reported in the review as non-significant.

The interventions across all the included studies ranged from 20 to 65 minutes per session, two to seven times per week.

The meta-analysis by Gao et al (2016) was conducted solely with studies of women. Hanson et al (2015) included eight studies of all-female samples, and five other studies in patient groups (type 2 diabetes mellitus, cardiovascular disease risk factors, and people with learning disabilities).

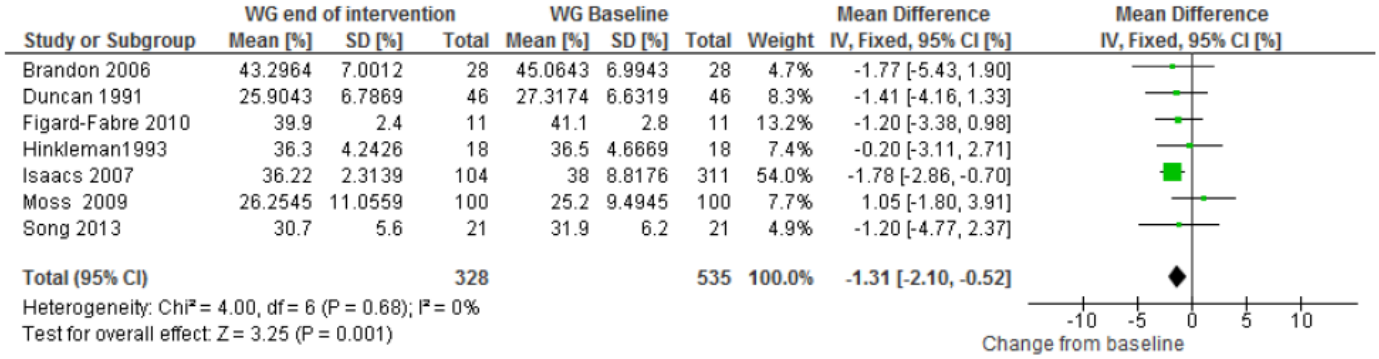
Adults | RCTs | BMI change | Hanson et al (2015) | Walking

Figure 73 Meta-analysis of RCTs in adults – Walking – Hanson and Jones 2015 – BMI change



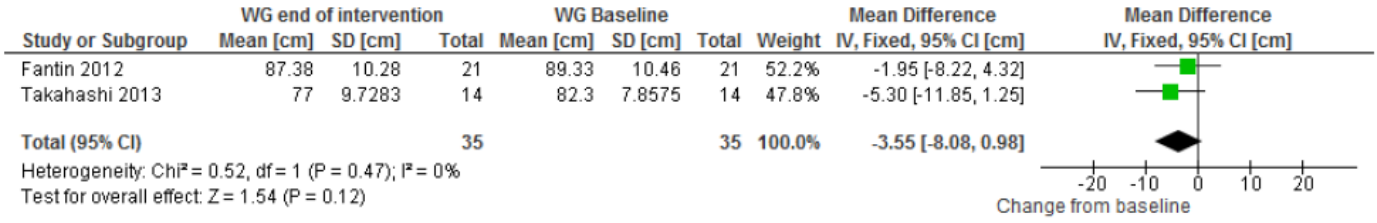
Adults | RCTs | % body fat | Hanson et al (2015) | Walking

Figure 74 Meta-analysis of RCTs in adults – Walking – Hanson and Jones 2015 – Percentage body fat



Adults | RCTs | Waist circumference | Hanson et al (2015) | Walking

Figure 75 Meta-analysis of RCTs in adults – Walking – Hanson and Jones 2015 – Waist circumference



Walking – studies not included in any meta-analyses

None identified.

3.3 Strength Training

3.3.1 Meta-analyses of RCTS

Table 89 Meta-analyses of RCTs in adults – Strength training

Adults – Strength training recreational activity					
Meta-analyses of RCTs					
SMD=standardised mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Visceral adipose tissue change	Ismail et al (2012)	Resistance exercise therapy programme vs. control 12 weeks–2 years	SMD	**0.09 (-0.17, 0.36)** Units=unclear **+VE**	Studies=13; n=950 I^2=62%

One meta-analysis of RCTs in adults investigating strength training and adiposity was identified. This reported a non-significant association between strength training interventions and change in visceral adipose tissue. The definition of resistance exercise used in the review was not clear but the majority of the included studies had interventions using weight machines commonly found in gyms with a progressive element to the training (increased repetitions or weight over the course of the programme).

No RCTs or prospective cohort studies not included in meta-analyses were identified.

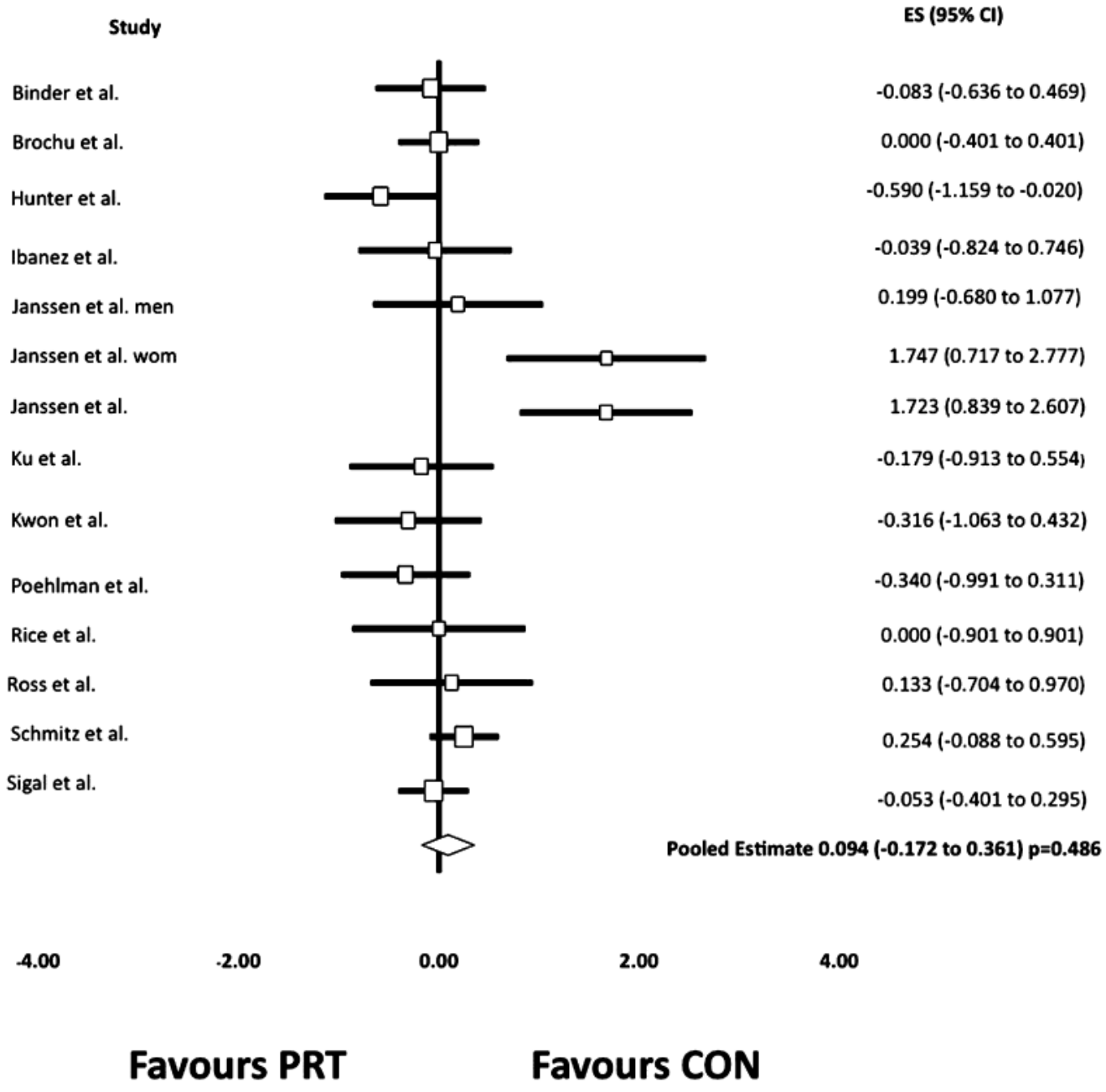
The corresponding forest plot is presented below.

Adults | RCTs | Visceral adipose tissue change | Ismail et al (2012) | Strength training

Forest plot for progressive resistance therapy studies (n=14). Graph depicts effect size and 95% confidence intervals for individual studies and the pooled estimate (Ismail et al 2012).

Please note – appears that 5th and 6th estimates on forest plots (Janssen et al. men and Janssen et al. women) are from same study population, therefore have listed studies=13 in results table of this literature review. Ismail et al (2012) report studies=14.

Figure 76 Meta-analysis of RCTs in adults – Strength training – Ismail et al 2012 – Visceral adipose tissue change



4. Possible mechanisms

As per preliminary discussions (June 2016):

- Energy expenditure leads to negative energy balance, assuming insufficient compensation by energy intake.
- Increased fat oxidation as a result of insulin sensitivity.
- Influences on appetite control: Increasing satiety sensitivity; altering food choice; modifying hedonic response to food.

5. Summary of evidence

5.1 Children

- **Total physical activity**: Only individual prospective cohort studies (not in meta-analyses) were identified. Eight studies provided 24 results: 17 reported inverse associations, of which five were statistically significant. Only one study measured total physical activity using accelerometry. For the prospective cohort studies with fewer than 500 participants, five reported significant inverse associations and the remaining reported non-significant associations.
- **Aerobic recreational activity**: The evidence for aerobic recreational physical activity and adiposity in children is largely consistent in reporting inverse relationships (decreasing physical activity Increases adiposity, and vice versa). Three published reviews conducted meta-analyses of RCTs (five results); three results reported significant inverse effects. The remaining two meta-analyses, both investigating active video gaming, reported non-significant effects (one inverse, one positive). The studies included in the meta-analyses of active video gaming appeared low quality. The four prospective cohort studies with more than 500 participants reported seven out of nine results as inverse associations (four of which were statistically significant). For the nine prospective cohort studies with fewer than 500 participants, mixed results were reported but the majority reported no association.
- **Strength training**: A single RCT was identified investigating strength training and adiposity in children. This was conducted in a small group of boys and reported a significant positive effect of the intervention relative to control group.

5.2 Adults

- **Total physical activity**: Only individual prospective cohort studies (not in meta-analyses) were identified. Eight studies provided 22 results: 20 reported inverse associations, of which ten were statistically significant. All studies measured total physical activity through self report. For the prospective cohort studies with fewer than 500 participants, eight out of 14 results reported inverse associations (five significant) and six reported no association.
- **Aerobic recreational activity**: The evidence for aerobic recreational physical activity and adiposity in adults is largely consistent in reporting inverse relationships. Five published review conducted meta-analyses of RCTS (nine results); eight results reported inverse effects (five were significant). In the 12 prospective cohort studies not in any meta-analyses with more than 500 participants, 20 out of 24 results reported inverse associations (of which 14 were statistically significant). In the smaller studies (fewer than 500 participants) the results were less consistent, with four out of ten reporting inverse associations and six out of ten reporting no association.
    - **Walking**: All fourteen meta-analyses of RCTs investigating walking and adiposity reported inverse effects, of which 12 were statistically significant.
- **Strength training**: The meta-analysis of 13 RCTs investigating strength training and change in visceral adipose tissue reported a non-significant positive effect. There were no individual studies identified.

5. Physical Inactivity

5.1 Sedentary behaviours

1. Evidence identified for 2017 update

Table 90 Published reviews identified for the 2017 update – Sedentary time

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	van Uffelen et al. 2010a [+]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	Y	
Supplementary literature search August 2016	1	Azevedo et al. 2016 [++]

Notes on the evidence:

- The 2007 Expert Report and the NICE (2014) report both considered 'sedentary behaviours' in general as an exposure with 'screen time' as a sub-category of sedentary behaviour. Both reports made separate judgements for 'sedentary time' and 'screen time'.
- The evidence base for screen time as an exposure is substantial. Results from individual studies not included in meta-analyses identified in the four published reviews above which pertain specifically to screen time are reported within the 'screen time' section of this literature review.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=1,000 participants, so only studies with more than 1,000 participants are reported in detail here.

2. Children

2.1 Meta-analyses of RCTS in Children

Table 91 Meta-analyses of RCTs in children – Sedentary behaviours

Children					
Meta-analyses of RCTs					
SMD = standardised mean difference; MD = mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
BMI or BMI z score change	Azevedo et al (2016)	Intervention to reduce sedentary behaviours vs. no intervention Majority <6 months	SMD	**-0.060 (-0.098, -0.022)** **+VE**	Studies=71; n=29,650 I^2=50%
BMI change		Intervention to reduce sedentary behaviours vs. no intervention Majority <6 months	MD	**-0.158 (-0.238, -0.077) kg/m^2** **+VE**	Studies=51; n=18,012 I^2=88%

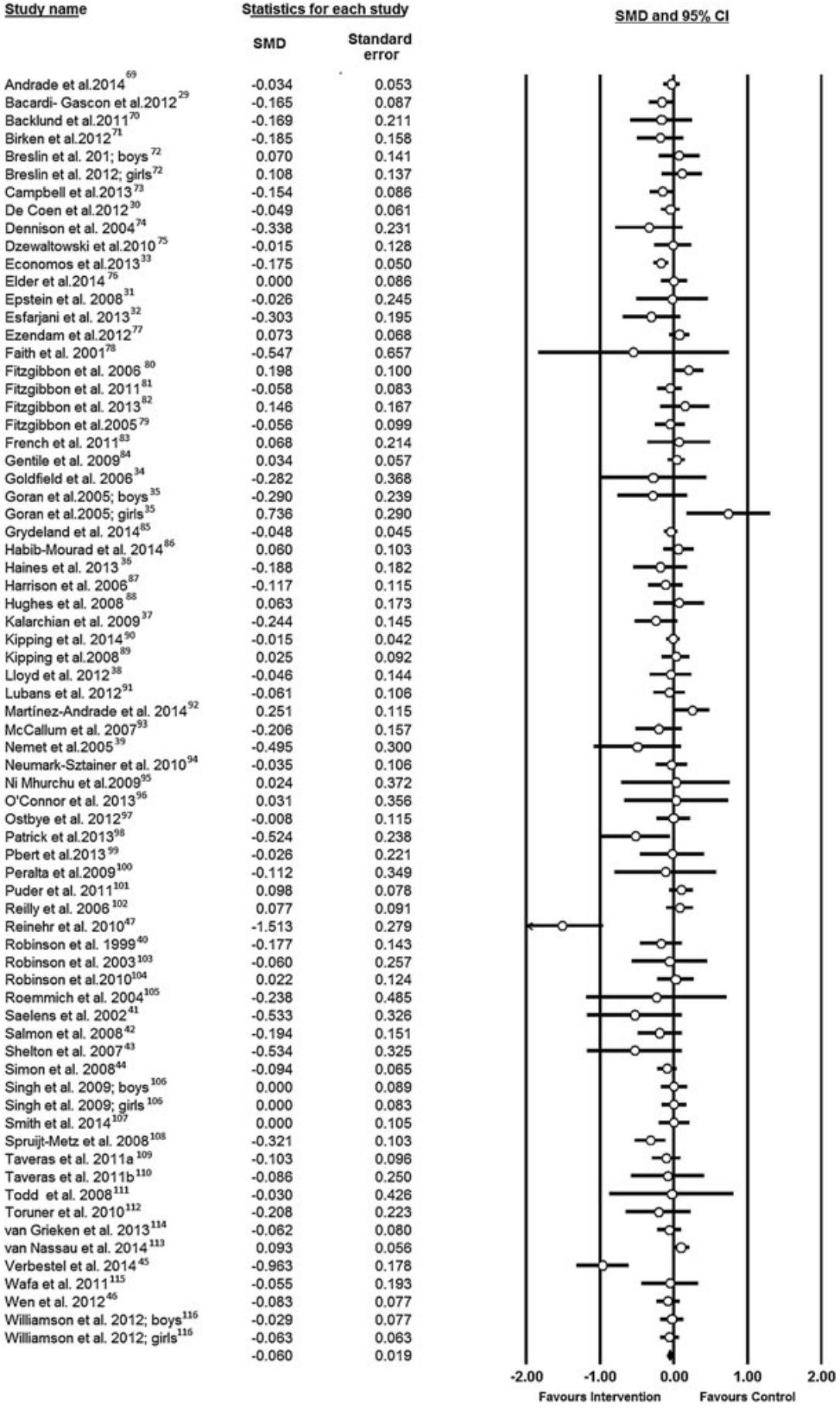
Two meta-analyses of RCTs in children were reported by one review. Both meta-analyses reported significant, positive effects (interventions to reduce sedentary behaviours led to a reduction in adiposity measures). The majority of the included studies were conducted in children aged five to 12 years old and lasted less than 6 months. Eight of the 71 studies were in participants living with overweight or obesity.

Stratifying for age group (0–5 years, 5–12 years, 12–17 years), weight status at baseline (mixed weight, overweight or obese), intervention type (focus on sedentary behaviour only, including physical activity, including other behaviours), setting (educational, non-education, combined), duration (less than six months, more than six months), or risk of bias (low, high, unclear) did not affect the direction of the overall effect (remained positive) but some results did lose significance.

The authors noted that the corresponding funnel plot was asymmetric and results from Egger's test (intercept = -0.771, $p<0.05$) showed that there was publication bias.

Children | RCTs | BMI or BMI z score change | Azevedo et al (2016) | Reduced sedentary behaviour

Figure 77 Meta-analysis of RCTs in children – Sedentary behaviour – Azevedo et al 2016 – BMI or BMI z score change



2.2 Meta-analyses of prospective cohort studies

Nil

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Nil

3. Adults

3.1 Meta-analysis of RCTs in adults

Nil

3.2 Meta-analyses of prospective cohort studies in adults

Nil

3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 92 Results of individual prospective cohort studies in adults – Sedentary behaviours

Adults					
Prospective cohort studies not included in meta-analyses					
MD=mean difference; OR=odds ratio; RR=relative risk; HR=hazard ratio. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	De Cocker et al. 2010 *USDA DGAC (2015)*	Hours per weekday spent sitting down at baseline 6 years	Beta coefficient	**0.030 (-0.051, 0.112)** Units of weight unclear **+VE**	5,562
		Change in hours per weekday spent sitting down 6 years	Beta coefficient	**-0.005 (-0.062, 0.052)** Units of weight unclear **Unclear direction***	
% weight change	van Uffelen et al. 2010b *USDA DGAC (2015)*	Hours per day spent sitting down over 3 years (2001–2004) 6 years	Beta coefficient	**0.64 (-0.20, 1.48) %** **+VE**	8,233
		Hours per day spent sitting down over 3 years (2004–2007) 6 years	Beta coefficient	**-0.51 (-1.35, 0.33) %** **INV**	
BMI (attained)	Andersen et al. 2007 *Van Uffelen et al (2010a)*	Quartiles of leisure time physical activity at baseline relative to Q1 ("sedentary") *(females)* 15 years	Q2: **24.9 SD ±4.6** p>0.05 Q3: **24.9 SD ±4.5** p>0.05 Q4: **24.6 SD ±4.1** p>0.05 **NIL**		7708
		Quartiles of leisure time physical activity at baseline relative to Q1 ("sedentary") *(males)* 15 years	Q2: **25.9 SD ±3.8** p>0.05 Q3: **26.0 SD ±3.9** p>0.05 Q4: **25.8 SD ±3.6** p>0.05 **NIL**		6506
		Transition between quartiles of leisure time physical activity (Q1 = "sedentary") across study period relative to no change *(females)* 15 years	Becoming more sedentary: **26.0 SD ±5.0** p>0.05 Becoming less sedentary: **25.5 SD ±4.4** p>0.05 **+VE**		4,124
		Transition between quartiles of leisure time physical activity (Q1 = "sedentary") across study period relative to no change *(males)* 15 years	Becoming more sedentary: **27.0 SD ±4.4** p>0.05 Becoming less sedentary: **26.5 SD ±3.7** p>0.05 **+VE**		2,946
BMI change	Mortensen et al. 2006 *USDA DGAC (2015)*	Categorised as sedentary at baseline and follow up vs. non-sedentary at baseline and follow up	Beta coefficient	**0.09 (0.05, 0.13) kg/m^2** **+VE**	2,070

		8 years			
		Categorised as becoming non-sedentary across study period vs. non-sedentary at baseline and follow up 8 years	Beta coefficient	**-0.04 (-0.08, 0.00) kg/m^2 per year** **+VE**	2,070
		Categorised as becoming sedentary across study period vs. non-sedentary at baseline and follow up 8 years	Beta coefficient	**0.06 (0.03, 0.09) kg/m^2 per year** **+VE**	2,070
	Pinto Pereira et al. 2013 *USDA DGAC (2015)*	Per hour per day increase in sitting at work 5 years	MD	**-0.01 (-0.04, 0.02) kg/m^2** **INV**	6,562
Odds of weight gain	Ball et al. 2002 *Summerbell et al (2009)*	>52 hours per week sitting time vs. <33 hours 4 years	OR	**0.80 (0.70, 0.91)** **INV**	8,726
	Blanck et al. 2007 *Summerbell et al (2009)* and *USDA DGAC (2015)*	>6 hours per day of non-occupational sedentary behaviour vs. <3 hours *(female)* 7 years	OR	**1.06 (0.87, 1.30)** **+VE**	18,583
Risk of obesity	Hu et al. 2003 *Van Uffelen et al (2010a)* and *Summerbell et al (2009)*	2-5 hours per week sitting at work or away from home vs. 0-1 hours 6 years	RR	**1.02 (0.89, 1.18)** **+VE**	50,277
		>40 hours per week sitting at work or away from home vs. 0-1 hours 6 years	RR	**1.25 (1.02, 1.54)** **+VE**	50,277
		2-5 hours per week sitting at home vs. 0-1 hours 6 years	RR	**0.99 (0.83, 1.18)** **INV**	50,277
		>40 hours per week sitting at home vs. 0-1 hours 6 years	RR	**1.11 (0.85, 1.45)** **+VE**	50,277
	Nunez-Cordoba et al. 2013 *USDA DGAC (2015)*	Annual distance travelled in motor vehicles >20,000 km vs. <10,000 km 6.4 years	HR	**1.00 (0.85, 1.17)** **NIL**	6808
	Pulsford et al. 2013 *USDA DGAC 2015*	>40 hours sedentary time at work per week vs. 0-6 hours 6 years	OR	**1.10 (0.59, 1.96)** **+VE**	10,308
		>17 hours non-TV leisure time per week vs. 0-6 hours 6 years	OR	**0.88 (0.40, 1.95)** **INV**	
*See note in text regarding direction of association.					

Ten prospective cohort studies in adults with more than 1,000 participants investigating sedentary behaviours and adiposity were identified in three reviews. These provided 21 results across five outcomes: weight change; percentage weight change; BMI (attained and change); odds of weight gain; and risk of obesity. Twelve results reported positive associations (increased sedentary behaviours associated with increased adiposity) of which four were statistically significant; five results reported inverse associations, of which one was statistically significant; and three results reported no association.

One result (DeCocker et al 2010) reported a result with respect to change in hours per weekday spent sitting down; however it was not clear if this was respect to increased or decreased time and so it is not clear if the association reported is positive or inverse. It was also unclear what units were used to report change in weight.

The exposure varied between studies but broadly included time spent sitting at work, home, or in a motor vehicle. All the studies measured exposure through participants' self reports.

Hu et al (2003), Ball et al (2002), Blanck et al (2007), DeCocker et al (2010), and Van Uffelen (2010b) were in all-female cohorts.

Four other prospective cohort studies in adults were identified with fewer than 1,000 participants. These provided 13 results: 11 reported no association between sedentary behaviours and adiposity and two reported significant positive associations.
Studies n<1000: Sammel et al. 2003, Ekelund et al. 2008, Saunders et al. 2013 and Sugiyama et al. 2013.

4. Possible mechanisms

From preliminary discussions (June 2016):

- Lack of influences on appetite control, hormonal circulation, and oxidation effects as outlined in physical activity.
- Lack of energy balance offset from overconsumption.

5. Summary of evidence

5.1 Children

Two large meta-analyses from one review of RCTs in children reported significant, positive effects of interventions designed to reduce sedentary behaviours leading to reductions in adiposity. The direction of effect was maintained when stratified for a variety of categories. No individual RCTs or prospective cohort studies were identified as the majority of evidence in children related specifically to screen time.

5.2 Adults

No meta-analyses of RCTs of prospective cohort studies in adults were identified. Ten prospective cohort studies with more than 1,000 participants reported 21 results: 12 reported positive associations (four were statistically significant), five reported inverse associations (one statistically significant), and three reported no association. For one results direction of association was unclear. Four additional prospective cohort studies with fewer than 1,000 participants were also identified and provided a less clear picture: two results reported significant, positive associations and 11 results reported no association.

5.2 Screen time

1. Evidence identified for 2017 update

Table 93 Published reviews identified for the 2017 update – Screen time

Source	No. of reviews	Authors [quality]
NICE (2014) report	5	Costigan et al. 2013 [++]; LeBlanc et al. 2012 [++]; Tremblay et al. 2011 [++]; Wahi et al. 2011 [++]; U.S Department of Agriculture Nutrition Evidence Library 2010a [++]
USDA DGAC (2015) scientific report [++]	Y	
Supplementary literature search August 2016	Nil	-
Relevant published reviews from 'sedentary behaviour' section	3	van Uffelen et al. 2010a [+]; Summerbell et al. 2009 [++]; Marshall et al. 2004 [+]

Notes on the evidence:

- The 2007 Expert Report and the NICE (2014) report both considered 'sedentary time' in general as an exposure with 'screen time' as a sub-category of sedentary behaviour. Both reports made separate judgements for 'sedentary time' and 'screen time'.
- The evidence base for screen time as an exposure is substantial and reported separately to sedentary time in general in this literature review.
- Results from individual studies not included in meta-analyses that pertain specifically to screen time (rather than sedentary time in general) identified from the published reviews in the sedentary time section are included in the results here. Those reviews are: Van Uffelen et al (2010a) and Summerbell et al (2009).
    - For reference, of the studies not included in meta-analyses identified in Azevedo et al (2016), none specifically pertained to screen time as an exposure. [Azevedo et al (2016) is a review that is included in the sedentary time exposure section.]
- Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.
- Included within USDA (2010) and Summerbell et al (2009), one additional published review was identified: Marshall et al (2004) (quality rating: [+]).
    - Summerbell et al (2009) report that the eight comparisons in the Marshall et al (2004) meta-analysis comprise six study populations, of which two are cross sectional analyses reported two years apart. Summerbell et al (2009) reports separately the results of the four prospective cohort studies considered relevant to their scope– as these studies are encompassed within the meta-analysis result, their individual results are not reported here.
- Due to the large number of individual studies identified for this exposure, an additional criterion has been imposed (see protocol in the **Appendix**) of n=1,000, so only studies with more than 1,000 participants are reported in detail here.

2. Children

2.1 Meta-analysis of RCTs in children

Table 94 Meta-analyses of RCTs in children – Screen time

Children					
Meta-analyses of RCTs					
MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
BMI change	Tremblay et al (2011)	Intervention to decrease screen time vs. no intervention Duration not reported	MD	**-0.89 (-1.67, -0.11) kg/m^2** **+VE**	Studies=4; n=326 I^2=46%
	Wahi et al (2011)	Intervention to decrease screen time vs. no intervention 1.5–24 months	MD	**-0.10 (-0.28, 0.09) kg/m^2** **+VE**	Studies=6; n=708 I^2=38%

Two reviews conducted meta-analyses of RCTs in children investigating the effect of interventions to decrease screen time on BMI change. Both reported a positive effect in the predicted direction (reduced screen time leading to reductions in adiposity measures), with one reaching statistical significance. There was no overlap in studies between the two meta-analyses.

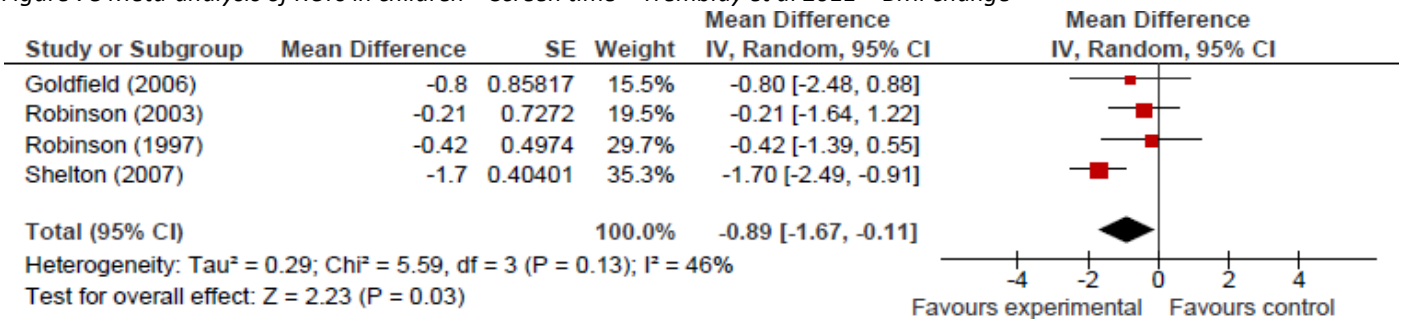
Mean age at baseline across both meta-analyses ranged from 4 to 11 years old. The majority of interventions took place within a school setting and focused on reducing time spent sitting watching television. One study in Wahi et al (2011) included physical activity as a co-intervention. One study in Tremblay et al (2011) also focused on reducing video game playing screen time alongside reducing television screen time.

The forest plots corresponding to the above meta-analyses are presented below.

Children | RCTs | BMI change | Tremblay et al (2011) | Decreased screen time

Meta-analysis of randomized controlled studies examining decreases in sedentary behaviour and effect on body mass index (Tremblay et al 2011).

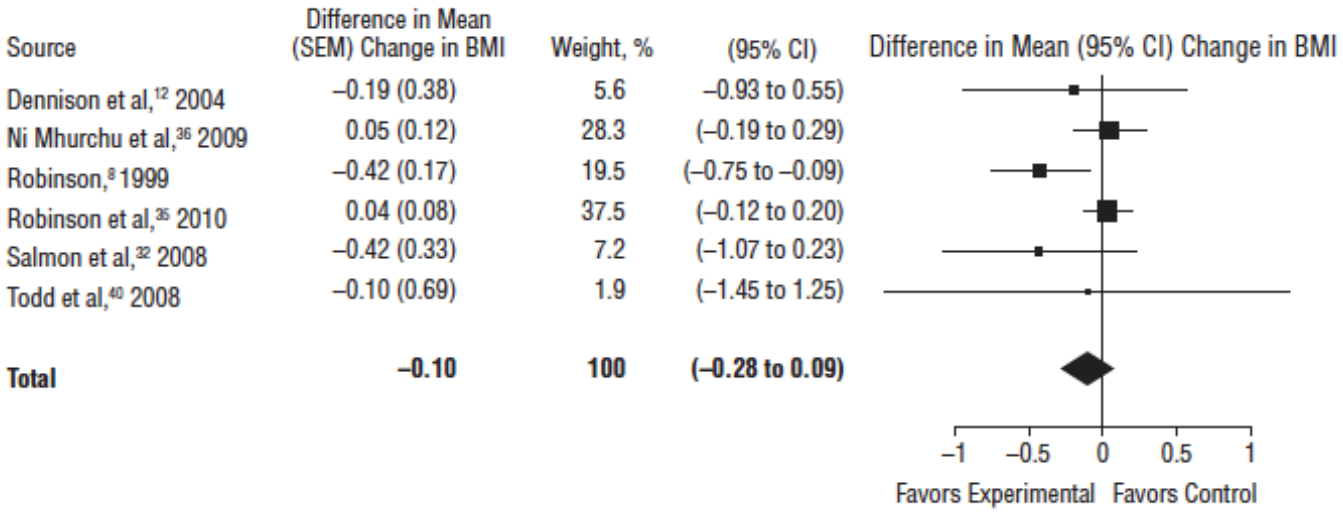
Figure 78 Meta-analysis of RCTs in children – Screen time – Tremblay et al 2011 – BMI change



Children | RCTs | BMI change | Wahi et al (2011) | Decreased screen time

Forest plot of primary outcome, unadjusted difference in mean change in body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared). Heterogeneity, τ^2=0.02; $\chi^{2/5}$=8.05 (**P**=.15); I^2=38%. Test for overall effect, **Z**=1.0 (**P**=.32). CI indicates confidence interval (Wahi et al 2011).

Figure 79 Meta-analysis of RCTs in children – Screen time – Wahi et al 2011 – BMI change



2.2 Meta-analyses of prospective cohort studies in children

Table 95 Meta-analyses of prospective cohort studies in children – Screen time

Children					
Meta-analyses of prospective cohort studies					
r_c=fully corrected sample-weighted mean effect size. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Intervention description***	***Results***		
Body fatness	Marshall et al (2004)	Increased time spent watching TV Unclear follow up period	r_c	**0.053 (0.030, 0.052)** Units=not reported **+VE**	Studies=6; n=15,797 Q=13.1

One published review conducted a meta-analysis of prospective cohort studies in children (this published review was identified within Summerbell et al 2009 and in USDA 2010). The result reported a positive association for increased time spent watching TV and increased 'body fatness' (outcome measurement was not clear). The result was statistically significant but the effect size was small and may not be clinically meaningful.

The review reports eight comparisons used in meta-analysis, although it is not clear which studies are included. Summerbell et al (2009) report that the eight comparisons comprise six study populations, of which two are cross sectional analyses reported two years apart.

There was no forest plot to accompany this meta-analysis.

2.3 Individual RCTs in children, not in meta-analyses

There are four RCTs in children not included in meta-analyses identified as part of the reviews. All had fewer than 1,000 participants. Two reported inverse effects and two reported no effects.
Studies n<1000: Epstein et al. 1995, Epstein et al. 2008, Epstein et al. 2000 and Kipping et al. 2008.

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 96 Results of individual prospective cohort studies in children – Screen time

Children					
Prospective cohort studies					
SE = standard error; SEM = standard error of the mean; r = correlation coefficient; OR = odds ratio; NS = not significant. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
BMI z score change	Viner et al. 2006 *Costigan et al (2013)* and *USDA DGAC (2015)*	Hours of screen time per day at baseline 14 years	Beta coefficient	**0.15 (0.03, 0.27)** p=0.01 **+VE**	4,373
	Borradaile et al. 2008 *Tremblay et al (2011)*	Change in daily sedentary activity, per 10 hours per day 2 years	Regression coefficient	**-0.01 SE ±0.02** p=0.35 **INV**	1,092
	Hesketh et al. 2009 *Tremblay et al (2011)*	Total screen time 3 years	Beta coefficient	**0.003 (-0.001, 0.01)** p=0.06 **+VE**	1,234
	Zimmerman et al. 2010 *Le Blanc et al (2012)*	Entertainment TV viewing at baseline, hours per day *(age 0-6 years at baseline)* 5 years	Coefficient	**0.11 (0.00, 0.21)** p<0.05 **+VE**	1,118
		Educational TV viewing at baseline, hours per day *(age 0-6 years at baseline)* 5 years	Coefficient	**0.03 (-0.08, 0.13)** **+VE**	
		Entertainment TV viewing at baseline, hours per day *(age 7-14 years at baseline)* 5 years	Coefficient	**-0.03 (-0.10, 0.04)** **INV**	836*
		Educational TV viewing at baseline, hours per day *(age 7-14 years at baseline)* 5 years	Coefficient	**-0.01 (-0.11, 0.10)** **INV**	
BMI z score (attained)	Bhargava et al. 2008 *Tremblay et al (2011)*	(Natural log of) TV watching minutes per day at baseline 4 years	Coefficient	**0.032 SE ±0.006** p<0.05 **+VE**	7,635
BMI percentile change	Kaur et al. 2003 *Tremblay et al (2011)* and *Summerbell et al (2009)*	Hours of TV watched per day at baseline 3 years	Regression coefficient	**0.47 SE ±0.21** p=0.02 **+VE**	2,223
BMI acceleration	Danner 2008 *Trembaly et al (2011)*	Hours spent watching TV at baseline 6 years	Coefficient	**0.0016 SE ±0.0002** p<0.001 **+VE**	7,334
BMI change	Berkey et al. 2003 *Tremblay et al (2011)*	Per hour increase of TV and video games per day *(girls)* 1 year	Beta coefficient	**0.031 (0.005, 0.057) kg/m^2** **+VE**	6,767
		Per hour increase of TV and video games per day *(boys)* 1 year	Beta coefficient	**-0.003 (-0.033, 0.026) kg/m^2** **INV**	5,120
BMI change (from age 9)	Henderson 2007 *Trembaly et al (2011)*	Per additional hour of TV viewing at baseline *(black girls)* 1–4 years	Beta coefficient	**0.00 SEM ±0.01** p=0.842 **NIL**	2,379

		Per additional hour of TV viewing at baseline *(white girls)* 1–4 years	Beta coefficient	**0.03 SEM ±0.01** p=0.005 **+VE**	
BMI change (from age 14)		Per additional hour of TV viewing at baseline years *(black girls)* 1–5 years	Beta coefficient	**0.00 SEM ±0.01** p=0.600 **NIL**	
		Per additional hour of TV viewing at baseline *(white girls)* 1–5 years	Beta coefficient	**-0.15 SEM ±0.01** p=0.143 **INV**	
BMI change per year	Parsons et al. 2008 *USDA DGAC (2015)*	TV viewing frequency "often" vs. "sometimes" at aged 11 years *(girls)* 22 years	Regression coefficient	**0.012 SE ±0.007** p>0.05 **+VE**	11,301
		TV viewing frequency "often" vs. "sometimes" at aged 11 years *(boys)* 22 years	Regression coefficient	**0.002 SE ±0.006** p>0.05 **+VE**	
		TV viewing frequency "often" vs. "sometimes" at aged 16 years *(girls)* 17 years	Regression coefficient	**0.013 SE ±0.005** p=0.009 **+VE**	
		TV viewing frequency "often" vs. "sometimes" at aged 16 years *(boys)* 17 years	Regression coefficient	**0.011 SE ±0.004** p=0.006 **+VE**	
BMI (attained)		TV viewing frequency "often" vs. "sometimes" at aged 11 years *(girls)* 22 years	Regression coefficient	**0.36 SE ±0.16** p=0.02 **+VE**	
		TV viewing frequency "often" vs. "sometimes" at aged 11 years *(boys)* 22 years	Regression coefficient	**0.11 SE ±0.13** p>0.05 **+VE**	
		TV viewing frequency "often" vs. "sometimes" at aged 16 years *(girls)* 17 years	Regression coefficient	**0.28 SE ±0.12** p=0.02 **+VE**	
		TV viewing frequency "often" vs. "sometimes" at aged 16 years *(boys)* 17 years	Regression coefficient	**0.12 SE ±0.10** p>0.05 **+VE**	
	Hancox et al. 2006 *Tremblay et al (2011)* and *Summerbell et al (2009)*	Mean TV viewing reported at preceding annual follow ups 12 years	r	**0.1** p=0.002 **+VE**	1,037
	Hesketh et al. 2007 *Tremblay et al (2011)*	Per additional hour per week of TV viewing at baseline 3 years	Beta coefficient	**0.02 (0.01, 0.02)** **+VE**	1,151
Odds of excess weight gain	O'Loughlin et al. 2000 *Summerbell et al (2009)*	Playing video games every day 1 year	OR	Girls: **2.48 (1.04, 5.98)** **+VE** Boys: **Not reported (NS)** **NIL**	2,318
Odds of overweight or obesity	Hesketh et al. 2007 *Tremblay et al (2011)*	Per additional hour per week of TV viewing 3 years	OR	**1.03 (1.02, 1.05)** **+VE**	1,151
Odds of overweight	Mamun et al. 2013 *USDA DGAC (2015)*	>3 hours per day of TV viewing at baseline and follow up vs. <3 hours at baseline and follow up 7 years	OR	**1.09 (0.81, 1.45)** **+VE**	2,439
		Increase from <3 hours per day of TV viewing at baseline to >3	OR	**1.09 (0.76, 1.57)** **+VE**	2,439

		hours per day at follow up vs. <3 hours at baseline and follow up 7 years			
		Decrease from >3 hours per day of TV viewing at baseline to <3 hours per day at follow up vs. <3 hours at baseline and follow up 7 years	OR	**0.72 (0.53, 0.97)** **+VE**	2,439
Odds of obesity	Mamun et al. 2013 *USDA DGAC (2015)*	>3 hours per day of TV viewing at baseline and follow up vs. <3 hours at baseline and follow up 7 years	OR	**2.31 (1.52, 3.51)** **+VE**	2,439
		Increase from <3 hours per day of TV viewing at baseline to >3 hours per day at follow up vs. <3 hours at baseline and follow up 7 years	OR	**2.33 (1.41, 3.85)** **+VE**	2,439
		Decrease from >3 hours per day of TV viewing at baseline to <3 hours per day at follow up vs. <3 hours at baseline and follow up 7 years	OR	**1.52 (0.99, 2.35)** **INV**	2,439
	Reilly et al. 2005 *Le Blanc et al (2012)* and *Summerbell et al (2009)*	>8 hours of TV viewing per week vs. <4 hours at age 3 years 4 years	OR	**1.55 (1.13, 2.12)** **+VE**	5,493
	Gable et al. 2007 *Tremblay et al (2011)* and *Summerbell et al (2009)*	Per additional hour of TV per week at baseline 3 years	OR	**1.02 (1.00, 1.04)** **+VE** ***Borderline signif***	8,000
Probability of being overweight	Pagani et al. 2010 *Le Blanc et al (2012)*	Per additional hour of watching TV at baseline ~7.5 years	**0.05 (0.01, 0.09)** **+VE**		1,314
		Increase in total hours watching TV from baseline 2.5 years old to 4.5 years old ~7.5 years	**0.03 (0.01, 0.05)** **+VE**		1,314
Incident obesity	Boone et al. 2007 *Costigan et al (2013)*	Change in hours per week of screen time *(girls)* 6 years	Coefficient	**0.0119 (0.0051, 0.0186)** p=0.001 **+VE**	4,276
		Change in hours per week of screen time *(boys)* 6 years	Coefficient	**0.0062 (0.009, 0.0115)** p=0.021 **+VE**	4,879
*Results from Zimmerman et al (2010) were stratified by age group. Prior to stratification, more than 1,000 participants were included.					

Fifteen cohorts (18 publications) in children with more than 1,000 participants were identified providing 41 results across eight outcomes: BMI z score (change and attained); BMI percentile change; BMI acceleration; BMI (change and attained); odds of excess weight gain; odds of overweight and/or obesity; probability of being overweight; and incident obesity. Thirty two results reported positive associations (increased screen time leading to increased adiposity), of which 23 were statistically significant and one was borderline significant. Six results reported non-significant inverse associations and three results reported no association.

Average age at baseline across the studies ranged from 29 months to 16 years. One study (Viner et al 2006) followed up participants into adulthood (aged 30). Henderson et al (2007) conducted their study in an all-female cohort.

There are 18 additional prospective cohort studies in children with fewer than 1,000 participants, providing 26 results. Fourteen reported positive associations (of which eight were significant), one reported a significant inverse association in girls only, and 11 reported no association.

Studies n<1000: Barnett et al. 2010, Hume et al. 2009, Jago et al. 2005, Lumeng et al. 2006, Proctor et al. 2003, Burke et al. 2006, Chen et al. 2007, Elgar et al. 2005, Hancox et al. 2004, Janz et al. 2005, Maffeis et al. 1998, Must et al. 2007, O'Brien et al. 2007, Bogaert et al. 2003, Skinner et al. 2004, Skinner et al. 2003, Kettaneh et al. 2005 and Davison et al. 2006.

3. Adults

3.1 Meta-analysis of RCTs in adults

Nil

3.2 Meta-analyses of prospective cohort studies in adults

Nil

3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 97 Results of individual prospective cohort studies in adults – Screen time

Adults					
Prospective cohort studies					
MD=mean difference; OR=odds ratio; RR=relative risk. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Mozaffarian et al. 2011 *USDA DGAC (2015)*	Per hour per day increase in TV viewing 20 years	Beta coefficient	**0.31 (0.20, 0.42) lb** +VE	120,877
	Raynor et al. 2006 *USDA DGAC (2015)*	Frequency of TV viewing at baseline 1 year	Beta coefficient	**0.081 kg** *t*=2.532 p=0.011 +VE	1,422
		Change in frequency of TV viewing across study period 1 year	Beta coefficient	**0.123 kg** *t*=3.885 p=0.000 +VE	1,422
BMI change	Pinto Pereira et al. 2013 *USDA DGAC (2015)*	Per hour per day increase in TV viewing 5 years	MD	**0.06 (0.01, 0.12) kg/m^2** +VE	6,562
Waist circumference	Stamatakis et al. 2012 *USDA DGAC (2015)*	Watching TV 3–4 times per week vs. <2 times at baseline 21 years	Beta coefficient	**0.351 (-0.659, 1.361) cm** +VE	5,972
		Watching TV >5 times per week vs. <2 times at baseline 21 years	Beta coefficient	**1.166 (0.325, 2.008) cm** +VE	5,972
	Wijndaele et al. 2010 *USDA DGAC (2015)*	Per 10 hours per week of TV viewing at baseline *(female)* 5 years	Beta coefficient	**0.04 (-0.31, 0.39) cm** +VE	2,143
		Per 10 hours per week of TV viewing at baseline *(male)* 5 years	Beta coefficient	**-0.25 (-0.56, 0.06) cm** INV	1,703
		Change in TV viewing (hours per week) *(female)* 5 years	Beta coefficient	**0.68 (0.30, 1.05) cm** +VE	2,143
		Change in TV viewing (hours per week) *(male)* 5 years	Beta coefficient	**0.43 (0.08, 0.78) cm** +VE	1,703
Odds of overweight or obesity	Meyer et al. 2008 *USDA DGAC (2015)*	"Medium" TV exposure at baseline 6 years	OR	**1.03 (0.92, 1.15)** +VE	12,678
		"High" TV exposure at baseline 6 years	OR	**0.93 (0.83, 1.04)** INV	12,678
Risk of obesity	Hu et al. 2003 *Van Uffelen et al (2010a)* and *Summerbell et al (2009)*	2–5 hours per week watching TV vs. 0–1 hours 6 years	RR	**1.22 (1.06, 1.42)** +VE	50,277
		>40 hours per week watching TV vs. 0–1 hours	RR	**1.94 (1.51, 2.49)** +VE	50,277

		6 years			
	Pulsford et al. 2013 *USDA DGAC (2015)*	>19 hours TV viewing per week vs. 0-6 hours 6 years	OR	**0.97 (0.41, 2.29)** **INV**	1,071

Eight prospective cohort studies in adults with more than 1,000 participants investigated screen time and adiposity. These provided 15 results across five outcomes: weight change; BMI change; waist circumference; odds of overweight or obesity; and risk of obesity. Twelve results reported positive associations, with increased screen time leading to increased adiposity; nine were statistically significant. Three results reported inverse associations; none were statistically significant.

Hu et al (2003) used data from the all-female Nurses' Health Study cohort. Mozaffarian et al (2011) also used data from the Nurses' Health Study cohort, pooling it with data from the Nurses' Health Study II and the Health Professionals Follow up Study. Pinto-Pereira et al (2013) and Stamatakis et al (2012) both used data from the British Birth Cohort. Raynor et al (2006) used data from the National Weight Control Register; Wijndaele et al (2010) used data from AusDiab; Meyer et al (2008) used data from ARIC; and Pulsford et al (2013) used data from the Whitehall II cohort.

Two additional prospective cohort studies in adults with fewer than 1,000 participants were identified providing four results: one reported a significant, positive association and three reported no association.
Studies n<1000: Ding et al. 2012 and French et al. 2012.

4. Possible mechanisms

As per preliminary discussions in June 2016:

- Time spent watching television displaces opportunities for more active pursuits.
- Increases exposure to promotion of foods that may promote weight gain.
- May be accompanied by relatively uninhibited consumption of energy dense foods, which may be eaten in large portion sizes.

5. Summary of evidence

5.1 Children

The evidence for increased screen time increasing adiposity in children is largely consistent. Two meta-analyses of RCTs aimed at reducing screen time reported positive effects (reduced screen time leading to reduced adiposity), of which one was statistically significant. One meta-analysis of prospective cohort studies reported a significant, but small, positive association. Fifteen prospective cohort studies (18 publications) reported 32 out of 41 results as positive associations, of which 23 were statistically significant. For prospective cohort studies with fewer than 500 participants the majority 4/26 results) reported positive associations, of which eight were significant; one result reported a significant inverse association.

5.2 Adults

There were no meta-analyses of RCTs or prospective cohort studies in adults investigating screen time and adiposity. Eight prospective cohort studies provided 15 results, of which 12 reported positive associations (nine were statistically significant). There were two prospective cohort studies with fewer than 500 participants providing four results: one reported a significant positive association and three reported no association.

6. Energy density of the diet

1. Evidence identified for 2017 update

Table 98 Published reviews identified for the 2017 update – Energy density of the diet

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Fogelholm et al. 2012 [+]; Johnson et al. 2009 [+]
USDA DGAC (2015) scientific report [++]	N	
Supplementary literature search August 2016	1	Rouhani et al. 2016 [++]

Notes on the evidence:

- The calculation of energy density varies between the included studies. All studies include solid foods; however, there is variation in inclusion of liquid foods (for example, soups) and beverages (for example, milk, hot drinks, water). Where possible, this information is included in **Sections 2** and **3** of this exposure.
- No meta-analyses of RCTs or individual RCTs (in children or adults) were identified. All the available evidence is from prospective cohort studies.

2. Children

2.1 Meta-analysis of RCTs in children

Nil

2.2 Meta-analyses of prospective cohort studies in children

Nil

2.3 Individual RCTs in children, not in meta-analyses

Nil

2.4 Individual prospective cohort studies in children, not in meta-analyses

Table 99 Results of individual prospective cohort studies in children – Energy density of the diet

Children					
Prospective cohort studies					
ED=energy density; FMI=fat mass index (calculated differently between studies); OR=odds ratio; SD=standard deviation. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight change	Butte et al. 2007 *Rouhani et al (2016)* and *Johnson et al (2009)*	Per 1 kcal per gram ED 1 year	Beta coefficient	**0.23 SD±0.35 kg per year** p=0.5 **+VE**	798
BMI z score	Durao et al. 2014 *Rouhani et al (2016)*	Intake of energy dense snacks 2 years	Beta coefficient	**-0.030 (-0.095, 0.035)** **INV**	589
	Kring et al. 2008 *Rouhani et al (2016)*	Dietary ED (kJ per gram) *(girls)* 3 years	Beta coefficient	**0.07 (-0.04, 0.18)** **+VE**	217
		Dietary ED (kJ per gram) *(boys)* 3 years	Beta coefficient	**-0.05 (-0.16, 0.06)** **INV**	181
	Alexy et al. 2004 *Rouhani et al (2016)*	Clusters (Constant; Medium; High; Low) of ED intake 10 years	Constant 4.1kJ/g: **-0.29 SD±1.11** Medium 4.0 kJ/g: **0.11 SD±1.08** High 4.1 kJ/g: **0.11 SD±1.09** Low 3.7 kJ/g: **0.23 SD±0.90** p>0.05 **INV**		228
	Gunther et al. 2011 *Rouhani et al (2016)*	Tertiles of energy density kJ per gram 3 years	Tertile 1: **0 (-0.1, 0.2)** Tertile 2: **0 (-0.1, 0.1)** Tertile 3: **0 (-0.1, 0.2)** p for trend=0.8 **NIL**		219
Odds of FMI z score >80th percentile	Ambrosini et al. 2012 *Rouhani et al (2016)*	Per 1 SD increase in dietary pattern score (characterised by energy density) over 4 years 8 years	OR	**1.13 (1.01, 1.27)** **+VE**	2,245
		Highest vs. lowest quintile of dietary pattern score (characterised by energy density) over 4 years 8 years	OR	**1.22 (1.10, 1.35)** **+VE**	
Odds of being in top 20% of FMI	Johnson et al. 2008b *Rouhani et al (2016)* and *Johnson et al (2009)*	Dietary ED (kJ per gram) at age 5 years 4 years	OR	**1.12 (0.90, 1.40)** **+VE**	459
		Dietary ED (kJ per gram) at age 7 years 4 years	OR	**1.36 (1.09, 1.69)** **+VE**	
Odds of being in highest FMI category	McCaffrey et al. 2008 *Rouhani et al (2016)* and *Johnson et al (2009)*	ED kJ per gram (all food and beverages, including water) Approx. 8 years	OR	**1.23 (0.53, 2.90)** **+VE**	48

		ED kJ per gram (all solid and liquid foods, plus milk) Approx. 8 years	OR	**2.16 (1.10, 4.25)** **+VE**	

Eight prospective cohort studies investigating dietary energy density and adiposity in children were identified in two reviews. They provided 12 results across two outcomes: BMI z score and odds of adiposity (reported as various categories of fat mass index (FMI)). Eight results reported positive associations (four were statistically significant), three reported non-significant inverse associations, and one reported no association.

FMI was calculated differently between studies as per table below.

Study	Calculation of Fat Mass Index
Ambrosini et al (2012)	Fat mass (kg) divided by height (m) raised to an optimum power (*X*) to remove the relation between FMI and height: **fat mass/height^{X}**.
Johnson et al (2008)	Fat mass (kg) divided by height (m) raised to 5.8: **fat mass/height$^{5.8}$**.
McCaffrey et al (2008)	Fat mass (kg) divided by height (m) squared: **fat mass/height^{2}**.

The variables included in the calculation of energy density varied between studies: Alexy et al (2004), Durao et al (2014), and Iqbal-Kring et al (2008) included solid and liquid food and beverages, whereas Ambrosini et al (2012), Butte et al (2007), Gunther et al (2011), and Johnson et al (2008) included solid food only. McCaffrey et al (2008) reported separate results for energy density calculations including all food and beverages (including water) and calculations including all solid and liquid food (including milk and soups) but excluding beverages; both of these are presented in the main results table.

Durao et al (2015) included salty snacks, soft drinks, cakes, and sweets in their dietary assessment (via food frequency questionnaire). Gunther et al (2011) did not define the thresholds for tertiles of dietary energy density; however, the mean energy density across the whole sample was 6.9 kJ per gram. Alexy et al (2004) identified four intake categories via cluster analysis defined primarily by fat intake; the 'low' intake category was significantly different with respect to energy density relative to the other categories. Fat intake in the 'constant' cluster was similar to the 'medium' cluster, but the intra-individual standard deviation was smaller in the constant cluster.

3. Adults

3.1 Meta-analysis of RCTs in adults

Nil

3.2 Meta-analyses of prospective cohort studies in adults

Table 100 Meta-analyses of prospective cohort studies in adults – Energy density of the diet

Adults					
Meta-analyses of prospective cohort studies					
MD=mean difference. Significant results are highlighted in **red**.					
Outcome	***Publication***	***Exposure description***	***Results***		
Weight change	Rouhani et al (2016)	High energy dense diet vs. low energy dense diet 6–8 years	MD	**2.26 (1.00, 3.53) kg** +VE	Studies=3; n=52,919 I^2=26%

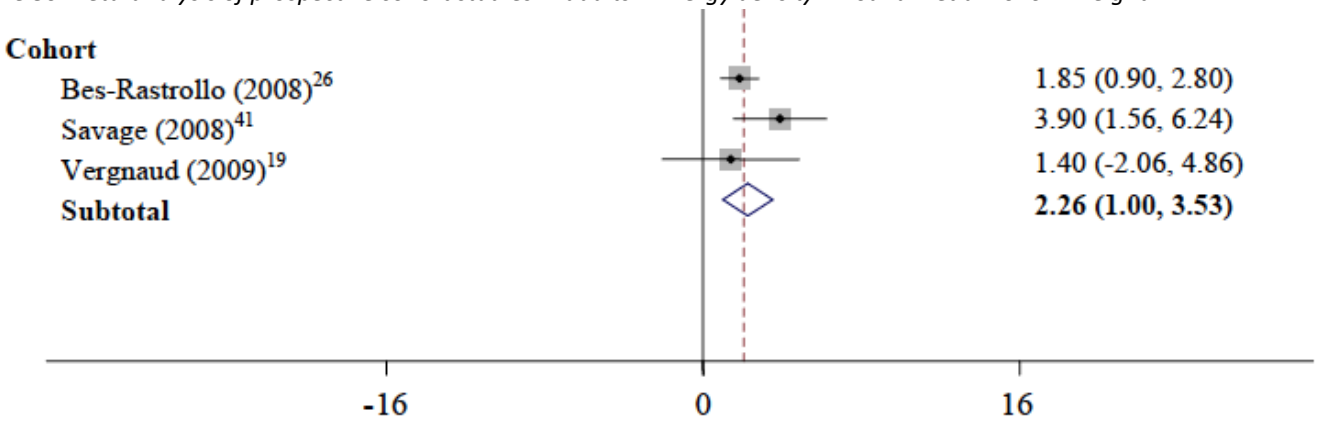
One review conducted a meta-analysis of prospective cohort studies in adults investigating dietary energy density and adiposity. The result reported a marginally significant positive association when comparing the highest and lowest NTILES reported in each study.

The study by Bes-Rastrollo et al. 2008, conducted with the Nurses' Health Study cohort, had the largest sample size (n=50,026) and the greatest difference between highest and lowest energy density categories (2.46 kcal per gram vs. 0.78 kcal per gram). The study by Savage et al. 2008 was also in an all-female population. All the included studies calculated energy density by including solid foods only. The corresponding forest plot is presented below.

Adults | Prospective cohort studies | Weight | Rouhani et al 2016 | High vs. low energy density diet

Overall association between dietary energy density and mean body weight (kg).

Figure 80 Meta-analysis of prospective cohort studies in adults – Energy density – Rouhani et al 2016 – Weight



3.3 Individual RCTs in adults, not in meta-analyses

Nil

3.4 Individual prospective cohort studies in adults, not in meta-analyses

Table 101 Results of individual prospective cohort studies in adults – Energy density of the diet

Adults					
Prospective cohort studies					
ED=energy density; MD=mean difference; SE=standard error; ΔWC_{BMI}=waist circumference for a given BMI. Significant results are highlighted in **red**.					
Outcome	***Publication*** ***Review***	***Exposure description***	***Results***		***n***
Weight	Du et al. 2009 *Rouhani et al (2016)* and *Fogelholm et al (2012)*	Per 1 kcal per gram ED 6.5 years	MD	**-42 (-112, 28) g per year** **INV**	89,432
	Iqbal et al. 2006 *Rouhani et al (2016)* and *Fogelholm et al (2012)*	Per 1 MJ per gram ED *(females)* 5 years	Beta coefficient	**-70.5 SE ± 58.1 kg** p=0.22 **INV**	900
		Per 1 MJ per gram ED *(males)* 5 years	Beta coefficient	**23.5 SE ± 46.8 kg** p=0.62 **+VE**	862
Waist circumference	Du et al. 2009 *Rouhani et al (2016)* and *Fogelholm et al (2012)*	Per 1 kcal per gram ED 6.5 years	MD	**0.09 (0.01, 0.18) cm per year** **+VE**	89,432
ΔWC_{BMI}	Romaguera et al. 2010 *Rouhani et al (2016)* and *Fogelholm et al (2012)*	Per 1 kcal per gram ED *(females)* 5.5 years	Beta coefficient	**0.15 (0.09, 0.21) cm per year** **+VE**	28,937
		Per 1 kcal per gram ED *(males)* 5.5 years	Beta coefficient	**0.09 (0.05, 0.13) cm per year** **+VE**	19,694

Three individual prospective cohort studies in adults from two reviews investigated dietary energy density and adiposity. These provided six results, of which four reported positive associations (three statistically significant) and two reported non-significant inverse associations.

Du et al (2009) and Romaguera et al (2010) both used data from the same eight centres of the EPIC cohort: Florence, Norfolk, Amsterdam, Maastricht, Doetinchem, Potsdam, Copenhagen, and Aarhus. The discrepancy in included subjects appears to be due to Romaguera et al (2010) additionally excluding subjects more than 60 years old. Both the studies using the EPIC cohort data excluded beverages from their energy density calculations. Iqbal et al (2006) reported calculating energy density using water content; however it was not clear if the total calories were derived from food alone, or from beverages as well.

Iqbal et al (2006) reported on the outcome of weight in kilograms, although the effect size seems implausibly large.

4. Possible mechanisms

As per 2007 Expert Report:

- **Passive overconsumption**: In general people tend to consume roughly the same amount of food from day to day, measured by bulk and weight. Several human clinical studies have shown that high energy dense diets can undermine normal appetite regulation, termed 'passive overconsumption'. Higher energy density diets tend to leads to greater energy intake.

5. Summary of evidence

5.1 Children

No meta-analyses of RCTs or prospective cohort studies, or individual RCTs, in children were identified. Eight individual prospective cohort studies provided 12 results, of which eight reported positive associations (four statistically significant), three reported inverse associations, and one reported no association. There was variability between the studies with respect to method of calculating energy density and FMI.

5.2 Adults

One meta-analysis of prospective cohort studies in adults was identified, which reported a significant positive association between energy density and adiposity over six to eight years of follow up. Two of the three studies in the meta-analysis were in all-female populations. Three individual prospective cohort studies provided six results, of which four reported positive associations (three were statistically significant) and two reported non-significant inverse associations. Two studies used data from eight centres in the EPIC cohort.

Evidence by exposure: Part 2 – De-prioritised exposures

Part 2 contains the evidence for the de-prioritised exposures. The evidence for exposures in this section is derived from the NICE (2014) report, the USDA DGAC (2015) scientific report, or the preliminary search (August 2015); evidence from a supplementary search (August 2016) for meta-analyses published after the NICE (2014) report cut-off are not included (please see the protocol in **Appendix**).

The non-prioritised exposures are: Vegetarian/vegan diets, adherence to dietary guidelines, dietary variety, breakfast, family meals, eating in the evening, eating frequency, snacking, pulses (legumes), nuts, fish, confectionary, water, non-nutritively sweetened drinks (NNS), fruit juice, coffee and tea, alcoholic drinks, total carbohydrate, glycaemic load, total protein, caffeine, catechins, and sleep.

Presentation format of the evidence

The structure for each exposure section follows this approximate outline:

1. Available evidence
2. Summary of the evidence *[This section is stratified by children and adults where possible]*
3. Issues in interpretation of the evidence
4. Possible mechanisms

Notes on the evidence tables:

- Not all studies in a published review were included in the NICE (2014) report, as some were judged to be outside the NICE report scope. Where this was the case, an asterisk in the table indicates the number of the total studies that were deemed relevant to the scope and included in the NICE judgement.
- The association column in the summary table relates to the conclusion of the published review as reported by NICE, and is based on the relevant included studies.
- The abbreviation 'NR' denotes where data are not reported by the published review.
- The quality rating of published reviews corresponds to the NICE (2014) report rating (see protocol in the **Appendix** of this literature review and Appendix D of the NICE (2014) report):
  [-] Low quality
  [+] Moderate quality
  [++] High quality

7. Patterns of diet

7.1 Vegetarian/vegan

1. Available evidence

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	U.S Department of Agriculture Nutrition Evidence Library 2010c [+]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
USDA 2010	Adults	RCT: 0 Cohort: 7 (3*, n=22,365) Other: 11	1 study significantly less weight gain in vegans, vegetarians intermediate; 1 study significantly lower BMI in vegetarians; 1 study no significant association.	Inverse association

* Relevant studies included

Adults

- Cohort studies
  - USDA (2010) included 3 relevant cohorts.
    - 1 study (n=21,966) found that mean annual weight gain was significantly less in vegans than in meat-eaters, vegans: 284 g in men and 303 g in women, meat eaters: 406 g in men and 423 g in women; $p<0.05$, but not lacto-ovo vegetarians, vegetarians: 386 g for men and 392 g for women.
    - 1 study found significantly lower BMI in vegetarians (mainly lacto-ovo) than omnivores (data not reported (NR)).
    - 1 study found no difference in BMI between healthy lacto-ovo vegetarians and omnivores (data NR).

3. Issues in interpretation of evidence

- Two of the cohort studies identified in USDA (2010) did not describe a follow-up period, and they seemed likely to have assessed BMI cross-sectionally.

4. Potential mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

7.2 Adherence to dietary guidelines

1. Available evidence

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Fogelholm et al. 2012 [+]; Kuhl et al. 2012 [-]; Smithers et al. 2011 [+]
USDA DGAC (2015) scientific report [++]	Y	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Fogelholm et al. 2012	Adults	RCT: 0 Cohort: 5 (2*, n=8,786)	2 studies inverse association with weight gain.	Inverse association
Kuhl et al. 2012	Children	RCT: 0 Cohort: 1 (n=7,758)	No significant association between dietary patterns and BMI.	Not reported
Smithers et al. 2011	Children	RCT: 0 Cohort: 2 (n=5,292) Other: 8	1 study positive association with BMI; 1 study found higher "infant guidelines" pattern score partially associated with increased lean mass.	Inconclusive
Additional to NICE report				
USDA DGAC 2015	Adults and children	RCT: 0 Cohort: 3 adults, 2 children (n unclear)	Adults – 2 studies inverse association with BMI, WC and weight gain risk; 1 study inverse association in white adults, positive association in black adults. Children – 1 study inverse association with BMI, 1 study positive association.	Inconclusive

* Relevant studies included

Evidence from NICE 2014 report

Adults

- Cohort studies
  - Fogelholm et al. (2012) included 2 cohorts (n=8,786) assessing the effect of adherence to US dietary guidelines over 8 to 20 years. Both cohorts found a significant inverse association between adherence to the dietary guidelines and weight gain; 1 found that a 1-unit improvement in adherence score was associated with 0.22 kg to 0.27 kg at 8 years (reviewer calculated, p for trend <0.01), with the other finding 2.7 kg lower weight gain with high adherence (reviewer calculated; follow up period unclear, 7 or 20 years).

Children

- Cohort studies
  - Kuhl et al. (2012) identified 1 cohort study (n=7,758) which found no association between junk, healthy, traditional and fussy dietary patterns at age 3 and BMI at age 7 (data NR).
  - Smithers et al. (2011) identified 2 cohort studies. 1 (n=782) found that higher "infant guidelines" pattern score at 12 months was associated with increased lean mass, but not with fat mass or BMI at age 4 (data NR). 1 (n=4,510) found that a pattern including meat at age 3, but not other patterns (staples, noodles & pasta, fruit and vegetables, breakfast foods, snacks, no further detail provided), were associated with increased odds of BMI>85th percentile: OR = 1.37 (95% CI 1.04 to 1.81).

Evidence from USDA DGAC 2015

Adults

- 1 study found that there was an inverse association between quintiles of each healthy eating index score and BMI ($p<0.001$). There was also an inverse association with waist circumference ($p<0.001$).
- 1 study found that a 10-point increase in diet quality index score was associated with a 10% lower risk of gaining 10 kg in normal-weight white adults; however, the same magnitude increase in score was associated with a 15% higher risk in black adults living with obesity ($p<0.001$).
- 1 study found that an increase of one dietary guideline unit was associated with lower weight gain ($p=0.004$), and lower BMI gain ($p=0.002$). An increase of 1 unit was associated with a lower probability of becoming overweight or obese: OR = 0.93 (95% CI = 0.88 to 0.99). Similarly, an increase of 1 unit was associated with a lower probability of becoming obese: OR =0.89 (95% CI = 0.80 to 0.99). An increase of one unit was also associated with lower waist circumference gain ($p=0.01$) and lower waist-to-hip ratio gain ($p=0.02$).

Children

- 1 study found that higher dietary quality was associated with a higher energy intake, and children with a lower diet quality had lower BMI and Fat Mass Index (FMI) Z-scores at baseline ($p<0.01$) but not at onset of puberty.
- 1 study found that girls in the highest vs. lowest quintile of DASH ("Dietary Approaches to Stop Hypertension") score had an adjusted mean BMI of 24.4 vs. 26.3 kg/m^2 ($p<0.05$).

3. Issues in interpretation of evidence

- It was unclear whether the individual cohort studies used the same definitions of dietary guidelines.

4. Potential mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

7.3 Dietary variety

1. Available evidence

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Vadiveloo et al. 2013 [+]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Vadiveloo et al. 2013	Adults	RCT: 3 (0*) Cohort: 1 (n=100,886) Other: 22	Diversity associated with lower BMI in men, but higher BMI in women.	Inconclusive

*Relevant studies included

Adults

- Cohort studies
  - Vadiveloo et al. (2013) identified 1 cohort study (n=100,886) that found that eating more of 23 recommended foods at least weekly was associated with lower mean BMI after 8 to 12 years in men: mean difference in BMI for highest vs. lowest score quintile for men: -0.2 kg/m^2, $p<0.001$; but higher BMI for women: 0.3 kg/m^2, $p<0.001$.

3. Issues in interpretation of evidence

Nil

4. Potential mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

7.4 Breakfast consumption

1. Available evidence (via NICE 2014)

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Mesas et al. 2012 [+]; U.S Department of Agriculture Nutrition Evidence Library 2010a [+]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Mesas et al. 2012	Adults and children	RCT: 0 Cohort: 10 (2 adults, n=20,698/ 8 children, n unclear) Other: 76	Adults – 1 study inverse association between eating breakfast and weight gain; 1 study skipping breakfast positively associated with BMI gain. Children – 3 studies inverse association (1 in overweight children only), 1 study positive association, 4 studies no significant association.	Inverse association
USDA 2010	Adults and children	RCT: 1 (0*) Cohort: 16 (3 adults, n=27,116/ 13 children, n unclear) Other: 1	Adults – 2 studies in Mesas et al. (2012). 1 study inverse association between % energy from breakfast and weight change. Children – 9 studies (4 cohorts) inverse association, 1 study positive association, 3 studies no significant association.	Inverse association

* relevant studies included

Adults

- Cohort studies
  - Mesas et al. (2012) included 2 cohort studies (n=20,698). One found that eating breakfast was associated with reduced risk of gaining 5 kg or more over 10 years compared to not eating breakfast: HR = 0.91 (95% CI 0.85 to 0.97). The other found that skipping breakfast was associated with increases risk of 5% or greater BMI gain over the course of a year: OR = 1.34 (95% CI 1.12 to 1.61).
  - USDA (2010) included 3 studies, 2 reported in Mesas et al. (2012). The third (n=6,764) found a small inverse association between % energy from breakfast and weight change: beta = -0.021 (95% CI -0.035 to -0.007).

Children

- Cohort studies
  - Mesas et al. (2012) included 8 cohort studies. 2 cohorts found that eating breakfast was inversely associated with excess weight; 1 found that skipping breakfast was inversely associated with weight in overweight children only; 1 found that eating breakfast was inversely associated with weight in overweight children only; and 4 found no association.
    - 1 study (n=7,788) found that eating breakfast >4 days/week compared with <4 days/week was associated with lower frequency of chronic obesity: OR = 0.59 (95%

CI 0.52 to 0.68).
    - 1 study (n=9,919) found an association with BMI Z score and number of days eating breakfast at baseline: β = -0.02 (p<0.001) and changing breakfast consumption over the 5 year follow up: β = -0.01 (p<0.01).
    - 1 cohort (n= 2,371) found eating breakfast ≥2 days/week was associated with a decrease in BMI Z score in girls with baseline BMI in the 95th percentile: B = -0.04 (95% CI -0.08 to -0.01) and the 97th percentile: B = -0.05 (95% CI -0.10 to 0.01).
    - 1 cohort (n=14,586) skipping breakfast (never eating) compared with eating breakfast ≥5 days/week was associated with a decrease in BMI after 1 year in overweight boys: beta = -0.70 (p=0.01) and girls: beta = -0.47 (p=0.01) only.
    - 4 cohorts (n=5,103) did not find an association between breakfast frequency and BMI at 5 year follow up, obesity or BMI z score or risk of overweight (data NR).
  - USDA (2010) included 13 studies (based on 7 cohorts, n range 355 to 14,586). 9 studies (from 4 cohorts) found an inverse association, 1 study found a positive association, and 3 found no significant association.
    - Inverse association: effects of breakfast consumption ranged from inverse association with overweight at 5 years, boys: OR=0.89 (95% CI 0.82 to 0.97), p<0.05; girls: OR=0.89 (95% CI 0.83 to 0.97), p<0.05; to predicting reduced BMI z score after 8 years, β=-0.01 (p<0.05).

3. Issues with interpretation of evidence

- One review in adults noted that it was difficult to separate the impact of eating breakfast per se, and what the breakfast contained (e.g. fibre, nutrients).

4. Potential mechanisms

- Breakfast foods are often low energy-dense. If breakfast is not eaten, subsequent foods may have higher energy density.
- Eating a greater proportion of the daily energy intake earlier in the day may be associated with a higher metabolic rate from increased dietary-induced thermogenesis (Bo et al., 2015).
- Eating breakfast may be predispose greater physical activity in the morning (Chowdhury et al., 2016).

7.5 Family meals

1. Available evidence

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Hammons et al. 2011 [+]
USDA DGAC (2015) scientific report [++]	Y	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Hammons et al 2011	Children	RCT: 0 Cohort: 4 (n=29,961) Other: 4	Meta-analysis: shared family meals associated with reduced risk of overweight.	Inverse association
Additional to NICE report				
USDA DGAC 2015	Children	RCT: 1 Cohort: 5 (n unclear)	RCT: weight reduced despite no change in shared meals frequency. Cohort: 1 cohort inverse association between family meals and likelihood of being persistently overweight; 3 cohorts no significant association.	Inconclusive

Evidence from NICE 2014 report

Children

- Cohort studies
  - Hammons & Fiese (2011) conducted a meta-analysis of 8 studies of mixed study designs (4 cohorts and 4 cross-sectional studies) and found that children who took part in ≥3 shared family meals per week were less likely to be overweight compared with those who ate fewer family meals: OR = 0.88 (95% CI 0.81 to 0.97), I^2=48%, p=0.06.
    - Meta-analysis of cohort studies only showed that shared family meals were associated with reduced risk of overweight over 2 to 5 years: OR = 0.93 (95% CI 0.90 to 0.95).

Evidence from USDA DGAC 2015

Children

- RCT – increasing frequency of family shared meals
  - 1 RCT lasting 6 months included an intervention that simultaneously focused on four household routines, including family shared meals. Family meal frequency did not change; however, a reduction in body weight occurred (results NR).
- Cohort studies
  - 5 studies from 4 cohorts were identified that ranged in duration from 1 to 5 years.
  - 3 of 4 cohorts found no significant association between the frequency of family shared meals and BMI or weight status.
  - 1 study found that among overweight children, eating more family breakfast and dinner meals was associated with lower likelihood of becoming overweight or remaining overweight over a 4-year period (data NR).
  - 1 study found that children who ate fewer family meals were more likely to be persistently overweight (between kindergarten and third grade), OR = 1.08. Children who typically ate more breakfast meals (but not dinner) with their families had a lower rate of increase in BMI over 5 years (data NR).

3. Issues in interpretation of evidence

- Studies did not use a standard definition for family shared meals, which may contribute to inter-study variability. Not all studies assessed all meals. No study identified by USDA DGAC 2015 assessed the quality or source of meals consumed.
- The cohort studies in Hammons and Fiese (2011) were adjusted for confounders including socioeconomic status in 3 studies, physical activity in 2 studies, and energy intake in 1 study.

4. Potential mechanisms

- Foods eaten with family may more closely adhere to nutrition guidelines. Parents may act as positive role models in food intake.

7.6 Eating in the evening

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 2 (n=13,411)	2 studies no significant association between eating after 5pm/night eating and weight change.	No association

Adults

- Cohort studies
    - Summerbell et al. (2009) included 2 cohorts; both found no association between eating in the evening and change in weight over a 6 to 10 year follow up (data NR).

3. Issues in interpretation of evidence

- One study assessed the percentage of daily energy intake consumed after 5pm, which may not be a meaningful indicator. The other assessed whether people got up at night to eat.

4. Potential mechanisms

- Food consumed in the morning causes increased dietary-induced thermogenesis than food consumed in the evening (Bo et al. 2015).

7.7 Eating frequency

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Mesas et al. 2012 [+]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Mesas et al. 2012	Adults and children	RCT: 0 Cohort: 4 (2 adults, n=27,211; 2 children, n=2,476) Other: 35	Adults: 1 study increased risk of weight gain with greater frequency; 1 study no significant association. Children: 2 studies mixed associations with BMI z-score for higher meal frequency	Inconclusive (adults and children)

Adults

- Cohort studies
    - Mesas et al. (2012) included 2 cohort studies (n=27,211).
        - One study found daily eating frequency was not associated with weight change, beta coefficients = 0.02 (p=0.86) for men and 0.11 (p=0.21) for women (units NR). This study adjusted for total energy intake.
        - The other study found a higher risk of 5 kg weight gain after 10 years for eating 4 meals/day, HR = 1.07 (95% CI 1.02 to 1.14) or ≥5 meals/day, HR = 1.15 (95% CI 1.06 to 1.25) compared with eating 3 meals a day.

Children

- Cohort studies
    - Mesas et al. (2012) included 2 cohort studies in children (range 8 to 12 years; n=2,476).
        - One study found that eating 3 or more meals a day was associated with lower BMI z scores compared to eating fewer than 3 meals a day, beta = -0.0472 (p<0.0001); odds of overweight was non-significant: OR 0.91 (95% CI 0.79, 1.05). This study adjusted for average daily energy intake.
        - The other study found eating 4 to 5 meals a day was associated with an increase in BMI z score after 10 years compared to eating 6 times or more a day, beta = 0.24 (p=0.028) (not adjusted for energy intake). This study did not adjust for average daily energy intake.

3. Issues in interpretation of evidence

- Of the studies in Mesas et al. (2012) in adults, the one that found no association adjusted for energy intake and the one finding a positive association did not adjust for energy intake. This suggests that the effect could be related to an increased energy intake with more eating occasions.
- One of the two studies in children adjusted for energy intake.
- The studies in children were of a relatively small size, which precludes firm conclusions.

4. Potential mechanisms

- Increasing eating frequency may lead to eating in the absence of hunger, which is likely to increase energy intake beyond needs.
- Conversely, reducing eating frequency may lead to uncontrolled later eating if hunger is excessive.
- Results may relate to the foods consumed (core foods vs. ‘snack foods’).

7.8 Snacking

1. Available evidence (via NICE 2014 report)

This exposure contains evidence on both snacking (eating outside a meal) and consumption of 'snack foods' (undefined).

Source	No. of reviews	Authors [quality]
NICE (2014) report	4	Larson et al. 2013 [+]; Mesas et al. 2012 [+]; U.S Department of Agriculture Nutrition Evidence Library 2010a [+]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Larson et al 2013	Children	RCT: 0 Cohort: 7 (n=28,958) Other: 25	2 studies positive association; 2 inverse association; 3 no significant association.	Inconclusive
Mesas et al. 2012	Adults and children	RCT: 0 Cohort: 8 (4 adults, n=73,068 /4 children, n=19,562) Other: 36	Adults – 4 studies positive associations. Children – 3 studies no significant association, 1 study mixed findings, generally positive.	Inconclusive
USDA 2010	Children	RCT: 0 Cohort: 5 (n=16,634) Other: 1	2 studies positive association; 3 studies no significant association, generally positive.	Positive association
Summerbell et al. 2009	Adults and children	RCT: 0 Cohort: 4 (1 adults n=7,147 /3 children n=17,974)	Adults – 1 study reported no significant association. Children – 2 studies positive association in at least 1 analysis; 1 study inverse association before adjustment.	No association

Adults

- Cohort studies
  - Mesas et al. (2012) included 4 cohort studies (n=73,068) that found positive associations between snacking and weight-related outcomes. Associations ranged from small: 0.06 cm increase in waist circumference (95% CI 0.003 to 0.11) per 60 kcal snack food consumption over 5 years in women; to large: risk of gaining ≥5 kg/year OR = 2.75 (95% CI 1.17 to 6.50) for usual snacking between meals vs. no usual snacking over 4.6 years.
  - Summerbell et al. (2009) included one study which reported no significant association between weight change and eating frequency at baseline, regression-coefficients = 0.0211 (95% CI -0.2331, 0.2653) in men, and 0.1101 (95% CI -0.0654, 0.2847) in women.

Children

- Cohort studies
  - Larson et al (2013) identified 7 cohort studies (n=28,958).

        - 2 studies (n=2,175) found a positive association. One study found that that adherence to the sedentary-snacking pattern at baseline was positively associated with BMI z-score and the likelihood that children were obese (data NR). 1 found that increases in BMI from age 5 to 9 were predicted by higher intakes of fat from energy-dense snacks among girls from families in which one or both parents were overweight (data NR).
        - 2 studies (n= 15,847) found inverse associations in some, but not all, groups of children. One study found that among boys, consumption of reduced-fat snack food was associated with less weight gain (data NR); the other found that among boys snacking was inversely associated with becoming overweight between ages 3 and 6 (data NR).
        - 3 studies (n=10,936) found no association.
    - Mesas et al. (2012) included 4 cohorts (n=9,562). Three studies found no significant association.
        - One study (n=4,393) had mixed findings. It found a consistent (5/6 comparisons significant) positive direction of effect for comparisons of frequent (usually or often) snacking versus not frequent snacking: OR range = 1.3 (95% CI 0.9 to 1.8) to 3.0 (95% CI 1.7 to 5.5). Frequently replacing meals by snacks was associated with overweight in boys, OR = 1.9 (95% CI 1.1 to 3.2) but not girls.
    - USDA (2010) included 5 cohorts (n=16,634) with overlap with the studies in Mesas et al. (2012).
        - 2 studies found significant positive associations. One study (n=1,188) found that BMI was associated with changes in the frequency of low-quality snacking over time: -0.31 (0.14), t=-2.22 ($p<0.05$) – while snacking increased in the sample over time, low-quality snacking remained relatively stable in participants living with obesity. The other study (n=173) found that girls who snacked more frequently had higher intake of fat from energy dense snacks ($p<0.05$), which was reported to predict their increase in BMI from age five to nine ($p<0.05$). It was not clear if either of these studies were cross sectional.
        - 3 studies found no association.
    - Summerbell et al. (2009) included 3 cohorts (n=17,974), 2 that found positive associations and 1 mixed.
        - One study (n=355) found that the number of snacks per day at baseline was significantly associated with BMI at four year follow-up, regression coefficient = 0.13 ($p<0.05$).
        - One study (n=737) reported that children who snacked at fixed times at baseline (age 3) had significantly increased odds of obesity at follow up (adolescence) compared to those with no fixed snacking pattern, OR = 2.12 (95% CI 1.25 to 3.61).
        - The largest study (n=16,882) found a weak inverse association in girls only between consumption of snack foods and changes in BMI z-score, regression coefficient = -0.006 ($p<0.05$); the association was no longer significant after adjusting for dieting status and maternal overweight status.

3. Issues in interpretation of evidence

- The studies in adults had differing definitions of snacking, with 2 considering eating between meals snacking, 1 considering variety of snack foods consumed (not further defined), and the fourth considering consumption of specific snack foods (not further defined in the review). The studies were reported to have adjusted for confounders, with 2 adjusting for energy intake.
- One large study (n=14,977) in children included by all 3 reviews was reported as having different findings in these reviews. This may be due to different reviews focusing on different aspects of the analyses.

- Reviewers of one paper in children suggested that results might be influenced by reverse causality or biased self-reporting (overweight youth reducing their snacking for weight loss, or under-reporting snack intake, more often than youth at a healthy weight).

4. Potential mechanisms

- See eating frequency.
- Effects may depend on whether snacks are energy-dense and additional to energy requirements, or form part of energy requirements.

8. Foods and drinks

8.1 Pulses (legumes)

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	U.S Department of Agriculture Nutrition Evidence Library 2010d [+]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
USDA 2010	Adults	RCT: 3 (2*, n=83) Cohort: 1 (n=1,418) Other: 5	RCTs: no significant difference in weight for chickpea supplementation vs. wheat. Cohort: high soy food intake in childhood and adulthood associated with lower BMI in adulthood.	Inconclusive
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 2 (n=23,688)	Highest vs. lowest level of legumes associated with weight loss in men only.	No association

*relevant studies included

Adults

- RCTS – increasing consumption of pulses
  - USDA (2010) identified 2 small crossover RCTs (n=83) comparing supplementing the diet with 140 g/day chickpeas vs. supplementing with wheat. There was no significant difference in weight between the chickpea- and wheat-supplemented diets at 5 weeks (p>0.2 for 1 RCT).
- Cohort Studies
  - USDA (2010) identified 1 cohort, which found that high soy food intake in childhood and adulthood was associated with lower BMI in adulthood (p<0.0001). There was also an inverse association between highest vs. lowest adult soy consumption and BMI: -0.9 kg/m^2, p=0.002.
  - Summerbell et al. (2009) identified 2 prospective cohorts (n=23,688), one of which found that consumption of legumes was associated with weight loss in men: OR = 0.68 (95% CI 0.49 to 0.94); but not women: OR = 0.71 for highest vs. lowest legume consumption, while the other found no effect (p=0.96), over about 2 to 2.3 years.

3. Issues in interpretation of the evidence

- The RCTs identified may have been too small and short to detect an effect.
- In the cohort identified by the USDA (2010o), it was unclear whether adult intake measurement preceded outcome measurement or whether the assessments were cross-sectional.

4. Potential Mechanisms

As summarised in 2007 Expert Report

- Pulses (legumes) are a source of dietary fibre:
    - Fibre consumption may increase satiation by increasing chewing, slowing gastric emptying and elevating stomach distension, and stimulation of cholecystokinin.
    - The increased viscosity of soluble fibre can reduce the overall rate and extent of digestion, which may also result in reduced energy from protein and fat and a blunted post-prandial glycaemic and insulinaemic response to carbohydrates.
    - Fibre-induced delayed absorption and the resultant presence of macronutrients in the distal small intestine, known as the ileal brake, mediate the release of several gut hormones.

8.2 Nuts

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Flores-Mateo et al. 2013 [+]; Fogelholm et al. 2012 [+]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Flores-Mateo et al. 2013	Adults	RCT: 31 (unclear*) Cohort: 0 Other: 1	No significant association with nut-rich diets (direction all inverse).	No association
Fogelholm et al. 2012	Adults	RCT: 0 Cohort: 3 (n=180,930)	3 studies significant inverse associations with weight gain.	Inverse association
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 3 (n=32,553)	1 study inverse association with weight gain; 1 study no significant association; 1 unclear.	No association

* Relevant studies included

Adults

- RCTs – increasing nut consumption
    - Flores-Mateo (2013) included 31 small RCTs (some crossover RCTs) and 1 quasi-experimental trial, lasting 2 weeks to 3 years. It found no significant effect of diets including nuts compared to control diets (usually isocaloric, and usually habitual diet) on body weight, BMI or WC; although direction of effects were all inverse, e.g. body weight: 28 trials, n=1,836; WMD = -0.47 kg (95% CI -1.17 to 0.22 kg).
- Cohort studies
    - Fogelholm et al. (2012) included 3 cohorts (n=180,930) lasting from 2.3 to 20 years. All 3 cohorts found significant inverse associations with weight gain. The effect of higher nut intake ranged from small: 0.26 kg less weight gain (95% CI 0.08 to 0.44 kg) over 4 years, to relatively large: ≥2 times a week vs. never or almost never eating nuts OR = 0.69 (95% CI 0.53 to 0.90) for weight gain ≥5 kg over 2 years.
    - Summerbell et al. (2009) included 3 cohort studies (n=32,553) with follow-ups of 2.2 to 2.3 years.
        - 1 of the cohorts found a significant inverse association between nuts and weight gain: 50 g of nuts ≥ 2 times/week vs. never or rarely eating nuts OR = 0.69 (95% CI 0.53 to 0.90) for weight gain ≥5 kg over 2 years.
        - 1 cohort investigated the highest vs. lowest consumption of nuts and seeds, OR = 0.33 (95% CI 0.12 to 0.90) in women but not significant in men; exact exposure or outcomes being compared unclear.
        - The third cohort found no significant effect on mean change in body weight, OR = 0.73 in lowest consumption group vs. OR = 0.57 in highest consumption group (units NR); p for trend=0.07, adjusted for total energy intake.

3. Issues in interpretation of evidence

- Some of the RCTs may be in populations living with overweight or obesity.
- There was some overlap in the cohorts included in Fogelholm et al. (2012) and Summerbell et al (2009).
- Studies in Fogelholm et al. (2012) were adjusted for various confounders, but apparently not total energy intake.
- The cohort studies in Summerbell et al (2009) were reported to be adjusted – whether this includes adjustment for energy intake is unclear; the cohort with non-significant results was explicitly adjusted for total energy intake.

4. Potential mechanisms

From 2005 SLR:

- Antioxidants, vitamin E and magnesium present in nuts and seeds may be implicated in insulin metabolism.

8.3 Fish

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 3 (n= 27,473)	3 cohorts no significant association.	No association

Adults

- Cohort studies
    - Summerbell et al (2009) included 3 studies, all of which found no significant association between the highest vs. lowest level of fish intake and weight or waist circumference change over 2.2 to 6 years.
        - Weight change lowest vs. highest consumption: OR = 0.92 for women, OR = 1 for men
        - Mean change in body weight: OR = 0.71 in the lowest consumption group vs. OR = 0.88 in the highest consumption group, p = 0.92
        - Change in waist circumference: regression coefficient = -0.07 for women, -0.08 for men.

3. Issues in interpretation of the evidence

None reported

4. Potential Mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

8.4 Confectionery (candy)

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults and children	RCT: 0 Cohort: 6 (4* adults n=19,144 adults, 1* children, n=881)	Adults: 1 study positive association in men with risk of weight gain/risk of small weight loss; in women reduced odds of large weight loss. Children: No significant association with risk of overweight.	Inconclusive

* Relevant studies included

Adults

- Cohort studies
  - Summerbell et al. (2009) identified 4 cohort studies (n=19,144) with 2 to 12 years' follow up on the consumption of 'sweets' (including confectionery, ice cream and sugar) or a dietary pattern high in sweets on weight related outcomes.
    - One study in women found an inverse association; higher consumption of sweets (candy and desserts) associated with reduced risk of large weight gain (over 10 pounds): OR = 0.74 (95% CI 0.6 to 0.91), p=0.004.
    - The largest study (n=17,369) found a positive association in men and women; men with higher sweets consumption were at increased risk of large weight gain (not defined): OR = 1.48 (95% CI 1.03 to 2.13), p<0.05 and at increased risk of small weight loss (not defined): OR = 1.43 (95% CI 1.07 to 1.90), p<0.05. Women in this study with higher consumption of sweets were less likely to experience large weight loss: OR = 0.67 (95% CI 0.49 to 0.92), p<0.05.
    - The two other studies found no significant association.

Children

- Cohort studies
  - Summerbell et al. (2009) identified 1 cohort study (n=811) that found no significant association between maternally reported frequency of sweets intake (candy and desserts) at baseline and risk of being overweight at 10-year follow-up (data NR).

3. Issues in interpretation of evidence

- Summerbell et al. (2009) noted that the inverse relationship seen in 2 studies in adults may to some extent reflect reverse causality (those prone to weight gain may be more likely to avoid sweets), or biased reporting. The reason for the association between high sweets intake and both weight gain and weight loss in men in one study is unclear. The weight loss could be due to an increased risk of diabetes associated with increased sweets (and therefore sugar) intake, or result from a change in diet in those with a previously high sweet intake.

- The small size of the study on children and the lack of assessment of confectionery alone means that no firm conclusions can be drawn.

4. Potential mechanisms

Due to the limited nature of the evidence, potential mechanisms were not explored further for this exposure.

8.5 Water

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Muckelbauer et al. 2013 [++]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Muckelbauer et al. 2013	Adults	RCT: 3 (2*, n=52) Cohort: 0 Other: 8	No significant effect of increased water consumption on body weight.	Inconclusive
Summerbell et al. 2009	Children	RCT: 0 Cohort: 1 (n=1,432)	No significant association between water and fat mass.	No association

*Relevant studies included

Adults

- RCTs – increasing water intake
    - Muckelbauer et al. (2013) identified 2 small short-term crossover RCTs. The first (n=32) found no effect of additional water consumption (average 685 mL daily) versus replacing water with caffeine free diet cola for 3 days on body weight: mean difference between intervention and control = 0.1 kg (SD NR), p=0.146. The second RCT (n=20) also showed no effect of increased water consumption (average 2.1 L daily) over 2 weeks: mean difference between intervention and control = 0.18 kg (SD 1.5), p=0.613.

Children

- Cohort studies
    - Summerbell et al. (2009) identified 1 prospective cohort study (n=1,432) that found no significant association between servings of water consumed (not further defined) at the age of 5 or 7 years and change in fat mass (units NR) at the age of 9 years: regression coefficient = 0.25 (p=0.22) and 0.06 (p=0.58) respectively.

3. Issues in interpretation of evidence

- The studies in Muckelbauer et al. (2013) are likely to have been too small and short-term to show an effect on body weight.

4. Potential mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

8.6 Non-nutritively sweetened drinks

1. Available evidence

Source	No. of reviews	Authors [quality]
NICE (2014) report	4	Wiebe et al. 2011 [++]; Brown et al. 2010 [-]; U.S Department of Agriculture Nutrition Evidence Library 2010c [+]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	Y	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Wiebe et al. 2011	Adults	RCT: 53 (1*, n=133) Cohort: 0	No significant difference in BMI change between aspartame and sucrose.	No association
Brown et al. 2010	Children	RCT: 3 (1*, n=103) Cohort: 6 (n=16,119) Other: 9	RCT: No significant difference in BMI 25 weeks after SSB replacement. Cohort: 6 studies had inconsistent results.	Inconclusive
USDA 2010	Adults	RCT: 1 (0*) Cohort: 1 (n=3,371) Other: 1	Cohort: significant positive association over 7 to 8 years.	Positive association
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 3 (n=111,190)	3 studies significant positive associations.	Positive association
Additional to NICE report				
USDA DGAC 2015	Adults and children	RCT: not specified Cohort: 5 adults, 4 children (n unclear)	Adults – RCTs: low-calorie sweeteners reduced body weight over 3 to 78 weeks. Cohort: low-calorie sweetener intake significantly associated with higher BMI, but not body weight or fat mass. Children – RCTs: low-calorie sweeteners reduced body weight: 1.06 kg (95% CI -1.17 to -0.56).	

*relevant studies included

Evidence from NICE 2014

Adults

- RCT – aspartame vs. sucrose
  - Wiebe et al. (2011) identified 1 RCT (n=133, all female) that found no significant difference between aspartame (3.56 g/day) and sucrose (42 g/day) in BMI change over 4 weeks: mean difference -0.3kg/m^2 (95% CI -1.1 to 0.5).
- Cohort studies
  - USDA (2010) included 1 cohort study (n=3,371), which found significant positive associations with weight-related outcomes over 7 to 8 years; obesity OR = 2.03 (CI NR, p=0.0005) for consuming more than 21 non-nutritively sweetened beverages a week compared with none.

- Summerbell et al. (2009) included 3 prospective cohort studies (n=111,190) that found significant positive associations with weight change over 1 to 4 years, 1 of which (n=556) was no longer significant after adjustment for confounders including baseline BMI; correlation between saccharin intake and change in weight in women over 4 years: r=0.0024 (95% CI 0.00176 to 0.0030); difference in mean weight gain of 0.67 kg over 1 year between users vs. non-users of non-nutritive sweeteners. In 1 study the association was particularly strong with higher weight at baseline.

Children

- RCT – replacing sugar-sweetened beverages with non-nutritively sweetened beverages/water
  - Brown et al. (2010) included 1 small RCT (n=103) that found no significant difference in BMI overall 25 weeks after SSB replacement (data NR).
- Cohort studies
  - Brown et al. (2010) identified 6 cohort studies assessing the effect of non-nutritive sweeteners (assessed as non-nutritively sweetened beverage intake) on body weight and related outcomes in children and young people. The cohort studies had inconsistent findings in terms of direction of effect and significance (data NR).

Evidence from USDA DGAC 2015

- In addition to the reviews identified by NICE, the USDA DGAC 2015 identified one review by Miller and Perez (2014), which contained RCTs and cohort studies (5 cohorts in adults, 4 cohorts in children).
  - RCTs (number not specified): over 3 to 78 weeks, low-calorie sweeteners reduced body weight in adults: -0.72 kg (95% CI -1.15 to -0.30) and children: -1.06 kg (95% CI -1.17 to -0.56).
  - Cohort studies: low-calorie sweetener intake was significantly associated with higher BMI: 0.03kg/m^2 (95% CI 0.01 to 0.06), but not body weight or fat mass.

3. Issues in interpretation of the evidence

- The RCT in Wiebe et al. (2011) may have been too small and short to detect an effect.
- The RCT in Brown et al. (2010) could not determine the effect of non-nutritive sweeteners specifically, replaced sugar-sweetened beverages with non-nutritively sweetened beverages or water.
- Reviews of observational evidence suggesting that non-nutritive sweeteners are positively associated with weight are likely to reflect reverse causality; people with higher body weights may consume more low-calorie sweetener-containing foods and beverages as a weight-control strategy.

4. Potential mechanisms

- NNS may reduce energy intake if they replace sugar-containing drinks and foods.
- A review published after the NICE report (Rogers et al., 2015) of human and animal studies concluded that low-energy sweeteners do not increase body weight, and that sweet taste alone is unlikely to signal a learned association with energy content, and therefore stimulation of gut receptors.

8.7 Fruit Juice

1. Available evidence (via 2014 NICE report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Summerbell et al. 2009 [++]; U.S Department of Agriculture Nutrition Evidence Library 2010a [++]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults and children	RCT: 0 Cohort: 7, 1 adults (n=7,194), 6 children (n=20,114)	Adults – no significant association. Children – 5 of 6 studies no significant association. 1 study significant inverse association.	No association
USDA 2010	Children	RCT: 0 Cohort: 12 (n=47,201)	2 studies positive association in overweight children; 1 study positive association in girls only; 9 studies no significant association.	Inconsistent

Adults

- Cohort studies
  - Summerbell et al. (2009) identified a single prospective cohort study, which found no link between sweetened juice consumption on weight-related outcomes over 28 months (data NR).

Children

- Cohort studies
  - Summerbell et al. (2009) and USDA (2010) identified cohort studies on the relationship between 100% unsweetened fruit juice consumption and weight-related outcomes.
  - The majority of studies included in the reviews had non-significant findings over 3 to 11 years of follow-up, with mixed directions of effect, for BMI, obesity or fat mass. Effect sizes in individual studies were generally small, with regression coefficients ranging from 0.001kg/m^2 for BMI per ounce per day over 8 months to 0.25 for change in fat mass per serving of juice (not further defined in the review) over 2 years.
    - Some studies suggested a possible positive association between fruit juice and weight-related outcomes in those at risk of overweight or obesity.

3. Issues in interpretation of evidence

- Results from 1 study in the Summerbell et al. (2009) review and 2 studies in the USDA (2010s) review were explicitly reported as being adjusted for energy intake; but adjustments for the other studies were unclear. Adjusting for energy intake may remove any association.

- The reviews did not provide definitions of fruit juice, and may have included a mixture of fruit juice types (e.g. sweetened and unsweetened; 100% fruit juice and juices from concentrates). Summerbell et al. (2009) did not identify any studies of unsweetened fruit juice in adults.

4. Potential Mechanisms

From 2007 Expert Report:

There may be some overlap between sweetened fruit juice and sugar-sweetened beverages. The same mechanisms for both drink types are proposed to operate.

- Increasing energy intake without increasing satiety (for a positive relationship)
- Reducing energy intake by replacing sugar-sweetened beverage consumption (for an inverse relationship)

8.8 Coffee and tea

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

One study relates to coffee. One relates to hot beverages including coffee and tea.

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 2 (n=30,038)	1 study no significant association with subsequent overweight. 1 study (coffee) significant increases risk of weight gain in women, inverse risk in men.	No association

Adults

- Cohort studies
  - Summerbell et al. (2009) identified 2 cohorts.
    - One cohort (n=17,369) found no association between highest vs. lowest consumption (g/day) hot drink consumption (including tea and coffee) and subsequent excess weight gain and obesity (not defined) over 2.2 years: OR = 1.01 in women and OR = 1 in men.
    - One other cohort (n=12,669) found that drinking more than 8 cups of coffee a day was associated with a significant increase in risk of substantial weight gain in women, but with a reduced risk in men (data NR) after 5.7 years.

3. Issues in interpretation of evidence

- The study on coffee did not adjust for potential confounders

4. Potential Mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

8.9 Alcoholic drinks

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	4	Bendsen et al. 2013 [+]; Sayon-Orea et al. 2011 [+]; U.S Department of Agriculture Nutrition Evidence Library 2010b [++]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Bendsen et al. 2013	Adults	RCT: 9 (7*, n=157) Cohort: 10 (n=215,997) Other: 28	RCTs: Beer intake associated with greater body weight in men Cohort: Most studies either showed positive or no significant association between beer intake and obesity in men; results were less consistent in women.	Inconclusive (moderate beer drinking) Positive association (heavy beer drinking)
Sayon-Orea et al. 2011	Adults and adolescents	RCT: 1 (0*) Cohort: 13 (n=207,533) Other: 19	5 analyses positive association with weight; 2 analyses no significant association; 2 analyses inverse association in women only.	Inconclusive
USDA 2010	Adults	RCT: 1 (0*) Cohort: 7 (n=124,768)	5 studies no/inverse association in moderate drinkers. 2 studies positive associations with heavier drinking.	No association (moderate drinking) Positive association (heavy drinking)
Summerbell et al. 2009	Adults and adolescents	RCT: 0 Cohort: 20 (n= 375,421)	14 studies no significant association; 6 studies mixed directions of effect.	No association

* Relevant studies included

Adults

- RCTs
  - Bendsen et al. (2013) identified 9 RCTs comparing alcoholic beer versus no alcohol, or alcoholic beer versus low-alcohol or non-alcoholic beer over 21 to 126 days (7 included, n = 157). These RCTs individually found that drinking alcoholic beer was associated with greater body weight over 21 to 126 days ($p<0.05$), and this was supported by meta-analysis; mean difference = 0.73 kg (95% CI 0.53 to 0.92), I^2 = 0%.
  - The 3 RCTs (n=120; mainly men) comparing alcoholic beer (330 to 1,125 mL/day; 20 to 41 g/day ethanol) versus no alcohol found no significant effect of beer on weight-related outcomes (body weight or fat mass) over 21 to 30 days (data NR); overall meta-analysis mean difference = 0.54 kg (95% CI -1.00 to 4.50), I^2=0%.
- Cohort

- Bendsen et al. (2013) identified 10 cohort studies (n=215,997). Results were presented by gender.
  - Women: 1 study found an inverse association with 10 year BMI change = 0.44kg/m^2 for drinking ≥5 days/week vs. non-drinkers; 1 study found no association. 3 studies found positive associations with WC, e.g. drinking >days/week associated with 1.3cm greater WC at 6 years vs. non-drinkers, 2 studies found inverse associations (data NR) and 2 studies found no association.
  - Men: 1 study found a positive association (U-shaped) with obesity (data NR); 1 an inverse association: -0.11 kg/m^2 lower change in BMI for drinking ≥5 days/week vs. non-drinkers; and 1 no association. 3 studies found positive associations with WC, e.g. regression coefficient = 0.0038 cm change in WC per 250mL beer/cider. 4 studies found no association.
- Sayon-Orea et al. (2011) included 13 cohorts (n=207,533). 5 studies found a positive association between alcohol intake and weight gain/BMI, e.g. risk of obesity at 3.6 years OR = 1.42 for male drinkers compared with non-drinkers. 2 studies found an inverse association in women only; risk of obesity at 12.9 years in women drinking ≥2.2 drinks/day OR = 0.73 vs. non-drinkers; risk of major weight gain at 10 years for women drinking 1 to 6.9 drinks/week OR = 0.7. 2 studies found no association.
  - 3 studies on WC found a positive association, 1 study found an inverse association, 2 studies found no association (data NR).
- USDA (2010) included 7 prospective cohorts with a follow-up of 4 to 10 years. Of these cohorts, 5/7 found no significant association or a significant inverse association between alcohol consumption and weight gain; e.g. risk of major weight gain (≥10 kg) OR = 0.7 (95% CI 0.5 to 0.9) in female moderate drinkers (1 to 6.9 drinks/week) vs. non-drinkers.
  - The other 2 studies found positive associations with increased weight gain >4% or ≥5kg over 5 to 8 years at heavier drinking (above about 20 to 26 units a week, or about 3 to 4 units per day): OR = 0.86 to 0.96 in light to moderate drinkers and OR = 1.07 to 1.29 in heavier drinkers vs. non-drinkers.
- Summerbell et al. (2009) included 20 prospective cohorts with follow-up between 1 and 18 years. The majority (14/20) found no significant association between alcohol consumption and weight-related outcomes (mixed directions of effect); 6 studies also showed mixed directions of significant effects (data NR).

3. Issues in interpretation of evidence

- Assessments of the effect of alcohol consumption may be particularly challenging for a number of reasons, including that individuals may abstain from alcohol for medical reasons that may affect weight-related outcomes.
- Self-reported alcohol consumption may be particularly prone to under-reporting.
- Bendsen et al. (2013) was funded by the Dutch Beer Institute.

4. Potential mechanisms

From WCRF/AICR 2005 SLR:

- Alcohol is an energy-dense nutrient (7kcal/g), the oxidation of which takes precedence over other substrates and thus has the potential for displacing fat oxidation and promoting fat storage.
- Alcohol may stimulate appetite, the mechanisms for which remain unclear but have been postulated to occur via the stimulation of the hedonic components of appetite control or by inhibition of satiation.

9. Dietary Constituents

9.1 Total carbohydrate

1. Available evidence (via NICE 2014 Report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of Evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults and children	RCT: 0 Cohort: 16 (7 adults, n=79,083, 9 children, n=2,625)	Adults: 4 studies no significant association. 2 studies inverse association with weight gain. 1 study positive association with change in body weight/fat.	No association
			Children: 6 studies no significant association. 3 studies inverse association with BMI change or body composition.	

Adults

- Cohort studies
    - Summerbell et al. (2009) included 7 cohorts (n=79,083) with 1 to 12 years' follow-up. 4 studies (n=44,180) found no significant association between carbohydrate intake and weight-related outcomes.
        - 2 studies (n=34,849) found an inverse association with weight gain over 4 to 10 years: regression coefficient = -0.001 (95% CI 0.0024 to 0.0004), and 1 study (n=54) found a positive association with change in body weight and body fat, correlation coefficients between 0.30 to 0.35 depending on measurement.

Children

- Cohort studies
    - Summerbell et al. (2009) included 9 cohorts (n=2,625) with 1 to 15 years' follow up. Most of the studies (6/9; n=1,282) found no association between total carbohydrate intake and various weight related outcomes in children and young people (mixed directions of effect where reported).
        - Three studies (n=1,343) found significant inverse relationships between total carbohydrate and a weight related outcome: 1) −0.044 kg/year weight change per 1% increase in energy from carbohydrates; 2) −11.70 kg/m^2 (95% CI −20.5 to −2.9) BMI change over 6 years per 1% increase in energy from carbohydrates; 3) -0.003 change in subscapular skinfold per 1kJ/g increase in carbohydrate intake.

3. Issues in interpretation of evidence

- The cohort studies assessed carbohydrate intake in various ways (% energy as carbohydrate or carbohydrate intake in grams).

4. Potential Mechanisms

Due to the limited nature of the evidence, potential mechanisms were not explored further for this exposure.

9.2 Glycaemic load

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	U.S Department of Agriculture Nutrition Evidence Library 2010c [+]
USDA DGAC (2015) scientific report [++]	N	

Note on quality assessment of USDA 2010: Quality assessments for reviews identified via the NICE (2014) report are taken from the NICE (2014) report (see protocol in **Appendix**). Assessments were made on individual exposure sections, not on the report as a whole, hence it appears that inconsistent assessment grades are given.

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
USDA 2010	Adults	RCT: 13 (1*, n=203) Cohort: 2 (1*, n=376) Other: 7	RCT: No significant effect on weight change. Cohort: Positive association in women only.	Inconclusive

*Relevant studies included

Adults

- RCTs
    - USDA (2010) included one RCT (n=203) comparing a high glycaemic index (GI) and a low GI diet (difference in GI 35 to 40 units). There was no significant difference in weight change over 18 months between the diets: low GI -0.41kg diet vs. high GI diet -0.26kg (p=0.93).
- Cohorts
    - USDA (2010j) included one cohort study (n=376) that found a positive association between GI and weight-related outcomes over 6 years, in women only: 2% increase in body weight (95% CI 0.1% to 4%) and 0.9% increase in %body fat (95% CI 0.04% to 1.7%) per 10-unit increase in baseline GI. Other measures of adiposity in women, and all measures of adiposity in men, were not significantly associated with GL.

3. Issues in interpretation of evidence

- The RCT had a high loss to follow-up (40%).

4. Potential Mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

9.3 Total protein

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	3	Schwingshackl et al. 2013 [++]; Santesso et al. 2012 [++]; Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Schwingshackl et al 2013	Adults	RCT: 15 (unclear*, maximum 3, n=107) Cohort: 0	RCTs: No significant differences between high and low protein groups at 1-2 years follow-up.	No association
Santesso et al. 2012	Adults	RCT: 74 (6*, n=143) Cohort: 0	RCTs: Higher protein diets associated with small to moderate weight change.	Inverse association
Summerbell et al. 2009	Adults and children	RCT: 0 Cohort: 19 (8 adults, n=81,286; 11 children, n=2,396)	Adults – 1 study positive association with weight gain in whites only, 7 studies no significant association (mixed directions). Children – 6 studies positive associations in at least one analysis; 5 studies no significant association (mixed directions).	No association

* Relevant studies included

Adults

- RCTs – high vs. low protein diets
  - Schwingshackl et al (2013) included RCTs with follow-up >1 year. In relevant cohorts, there were no significant differences between high and low protein groups (% energy from protein: 25-40% vs. 10-20%) in weight, WC, or fat mass at 1 to 2 years' follow up. Weight: WMD -0.39 kg (95% CI -1.43 to +0.65); WC: WMD -0.98 cm (95% CI -3.32 to +1.37); fat mass: WMD -0.59 kg (95% CI -1.32 to +0.13). The direction of the effects was towards a benefit with the higher protein diets.
  - Santesso et al. (2012) included RCTs of ≥28 days' length comparing higher versus lower protein diets and found that higher protein diets (median 27% energy from protein) were associated with small to moderate weight, BMI, and WC reductions compared with lower protein diets (median 18% energy from protein). Weight change: SMD -0.36 (95% CI -0.56 to -0.17); BMI change: SMD -0.37 (95% CI -0.56 to -0.19); WC change: SMD -0.43 (95% CI -0.69 to -0.16).
    - Higher protein diets (median 27% energy from protein) compared to low protein diets (median 18% energy from protein) resulted in 1.21 kg (95% CI -1.88 to -0.57) greater weight loss and 0.51 kg/m^2 (95% CI -0.77 to -0.26) greater BMI reduction at 3 months. Meta-regression suggested that those with a higher BMI at the start of a study had greater weight loss.
- Cohort studies
  - Summerbell et al. (2009) identified 8 cohort studies (n=81,286) in adults lasting 1 to 12 years. Most (7/8 studies) had non-significant findings, with most (3 studies) finding a positive direction of effect where reported, although 1 large study reported an inverse direction of effect for WC.

The one significant association was positive: 2 kg difference in mean weight between highest and lowest quintiles of protein intake (not quantified) over 10 years in white individuals, p<0.01; findings in black individuals non-significant.

Children

- Cohort studies
  - Summerbell et al. (2009) included 11 prospective cohorts (n=2,396; possible overlap of 3 small cohorts), 6 (n=942) of which showed a positive association between protein intake and at least 1 weight-related outcome in at least 1 analysis (e.g. in either boys or girls). The other 5 cohorts (n=1,454) were non-significant. Effect sizes ranged from a small non-significant inverse association of kJ/g protein intake with skinfold thickness (sole inverse association, regression coefficient -0.001, p=0.79) to a relatively large association between high protein intake at 12 months and BMI above the 75th percentile at 7 years: OR = 2.39 (95% CI 1.14 to 4.99), p=0.02.

3. Issues in interpretation of evidence

- Analyses in Schwingshackl et al (2013) may have lacked power to detect small effects.
- Studies in Santesso et al. (2012) used a different methodology from Schwingshackl et al (2013), which may account for discrepancies; Santesso et al. (2012) also included shorter-term studies.
- Most RCTs were in individuals living with overweight or obesity and aimed at weight loss. Total energy intake was similar in the higher and lower protein groups, though there was a difference for some RCTs.

4. Potential Mechanisms

- Protein has been shown to have beneficial effects on satiety.
- In adults, high-protein intake has been shown to be a significant predictor of fat free mass retention, but may not impact on fat mass (Schwingshackl et al 2013).
- In children, high protein intake has been associated with risk of obesity (see Koletzko et al. 2016).

9.4 Caffeine

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Summerbell et al. 2009 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of evidence

Published review	Population	Included studies	Results	Summary
Summerbell et al. 2009	Adults	RCT: 0 Cohort: 3 (n=32,612)	2 studies no significant association with weight change; 1 study women gaining weight significantly more likely to consume caffeine.	No association

Adults

- Cohort studies
    - Summerbell et al. (2009) identified 3 prospective cohort studies (n=32,612) with follow up of between 1 and 12 years. Two out of the 3 studies (n=556 and n=31,940) found no significant association between caffeine intake and weight change over 1 to 4 years (regression coefficients 0.143 and 0.0003, units not specified). The third small study (n=116) found no association between caffeine and BMI change in men (figures NR), but found women in a 'BMI-gain' group (not further defined) were more likely to consume caffeine: OR = 0.2 (95% CI 0.04 to 0.94), p=0.04.

3. Issues in interpretation of evidence

- Method of dietary assessment varied.
- All studies adjusted for some confounders, but not for physical activity level.

4. Potential Mechanisms

Due to the limited nature of the epidemiological evidence, potential mechanisms were not explored further for this exposure.

9.5 Catechins

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	1	Phung et al. 2010 [++]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Phung et al. 2010	Adults	RCT: 15 (4*, n=388) Cohort: 0	Meta-analysis: Green tea catechins with caffeine showed significant reductions in BMI, body weight, and WC vs. caffeine-matched control.	Inverse association

* Relevant studies included

Adults

- RCTs – increasing intake of catechins
    - Phung et al. (2010) included 4 RCTs (n=388) on green tea catechins with caffeine. Meta-analysis found that green tea catechins (583 mg to 714 mg/day) with caffeine (70 to 114 mg/day) consumed for 3 to 12 weeks reduced BMI: -0.55 kg/m^2 (95% CI -0.65 to -0.40), body weight: -1.38 kg (95% CI -1.70 to -1.06), and WC: -1.93 cm (95% CI -2.82 to -1.04) compared with dose matched caffeine control (0 to 126 mg catechins plus 70 to 114 mg caffeine).

3. Issues in interpretation of evidence

- The meta-analysis included some RCTs that provided catechins as capsules rather than as tea.
- Some RCTs were in populations with comorbidities including obesity and diabetes.
- The clinical significance of effects is modest at best. Current data do not suggest that green tea catechins alone affect anthropometric measurements.

4. Potential Mechanisms

- The principal catechin, epigallocatechin gallate (EGCG) may have a positive impact on glucose tolerance and thermogenesis (McKay and Blumberg, 2007).
- However, Phung et al. (2010) note that the trial that evaluated EGCG alone showed non-significant increases in BMI and body weight when compared with placebo. This suggests that the effect of green tea catechins might be due to the combination, rather than to any single catechin, and merits further investigation.

10 Other

10.1 Sleep

1. Available evidence (via NICE 2014 report)

Source	No. of reviews	Authors [quality]
NICE (2014) report	2	Magee et al. 2012 [+]; Chen et al. 2008 [+]
USDA DGAC (2015) scientific report [++]	N	

2. Summary of the evidence

Published review	Population	Included studies	Results	Summary
Magee et al 2012	Adults and children	RCT: 0 Cohort: 20 (11 adults, n=120,690, 7 children, n=10,959)	Adults – 4 studies significant inverse association with sleep duration; 4 studies significant U-shaped association; 5 no significant association. Children – 7 studies significant inverse associations with sleep duration.	Inconclusive (adults) Inverse association (children)
Chen et al. 2008	Children	RCT: 0 Cohort: 3 (n=10,189) Other: 14	3 studies significant inverse associations with sleep duration.	Inverse association (children)

Adults

- Cohort studies
  - Magee et al (2012) included 13 studies examining sleep duration.
    - 4 studies found a significant relationship between short sleep duration (generally ≤5 hours) and weight-related outcomes, although 1 was in post-partum mothers. Effect sizes ranged from small: BMI change: beta=0.015 kg/m^2 (95% CI 0.03 to 0.27) with short sleep duration to large: short sleep at age 27 associated with increased obesity risk, OR = 8.2 (95% CI 1.9 to 36.3).
    - 4 studies found a significant U-shaped relationship, with both short and long sleep duration (generally ≥9 hours) associated with weight-related outcomes. Effect sizes were moderate, e.g.1.84kg (95% CI 1.13 to 2.62) weight gain, and 35% greater likelihood of a 5kg weight gain.
    - 5 studies found no significant relationship, including 1 study measuring sleep duration objectively.

Children

- Cohort studies
  - Magee et al (2012) included 7 studies that all reported a significant inverse association between sleep duration and weight-related outcomes at follow-up from 3 to 27 years.
    - Effect sizes were moderate, e.g. sleep duration at age 5 was associated with reduced obesity odds at age 32: OR = 0.65 (95% CI 0.43 to 0.97), p=0.034; <10.5h sleep at age 3 was associated with higher odds of obesity at age 7, OR = 1.45 (95% CI 1.10 to 1.89), p<0.01.
  - Chen et al. (2008) included 3 cohort studies that all found a significant inverse association between sleep duration and weight-related outcomes (data NR).

- Meta-regression of cohort, cross-sectional and case-control studies (mainly the latter two) found that odds overweight/obesity decreased per 1 hour increase in sleep duration: pooled OR = 0.91 (95% CI 0.84 to 1.00), p=0.044.
- ≥2 hours less sleep than recommended was associated increased odds of overweight/obesity, pooled OR = 1.92 (95% CI 1.15 to 3.20).

3. Issues in interpretation of evidence

- Only one study assessing short sleep duration in adults in Magee et al (2012) used an objective measure of sleep. Only studies using objectively measured weight outcomes reported a U-shaped relationship between sleep and weight in adults.
- Studies in children did not use consistent definitions of short sleep duration.
- Meta-analysis in Chen et al. (2008) included cross-sectional studies, which may indicate reverse causality to some extent.
- Magee et al (2012) noted that there appear to be age related changes in the association between sleep duration and weight, for unclear reasons.

4. Potential mechanisms

- Short sleep duration may increase appetite, and reward response to energy-dense foods in particular (see Chaput 2010).
- Short sleep duration may be associated with decreased energy expenditure from exercise engagement and non-exercise activity thermogenesis.

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Appendix

Protocol for the Diet, Nutrition and Physical Activity: Energy Balance and Body Fatness Literature Review

Prepared by WCRF International, July 2016

1. Background

In recent years, evidence showing a link between greater body fatness and cancer risk has strengthened, with the WCRF/AICR Continuous Update Project (CUP) concluding there is strong evidence that greater body fatness increases the risk of 11 cancers. Furthermore, rates of overweight and obesity have continued to rise in both adults and children in many parts of the world[1].

Therefore it was decided to update the WCRF/AICR 2007 Expert Report[2] chapter 8 on the determinants of weight gain, overweight and obesity for the report, Diet, Nutrition, Physical Activity and Cancer: a Global Perspective, our 3rd Expert Report, to be published in 2018.

2007 Expert Report conclusions from the evidence for weight gain, overweight and obesity based on the 2005 WCRF/AICR systematic literature review (SLR) (see: Summerbell et al 2009[3]) and Expert Panel discussion:

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND WEIGHT GAIN, OVERWEIGHT, AND OBESITY

In the judgement of the Panel, the factors listed below modify the risk of weight gain, overweight, and obesity. Judgements are graded according to the strength of the evidence.

Factors that decrease risk promote appropriate energy intake, and those that increase risk promote excess energy intake, relative to the level of energy expenditure.

	DECREASES RISK	INCREASES RISK
Convincing	**Physical activity**	**Sedentary living[1]**
Probable	**Low energy-dense foods[2]** **Being breastfed[4]**	**Energy-dense foods[2 3]** **Sugary drinks[5]** **'Fast foods'[6]** **Television viewing[7]**
Limited — suggestive		
Limited — no conclusion	Refined cereals (grains) and their products; starchy roots, tubers, and plantains; fruits; meat; fish; milk and dairy products; fruit juices; coffee; alcoholic drinks; sweeteners	
Substantial effect on risk unlikely	None identified	

1 Sedentary living comprises both high levels of physical inactivity and low levels of physical activity (in terms of intensity, frequency, and duration). Also see box 5.2.
2 The direct epidemiological evidence for low energy-dense foods is from wholegrain cereals (grains) and cereal products, non-starchy vegetables, and dietary fibre. The direct epidemiological evidence for energy-dense foods is from animal fat and fast foods. These are interpreted as markers of the energy density of diets, based on compelling physiological and mechanistic evidence (box 8.1).
3 Some relatively unprocessed energy-dense foods (which tend to be eaten sparingly), such as nuts, seeds, and some vegetable oils, are valuable sources of nutrients.
4 The evidence relates principally to obesity in childhood, but overweight and obesity in children tend to track into adult life: overweight children are liable to become overweight and obese adults.
5 The evidence relates to all drinks containing added caloric sweeteners, notably sucrose and high-fructose corn syrup. Fruit juices are also sugary drinks and could have similar effects, but the evidence is currently limited.
6 'Fast foods' characteristically are consumed often, in large portions, and are energy dense (box 8.2).
7 Television viewing (box 8.4) is here identified as a sedentary activity (box 5.2). It is also associated with consumption of energy-dense foods (box 8.1). The evidence relates specifically to childhood and adolescence, and is taken also to apply to adults.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

[1] NCD Risk Factor Collaboration (NCD-RisC). 'Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants'. 2016. *Lancet*, 387: 1377-96.
[2] World Cancer Research Fund / American Institute for Cancer Research. 2007. "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective." In. Washington DC: AICR.
[3] Summerbell, C. D., W. Douthwaite, V. Whittaker, L. J. Ells, F. Hillier, S. Smith, S. Kelly, L. D. Edmunds, and I. Macdonald. 2009. 'The association between diet and physical activity and subsequent excess weight gain and obesity assessed at 5 years of age or older: a systematic review of the epidemiological evidence', *Int J Obes (Lond)*, 33 Suppl 3: S1-92.

2. Research question

The research question addressed by this literature review is: 'What are the food-, nutrition- and physical activity-related determinants of weight gain, overweight and obesity in humans?'.

3. Approach and rationale

3.1 Agreed approach

- To conduct a 'review of published reviews'.
- To identify published reviews addressing the research question.
- One evidence review was identified which was published in 2014 by the National Institute of Health and Care Excellence (NICE) [4], entitled 'Maintaining a healthy weight and preventing excess weight gain in children and adults: An evidence review of modifiable diet and physical activity components, and associated behaviours'. This was used as a source for identifying published reviews.
- To obtain the published reviews in the NICE (2014) report.
- To use meta-analyses in published reviews where possible. If not available, then to summarise evidence from individual studies but not conduct meta-analyses.
- To update the gaps in evidence where necessary, e.g. where the NICE (2014) report does not cover an exposure of interest.
- To apply the WCRF/AICR criteria for judging the evidence as used for CUP Reports related to specific cancer sites.

3.2 Rationale

- **A 'review of published reviews'**: Due to the large number of individual studies covering a wide range of exposures and the existence of a large number of reviews addressing relevant questions it was decided to take a pragmatic approach based primarily on a review of reviews.
- **Avoiding duplication of work**: WCRF/AICR internal policy for all its CUP reports is to not duplicate work, or conduct a review, if one of adequate quality already exists. The NICE (2014) report has been identified and has sufficient overlap of scope with the WCRF/AICR research question to negate conducting a separate review.
- **Building on 2005 WCRF/AICR SLR**: The NICE (2014) report is a 'review of reviews' of epidemiological research that is based on the 2005 WCRF/AICR SLR for the 2007 Expert Report. It can therefore be seen as an update to the SLR conducted for the 2007 Expert Report.
    - The exposures of 'lactation' and 'having been breastfed' are not included in the NICE (2014) report. Evidence for these exposures will be sought separately (see **Section 4** and **Section 5** of this protocol).
    - The NICE (2014) report does not review the mechanisms linking the exposures with the outcomes. For this literature review, evidence for biological plausibility will be addressed (see **Section 9** of this protocol).
- **Criteria for judging the evidence**: The criteria for judging the evidence developed for the 2007 Expert Report and used throughout the CUP process will be applied to the evidence identified as part of this literature review. This ensures consistency across the work of the CUP.

[4] National Clinical Guideline, Centre. 2014. 'National Institute for Health and Clinical Excellence: Guidance.' in, *Obesity: Identification, Assessment and Management of Overweight and Obesity in Children, Young People and Adults: Partial Update of CG43* (National Institute for Health and Care Excellence (UK). Copyright (c) National Clinical Guideline Centre, 2014.: London).

4. Preliminary work to identify exposures of interest – completed by June 2016

Preliminary work was carried out to identify exposures of priority.

4.1 Initial exposures of interest

This literature review addresses a range of factors, with a focus on possible interactions, in addition to single isolated factors. The literature review will focus on causal factors included in the 2007 Expert Report, the NICE (2014) report, and other narrative and mechanistic published reviews. The list of exposures was agreed through discussion by the CUP Secretariat. Factors that relate primarily to policy, such as environmental factors, will not be included.

The exposures of interest were: Mediterranean diet, lactation, having been breastfed, breakfast, family meals, eating in the evening, eating frequency, snacking, wholegrains, refined grains, fruits and vegetables, pulses (legumes), nuts, meat, fish, dairy, fast foods, confectionery, water, sugar sweetened beverages, non-nutritively sweetened beverages, fruit juice, coffee and tea, alcoholic drinks, total carbohydrate, foods containing dietary fibre, free sugars, glycaemic load, dietary fat, total protein, caffeine, catechins, physical activity, sedentary time, screen time, energy density of the diet

4.2 Process for identifying exposures of priority

The plan was to use a less intensive method to identify exposures that may be determinants of weight gain, overweight and obesity. Then conduct a more detailed assessment.

To identify exposures of priority, the following process was undertaken:

- Evidence for each exposure was identified from the NICE (2014) report.
- This was supplemented with additional evidence from the United States Department of Agriculture Dietary Guidelines for Americans (USDA DGAC) 2015 scientific report[5].
    - ***Rationale****: The NICE (2014) report includes evidence from the USDA DGAC (2010) scientific report where relevant. In 2015, the USDA updated their dietary guidelines and published the USDA DGAC (2015) scientific report. Where an exposure in the NICE (2014) report has evidence from the USDA DGAC (2010) scientific report, the updated USDA DGAC (2015) scientific report were checked for additional evidence.*
- The exposures of 'lactation' and 'having been breastfed' were not included in the NICE (2014) report and so a separate preliminary literature search was conducted to identify relevant evidence.
    - The search strategy for these exposures followed that of the 2005 WCRF/AICR SLR (see also **Section 10.1** of this protocol). The search was conducted in August 2015. The start date of the search was 1st January 2006 (after the cut-off for the 2005 WCRF/AICR SLR of 31st December 2005) and the end date was August 2015.
- The combined evidence based on summaries of evidence presented in the published reviews (meta-analyses or narrative summaries) was presented to the CUP Panel for discussion in June 2016.
- Exposures that did not show evidence of an association were de-prioritised. Exposures were prioritised when there was evidence at least suggestive of a direction of effect, or if there was a conclusion of 'Limited – suggestive' or higher from the 2007 Expert Report.

[5] U.S Department of Agriculture Nutrition Evidence Library. 2015. "2015 Dietary Guidelines Advisory Committee: Systematic Reviews of the Individual Diet and Physical Activity Behavior Change Subcommittee." In. Alexandria, VA: Department of Agriculture, Center for Nutrition Policy and Promotion.

4.3 List of prioritised exposures

The agreed prioritised exposures as per the preliminary work are:

- Mediterranean diet
- Lactation
- Having been breastfed
- Wholegrains
- Refined grains
- Fruits and vegetables
- Meat
- Dairy products
- Fast foods
- Sugar sweetened beverages
- Foods containing dietary fibre
- Free sugars
- Dietary fat
- Physical activity
- Sedentary time
- Screen time
- Energy density of the diet

The agreed de-prioritised exposures as per the preliminary work are:

- Vegetarian/vegan diets
- Adherence to dietary guidelines
- Dietary variety
- Breakfast
- Family meals
- Eating in the evening
- Eating frequency
- Snacking
- Pulses (legumes)
- Nuts
- Fish
- Confectionary
- Water
- Non-nutritively sweetened beverages
- Fruit juice
- Coffee and tea
- Alcoholic drinks
- Total carbohydrate
- Glycaemic load
- Total protein
- Caffeine
- Catechins
- Sleep

4.4 Agreed next steps

- The plan for a supplementary literature search to update the evidence beyond the cut-off of the NICE (2014) report was agreed (see **Section 5** of this protocol).
- The CUP Panel will discuss the updated evidence for the prioritised exposures at the March 2017 CUP Panel meeting.

5. Search strategy

There will be four sources of evidence for this literature review: the NICE (2014) report; the USDA DGAC (2015) scientific report; the preliminary literature search (conducted August 2015); and the supplementary literature search (to be conducted August 2016).

NICE (2014) report

Evidence from the NICE (2014) report will be included for all exposures, except 'lactation' and 'having been breastfed' (these are not part of the NICE (2014) report scope).

USDA Dietary Guidelines Advisory Committee (2015) scientific report

Where available, evidence from the USDA DGAC (2015) scientific report will be included (see **Section 4.2** of this protocol).

The preliminary literature search (conducted August 2015)
Evidence from the preliminary literature search will be included for the exposures 'lactation' and 'breastfeeding' (see **Section 4.2** and **Section 10.1** of this protocol).

The supplementary literature search
To update the evidence beyond the cut-off of the NICE (2014) report, a supplementary literature search will be undertaken by the team at Imperial College London. The search strategy will be based on that used for the NICE (2014) report (see Appendix A—D page 9 of the NICE (2014) report). The Pubmed database will be searched. The date range of the supplementary literature search will be 1st October 2013 to present. Prioritised and de-prioritised exposures will be included in the search; published reviews pertaining to prioritised exposures will be subjected to the inclusion/exclusion criteria as per **Section 6**. Published reviews pertaining to de-prioritised exposures will be stored for future reference as part of the CUP database.

The search terms that will be used can be found in **Section 10.2** of this protocol.

6. Selection of published reviews

The published reviews identified via the supplementary literature search will initially be assessed for relevance based on title and abstract by at least two people. The full texts for the remaining published reviews will then be obtained. Published reviews matching the pre-defined criteria will be included in the literature review (see below). Where a published 'review of reviews' is identified, the reviews therein (and, as necessary, individual primary studies) will be subject to inclusion/exclusion criteria below. Inclusion will be verified by at least two people.

Evidence types	Published reviews identified via the supplementary search (August 2016) will be included if they have conducted a meta-analysis of randomised controlled trials or prospective cohort studies. Other published reviews (identified via NICE (2014) report) or primary studies will be included that are (of): • Prospective cohort studies lasting at least 12 months. • Randomised controlled trials (RCTs) or interventions of any duration (following the NICE report), except those with weight loss as an outcome. • Ecological studies, which are longitudinal and able to demonstrate a trend over time. Correlational or cross-sectional data may be used as supporting evidence. Studies will be excluded that are: • Case-control studies or retrospective studies.
Exposures	Prioritised exposures are: Mediterranean diet; lactation; having been breastfed; wholegrains; refined grains; fruits and vegetables; meat; dairy products; fast foods; sugar sweetened beverages; foods containing dietary fibre; free sugars; dietary fat; physical activity; sedentary time; screen time; energy density of the diet Exposures/interventions/settings not included are: interventions offered by national health services, local authorities, early learning settings, schools, workplaces, self-help, commercial or community programmes, programmes for

	overweight or obesity people, management of medical conditions and health profession led interventions. Also, interventions comparing different behaviours e.g. diet vs. physical activity.
Outcomes	Outcomes will be included that are: • Any measure of body fatness or weight (e.g. BMI, waist circumference, % overweight, % obesity, fat mass). • Weight gain (e.g. change in weight, change in BMI, change in waist circumference). Statistical methods include but are not limited to OR, RR, regression coefficients as well as absolute changes in kg or cm. Outcomes will be excluded that are: • Weight or fat loss, as the focus of this report is on the determinants of weight gain and overweight, rather than treatment. • Diseases associated with obesity. • Energy intake. Studies controlling for energy intake will be examined on a case-by-case basis. • Process measures such as acceptability of information.
Populations	The populations studied will be limited to free-living adults and children not undergoing treatment for weight loss. The focus is on the general population. This includes infants (pre-weaning). Cancer survivors will not be studied. Populations excluded: pregnant women; adults or children receiving treatment for underweight; population solely selected on bases of being overweight or obese; subgroups of the general population such as post-pregnancy (except for the exposure 'lactation'), learning difficulties, mental health conditions, and disabilities; patient groups e.g. people living with diabetes, people living with metabolic syndrome; people with genetic predisposition to obesity.
Language	Research will be included that is published in English only.

7. Quality of published reviews

The quality of included published reviews will be reported. For published reviews identified via the NICE (2014) report, the quality rating as assessed by the NICE (2014) report will be used. This has three levels:
[-] Low quality
[+] Moderate quality
[++] High quality

The full checklist used is in Appendix D of the NICE (2014) report (please see reference section of this protocol).

For published reviews identified from other sources (see **Section 5** of this protocol), the quality criteria used in the NICE (2014) report will be applied. Question eight of this criteria list relates to applicability of the

published review to the UK population; this has been amended for the purposes of the WCRF/AICR literature review to the applicability of the published review to a general population.

Where published 'reviews of reviews' are identified, a quality assessment will be carried out. This will be a version of the quality assessment used by NICE (2014) report modified by WCRF International for the purposes of this literature review; the modified template is presented below. A quality assessment will also be carried out on the published reviews found within the 'reviews of reviews', as outlined above.

The derived quality ratings will be verified by at least two people.

Rapid quality assessment for 'reviews of reviews' – modified from NICE (2014) report, appendix D

1	Does the review of reviews address an appropriate and clearly-focused question that is relevant to one (or more) exposure(s) of interest?	Yes	No	Unclear
2	Does the review of reviews include reviews that are relevant to the exposure(s) of interest? • *e.g. are there clearly stated inclusion/exclusion criteria?*	Yes	No	Unclear
3	Is the literature search sufficiently rigorous to identify all the relevant reviews? *Must meet following criteria for a yes:* • *At least two electronic sources should be searched* • *Must include years and databases searched* • *Key words must be stated*	Yes	No	Unclear
4	Is the quality of included reviews (or the primary studies therein) appropriately assessed and reported? *Must meet following criteria for a yes:* • *Methods of assessment provided* • *Quality of included studies reported* • *Quality of included studies considered in conclusions*	Yes	No	Unclear
5	Is an adequate description of the analytical methodology used, or approach to synthesis, included and are the methods used appropriate to the question? • *e.g. has the review of reviews taken appropriate steps to account for all the data/studies in each review in their interpretation?* • *Has the review of reviews attempted to identify overlap of primary studies between reviews?*	Yes	No	Unclear
6	Were the characteristics of the included reviews provided? • *e.g. data should be provided on included study design, results/conclusions, effect size (as available), participants, heterogeneity; might be in table format*	Yes	No	Unclear
7	Were potential conflicts of interest reported? *Potential sources of support should be clearly acknowledged for the review of reviews and considered for the included reviews (and studies therein).*	Yes	No	Unclear
8	Can the results be applied to a general population? • *Answer yes if majority of reviews or primary studies in healthy populations, or representative populations, where results can be generalised*	Yes	No	Unclear

8. Data extraction

8.1 Included published reviews

All identified published reviews will be subjected to the pre-defined inclusion/exclusion criteria as outlined in **Section 6** of this protocol. This process will be checked by at least two people.

The included published reviews for each exposure will be reported in the following table:

Source	No. of reviews	Authors [quality]
NICE (2014) report	[number]	[published reviews]
USDA DGAC (2015) scientific report	Y/N	

Supplementary literature search August 2016	[number]	[published reviews]

For the exposures 'lactation' and 'having been breastfed' an additional row will be added to the above table to report the results from the preliminary literature search.

8.2 Results from meta-analyses

The results of meta-analyses will be extracted from the included published reviews for each exposure and reported in the literature review. The data extraction will be checked by at least two people.

Where a meta-analysis includes individual studies which do not fit the pre-defined criteria – for example a given meta-analysis includes five prospective cohort studies (meets inclusion criteria) and two cross sectional studies (do not meet inclusion criteria), or a given meta-analysis includes seven studies in the general population (meets inclusion criteria) and four studies in overweight subjects (do not meet the inclusion criteria) – the inclusion of this result will be addressed on a case by case basis. As a guiding principle, if the majority of studies included in the meta-analysis meet the pre-defined criteria, the result will be included and the caveats outlined in the text.

The results of meta-analyses from included published reviews for each exposure will be reported in the following table:
**Note – evidence for children will be reported in separate tables to evidence for adults.*
**Note – meta-analyses of RCTs will be reported in separate tables to meta-analyses of prospective cohort studies.*

[insert population: adults or children]					
Meta-analyses of [insert study design]					
[to insert abbreviations used in table]					
Outcome	***Publication***	***Intervention*** [or exposure] ***description***	***Results***		
[example]			[statistic used]	[result and direction]	[no. of studies, participants, I^2]

8.3 Results from individual studies

For included published reviews which do not present meta-analyses (identified via the NICE (2014) report), the individual studies of the published reviews will be extracted and subjected to the pre-defined inclusion/exclusion criteria as used for published reviews (see **Section 6** of this protocol). This process will be checked by at least two people.

It is anticipated that some exposures will yield a high number of individual studies. Due to capacity constraints, it may be necessary to impose an additional exclusion criterion capping the number of individual studies reported in the results tables. This will be based on study size (number of participants), with smaller studies being omitted from the results tables (for example, prospective cohort studies with fewer than 500 participants). This will be addressed on an exposure-by-exposure basis. Where this additional criterion is applied, it will be outlined in the text.

The results of the included individual studies for each exposure will be extracted and reported in the literature review. The data extraction will be checked by at least two people.

The results of individual studies (identified via included reviews) for each exposure will be reported in the following table:
**Note – evidence for children will be reported in separate tables to evidence for adults.*
**Note – RCTs will be reported in separate tables to prospective cohort studies.*

[insert population: adults or children]				
[insert study design]				
[to insert abbreviations used in table]				
Outcome	***Publication*** *Review*	***Intervention*** [or exposure] ***description***	***Results***	***n***
[example]				

9. Evidence of biological plausibility

9.1 Rationale for including evidence of biological plausibility

- As part of the process of judging the evidence, the CUP Panel will consider the biological plausibility of a given observed association, for example if an association is observed between sugar sweetened drinks and weight gain, the potential physiological, psychological or broader social mechanisms through which that association is operating will be considered. This is part of the criteria for grading the evidence as used when judging the evidence for cancers and forms a critical component of judging causality.
- It was agreed as part of the preliminary work that evidence able to demonstrate biological plausibility should be sought to complement the epidemiological evidence. This process will not follow the same systematic criteria for sourcing epidemiological and intervention evidence.

9.2 Sources of evidence of biological plausibility

- Included published reviews which offer a review of biological plausibility. To follow up primary studies listed in references if insufficient detail is provided.
- Other published reviews relevant to the exposure (which may have been excluded from the epidemiological evidence review) which offer a review of biological plausibility. To follow up primary studies listed in references if insufficient detail is provided.
- Studies identified by CUP Panel members during discussions.
- Study types that will be included:
    - Human feeding studies
    - Live animal models
    - In vitro studies

9.3 Reporting of evidence of biological plausibility

- **For exposures judged as 'Convincing', 'Probable' or 'Limited – suggestive'**: The level of evidence should be reasonably broad, with the minimum detail necessary to support a link.
- **For exposures judged as 'Limited – no conclusion'**: There will be no formal review of the evidence for biological plausibility.
- **Appearance in document**: Text will be reported in literature review under subtitle of "Potential mechanisms".

10. Other information

10.1 Preliminary literature search (conducted August 2015)

Databases used to search for epidemiological evidence will be:

- Cochrane Database of Systematic Reviews
- PubMed.

Following the 2005 WCRF/AICR SLR, the search terms relating to weight gain, overweight and obesity will be paired with search terms relating to the causal factor of interest (using operator AND) in PubMed. The standard search is:
Weight Gain [MeSH] OR Weight Loss [MeSH] OR obes*[tiab] OR adipos*[tiab] OR weight gain[tiab] OR overweight[tiab] OR overeat*[tiab] OR overconsum*[tiab] OR weight change[tiab]
AND review
Filter: humans.

10.2 Supplementary literature search (to be conducted August 2016)

Search terms to be used in the supplementary literature search

#1 Obesity
#2 Overweight
#3 Weight Gain
#4 Ideal Body Weight
#5 (prevent* OR reduc* OR tackl* OR address*) AND (obes* OR "weight gain" OR "excess weight" OR overweight)
#6 (maintain* OR maintenance OR prevent* OR reduc* OR control* OR manag* OR monitor* OR healthy OR normal OR average) AND (weight OR bmi OR body mass index OR body fat OR waist circumference OR adiposity)
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#8 Primary Prevention
#9 Risk Factors
#10 Health Promotion
#11 Health Behavior
#12 Health Education
#13 Health Communication
#14 Information Dissemination
#15 Marketing of Health Services
#16 Health Knowledge
#17 Risk Reduction Behavior
#18 (promot* OR advert* OR marketing OR program* OR campaign* OR scheme* OR initiative* OR strateg* OR communicat* OR message)
#19 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 Diet
#21 beverages OR food
#22 Food Habits
#23 Feeding Behavior
#24 Energy Intake
#25 (diet* OR food* OR eat*)[ti]
#26 Exercise
#27 Motor Activity
#28 Physical Fitness
#29 (physical* OR exercis* OR fit* OR aerobic)[ti]

#30 Life Style
#31 Sedentary Lifestyle
#32 Size Perception
#33 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
#34 #19 OR #33
#35 #7 AND #34
#36 Meta-Analysis[OT]
#37 meta analy*[TI]
#38 metaanaly*[TI]
#39 Meta-Analysis
#40 "Systematic Literature Review"
#41 #36 OR #37 OR #38 OR #39 OR #40
#42 Animal
#43 Human
#44 #42 NOT (#42 AND #43)
#45 Comment[PT] OR Letter[PT] OR Editorial[PT]
#46 #44 OR #45
#47 #35 NOT #46
#48 #47 AND ("2013/10/01"[PDat] : "3000/12/31"[PDat])
#49 #48 AND #41