

# Chapter 4: Diabetes and glycaemia

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# Background

In healthy individuals, blood glucose levels are normally tightly regulated around 4 mM (4 mmol/L or 72 mg/dL), with time of day, and meal-associated fluctuations of just a few millimoles. Blood glucose levels outside the normal range may be an indicator of a medical condition, with persistently high levels (hyperglycaemia) reflecting some sort of pathology. Diabetes mellitus (DM) is a condition which is characterised by hyperglycaemia. There are considered to be two main types of diabetes, Type 1 and Type 2. Type 1 diabetes tends to occur in younger individuals (generally before the age of 40) and is characterised by a lack of insulin production by the pancreas. Type 2 diabetes, commonly referred to as adult- or maturity-onset diabetes is characterised by insufficient insulin production or an inappropriate responsiveness of body tissues to insulin (insulin resistance). Type 2 diabetes is more common, affecting in the region of 90% of all those with diabetes (Diabetes UK, 2012). Since Type 2 diabetes is more prevalent and much more closely linked with deleterious aspects of lifestyle, including diet, this type of diabetes is the focus of this review. Henceforth, the term 'diabetes' in this review will refer to Type 2 diabetes (DM) unless otherwise stated.

Audit data from the Quality and Outcomes Framework (QOF) which was introduced in 2004 and which uses General Practitioner (GP) diabetes registrations, indicate that in the region of 2.9 million people in the UK currently have a diagnosis of diabetes (Diabetes UK, 2012). The prevalence rates for diabetes since 1996 indicate a marked rise in the number of people diagnosed with the condition, and current estimates suggest that by 2025 more than 4 million individuals will have diabetes (Diabetes UK, 2012). The majority of these cases will be Type 2 diabetes, and this is thought to be partly due to rising rates of obesity, but also a reflection of the age profile of the UK population. Diabetes has serious micro- and macro-vascular complications, which tend to increase with lack of diabetic control. It is a major cause of renal failure, limb amputations and blindness. Treating DM takes approximately 10% of the current NHS budget (Diabetes UK, 2012).

The World Health Organization (WHO)/International Diabetes Federation (IDF) criteria for a diagnosis of DM are based on the presence of symptoms (i.e. polyuria, polydipsia and unexplained weight loss) combined with tests that yield a positive result for either a random venous plasma glucose concentration  $>11.1$  mmol/L or a fasting plasma glucose concentration  $>7.0$  mmol/L (whole blood  $>6.1$  mmol/L) or two hour plasma glucose concentration  $>11.1$  mmol/L two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT) (World Health Organisation, 2006). In the absence of overt symptoms, repeat and/or multiple positive results on the previous tests are to be used. This battery of tests has recently been supplemented with the potential to use glycated haemoglobin values. Recent World Health Organisation guidelines (2011) recommend using an HbA1c of 48 mmol/mol (6.5%) as the cut point for diagnosing DM, although they caution that a value of less than 48 mmol/mol (6.5%) does not exclude DM diagnosed using glucose tests (World Health Organisation, 2011).

Despite the existence of clear diagnostic criteria for DM, it should be recognised that the development of DM may take some years to emerge, with a progression from normo-glycaemia, through varying degrees of dysregulation (prediabetes) resulting in overt DM. A number of intermediate or prediabetic states have been identified for which there are established guidelines for diagnosis. Impaired Glucose Tolerance (IGT) is a stage of impaired glucose regulation (fasting plasma glucose  $<7.0\text{mmol/L}$  and OGTT two hour value  $>7.8\text{mmol/L}$  but  $<11.1\text{mmol/L}$ ). Impaired Fasting Glycaemia (IFG) has been introduced to classify individuals who have fasting glucose values above the normal range but below those diagnostic of DM (fasting plasma glucose  $>6.1\text{mmol/L}$  but  $<7.0\text{mmol/L}$ ) (World Health Organisation, 2006). In the US, almost 7% of adults have either IGT or IFG and these states are generally much more common than type 2 DM (Harris *et al.*, 1998). Whilst it is not a foregone conclusion that individuals with either of these prediabetic states will progress to DM, these states are associated with increased mortality compared with age- and gender-matched populations who have normal glucose tolerance. Much of this increased mortality risk is associated with cardiovascular disease (Barr *et al.*, 2007).

A considerable body of research has indicated that both Type 1 and Type 2 DM are strong independent risk factors for cardiovascular disease (Sarwar *et al.*, 2010). Often, cardiovascular disease and DM exist together as they share common modifiable risk factors such as obesity and in particular elevated central adiposity.

The value of prevention of progression from normal and prediabetic states through DM using dietary and other lifestyle approaches rather than through pharmacological routes has been highlighted by Hu (Hu, 2011). Gillies *et al.* (Gillies *et al.*, 2007) reviewed randomised controlled trials of the impact of interventions to prevent the progression from the prediabetic state to DM and concluded on the basis of evidence from 17 trials that lifestyle management was equally, if not more effective than pharmacological therapy. Whilst it is recognised that body weight control is a key factor in the prevention of progression to DM (Pi-Sunyer, 2007; American Diabetes Association and National Institute of Diabetes Digestive and Kidney Diseases, 2002), the identification of which dietary aspects improve glycaemia, insulinaemia and insulin resistance in individuals with normal or moderately compromised glycaemic control is worthy of attention.

## **Previous studies in COMA reports**

The two tables below list studies included in previously published reports from the Committee of Medical Aspects of Food Policy (Committee on Medical Aspects of Food Policy, 1989; Committee on Medical Aspects of Food Policy, 1991; Committee on Medical Aspects of Food Policy, 1994) that concerned the relationship between dietary carbohydrates and DM and/or glycaemia. Studies were initially scanned by title and abstract for relevance. Those deemed non-relevant were omitted and those of relevance were passed through the inclusion/ exclusion criteria used in this review.

## ***Papers from COMA reports that did not meet inclusion criteria***

The papers, published before 1990, noted in the first table would not have been eligible for inclusion in this review for the reasons listed.

Table 4.1 Previous studies in COMA reports\*: excluded studies

Authors, Year	Intervention description	Intervention duration/ follow up	Exclusion code that would be applied in this review	Exclusion detail
(Bolton <i>et al.</i> , 1981)	1) Whole oranges 2) Orange juice  1) Whole grapes 2) Grape juice  1) Grape juice 2) Grape juice with different osmolarity	Not reported	2	Subjects were not reported to have been randomly allocated to groups.
(Crapo and Kolterman, 1984)	1) Sucrose diet 2) Fructose diet	2 weeks	2	Subjects were not reported to have been randomly allocated to groups.
(Goulder <i>et al.</i> , 1978)	1) Addition of guar to a test meal	Acute meal study	2	The study was not a randomised controlled trial.
(Huttunen <i>et al.</i> , 1976)	1) Usual diet + sucrose 2) Usual diet + xylitol 3) Usual diet + fructose	2 years	2	Subjects were not reported to have been randomly allocated to groups.
(Keen <i>et al.</i> , 1979)	Not applicable	Not applicable	2	The study was not a randomised trial or cohort/prospective study (cross-sectional survey).
(Lock <i>et al.</i> , 1980)	1) Usual diet + sucrose 2) Usual diet + dried glucose syrup	2 years	2	Subjects were not reported to have been randomly allocated to groups.
(Mann and Truswell, 1972)	1) Basal diet 2) Basal + starch diet 3) Basal + sucrose diet	14 days	6	Subjects did not fit the definition of 'healthy' – all had been admitted to hospital with non-metabolic conditions such as cerebral vascular accident and nerve palsy.
(Peterson <i>et al.</i> , 1986)	1) Control diet 2) Sucrose diet	6 weeks	6	Subjects did not fit the definition of 'healthy' – all had DM.
(Reiser <i>et al.</i> , 1979)	1) Diet comprised 30% of calories from sucrose 2) Diet comprised 30% of calories from wheat starch	6 weeks	2	Subjects were not reported to have been randomly allocated to groups.
(Reiser <i>et al.</i> , 1986)	1) Low sugar diet 2) High sugar diet	20 weeks	2	All subjects received the same diet over the same period of time.
(Rosenthal <i>et al.</i> , 1985)	1) High-complex-carbohydrate, high-fibre, low-fat, low-cholesterol diet	26 days	2	The study did not have a 'control' group - all subjects received the same intervention.
(Vinik and Jenkins, 1988)	Not applicable	Not applicable	1	The publication was a review/ not original research.
(Werner <i>et al.</i> , 1984)	1) Usual diet + sucrose 2) Usual diet + saccharine	6 weeks	6	Subjects did not fit the definition of 'healthy' – all had radiolucent gall stones.
(Yudkin, 1964)	Not applicable	Not applicable	1	The publication was a review/ not original research.

\*(Committee on Medical Aspects of Food Policy, 1989; Committee on Medical Aspects of Food Policy, 1991; Committee on Medical Aspects of Food Policy, 1994)





## Papers from COMA reports that met inclusion criteria

The following paper would have been eligible for inclusion in this review, had it been published after 1990.

Table 4.2 Previous studies in COMA reports\*: included study

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Intervention duration	Intervention Style	Total number of participants	Intervention description
(Reiser <i>et al.</i> , 1981)	Generally healthy  Exaggerated insulin response to glucose load	US  50% Male  Age: (38.6) males (35.1) females	Crossover	6 weeks	All food provided	24	1) Diet containing 5% of total calories as sucrose 2) Diet containing 18% of total calories as sucrose 3) Diet containing 33% of total calories as sucrose

\*(Committee on Medical Aspects of Food Policy, 1989; Committee on Medical Aspects of Food Policy, 1991; Committee on Medical Aspects of Food Policy, 1994)

Reiser *et al.* (Reiser *et al.*, 1981) tested the effects of dietary sucrose on serum insulin and glucose in a sample of carbohydrate-sensitive subjects (n=24). Subjects were randomly allocated to receive a diet containing 5%, 18% or 33% of total calories as sucrose and as such, were fed each of these diets for a period of 6 weeks. The authors reported statistically significantly higher insulin values on the three diets in males compared to females; these values also tended to increase as the level of sucrose in the diet increased. Additionally, higher glucose values were observed on the 18% and 33% sucrose diets than the 5% diet. In comparison to the 5% sucrose diet group, the 18% and 33% sucrose diet groups experienced a statistically significantly higher insulin response after 1 hour and 0.5, 1, 2 and 3 hours, respectively. Glucose response was also statistically significantly greater, except after 2 hours, following the 18% and 33% sucrose diets (Reiser *et al.*, 1981). However, fasting serum glucagon did not statistically significantly alter between groups.

# Summary of the evidence base

## Cohort studies

Forty six publications on 29 separate cohort studies provided data for this chapter on incident DM type 2, glycaemia, insulinaemia, insulin resistance and glycated proteins (Table 4.3).

Seventeen cohort studies were conducted in the USA, 4 in the UK, 2 in Finland, 1 in the Netherlands and Finland, 1 in Germany, 2 in Australia and 1 in China. The majority studied populations that were middle-aged (40+ years) at study entry. Seven studies included participants that were younger adults (<30 years) at baseline (Twisk *et al.*, 2001; Krishnan *et al.*, 2007; Van Dam *et al.*, 2006; Palmer *et al.*, 2008; Hodge *et al.*, 2004; de Munter *et al.*, 2007; Schulze *et al.*, 2004b; Schulze *et al.*, 2004a; Monterrosa *et al.*, 1995; Marshall *et al.*, 1997; Gunderson *et al.*, 2007; Carnethon *et al.*, 2004; Ludwig *et al.*, 1999; Mirmiran *et al.*, 2008).

Thirteen cohort studies were single gender. Eight were female only (Van Dam *et al.*, 2006; Krishnan *et al.*, 2007; Palmer *et al.*, 2008; Meyer *et al.*, 2000; Halton *et al.*, 2008; de Munter *et al.*, 2007; Halton *et al.*, 2006; Salmeron *et al.*, 2001; Liu *et al.*, 2000a; Salmeron *et al.*, 1997b; Colditz *et al.*, 1992; Schulze *et al.*, 2004a; de Munter *et al.*, 2007; Schulze *et al.*, 2004b; Villegas *et al.*, 2007; Villegas *et al.*, 2008; Gunderson *et al.*, 2007; Janket *et al.*, 2003; Ventura *et al.*, 2006). Six included males only (Wannamethee *et al.*, 2009; Fung *et al.*, 2002; Salmeron *et al.*, 1997a; Leonetti *et al.*, 1996; Kochar *et al.*, 2007; Feskens *et al.*, 1995; Feskens *et al.*, 1991).

The Finnish Diabetes Prevention Study (Lindstrom *et al.*, 2006) had the shortest follow-up period (3 years), and one publication from the Finnish Mobile Clinic Health Surveys cohort (Montonen *et al.*, 2005) reported the longest follow-up period (23 years); the mean duration being 10.1 years, across all publications.

In order of size of the baseline cohort, the US Nurse's Health Studies I and II were the largest, with 121700 and 116671 female participants respectively (Halton *et al.*, 2008; de Munter *et al.*, 2007; Halton *et al.*, 2006; Salmeron *et al.*, 2001; Liu *et al.*, 2000a; Salmeron *et al.*, 1997b; Colditz *et al.*, 1992; de Munter *et al.*, 2007; Schulze *et al.*, 2004b; Schulze *et al.*, 2004a). However, five other cohort studies had in excess of 40000 participants (Villegas *et al.*, 2007; Villegas *et al.*, 2008; Palmer *et al.*, 2008; Van Dam *et al.*, 2006; Krishnan *et al.*, 2007; Fung *et al.*, 2002; Salmeron *et al.*, 1997a; Meyer *et al.*, 2000; Hodge *et al.*, 2004). Five cohorts were small, with less than 1000 participants (Twisk *et al.*, 2001; Leonetti *et al.*, 1996; Schroeder *et al.*, 2007; Feskens *et al.*, 1995; Lindstrom *et al.*, 2006; Ventura *et al.*, 2006; Feskens *et al.*, 1991).

Three studies employed a food diary dietary assessment method (Prynne *et al.*, 2009; Schroeder *et al.*, 2007; Lindstrom *et al.*, 2006), two studies used dietary recalls (Monterrosa *et al.*, 1995; Marshall *et al.*, 1997; Ventura *et al.*, 2006), four studies used a dietary history approach (Twisk *et al.*, 2001; Montonen *et al.*, 2003; Montonen *et al.*, 2005; Montonen *et al.*, 2007; Feskens *et al.*, 1995; Gunderson *et al.*, 2007; Feskens *et al.*, 1991), but the majority used a food frequency questionnaire to assess dietary exposure.

With observational studies, especially in the field of diet and nutrition, there is substantial potential for biases caused by incomplete adjustment for confounding, measurement error in the exposure estimate, and other biases in participant selection or data collection. The bias could be large in size, and act in either direction, either towards or away from the null. These studies should therefore be interpreted with caution.

## **Trial design**

One hundred and fourteen publications on 101 separate trials provided data for this chapter (Table 4.4). Outcomes from these trials included, glycaemia (fasting and area under the curve), insulinaemia (fasting and area under the curve [AUC]), insulin resistance and glycated proteins.

Trials were conducted in a wide range of countries: Argentina (1), Australia (7), Brazil (1), Canada (4), Denmark (5), Europe (2), Finland (2), France (4), Germany (2), Israel (1), Italy (1), Korea (1), New Zealand (2), Norway (1), Spain (5), Sweden (3), Switzerland (2), the Netherlands (3), UK (11), USA (45).

Twenty six studies included female participants only and 10 studies males only. Three studies included adolescents only (aged range 12 – 21years) (Ebbeling *et al.*, 2003; Demol *et al.*, 2009; Davis *et al.*, 2009).

The majority of the studies recruited overweight or obese participants (average Body Mass Index (BMI) of all participants  $>26\text{kg/m}^2$ ), however in 6 trials the average BMI was 25 or less (Ryle *et al.*, 1990; Helge, 2002; Aller *et al.*, 2004; Landin *et al.*, 1992; Bantle *et al.*, 2000; Letexier *et al.*, 2003).

Most of the studies used the parallel group design, with just 12 studies using a cross-over design.

Twenty three of the studies reported that they were industry-funded.

Fifty three studies focussed on the impact of manipulations of the energy-yielding macronutrients, typically the effect of consuming a high carbohydrate, low fat diet compared to a lower carbohydrate diet which was higher in either fat and/or protein. Six studied the effects of diets high or low in sugars, or type of sugar (glucose vs. fructose), or replacement of sugars with complex carbohydrate. Twenty seven trials studied interventions that compared the effect of variation in type or amount of dietary fibre, with relatively few of these using diets that were naturally high in dietary fibre. Most of these studies manipulated the dietary fibre content within intervention groups by using some sort of fibre isolate or fibre-rich component such as bran. Four studies included one or more groups that explored the effects of wholegrain foods, although this was not always explicit. Fifteen studies used interventions that differed by glycaemic index or load.

## Risk of bias

A summary of the risk of bias assessment is provided in Table 4.5. Criteria for judging whether a risk of bias was evident were based on the Cochrane Handbook. A judgement of 'unclear' was provided if there was insufficient evidence within the paper to make a clear judgement.

Judgements concerning whether there was evidence of a risk of bias in terms of outcome assessment (the experimenters involved in assessing the outcome were aware which intervention had been followed by each participant) are reported as the final column in each of the specific results tables.

All trials included were randomised controlled trials. All were judged to be either 'unbiased' or 'unclear' in terms of allocation sequence generation and all, bar two, were judged to be 'unbiased' or 'unclear' with regard to allocation concealment. The two exceptions, those viewed as 'biased', were studies by Brehm *et al.* (Brehm *et al.*, 2003) and Gray *et al.* (Gray *et al.*, 2008). Blinding of participants and researchers to the various dietary approaches was more difficult to achieve, as might be anticipated with dietary intervention trials. Nineteen papers were judged as 'unbiased' in respect of participants' awareness of the dietary intervention, and 25 trials were judged to be 'unbiased' in respect of researchers' awareness (these generally overlapped).

There was some evidence of incomplete outcome reporting in 38 publications and selective outcome reporting in 10 publications.

Table 4.3 Characteristics of cohort studies

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
<b>1946 British Birth Cohort</b>	(Prynne <i>et al.</i> , 2009)	Members of the Medical Research Council National Survey of Health and Development Mean age: 36 % Male: 46 Country: UK Ethnicity: Primarily white	Population-based cohort	17	Diet was assessed using validated 5-day food diary records at 3 different time points.	Not reported.	5362	Not reported
<b>Atherosclerosis Risk in Communities (ARIC) Study</b>	(Paynter <i>et al.</i> , 2006)	Middle age adults Mean age: 54 (45-64) % Male: 44 Country: USA Ethnicity: Multi-ethnic	Community cohort	9	Diet was assessed twice using a validated 61-item FFQ. The FFQ referred to diet over the previous year.	Diabetes was classified as having fasting glucose level $\geq 126$ mg/dL or non-fasting glucose level $\geq 200$ mg/dL, reported a physician diagnosis, reported taking diabetes medication in the 2 weeks prior to the examination or responded positively to "has a Doctor ever told you that you had diabetes?"	15792	Not reported
	(Stevens <i>et al.</i> , 2002)	Middle age adults Mean age: 54 (45-64) % Male: 44 Country: USA Ethnicity: Multi-ethnic	Community cohort	9	Diet was assessed twice using a validated 66-item FFQ. The FFQ referred to diet over the previous year.	Diabetes was classified as having fasting glucose level $\geq 126$ mg/dL or non-fasting glucose level $\geq 200$ mg/dL, reported a physician diagnosis or reported taking diabetes medication in the 2 weeks prior to the examination.	15792	Not reported
<b>Black Women's Health Study</b>	(Krishnan <i>et al.</i> , 2007)	Black women from across all regions of the United States Mean age: 45 (21-69) %Male: 0 Country: USA Ethnicity: Black	Volunteers	8	Diet was assessed from a validated 68-item FFQ. The FFQ referred to diet over the previous year.	Incident cases of diabetes were self-reported.	59000	20
	(Palmer <i>et al.</i> , 2008)	Black women from across all regions of the United States Mean age: 45 (21-69) %Male: 0 Country: USA Ethnicity: Black	Volunteers	10	As above	Incident cases of diabetes were self-reported.	59000	20
	(Van Dam <i>et al.</i> , 2006)	Black women from across all regions of the United States Mean age: 45 (21-69) %Male: 0 Country: USA Ethnicity: Black	Volunteers	8	As above	Incident diabetes was self-reported.	59000	20
<b>Blue Mountains Eye Study</b>	(Barclay <i>et al.</i> , 2007)	Mean age: 65 %Male: 44 Country: Australia Ethnicity: Primarily White	Community cohort	10	Diet was assessed from a validated 145-item FFQ.	Diabetes was identified by self-reports and use of diabetes medication or fasting glucose concentration $\geq 126$ mg/dL.	3654	29

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
<b>British Regional Heart Study</b>	(Wannamethee <i>et al.</i> , 2009)	Non-diabetic men at baseline Mean age: 49.5 (40-59) %Male: 100 Country: UK Ethnicity: Primarily white	Population-based cohort	7	Diet was assessed from a validated 7-day dietary recall.	Diabetes was self-reported and subsequently, confirmed by primary care records.	7735	1
<b>EPIC Norfolk</b>	(Simmons <i>et al.</i> , 2006)	Men and women in the Norfolk region, slightly healthier than the general UK population. Mean age: 40-79 %Male:45 Country: UK Ethnicity: Primarily white	Community cohort	4.6	Diet was assessed from a validated 130-item FFQ. This FFQ referred to diet over the previous year.	Incident cases of diabetes were established from follow-up health checks, hospital and general practice registers and prescribing data and a HbA1c level > 7% at baseline or follow-up.	25633	41
	(Simmons <i>et al.</i> , 2007)	Men and women in the Norfolk region, slightly healthier than the general UK population. Mean age: 40-79 %Male:45 Country: UK Ethnicity: Primarily white	Community cohort	4.6	As above	Incident cases of diabetes were established from follow-up health checks, hospital and general practice registers and prescribing data and a HbA1c level > 7% at baseline or follow-up.	25633	41
<b>EPIC Potsdam</b>	(Fisher <i>et al.</i> , 2009)	Men and women from general population of Potsdam Mean age: 50 (35-65) %Male:40 Country: Germany Ethnicity: Primarily white	Community cohort	7.1	Diet was assessed from a validated 148-item self-administered FFQ. The FFQ referred to diet over the past 12 months.	Not reported	27548	Not reported
	(Schulze <i>et al.</i> , 2007a)	Men and women from general population of Potsdam Mean age: 50 (35-65) %Male:40 Country: Germany Ethnicity: Primarily white	Community cohort	5	Diet was assessed from a validated self-administered FFQ. The FFQ referred to diet over the past 12 months.	Incident diabetes was identified by self-reports of a diagnosis, diabetes medication, or dietary treatment because of diabetes, which were confirmed by a physician.	27548	9
	(Schulze <i>et al.</i> , 2007b)	Men and women from general population of Potsdam Mean age: 50 (35-65) %Male:40 Country: Germany Ethnicity: Primarily white	Community cohort	11	Diet was assessed from a validated 148-item self-administered FFQ. The FFQ referred to diet over the past 12 months.	Incident diabetes was identified by self-reports, which were confirmed by a physician diagnosis and a diagnosis date.	27548	9
	(Schulze <i>et al.</i> , 2008)	Men and women from general population of Potsdam Mean age: 50 (35-65) %Male:40 Country: Germany Ethnicity: Primarily white	Community cohort	11	Diet was assessed from a validated 148-item self-administered FFQ. The FFQ referred to diet over the past 12 months.	Incident diabetes was identified by self-reports of a diagnosis, diabetes medication, or dietary treatment because of diabetes, which were confirmed by a physician.	27548	9

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
<b>Finnish Mobile Clinic Health Surveys (health examination in various regions of Finland)</b>	(Montonen <i>et al.</i> , 2003)	Men and women free of diabetes at baseline Mean age: 40-69 %Male:53 Country: Finland Ethnicity: Not reported	Population-based cohort	10	Diet was assessed once with dietary histories and this method was reported to be validated. The dietary history referred to diet over the previous year.	Subjects provided information on their previous history of diabetes, when appropriate. For those without a previous history, an oral-glucose-tolerance test was conducted and the WHO diagnostic criteria used.	10054	Not reported
	(Montonen <i>et al.</i> , 2005)	Men and women free of diabetes at baseline Mean age: 40-69 %Male:53 Country: Finland Ethnicity: Not reported	Population-based cohort	23	Diet was assessed once with dietary histories and this method was reported to be validated. The dietary history referred to diet over the previous year.	Subjects provided information on their previous history of diabetes, when appropriate. For those without a previous history, an oral-glucose-tolerance test was conducted and the WHO diagnostic criteria used.	10054	Not reported
	(Montonen <i>et al.</i> , 2007)	Men and women free of diabetes at baseline Mean age: 40-69 %Male:53 Country: Finland Ethnicity: Not reported	Population-based cohort	12	Diet was assessed once with dietary histories and this method was reported to be validated. The dietary history referred to diet over the previous year.	Incident diabetes was identified through a nationwide registry of patients receiving drug reimbursement for hypoglycaemic agents. Medical certificates for subjects were examined to ensure they met the WHO diagnostic criteria for type 2 diabetes.	10054	Not reported
<b>Health Professionals' Follow-Up Study</b>	(Fung <i>et al.</i> , 2002)	Male health professionals Mean age: 40-75 %Male:100 Country: USA Ethnicity: Primarily white	Occupational cohort	12	Diet was assessed from a validated FFQ administered at baseline and then twice thereafter... The FFQ referred to the diet over the previous year.	Diabetes was self-reported and then confirmed by meeting one of the following: 1) elevated plasma glucose concentration (fasting plasma glucose $\geq$ 7.8mmol/L or random plasma glucose $\geq$ 11.1mmol/L) and a classic symptom of diabetes; 2) $\geq$ 2 elevated plasma glucose concentrations on separate occasions; or 3) treatment for diabetes.	51529	~6
	(Salmeron <i>et al.</i> , 1997a)	Male health professionals Mean age: 40-75 %Male:100 Country: USA Ethnicity: Primarily white	Occupational cohort	6	Diet was assessed from a validated 131-item FFQ administered at baseline and then 4 years subsequently. The FFQ referred to the diet over the previous year.	Incident diabetes was self-reported and met the criteria for the WHO and National Diabetes Data Group.	51529	Not reported
<b>Health, Aging, and Body Composition Study</b>	(Sahyoun <i>et al.</i> , 2008)	Random sample of older adults residents Mean age: 75 %Male: 46 Country: USA Ethnicity: Multi-ethnic	Community cohort	4	Diet was assessed from a 108-item FFQ by a trained interviewer. The FFQ included an age-appropriate food list based on the third NHANES 24-	Incident diabetes was defined as: 1) annual report of physician diagnosis; 2) use of hypoglycaemic medication in years 2, 3, 5 and 6; or 3) fasting serum glucose $\geq$ 126 mg/dL in years 2, 4 or 6.	3075	Not reported

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Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
					hour recall.			
<b>Insulin Resistance Atherosclerosis Study</b>	(Mayer-Davis <i>et al.</i> , 2006)	Multicentre observational study Mean age: 55 (40-69) %Male: 46 Country: USA Ethnicity: Multi-ethnic	Population-based cohort	5.2	Diet was assessed using a validated 114-item FFQ administered twice. The FFQ referred to diet over the previous year.	Incident diabetes was determined by a 2-hour oral glucose tolerance test and confirmed by WHO criteria or identified if subjects were taking hypoglycaemic medication.	1625	19
	(Schulz <i>et al.</i> , 2006)	Multicentre observational study Mean age: 55 (40-69) %Male: 46 Country: USA Ethnicity: Multi-ethnic	Population-based cohort	5	As above	Incident cases of diabetes were ascertained if subjects met the WHO criteria for diabetes on the follow-up oral glucose tolerance test or if subjects were taking hypoglycaemic medication.	1625	Not reported
<b>Iowa Women's Health Study</b>	(Meyer <i>et al.</i> , 2000)	Postmenopausal women Mean age: 61 (55-69) %Male: 0 Country: USA Ethnicity: Primarily white	Community cohort	6	Diet was assessed by using a validated 127-item FFQ administered once. The FFQ referred to diet over the previous year.	Diabetes incidence was self-reported.	41836	21
<b>Japanese-American Men Diabetes Study</b>	(Leonetti <i>et al.</i> , 1996)	Japanese-American men - some had diabetes, some had impaired glucose tolerance and some had normal glucose tolerance. Mean age: 45-74 %Male:100 Country: USA Ethnicity: Japanese	Community cohort	5	Diet was assessed from a FFQ interview regarding usual dietary consumption over the 1-2 month interval prior to the study. It was administered once and was not reported to be validated.	Classification for diabetes was based on self- reports, information from subjects' physicians and results of a 2-hour 75g oral glucose tolerance test using WHO criteria.	229	5.6
<b>Melbourne Collaborative Cohort Study</b>	(Hodge <i>et al.</i> , 2004)	Mean age: 54 (27-75) %Male: 41.1 Country: Australia Ethnicity: Multi-ethnic	Population-based cohort	4	Diet was assessed from a validated 121-item FFQ. The FFQ referred to diet over the previous month	Incident cases of diabetes were identified through self-reports and subsequent to this, a diagnosis date. Doctors were also required to confirm a diagnosis.	41528	14
<b>Middle-aged Runners Study</b>	(Schroeder <i>et al.</i> , 2007)	Chronically endurance-trained runners Mean age: 51 %Male: 62 Country: USA Ethnicity: Not stated	Community cohort	10	Diet was assessed using 3- day food diary records administered once.	Not reported	91	Not reported
<b>Multi-Ethnic Study of Atherosclerosis (MESA)</b>	(Nettleton <i>et al.</i> , 2009)	Mean age:45-84 %Male: 47 Country: USA Ethnicity: Multi-Ethnic	Population-based cohort	7	Diet was assessed from a validated 114-item FFQ administered once. The FFQ referred to the diet over the previous year.	Incident cases of diabetes were self-reported, classified as fasting glucose > 126 mg/dL at any examination or use of hypoglycaemic medication.	6841	Not reported
<b>Nurses' Health Study</b>	(Colditz <i>et al.</i> , 1992)	Female Health Professionals Mean age: 30-55	Occupational cohort	6	Diet was assessed from a validated 126-item FFQ for	Diabetes was self-reported and then confirmed by meeting one of the following: 1)	121700	19

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Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
		%Male: 0 Country: USA Ethnicity: Primarily white			intakes over the previous year.	elevated plasma glucose concentration (fasting plasma glucose $\geq$ 7.8mmol/L, random plasma glucose $\geq$ 11.1mmol/L, or plasma glucose $\geq$ 11.1mmol/L $\geq$ 2 hours after an oral-glucose-tolerance test) and a classic symptom of diabetes; 2) $\geq$ 2 elevated plasma glucose concentrations on separate occasions; or 3) use of hypoglycaemic medication.		
	(Halton <i>et al.</i> , 2006)	Female Health Professionals Mean age: 30-55 %Male: 0 Country: USA Ethnicity: Primarily white	Occupational cohort	20	Diet was assessed from a validated 61-item FFQ for intakes over the previous year. This FFQ was revised in subsequent cycles to include about twice this number of items.	As above	121700	Not reported
	(Halton <i>et al.</i> , 2008)	Female Health Professionals Mean age: 30-55 %Male: 0 Country: USA Ethnicity: Primarily white	Occupational cohort	20	Diet was assessed from a validated 126-item FFQ for intakes over the previous year. During 20 years of follow-up, diet was assessed 6 times.	As above	121700	Not reported
	(Liu <i>et al.</i> , 2000a)	Female Health Professionals Mean age: 30-55 %Male: 0 Country: USA Ethnicity: Primarily white	Occupational cohort	10	Diet was assessed from a validated 126-item FFQ for intakes over the previous year.	As above	121700	Not reported
<b>Nurses' Health Study (continued)</b>	(Salmeron <i>et al.</i> , 1997b)	Female Health Professionals Mean age: 30-55 %Male: 0 Country: USA Ethnicity: Primarily white	Occupational cohort	6	Diet was assessed from a validated 134-item FFQ for intakes over the previous year.	As above	121700	Not reported
<b>Nurses' Health Study I and II</b>	(de Munter <i>et al.</i> , 2007)	Female Health Professionals Mean age: 30-55 (NHS I) and 24-44 (NHS II) %Male: 0 Country: USA Ethnicity: Primarily white	Occupational cohort	18	Diet was assessed from a validated, semi-quantitative FFQ for intakes over the previous year.	As above	238309	Not reported
<b>Nurses' Health Study II</b>	(Schulze <i>et al.</i> , 2004a)	Female Health Professionals Mean age: 24-44 %Male: 0 Country: USA	Occupational cohort	8	Diet was assessed from a validated 133-item FFQ administered three times. The FFQ referred to diet	As above	116671	<10

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Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
	(Schulze <i>et al.</i> , 2004b)	Ethnicity: Primarily White Female Health Professionals Mean age: 24-44 %Male: 0 Country: USA Ethnicity: Primarily White	Occupational cohort	8	over the previous year. As above	As above	116671	<10
<b>Physicians' Health Study I</b>	(Kochar <i>et al.</i> , 2007)	Male Health Professionals Mean age: 54 (40-84) %Male: 100 Country: USA Ethnicity: not stated	Occupational cohort	19.1	Diet was assessed from a validated FFQ for intake over the previous year.	Incident diabetes was self-reported.	22071	Not reported
<b>San Antonio Heart Study/ San Antonio Heart Study follow-up</b>	(Monterrosa <i>et al.</i> , 1995)	Mean age: 25-64 %Male: 42.3 Country: USA Ethnicity: Multi-ethnic	Community cohort	8	Diet was assessed by 24-hour dietary recall administered once and it was not reported to be validated.	Diabetes was defined as: fasting plasma glucose $\geq$ 140 mg/dL, 2-hour post-glucose load plasma glucose $\geq$ 200 mg/dL or use of insulin or oral antidiabetic drugs.	2217	22.8
<b>San Luis Valley Diabetes Study</b>	(Marshall <i>et al.</i> , 1997)	Hispanic and non-Hispanic white person living in southern Colorado Mean age: 52 (20-74) %Male: 46.8 Country: USA Ethnicity: Multi-ethnic	Community cohort	4.3	Diet was assessed by 24-hour dietary recall administered once.	Not reported.	1351	26
<b>Seven Countries Study</b>	(Feskens <i>et al.</i> , 1995)	Longitudinal study of men from the Finland and Netherlands cohorts Mean age: 70-89 %Male: 100 Country: Finland and the Netherlands Ethnicity: Not reported	Population-based cohort	30	Diet was assessed from a dietary history administered twice. Interviews were conducted by experienced nutritionists and dieticians.	Subjects with a 2-hour plasma glucose level $\geq$ 11.1mmol/L were diagnosed as having incident diabetes and those with 2-hour plasma glucose from 7.8-11.1 mmol/L as having impaired glucose tolerance.	2589	Not reported
<b>Shanghai Women's Health Study</b>	(Villegas <i>et al.</i> , 2007)	Middle-aged Chinese women with no history of type 2 DM, CVD or cancer at baseline. Mean age: 40-70 %Male: 0 Country: China Ethnicity: not stated	Population-based cohort	4.6	Diet was assessed from a validated 77-item FFQ administered twice.	Incident diabetes was firstly identified through outcome follow-up surveys. It was then confirmed if subjects had been previously diagnosed and met one of the following criteria: fasting glucose level $\geq$ 126 mg/dL on 2 separate occasions or an oral glucose tolerance test $\geq$ 200 mg/dL or use of hypoglycaemic medication.	74942	0.2
<b>The CARDIA Study</b>	(Gunderson <i>et al.</i> , 2007)	Prospective bi-racial cohort Mean age: 18-30 %Male: 45.5 Country: US	Population-based cohort	20		Incident diabetes was defined by elevated fasting plasma glucose levels in years 7, 10, 15 or 20 and use of diabetes medication or self-reported diabetes at year 5, 7, 10, 15 or 20	5115	6.45

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Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Length of follow-up (years)	Dietary assessment methods	Criteria for defining diabetes/ glycaemia	Initial cohort size	Losses to follow-up (%)
		Ethnicity: Black and White				(but not during pregnancy).		
	(Ludwig <i>et al.</i> , 1999)		Population-based cohort	10		Not reported.	5115	Not reported
<b>The Framingham Heart Study</b>	(Dhingra <i>et al.</i> , 2007)	Mean age: 53 %Male: 43 Country: USA Ethnicity: not stated	Community cohort	4	Diet was assessed using a validated general questionnaire administered three times.	Not reported	8997	Not reported
<b>The Women's Health Study</b>	(Janket <i>et al.</i> , 2003)	US female health professionals free of CVD, cancer and hypertension at baseline. Mean age: 54 %Male: 0 Country: USA Ethnicity: Primarily White	Occupational cohort	6	Diet was assessed once using a validated 131-item FFQ.	Diabetes was self-reported and thereafter confirmed according to guidelines by the American Diabetes Association.	39876	Not reported
<b>Whitehall II Study</b>	(Mosdol <i>et al.</i> , 2007)	Participants from 20 civil service departments in London and free of diabetes at baseline. Mean age: 50 %Male: 71 Country: England Ethnicity: White	Occupational cohort	13	Diet was assessed from a validated 127-item FFQ for intakes over the previous year. It was administered once.	Incident diabetes was identified through self- reports of diagnosis and diabetic treatment in the certain phases as well as a 2-hour oral glucose tolerance test at phases 3, 5 and 7.	10308	Not reported
<b>Zutphen Elderly Study</b>	(Feskens <i>et al.</i> , 1991)	Middle-aged men in Zutphen, an old industrial town in eastern part of the Netherlands. Mean age: 64-84 %Male: 100 Country: The Netherland Ethnicity: not stated	Population-based cohort	4	Diet was assessed once with a validated dietary history for intake over the past 6-12 months.	Incident cases of diabetes were identified through oral glucose tolerance tests conducted every year; results of these tests were then confirmed by WHO criteria.	340	Not reported

Table 4.4 Trial characteristics (studies shaded in grey were conducted on children and adolescents)

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Abete <i>et al.</i> , 2008)	No medical conditions which influence outcomes No medication Weight stable	Spain 56% Male Age: (36) BMI: (32)	Parallel Group	8 weeks Energy-restricted, plus 1 yr maintenance	Free living diet plan	32	1. Higher GI diet  2. Lower GI diet	1. Individually prescribed diet within a strict dietary frame-work repeated on a 3 day rotation basis. 84% of CHO provided by rice and potatoes. 2. Individually prescribed diet within a strict dietary frame-work repeated on a 3 day rotation basis. 84% of CHO provided by pasta and legumes.	1. %Energy: C 47.8 P 19.6 F 32.6 Fibre g/d:18.5 GI 60-65 units  2. %Energy: C 50.2 P 18.3 F 31.5 Fibre g/d:24.9 GI 40-45 units	Yes	Government funding
(Aller <i>et al.</i> , 2004)	Age 18-70y Generally healthy No hypertension, T2DM, statins or steroids Not hyperlipidaemic/hypercholesterolaemic Weight stable	Spain 36% Male Age: (47) BMI: (25)	Parallel Group	3 months	Free living diet plan	53	1. High fibre  2. Low fibre	1. Fibre 30.5g/d: 4.11g soluble fibre (pectins, gums and mucilages) and 25.08g insoluble (hemicellulose, cellulose and lignins). High fibre intake reached through breakfast cereal consumption 60g/d plus 2 apples/d 2. Fibre 10.4g/d: 1.97g soluble fibre (pectins, gums and mucilages) and 8.13g insoluble fibre (hemicellulose, cellulose and lignins)	1. g/d: F 72.6 Energy 1707 kcal/d Fibre g/d:25.95  2. g/d: F 73.4 Energy 1633 kcal/d Fibre g/d:9.06	Yes	Not reported
(Andersson <i>et al.</i> , 2007)  Uppsala Wholegrain Trial	≥ 1 CHD risk factor Age 30-70y BMI 26-35	Sweden 27% Male Age: 35 - 70(59) BMI: (28)	Crossover (washout 6 weeks)	6 weeks	Supplement	34	1. Wholegrain products  2. Refined grain products	1. Usual diet + whole grain foods (Bread, bread, muesli & pasta) Minimum 50% wholegrain in provided foods = 112g wholegrain/day 2. Usual diet + refined grain foods (Bread, muesli & pasta)	1. g/d: C 143 P 28 F 8 Energy: 3180kJ/d Fibre g/d:18  2. g/d: C 145 P 23 F 14 Energy: 3340kJ/d Fibre g/d:6	Yes	Swedish Diabetes Association and Government and research institute funding
(Bantle <i>et al.</i> , 2000)	Age >18y BMI <32 No CHD Normal glucose tolerance Not hyperlipidaemic/hypercholesterolaemic	USA 50% Male Age: (41) BMI: (25)	Crossover (washout not reported)	6 weeks	All food provided	24	1. High-fructose diet  2. High-glucose diet	1. 55% of energy as carbohydrate, 15% of energy as protein, and 30% of energy as fat (17% total energy as fructose). Crystalline fructose was added to diet. 2. 55% of energy as carbohydrate, 15% of energy	1. g/d: C 276 P 76 F 66 Energy 2004 kcal/d Fibre g/d:23  2. g/d: C 276 P 76 F 66 Energy 2001 kcal/d	No, intended diet only	National Institute of Health (NIH)

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
								as protein, and 30% of energy as fat (3% total energy as fructose). Crystalline glucose was added to diet.	Fibre g/d:23		
(Bell <i>et al.</i> , 1990)	Age 24-59y Body weight >130% of ideal Cholesterol between the 50th and 90th centile Free of chronic disease No medications which influence outcomes	USA  100% Male  Age: mean not reported  BMI: mean not reported	Parallel Group	6 weeks	Substitution	60	1. Placebo  2. Pectin enriched cereal  3. Psyllium enriched cereal	1. Step 1 diet with 57g of cornflakes consumed each morning. 2. Step 1 diet with 57g of cornflakes containing oat bran, sugar-beet fibre, white wheat bran and high-methoxyl pectin consumed each morning. 50% total soluble fibre in cereal was from pectin. 3. Step 1 diet with 57g of cornflakes containing oat bran, sugar-beet fibre, white wheat bran and psyllium consumed each morning. 50% total soluble fibre in cereal was from psyllium.		Yes	General Mills Inc.
(Bellisle <i>et al.</i> , 2007)	Age >18y BMI >25 Free of chronic disease No medication Women	France  0% Male  Age: 20 - 72  BMI:25 - 40	Parallel Group	12 weeks	Free living diet plan	96	1. Low GI  2. Control	1. Weight watchers program with a focus on low GI foods. 2. Weight watchers program		Yes	Weight Watchers International Inc
(Bhargava, 2006) The Women's Health Trial: Feasibility Study in Minority Populations	Age 50-80y Post-menopausal Women	UK and USA  0% Male  Age: 50 - 79  BMI: 29	Parallel Group	12 months	Free living diet plan	2208	1. Low fat  2. Control	1. Reduce fat intake to 20% and increase fruit, vegetable and grain consumption. 2. No intervention	1. 5430 kJ, E%: F 20, 13g/d saturated fat, 13g/d fibre 2. 6149 kJ, 20g/d saturated fat, 12g/d fibre	Yes	National Cancer Institute
(Birketvedt <i>et al.</i> , 2000)	Age 18-70y BMI >27.5 Generally healthy	Norway  0% Male  Age: (40)	Parallel Group	24 weeks	Supplement	53	1. Energy restricted diet + mixed fibre tablets  2. Energy	In both groups: 24 tablets/d for 8 weeks then 15 tablets/d up to 24 weeks + 1200kcal, 15g fibre weight reducing diet 1. Supplement tablets		Yes	Not reported

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
		BMI: (28)					restricted diet + placebo tablets	contained grain/citrus fibre. 6g fibre, 15% soluble/85% insoluble. 2. Placebo tablets content not reported			
(Black <i>et al.</i> , 2006)	BMI <35 No CHD, T2DM or hypertension Not hyperlipidaemic/hypercholesterolaemic	UK 100% Male Age: (33) BMI: (27)	Crossover (washout 4 weeks)	6 weeks	All food provided	14	1. High sucrose diet  2. Low sucrose diet	1. 25% energy provided as sucrose (solid food & beverages). 55% CHO, 10-15% PRO, 30-35% FAT, 18g/d fibre 2. 10% energy provided as sucrose (solid food & beverages). 55% CHO, 10-15% PRO, 30-35% FAT, 18g/d fibre	1. %Energy: C 55 P 11 F 33 Energy 2484 kcal/d Fibre g/d:17  2. %Energy: C 55 P 12 F 33 Energy 3176 kcal/d Fibre g/d:18	Yes	Government funding and The Sugar Bureau and Suikerstichting
(Bowden <i>et al.</i> , 2007)	All BMI categories No CHD, T2DM or hypertension No medications which influence outcomes Sedentary only Without metabolic syndrome University students	USA 34% Male Age: (20) BMI: mean not reported	Parallel Group	12 weeks	Free living diet plan	108	1. Standard diet, lower body fat participants 2. Standard diet, higher body fat participants 3. High protein diet, lower body fat participants 4. High protein diet, higher body fat participants	1. 55% CHO, 15% PRO, 30% FAT, no energy restriction 2. 55% CHO, 15% PRO, 30% FAT, 500kcal/d energy restriction 3. 45% CHO, 25% PRO, 30% FAT, no energy restriction 4. 45% CHO, 25% PRO, 30% FAT. 500kcal/d energy restriction.	1. %Energy: C 51.12 P 16.03 F 32.72 Energy 1620.77 kcal/d 2. %Energy: C 53.92 P 15.62 F 30.54 Energy 1464.78 kcal/d 3. %Energy: C 41.21 P 25.06 F 33.71 Energy 1221.88 kcal/d 4. %Energy: C 42.73 P 26.64 F 30.64 Energy 1487 kcal/d	Yes	University funding
(Brehm <i>et al.</i> , 2003) American LC study I	Age >18y BMI 30-35 Familial CVD/CHD Generally healthy No hypertension or T2DM Weight stable	USA 0% Male Age: (44) BMI: (34)	Parallel Group	6 months	Free living diet plan	53	1. Low carbohydrate  2. Moderate fat	1. Ad libitum food intake. Max CHO intake 20g/d. CHO increased to 40-60g/d if ketosis was induced after 2 weeks. 2. American Heart Association Step 1 diet + restrict to 1200kcal/d. Intended intake: 55% CHO, 15% PRO, 30% FAT	1. %Energy: C 30 P 23 F 46 Energy 1302 kcal/d Fibre g/d:8.4 2. %Energy: C 53 P 18 F 29 Energy 1247 kcal/d Fibre g/d:12.35	Yes	American Heart Association, research institute funding and NIH
(Cairella <i>et al.</i> , 1995)	BMI >30 No CHD Sedentary	Italy 27% Male	Parallel Group	60 days	Supplement	30	1. Balanced diet + fibre tablets	1. Fibre tablets (vegetable, citrus, cereal fibre, 6g/d) + balanced diet following 2	1. Fibre g/d:6	Yes	Not reported

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	occupation	Age: (36) BMI:31 - 47(37)					2. Balanced diet + placebo tablets	week VLCD 2. Placebo tablets, plus balanced diet following 2 week VLCD			
(Chen <i>et al.</i> , 2006)  American Fibre Study	Age 30-65y Good compliance during run-in No antihypertensive / cholesterol lowering No CHD/CVD, T2DM or hypertension Not hyperlipidaemic/ hyperchol-esterolaemic	USA 40% Male Age: (48) BMI: (29)	Parallel Group	12 weeks	Substitution	110	1. High fibre  2. Low fibre	1. 60g oat bran in a muffin and 84g of oatmeal squares cereal daily. Soluble fibre 8.1g/d, beta-glucan 7.3g/d, insoluble fibre 7.7g/d 2. 93g refined wheat in a muffin and 42g of corn flakes cereal daily. Soluble fibre 0.9g/d, beta glucan 0g/d, insoluble fibre 1.5g/d	1. g/d: C 113.3 P 24 F 13.7 Energy 652 kcal/d Fibre g/d:15.9 2. g/d: C 108.4 P 10.8 F 11 Energy 567 kcal/d Fibre g/d:2.7	Yes	NIH and research institute funding
(Claessens <i>et al.</i> , 2009)	BMI >27 No hypertension Normal glucose tolerance Normal lipid profile Weight loss >5% during run-in Weight stable	The Netherlands 28% Male Age: 30 - 60(45) BMI: (33)	Parallel Group	12 weeks	Supplement	60	1. High carbohydrate supplement 2. High protein supplement - casein 3. High protein supplement - whey	1. 50g/d consumed as a flavoured drink 2. 50g/d consumed as a flavoured drink 3. 50g/d consumed as a flavoured drink		Yes	Kerry Bio-Science, Almere, The Netherlands
(Clifton <i>et al.</i> , 2008)  Australian Protein Study	27-40 Female adults	Australia 0% Male Age: (49) BMI: (33)	Parallel Group	12 weeks intensive, plus 12 month follow up	Free living diet plan	119	1. High protein diet  2. High carbohydrate diet	1. 46% CHO, 34% PRO, 20% FAT 2. 64% CHO, 17% PRO, 20% FAT	1. %Energy: C 46.4 P 23.2 F 28.5 g/d: C 179 P 94.6 F 51.4 Energy: 6583kJ/d Fibre g/d:3.9 2. %Energy: C 50.8 P 19.6 F 27.5 g/d: C 189.5 P 77 F 48.4 Energy: 6391kJ/d Fibre g/d:4.3	Yes	Meat and Livestock Australia
(Clifton <i>et al.</i> , 2004)	BMI >27 No medications which influence outcomes	Australia 0% Male	Parallel Group	12 weeks	Free living diet plan	70	1. Very low fat	1. Diet was closely prescribed and key foods were provided	1. %Energy: C 65.4 P 21.7 F 11.6 Energy: 6004kJ/d Fibre g/d:31.2	Yes	Meadow Lea Foods, Australia

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	No T2DM	Age: (47) BMI: (35)					2. High MUFA	2. Diet was closely prescribed and key foods were provided	2. %Energy: C 43.7 P 21.3 F 35.3 Energy: 5972kJ/d Fibre g/d:32		
(Colette <i>et al.</i> , 2003)	BMI >25 No medications which influence outcomes No T2DM	France 28% Male Age: (48) BMI: (35)	Parallel Group	8 weeks	Free living diet plan	52	1. High carbohydrate diet  2. High MUFA diet	1. Hypocaloric diet (-30% energy intake). 55%CHO, 20%PRO, 25% FAT (10%MUFA, (7.5%SFA, 7.5%PUFA) 2. Hypocaloric diet (-30% energy intake). 40%CHO, 20%PRO, 40%FAT (25%MUFA, 7.5%SFA 7.5%PUFA).	1. %Energy: C 52.4 P 20.9 F 25.8 Energy: 6000kJ/d Fibre g/d:17  2. %Energy: C 40.3 P 20.2 F 39.4 Energy: 7200kJ/d Fibre g/d:18	Yes	Not reported
(Cornier <i>et al.</i> , 2005)	Normoglycaemic	USA 0% Male Age: 23 - 53(42) BMI:30 - 35(32)	Parallel Group	16 weeks	All food provided	21	1. High carbohydrate, low fat 2. Low carbohydrate, high fat	1. 60%CHO, 20%PRO, 20%FAT 2. 40%CHO, 20%PRO, 40%FAT	1. %Energy: C 60 P 20 F 20 2. %Energy: C 40 P 20 F 40	No, intended diet only	Research institute funding, American Diabetes Association and American Heart Association
(Crujeiras <i>et al.</i> , 2007)	<3kg Δ weight in previous 3m Generally healthy No medication	Spain 56.6% Male Age: (36) BMI: (32)	Parallel Group	8 weeks	Free living diet plan	30	1. Hypocaloric diet + legumes 2. Hypocaloric control diet	1. Energy deficit of 30%. Intended diet: 50%CHO, 20% PRO, 30% FAT. Non-soybean legume servings 4 days/week 2. Energy deficit of 30%. Intended diet: 50%CHO, 20% PRO, 30% FAT	1. %Energy: C 50.2 P 18.9 F 33.4 Energy 2479 kcal/d 2. %Energy: C 50.7 P 18.9 F 30.8 Energy 2479 kcal/d	Yes	Government funding and University funding
(Dale <i>et al.</i> , 2009)	BMI >27.5	New Zealand 0% Male Age: (45) BMI: (32)	Factorial	2 years	Free living diet plan	200	1. High MUFA diet  2. High carbohydrate diet	1. 40%CHO, 25%PRO, 21%MUFA 2. 55%CHO, 15-20%PRO, 25-30%FAT	1. %Energy: C 43 P 22 F 31 g/d: C 185 P 88 F 61 Energy: 6985kJ/d Fibre g/d:23 2. %Energy: C 47 P 22 F 27 g/d: C 183 P 77 F 46 Energy: 6192kJ/d Fibre g/d:23	Yes	Health Research Council of New Zealand
(Dansinger <i>et al.</i> , 2005)	≥1 cardiac risk factor BMI 27-42 Free of chronic disease No insulin therapy No medications	USA 49% Male Age: (49) BMI: (35)	Parallel Group	12 months	Free living diet plan	160	1. Atkins  2. Zone  3. Weight	1. Carbohydrate restriction (%E 41 CHO) . 2. Macronutrient balance (%E 42 CHO). 3. Calorie restriction (%E 46	1. g/d: C 190 P 82 F 80.5 Energy 1846 kcal/d Fibre g/d:13 2. g/d: C 198 P 90.4 F 66 Energy 1886 kcal/d Fibre g/d:17.4 3. g/d: C 202 P 80 F 58	Yes	NIH

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	which influence outcomes						watchers	CHO).	Energy 1755 kcal/d Fibre g/d:14		
							4. Ornish	4. Fat restriction. (%E 55 CHO) For all participants dietary advice was strictly followed for the first 2 months. Participants then selected their own adherence levels.	4. g/d: C 237 P 74 F 54.5 Energy 1711 kcal/d Fibre g/d:14.5		
(Das <i>et al.</i> , 2007)  CALERIE	BMI 25-30 Generally healthy No medications which influence outcomes Not extremely athletic/active Weight stable	USA  % Male: not reported  Age: (35)  BMI: (28)	Parallel Group	12 months	All food provided	34	1. Energy restricted high GL diet 2. Energy restricted low GL diet	1. 30% calorie restriction. Fibre 15 g/1000kcal. Estimated GI=86, GL=116 g/1000 kcal 2. 30% calorie restriction. Fibre 15 g/1000 kcal. Estimated GI=53, GL=45 g/1000kcal	1. %Energy: C 60 P 20 F 20 2. %Energy: C 40 P 30 F 30	Yes	NIH and Government funding
(Davis <i>et al.</i> , 2009)	Age 11-18y BMI >85th centile No medications which influence outcomes No recent weight loss program No T2DM	USA  50% Male  Age: 14 - 18(16)  BMI: mean not reported	Parallel Group	16 weeks	Free living diet plan	44	1. Control  2. High fibre, low sugar diet	1. No intervention  2. ≤10% added sugar, >14 g/1000 kcal dietary fibre/d	1. g/d: C 282 P 80 F 80.3 Energy 2146.6 kcal/d Fibre g/d:17.1 2. g/d: C 234 P 71.7 F 61.5 Energy 1752.1 kcal/d Fibre g/d:17.9	Yes	NIH and research institute funding
(de Luis <i>et al.</i> , 2008)  Spanish Hypocaloric Diet Study	BMI >30 No CHD, T2DM or hypertension	Spain  24.5% Male  Age: (46)  BMI: (34)	Parallel Group	2 months	Free living diet plan	204	1. Low fat  2. Low carbohydrate	1. Intended diet: 1500 kcal/d. 52% CHO, 20% PRO, 27% FAT 2. Intended diet: 1507kcal/d. 38% CHO, 26% PRO, 36% FAT	1. %Energy: C 52 P 20 F 27 Energy 1500 kcal/d 2. %Energy: C 38 P 26 F 36 Energy 1507 kcal/d	No, intended diet only	Not reported
(de Luis <i>et al.</i> , 2009b)  Spanish Hypocaloric Diet Study	BMI >30 No CHD, T2DM or hypertension	Spain  28% Male  Age: (46)  BMI: (35)	Parallel Group	3 months	Free living diet plan	118	1. Low carbohydrate  2. Low fat	1. Intended diet: 1507kcal/d. 38% CHO, 26% PRO, 36% FAT 2. Intended diet: 1500 kcal/d. 52% CHO, 20% PRO, 27% FAT	1. %Energy: C 30.8 Energy 1548 kcal/d 2. %Energy: F 25.3 Energy 1613 kcal/d	Yes	Not reported
(de Luis <i>et al.</i> , 2009a)  Spanish Hypocaloric Diet Study	BMI >30 No CHD or T2DM No medications which influence	Spain  22% Male  Age: (46)	Parallel Group	2 months	Free living diet plan	131	1. Low fat  2. Low carbohydrate	1. Intended diet: 1500 kcal/d. 52% CHO, 20% PRO, 27% FAT 2. Intended diet: 1507kcal/d. 38% CHO, 26% PRO, 36% FAT	1. %Energy: C 53 P 20 F 27 Energy 1500 kcal/d 2. %Energy: C 38 P 26 F 36 Energy 1507 kcal/d	No, intended diet only	Not reported

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	outcomes Not hyperlipidaemic/ hyperchol- esterolaemic	BMI: (35)									
(Demol <i>et al.</i> , 2009)	BMI >95th centile No medications which influence outcomes No recent weight loss program Without chronic disease	Israel 38% Male Age: 12 - 18(14) BMI: mean not reported	Parallel Group	12 weeks (9 month Follow up)	Free living diet plan	55	1. Low carbohydrate, high protein  2. Low carbohydrate, high fat  3. High carbohydrate, low fat	All groups prescribe energy restriction to 1200-1500 kcal/d 1. Low-carbohydrate, low-fat, protein-rich diet containing 60 g carbohydrate (up to 20%), 30% fat and 50% protein. 2. Low-carbohydrate, high-fat diet containing: 60 g carbohydrate (up to 20%), 60% fat and 20% protein 3. High-carbohydrate, low-fat diet containing: 50–60% carbohydrate, 30% fat and 20% protein	1. %Energy: C 20 P 50 F 30 g/d: C 60  2. %Energy: C 20 P 20 F 60 g/d: C 60  3. %Energy: C 50 P 20 F 30	No, intended diet only	Not reported
(Due <i>et al.</i> , 2008a)	<3kg Δ weight in previous 2m Age 18-35y BMI 28-36 Non smokers No T2DM Obesity trial	Denmark 43.5% Male Age: (28) BMI: (31)	Parallel Group	6 months	Free living diet plan - All food provided via supermarket	46	1. High MUFA  2. Low fat  3. Control	1. Dietary counselling and food provided from study supermarket. Prescribed 35-45%FAT, >20%MUFA. This diet <i>also</i> included more whole-grains, legumes and nuts. SFA:MUFA:PUFA% 7:20:8 2. Dietary counselling. Food provided from study supermarket. Prescribed 20-30%FAT. SFA:MUFA:PUFA% 8:8:5 3. Dietary counselling. Food provided from study supermarket. Moderate fat (35% energy) with >15% SFA. SFA:MUFA:PUFA% 15:10:4.	1. %Energy: C 44 P 15 F 39 Energy: 12.5 MJ/d  2. %Energy: C 58 P 16 F 23 Energy: 12.8 MJ/d  3. %Energy: C 50 P 16 F 32 Energy: 12.3 MJ/d  Fibre intake similar	Yes	H.A. Foundation; The Danish Heart Association; The Danish Diabetes Association; The Danish Pork Council foundations and research institute funding
(Due <i>et al.</i> , 2008b)	<3kg Δ weight in previous 2m Age 18-35y BMI 28-36 Non smokers No T2DM	Denmark 42% Male Age: (28)	Parallel Group	6 months	Free living diet plan - All food provided via supermarket	154	1. High MUFA	1. Dietary counselling and food provided from study supermarket. Prescribed 35-45%FAT, >20%MUFA This diet <i>also</i> included more whole-grains, legumes and	1. %Energy: C 43.3 P 15.3 F 38.4 Energy: 11500kJ/d	Yes	HA Foundation, The Danish Heart Association, The Danish Diabetes

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Obesity trial	Pre-menopausal Recently involved in weight loss trial	BMI: (31)						nuts. SFA:MUFA:PUFA% 7:20:8 2. Low fat 2. Dietary counselling. Food provided from study supermarket. Prescribed 20-30%FAT. 3. Control SFA:MUFA:PUFA% 8:8:5 3. Dietary counselling. Food provided from study supermarket. Moderate fat (35% energy) with >15% SFA. SFA:MUFA:PUFA% 15:10:4.	2. %Energy: C 57.6 P 15.8 F 23.6 Energy: 10500kJ/d 3. %Energy: C 49.8 P 15.9 F 32.1 Energy: 10900kJ/d		Association, The Danish Pork Council and research institute funding
(Due <i>et al.</i> , 2004)  The Danish Protein Swap Study	Previously overweight/obese	Denmark  24% Male  Age: (40)  BMI: (30)	Parallel Group	6 months strict, 6-12 month less strict, plus 24 month follow up	All food provided	50	1. High protein  2. Moderate protein	1. 25%PRO, <30%FAT  2. 12%PRO, <30%FAT	1. %Energy: C 48.9 P 21.2 F 30 Energy: 8400kJ/d 2. %Energy: C 54.7 P 13.9 F 31.4 Energy: 8200kJ/d	Yes	Research institute funding, The Federation of Danish Pig Producers and Slaughterhouse and The Danish Livestock and Meat Board
(Due <i>et al.</i> , 2005)  The Danish Protein Swap Study	Overweight/ Obese	Denmark  28% Male  Age: (40)  BMI: (30)	Parallel Group	6 months	All food provided	50	1. High protein  2. Moderate protein	1. 25%PRO, <30%FAT  2. 12%PRO, <30%FAT	1. %Energy: C 48.9 P 21.2 F 30 Energy: 8400kJ/d 2. %Energy: C 54.7 P 13.9 F 31.4 Energy: 8200kJ/d	Yes	Research institute funding, The Federation of Danish Pig Producers and Slaughterhouse; Danish Dairy Research Foundation; and The Danish Livestock and Meat Board
(Dyson <i>et al.</i> , 2007)	Age >18y BMI >25 No T2DM Weight stable	UK  23% Male  Age: (51)  BMI: (36)	Parallel Group	3 months	Free living diet plan	13	1. Low carbohydrate diet 2. Healthy eating diet	1. Healthy eating advice plus reduction in CHO to <40g/d  2. Dietary guidelines of Diabetes UK plus energy restriction.	1. %Energy: C 17 P 31 F 36 Energy 1313 kcal/d 2. %Energy: C 39 P 21 F 34 Energy 1593 kcal/d	Yes	Medisense UK, Abbott Laboratories
(Ebbeling <i>et</i>	Age 18-35y	USA	Parallel	6 months	Free living	73	1. Low GL	1. Ad libitum low GL foods.	Approx from figures:	Yes	National

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<i>al., 2007)</i>	BMI >30 Generally healthy No medication No recent weight loss program Non smokers No T2DM	21% Male  Age: 18 - 35(27)  BMI: mean not reported	Group	intensive, 12 month follow up. Monthly group workshops through-out 18 mo	diet plan		diet  2. Low fat diet	Target: 40% CHO, 25% PRO, 35% FAT.  2. General healthy eating advice. Target: 55% CHO, 25% PRO, 20% FAT. <i>Ad libitum</i> consumption.	1. %Energy: C 40 P 20 F 36 Energy 1600 kcal/d Fibre g/d:12 2. %Energy: C 53 P 21 F 25 Energy 1500 kcal/d Fibre g/d:10		Institute of Diabetes & Digestive & Kidney Diseases, Charles H. Hood Foundation and research institute funding
(Ebbeling <i>et al., 2003)</i>	BMI >95th centile Generally healthy	USA  28% Male  Age: 13 - 21(16)  BMI: (36)	Parallel Group	6 months strict, 6-12 month less strict	Free living diet plan	16	1. Low GL diet  2. Low fat diet	1. Low to moderate GL foods (non-starchy vegetables, fruits, legumes, nuts, dairy). Target 45-50%CHO, 30-35%FAT. Ad lib diet. GL (g/1000kcal) was 86, 6 at baseline, 68 at 6 months and 69 at 12 months 2. Conventional low fat diet. Increase grains, vegetables & fruit. Target energy reduction 250-500kcal/d. Targets:55-60%CHO, 25-30%FAT. GL (g/1000kcal) was 79 at baseline, 77 at 6 months and 79 at 12 months	1. %Energy: C 51 P 19 F 31 Energy 1522 kcal/d  2. %Energy: C 55 P 18 F 28 Energy 1604 kcal/d	Yes	National Institute of Diabetes & Digestive & Kidney Diseases, Charles H. Hood Foundation and NIH
(Ebbeling <i>et al., 2005)</i>	Age 18-35y BMI >27.5 Healthy	USA  12% Male  Age: mean not reported  BMI: mean not reported	Parallel Group	12 months	Free living diet plan	34	1. Low GI diet  2. Low fat diet	1. Ad lib low GI food, 45-50% CHO, 30-35%FAT. GL 53 g/1000kcal 2. Meal plans based on an exchange system, energy deficit of 250-500kcal/d. GL 77 g/1000 kcal	1. %Energy: C 47.2 P 21.1 F 33 Energy 1391 kcal/d Fibre g/d:20.7 2. %Energy: C 59.4 P 18.7 F 23.4 Energy 1409 kcal/d Fibre g/d:17.8	Yes	National Institute of Diabetes & Digestive & Kidney Diseases, Charles H. Hood Foundation and NIH
(Forcheron and Beylot, 2007)	Not extremely athletic/active	France  35% Male  Age: mean not reported  BMI: mean not	Parallel Group	6 months	Supplement	20	1. Fructans  2. Placebo	1. 10g mix of inulin and oligofructose 2. Maltodextrin 10g/d		Yes	Orafti

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
		reported									
(Foster <i>et al.</i> , 2003)	No medications which influence outcomes Without chronic disease	USA 32% Male Age: (44) BMI: (34)	Parallel Group	12 months	Free living diet plan	63	1. Low carbohydrate diet  2. Conventional diet plan	1. Atkins diet book provided. Low CHO, high FAT, high PRO  2. LEARN weight management diet. High CHO, low FAT, energy restricted diet (1200-1500kcal/d for women and 1500-1800kcal/d for men).	1. <20g CHO for 1 <sup>st</sup> 2 wks, rising until desired wt. achieved. 60% participants ketotic in first 8 wks, falling to 20% at 1 year 2. %Energy: C 60 P 15 F 25	No, intended diet only	NIH
(Frisch <i>et al.</i> , 2009)	Age 18-70y BMI 25-30 Generally healthy	Germany 31% Male Age: (47) BMI: (34)	Parallel Group	6 months, plus 6 month follow up  Weekly phone contact 1 <sup>st</sup> 6 mo, then continue diet for next 6 mo	Free living diet plan	200	1. Moderate carbohydrate diet  2. High carbohydrate diet	1. Prescribed diet: <40% CHO, 25% PRO, >35% FAT. Energy deficit >500kcal/d.  2. Conventional low fat diet. Prescribed diet: >55% CHO, 15% PRO, <30% FAT. Energy deficit >500kcal/d.	1. %Energy: C 40.9 P 19.3 F 36.5 Energy 1742 kcal/d 2. %Energy: C 49.5 P 17.7 F 29.7 Energy 1783 kcal/d	Yes	German Health Insurances and the Institute for Applied Telemedicine
(Garcia <i>et al.</i> , 2007)  The Arabinoxylan and Glucose Metabolism study	Age 20-70y BMI >26 Free of chronic disease Generally healthy Impaired glucose tolerance No medication	Germany 36% Male Age: 48 - 70(56) BMI: 26 - 46(30)	Crossover  (washout 6 weeks)	6 weeks	Supplement	14	1. Arabinoxylan 2. Placebo	1. Arabinoxylan 15g/d (10g within bread, 5g as powder). 2. Placebo powder and bread rolls		Yes	Federal Ministry of Education and Research Germany
(Garcia <i>et al.</i> , 2006)  The Arabinoxylan and Glucose Metabolism study	Age 20-70y BMI >26 Generally healthy Impaired glucose tolerance No chronic illness No medication	Germany 36% Male Age: 48 - 70(56) BMI: 26 - 46(30)	Crossover  (washout 6 weeks)	6 weeks	Supplement	14	1. Arabinoxylan 2. Placebo	1. Arabinoxylan 15g/d (10g within bread, 5g as powder). 2. Placebo powder and bread rolls		Yes	Federal Ministry of Education and Research Germany
(Gardner <i>et al.</i> , 2007) A to Z Weight Loss Study	Generally healthy Moderate alcohol intake No T2DM Pre-menopausal Weight stable	USA 0% Male Age: (41) BMI: 27 - 40(32)	Parallel Group	12 months  8 wks intensive weekly sessions, continue diets w. email and	Free living diet plan	311	1. Atkins: low carbohydrate  2. Zone: moderate carbohydrate  3. Ornish:	1. Atkins diet: very low in carbohydrate  2. Zone: reduced carbohydrate  3. Ornish: high carbohydrate	1. %Energy: C 17.7 P 27.7 F 54.7 Energy: 5781.97kJ/d Fibre g/d:11 2. %Energy: C 42 P 23.7 F 34.8 Energy: 6091.8kJ/d Fibre g/d:16.9 3. %Energy: C 63.1 P 16.9 F	Yes	NIH

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				telephone contact until 12month post randomisation			high carbohydrate	intake 4. LEARN program (data not extracted) – lifestyle, exercise, attitudes, relationships, nutrition	21.1 Energy: 5895kJ/d Fibre g/d:22.1		
(Genta <i>et al.</i> , 2009)	BMI >30 Generally healthy History of constipation Mild lipidaemias Pre-menopausal	Argentina  0% Male  Age: (41)  BMI: (34)	Parallel Group	120 days	Supplement	55	1. Fructooligosaccharide (Yacon) syrup low dose 2. Placebo  3. Fructooligosaccharide (Yacon) syrup high dose.	1. Provided 0.14 g fructooligosaccharides/ kg body weight/d from yacon syrup. 2. Placebo syrup  3. Provided 0.29 g fructooligosaccharides/ kg body weight/d from yacon syrup. No data were presented for this group as significant undesirable gastrointestinal side effects were observed.	1. %Energy: C 67.04 P 2.16 F 0.14	Yes	Research institute funding
(Golay <i>et al.</i> , 1996)	BMI >30 No endocrine disease	Switzerland  21% Male  Age: (43)  BMI: (40)	Parallel Group	6 weeks	All food provided	43	1. Low carbohydrate diet 2. Moderate carbohydrate diet	1. Hypocaloric diet (1000kcal/d) 15%CHO, plus aerobic exercise 1h/d 2. Hypocaloric diet (1000kcal/d) 45%CHO plus aerobic exercise 1h/d	1. %Energy: C 15 P 32 F 53 g/d: C 37 P 79 F 60 Energy: 4214kJ/d 2. %Energy: C 45 P 29 F 26 g/d: C 115 P 73 F 30 Energy: 4296kJ/d	No, intended diet only	Not reported
(Golay <i>et al.</i> , 2000)	Able to participate in physical activity BMI >30 Highly motivated to lose weight	Switzerland  24.1% Male  Age: (44)  BMI: (39)	Parallel Group	6 weeks	All food provided	54	1. Dissociated low energy diet  2. Balanced low energy diet	1. 1100 kcal/day. 47% carbohydrates and 25% lipids. Participants were not allowed to consume lipids and carbohydrates simultaneously. 2. 1100 kcal/day. 42% carbohydrates and 31% lipids. Participants were allowed to consume all macronutrients simultaneous	1. %Energy: C 47 P 27 F 25 g/d: C 123 P 71 F 29 Energy: 4600kJ/d  2. %Energy: C 42 P 27 F 31 g/d: C 114 P72 F 38 Energy: 4600kJ/d	No, intended diet only	Not reported
(Grau <i>et al.</i> , 2009)  NUGENOB	<3kg weight change 3 months prior Age 20-50y BMI >30 No hypertension, T2DM, alcoholics	Europe  25% Male  Age: (38)  BMI: (35)	Parallel Group	10 weeks	Free living diet plan	771	1. Low CHO, high fat diet  2. High carbohydrate, low fat diet	1. Hypoenergetic (-600 kcal/d) 40-45% CHO, 15% PRO, 40-45% FAT 2. Hypoenergetic (-600 kcal/d) 60-65% CHO, 15% PRO, 20-25% FAT	1. %Energy: C 43 P 17 F 40 Energy 1620 kcal/d Fibre g/d:19 2. %Energy: C 57 P 18 F 25 Energy 1561 kcal/d Fibre g/d:23	Yes	European Community

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	No surgically or drug-treated obesity Not hyperlipidaemic/hypercholesterolaemic										
(Gray <i>et al.</i> , 2008)  American LC study III	Age >18y BMI 30-35 Generally healthy No T2DM	USA  0% Male  Age: (44)  BMI: (34)	Parallel Group	3 months	Free living diet plan	42	1. Moderate fat   2. Low carbohydrate	1. American Heart Association Step 1 diet + restrict to 1200kcal/d. Intended intake: 55% CHO, 15% PRO, 30% FAT  2. Ad libitum food intake. Max CHO intake 20g/d. CHO increased to 40-60g/d if ketosis was induced after 2 weeks.	1. %Energy: C 54 P 18 F 28  2. %Energy: C 15 P 28 F 57	Yes	Research institute funding, Veterans Affairs Merit Award, the American Heart Association and NIH
(Helge, 2002)	Generally healthy Stable activity level	Denmark  100% Male  Age: (27)  BMI: (25)	Parallel Group	7 weeks	Free living diet plan	41	1. High fat + exercise 2. High carbohydrate + exercise  3. High fat	1. 21%CHO, 17%PRO, 62%FAT 2. 65% CHO, 15%PRO, 20%FAT 3. Data for this group will not be included, the lack of exercise element means it is not a useful comparison group	1. %Energy: C 21.8 P 16.6 F 61.6 Energy 3367 kcal/d 2. %Energy: C 64.9 P 14.6 F 20.3 Energy 3487 kcal/d	Yes	Research institute funding
(Howard <i>et al.</i> , 2006) The Women's Health Initiative Dietary Modification Trial	Age 50-79y Fat intake >32% Post-menopausal	USA  0% Male  Age: (62)  BMI: (29)	Parallel Group	6 years	Free living diet plan	48835 5.8% gave blood	1. Low fat   2. Control	1. Advice: reduce fat intake to 20%, increase fruit, vegetables and wholegrains  2. Received information relating to health and healthy diets	1. %Energy: C 53.9 P 17.7 F 28.8 Energy 1432 kcal/d Fibre g/d:19.6 2. %Energy: C 45.9 P 17.1 F 37 Energy 1546 kcal/d Fibre g/d:14.4	Yes	National Heart, Lung, and Blood Institute
(Jackson <i>et al.</i> , 1999)	Mild to moderate lipidaemias No CHD or T2DM No medications which influence outcomes Not extremely athletic/active	UK  % Male not reported Age: 35 - 65(52)  BMI:20 - 32(26)	Parallel Group	8 weeks	Supplement	54	1. Inulin 2. Placebo	1. Inulin powder added to usual diet 10g/d 2. Maltodextrin powder added to usual diet 10g/d		Yes	Raffinerie Tirlemontoise (ORAFIT)

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Jensen <i>et al.</i> , 2008)	Age 20-40y BMI 25-30 Generally healthy Moderate alcohol No hypertension No medical conditions which influence outcomes No medication Non smokers Not extremely athletic/active	Denmark 0% Male Age: 20 - 40 BMI: (28)	Parallel Group	10 weeks	Substitution	55	1. Low GI diet  2. High GI diet	1. Received low GI test foods in place of their usual CHO rich foods. GI of provided foods 72 2. Received high GI test foods in place of their usual CHO rich foods. GI of provided foods 95	1. %Energy: C 81.2 P 12.8 F 5.9 Energy: 4860kJ/d Fibre g/d:29.3 2. %Energy: C 81.7 P 12.6 F 5.7 Energy: 4886kJ/d Fibre g/d:32.2	Yes	Research institute funding
(Johnston <i>et al.</i> , 2004)	Generally healthy	USA 10% Male Age: 19 - 54 BMI: (29)	Parallel Group	6 weeks	All food provided	20	1. High protein, low fat 2. High carbohydrate, low fat	1. Low fat, energy restricted, 30%PRO 2. Low fat, energy restricted, 60%CHO	1. g/d: C 170 P 134 F 53 Energy 1700 kcal/d Fibre g/d:23 2. g/d: C 280 P 64 F 39 Energy 1700 kcal/d Fibre g/d:25	No, intended diet only	University funding and research institute funding
(Johnston <i>et al.</i> , 2006)	No medications which influence outcomes	USA 21% Male Age: 20 - 60 BMI: (34)>25	Parallel Group	6 weeks	All food provided	20	1. Low carbohydrate diet 2. Very low-carbohydrate diet	1. Nonketokegenic low carbohydrate diet. 40%CHO, 30%PRO, 30%FAT (SFA 9%) 2. 5%CHO (increased by 5g/wk in weeks 3-6), 30%PRO, 60%FAT (SFA 21%)	1. %Energy: C 42 P 31 F 30 g/d: C 157 P 117 F 50 Energy: 6250kJ/d Fibre g/d:30 2. %Energy: C 9 P 33 F 60 g/d: C 33 P 125 F 100 Energy: 6250kJ/d Fibre g/d:15	Yes	Research institute funding
(Keogh <i>et al.</i> , 2007)	Age 20-65y BMI 27-40 Moderate alcohol intake No hypertension or T2DM No medications which influence outcomes	Australia 32% Male Age: (49) BMI: (33)	Parallel Group	12 weeks  Active weight loss phase 1-12 week, monthly dietician meeting until week 52	Free living diet plan	44	1. Low carbohydrate diet 2. High carbohydrate diet	1. Energy restricted, low CHO diet, low in saturated fat. 2. Energy restricted, high CHO diet, low in saturated fat.	1. %Energy: C 33 P 40 F 27 Fibre g/d:26 2. %Energy: C 60 P 20 F 20 Fibre g/d:40	No, intended diet only	Research institute funding
(Keogh <i>et al.</i> , 2008)	≥ 1 metabolic syndrome risk factor Abdominal obesity No CHD or T2DM	Australia % Male: not reported Age: 24 - 64(50) BMI:27 - 44(34)	Parallel Group	8 weeks	Free living diet plan	117	1. Low carbohydrate, high SFA 2. High carbohydrate, low SFA	1. 30% energy restriction. Some key foods were provided top aid compliance. Intended diet: 4%CHO, 35%PRO, 61%FAT 2. 30% energy restriction. Some key foods were provided top aid compliance. Intended diet: 46%CHO,	1. %Energy: C 5 P 35 F 59 g/d: C 20 P 133 F 103 Energy: 6608kJ/d Fibre g/d:13 2. %Energy: C 47 P 24 F 28 g/d: C 172 P 87 F 47 Energy: 6590kJ/d Fibre g/d:32	Yes	Research institute funding



Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Kim <i>et al.</i> , 2008)	BMI 25-35 No chronic illness Normal glucose tolerance Normal lipid profile	Korea 0% Male Age: 20 - 35 BMI:25 - 35	Parallel Group	6 weeks	All food provided	47	1. White rice meal replacement	24%PRO, 30%FAT 1. Energy restricted diet (258kj/d), three meals per day replaced with supplement containing white rice plus soybean, seaweed, laver, vegetables. Cooked with milk.		Yes	Research institute funding
							2. Brown & black rice meal replacement	2. Energy restricted diet (258kj/d), three meals per day replaced with supplement containing brown and black rice plus soybean, seaweed, laver, vegetables. Cooked with milk.			
(Kirk <i>et al.</i> , 2009)	Impaired glucose tolerance Insulin resistant No chronic illness No medications which influence outcomes No T2DM Weight stable	USA 18% Male Age: (44) BMI: (37)	Parallel Group	11 weeks	All food provided	22	1. High carbohydrate	1. Energy deficit 1000kcal/d until 7% body weight loss (~6 weeks) followed by weight maintenance. CHO>180g/d	1. %Energy: C 65 P 15 F 20	No, intended diet only	NIH
							2. Very low carbohydrate	2. Energy deficit 1000kcal/d until 7% body weight loss (~6 weeks) followed by weight maintenance. CHO <50g/d	2. %Energy: C 10 P 15 F 75		
(Kirkwood <i>et al.</i> , 2007)	Age 30-50y BMI 25-40 Generally healthy Not on weight loss diet	Scotland 0% Male Age: (41) BMI: (32)	Parallel Group	12 weeks	Free living diet plan	109	1. Group 1: No advice 2. Group 2: Conventional weight loss diet 3. Group 3: Exercise 4. Group 4: Conventional weight loss diet + exercise	1. Comparison for group 2 2. Low fat, high carbohydrate, including sucrose, energy reduced diet 3. Intervention was exercise-based (comparison for group 4) 4. Low fat, high carbohydrate, including sucrose, energy reduced diet plus exercise	1. %Energy: C 49.6 P 17 F 33.1 Energy: 8100kj/d 2. %Energy: C 50.1 P 19.1 F 30.2 Energy: 7100kj/d 3. %Energy: C 44.2 P 18.9 F 36.7 Energy: 7400kj/d 4. %Energy: C 52.3 P 17.8 F 29 Energy: 7100kj/d	Yes	The Sugar Bureau
(Landin <i>et al.</i> , 1992)	Generally healthy Middle-aged adults Not extremely athletic/active Not obese	Sweden 100% Male Age: (52)	Crossover (washout 2 weeks)	6 weeks	Supplement	25	1. Guar gum 2. Placebo	1. Ten grams granulated guar given in a glass of water, 3 times a day before meals. 2. Granulated gelling starch given in a glass of water, 3 times a day before meals.	1. g/d: C 445 P 14 F 92 Energy 2875 kcal/d 2. g/d: C 445 P 14 F 92 Energy 2875 kcal/d	Yes	Research institute funding: Nordisk Insulin fond, the Swedish

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	WHR of 0.91	BMI: (25)									Nutrition Foundation and Goteborg Medical Society.
(Landry <i>et al.</i> , 2003)	Generally healthy No CHD Normal glucose tolerance Weight stable	Canada  100% Male  Age: (34)  BMI: (28)	Parallel Group	7 weeks	All food provided	37	1. High carbohydrate  2. Low carbohydrate, high fat diet	1. Ad libitum consumption of plentifully supplied foods.  2. Ad libitum consumption of plentifully supplied foods.	1. %Energy: C 60 P 16 F 27 Energy: 12000kJ/d 2. %Energy: C 46 P 16 F 41 Energy: 13000kJ/d	Yes	Knoll Pharmaceutical Company and the International Life Sciences Institute.
(Lasker <i>et al.</i> , 2008)	BMI >25 No medications which influence outcomes Non smokers	USA  38% Male  Age: (47)  BMI: (34)	Parallel Group	4 months	Free living diet plan	65	1. High carbohydrate  2. High protein	1. Energy restriction 500kcal/d  2. Energy restriction 500kcal/d	1. g/d: C 215.4 P 66.7 F 39.2 Energy: 5875kJ/d Fibre g/d:24.3 2. g/d: C 152.6 P 121.4 F 56.2 Energy: 6607kJ/d Fibre g/d:21.1	Yes	National Cattleman's Beef Association, The Beef Board and Kraft Foods
(Layman <i>et al.</i> , 2005)	BMI >26 Body weight <140% of ideal No medical conditions which influence outcomes No medications which influence outcomes	USA  0% Male  Age: 40 - 56(47)  BMI: (33)	Parallel Group	16 weeks	Free living diet plan	48	1. High protein diet  2. High protein diet + exercise  3. High carbohydrate diet 4. High carbohydrate diet + exercise	1. Carbohydrate: protein ratio designed to be <1.5.  2. Carbohydrate: protein ratio designed to be <1.5. Exercise recommendations were a minimum of 30minutes of walking 5d/week 3. Carbohydrate: protein ratio designed to be >3.5 4. Carbohydrate: protein ratio designed to be >3.5. Exercise recommendations were minimum of 30minutes of walking 5d/week	1. g/d: C 141 P 110 F 52 Energy: 6062kJ/d Fibre g/d: 18.6 2. g/d: C 127 P 102 F 46 Energy: 5540kJ/d Fibre g/d: 16 3. g/d: C 197 P 58 F 34 Energy: 5377kJ/d Fibre g/d:23	Yes	Illinois Council on Food and Agricultural Research, National Cattlemen's Beef Association, The Beef Board and Kraft Foods.
(Lehtimäki <i>et al.</i> , 2005)	Age 18-65y Healthy Not recently involved in any trial Stratified by apolipoprotein E genotype	Finland  42% Male  Age: (44)  BMI: (26)	Crossover (washout 0 days)	3 months	Supplement	130	1. Encapsulated microcrystalline chitosan 2. Starch capsules	1. 1.2 g chitosan twice daily (total 2.4g/d).  2. 1.2 g starch twice daily.		Yes	Research institute funding and the Finnish Cultural Foundation

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Leidy <i>et al.</i> , 2007)  American Protein Study	Age >18y BMI >25 Non smokers Normal blood profiles Normal glucose tolerance Stable activity level Weight stable Women	USA  0% Male  Age: 28 - 80  BMI:26 - 37	Parallel Group	12 weeks	Free living diet plan	54	1. High protein, energy restricted 2. Moderate protein, energy restricted	1. 750 kcal/d energy-deficit diet, 30% PRO  2. 750 kcal/d energy-deficit diet, 18% PRO	1. %Energy: C 45 P 30 F 25 Energy: 1560 kcal/d  2. %Energy: C 57 P 18 F 25 Energy: 1440 kcal/d	No, intended diet only	University funding and the National Pork Board
(Letexier <i>et al.</i> , 2003)	Generally healthy No medications which influence outcomes No T2DM	France  50% Male  Age: 23 - 32  BMI:19 - 25	Crossover  (washout 4 months)	6 weeks	Supplement	8	1. Inulin 2. Placebo	High-carbohydrate, low-fat diet (55% of total energy) plus 1. Inulin 10g/d 2. Maltodextrin 10g/d		Yes	European Union
(Lofgren <i>et al.</i> , 2005)	Age 20-50y BMI >30 No chronic illness No medications which influence outcomes	Sweden  0% Male  Age: (36)  BMI: (37)	Parallel Group	10 weeks	Not stated	40	1. High fat, moderate carbohydrate 2. High carbohydrate, low fat	1. Hypoenergetic (-600 kcal/d). 40-45%CHO, 15-20%PRO, 40-45%FAT. No alcohol permitted 2. Hypoenergetic (-600 kcal/d). 60-65%CHO, 15-20%PRO, 20-25%FAT. No alcohol permitted.	1. %Energy: C 38.9 P 19.6 F 41.5  2. %Energy: C 52.4 P 21.1 F 26.5	Yes	European Community
(Lovejoy <i>et al.</i> , 2003)  Ole Study	Age 18-70y BMI 25-35 Generally healthy Non smokers Not extremely athletic/active Weight stable	USA  100% Male  Age: (37)  BMI: (31)	Parallel Group	9 months	All food provided	45	1. Control  2. Fat reduced  3. Fat substituted	1. 33%FAT  2. 25%FAT. Diet designed to be 11% lower energy than control diet 3. 1/3 of dietary fat replaced by olestra (25% metabolizable fat). This group will not be included in the review.	1. %Energy: C 52 P 15 F 33 2. %Energy: C 58 P 17 F 25	No, intended diet only	Government funding and Procter & Gamble Co.
(Mahon <i>et al.</i> , 2007)	Age 50-80y BMI 25-35 Generally healthy No T2DM Post-menopausal	USA  0% Male  Age: (58)  BMI: (30)	Parallel Group	9 weeks	All food provided	57	1. Control 2. Energy restriction + beef 3. Energy restriction + chicken 4. Energy	1. Habitual diet 2. Energy restricted diet (1000 kcal/day) lacto-ovo vegetarian diet plus 250kcal/d from beef 3. Energy restricted diet (1000 kcal/day) lacto-ovo vegetarian diet plus 4. Energy	1. %Energy: C 47 P 20 F 33 Energy: 1570 kcal/d 2. %Energy: C 46 P 24 F 30 Energy: 1114 kcal/d 3. %Energy: C 51 P 25 F 24 Energy: 1098 kcal/d 4. %Energy: C 59 P 17 F 24 Energy: 1158 kcal/d	Yes	Cattlemen's Beef Board and the National Cattlemen's Beef Association, research institute

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								restriction + carbohydrate / fat	250kcal/d from chicken 4. Energy restricted diet (1000 kcal/day) lacto-ovo vegetarian diet plus 250kcal/d from carbohydrate/fat foods (shortbread cookies and sugar coated chocolates)		funding and University funding
(Maki <i>et al.</i> , 2007a)	Age >40y DBP 85-109mmHg Fibre <20g/d Mid upper arm circumference <42cm No CHD or T2DM SBP 130-179 mmHg. Waist circumference >96.5 (m) >88.9 (f)	USA 55% Male Age: >40 BMI: (32)	Parallel Group	12 weeks	Substitution	97	1. Oat beta-glucan cereal  2. Wheat cereal	1. 90g/d oat bran cereal + 60g/d oatmeal + 20g/d powdered oat beta-glucan. 7.7g/d beta glucan  2. 90g/d wheat cereal + 65g/d low fibre hot cereal oatmeal + 12g/d maltodextrin powder	1. g/d: C 124.3 P 20.3 F 8.9 Energy: 658 kcal/d Fibre g/d:17.3 2. g/d: C 139.5 P 10 F 2.1 Energy: 641 kcal/d Fibre g/d:1.9	Yes	Quaker Oats Company
(Maki <i>et al.</i> , 2007b)	<4.5kg Δ weight in previous 2m Age 18-65y Generally healthy No untreated hypertension Non smokers No T2DM Waist >87cm(F) or >90cm(M)	USA 32.6% Male Age: (50) BMI: (32)	Parallel Group	36 weeks	Free living diet plan	86	1. Ad libitum low GL diet  2. Low fat, energy restricted	1. Dietary advice ad libitum reduced-glycaemic-load (GI average = 48, GL = 8173 carb*GI) 2.Reduce fat intake, decrease portion sizes, target energy deficit 500-800 kcal/d (GI average = 51, GL= 12118 carb*GI)	1. g/d: C 69 P 97 F 80 Energy: 1365 kcal/d Fibre g/d:11 2. g/d: C 168 P 75 F 62 Energy: 1525 kcal/d Fibre g/d:12	Yes	Kraft Foods
(Marett and Slavin, 2004)	Age 18-55y Generally healthy	USA 52% Male Age: (29) BMI: mean not reported	Parallel Group	6 months	Supplement	54	1. Placebo  2. Larch arabinogalactan  3. Tamarack arabinogalactan	1. Rice starch 8.4g/d added to food or drinks 2. 8.4g/d Larch arabinogalactan (non viscous soluble fibre) added to food or drinks 3. 8.4g/d Tamarack arabinogalactan (non viscous soluble fibre) added to food or drinks		Yes	The Sota-Tec Fund
(McMillan-Price <i>et al.</i> , 2006)	<150 kg <5kg Δ weight in the previous 2m Age 18-40y BMI >25	Australia 24% Male Age: (32)	Parallel Group	12 weeks	All food provided	129	1. High CHO, high GI diet	All groups: 1400 kcal/d women and 1900 kcal/d men. 1. 55% CHO, 15% PRO, <30% FAT, fibre 30g/d. Diet based	1. %Energy: C 60 P 18 F 19 Energy: 9630kJ/d	Yes	Meat and Livestock Australia and National Heart Foundation of

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	Maintain current physical activity levels No chronic illness No medication	BMI: (31)						on high-GI whole grains, fibre-rich cereals/breads. GI 70, GL 127g  2. High CHO, low GI diet  3. High protein, high GI diet  4. High protein, low GI diet	Fibre g/d:23  2. %Energy: C 56 P 19 F 22 Energy: 9030kJ/d Fibre g/d:20 3. %Energy: C 42 P 28 F 27 Energy: 9220kJ/d Fibre g/d:19  4. %Energy: C 40 P 26 F 29 Energy: 8890kJ/d Fibre g/d:21		Australia
(Meckling <i>et al.</i> , 2004)	BMI >25 Generally healthy Highly motivated to lose weight No medications which influence outcomes	Canada 29% Male Age: 24 - 61 BMI: (32)	Parallel Group	10 weeks	Free living diet plan	40	1. Low fat  2. Low carbohydrate	1. Energy restriction was matched to the low CHO group 2. CHO 50-70 g/d plus concomitant energy restriction	1. %Energy: C 61.9 P 19.5 F 17.8. Energy: 6077kJ/d Fibre g/d:20.3 2. %Energy: C 15.4 P 26.2 F 55.5. Energy: 6421kJ/d Fibre g/d:8.9	Yes	Research institute funding
(Meckling and Sherfey, 2007)	BMI 25-30 No chronic illness No CHD/ T2DM No medication Pre-menopausal	Canada 0% Male Age: (43)  BMI: (30)	Parallel Group	12 weeks	Free living diet plan	60	1. Hypocaloric control diet  2. Hypocaloric control diet + exercise  3. Hypocaloric protein rich diet 4. Hypocaloric protein rich diet + exercise	1. Hypoenergetic (-500kcal/day). Target PRO:CHO ratio 1:3 (WHO standards) 2. Hypoenergetic (-500kcal/day). Target PRO:CHO ratio 1:3 (WHO standards). Supervised circuit training exercise 3d/week 3. Hypoenergetic (-500kcal/day). Target PRO:CHO ratio 1:1 (Fat intake >30%). 4.	1. %Energy: C 49.5 P 16 F 33.8 g/d: C 171 P 56 F 53 Energy: 5822kJ/d 2. %Energy: C 50.2 P 18.4 F 29.4 g/d: C 160 P 59 F 42 Energy: 5271kJ/d 3. %Energy: C 36.6 P 24.3 F 38.6 g/d: C 127 P 84 F 60 Energy: 5787kJ/d	Yes	Not reported
(Morgan <i>et al.</i> , 2009)	Age 18-70y BMI >25 Generally healthy	UK 30% Male	Parallel Group	6 months	Free living diet plan	300	1. Control  2. Atkins	1. No intervention 2. Atkins Diet - very low carbohydrate	1. %Energy: C 43 P 16 F 36 Energy: 7947kJ/d 2. %Energy: C 12 P 28 F 57 Energy: 6809kJ/d	Yes	The British Broadcasting Corporation

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		Age: 21 - 60(40)  BMI: (32)					3. Weight Watchers  4. Slim Fast  5. Rosemary Conley	3. Weight Watchers Pure Points programme (an energy-controlled low-fat healthy eating diet) 4. The Slim-Fast Plan (a low-fat meal replacement approach) 5. Rosemary Conley's 'Eat yourself Slim' Diet and Fitness Plan (energy controlled, low-fat healthy eating diet and weekly group exercise class) Group not included as a comparison as it includes an exercise component	3. %Energy: C 47 P 19 F 29 Energy: 6084kJ/d 4. %Energy: C 50 P 19 F 28 Energy: 6076kJ/d		
(Nestel <i>et al.</i> , 2004)	Moderate alcohol intake No medications which influence outcomes No supplement use Non smokers Not extremely athletic/active	Australia  47% Male  Age: (57)  BMI: (26)	Crossover  (washout 0 days)	6 weeks	Substitution	21	1. Chickpea based foods  2. Wheat based foods	1. Cooked chickpeas plus bread and biscuits baked with 30% chickpea flour. 2. Included whole-grain shredded wheat cereal plus bread and biscuits made from whole-grain flour.	1. %Energy: C 47 P 19 F 30 Energy: 7424kJ/d Fibre g/d:33 2. %Energy: C 44 P 19 F 31 Energy: 7524kJ/d Fibre g/d:26	Yes	Research institute funding
(Noakes <i>et al.</i> , 2006)	≥ 1 CHD risk factor BMI >28	Australia  17% Male  Age: (48)  BMI: (33)	Parallel Group	12 weeks	Free living diet plan	83	1. Very low carbohydrate 2. Very low fat 3. High unsaturated fat	All groups were iso-caloric with 30% energy restriction during weeks 1-8, weight maintenance weeks 9-12. 36% of key foods provided to aid compliance	1. %Energy: C 12.4 P 30.5 F 54.3. Energy: 7706kJ/d 2. %Energy: C 66 P 20.3 F 12.5. Energy: 7000kJ/d 3. %Energy: C 48.7 P 21.4 F 28. Energy: 7659kJ/d	Yes	The National Heart Foundation of Australia
(Noakes <i>et al.</i> , 2005)  Australian Protein Study	Age 20-65y BMI 27-40 No metabolic disease No T2DM	Australia  0% Male  Age: (49)  BMI: (32)	Parallel Group	12 weeks	Free living diet plan	119	1. High protein diet  2. High carbohydrate diet	1. 46%CHO, 34%PRO, 20%FAT (<10%SFA). Advise: 200g/d red meat + 100g/d lunch meat/chicken/fish 2. 64%CHO, 17%PRO, 20%FAT (<10%SFA). Advise: 80g/d chicken or pork plus bread.	1. %Energy: C 44.2 P 31.3 F 22.1 Energy: 5310kJ/d Fibre g/d:27.6 2. %Energy: C 60.8 P 17.8 F 20.1 Energy: 5219kJ/d Fibre g/d:26.1	Yes	Meat and Livestock Australia
(O'Brien <i>et al.</i> , 2005)	Age >18y BMI 30-35 No CHD, T2DM or	USA  0% Male	Parallel Group	3 months	Free living diet plan	42	1. Moderate fat	1. American Heart Association Step 1 diet + restrict to 1200kcal/d.	1. %Energy: C 53 P 18 F 29 Energy 1247 kcal/d Fibre g/d:12.35	Yes in alternative	University funding, NIH and American

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American LC study IV	hypertension No weight Δ >10% in past 6m	Age: (44)  BMI: (34)					2. Low carbohydrate	Intended intake: 55% CHO, 15% PRO, 30% FAT 2. Ad libitum food intake. Max CHO intake 20g/d. CHO increased to 40-60g/d if ketosis was induced after 2 weeks.	2. %Energy: C 30 P 23 F 46 Energy 1302 kcal/d Fibre g/d:8.4  Data from Brehm <i>et al.</i> 2003	publication	Heart Association Grant-in-Aid
(Olendzki <i>et al.</i> , 2009)	Age 18-70y BMI >25	USA  16% Male  Age: (48)  BMI: (31)	Parallel Group	3 months	Free living diet plan	31	1. Hypo-energetic high fibre 2. Hypoenergetic low saturated fat 3. Hypoenergetic high fibre and low saturated fat	In all conditions, energy restriction goal plus: 1. Increase fibre to 30g/day  2. saturated fat < 7%  3. low saturated fat <7% and high fibre > 30g	1. %Energy: C 51.4 P F 27.6 Energy: 1511 kcal/d Fibre g/d:24.6 2. %Energy: C 49.9 P F 27.5 Energy: 1523 kcal/d Fibre g/d:17.4 3. %Energy: C 52.1 P F 26.2 Energy: 1511 kcal/d Fibre g/d:23.7	Yes	Not reported
(Parnell and Reimer, 2009)	Age 18-70y BMI >25	Canada  18% Male  Age: (40)  BMI: (30)	Parallel Group	12 weeks	Supplement	48	1. Maltodextrin placebo 2. Oligofructose	No dietary prescription other than 1. Maltodextrin placebo 21g/d, added to drinks 2. 21g/d oligofructose (Raftilose) per day, added to drinks	1. g/d: C 259.1 P 94.6 F 93.6 Energy: 1800 kcal/d 2. g/d: C 189.2 P 71.3 F 54.6 Energy: 1600 kcal/d	Yes	Research institute and University funding
(Pasman <i>et al.</i> , 1997a)	BMI >30 Energy restriction during trial run-in Weight loss >5kg during run-in	The Netherlands  0% Male  Age: (41)  BMI: (33)	Parallel Group	14 months post 2 month weight loss phase	Supplement	39	1. Guar gum - High compliance  2. Control 3. Guar Gum - Low compliance	1. 20g guar gum in 2x10g doses daily to be consumed in afternoon and evening. Dissolved in 200ml water/coffee/orange juice. High compliance - consumed >80% supplements 2. Nothing was provided as placebo to the control group 3. 20g guar gum in 2x10g dose. 50-80% compliant	Nb. groups 1 and 3 are post-hoc defined – subjects not randomised to these groups initially 1.5.8 MJ/d 2. 6.6 MJ/d 3. 7.0 MJ/d	Yes	Sandoz Nutrition Ltd (Novartis Nutrition)
(Pasman <i>et al.</i> , 1997b)	BMI >30 Energy restriction during trial run-in Good compliance during run-in	The Netherlands  0% Male  Age: (35)	Parallel Group	14 months	Supplement	33	1. CHO/Cr-Pic (Chromium III)/Fibre/Caffeine 2. Carbohydrate	1. Group not comparable, multi-ingredient supplement. Data not extracted 2. 50g carbohydrate daily, dissolved in 250ml water	1. data not extracted 2. %Energy: C 50 P 13 F 36 Energy: 8100kJ/d Fibre g/d:12 3. %Energy: C 42 P 15 F 37 Energy: 7600kJ/d	Yes	Novartis Nutrition Ltd

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		BMI: (31)					supplement	(42% glucose, 58% maltodextrin)	Fibre g/d:15		
							3. Control	3. No supplement			
(Pereira <i>et al.</i> , 2004)	Age 18-35y BMI >25 Generally healthy No medications which influence outcomes No recent weight loss program Non smokers Not extremely athletic/active Weight stable	USA 23.7% Male Age: (31) BMI: mean not reported	Parallel Group	Mean interval from baseline to follow-up = 65d in low GL group and 69d in low fat	All food provided	39	1. Hypoenergetic low GL diet  2. Hypoenergetic low fat diet	1. Energy restricted low glycaemic load diet (60% of predicted requirements). GI 50, GL 82  2. Energy restricted low fat diet (60% of predicted requirements). 18%FAT. GI 82, GL 205. NCEP Step 1 diet	1. %Energy: C 43 P 27 F 30 Energy: 1500 kcal/d Fibre g/d:32 2. %Energy: C 65 P 17 F 18 Energy: 1500 kcal/d Fibre g/d:20	Yes	National Institute of Diabetes, NIH, Digestive and Kidney Diseases, Charles H. Hood Foundation and General Mills
(Petersen <i>et al.</i> , 2006)	Age 20-50y BMI >30 No hypertension or T2DM Not hyperlipidaemic/hypercholesterolaemic Weight stable	Europe 25% Male Age: (38) BMI: (35)	Parallel Group	10 weeks	Free living diet plan	771	1. Hypo-energetic high carbohydrate, low fat diet 2. Hypoenergetic low carbohydrate, high fat diet	1. Hypoenergetic (-600 kcal/d) 60-65% CHO, 15% PRO, 20-25% FAT  2. Hypoenergetic (-600 kcal/d) 40-45% CHO, 15% PRO, 40-45% FAT	1. %Energy: C 57 P 18 F 25 Energy: 1561kJ/d Fibre g/d:23  2. %Energy: C 43 P 17 F 40 Energy: 1620kJ/d Fibre g/d:19	Yes	European Community
(Peterson and Jovanovic-Peterson, 1995)	130-200% ideal body weight No hypertension Normal glucose tolerance during pregnancies Postpartum 1-4 yrs	USA 0% Male Age: 21 - 50(36) BMI: mean not reported	Crossover	6 weeks	Supplement	25	1. 40% CHO supplement bar 1st 2. 40% CHO supplement bar 2nd 3. 55% CHO supplement bar 1st 4. 55% CHO supplement bar 2nd	1. 180 kcal/bar. 20% protein, 40% CHO.  2. 180 kcal/bar. 20% protein, 40% CHO.  3. 180 kcal/bar. 20% protein, 55% CHO.  4. 180 kcal/bar. 20% protein, 55% CHO.		Yes	Bio-Foods Inc.
(Philippou <i>et al.</i> , 2008)	≥1 CHD risk factor Age 35-65y No chronic illness	UK 38% Male Age: mean not reported BMI: mean not	Parallel Group	12 weeks	Free living diet plan	18	1. Low GI  2. High GI	1. Healthy eating advice plus low GI diet (median GI: 51.3)  2. Healthy eating advice plus high GI diet (median GI: 59.3)	1. %Energy: C 46 P 17.1 F 32.8 Energy: 1773kJ/d 2. %Energy: C 49.4 P 19.6 F 29.2 Energy: 1308kJ/d	Yes	British Heart Foundation



Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
		reported									
(Philippou <i>et al.</i> , 2009b)	Age 18-65y BMI 27-45 Generally healthy Recently involved in weight loss trial and lost at least 5% body weight	UK  % Male: not reported Age: mean not reported  BMI: mean not reported	Parallel Group	4 months	Free living diet plan	43	1. High GI    2. Low GI	1. 4 month GI=64, GL=137. High GI foods at each meal (white/wholemeal bread, cornflakes, weetabix, potatoes, couscous, melon, pineapple and rice cakes) 2. 4 month GI=50 GL=90. Low GI food at each meal (seeded bread, brown pitta, muesli, sweet potatoes, pasta, noodles, basmati slow-cook rice, beans, lentils, apples and dried fruit)	1. %Energy: C 50 P 19 F 31 Energy: 1604 kcal/d Fibre g/d:11  2. %Energy: C 48 P 20 F 32 Energy: 1604 kcal/d Fibre g/d:13	Yes	Not reported
(Philippou <i>et al.</i> , 2009a)	≥1 cardiac risk factor (BMI 27-35 kg/m <sup>2</sup> , waist ≥94 cm, total cholesterol to high-density lipoprotein ratio ≥5.0, raised BP up to a maximum of 140/90 mm Hg) No medication	UK  100% Male  Age: 35 - 65  BMI: mean not reported	Parallel Group	6 months	Substitution	56	1. High GI   2. Low GI	Those with BMI>25 also received weight management advice 1. High GI, carbohydrate foods (e.g. white/wholemeal bread, cornflakes, weetabix, potatoes, couscous, risotto rice, melon, pineapple, rice cakes) 2. Low GI, carbohydrate foods (e.g. seeded bread, wholemeal pita, muesli, porridge, sweet potatoes, pasta, noodles, basmati slow-cook rice, beans, lentils, apples, dried fruit, nuts)	Both groups decreased EI (greater in low GI group), but no macronutrient differences between groups	Yes	British Heart Foundation
(Phillips <i>et al.</i> , 2008)	Age 18-50y BMI 29-39 Generally healthy No CHD, T2DM or hypertension Non smokers Not hyperlipidaemic/hypercholesterolaemic	USA  25% Male  Age: mean not reported  BMI: mean not reported	Parallel Group	6 weeks	All food provided	28	1. Low carbohydrate diet  2. Low fat diet	1. Iso-caloric groups. Low carbohydrate Atkins-style diet (20g/d CHO). 750kcal/d energy deficit weeks 1-4 weeks. 2. American Heart Association low fat diet (30% total energy from fat). 750kcal/d energy deficit weeks 1-4.	1. g/d: C 20  2.%Energy: F 30	No, intended diet only	NIH & the Medical College of Wisconsin Cardiovascular Centre
(Pittas <i>et al.</i> , 2006)  CALERIE	<15 lb Δ weight in previous 12m Age 24-42y Age 5-10y BMI 25-30 Fasting plasma	USA  21.8% Male  Age: 24 - 42(35)	Parallel Group	6 months	All food provided	34	1. Energy restricted high GL diet  2. Energy restricted low	1. 30% calorie restriction. Fibre 15 g/1000kcal. Estimated GI=86, GL=116 g/1000 kcal 2. 30% calorie restriction. Fibre 15 g/1000 kcal.	1. %Energy: C 60 P 20 F 20  2. %Energy: C 40 P 30 F 30	Yes	Research institute funding & U.S. Department of Agriculture

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Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	glucose <5.6mmol/L Generally healthy No chronic illness No familial diabetes No strong family history of CVD/CHD	BMI: (28)					GL diet	Estimated GI=53, GL=45 g/1000kcal			cooperative
(Raatz <i>et al.</i> , 2005)	Age 18-70y BMI 30-40 No medical conditions which influence outcomes No medication	USA 17.2% Male Age: mean not reported BMI: (36)	Parallel Group	36 weeks	Free living diet plan	42	1. High GI diet  2. Low GI diet  3. High fat diet	1. GI=63, GL=272 during feeding phase (12wk feeding phase, 24wk free living). Hypocaloric diet, feeding phase: 60%CHO, 15%PRO, 25%FAT. 2. GI=33, GL=178 during feeding phase (12wk feeding phase, 24wk free living). Hypocaloric diet, feeding phase: 60%CHO, 15%PRO, 25%FAT. 3. GI=59, GL=182 during feeding phase (12wk feeding phase, 24wk free living). Hypocaloric diet, feeding phase: 45%CHO, 15%PRO, 40%FAT.	Feeding phase intakes: 1.%Energy: C60 P15 F25 fibre 9.1g/4184 kJ  2.%Energy: C 60P15 F25 fibre 16.7g/4184 kJ  3. %Energy: C45 P15 F40 fibre 8.6g/4184 kJ	Yes	NIH and research institute funding
(Racette <i>et al.</i> , 1995)	Age 21-47y Body weight 140-180% of ideal Fat mass >35% body weight Generally healthy Pre-menopausal Weight stable	USA 0% Male Age: (39) BMI: (34)	Factorial	16 weeks	Free living diet plan	41	1. Low fat diet 2. Low carbohydrate diet 3. Low fat diet + exercise 4. Low carbohydrate diet + exercise	For all groups: For the first 12 weeks, the prescribed diet aimed to provide 75% of energy for resting metabolic rate (no food was provided). After the weight reduction phase there was a maintenance phase for 4 weeks with higher energy intake prescribed.	1. %Energy: C 59 P 24 F 18 Energy: 51500kJ/d 2. %Energy: C 27 P 24 F 49 Energy: 48000kJ/d 3. %Energy: C 57 P 24 F 19 Energy: 48600kJ/d 4. %Energy: C 26 P 25 F 49	Yes	The Quaker Oats Co., NIH and research institute funding
(Ryle <i>et al.</i> , 1990)	No diabetes	UK 64% Male Age: (26)	Crossover	6 weeks	All food provided	11	1. High glucose low soluble fibre 2. Low glucose high soluble fibre	1. High glucose and low soluble fibre. 75g supplement of high glucose drink (Lucozade) 2. low glucose high soluble fibre diet with 15g		Yes	Not reported

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Sacks <i>et al.</i> , 2009)	Age 30-70y BMI 25-40 No CVD or T2DM	BMI: (22)	Parallel Group	2 years	Free living diet plan	811	diet	supplement of guar gum.		Yes	NIH
		USA						ALL DIETS: energy deficit 750kcal/d			
		36% Male		Contact through-out 2 yrs			1. Low-fat, average-protein	1. 20% fat, 15% protein and 65% CHO.	1. %Energy: C 57.5 P 17.6 F 26.2 Energy: 1636 kcal/d		
		Age: (51) BMI: (33)					2. Low-fat, high-protein	2. 20% fat, 25% protein and 55% CHO.	2. %Energy: C 53.4 P 21.8 F 25.9 Energy: 1572 kcal/d		
							3. High-fat, average-protein	3. 40% fat, 15% protein and 45% CHO	3. %Energy: C 49.1 P 18.4 F 33.9 Energy: 1607 kcal/d		
							4. High-fat, high-protein	4. 40% fat, 25% protein and 35% CHO	4. %Energy: C 43 P 22.6 F 24.3 Energy: 1624 kcal/d		
(Salas-Salvado <i>et al.</i> , 2008)	Age 18-70y BMI >25 Generally healthy Highly motivated to lose weight No medication No recent weight loss program	Spain	Parallel Group	16 weeks		200	1. Mixed soluble fibre twice a day	1. Mixed fibre dose (3g Plantago ovata husk and 1g glucomannan) added to hypoenergetic diet (- 2.5MJ/d) twice a day.	1. %Energy: C 45 P 25 F 35	No, intended diet only	MADAUS, S.A. and the Carlos III Health Institute funding
		22% Male					2. Mixed soluble fibre 3 times a day	2. Mixed fibre dose (3g Plantago ovata husk and 1g glucomannan) added to hypoenergetic diet (- 2.5MJ/d) three times a day.	2. %Energy: C 45 P 25 F 35		
		Age: 18 - 70(48)					3. Placebo	3. 3g microcrystalline cellulose added to an energy restricted diet (reduced by 2.5MJ/d)	3. %Energy: C 45 P 25 F 35		
(Saltzman <i>et al.</i> , 2001)	BMI 25-35 Generally healthy Moderate alcohol intake No hypertension No medications which influence outcomes Non smokers Not extremely athletic/active Weight stable	USA	Parallel Group	6 weeks	All food provided	43	1. Control	1. Hypocaloric (minus 4.2 MJ/d). Same macronutrient composition as intervention but with 45g/1000 kcal of wheat products instead of oats.	1. g/d: C 234 P 82 F 69 Energy: 7833kJ/d Fibre g/d:12.5	Yes	Quaker Oats Company, NIH and Government funding
		49% Male					2. Oats	2. Hypocaloric (minus 4.2 MJ/d). Same macronutrient composition as control but with 45g/1000 kcal of rolled oats.	2. g/d: C 229 P 79 F 67 Energy: 7645kJ/d Fibre g/d:16.3		
(Saris <i>et al.</i> , 2000)	Age 20-55y BMI 26-35 Generally healthy Moderate alcohol intake	Denmark	Parallel Group	6 months	All food provided	398	1. Low-fat, high-simple carbohydrate diet	For all groups, diets ad libitum. 60-70% food provided via study supermarket.	1. %Energy: C 51.6 P 15.3 F 25.7 Energy: 10.8kJ/d	Yes	EU-FAIR and European Sugar industries.
		49.1% Male					2. Low-fat		2. %Energy: C 49.3 P 18.8 F		
CARMEN		Age: (39)									

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Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	No weight loss >5kg in past 6m Not extremely athletic/active Not on weight loss diet	BMI: (30)					high-complex carbohydrate diet 3. Control diet	3. Control diet corresponds to average national intake.	26.4 Energy: 10.5kJ/d 3. %Energy: C 47.7 P 17.2 F 31.3 Energy: 9.6kJ/d		
(Schwab <i>et al.</i> , 2006)	Abnormal glucose metabolism Age 30-65y BMI <35 No CHD No insulin treatment Not taking lipid lowering drugs Plasma glucose <8mmol/L Total Cholesterol <7.5mmol/L Triacylglycerol <4mmol/L	Finland 43.9% Male Age: (53) BMI: (29)	Parallel Group	12 weeks	Supplement	70	1. Pectin  2. Polydextrose 3. Placebo	1. Sugar-beet pectin, drinks. 400ml/day, containing 16g pectin, of which 76% soluble fibre 2. Polydextrose, drinks. 400ml/day, containing 40g/d polydextrose 3. Placebo drinks 400ml/d	1. %Energy: C 51.3 P 17.8 F 28.4 Energy: 7768kJ/d 2. %Energy: C 51.3 P 17.8 F 26.4 Energy: 7978kJ/d 3. %Energy: C 53.2 P 18.8 F 26.3 Energy: 7978kJ/d	Yes	Danisco Ltd
(Segal-Isaacson <i>et al.</i> , 2004)	BMI >25 No CHD or T2DM No medications which influence outcomes Post-menopausal Weight stable	USA 0% Male Age: (52) BMI: (33)	Crossover (washout 0 days)	6 weeks	All food provided	4	1. Low fat diet  2. Very low carbohydrate	1. High protein, low fat diet. Resting energy expenditure - 200kcal = approx 1400 kcal/d. Carbohydrates were provided as low GI starches and fruit. 2. Atkins type diet. Resting energy expenditure -200kcal = approx 1400 kcal/d	1. %Energy: C 50 P 30 F 20 2. %Energy: C 5 P 30 F 65	No, intended diet only	The Robert C. Atkins Foundation and research institute funding
(Seshadri <i>et al.</i> , 2005)	Age >18y BMI >35 Free of severe chronic disease No medications which influence outcomes No uncontrolled diabetes	USA 85% Male Age: mean not reported BMI: mean not reported	Parallel Group	6 months	Free living diet plan	132	1. Low carbohydrate diet 2. Standard diet, energy restricted	1. Limit CHO intake to <30g/d 2. National Heart, Lung and Blood Institute obesity management guidelines. Calorie restriction 500kcal/d.	1. %Energy: C 31 P 25 F 44 Energy: 1343 kcal/d 2. %Energy: C 51 P 16 F 32 Energy: 1590 kcal/d	Yes	Veteran Affairs Healthcare Network Competitive Pilot Project Grant
(Sharman <i>et al.</i> , 2004)  American VLC study	Generally healthy No medications which influence outcomes Non smokers Not extremely athletic/active	USA 100% Male Age: (33) BMI: (34)	Crossover (washout 0 days)	6 weeks	Free living diet plan	15	1. Low fat  2. Very low carbohydrate	1. <30%FAT, hypoenergetic (-500 kcal/d) <10% SAFA, <300mg cholesterol 2. <10%CHO, hypoenergetic (-500 kcal/d)	1. %Energy: C 56 P 20 F 23 Energy: 6540kJ/d Fibre g/d:17 2. %Energy: C 8 P 28 F 63 Energy: 7770kJ/d Fibre g/d:8	Yes	The Robert C. Atkins Foundation

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Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	Not on weight loss diet Weight stable										
(Sichieri <i>et al.</i> , 2007)	Age 25-45y BMI 23-30 Generally healthy No T2DM Parity ≥1 Pre-menopausal	Brazil  0% Male  Age: (37)  BMI: (27)	Parallel Group	18 months  Monthly contact	Substitution	203	1. Low GI/GL diet  2. High GI/GL diet	1. Energy restriction 100-300kcal/d. Staple foods provided. At 18m, GI=30, GL=104 2. Energy restriction 100-300kcal/d. Staple foods provided. At 18m, GI=72, GL=280	1. %Energy: C 60 P F 27 Energy: 11200kJ/d Fibre g/d:36 2. %Energy: C 62 P F 26 Energy: 14000kJ/d Fibre g/d:45	Yes	NIH and research institute funding
(Singh <i>et al.</i> , 1992)											
Data not included in review – concerns about veracity											
(Sloth <i>et al.</i> , 2004)  The Danish GI study	Age 20-40y BMI 25-30 Generally healthy Moderate alcohol intake No medical conditions which influence outcomes No medication, hypertension, smokers Not extremely athletic/active	Denmark  0% Male  Age: 20 - 40  BMI: (28)	Parallel Group	10 weeks	Substitution	55	1. Low GI diet  2. High GI diet	1. Received low GI test foods in place of their usual CHO rich foods 2. Received high GI test foods in place of their usual CHO rich foods	1. %Energy: C 81.2 P 12.8 F 5.9 Energy: 4860kJ/d Fibre g/d:29.3 2. %Energy: C 81.7 P 12.6 F 5.7 Energy: 4886kJ/d Fibre g/d:32.2	Yes	Research institute funding
(Sloth <i>et al.</i> , 2009)  Monounsaturated Fatty acids in Obesity trial	<3kg Δ weight in previous 2m Age 18-35y BMI 28-36 Non smokers No T2DM Pre-menopausal	Denmark  48% Male  Age: (28)  BMI: 28-36	Parallel Group  (washout 3 weeks)	6 months	All food provided in supermarket	56	1. Control  2. Low fat  3. High MUFA	1. Dietary counselling. Food provided from study supermarket. Moderate fat (35% energy) with >15% SFA. SFA:MUFA:PUFA% 15:10:4. 2. Dietary counselling. Food provided from study supermarket. Prescribed 20-30%FAT. SFA:MUFA:PUFA% 8:8:5 3. Dietary counselling and food provided from study supermarket. Prescribed 35-45%FAT, >20%MUFA	1. %Energy: C 50 P 16 F 29 Energy: 10850kJ/d Fibre g/d:28 2. %Energy: C 57 P 16 F 22 Energy: 9625kJ/d Fibre g/d:36 3. %Energy: C 43 P 15 F 35 Energy: 11799kJ/d Fibre g/d:39	Yes	Research institute funding, The H. A. Foundation, the Danish Heart Association, the Danish Diabetes Association, LMC and the Danish Pork Council

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Intervention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Smith <i>et al.</i> , 2008)	<5kg Δ weight in previous 3m Age 22-66y BMI <30 Free of chronic disease Generally healthy Mild to moderate lipidaemias No medications which influence outcomes Non smokers	USA  29% Male  Age: mean not reported  BMI: mean not reported	Parallel Group	6 weeks	Supplement	90	1. Beta glucan, low molecular weight	This diet <i>also</i> included more whole-grains, legumes and nuts. SFA:MUFA:PUFA% 7:20:8  1. Low molecular weight barley B-glucan. 6g B-glucan per day was given as a dietary supplement powder, consumed as a beverage with morning and evening meals.		Yes	NIH
							2. Beta glucan, high molecular weight	2. High molecular weight barley B-glucan. 6g B-glucan per day was given as a dietary supplement			
(Sorensen <i>et al.</i> , 2005)	Age 20-50y BMI 25-30 Generally healthy Not on weight loss diet	Denmark  15% Male  Age: mean not reported  BMI: 28	Parallel Group	10 weeks	Supplement	42	1. Sucrose	1. Sucrose-containing food and drinks provided ~2g/kg/day (~23% total energy). 80% of sucrose within drinks and 20% within food.	From supplements: 1. g/d: C 176 P 9 F 9 Energy: 3349kJ/d 2. g/d: C 31 P 9 F 9 Energy: 963kJ/d	Yes	Research institute funding and Danisco Sugar.
(Surwit <i>et al.</i> , 1997)	Generally healthy No medications which influence outcomes Non smokers Sedentary only	UK 0% Male Age: mean not reported BMI: mean not reported	Parallel Group	6 weeks	All food provided	52	1. High sucrose diet	1. Hypoenergetic diet: low fat high sucrose diet (43% TE from sucrose)	1. %Energy: C 73.3 P 18.7 F 10.8. Energy: 4552.2kJ/d Fibre g/d:10.4 2. %Energy: C 70.9 P 19.3 F 10.6. Energy: 4840.9kJ/d Fibre g/d:14.9	Yes	NIH and The Sugar Association, Inc and the Kellogg Company, Inc
							2. Low sucrose diet	2. Hypoenergetic diet: low fat, low sucrose diet (4% TE from sucrose)			
(Swinburn <i>et al.</i> , 2001)	Age >40y Impaired glucose tolerance (2-h blood glucose 7.8-11.0 mmol/L) or high normal blood glucose (7.0-7.8 mmol/L)	New Zealand  74% Male  Age: >40 - (53)  BMI: mean not reported	Parallel Group	12 months  With 5 yr follow up	Free living diet plan	176	1. Low fat	1. Reduced fat, ad libitum E diet	1. %Energy: C 54.5 P 18.6 F 25.9 Energy: 1832 kcal/d Fibre g/d:20.5	Yes	Auckland Medical Research Foundation, National Heart Foundation of New Zealand, and the Lotteries Medical Board
New Zealand Diabetic Workforce Study							2. Control	2. No intervention – usual diet	2. %Energy: C 45.6 P 16.5 F 33.8 Energy: 2307 kcal/d Fibre g/d:20.3		
(Thompson	BMI 30-40	USA	Parallel	48 weeks	Free living	90	1. Energy	1. Calorie deficit of	1. %Energy: C 54.5 P 18.8 F	Yes	National Dairy

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<i>et al.</i> , 2005)	No medications which influence outcomes No supplement use Weight stable	14% Male  Age: mean not reported  BMI: mean not reported	Group		diet plan		restricted diet  2. Energy restriction + dairy  3. Energy restriction + dairy + fibre	500kcal/d. 50%CHO, 20%PRO, 30%FAT. Dairy 2 servings/d  2. Calorie deficit of 500kcal/d. 50%CHO, 20%PRO, 30%FAT. Dairy 4 servings/d (at least 2 fluid milk).  3. Calorie deficit of 500kcal/d. 50%CHO, 20%PRO, 30%FAT. Dairy 4 servings/d, high fibre	26.3 Energy: 1437.1 kcal/d Fibre g/d:18.8  2. %Energy: C 53.6 P 21.5 F 24.6 Energy: 1490.1 kcal/d Fibre g/d:17.6 3. %Energy: C 58.1 P 20.9 F 20.6 Energy: 1510.2 kcal/d Fibre g/d:28.9		Council and research institute funding
(Tinker <i>et al.</i> , 2008) The Women's Health Initiative Dietary Modification Trial	Age 50-79y Fat intake >32% Post-menopausal No type 2DM No cancer	USA  0% Male  Age: (62)  BMI: (29)	Parallel Group	12 month intensive 8 years follow up	Free living diet plan	48835	1. Control  2. Low fat	1. Received information relating to health and healthy diets  2. Advice: reduce fat intake to 20%, increase fruit, vegetables and grains	1. %Energy: C 48 P 16.8 F 35 Energy: 1594 kcal/d Fibre g/d:15.5  2. %Energy: C 58.5 P 17.6 F 24.2 Energy: 1502 kcal/d Fibre g/d:18.5	Yes	NIH
(Wolever and Mehling, 2003)  American GI & carbohydrate study	≥1 diabetes risk factor Age 30-65y BMI <40 Impaired glucose tolerance Not hyperlipidaemic/ hypercholesterolaemic	USA  % Male: not reported  Age: (56)  BMI: (30)	Parallel Group	4 months	Free living diet plan	37	1. High carbohydrate, high GI  2. High carbohydrate, low GI  3. Low carbohydrate, high MUFA	1. Ad libitum diet, 55%CHO, 30%FAT. At least one serving of a high GI food with each meal. Provided foods included breakfast cereal, breads, polished rice, crackers and instant potato  2. Ad libitum diet, 55%CHO, 30%FAT, At least one serving of a low GI food with each meal.  3. Ad libitum diet. 45%CHO, 40%FAT (20%MUFA).	1. %Energy: C 52.8 P 17.4 F 27.9 Energy: 1712 kcal/d Fibre g/d:22.7  2. %Energy: C 54.8 P 19.4 F 24.7 Energy: 1693 kcal/d Fibre g/d:36.2  3. %Energy: C 47.4 P 16.4 F 35.4 Energy: 1877 kcal/d Fibre g/d:23.7	Yes	Canadian Diabetes Association and the International Olive Oil Council
(Wolever and Mehling, 2002)  American GI & carbohydrate study	≥1 diabetes risk factor Age 30-65y BMI <40 Impaired glucose tolerance Not hyperlipidaemic/ hypercholesterolaemic	USA  20% Male  Age: (57)  BMI: (30)	Parallel Group	4 months	Free living diet plan	37	1. High carbohydrate, high GI  2. High carbohydrate, low GI  3. Low	1. Ad libitum diet. 55%CHO, 30%FAT. At least one serving of a high GI food with each meal. Provided foods included breakfast cereal, breads, polished rice, crackers and instant potato  2. Ad libitum diet. 55%CHO, 30%FAT. At least one serving of a low GI food with each meal.  3. Low	1. %Energy: C 52.8 P 17.4 F 27.9 Energy: 1712 kcal/d Fibre g/d:22.7  2. %Energy: C 54.8 P 19.4 F 24.7 Energy: 1693kcal/d Fibre g/d:36.2  3. %Energy: C 47.4 P 16.4 F	Yes	Canadian Diabetes Association and the International Olive Oil Council

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							carbohydrate, high MUFA	3. Ad libitum diet. 45%CHO, 40%FAT (20%MUFA).	35.4 Energy: 1877 kcal/d Fibre g/d:23.7		
(Wood <i>et al.</i> , 2007)  American Soluble Fibre Study	<2.5kg Δ weight in previous 6m Age 20-69y BMI 25-35 DBP <90mmHg No CHD or T2DM Not taking lipid lowering drugs SBP <160mmHg	USA  100% Male  Age: 20 - 69(39)  BMI:25 - 35(30)	Parallel Group	12 weeks	Free living diet plan	30	1. Low carbohydrate diet + konjac-mannan 2. Low carbohydrate diet + maltodextrin	1. Ad libitum diet: 13% CHO, 27% PRO, 60% FAT. Supplement: Konjac-mannan 3g/d 2. Ad libitum diet: 13% CHO, 27% PRO, 60% FAT. Supplement: Maltodextrin 3g/d	1. %Energy: C 12.5 P 28.4 F 60.7 Energy: 6866kJ/d Fibre g/d:12.7 2. %Energy: C 13.3 P 27.1 F 59.6 Energy: 7017kJ/d Fibre g/d:9.6	Yes	Nutraquest and University funding
(Zaveri and Drummond, 2009)	Age 25-50y BMI 25-35 Free of chronic disease Generally healthy Not on weight loss diet	Scotland  100% Male  Age: [39.6] BMI: [29.8]	Parallel Group	12 weeks	Supplement	45	1. Control 2. Cereal bar  3. Almond snack	1. Healthy eating advice 2. Healthy eating advice plus 2 cereal bars daily (30g each) 3. Healthy eating advice plus 28g almonds/day. Group not relevant to this review so results not extracted.	Cereal bars provided: g/d C 44 P 3.0 F 4.7 Energy: 227 kcal/d	No, intended diet only	Kellogg Group



Table 4.5 Risk of bias assessment for randomised controlled trials

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome data	Selective outcome reporting	Any other bias
(Abete <i>et al.</i> , 2008)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Aller <i>et al.</i> , 2004)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Andersson <i>et al.</i> , 2007)	Unclear	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Bantle <i>et al.</i> , 2000)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Bell <i>et al.</i> , 1990)	Unclear	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Bellisle <i>et al.</i> , 2007)	Unclear	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Bhargava, 2006)	Unclear	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Birketvedt <i>et al.</i> , 2000)	Unclear	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Black <i>et al.</i> , 2006)	No Bias	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Bowden <i>et al.</i> , 2007)	No Bias	Unclear	Bias	Bias	Bias	No Bias	No Bias
(Brehm <i>et al.</i> , 2003)	No Bias	Bias	Bias	Unclear	Unclear	No Bias	No Bias
(Cairella <i>et al.</i> , 1995)	No Bias	Unclear	No Bias	No Bias	Unclear	Bias	Bias
(Chen <i>et al.</i> , 2006)	No Bias	No Bias	No Bias	No Bias	No Bias	Bias	Bias
(Claessens <i>et al.</i> , 2009)	Unclear	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Clifton <i>et al.</i> , 2008)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Clifton <i>et al.</i> , 2004)	No Bias	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Colette <i>et al.</i> , 2003)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Cornier <i>et al.</i> , 2005)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Crujeiras <i>et al.</i> , 2007)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Dale <i>et al.</i> , 2009)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Dansinger <i>et al.</i> , 2005)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Davis <i>et al.</i> , 2009)	No Bias	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(de Luis <i>et al.</i> , 2008)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(de Luis <i>et al.</i> , 2009b)	No Bias	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Demol <i>et al.</i> , 2009)	Unclear	Unclear	Bias	Bias	No Bias	Bias	Bias
(Due <i>et al.</i> , 2008a)	No Bias	No Bias	Bias	Bias	Unclear	No Bias	No Bias
(Due <i>et al.</i> , 2008b)	No Bias	No Bias	Bias	Bias	Bias	No Bias	No Bias
(Due <i>et al.</i> , 2004)	No Bias	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Due <i>et al.</i> , 2005)	No Bias	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Dyson <i>et al.</i> , 2007)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Ebbeling <i>et al.</i> , 2007)	No Bias	No Bias	Bias	No Bias	No Bias	No Bias	No Bias
(Ebbeling <i>et al.</i> , 2003)	Unclear	Unclear	Bias	Bias	No Bias	Bias	Bias
(Ebbeling <i>et al.</i> , 2005)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome data	Selective outcome reporting	Any other bias
(Forcheron and Beylot, 2007)	Unclear	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Foster <i>et al.</i> , 2003)	No Bias	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Frisch <i>et al.</i> , 2009)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Garcia <i>et al.</i> , 2007)	Unclear	Unclear	No Bias	Bias	No Bias	No Bias	No Bias
(Garcia <i>et al.</i> , 2006)	Unclear	Unclear	No Bias	Bias	No Bias	No Bias	No Bias
(Gardner <i>et al.</i> , 2007)	No Bias	Unclear	Bias	No Bias	No Bias	No Bias	No Bias
(Genta <i>et al.</i> , 2009)	Unclear	Unclear	No Bias	No Bias	Bias	No Bias	No Bias
(Golay <i>et al.</i> , 1996)	Unclear	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias
(Golay <i>et al.</i> , 2000)	Unclear	Unclear	Unclear	Bias	Bias	No Bias	No Bias
(Grau <i>et al.</i> , 2009)	No Bias	Unclear	Bias	Bias	Bias	Unclear	Unclear
(Gray <i>et al.</i> , 2008)	No Bias	Bias	Bias	Unclear	Unclear	No Bias	No Bias
(Helge, 2002)	Unclear	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Howard <i>et al.</i> , 2006)	No Bias	Unclear	Bias	No Bias	No Bias	No Bias	No Bias
(Jackson <i>et al.</i> , 1999)	No Bias	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Jensen <i>et al.</i> , 2008)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Johnston <i>et al.</i> , 2004)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Johnston <i>et al.</i> , 2006)	No Bias	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Keogh <i>et al.</i> , 2007)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Keogh <i>et al.</i> , 2008)	No Bias	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Kim <i>et al.</i> , 2008)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Kirk <i>et al.</i> , 2009)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Kirkwood <i>et al.</i> , 2007)	Unclear	Unclear	Unclear	Unclear	Unclear	Bias	Bias
(Landin <i>et al.</i> , 1992)	Unclear	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Landry <i>et al.</i> , 2003)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Lasker <i>et al.</i> , 2008)	No Bias	Unclear	Bias	Unclear	No Bias	Bias	Bias
(Layman <i>et al.</i> , 2005)	No Bias	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Lehtimäki <i>et al.</i> , 2005)	No Bias	No Bias	No Bias	No Bias	No Bias	No Bias	No Bias
(Leidy <i>et al.</i> , 2007)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Letexier <i>et al.</i> , 2003)	Unclear	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Lofgren <i>et al.</i> , 2005)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Lovejoy <i>et al.</i> , 2003)	No Bias	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(de Luis <i>et al.</i> , 2009a)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Mahon <i>et al.</i> , 2007)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Maki <i>et al.</i> , 2007a)	Unclear	Unclear	No Bias	No Bias	Bias	No Bias	No Bias

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome data	Selective outcome reporting	Any other bias
(Maki <i>et al.</i> , 2007b)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Marett and Slavin, 2004)	Unclear	Unclear	No Bias	No Bias	Bias	No Bias	No Bias
(McMillan-Price <i>et al.</i> , 2006)	No Bias	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Meckling <i>et al.</i> , 2004)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Meckling and Sherfey, 2007)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Morgan <i>et al.</i> , 2009)	Unclear	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Nestel <i>et al.</i> , 2004)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Noakes <i>et al.</i> , 2006)	No Bias	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Noakes <i>et al.</i> , 2005)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(O'Brien <i>et al.</i> , 2005)	Unclear	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Olendzki <i>et al.</i> , 2009)	No Bias	Unclear	Bias	Bias	Bias	Unclear	Unclear
(Parnell and Reimer, 2009)	No Bias	No Bias	No Bias	No Bias	Unclear	Unclear	Unclear
(Pasman <i>et al.</i> , 1997a)	Unclear	Unclear	Bias	Unclear	Bias	Bias	Bias
(Pasman <i>et al.</i> , 1997b)	Unclear	Unclear	No Bias	No Bias	Bias	No Bias	No Bias
(Pereira <i>et al.</i> , 2004)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Petersen <i>et al.</i> , 2006)	No Bias	No Bias	Bias	Bias	Unclear	No Bias	No Bias
(Peterson and Jovanovic-Peterson, 1995)	Unclear	Unclear	No Bias	Bias	Bias	No Bias	No Bias
(Philippou <i>et al.</i> , 2008)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Philippou <i>et al.</i> , 2009b)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Philippou <i>et al.</i> , 2009a)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Phillips <i>et al.</i> , 2008)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Pittas <i>et al.</i> , 2006)	No Bias	Unclear	Bias	No Bias	Unclear	Unclear	Unclear
(Raatz <i>et al.</i> , 2005)	Unclear	Unclear	Bias	Unclear	Bias	Bias	Bias
(Racette <i>et al.</i> , 1995)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Ryle <i>et al.</i> , 1990)	Unclear	Unclear	Unclear	Unclear	No Bias	Unclear	Unclear
(Sacks <i>et al.</i> , 2009)	No Bias	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Salas-Salvado <i>et al.</i> , 2008)	No Bias	No Bias	No Bias	No Bias	No Bias	No Bias	No Bias
(Saltzman <i>et al.</i> , 2001)	No Bias	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Saris <i>et al.</i> , 2000)	No Bias	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Schwab <i>et al.</i> , 2006)	Unclear	Unclear	No Bias	No Bias	Unclear	No Bias	No Bias
(Segal-Isaacson <i>et al.</i> , 2004)	Unclear	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Seshadri <i>et al.</i> , 2005)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Sharman <i>et al.</i> , 2004)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Sichieri <i>et al.</i> , 2007)	No Bias	Unclear	Bias	Unclear	Bias	No Bias	No Bias

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome data	Selective outcome reporting	Any other bias
(Sloth <i>et al.</i> , 2004)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Sloth <i>et al.</i> , 2009)	No Bias	No Bias	Bias	Bias	Unclear	Unclear	Unclear
(Smith <i>et al.</i> , 2008)	No Bias	Unclear	No Bias	No Bias	No Bias	Bias	Bias
(Sorensen <i>et al.</i> , 2005)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Surwit <i>et al.</i> , 1997)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Swinburn <i>et al.</i> , 2001)	No Bias	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Thompson <i>et al.</i> , 2005)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Tinker <i>et al.</i> , 2008)	No Bias	Unclear	Bias	No Bias	No Bias	No Bias	No Bias
(Wolever and Mehling, 2003)	No Bias	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Wolever and Mehling, 2002)	No Bias	Unclear	Bias	Unclear	Unclear	Bias	Bias
(Wood <i>et al.</i> , 2007)	No Bias	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Zaveri and Drummond, 2009)	No Bias	Unclear	Bias	Unclear	No Bias	No Bias	No Bias

# Incident diabetes mellitus type 2

## Incident diabetes mellitus and total carbohydrate (g/day and % energy from carbohydrate)

### Summary of cohort results

#### % Energy from carbohydrate and diabetes

Data were extracted from 7 publications presenting results from 7 cohort studies which were conducted in Holland and Finland, the USA, Finland, Germany and China (Gunderson *et al.*, 2007; Villegas *et al.*, 2007; Lindstrom *et al.*, 2006; Monterrosa *et al.*, 1995; Schulze *et al.*, 2004a; Schulze *et al.*, 2008; Feskens *et al.*, 1995). It was not possible to undertake a meta-analysis because 5 of the 7 studies either did not present sufficient information by which a dose-response trend could be estimated (Villegas *et al.*, 2007; Feskens *et al.*, 1995) or the results provided were unadjusted (Gunderson *et al.*, 2007); (Lindstrom *et al.*, 2006); (Monterrosa *et al.*, 1995). The remaining two studies from NHS II and EPIC Potsdam were insufficient to conduct a meta-analysis (Schulze *et al.*, 2004a; Schulze *et al.*, 2008).

Two cohort studies provided evidence of increased risk of DM with increasing carbohydrate energy. Villegas *et al.*, reporting from the Shanghai Women's Health Study, found that those in the highest fifth of %energy from carbohydrate had a 30% increased risk of DM compared to those in the lowest fifth of intake (Villegas *et al.*, 2007). Gunderson *et al.* from the CARDIA Study found that cases of DM had somewhat higher % energy from carbohydrate at recruitment than those who remained free of DM (Gunderson *et al.*, 2007). However, this result was not adjusted for age, BMI, or any other potential confounder.

Two studies, one from the Seven Countries Study and the other from The Finnish Diabetes Prevention Study, reported that cases at recruitment consumed less carbohydrate (Feskens *et al.*, 1995); (Lindstrom *et al.*, 2006), but both cohorts provided minimally adjusted results.

Monterrosa *et al.* presented mean % energy reported at baseline for subsequent cases and non cases of DM, for men and women separately. Participants were from the San Antonio Heart Study follow-up, a multi-ethnic US cohort, free of DM at recruitment. Overall there was no relationship between % energy from carbohydrate and risk of incident DM. Similarly, Schulze *et al.* (NHS II) and Schulze *et al.* (EPIC Potsdam) both reported no association between carbohydrate percent and risk of incident DM in these two large cohorts, after adjusting for important confounders. These are the two most reliable results because they take account of confounding (Schulze *et al.*, 2004a; Schulze *et al.*, 2008).

Collectively, these studies present conflicting results. However, the larger studies that took important covariates into consideration indicate a lack of association between percentage carbohydrate intake and risk of DM.

### **Total carbohydrate reported as g/day and diabetes**

Data were extracted from 9 publications presenting results from the following 8 cohort studies: The Shanghai Women's Cohort Study, the Blue Mountains Eye Study, the Finnish Mobile Clinic Health Surveys, the Japanese-American Men Diabetes Study, the Melbourne Collaborative Cohort Study, the Iowa Women's Health Study, EPIC Potsdam and HPFS (Villegas *et al.*, 2007; Barclay *et al.*, 2007; Montonen *et al.*, 2007; Leonetti *et al.*, 1996; Hodge *et al.*, 2004; Meyer *et al.*, 2000; Schulze *et al.*, 2008; Salmeron *et al.*, 1997a; Salmeron *et al.*, 1997b). These studies were conducted in Australia, Germany, Finland, USA, and China.

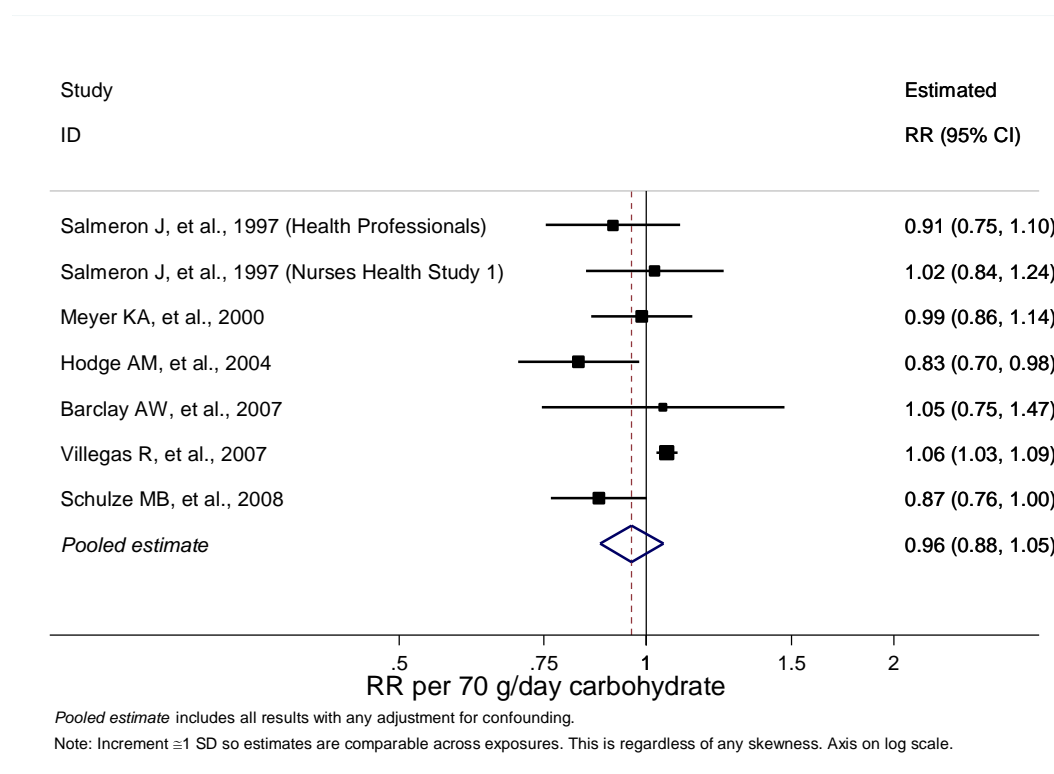
Two studies were excluded from the meta-analysis because results were unadjusted for any potential confounders (Leonetti *et al.*, 1996; Montonen *et al.*, 2007).

Leonetti *et al.* reported that carbohydrate intakes were somewhat higher in participants who developed DM compared to cohort members that remained DM free, but these results are unadjusted for potential confounding factors (Leonetti *et al.*, 1996). Montonen *et al.* reported lower carbohydrate intakes in cases, but was similarly unadjusted for confounding (Montonen *et al.*, 2007).

The remaining seven studies were all included in a meta-analysis. One study presented results for men and women separately (Schulze *et al.*, 2008). These subgroups were first combined using fixed effects meta-analysis before joining with the other studies in the random effects meta-analysis. To include the Shanghai Women's Health Study in the meta-analysis (Villegas *et al.*, 2007), we assumed that the median intake for the lowest category was half the upper limit of the lowest category, and the median of the highest category was 1.5 times the lower limit of the highest category.

The pooled estimate of relative risk (RR) from the cohort studies was 0.96 (95% CI: 0.88 to 1.05) per 70 g/day of total carbohydrate (p=0.4).

Figure 4.1 Forest plot for total carbohydrate and incident diabetes mellitus type 2



There was substantial heterogeneity between the cohort studies ( $I^2=65\%$  [95% CI: 22% to 85%],  $Q=17$ ,  $df=6$ ,  $p=0.008$ ). Villegas *et al.* (2007) had a strong influence on the results. With this study excluded, the excess heterogeneity reduced to 0% and the estimate became statistically significant ( $RR=0.92$ , 95% CI: 0.86 to 0.99) per 70 g/day of total carbohydrate ( $p=0.03$ ) (Villegas *et al.*, 2007). Risk estimates in this cohort were markedly elevated in particular sub groups of women. This was notable in those women who were at increased risk of insulin resistance, with low levels of physical activity and  $BMI > 25 \text{ kg/m}^2$ . It should be recognised that there are differences in the main sources of carbohydrate consumed (noodles or steamed bread, bread, potatoes, and sweet potatoes) and/or other differences in dietary practices in this Chinese population compared to the other European, American and Australian cohorts.

There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). There were many differences between subgroups, but this was dictated by which group contained the Shanghai Women's Health Study (Villegas *et al.*, 2007), a large study with quite different results from the others. There were insufficient studies to investigate the possibility of small-study effects such as publication bias from the contour-enhanced funnel plot.

Table 4.6: Subgroup analyses of total carbohydrate and incidence of diabetes mellitus type 2. Relative risks are per 70 g/day.

Subgroup	subgroup	RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> *	P <sub>het</sub> **
subjects' gender	Male	0.88 (0.78, 0.99)	0%	2	.6	.04
	Mixed	0.89 (0.72, 1.10)	33%	2	.2	
	Female	1.05 (1.02, 1.08)	0%	4	.5	
subjects' gender in same study	Male	0.86 (0.73, 1.00)		1		.06
	Female	0.92 (0.72, 1.18)		1		
length of follow-up	<10 years	0.95 (0.87, 1.05)	71%	6	.004	
	>=10 years	1.05 (0.75, 1.47)		1		.9
geographic location	Americas	0.97 (0.88, 1.07)	0%	3	.7	
	EU	0.87 (0.76, 1.00)		1		
	Other	0.97 (0.81, 1.17)	75%	3	.02	.6
adjusted for age	yes	0.96 (0.88, 1.05)	65%	7	.008	
	no			0		
adjusted for alcohol	yes	0.95 (0.87, 1.05)	71%	6	.004	
	no	1.05 (0.75, 1.47)		1		.7
adjusted for anthropometry	yes	0.95 (0.87, 1.05)	71%	6	.004	
	no	1.05 (0.75, 1.47)		1		.7
adjusted for energy intake	yes	0.95 (0.83, 1.07)	80%	4	.002	
	no	0.97 (0.86, 1.10)	0%	3	.6	.8
adjusted for family history	yes	0.92 (0.83, 1.02)	8%	4	.4	
	no	0.98 (0.87, 1.11)	75%	3	.02	.5
adjusted for physical activity	yes	0.96 (0.88, 1.05)	65%	7	.008	
	no		65%	0		
adjusted for gender	yes	0.98 (0.90, 1.07)	54%	6	.06	
	no	0.87 (0.76, 1.00)		1		.3
adjusted for smoking	yes	0.99 (0.91, 1.07)	51%	6	.07	
	no	0.83 (0.70, 0.98)		1		.2
adjusted for age and anthropometry	yes	0.95 (0.87, 1.05)	71%	6	.004	
	no	1.05 (0.75, 1.47)		1		.7

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup



## ***Exposure definition and assessment***

The Finnish Diabetes Prevention Study (Lindstrom *et al.*, 2006) assessed diet by food diary, the San Antonio Heart Study (Monterrosa *et al.*, 1995) by dietary recall, and the Seven Countries Study (Feskens *et al.*, 1995), The Finnish Mobile Clinic Health Survey (Montonen *et al.*, 2007) and the Cardia Study (Gunderson *et al.*, 2007) used the dietary history interview approach. The remaining studies used FFQs. Total carbohydrate nature (ratio of starches to sugars) and source may vary greatly between cohort studies depending on the study country.

## ***Adjustment for appropriate confounders***

The Cardia Study (Gunderson *et al.*, 2007) and the study of Japanese Americans (Leonetti *et al.*, 1996) provided unadjusted consumption data in cases and non-cases only, and no estimate of risk of DM in association with diet. Similarly Montonen *et al.* did not take important confounders into account (Montonen *et al.*, 2007). These unadjusted results should be interpreted cautiously.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## **Summary of RCT results**

Two randomized controlled trials, the Women's Health Initiative Dietary Modification Trial and the New Zealand Diabetic Workforce Study, reported incident DM 2 events in relation to high or low carbohydrate diets (Tinker *et al.*, 2008; Swinburn *et al.*, 2001).

Swinburn and colleagues (Swinburn *et al.*, 2001) randomly allocated participants (n=176) to a low fat group, a 1-year structured program which aimed to reduce total fat in participants' habitual diets, or a control group, in which participants received general healthy eating advice. After 1 year of the intervention, there were a statistically significantly smaller number of participants who had incident DM 2 or impaired glucose tolerance in the low fat group compared to those in the control group (Swinburn *et al.*, 2001). No statistically significant differences were observed at the 2, 3 or 5 year follow-ups, however. It is important to note that participants in the low fat group lost weight throughout the trial, whereas the control group did not.

In the study by Tinker *et al.* (Tinker *et al.*, 2008), participants were randomised to either an intensive intervention group which included individual sessions designed to reduce fat intake to 20% of total energy and increase consumption of fruits, vegetables and grains or a comparison group which received diet-related education materials only.

The percentage of participants in each group experiencing incident DM events was very similar and the hazard ratio which compared the low-fat intervention group with the comparison group did not show a statistically significant difference in DM incidence between the groups.

Results from this trial should be interpreted with caution as dietary components were altered other than a switch between fat and carbohydrate content and the low fat diet group experienced weight loss but the comparison group did not.

Table 4.7 Incident diabetes mellitus type 2 and total carbohydrate (g/day and % energy): cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
<b>Percent energy from total carbohydrate</b>															
14639 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	(26) /338	20 years	Dietary history	Carbohydrate total (% energy)	Plasma glucose OGTT (75g/120mins) Clinic tested			% Energy		Cases: (n: 26) 46.5% Non-cases: (n: 241) 48.8%			age, cohort
13720 (Gunderson <i>et al.</i> , 2007) The CARDIA Study	USA, Not diabetic	18-30 %M 0	(193) /2787	20 years (6.45)	Dietary history	Carbohydrate total (% energy)	Self-reported, use of insulin/oral hypoglycaemic medication, fasting plasma glucose ≥126 mg/dL or non- fasting plasma glucose ≥200 mg/dL (American Diabetes Association criteria)			% Energy		Cases: (n: 193) 48.5% (7.9) Non-cases: (n: 2215) 46.9% (7.4)			
14246 (Halton <i>et al.</i> , 2008) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4670) /121700	20 years	FFQ (127)	Carbohydrate total (% energy)	Multiple diagnosis methods American diabetes association Criteria		Q10 vs. Q1	% Energy	1.26 (1.07, 1.49)			0.003	age, alcohol, BMI, family history of DM, hormone replacement therapy, physical activity, smoking
14606 (Lindstrom <i>et al.</i> , 2006) The Finnish Diabetes Prevention Study	Finland, BMI >25, Middle- aged adults	40-64 (55) %M 33	(114) /522	3 years	Food diary	Carbohydrate total (% energy)	Multiple diagnosis methods Clinic tested			% Energy		Cases: (n: 114) 42 (7) Non-cases: (n: 386) 44 (7)			gender, group allocation
14123 (Monterrosa <i>et al.</i> , 1995) San Antonio Heart Study follow-up	USA, Multi- ethnic, Not diabetic	25-64 %M 41.8	(20) /2217	8 years (22.8)	Dietary recall	Carbohydrate total (% energy)	Fasting serum/blood glucose Clinic tested	Men		% Energy				0.69	age, alcohol, BMI, caffeine, cereal fibre, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, hyperchol- esterolaemia, hypertension, magnesium intake, oral contraceptive pill, physical activity, smoking,

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
14124 San Antonio Heart Study follow-up			(37) /2217					Women		% Energy		Cases: 40.77% Non-cases: 42.33%			postmenopausal hormone replacement therapy age, socioeconomic status/class
13536 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) /116671	8 years (<10)	FFQ (133)	Carbohydrate total (% energy)	Multiple diagnosis methods Confirmed self report		>55.9 (59.4) vs. <44.4 (41.3)	% Energy	0.89 (0.6, 1.33)			0.69	age, alcohol, BMI, caffeine, cereal fibre, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, hyperchol- esterolaemia, hypertension, magnesium intake, oral contraceptive pill, physical activity, smoking, postmenopausal hormone replacement therapy
13553 NHS II			(114) /116671					BMI <27	Q5 vs. Q1		0.78 (0.29, 2.11)				As above
13554 NHS II			(608) /116671					BMI >27	Q5 vs. Q1		0.94 (0.6, 1.46)				As above
13555 NHS II			(421) /116671					Seden- tary/ Low physical activity	Q5 vs. Q1		0.96 (0.55, 1.66)				As above
13556 NHS II			(320) /116671					High physical activity	Q5 vs. Q1		0.81 (0.45, 1.45)				As above
13557 NHS II			(459) /116671					No family history of diabetes	Q5 vs. Q1		0.81 (0.49, 1.34)				As above
13558 NHS II			(282) /116671					family history of Diabetes	Q5 vs. Q1		1.02 (0.53, 1.95)				As above
13632 (Schulze <i>et al.</i> , 2008)	Germany, Primarily White, Not diabetic	35-65 %M 40	(491) /27548	7 years (9)	FFQ (148)	Carbohydrate total (% energy)	Multiple diagnosis methods Confirmed self	Men	(46.4) vs. (30.9)	%Total energy	0.83 (0.62, 1.12)			0.313	age, alcohol, BMI, smoking, education, physical activity,

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
EPIC Potsdam							report								occupational physical activity, energy intake, waist
13633 EPIC Potsdam			(355) /27548					Women	(51.4) vs. (36.7)	%Total energy	0.87 (0.61, 1.23)			0.497	As above
17570 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70 %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Carbohydrate total (% energy)	Fasting serum/blood glucose American diabetes association Criteria, Confirmed self report		Q5 vs. Q1		1.31 (1.10, 1.5)				age, alcohol, BMI, energy intake, Income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
<b>Total carbohydrate (grams)</b>															
*13336 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(138) /3654	10 years (29)	FFQ (145)	Carbohydrate total (grams/day)	Self-reported DM and current use of insulin/oral hypoglycaemic medication, or fasting glucose ≥126 mg/dL (WHO criteria)		Contin- uous risk estimate	200 g/day	1.14 (0.43, 3)		0.79		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglyceride
*14235 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Carbohydrate total (grams/day)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Contin- uous risk estimate	200 g/day	0.58 (0.36, 0.95)		0.03		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
14623 (Leonetti <i>et al.</i> , 1996) Japanese- American Men Diabetes Study	USA, Asian, Not diabetic	45-74 %M 100	(9) /229	5 years (5.6)	FFQ Interview (89)	Carbohydrate total (grams/day)	Plasma glucose OGTT (75g/120mins) Confirmed self report	Impaired glucose tolerance at baseline		g/day		Cases: (n: 9) 258.1g (83.2) Non-cases: (n: 23) 238.8g (72.2)			
*13756 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Carbohydrate total (grams/day)	Self-reported		>243.8 (259) vs. <192.1 (176)	g/day	0.93 (0.76, 1.13)			0.22	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
13221	Finland, Not	40-69	(177)	12	Dietary	Carbohydrate	Diagnosis criteria			g/day		Cases: (n:			Energy intake

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
(Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	diabetic	%M 53	/10054	years	history	total (grams/day)	not reported Registry data					177) 304g (58.5) Non-cases: (n: 4127) 315g (60)			
*13569 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(915) /121700	6 years	FFQ (134)	Carbohydrate total (grams/day)	Multiple diagnosis methods Confirmed self report		(231) vs. (155)	g/day	1.04 (0.83, 1.3)	Cases: (n: 9) 224g (67.3) Non-cases: (n: 23) 302g (62.6)			age, BMI
*13468 (Salmeron <i>et al.</i> , 1997a) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(523) /51529	6 years	FFQ (131)	Carbohydrate total g/day	Multiple diagnosis methods Confirmed self report		(288) vs. (182)	g/day	0.85 (0.62, 1.15)			0.33	age, alcohol, BMI, family history of DM, physical activity, smoking
*13634 (Schulze <i>et al.</i> , 2008) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(491) /27548	7 years (9)	FFQ (148)	Carbohydrate total (grams/day)	Multiple diagnosis methods Confirmed self report	Men	(339) vs. (157)	g/day	0.63 (0.39, 1)			0.05	age, alcohol, BMI, smoking, education, physical activity, occupational physical activity, energy intake, waist
*13635 EPIC Potsdam			(355) /27548					Women	(266) vs. (129)	g/day	0.78 (0.45, 1.35)			0.527	As above
*13063 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70 %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Carbohydrate total (g/d)	Fasting serum/blood glucose American diabetes association Criteria, Confirmed self report		Q5 vs. Q1		1.28 (1.09, 1.5)				age, alcohol, BMI, energy intake, income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13072 Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70 %M 0	(Sub- group cases not reported; total cohort cases 1608) /74942	4.6 years (0.2)	FFQ (77)	Carbohydrate total (g/d)	Fasting serum/blood glucose American diabetes association Criteria, Confirmed self report	WHR <0.85 (F) <0.90(M)	Q5 vs. Q1		1.23 (1, 1.52)			0.01	age, alcohol, BMI, energy intake, income, occupation, physical activity, hypertension, smoking, education
13073 Shanghai Women's								WHR >0.85 (F) >0.90(M)	Q5 vs. Q1		1.38 (1.07, 1.79)			0.01	age, alcohol, BMI, energy intake, income, occupation, physical

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
Health Study															activity, hypertension, smoking, education
13080 Shanghai Women's Health Study								BMI <25	Q5 vs. Q1		1.22 (0.94, 1.58)			0.24	age, alcohol, energy intake, income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13081 Shanghai Women's Health Study								BMI >25	Q5 vs. Q1		1.41 (1.14, 1.73)			0.24	age, alcohol, energy intake, income, occupation, physical activity, hypertension, smoking, waist:hip ratio, Education
13091 Shanghai Women's Health Study								Seden- tary/ Low physical activity	Q5 vs. Q1		1.54 (1.13, 2.1)			<0.001	age, alcohol, BMI, energy intake, income, occupation, hypertension, smoking, waist:hip ratio, education
13097 Shanghai Women's Health Study								Med/ High physical activity	Q5 vs. Q1		1.19 (0.99, 1.44)			<.0001	age, alcohol, BMI, energy intake, income, occupation, hypertension, smoking, waist:hip ratio, education
13110 Shanghai Women's Health Study								Insulin Resist- ance Low Risk	Q5 vs. Q1		1.41 (1.2, 1.67)			<.0001	age, alcohol, energy intake, income, occupation, hypertension, smoking, education
13115 Shanghai Women's Health Study								Insulin Resist- ance High Risk	Q5 vs. Q1		2.04 (1.11, 3.75)			<0.001	age, alcohol, energy intake, income, occupation, hypertension, smoking, education

\*This result was used in the meta-analysis of carbohydrate (grams/d) and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

Table 4.8 Incident diabetes mellitus type 2 and high carbohydrate diets: RCT data

Result ID/Author	Intervention group	Completers/ Allocated	% of group experiencing event	Outcome/ Assessment method	Contrast	RR (95% CI)	p	p value difference between groups	Result- specific follow-up	Weight Change	Outcome Assessment Bias
17626 (Swinburn <i>et al.</i> , 2001) New Zealand Diabetic Workforce Study	Low fat diet	70/70	47%	Incident DM 2 or impaired glucose tolerance				<0.05	1 year	Decrease	unclear
	Control diet	66/66	67%	Plasma glucose OGTT (75g/ 120 mins) WHO criteria						No change	
17627	Low fat diet	70/70	Not reported	Incident DM 2 or impaired glucose tolerance				NS	2 years	Decrease	
	Control diet	66/66	Not reported	Plasma glucose OGTT (75g/ 120 mins) WHO criteria						No change	
17628	Low fat diet	70/70	Not reported	Incident DM 2 or impaired glucose tolerance				NS	3 years	Decrease	
	Control diet	66/66	Not reported	Plasma glucose OGTT (75g/ 120 mins) WHO criteria						No change	
17629	Low fat diet	70/70	Not reported	Incident DM 2 or impaired glucose tolerance				NS	5 years	Decrease	
	Control diet	66/66	Not reported	Plasma glucose OGTT (75g/ 120 mins) WHO criteria						No change	
17625 (Tinker <i>et al.</i> , 2008) The women's health initiative dietary modification trial	Low fat	18376/19541	7.1	Incident DM 2	Control (reference) vs. Low fat	0.96 (0.90, 1.03)	0.25		8.1 years	Decrease	No bias
	Control	27511/29294	7.4	Self-reported and use of insulin/oral hypoglycaemic medication						No change	



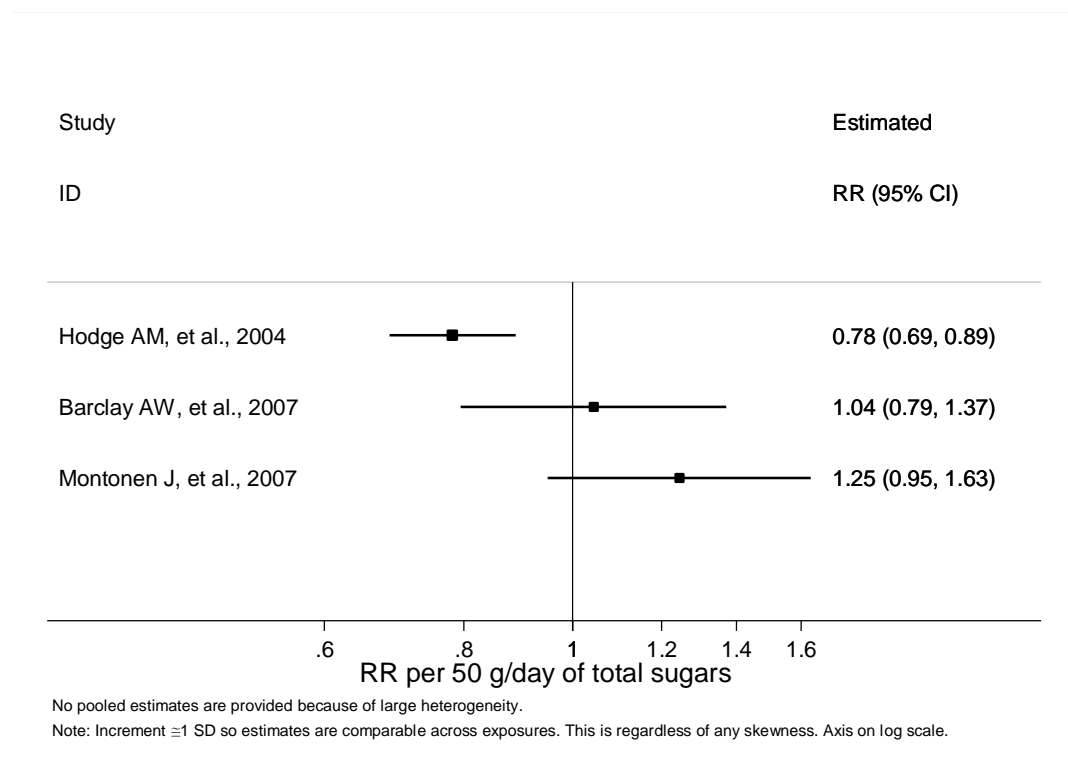
# Incident diabetes mellitus type 2 and total sugars

## Summary of cohort results

Data were extracted from 5 publications presenting results from 5 cohort studies conducted in Australia (2), Holland and Finland, USA, and Finland (Barclay *et al.*, 2007;Montonen *et al.*, 2007;Hodge *et al.*, 2004;Janket *et al.*, 2003), where the consumption estimates were expressed as grams per day of total sugars, or mono and disaccharides combined. The Seven Countries Study expressed total sugars consumption as a percentage of energy intake (Feskens *et al.*, 1995), and observed little difference between cases and non-cases of DM.

One study could not be included in the meta-analysis because no information was presented by which the intake could be calculated (Janket *et al.*, 2003), so no dose-response trend could be estimated. This study (The Women’s Health Study), reported weak evidence of decreasing risk of DM in association with increasing intakes of total sugars, with similar point estimates across the various sub groups studied. One other study only reported baseline intake of mono and disaccharides in those subsequently developing or not developing DM (Feskens *et al.*, 1995). Overall, the direction of effect is inconsistent in the cohort studies reporting data on total sugars intake.

Figure 4.2 Forest plot for total sugars and incident diabetes mellitus type 2



Three studies were included in a meta-analysis that provided data on total sugars consumption. There was substantial heterogeneity between the cohort studies ( $I^2=82\%$  [95% CI: 44% to 94%],  $Q=11.1$ ,  $df=3$ ,  $p=0.004$ ), so this presents too much heterogeneity to reliably interpret a pooled estimate. However, there were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. All three studies had a strong influence on the pooled estimate because all the results were so different. There were insufficient studies to explore any small-study effect such as publication bias.

### ***Exposure definition and assessment***

Three cohort studies used a FFQ to estimate sugars consumption, 2 used the dietary history approach.

### ***Adjustment for appropriate confounders***

Other than the Seven Countries Study (Janket *et al.*, 2003), which reported mean consumption data in cases and non-cases adjusted only for age and cohort, the other studies included important covariates in their analyses (age, gender, and a measure of adiposity).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No trials provided data on sugars intakes with incident DM as an outcome.

Table 4.9 Incident diabetes mellitus type 2 and total sugars: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
*13337 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(138) /3654	10 years (29)	FFQ (145)	Sugars, total (g/d)	Self-reported diabetes and current use of insulin/oral hypoglycaemic medication, or fasting glucose $\geq 126$ mg/dL (WHO criteria)		Continuous risk estimate	100 g/day	1.09 (0.63, 1.88)		0.767		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglycerides.
14641 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	(26) /338	20 years	Dietary history	Mono and disaccharides	Plasma glucose OGTT (75g/120mins) Clinic tested			% Energy		Cases: (n: 26) 23.8 Non-cases: (n: 241) 24.7			age, cohort
*14236 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Sugars, total (g/d)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	100 g/day	0.61 (0.47, 0.79)		<0.001		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13781 (Janket <i>et al.</i> , 2003) The Women's Health Study	USA, Primarily White	(54) %M 0	(918) /39876	6 years	FFQ (131)	Sugars, total (g/d)	Self-reported		Q5 vs. Q1		0.86 (0.69-1.06)			0.17	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity
13775 The Women's Health Study			(271) /39876					No diseased at baseline	Q5 vs. Q1		0.77 (0.52, 1.15)			0.26	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
13787 The Women's Health Study			(117) /39876					BMI <25	Q5 vs. Q1		0.86 (0.47, 1.58)			0.36	alcohol, BMI, family history of DM, hypertension, hypercholesterolaemia, physical activity, smoking
13793 The Women's Health Study			(776) /39876					BMI >25	Q5 vs. Q1		0.88 (0.7, 1.11)			0.38	alcohol, BMI, family history of DM, hypertension, hypercholesterolaemia, physical activity, smoking
*13234 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69  %M 53	(177) /10054	12 years	Dietary history	Sugars, total (g/d) Sum of mono and disaccharides	Diagnosis criteria not reported Registry data		(171) vs. (92)	g/day	1.56 (0.99, 2.46)			0.10	age, BMI, diet pattern- conservative, diet pattern- prudent, energy intake, family history of DM, region, physical activity, gender, smoking

\*This result was used in the meta-analysis of total sugars and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

## **Incident diabetes mellitus type 2 and specific mono- and disaccharide intakes**

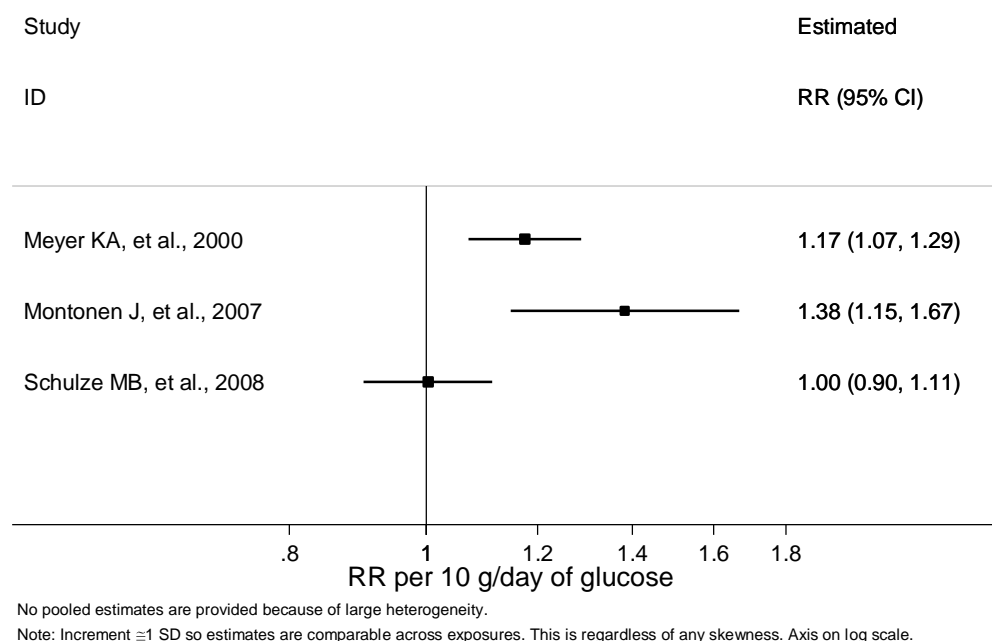
Data on the relationship between consumption of glucose, fructose, lactose, maltose and sucrose and risk of incident DM are provided in this section. Meta-analyses were possible for glucose, fructose and sucrose.

### **Summary of cohort results**

#### **Dietary glucose and diabetes**

Data were extracted from four publications presenting results from four cohort studies: the Finnish Mobile Clinic Health Surveys, The Women's Health Study, the Iowa Women's Health Study and EPIC Potsdam, conducted in the USA, Finland and Germany (Montonen *et al.*, 2007; Janket *et al.*, 2003; Meyer *et al.*, 2000; Schulze *et al.*, 2008). One study could not be included in a meta-analysis because no information was presented by which the intake could be calculated (Janket *et al.*, 2003), so no dose-response trend could be estimated. This study (The Women's Health Study), reported no association between glucose intakes and risk of DM, with similar point estimates across the various sub groups studied. The remaining three studies were all included in the meta-analysis. One paper presented results for two male and female subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Schulze *et al.*, 2008). All cohorts reported risk estimates that were greater than one, which suggests that increasing intakes may be associated with increasing risk. However, confidence intervals were generally wide in each study and the point estimates for the highest category of intake (>25g/day) were statistically significant only for two studies (Meyer *et al.*, 2000; Montonen *et al.*, 2007).

Figure 4.3 Forest plot for dietary glucose and incident diabetes mellitus type 2



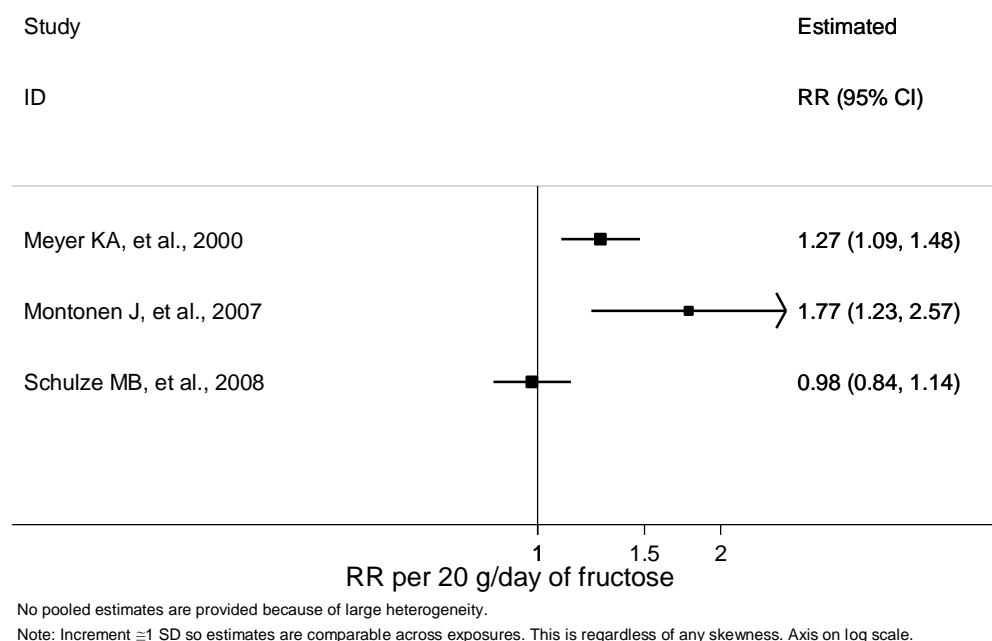
There was substantial heterogeneity between the cohort studies ( $I^2=80\%$  [95% CI: 38% to 94%],  $Q=10.1$ ,  $df=3$ ,  $p=0.006$ ), so the pooled estimate conveys little meaning and is not presented. There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. All three studies had a strong influence on the pooled estimate because all the results were so different. There were insufficient studies to explore any small-study effect such as publication bias.

## Dietary fructose and diabetes

Data were extracted from four publications presenting results from four cohort studies: the Finnish Mobile Clinic Health Surveys, The Women's Health Study, the Iowa Women's Health Study and EPIC Potsdam, conducted in the USA, Finland and Germany (Montonen *et al.*, 2007; Janket *et al.*, 2003; Meyer *et al.*, 2000; Schulze *et al.*, 2008). One study could not be included because no information was presented by which the intake could be calculated (Janket *et al.*, 2003), so no dose-response trend could be estimated. This study (The Women's Health Study), reported no association between fructose intakes and risk of DM, with similar point estimates across the various sub groups studied. The remaining three studies were all included in the meta-analysis. One paper presented results for two male and female subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Schulze *et al.*, 2008).

Confidence intervals were generally wide in each study and the point estimates for the highest category of intake ( $>29\text{g/day}$ ) were statistically significant only for two studies (Meyer *et al.*, 2000; Montonen *et al.*, 2007).

Figure 4.4 Forest plot for dietary fructose and incident diabetes mellitus type 2



There was substantial heterogeneity between the cohort studies ( $I^2=83\%$  [95% CI: 47% to 94%],  $Q=11.5$ ,  $df=2$ ,  $p=0.003$ ), so the pooled estimate has little meaning and is therefore not presented. There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. All three studies had a strong influence on the pooled estimate, because they were all so different in their results. There were insufficient studies to explore any small-study effect such as publication bias.

### Dietary lactose and diabetes

Three cohort studies provided data on lactose consumption and risk of DM: The Women's Health Study, the Finnish Mobile Clinic Health Surveys and the Iowa Women's Health Study; two from the USA and one conducted in Finland (Janket *et al.*, 2003; Montonen *et al.*, 2007; Meyer *et al.*, 2000). These studies could not be included in a meta-analysis since one study provided no information by which the intake could be calculated (Janket *et al.*, 2003), so no dose-response trend could be estimated. In all of these studies, the point estimate for the highest consumption category compared to the lowest was close to one, which indicates no association between dietary lactose consumption and risk of DM.

## **Dietary maltose and diabetes**

Two cohort studies provided data on maltose consumption and risk of DM: the Finnish Mobile Clinic Health Surveys and the Iowa Women's Health Study; one from the USA and one conducted in Finland (Montonen *et al.*, 2007; Meyer *et al.*, 2000). With just two studies, these could not be included in a meta-analysis. In both of these studies, the point estimate for the highest consumption category compared to the lowest was less than one, which suggest decreased risk of DM with increasing consumption. However, neither of these point estimates achieved statistical significance.

## **Dietary sucrose and diabetes**

Data were extracted from six publications presenting results from the following six cohort studies: the Finnish Mobile Clinic Health Surveys, The Women's Health Study, the Iowa Women's Health Study, EPIC Potsdam, San Antonio Heart Study Follow Up and the Nurses' Health Study (Montonen *et al.*, 2007; Janket *et al.*, 2003; Meyer *et al.*, 2000; Schulze *et al.*, 2008; Colditz *et al.*, 1992). Three studies were conducted in the USA, one in Finland and one in Germany. One study could not be included because no confidence intervals were given for the relative risks (Colditz *et al.*, 1992). This study (The Nurse's Health Study) found no association between sucrose consumption and risk of DM in obese and non-obese women.

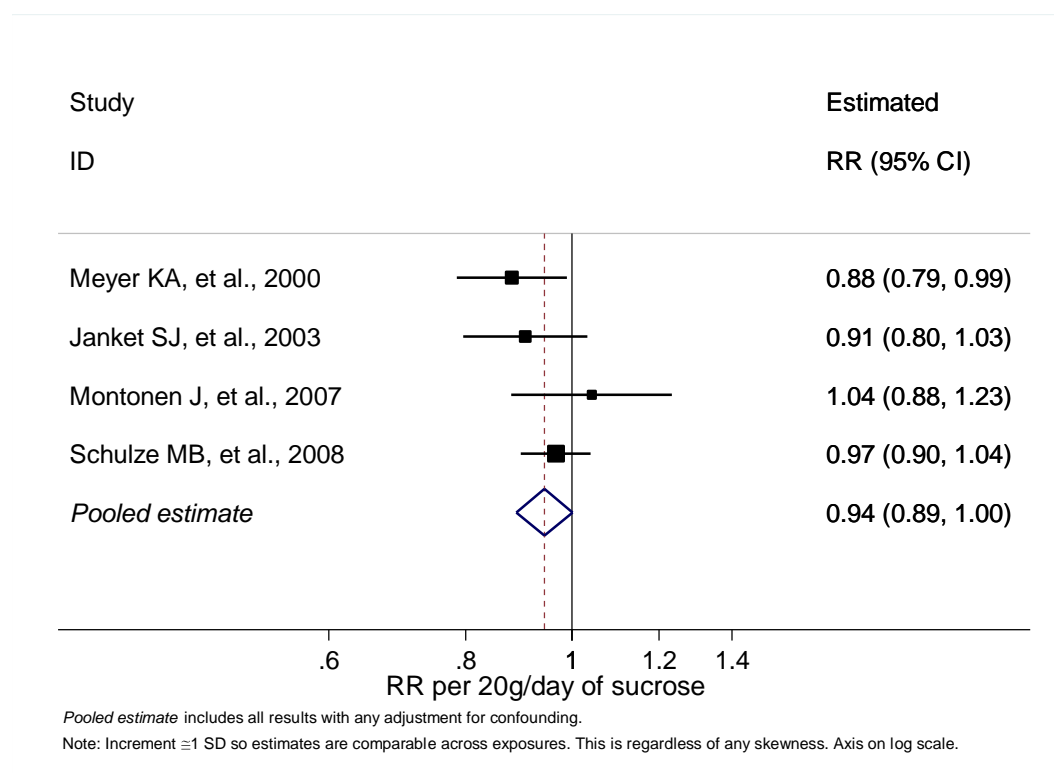
The San Antonio Heart Follow-up Study (Monterrosa *et al.*, 1995) provided sucrose consumption data expressed as the percentage of total energy intake in cases and non-cases of DM occurring within the cohort. The differences between cases and non-cases by gender appear to be small, but no information concerning statistical significance of the difference was provided.

The remaining four studies were all included in the meta-analysis. One paper presented results for two male and female subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Schulze *et al.*, 2008).

The pooled estimate of relative risk from the cohort studies was 0.94 (95% CI: 0.89 to 1.00) per 20 g of sucrose per day ( $p=0.05$ ).



Figure 4.5 Forest plot for dietary sucrose and incident diabetes mellitus type 2



There was little heterogeneity between the cohort studies ( $I^2=13\%$  [95% CI: 0% to 87%],  $Q=3.5$ ,  $df=3$ ,  $p=0.3$ ). There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. No single study dominated the results. There were insufficient studies to explore any small-study effect such as publication bias.

### Exposure definition and assessment

Four of the six cohort studies that reported dietary intake data on specific mono and disaccharides captured dietary data using comprehensive FFQs that ranged in size from 61 to 148 items (Schulze *et al.*, 2008; Janket *et al.*, 2003; Meyer *et al.*, 2000; Colditz *et al.*, 1992). There is no evidence to suggest that this approach is more or less flawed than the dietary history or recall techniques used in the other 2 studies.

### Adjustment for appropriate confounders

The five studies that reported risk estimates for specific sugars all included the important covariates age, gender (where appropriate) and a measure of adiposity in their models.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No studies provided data.

Table 4.10 Incident diabetes mellitus type 2 and sugars: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	P trend	Adjustments
13778 (Janket <i>et al.</i> , 2003) The Women's Health Study	USA, Primarily White	(54) %M 0	(918) /39876	6 years	FFQ (131)	Glucose	Self-reported		Q5 vs. Q1		1.04 (0.85, 1.28)		0.91	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity
13784 The Women's Health Study			(271) /39876					No diseased at baseline	Q5 vs. Q1		1.12 (0.76, 1.65)		0.55	As above
13790 The Women's Health Study			(117) /39876					BMI <25	Q5 vs. Q1		1.04 (0.59, 1.85)		0.87	alcohol, BMI, family history of DM, hypertension, hypercholesterolaemia, physical activity, smoking
13796 The Women's Health Study			(776) /39876					BMI >25	Q5 vs. Q1		1.08 (0.86, 1.35)		0.85	alcohol, BMI, family history of DM, hypertension, hypercholesterolaemia, physical activity, smoking
*13758 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Glucose	Self-reported		>25.8 (30) vs. <13.9 (11.1)	g/day	1.3 (1.08, 1.57)		0.0007	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13238 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(177) /10054	12 years	Dietary history	Glucose	Diagnosis criteria not reported Registry data		(27.5) vs. (5.6)	g/day	1.91 (1.22, 2.98)		0.001	age, BMI, diet pattern- conservative, diet pattern-prudent, energy intake, family history of DM, region, physical activity, gender, smoking

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	P trend	Adjustments
*14250 (Schulze <i>et al.</i> , 2008) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65  %M 40	(491) /27548	7 years (9)	FFQ (148)	Glucose	Multiple diagnosis methods  Confirmed self report	Men	(31.4) vs. (6.6)	g/day	1.1 (0.81, 1.5)		0.721	age, alcohol, BMI, education, energy intake, Fibre, magnesium Intake, MUFA:SFA, occupation, physical activity, PUFA:SFA, gender, smoking, waist
*14254 EPIC Potsdam			(355) /27548					Women	(24.3) vs. (9.6)	g/day	0.88 (0.58, 1.33)		0.599	As above
13236 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69  %M 53	(177) /10054	12 years	Dietary history	Fructose and glucose g/day	Diagnosis criteria not reported Registry data		(56.2) vs. (11.7)	g/day	1.87 (1.19, 2.93)		0.003	age, BMI, diet pattern- conservative, diet pattern-prudent, energy intake, family history of DM, region, physical activity, gender, smoking
13777 (Janket <i>et al.</i> , 2003) The Women's Health Study	USA, Primarily White	(54)  %M 0	(918) /39876	6 years	FFQ (131)	Fructose	Self-reported		Q5 vs. Q1		0.96 (0.78, 1.19)		0.86	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity
13783 The Women's Health Study			(271) /39876					No diseased at baseline	Q5 vs. Q1		1.24 (0.84, 1.85)		0.3	As above
13789 The Women's Health Study			(117) /39876					BMI <25	Q5 vs. Q1		0.9 (0.51, 1.59)		0.94	alcohol, BMI, family history of DM, hypertension, hypercholesterolaemia, physical activity, smoking
13795 The Women's Health Study			(776) /39876					BMI >25	Q5 vs. Q1		1 (0.79, 1.26)		0.87	As above
*13760 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic,	55-69 (61)  %M 0	(1141) /41836	6 years (21)	FFQ (127)	Fructose g/day	Self-reported		>30 (35.5) vs. <15.9 (12.5)	g/day	1.27 (1.06, 1.54)		0.0015	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	P trend	Adjustments
	Post-menopausal													
*13237 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(177) /10054	12 years	Dietary history	Fructose g/day	Diagnosis criteria not reported Registry data		(28.8) vs. (6)	g/day	1.9 (1.2, 3.01)		0.004	age, BMI, diet pattern- conservative, diet pattern-prudent, energy intake, family history of DM, region, physical activity, gender, smoking
*14251 (Schulze <i>et al.</i> , 2008) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(491) /27548	7 years (9)	FFQ (148)	Fructose g/day	Multiple diagnosis methods Confirmed self report	Men	(40.6) vs. (8.4)	g/day	1 (0.74, 1.35)		0.987	age, alcohol, BMI, education, energy intake, fibre, magnesium intake, MUFA:SFA, occupation, physical activity, PUFA:SFA, gender, smoking, waist
*14255 EPIC Potsdam			(355) /27548					Women	(34.8) vs. (11)	g/day	1.09 (0.75, 1.58)		0.877	As above
13779 (Janket <i>et al.</i> , 2003) The Women's Health Study	USA, Primarily White	(54) %M 0	(918) /39876	6 years	FFQ (131)	Lactose	Self-reported		Q5 vs. Q1		0.99 (0.8, 1.22)		0.33	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity
13785 The Women's Health Study			(271) /39876					No diseased at baseline	Q5 vs. Q1		0.93 (0.62, 1.38)		0.34	As above
13791 The Women's Health Study			(117) /39876					BMI <25	Q5 vs. Q1		0.6 (0.34, 1.08)		0.13	As above
13797 The Women's Health Study			(776) /39876					BMI >25	Q5 vs. Q1		1.06 (0.84, 1.33)		0.57	As above
13761 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Lactose	Self-reported		>101.8 vs. <11.9	g/day	0.94 (0.77, 1.14)		0.24	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	P trend	Adjustments
13239 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69  %M 53	(177) /10054	12 years	Dietary history	Lactose	Diagnosis criteria not reported Registry data		(58.4) vs. (22.4)	g/day	0.99 (0.6, 1.62)		0.89	age, BMI, diet pattern- conservative, diet pattern-prudent, energy intake, family history of DM, region, physical activity, gender, smoking
13762 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61)  %M 0	(1141) /41836	6 years (21)	FFQ (127)	Maltose	Self-reported		>1.85 (2.28) vs. <0.92 (0.71)	g/day	0.98 (0.81, 1.19)		0.6	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
13240 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69  %M 53	(177) /10054	12 years	Dietary history	Maltose	Diagnosis criteria not reported Registry data		(5.6) vs. (1.6)	g/day	0.71 (0.45, 1.12)		0.08	age, BMI, diet pattern- conservative, diet pattern-prudent, energy intake, family history of DM, region, physical activity, gender, smoking
14258 (Colditz <i>et al.</i> , 1992) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55  %M 0	(252) /121700	6 years (19)	FFQ (61)	Sucrose	Multiple diagnosis methods	BMI <29	Q5 vs. Q1		1.16 (0.77, 1.76)		0.76	age, alcohol, BMI, family history of DM, prior weight change, assessment period
14259 NHS			(450) /121700					BMI >29	Q5 vs. Q1		0.9 (0.64, 1.28)		0.2	As above
*13776 (Janket <i>et al.</i> , 2003) The Women's Health Study	USA, Primarily White	(54)  %M 0	(918) /39876	6 years	FFQ (131)	Sucrose	Self-reported		Q5 vs. Q1		0.84 (0.67, 1.04)		0.16	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity
13782 The Women's Health Study			(271) /39876					No diseased at baseline	Q5 vs. Q1		0.59 (0.39, 0.88)		0.05	As above
13788 The Women's Health Study			(117) /39876					BMI <25	Q5 vs. Q1		0.77 (0.44, 1.36)		0.7	As above

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	P trend	Adjustments
13794 The Women's Health Study			(776) /39876					BMI >25	Q5 vs. Q1		0.87 (0.7, 1.12)		0.25	As above
*13759 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Sucrose g/day	Self-reported		>51 (57.7) vs. <31.2 (25.8)	g/day	0.81 (0.67, 0.99)		0.027	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13235 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(177) /10054	12 years	Dietary history	Sucrose g/day	Diagnosis criteria not reported Registry data		(79.5) vs. (28.5)	g/day	1.12 (0.71, 1.76)		0.61	age, BMI, diet pattern- conservative, diet pattern-prudent, energy intake, family history of DM, region, physical activity, gender, smoking
*14249 (Schulze <i>et al.</i> , 2008) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(491) /27548	7 years (9)	FFQ (148)	Sucrose g/day	Multiple diagnosis methods Confirmed self report	Men	(102) vs. (22.5)	g/day	0.72 (0.5, 1.04)		0.063	age, alcohol, BMI, education, energy intake, fibre, magnesium Intake, MUFA:SFA, occupation, physical activity, PUFA:SFA, gender, smoking, waist
*14253 EPIC Potsdam			(382) /27548					Women	(83.4) vs. (28.2)	g/day	1.31 (0.74, 1.74)		0.492	As above
14125 (Monterrosa <i>et al.</i> , 1995) San Antonio Heart Study follow-up	USA, Multi- ethnic, Not diabetic	25-64 %M 41.8	(20) /2217	8 years (22.8)	Dietary recall	Sucrose % energy	Fasting serum/blood glucose Clinic tested	Men		% Energy		Cases: 8.08% Non-cases: 7.61%		age, socioeconomic status/class
14126 San Antonio Heart Study follow-up			(37) /2217					Women		% Energy		Cases: 8.38% Non-cases: 8.25%		age, socioeconomic status/class

\*This result was used in the meta-analysis of dietary glucose/ fructose/ sucrose and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort

Incident diabetes mellitus type 2 and starch, polysaccharides, “complex” and refined carbohydrates

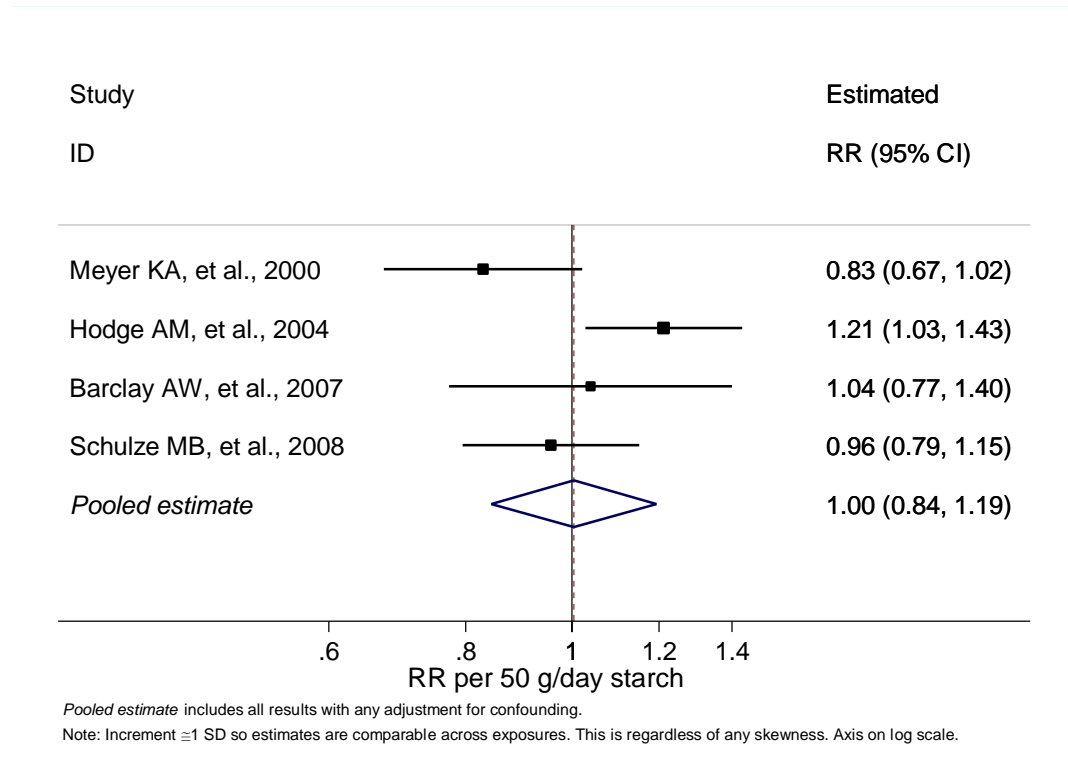
Summary of cohort results

Data were extracted from eight publications presenting results for dietary starch and DM. Of these; two reported polysaccharides and complex carbohydrates cases (Feskens *et al.*, 1995;Leonetti *et al.*, 1996) and one reported no risk estimate (Monterrosa *et al.*, 1995).

The remaining five publications presented risk estimates for dietary starch (expressed as grams per day) from five cohort studies: the Blue Mountains Eye Study, the Melbourne Collaborative Cohort Study, The Women’s Health Study, Iowa Women’s Health Study and EPIC Potsdam (Barclay *et al.*, 2007;Hodge *et al.*, 2004;Janket *et al.*, 2003;Meyer *et al.*, 2000;Schulze *et al.*, 2008). One study could not be included in the meta-analysis because insufficient information was presented by which a dose-response trend could be estimated (Janket *et al.*, 2003). This study (the Women’s Health Study) provided no evidence of an association between starch intakes and risk of DM. The remaining four studies were all included in the meta-analysis. One study presented results for men and women separately (Schulze *et al.*, 2008). These subgroups were first combined using fixed effects meta-analysis before joining with the other studies in the random effects meta-analysis.

The pooled estimate of relative risk from the cohort studies was 1.00 (95% CI: 0.84 to 1.19) per 50 g/day of starch (p=0.96).

Figure 4.6 Forest plot for starch and incident diabetes mellitus type 2



There was considerable heterogeneity between the cohort studies ( $I^2=65\%$  [95% CI: 0% to 88%],  $Q=8.5$ ,  $df=3$ ,  $p=0.04$ ), so the pooled estimate should be interpreted cautiously. There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. No single study dominated the results. There were insufficient studies to explore small-study effect such as publication bias using a funnel plot or a hypothesis test.

The San Antonio Heart Follow-up Study (Monterrosa *et al.*, 1995) provided starch consumption data expressed as the percentage of total energy intake in participants who subsequently became cases and non-cases of DM within the cohort. The difference between male cases and non-cases appears to be small, but no information concerning statistical significance of the difference was provided. In women, the cases obtained a 2% higher percentage of energy from starch than the non-cases, but no information concerning statistical significance of this difference was provided.

The Seven Countries Study and the study of Japanese-American Men provided consumption data for polysaccharides and “complex” and refined carbohydrates in cases and non-cases (Feskens *et al.*, 1995; Leonetti *et al.*, 1996), but not for starch specifically. Somewhat lower intakes of polysaccharides and “complex” carbohydrates were reported in the participants that became cases of DM compared to the non-cases, although no indication of the statistical significance of the difference was provided. It’s important to note that these estimates are unadjusted means for the Japanese-American men, and minimally adjusted in the Seven Countries Study.

Collectively, the data from these cohort studies do not provide evidence of an association between starch intakes and risk of DM.

### ***Exposure definition and assessment***

Six of the eight cohort studies that reported dietary intake data on starch, polysaccharides or “complex” carbohydrates used comprehensive FFQs that ranged in size from 61 to 148 items (Schulze *et al.*, 2008; Janket *et al.*, 2003; Meyer *et al.*, 2000; Colditz *et al.*, 1992; Barclay *et al.*, 2007; Hodge *et al.*, 2004). There is no evidence to suggest that this approach is more or less flawed than the dietary history or recall techniques used in the other 2 studies (Feskens *et al.*, 1995; Monterrosa *et al.*, 1995).

The definition and use of the term “complex” carbohydrate is variable from study to study and has changed over time. Definitions of “complex” carbohydrates were not provided by the authors of the included studies, although it is generally recognised that “complex” carbohydrates are composed of complex sugar chains, with these chains acting as an energy store or fibrous structure in plants (Committee on Medical Aspects of Food Policy, 1989). As such, rich food sources include grains, legumes, fruits and vegetables (Shah *et al.*, 1994; Shah *et al.*, 1996; Poppitt *et al.*, 2002). According to the WHO and as stated in The Crevalcore and Montegiorgio cohort from the Seven Countries Study (Farchi *et al.*, 1995), intakes of “complex” carbohydrates should make up 50-70% of total carbohydrate intake.



### ***Adjustment for appropriate confounders***

The study by Barclay *et al.* of an Australian cohort adjusted for age, family history of DM, blood lipids, physical activity and smoking but not adiposity (Barclay *et al.*, 2007). The other 3 studies that reported risk estimates for starch, that were included in the meta-analysis, all included the important covariates age, gender (where appropriate) and a measure of adiposity in their models.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning starch, polysaccharides, “complex” and refined carbohydrates and incident DM 2.

Table 4.11 Incident diabetes mellitus type 2 and starch, polysaccharides and “complex” and refined carbohydrates: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
14127 (Monterrosa <i>et al.</i> , 1995) San Antonio Heart Study follow-up	USA, Multi- ethnic, Not diabetic	25-64 %M 41.8	(20) /2217	8 years (22.8)	Dietary recall	Starch (%/energy)	Fasting serum/blood glucose Clinic tested	Men		% Energy		Cases: 8.36 Non-cases: 8.85			age, socioeconomic status/class
14128 (Monterrosa <i>et al.</i> , 1995) San Antonio Heart Study follow-up	USA, Multi- ethnic, Not diabetic	25-64 %M 41.8	(37) /2217	8 years (22.8)	Dietary recall	Starch (%/energy)	Fasting serum/blood glucose Clinic tested	Women		% Energy		Cases: 10.38 Non-cases: 8.58			age, socioeconomic status/class
*13338 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(138) /3654	10 years (29)	FFQ (145)	Starch, total	Self-reported DM and current use of insulin/oral hypoglycaemic medication, or fasting glucose ≥126 mg/dL (WHO criteria)		Continuo us risk estimate	100 g/day	1.08 (0.6, 1.97)		0.795		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglycerides
*14237 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Starch, total	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuo us risk estimate	100 g/day	1.47 (1.06, 2.05)		0.02		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13780 (Janket <i>et al.</i> , 2003) The Women's Health Study	USA, Primarily White	(54) %M 0	(918) /39876	6 years	FFQ (131)	Starch, total	Self-reported		Q5 vs. Q1		0.88 (0.71, 1.09)			0.61	age, alcohol, BMI, family history of DM, hypertension, hormone replacement therapy, hypercholesterolaemia, smoking, supplements, physical activity
13786 The Women's Health Study			(271) /39876					No diseased at baseline	Q5 vs. Q1		0.78 (0.5, 1.21)			0.59	As above

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
13792 The Women's Health Study			(117) /39876					BMI <25	Q5 vs. Q1		1.03 (0.59, 1.81)			0.54	alcohol, BMI, family history of DM, hypertension, hypercholesterolaemia, physical activity, smoking
13798 The Women's Health Study			(776) /39876					BMI >25	Q5 vs. Q1		0.85 (0.67, 1.08)			0.98	As above
*13757 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61)  %M 0	(1141) /41836	6 years (21)	FFQ (127)	Starch, total	Self-reported		>76.8 (85.3) vs. <50.5 (43.4)	g/day	0.83 (0.69, 1)			0.12	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*14248 (Schulze <i>et al.</i> , 2008) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65  %M 40	(491) /27548	7 years (9)	FFQ (148)	Starch, total	Multiple diagnosis methods Confirmed self report	Men	(161.4) vs. (71)	g/day	0.79 (0.5, 1.24)			0.26	age, alcohol, BMI, education, energy intake, Fibre, magnesium Intake, MUFA:SFA, occupation, physical activity, PUFA:SFA, smoking, waist
*14252 EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65  %M 40	(355) /27548	7 years (9)	FFQ (148)	Starch, total	Multiple diagnosis methods Confirmed self report	Women	(122.3) vs. (51.9)	g/day	1.38 (0.84, 2.26)			0.332	As above
14643 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59  %M 100	(26) /338	20 years	Dietary history	Polysaccharides (>10), unspecified	Plasma glucose OGTT (75g/120mins) Clinic tested			% Energy		Cases: (n: 26) 22.7% Non-cases: (n: 241) 24.1%			age, Cohort
14624 (Leonetti <i>et al.</i> , 1996) Japanese- American Men Diabetes	USA, Asian, Not diabetic	45-74  %M 100	/229	5 years (5.6)	FFQ Interview (89)	Complex carbohydrates	Plasma glucose OGTT (75g/120mins) Confirmed self report	Confirmed self report Normal glucose tolerance at baseline		g/day		Cases: (n: 9) 224g (67.3) Non-cases: (n: 23) 302g (62.6)			

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
Study															
14625 (Leonetti <i>et al.</i> , 1996) Japanese- American Men Diabetes Study	USA, Asian, Not diabetic	45-74  %M 100	(1)	5 years (5.6)	FFQ Interview (89)	Refined carbohydrates	Plasma glucose OGTT (75g/120mins)	Confirmed self report Normal glucose tolerance at baseline		g/day		Cases: (n: 9) 34.1 (22.7) Non-cases: (n: 23) 35.9 (23.5)			

\*This result was used in the meta-analysis of starch and Incident DM 2

## Incident diabetes mellitus type 2 and dietary fibre

The Association of Official Analytical Chemists (AOAC) methods of dietary fibre estimation include polysaccharides, oligosaccharides, lignin and associated plant substances that are resistant to digestion. This is the most commonly applied enzymatic-gravimetric method throughout most of Europe and the Americas. However, in the UK until recently, the Englyst method of dietary fibre analysis has been the preferred approach. This method, developed by Hans Englyst and colleagues, is based on an enzymatic-chemical approach and includes only non-starch polysaccharides (NSP), which are considered to be the dominant and most active fraction of 'dietary fibre'. Since it includes only NSP, this approach produces smaller estimates than AOAC. The Southgate method (Southgate, 1969) used in earlier editions of the UK Composition of Foods tables, produces dietary fibre estimates for foods which are greater than the Englyst method as it includes the sum of polysaccharides (including pectins, hemicelluloses and cellulose) and lignin.

### Summary of cohort results

#### Fibre and diabetes

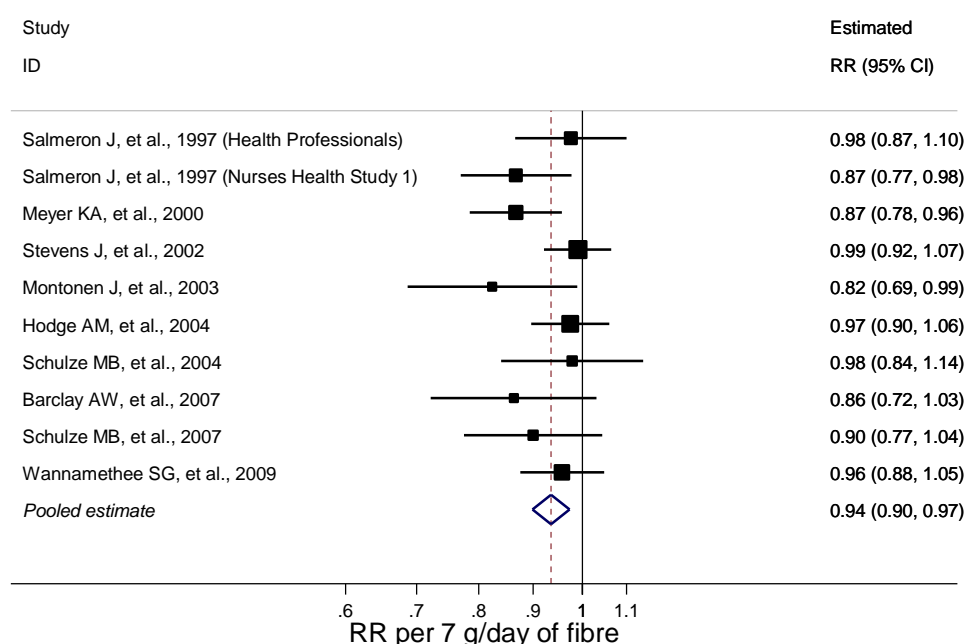
Data were extracted from 11 publications presenting dietary fibre intakes expressed as grams per day, from 11 cohort studies: Blue Mountains Eye Study, the Melbourne Collaborative Cohort Study, the Finnish Diabetes Prevention Study, Iowa Women's Health Study, the Finnish Mobile Clinic Health Surveys, HPFS, NHS, EPIC Potsdam, NHS II, ARIC and the British Regional Heart Study, (Barclay *et al.*, 2007;Stevens *et al.*, 2002;Schulze *et al.*, 2007b;Lindstrom *et al.*, 2006;Hodge *et al.*, 2004;Wannamethee *et al.*, 2009;Schulze *et al.*, 2004a;Montonen *et al.*, 2003;Meyer *et al.*, 2000;Salmeron *et al.*, 1997a;Salmeron *et al.*, 1997b). Studies were conducted in Finland, the USA, Australia, Germany, and the UK.

The Finnish Diabetes Prevention Study was excluded from the meta-analysis because the results were not adjusted for confounding (Lindstrom *et al.*, 2006). This study reported similar gender and group allocation-adjusted fibre intake data for cases and non-cases.

All remaining ten studies were included in the meta-analysis. So that one paper could be included in the meta-analysis, we assumed that the median intake of the lowest exposure category was half the upper limit of that category, and that the median intake of the upper exposure category was 1.5 times the lower limit of that category (Wannamethee *et al.*, 2009). Another paper presented results for two subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Stevens *et al.*, 2002).

The pooled estimate of relative risk from the cohort studies was 0.94 (95% CI: 0.90 to 0.97) per 7 g of dietary fibre per day ( $p=0.001$ ).

Figure 4.7 Forest plot for dietary fibre and incident diabetes mellitus type 2



Pooled estimate includes all results with any adjustment for confounding.

Note: Increment  $\pm 1$  SD so estimates are comparable across exposures. This is regardless of any skewness. Axis on log scale.

There was little heterogeneity between the cohort studies ( $I^2=19\%$  [95% CI: 0% to 60%],  $Q=11.1$ ,  $df=9$ ,  $p=0.3$ ). There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 4.12: Subgroup analyses of fibre and incidence of diabetes. Relative risks are per 7 g/day.

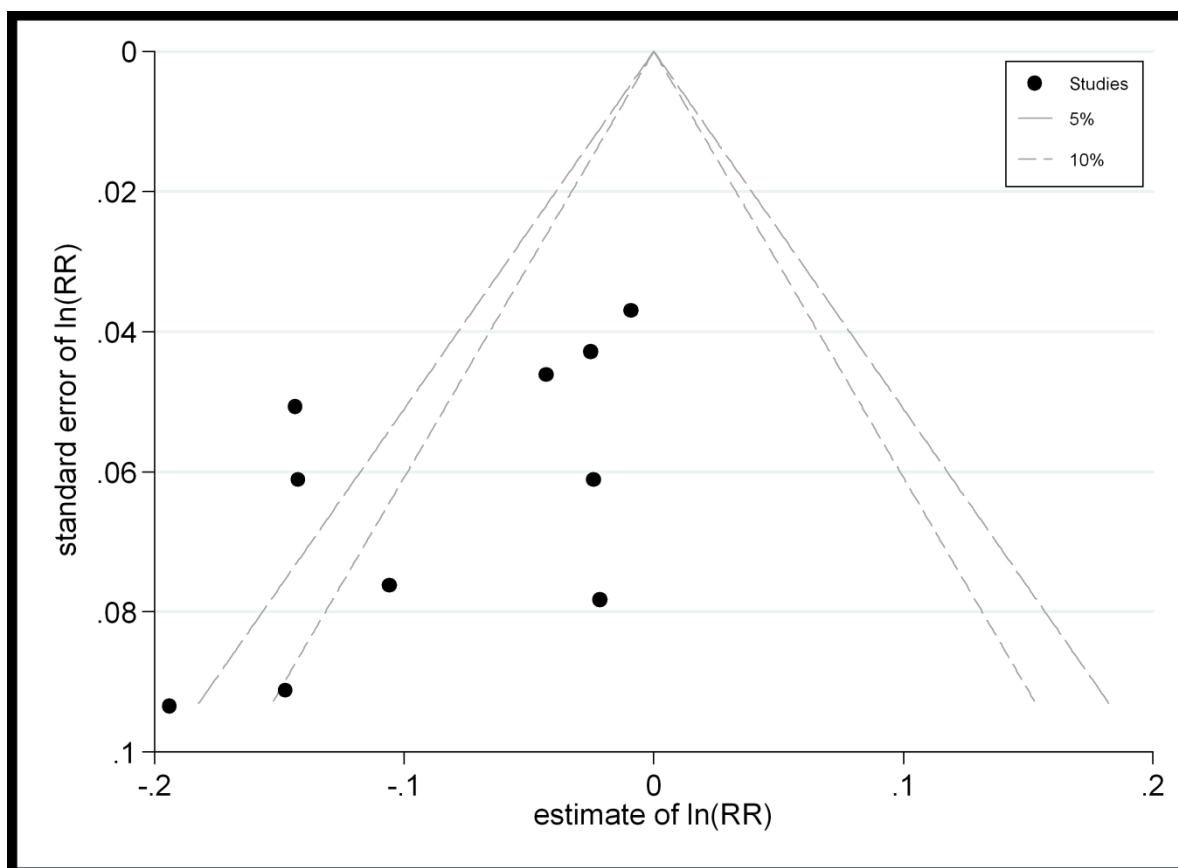
Subgroup	subgroup	RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> *	P <sub>het</sub> **
Subjects' gender	Male	0.96 (0.90, 1.04)	0%	2	.8	.3
	Mixed	0.94 (0.89, 1.00)	28%	5	.2	
	Female	0.89 (0.83, 0.95)	0%	3	.4	
Subjects' gender in same study	Male			0		
	Female			0		
method used to assess fibre	AOAC	0.93 (0.89, 0.97)	27%	9	.2	
	not AOAC	0.96 (0.88, 1.05)		1		.6
length of follow-up	<10 years	0.95 (0.91, 0.98)	13%	8	.3	
	>=10 years	0.84 (0.74, 0.96)	0%	2	.7	.7
geographic location	Americas	0.94 (0.88, 1.00)	43%	5	.1	
	EU	0.92 (0.85, 0.99)	11%	3	.3	
	Other	0.94 (0.85, 1.05)	32%	2	.2	.5
adjusted for age	yes	0.94 (0.90, 0.97)	19%	10	.3	
	no		19%	0		
adjusted for alcohol	yes	0.93 (0.90, 0.97)	2%	7	.4	
	no	0.91 (0.80, 1.03)	58%	3	.09	1
adjusted for anthropometry	yes	0.94 (0.90, 0.98)	22%	9	.2	
	no	0.86 (0.72, 1.03)		1		.4
adjusted for energy intake	yes	0.93 (0.88, 0.98)	15%	6	.3	
	no	0.94 (0.87, 1.01)	38%	4	.2	.7
adjusted for family history	yes	0.94 (0.89, 0.99)	0%	5	.4	
	no	0.92 (0.87, 0.99)	44%	5	.1	.8
adjusted for physical activity	yes	0.94 (0.91, 0.98)	12%	9	.3	
	no	0.82 (0.69, 0.99)		1		.2
adjusted for gender	yes	0.94 (0.90, 0.97)	19%	10	.3	
	no			0		
adjusted for smoking	yes	0.93 (0.89, 0.97)	22%	9	.3	
	no	0.97 (0.90, 1.06)		1		.4
adjusted for age and anthropometry	yes	0.94 (0.90, 0.98)	22%	9	.2	
	no	0.86 (0.72, 1.03)		1		.4

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup

There was no evidence of any small-study effect such as publication bias, as is shown by the contour-enhanced funnel plot below:

*Figure 4.8 Contour-enhanced funnel plot for publications presenting incident diabetes mellitus type 2 and dietary fibre*



### **Fibre density (grams/unit energy/day)**

Three cohort studies: The Seven Countries Study, The Finnish Diabetes Prevention Study and EPIC Norfolk, (Feskens *et al.*, 1995; Simmons *et al.*, 2006; Lindstrom *et al.*, 2006) provided risk estimates for dietary fibre intake expressed as fibre density (grams per unit of energy – generally 1000 kcal). The fibre density results of these studies are broadly consistent with those on fibre intake expressed as grams per day.

Of the studies which report DM and fibre intake or fibre density, the two cohorts from the UK are worthy of particular note. The British Regional Heart Study (Wannamethee *et al.*, 2009) reported a risk estimate of 0.82 (95% CI: 0.51, 1.32) comparing the highest (>31g/d) category of dietary fibre consumers against the lowest (<20g/d). The authors of the EPIC Norfolk study (Simmons *et al.*, 2006) reported a reduction in risk of similar magnitude when comparing participants with dietary fibre intakes greater than 15g/4184kJ to those consuming less than this. The dietary fibre analysis in common use in the UK provides data on non-starch polysaccharides only, and it should be recognised that this represents lower levels of dietary fibre intake than would be apparent using the AOAC method adopted in the rest of Europe and the USA.



### ***Exposure definition and assessment***

Other than the British Regional Heart Study (Wannamethee *et al.*, 2009), which reported dietary fibre expressed as non-starch polysaccharides based on the methods of Englyst (Englyst and Cummings, 1988), the cohort studies included in the meta-analysis tend to have used dietary fibre values for food based on the AOAC enzymic-gravimetric methodology (AOAC method 985.29). In the Finnish Mobile Clinic Health Survey cohort, the method of fibre analysis used is not clear from the detail provided in the paper. However, individuals in the highest consumption quartile reported intakes between 33 and 118g fibre per day, with a mean intake of 40g/d which indicates very high consumption levels (Montonen *et al.*, 2003). Despite these apparently high intakes however, in the meta-analysis no single study had a dominant influence on the pooled estimate.

### ***Adjustment for appropriate confounders***

Studies included in the meta-analysis that provided an estimate of risk associated with dietary fibre all adjusted for age, gender (where appropriate) and adiposity (generally BMI).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning dietary fibre and incident DM 2.

Table 4.13 Incident diabetes mellitus type 2 and dietary fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follo w Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
*13339 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(138) /3654	10 years (29)	FFQ (145)	Dietary Fibre, g/d	Self-reported diabetes and current use of insulin/oral hypoglycaemic medication, or fasting glucose $\geq 126$ mg/dL (WHO criteria)		Continuous risk estimate	5 g/day	0.9 (0.79, 1.02)		0.109		age, family history of DM, HDL-C, physical activity, gender, smoking, Blood triglyceride
*14238 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Dietary Fibre, g/d (AOAC method)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	20 g/day	0.93 (0.73, 1.18)		0.53		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
14607 (Lindstrom <i>et al.</i> , 2006) The Finnish Diabetes Prevention Study	Finland, BMI >25, Middle-aged adults	40-64 (55) %M 33	(386) /522	3 years	Food diary	Dietary Fibre (AOAC method?)	Multiple diagnosis methods Clinic tested			g/day		Cases: (n: 386) 20(8) Non-cases: (n: 114) 19 (6)			gender, Group allocation
*13765 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not diabetic, Post-menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Dietary Fibre, g/d (AOAC method)	Self-reported		>23.6 (26.5) vs. <15.3 (13.27)	g/day	0.78 (0.64, 0.96)			0.005	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13164 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle-aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Dietary Fibre, g/d (method unclear)	Diagnosis criteria not reported Registry data, WHO criteria		33.2-118 (40) vs. 2.6-19.2 (16)	g/day	0.51 (0.26, 1.00)			0.04	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
13205 Finnish Mobile Clinic			(24) /4316					Age <50	Q4 vs. Q1		0.35 (0.09, 1.41)				BMI, energy intake, fruit, region, gender, smoking, vegetable

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follo w Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
Health Surveys															intake
13206			(132) /4316					Age >50	Q4 vs. Q1		0.52 (0.26, 1.03)				As above
13207			(54) /4316					Men	Q4 vs. Q1		0.43 (0.18, 1.02)				age, BMI, energy intake, fruit, region, smoking, vegetable intake
13208			(102) /4316					Women	Q4 vs. Q1		0.61 (0.27, 1.39)				As above
13209			(33) /4316					BMI <27	Q4 vs. Q1		1.07 (0.38, 2.99)				As above
13210			(123) /4316					BMI >27	Q4 vs. Q1		0.37 (0.17, 0.8)				As above
13211			(124) /4316					Non-smokers	Q4 vs. Q1		0.56 (0.27, 1.14)				As above
13212			(32) /4316					Smokers	Q4 vs. Q1		0.39 (0.12, 1.24)				As above
13213			(84) /4316					No hypertensives	Q4 vs. Q1		0.65 (0.3, 1.43)				age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
13214			(72) /4316					Hypertension	Q4 vs. Q1		0.39 (0.15, 1.02)				As above
13215			(68) /4316					No hyperchol- esterolaemia	Q4 vs. Q1		0.44 (0.19, 1.02)				As above
13216			(88) /4316					With hyperchol- esterolaemia	Q4 vs. Q1		0.59 (0.26, 1.33)				As above
13218			(Subgroup cases not reported) /4316					Highest tertile of Refined Grain	Q3 vs. Q1	g/day	0.52 (0.18, 1.51)				As above
13217			(Subgroup cases not reported) /4316					Lowest tertile of Refined Grain	Q3 vs. Q1		0.52 (0.24, 1.12)				As above
*13469 (Salmeron <i>et al.</i> , 1997a) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(523) /51529	6 years	FFQ (131)	Dietary Fibre, g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(29.7) vs. (13.4)	g/day	0.98 (0.73, 1.33)			0.7	age, alcohol, BMI, family history of DM, physical activity, smoking

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follo w Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
*13570 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(918) /121700	6 years	FFQ (134)	Dietary Fibre, g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(24.1) vs. (11.8)	g/day	0.78 (0.62, 0.98)			0.02	age, alcohol, BMI, family history of DM, physical activity, smoking
*13579 (Schulze <i>et al.</i> , 2007b) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(844) /27548	7 years (9)	FFQ (148)	Dietary Fibre, g/d (AOAC method)	Medication Use Confirmed self report		(27.9) vs. (15.8)	g/day	0.86 (0.65, 1.14)			0.19	age, alcohol, waist, BMI, CHO, smoking, education, FAT, physical activity, gender, energy intake
*13537 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) /116671	8 years (<10)	FFQ (133)	Dietary Fibre, g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		>22 (24.9) vs. <14.2 (12.5)	g/day	1 (0.75, 1.34)			0.8	age, alcohol, BMI, caffeine, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, Hyperchol- esterolaemia, hypertension, magnesium Intake, oral contraceptive pill, physical activity, smoking, postmenopausal HRT
*13219 (Stevens <i>et al.</i> , 2002) ARIC	USA, Multi- ethnic	45-64 (54) %M 44	(Subgroup cases not reported; total cohort cases 1447) /15792	9 years	FFQ (66)	Dietary Fibre, g/d (Energy adjusted fibre intake. AOAC method)	Physician reports, use of diabetic medication, fasting glucose level ≥126 mg/dL or non- fasting glucose level ≥200 mg/dL.	Race - White	Continuous risk estimate	1 g/day	0.999 (0.987, 1.012)		0.915		age, BMI, centre, education, physical activity, gender, smoking
*13220 ARIC			Subgroup cases not reported					African- American	Continuous risk estimate	1 g/day	0.998 (0.98, 1.017)		0.849		age, BMI, centre, education, physical activity, gender, smoking
*13920 (Wannameth ee <i>et al.</i> , 2009) British Regional Heart Study	UK, Primarily White, Not diabetic	40-59 %M 100	(162) /7735	7 years (1)	FFQ	Dietary Fibre, g/d (Englyst method)	Diagnosis criteria not reported Confirmed self report		>31 vs. <20	g/day	0.82 (0.51, 1.32)				age, alcohol, waist, energy intake, myocardial infarction, stroke, physical activity, socioeconomic status/class, smoking,

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follo w Up (% loss)	Diet Assessm ent	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean Exposure	p	P trend	Adjustments
Statin use															
14645 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59  %M 100	(26) /338	20 years	Dietary history	Fibre density (g/unit energy. AOAC method)	Plasma glucose OGTT (75g/120mins ) Clinic tested			g/1000 kcal		Cases: (n: 26) 9.3 Non- cases: (n: 241) 10.1			age, cohort
14608 (Lindstrom <i>et al.</i> , 2006) The Finnish Diabetes Prevention Study	Finland, BMI >25, Middle- aged adults	40-64 (55)  %M 33	(386) /522	3 years	Food diary	Fibre density (g/unit energy. AOAC method)	Multiple diagnosis methods Clinic tested			g/1000 kcal		Cases: (n: 386) 12 (4) Non- cases: (n: 114) 11 (4)			gender, group allocation
13721 (Simmons <i>et al.</i> , 2006) EPIC Norfolk	UK, Primarily White, Not diabetic	40-74  %M 45	(394) /25633	4.6 years (41)	FFQ (130)	Fibre density (g/unit energy. Englyst and Cummings non-starch polysacch- arides)	Multiple diagnosis methods Confirmed self report		>15g vs. <15g	g/4184KJ	0.83 (0.44, 1.56)				age, BMI, family history of DM, fat intake, physical activity, socioeconomic status/class, gender, hypertension medication

\*This result was used in the meta-analysis of dietary fibre and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

## **Incident diabetes mellitus type 2 and bran/germ**

### **Summary of cohort results**

Data on bran and germ intake in relation to risk of DM are provided only by the Nurses Health Studies I and II (de Munter *et al.*, 2007; Liu *et al.*, 2000a). This evidence base is therefore limited. For both bran and germ consumption, risk of DM was reduced with increasing consumption in the models included in the tables below. However, it is apparent that dissociating the effects of bran and germ from each other and from cereal fibre generally is difficult. de Munter *et al.* (de Munter *et al.*, 2007) report that no significant association was observed for germ intake after adjustment for bran (data not included in table).

With just two studies, meta-analysis was not appropriate.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning bran/ germ and incident DM 2.

Table 4.14 Incident diabetes mellitus type 2 and bran/germ: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14105 (de Munter <i>et al.</i> , 2007) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4747) /121700	18 years	FFQ (126)	Bran, Total (naturally contained in whole grains and added)	Diagnosis criteria not reported Confirmed self report	(9.6) vs. (0.6)	g/day	0.57 (0.51, 0.63)	<0.001	age, alcohol, coffee, energy intake, DM, hormone replacement therapy, oral contraceptive pill, physical activity, PUFA:SFA, processed meat, smoking, sugar- sweetened beverages
14108 (de Munter <i>et al.</i> , 2007) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	26-44 %M 0	(1739) /116671	12 years	FFQ (133)	Bran, Total (naturally contained in whole grains and added)	Diagnosis criteria not reported Confirmed self report	(12) vs. (1.1)	g/day	0.64 (0.54, 0.76)	<0.001	As above
14106 (de Munter <i>et al.</i> , 2007) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4747) /121700	18 years	FFQ (126)	Germ, total (naturally occurring plus added)	Assessment method Diagnosis criteria not reported Confirmed self report	(1.5) vs. (0.2)	g/day	0.76 (0.69, 0.84)	<0.001	As above
14109 (de Munter <i>et al.</i> , 2007) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	26-44 %M 0	(1739) /116671	12 years	FFQ (133)	Germ, total (naturally occurring plus added)	Diagnosis criteria not reported Confirmed self report	(1.9) vs. (0.3)	g/day	0.94 (0.8, 1.1)	0.46	As above
13429 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Wheat germ	Self reported, and confirmed by the National Diabetes Data Group	5-6 vs. 0	times/week	0.85 (0.52, 1.37)	0.003	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake

## **Food sources of dietary fibre and incident diabetes mellitus type 2**

The following sections include cohort studies which report fibre from cereal foods, fruit, vegetables, potatoes and legumes. These results refer to fibre contained within and not fibre extracted from food sources. Interpretation of these results should therefore be considered in the context of whole food consumption and not necessarily fibre extracted from these foods.

## **Incident diabetes mellitus type 2 and fibre contained within cereals**

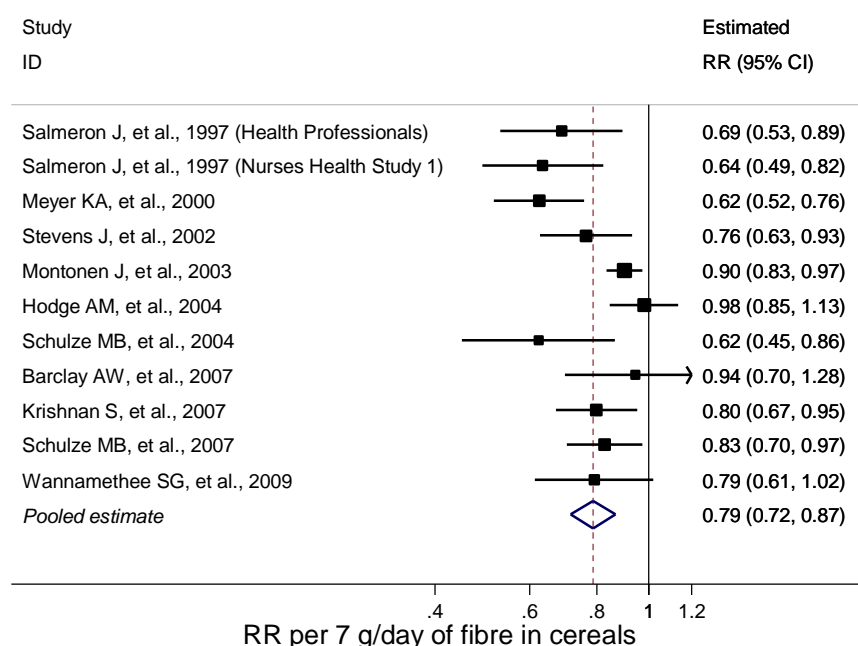
### **Summary of cohort results**

Data were extracted from 11 publications presenting results from 11 cohort studies: the Black Women's Health Study, the Blue Mountains Eye Study, ARIC, NHS II, EPIC Potsdam, the Melbourne Collaborative Cohort Study, the British Regional Heart Study, the Finnish Mobile Clinic Health Surveys, the Iowa Women's Health Study, HPFS and NHS (Krishnan *et al.*, 2007; Barclay *et al.*, 2007; Stevens *et al.*, 2002; Schulze *et al.*, 2007b; Hodge *et al.*, 2004; Wannamethee *et al.*, 2009; Schulze *et al.*, 2004a; Montonen *et al.*, 2003; Meyer *et al.*, 2000; Salmeron *et al.*, 1997a; Salmeron *et al.*, 1997b). Six of the 11 studies were conducted in the USA, two in Australia and three in Europe (one in the UK). All 11 studies were included in the meta-analysis. So that one paper could be included in the meta-analysis, we assumed that the median intake of the lowest exposure category was half the upper limit of that category, and that the median intake of the upper exposure category was 1.5 times the lower limit of that category, and these based on the assumption that quartiles of cereal fibre intake are in proportion to the quartiles for total fibre intake (Wannamethee *et al.*, 2009). Another paper presented results for two subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Stevens *et al.*, 2002).

The pooled estimate of relative risk from the cohort studies was 0.79 (95% CI: 0.72 to 0.87) per 7g of fibre from cereals per day ( $p < 0.001$ ).



Figure 4.9 Forest plot for fibre contained within cereals and incident diabetes mellitus type 2



Pooled estimate includes all results with any adjustment for confounding.

Note: Increment  $\pm 1$  SD so estimates are comparable across exposures. This is regardless of any skewness. Axis on log scale.

There was considerable heterogeneity between the cohort studies ( $I^2=65\%$  [95% CI: 32% to 81%],  $Q=28.2$ ,  $df=10$ ,  $p=0.002$ ), so the pooled estimate must be interpreted cautiously. However, all studies consistently reported an inverse association. There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 4.15: Subgroup analyses of fibre in cereals and incidence of diabetes. Relative risks are per 7 g/day.

Subgroup	subgroup	RR (95% CI)	$I^2$	n	$P_{het}^*$	$P_{het}^{**}$
subjects' gender	Male	0.74 (0.62, 0.89)	0%	2	.5	.02
	Mixed	0.89 (0.83, 0.95)	19%	5	.3	
	Female	0.68 (0.59, 0.78)	33%	4	.2	
method used to assess fibre	AOAC	0.78 (0.70, 0.88)	71%	9	<0.001	
	not AOAC	0.79 (0.61, 1.02)		1		.9
length of follow-up	<10 years	0.76 (0.68, 0.84)	60%	9	.01	
	$\geq 10$ years	0.90 (0.84, 0.97)	0%	2	.8	.6
geographic location	Americas	0.70 (0.64, 0.77)	6%	6	.4	

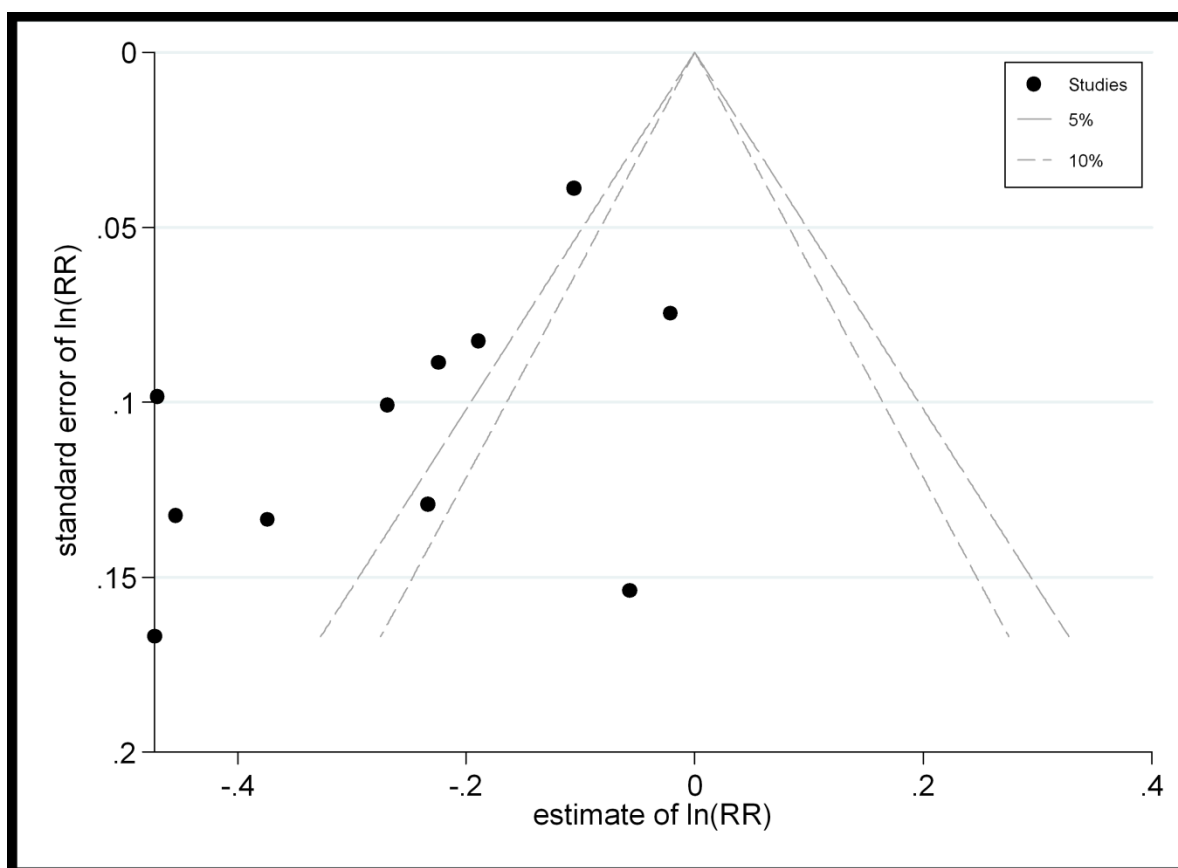
	EU	0.88 (0.82, 0.94)	0%	3	.5	
	Other	0.97 (0.85, 1.11)	0%	2	.8	.005
adjusted for age	yes	0.79 (0.72, 0.87)	65%	11	.002	
	no			0		
adjusted for alcohol	yes	0.74 (0.64, 0.86)	70%	7	.003	
	no	0.86 (0.79, 0.93)	17%	4	.3	.3
adjusted for anthropometry	yes	0.78 (0.70, 0.86)	67%	10	.001	
	no	0.94 (0.70, 1.28)		1		.4
adjusted for energy intake	yes	0.81 (0.72, 0.90)	70%	7	.003	
	no	0.74 (0.64, 0.86)	29%	4	.2	.5
adjusted for family history	yes	0.78 (0.66, 0.92)	66%	6	.01	
	no	0.79 (0.69, 0.90)	70%	5	.01	1
adjusted for physical activity	yes	0.77 (0.69, 0.85)	58%	10	.01	
	no	0.90 (0.83, 0.97)		1		.3
adjusted for gender	yes	0.79 (0.72, 0.87)	65%	11	.002	
	no			0		
adjusted for smoking	yes	0.77 (0.69, 0.85)	61%	10	.006	
	no	0.98 (0.85, 1.13)		1		.1
adjusted for age and anthropometry	yes	0.78 (0.70, 0.86)	67%	10	.001	
	no	0.94 (0.70, 1.28)		1		.4

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup

There was some evidence of a small-study effect, as shown by the contour-enhanced funnel plot below. This may reflect some publication bias, since the asymmetry tends towards the statistically significant studies.

Figure 4.10 Contour-enhanced funnel plot for publications presenting incident diabetes mellitus type 2 and fibre contained within cereals



### Exposure definition and assessment

The cohort studies included in this meta-analysis were predominantly conducted in the USA and other than one study (Montonen *et al.*, 2003) used FFQs to derive estimates of dietary fibre from cereal foods.

### Adjustment for appropriate confounders

Studies included in the meta-analysis all adjusted for age and gender (where appropriate) and most also for adiposity (generally BMI). Some studies additionally adjusted for dietary fibre from other major food groups. In the Nurse's Health Study II and in EPIC Potsdam, adjustment for other sources of dietary fibre (vegetable, fruit) did not alter the association between cereal fibre and risk of DM (Schulze *et al.*, 2004a; Schulze *et al.*, 2007b). In the Black Women's Study, the inclusion/exclusion of dietary glycaemic index, dietary fat and protein intakes in the model did not alter the point estimates found or statistical significance of the association (Krishnan *et al.*, 2007).

Additional adjustment for biomarkers of inflammation tended to attenuate the association between cereal fibre intake and risk of DM in the British Regional Heart Study (Wannamethee *et al.*, 2009) (data not extracted).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning fibre contained within cereals and incident DM 2.

Table 4.16 Incident diabetes mellitus type 2 and fibre contained within cereals: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
*13340 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(138) /3654	10 years (29)	FFQ (145)	Fibre within cereals g/d	Self-reported diabetes and current use of insulin/oral hypoglycaemic medication, or fasting glucose $\geq 126$ mg/dL (WHO criteria)		Continuous risk estimate	5 g/day	0.96 (0.78, 1.2)	0.742		age, family history of DM, HDL-C, physical activity, gender, smoking, Blood triglyceride
*14239 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Fibre within cereals g/d (AOAC method)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	10 g/day	0.97 (0.79, 1.2)	0.79		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13276 (Krishnan <i>et al.</i> , 2007) Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69 %M 0	(1938) /59000	8 years (20)	FFQ (68)	Fibre within cereals g/d (AOAC method)	Diagnosis criteria not reported Self-reported		(7.6) vs. (1.7)	g/day	0.82 (0.7, 0.96)		0.01	age, BMI, energy intake, family history of DM, fat intake, GI, physical activity, protein intake, smoking
13281			(166) /59000					BMI <25	Q5 vs. Q1		0.41 (0.24, 0.72)		0.003	As above
13282			(1772) /59000					BMI >25	Q5 vs. Q1		0.88 (0.75, 1.04)		0.11	As above
*13768 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not diabetic, Post-menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Fibre within cereals g/d (AOAC method)	Self-reported		>7.5 (9.43) vs. <3.4 (2.66)	g/day	0.64 (0.53, 0.79)		0.0001	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13169 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle-aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Fibre within cereals g/d (AOAC method)	Diagnosis criteria not reported Registry data, WHO criteria		24.5-111 vs. 0.47-12	g/day	0.39 (0.2, 0.77)		0.01	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
*13470 (Salmeron <i>et</i>	USA, Primarily	40-75	(523) /51529	6 years	FFQ (131)	Fibre within cereals g/d	Multiple diagnosis methods		(10.2) vs. (2.5)	g/day	0.7 (0.51, 0.96)		0.007	age, alcohol, BMI, family history of DM, physical activity, smoking

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
<i>al.</i> , 1997a) HPFS	White, Cancer free, No CHD, Not diabetic	%M 100				(AOAC method)	Confirmed self report							
*13573 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(915) /121700	6 years	FFQ (134)	Fibre within cereals g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(7.5) vs. (2)	g/day	0.72 (0.58, 0.9)		0.001	age, alcohol, BMI, family history of DM, physical activity, smoking
*13584 (Schulze <i>et al.</i> , 2007b) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(844) /27548	7 years (9)	FFQ (148)	Fibre within cereals g/d (AOAC method)	Medication Use Confirmed self report		(16.6) vs. (6.6)	g/day	0.73 (0.57, 0.94)		0.02	age, alcohol, waist, BMI, carbohydrate intake, smoking, education, fat intake, physical activity, gender, energy intake
*13538 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) /116671	8 years(< 10)	FFQ (133)	Fibre within cereals g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		>7.3 (8.8) vs. <3.8 (3.1)	g/day	0.64 (0.48, 0.86)		0.004	age, alcohol, BMI, caffeine, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, Hypercholesterolaemia, hypertension, magnesium Intake, oral contraceptive pill, physical activity, smoking, postmenopausal hormone replacement therapy, fibre from other sources
*13258 (Stevens <i>et al.</i> , 2002) ARIC	USA, Multi- ethnic	45-64 (54) %M 44	(Subgrou p cases not reported; total cohort cases 1447) /15792	9 years	FFQ (66)	Fibre within cereals g/d (Energy adjusted fibre intake. AOAC method)	Physician reports, use of diabetic medication, fasting glucose level ≥126 mg/dL or non-fasting glucose level ≥200 mg/dL.	African- American	Continuous risk estimate	1 g/day	0.982 (0.927, 1.039)	0.525		age, BMI, centre, education, physical activity, gender, smoking
*13257 ARIC								Race - White	Continuous risk estimate	1 g/day	0.956 (0.925, 0.987)	0.006		As above
*14100 (Wannameth ee <i>et al.</i> , 2009) British Regional Heart Study	UK, Primarily White, Not diabetic	40-59 %M 100	(162) /7735	7 years (1)	FFQ	Fibre within cereals g/d (Englyst method)	Diagnosis criteria not reported Confirmed self report		High vs. <6.9	g/day	0.7 (0.44, 1.12)			age, alcohol, waist, energy intake, MI, stroke, physical activity, socioeconomic status/class, smoking, Statin use

\*This result was used in the meta-analysis of fibre contained within cereals and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

# Incident diabetes mellitus type 2 and fibre contained within fruits

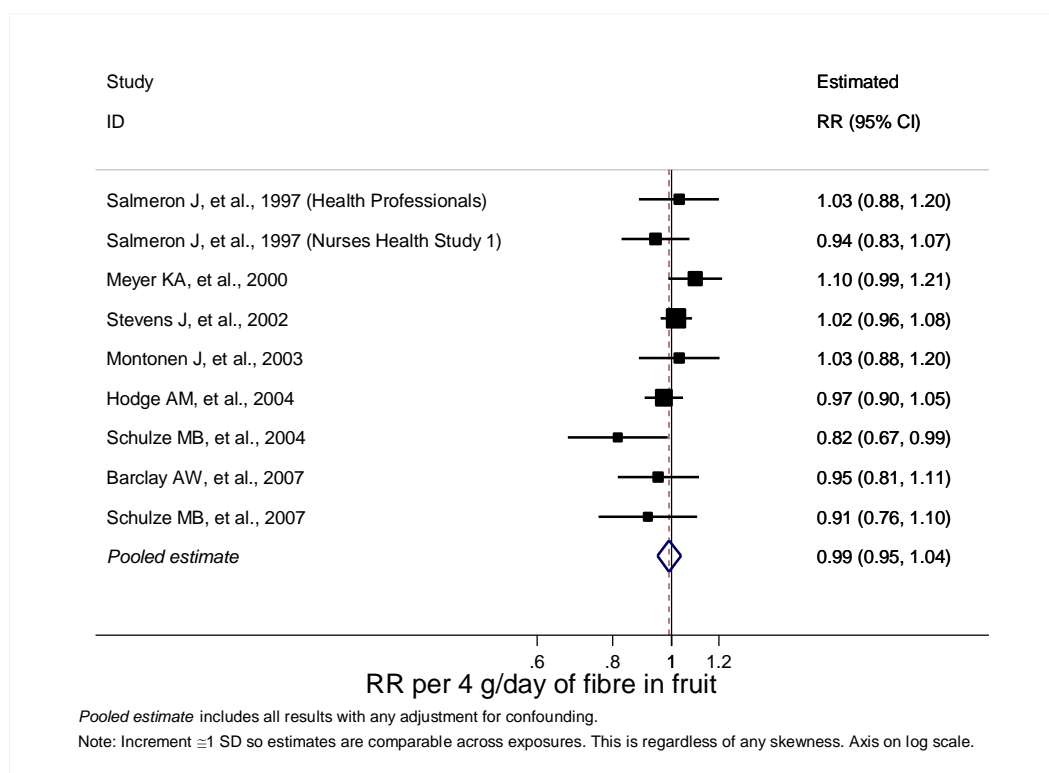
## Summary of cohort results

Data were extracted from nine publications presenting results from the following nine cohort studies: Blue Mountains Eye Study, ARIC, NHS II, EPIC Potsdam, the Finnish Mobile Clinic Health Surveys, the Melbourne Collaborative Cohort Study, the Iowa Women's Health Study, HPFS and NHS (Barclay *et al.*, 2007;Stevens *et al.*, 2002;Schulze *et al.*, 2007b;Hodge *et al.*, 2004;Schulze *et al.*, 2004a;Montonen *et al.*, 2003;Meyer *et al.*, 2000;Salmeron *et al.*, 1997a;Salmeron *et al.*, 1997b). Five of the studies were conducted in the USA, two in Australia and two in Europe (Finland and Germany). All nine studies were included in the meta-analysis. Individually, point estimates comparing the highest against the lowest intake categories tended to be close to or slightly less than one, but none showed a statistically significant association. The Nurses' Health Study II did report a significant test for trend across quantiles, which provides some evidence of reducing risk with increasing fibre from fruit sources (Schulze *et al.*, 2004a).

One paper presented results for two subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Stevens *et al.*, 2002).

The pooled estimate of relative risk from the cohort studies was 0.99 (95% CI: 0.95 to 1.04) per 4g of fibre from fruit per day (p=0.7).

Figure 4.11 Forest plot for fibre contained within fruits and incident diabetes mellitus type 2





There was little heterogeneity between the cohort studies ( $I^2=26\%$  [95% CI: 0% to 66%],  $Q=10.8$ ,  $df=8$ ,  $p=0.2$ ). There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 4.17: Subgroup analyses of fibre in fruit and incidence of diabetes. Relative risks are per 4 g/day.

subgroup	subgroup	RR (95% CI)	$I^2$	n	$P_{het}^*$	$P_{het}^{**}$
subjects' gender	Male	1.03 (0.88, 1.20)		1		.9
	Mixed	0.99 (0.95, 1.04)	0%	5	.7	
	Female	0.96 (0.82, 1.13)	76%	3	.02	
subjects' gender in same study	Male			0		
	Female			0		
method used to assess fibre	AOAC	0.99 (0.95, 1.04)	26%	9	.2	
	not AOAC			0		
length of follow-up	<10 years	0.99 (0.94, 1.04)	42%	7	.1	
	$\geq 10$ years	0.99 (0.89, 1.11)	0%	2	.5	1
geographic location	Americas	1.00 (0.93, 1.08)	53%	5	.07	
	EU	0.98 (0.87, 1.11)	0%	2	.3	
	Other	0.97 (0.91, 1.03)	0%	2	.8	.8
adjusted for age	yes	0.99 (0.95, 1.04)	26%	9	.2	
	no			0		
adjusted for alcohol	yes	0.98 (0.91, 1.05)	47%	6	.09	
	no	1.01 (0.96, 1.07)	0%	3	.7	.6
adjusted for anthropometry	yes	0.99 (0.95, 1.04)	33%	8	.2	
	no	0.95 (0.81, 1.11)		1		.7
adjusted for energy intake	yes	0.98 (0.90, 1.07)	56%	5	.06	
	no	1.00 (0.96, 1.05)	0%	4	.6	.9
adjusted for family history	yes	0.96 (0.91, 1.01)	0%	5	.4	
	no	1.03 (0.98, 1.08)	4%	4	.4	.09
adjusted for physical activity	yes	0.99 (0.94, 1.04)	34%	8	.2	
	no	1.03 (0.88, 1.20)		1		.7
adjusted for gender	yes	0.99 (0.95, 1.04)	26%	9	.2	
	no			0		
adjusted for smoking	yes	0.99 (0.94, 1.05)	31%	8	.2	
	no	0.97 (0.90, 1.05)		1		.7
adjusted for age and anthropometry	yes	0.99 (0.95, 1.04)	33%	8	.2	
	no	0.95 (0.81, 1.11)		1		.7

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup

There were insufficient studies to explore small-study bias such as publication bias through funnel plots or hypothesis tests.

### ***Exposure definition and assessment***

The cohort studies included in this meta-analysis were predominantly conducted in the USA and other than the Finnish Mobile Clinic Health Surveys study (Montonen *et al.*, 2003) used FFQs to derive estimates of dietary fibre from fruit. It is not clear from the methods sections of papers whether the fruit component of mixed, or recipe dishes has been used to derive the amount of dietary fibre from fruit.

### ***Adjustment for appropriate confounders***

Studies included in the meta-analysis all adjusted for age and gender (where appropriate) and most also for adiposity (generally BMI), the exception being the Blue Mountains Eye Study (Barclay *et al.*, 2007). This potential incomplete adjustment for confounding could generate a bias in the estimate of risk. The bias could be large in size, and act in either direction, either towards or away from the null. The Finnish Mobile Clinic Health Surveys study (Montonen *et al.*, 2003) adjusted for fruit, berries and vegetables, but not for fibre intake from non-fruit sources specifically. In the ARIC study, the authors commented in the text that the additional inclusion of cereal fibre in the model did not alter the point estimates found (Stevens *et al.*, 2002).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning fibre contained within fruits and incident DM 2.

Table 4.18 Incident diabetes mellitus type 2 and fibre contained within fruits: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
*13341 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65)  %M 44	(138) / 3654	10 years (29)	FFQ (145)	Fibre within fruit g/d	Self-reported diabetes and current use of insulin/oral hypoglycaemic medication, or fasting glucose ≥126 mg/dL(WHO criteria)		Continuous risk estimate	5 g/day	0.94 (0.78, 1.15)	0.566		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglycerides
*14240 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54)  %M 41.1	(365) / 41528	4 years (14)	FFQ (121)	Fibre within fruit g/d (AOAC method)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	10 g/day	0.93 (0.77, 1.11)	0.4		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13769 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61)  %M 0	(1141) / 41836	6 years (21)	FFQ (127)	Fibre within fruit g/d (AOAC method)	Self-reported		>7.02- (8.72) vs. <2.55 (1.71)	g/day	1.17 (0.96, 1.42)		0.081	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist hip ratio
*13170 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle- aged adults, Not diabetic	40-69  %M 53	(156) / 4316	10 years	Dietary history	Fibre within fruit g/d (AOAC method)	Diagnosis criteria not reported Registry data, WHO criteria		3.4-36.8 vs. 0-0.99	g/day	0.92 (0.4, 2.13)		0.87	age, BMI, energy intake, Fruit intake, region, gender, smoking, vegetable intake, intake of berries
*13471 (Salmeron <i>et al.</i> , 1997a) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75  %M 100	(523) / 51529	6 years	FFQ (131)	Fibre within fruit g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(8.3) vs. (1.2)	g/day	1.01 (0.76, 1.36)		0.68	age, alcohol, BMI, family history of DM, physical activity, smoking

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
*13571 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(915) / 121700	6 years	FFQ (134)	Fibre within fruit g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(7.6) vs. (1.4)	g/day	0.87 (0.7, 1.08)		0.39	age, alcohol, BMI, family history of DM, physical activity, smoking
*13540 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) / 116671	8 years (<10)	FFQ (133)	Fibre within fruit g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		>4.8 (6.2) vs. <1.6 (1.1)	g/day	0.79 (0.6, 1.02)		0.040	age, alcohol, BMI, caffeine, cereal fibre, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, Hypercholesterolaemia, hypertension, magnesium Intake, oral contraceptive pill, physical activity, smoking, postmenopausal hormone replacement therapy, fibre from other sources
*13596 (Schulze <i>et al.</i> , 2007b) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(844) / 27548	7 years (9)	FFQ (148)	Fibre within fruit g/d (AOAC method)	Medication Use Confirmed self report		(4.7) vs. (0.2)	g/day	0.89 (0.71, 1.13)		0.36	age, alcohol, waist, BMI, smoking, education, physical activity, gender, EI
*13260 (Stevens <i>et al.</i> , 2002) ARIC	USA, Multi- ethnic	45-64 (54) %M 44	(Sub-group cases not reported; total cohort cases 1447) / 15792	9 years	FFQ (66)	Fibre within fruit g/d (Energy adjusted fibre intake. AOAC method)	Physician reports, use of diabetic medication, fasting glucose level ≥126 mg/dL or non- fasting glucose level ≥200 mg/dL.	African- American	Continuous risk estimate	1 g/day	1.009 (0.985, 1.033)	0.479		age, BMI, centre, education, physical activity, gender, smoking
*13259 ARIC			(Sub-group cases not reported)					Race - White	Continuous risk estimate	1 g/day	1.002 (0.983, 1.021)	0.841		age, BMI, centre, education, physical activity, gender, smoking

\*This result was used in the meta-analysis of fibre contained within fruits and Incident DM 2

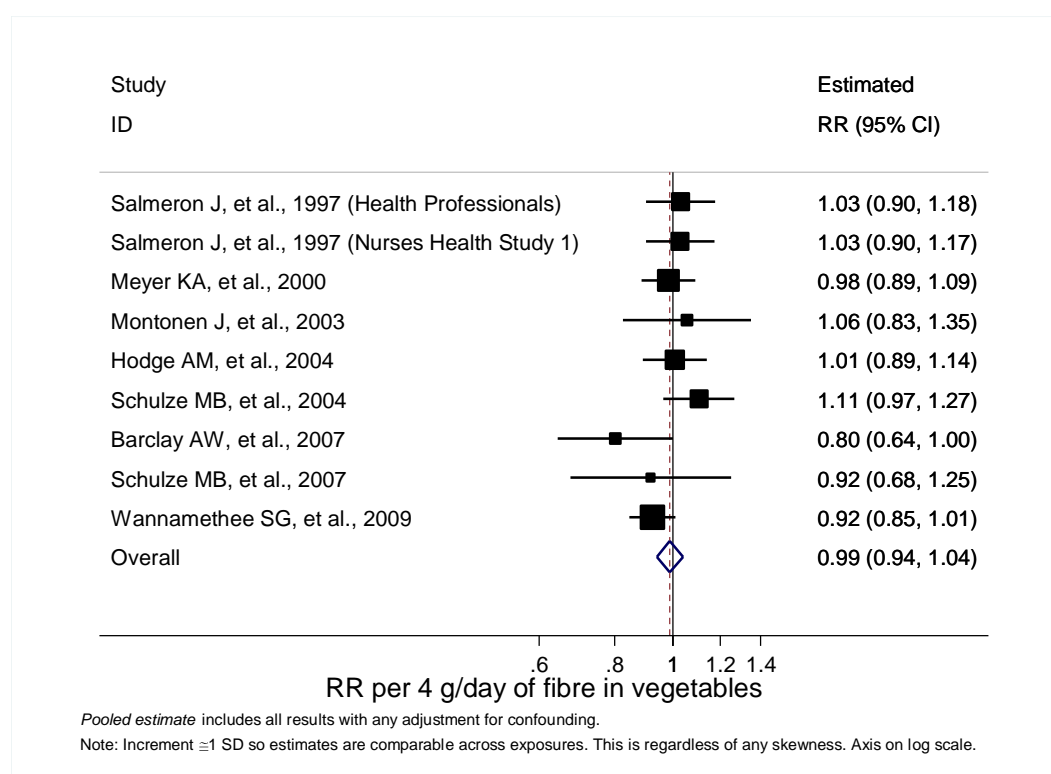
# Incident diabetes mellitus type 2 and fibre contained within vegetables and potatoes

## Summary of cohort results

Data were extracted from nine publications presenting results from nine cohort studies: the Blue Mountains Eye Study, EPIC Potsdam, NHS II, the Finnish Mobile Clinic Health Surveys, the Melbourne Collaborative Cohort Study, the Iowa Women's Health Study, the British Regional Heart Study, NHS and HPFS (Barclay *et al.*, 2007; Schulze *et al.*, 2007b; Hodge *et al.*, 2004; Wannamethee *et al.*, 2009; Schulze *et al.*, 2004a; Montonen *et al.*, 2003; Meyer *et al.*, 2000; Salmeron *et al.*, 1997a; Salmeron *et al.*, 1997b). Four studies were conducted in the USA, two in Australia and three in Europe (UK, Germany and Finland). All nine studies were included in the meta-analysis. So that one paper could be included in the meta-analysis, we assumed that the median intake of the lowest exposure category was half the upper limit of that category, and that the median intake of the upper exposure category was 1.5 times the lower limit of that category, and these based on the assumption that quartiles of vegetable fibre intake are in proportion to the quartiles for total fibre intake (Wannamethee *et al.*, 2009).

The pooled estimate of relative risk from the cohort studies was 0.99 (95% CI: 0.94 to 1.04) per 4 g of fibre from vegetables per day (p=0.7).

Figure 4.12 Forest plot for fibre contained within vegetables and incident diabetes mellitus type 2



There was very little heterogeneity between the cohort studies ( $I^2=16\%$  [95% CI: 0% to 58%],  $Q=9.5$ ,  $df=8$ ,  $p=0.3$ ).

There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 4.19: Subgroup analyses of fibre in vegetables and incidence of diabetes. Relative risks are per 4 g/day.

Subgroup	subgroup	RR (95% CI)	$I^2$	n	$P_{het}^*$	$P_{het}^{**}$
subjects' gender	Male	0.97 (0.87, 1.07)	44%	2	.2	.5
	Mixed	0.96 (0.86, 1.07)	20%	4	.3	
	Female	1.03 (0.96, 1.10)	0%	3	.4	
method used to assess fibre	AOAC	1.01 (0.96, 1.06)	0%	8	.5	
	not AOAC	0.92 (0.85, 1.01)		1		.1
length of follow-up	<10 years	0.99 (0.95, 1.04)	0%	7	.4	
	$\geq 10$ years	0.92 (0.70, 1.20)	62%	2	.1	.5
geographic location	Americas	1.03 (0.97, 1.09)	0%	4	.6	
	EU	0.94 (0.87, 1.02)	0%	3	.6	
	Other	0.92 (0.74, 1.14)	68%	2	.08	.7
adjusted for age	yes	0.99 (0.94, 1.04)	16%	9	.3	
	no			0		
adjusted for alcohol	yes	0.99 (0.95, 1.04)	0%	7	.4	
	no	0.92 (0.70, 1.20)	62%	2	.1	.3
adjusted for anthropometry	yes	1.00 (0.95, 1.04)	0%	8	.5	
	no	0.80 (0.64, 1.00)		1		.1
adjusted for energy intake	yes	0.99 (0.93, 1.04)	7%	6	.4	
	no	0.97 (0.86, 1.11)	52%	3	.1	.9
adjusted for family history	yes	1.01 (0.94, 1.10)	33%	5	.2	
	no	0.96 (0.90, 1.02)	0%	4	.7	.2
adjusted for physical activity	yes	0.99 (0.94, 1.04)	24%	8	.2	
	no	1.06 (0.83, 1.35)		1		.6
adjusted for gender	yes	0.99 (0.94, 1.04)	16%	9	.3	
	no			0		
adjusted for smoking	yes	0.99 (0.93, 1.05)	26%	8	.2	
	no	1.01 (0.89, 1.14)		1		.8
adjusted for age and anthropometry	yes	1.00 (0.95, 1.04)	0%	8	.5	
	no	0.80 (0.64, 1.00)		1		.1

\*  $P$  for heterogeneity within each subgroup

\*\*  $P$  for heterogeneity between each subgroup

There were insufficient studies to explore small-study bias such as publication bias through funnel plots.

One cohort study only provided data on risk of DM in relation to dietary fibre derived from potatoes (Hodge *et al.*, 2004). There was no evidence of any association.

### ***Exposure definition and assessment***

The cohort studies included in this meta-analysis, other than the Finnish Mobile Clinic Health Surveys study (Montonen *et al.*, 2003), used FFQs to derive estimates of dietary fibre from vegetables. It is not clear from the methods sections of studies whether the vegetable component of mixed, or recipe dishes has been used to derive the amount of dietary fibre from vegetables. Additionally, the food group classifications used in studies may vary, with some studies including legumes within the vegetable category (as in the study by Barclay and colleagues (Barclay *et al.*, 2007). Estimates for fibre contained within vegetables may or may not include fibre derived from potatoes. This detail was only reported in the Melbourne collaborative cohort study which reported that fibre from potatoes was not included (Hodge *et al.*, 2004).

This means it is difficult to separate any protective effect of vegetable fibre from the potential influence related to consumption of legumes or potatoes.

### ***Adjustment for appropriate confounders***

Studies included in the meta-analysis all adjusted for age and gender (where appropriate) and most also for adiposity (generally BMI). The exception being the Blue Mountains Eye Study (Barclay *et al.*, 2007), which did not include BMI in the list of adjustments in the model. Some studies additionally adjusted for dietary fibre from other major food groups. In the Nurse's Health Study II and in EPIC Potsdam adjustment for other sources of dietary fibre did not alter the association between vegetable fibre and risk of DM (Schulze *et al.*, 2004a; Schulze *et al.*, 2007b).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning fibre contained within vegetables and potatoes and incident DM 2.



Table 4.20 Incident diabetes mellitus type 2 and fibre contained within vegetables and potatoes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/Tot al	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
*13342 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65) %M 44	(138) / 3654	10 years (29)	FFQ (145)	Fibre within vegetables g/d	Self-reported diabetes and current use of insulin/oral hypoglycaemic medication, or fasting glucose $\geq 126$ mg/dL (WHO criteria)		Continuous risk estimate	5 g/day	0.76 (0.57, 0.99)	0.048		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglyceride
13343			(Sub-group cases not reported; total cohort cases 138) / 3654					Age <70	Continuous risk estimate	5 g/day	0.78 (0.56, 1.07)	0.123		age, family history of DM, HDL-C, physical activity, gender, smoking, Blood triglyceride
13344			As above					Age >70	Continuous risk estimate	5 g/day	0.69 (0.4, 1.21)	0.199		age, family history of DM, HDL-C, physical activity, gender, smoking, Blood triglyceride
*14241 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) / 41528	4 years (14)	FFQ (121)	Fibre within vegetables g/d (AOAC method)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	5 g/day	1.01 (0.87, 1.18)	0.89		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13770 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not diabetic, Post-menopausal	55-69 (61) %M 0	(1141) / 41836	6 years (21)	FFQ (127)	Fibre within vegetables g/d (AOAC method)	Self-reported		>10.14 (11.74) vs. <5.75 (4.71)	g/day	0.97 (0.8, 1.18)		0.77	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/Tot al	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
*13171 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle- aged adults, Not diabetic	40-69 %M 53	(156) / 4316	10 years	Dietary history	Fibre within vegetables g/d (AOAC method)	Diagnosis criteria not reported Registry data, WHO criteria		6.8-26.5 vs. 0.11-3.7	g/day	0.19 (0.46, 3.04)		0.86	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
*13472 (Salmeron <i>et al.</i> , 1997a) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(523) / 51529	6 years	FFQ (131)	Fibre within vegetables g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(11.3) vs. (3.5)	g/day	1.12 (0.84, 1.49)		0.65	age, alcohol, BMI, family history of DM, physical activity, smoking
*13572 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(915) / 121700	6 years	FFQ (134)	Fibre within vegetables g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		(9.6) vs. (3.4)	g/day	1.17 (0.93, 1.46)		0.54	age, alcohol, BMI, family history of DM, physical activity, smoking
*13603 (Schulze <i>et al.</i> , 2007b) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(844) / 27548	7 years (9)	FFQ (148)	Fibre within vegetables g/d (AOAC method)	Medication Use Confirmed self report		(3.4) vs. (0.7)	g/day	0.93 (0.75, 1.17)		0.64	age, alcohol, waist, BMI, smoking, education, physical activity, gender, energy intake
*13539 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) / 116671	8 years (<10)	FFQ (133)	Fibre within vegetables g/d (AOAC method)	Multiple diagnosis methods Confirmed self report		>8.6 (10.4) vs. <4.2 (3.4)	g/day	1.12 (0.87, 1.46)		0.192	age, alcohol, BMI, caffeine, cereal fibre, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, Hypercholesterolaemia, hypertension, magnesium intake, oral contraceptive pill, physical activity, smoking, postmenopausal hormone replacement therapy, fibre from other sources
*14101 (Wannameth <i>et al.</i> , 2009) British Regional Heart Study	UK, Primarily White, Not diabetic	40-59 %M 100	(169) / 7735	7 years (1)	FFQ	Fibre within vegetables g/d (Englyst method)	Diagnosis criteria not reported Confirmed self report		High vs. <11.3	g/day	0.74 (0.46, 1.19)			age, alcohol, waist, energy intake, Myocardial infarction, stroke, physical activity, socioeconomic status/class, smoking, Statin use

This document was prepared for consideration by the Scientific Advisory Committee on Nutrition. It does not necessarily represent the final views of SACN or the advice/policy of Public Health England and Health Departments.

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
14242 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) / 41528	4 years (14)	FFQ (121)	Fibre within potatoes g/d (AOAC method)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	1 g/day	1.04 (0.92, 1.17)	0.57		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change

\*This result was used in the meta-analysis of fibre contained within vegetables and Incident DM 2

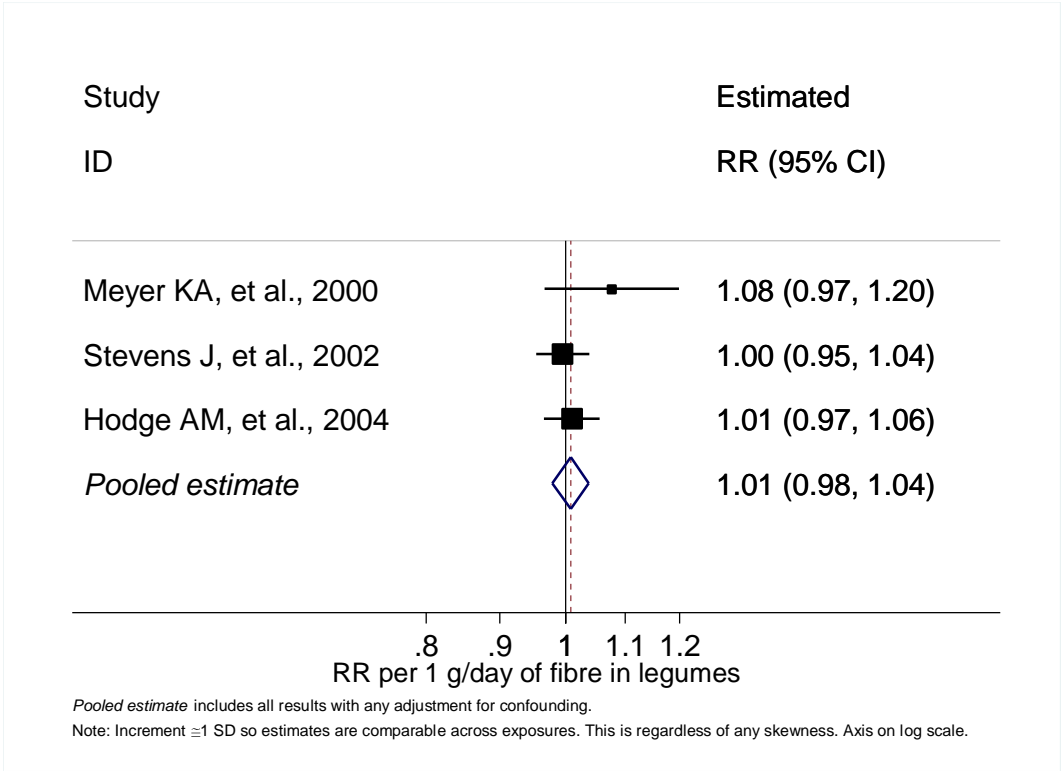
# Incident diabetes mellitus type 2 and fibre contained within legumes

## Summary of cohort results

Data were extracted from three publications presenting results from three cohort studies, namely ARIC, the Iowa Women’s Health Study and the Melbourne Collaborative Cohort Study (Stevens *et al.*, 2002;Hodge *et al.*, 2004;Meyer *et al.*, 2000). All three studies that provide risk estimates for fibre intakes from legumes were included in the meta-analysis. One paper presented results for two subgroups, but not overall. These two results were first combined using a fixed effects meta-analysis before combining with the other studies in a random effects meta-analysis (Stevens *et al.*, 2002).

The pooled estimate of relative risk from the cohort studies was 1.01 (95% CI: 0.98 to 1.04) per 1g of fibre from legumes per day (p=0.6).

Figure 4.13 Forest plot for fibre contained within legumes and incident diabetes mellitus type 2



There was no excess heterogeneity between the cohort studies ( $I^2=0\%$  [95% CI: 0% to 88%],  $Q=1.8$ ,  $df=2$ ,  $p=0.4$ ).

There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. No single study had a dominant influence on the pooled estimate. There were insufficient studies to explore any small-study effect such as publication bias.

### ***Exposure definition and assessment***

All three cohort studies assessed dietary fibre intakes derived from legumes through analysis of FFQ data.

### ***Adjustment for appropriate confounders***

All three cohort studies adjusted for age, gender (where appropriate) and BMI or weight change. In the ARIC study, the authors commented in the text that the additional inclusion of cereal fibre in the model did not alter the point estimates found (Stevens *et al.*, 2002). The other 2 cohort studies did not adjust for other sources of dietary fibre.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning fibre contained within legumes and incident DM 2.

Table 4.21 Incident diabetes mellitus type 2 and fibre contained within legumes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
*14243 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Fibre within legumes g/d (AOAC method)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	1 g/day	1.01 (0.97, 1.06)	0.62		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13771 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Fibre within legumes g/d (AOAC method)	Self-reported		>1.21 (1.74) vs. <0.31 (0.095)	g/day	1.1 (0.91, 1.33)		0.17	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13261 (Stevens <i>et al.</i> , 2002) ARIC	USA, Multi- ethnic	45-64 (54) %M 44	(Subgroup cases not reported; total cohort cases 1447) /15792	9 years	FFQ (66)	Fibre within legumes g/d (Energy adjusted fibre intake. AOAC method)	Physician reports, use of diabetic medication, fasting glucose level $\geq 126$ mg/dL or non- fasting glucose level $\geq 200$ mg/dL.	Race - White	Continuous risk estimate	1 g/day	1.007 (0.959, 1.058)		0.774	age, BMI, centre, education, physical activity, gender, smoking
*13262 ARIC								African- American	Continuous risk estimate	1 g/day	0.961 (0.882, 1.047)		0.366	As above

\*This result was used in the meta-analysis of fibre contained within legumes and Incident DM 2

# Incident diabetes mellitus type 2 and soluble and insoluble fibre

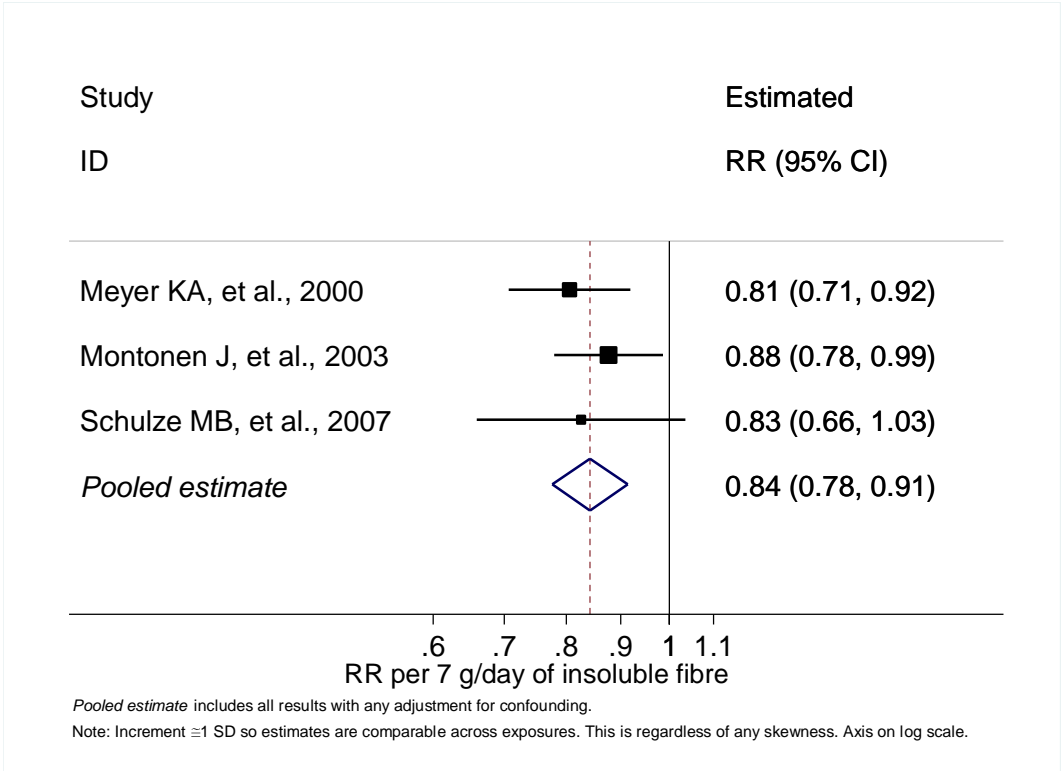
## Summary of cohort results

Data were extracted from three publications presenting results from the following three cohort studies: EPIC Potsdam, the Finnish Mobile Clinic Health Surveys and the Iowa Women’s Health Study (Schulze *et al.*, 2007b;Montonen *et al.*, 2003;Meyer *et al.*, 2000). These studies were conducted in Germany, Finland and the USA.

Two meta-analyses were conducted, for insoluble and soluble dietary fibre respectively and all three studies were included in both the meta-analyses.

The pooled estimate of relative risk from the cohort studies was 0.84 (95% CI: 0.78 to 0.91) per 7g of insoluble fibre per day (p<0.001).

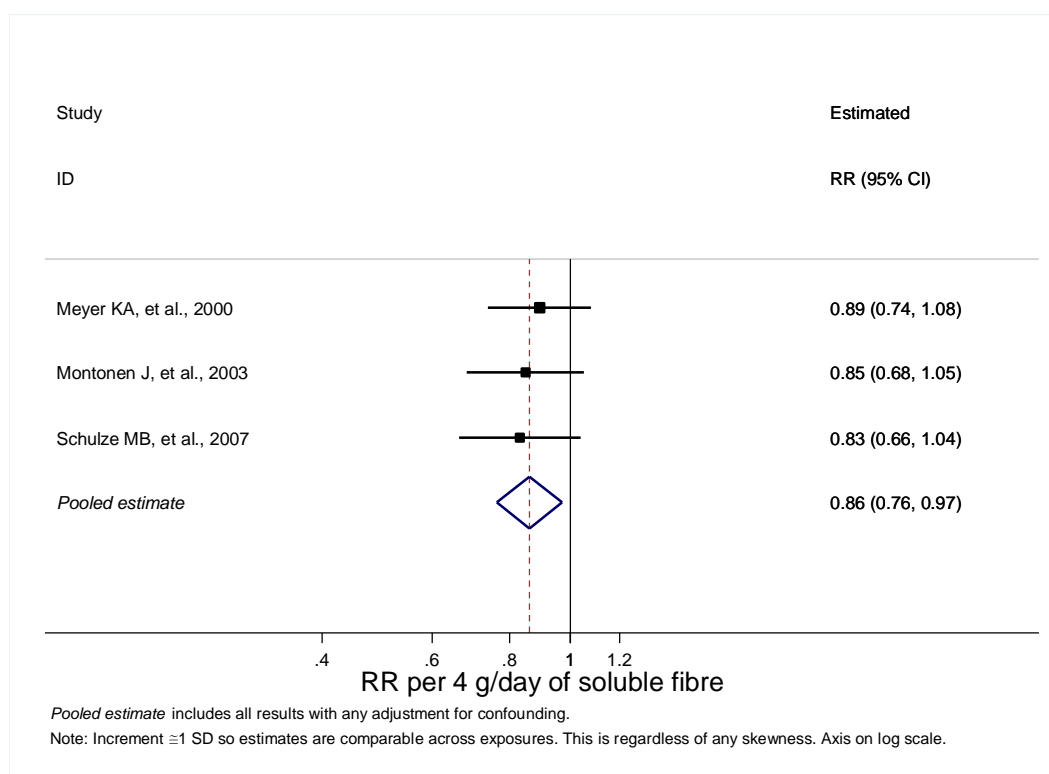
Figure 4.14 Forest plot for insoluble fibre and incident diabetes mellitus type 2



There was no excess heterogeneity between the cohort studies ( $I^2=0\%$  [95% CI: 0% to 78%],  $Q=0.9$ ,  $df=2$ ,  $p=0.6$ ).

The pooled estimate of relative risk from the cohort studies was 0.86 (95% CI: 0.76 to 0.97) per 4 g of soluble fibre per day (p=0.01).

Figure 4.15 Forest plot for soluble fibre and incident diabetes mellitus type 2



There was no excess heterogeneity between the cohort studies ( $I^2=0\%$  [95% CI: 0% to 18%],  $Q=0.3$ ,  $df=2$ ,  $p=0.9$ ).

For both meta-analyses, there were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. No single study had a dominant influence on the pooled estimate. There were insufficient studies to explore any small-study effect such as publication bias.

### Exposure definition and assessment

Insoluble dietary fibre (insoluble in water) includes hemicellulose, cellulose and lignin. Foods that are rich sources of insoluble dietary fibre include whole grain breakfast cereals, and certain vegetables such as celery and carrots. Food sources rich in soluble dietary fibre components include legumes (beans and lentils), vegetables (such as brassicas), and fruits (such as apples and berries). Two cohorts assessed dietary fibre intakes through FFQs (Schulze *et al.*, 2007b; Meyer *et al.*, 2000), and one, the Finnish Mobile Clinic Health Surveys, through the dietary history method (Montonen *et al.*, 2003).



### ***Adjustment for appropriate confounders***

All three cohort studies adjusted for age, gender (where appropriate) and BMI or weight change. Some studies additionally adjusted for dietary fibre from other major food groups. In the EPIC Potsdam study the association with soluble fibre became attenuated with additional adjustment for insoluble fibre intake (RR, 0.83; 95% CI, 0.57-1.22) (Schulze *et al.*, 2007b). Insoluble fibre intake was not associated with DM risk either with or without inclusion of soluble fibre intake in the model. In the other cohort studies, risk estimates were not provided with and without inclusion of soluble/insoluble fibre in the model.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning soluble and insoluble fibre and incident DM 2.

Table 4.22 Incident diabetes mellitus type 2 and soluble/ insoluble fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
*13767 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Insoluble fibre (AOAC method) g/day	Self-reported	>17.7 (19.84) vs. <11.4 (9.93)	g/day	0.75 (0.61, 0.91)	0.0012	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13166 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle-aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Insoluble Non- cellulose polysaccharides. (AOAC method g/day)	Diagnosis criteria not reported Registry data, WHO criteria	16.6-69.3 vs. 1.1-8.7	g/day	0.47 (0.25, 0.91)	0.03	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
13167						Cellulose (AOAC method)		5.4-15.2 vs. 0.48-3.2	g/day	0.6 (0.29, 1.12)	0.19	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
13168						Lignin (AOAC method) g/day		4.2-14.5 vs. 0.48-2.3	g/day		0.16	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
*13582 (Schulze <i>et al.</i> , 2007b) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(844) /27548	7 years (9)	FFQ (148)	Insoluble fibre (AOAC method) g/day	Medication Use Confirmed self report	(18.4) vs. (10.3)	g/day	0.82 (0.61, 1.08)	0.1	age, alcohol, waist, BMI, carbohydrate intake, smoking, education, fat intake, physical activity, gender, EI
*13766 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Soluble fibre (AOAC method) g/day	Self-reported	>7.2 (8.01) vs. <4.8 (4.19)	g/day	0.89 (0.73, 1.08)	0.23	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
*13165 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle-aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Soluble fibre (AOAC method) g/day	Diagnosis criteria not reported Registry data, WHO criteria	7.4-22.7 vs. 0.53-4.5	g/day	0.57 (0.29, 1.12)	0.21	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
*13581 (Schulze <i>et al.</i> , 2007b) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(844) /27548	7 years (9)	FFQ (148)	Soluble fibre (AOAC method) g/day	Medication Use Confirmed self report	(9.6) vs. (5.3)	g/day	0.78 (0.6, 1.01)	0.09	age, alcohol, waist, BMI, carbohydrate intake, smoking, education, fat intake, physical activity, gender, energy intake

\*This result was used in the meta-analysis of insoluble/ soluble fibre and Incident DM 2

## **Incident diabetes mellitus type 2 and nutrient-based dietary patterns**

### **Summary of cohort results**

Information from one publication on the Nurse's Health Study provided evidence concerning the long term effects of low carbohydrate diets on risk of developing DM (Halton *et al.*, 2008). This was approached through the derivation of a low-carbohydrate-diet score which was based on the percentage of energy as carbohydrate, fat, and protein in the diets of the 85,059 female participants. The higher the score, the more closely the participant followed a low carbohydrate diet. The authors concluded that there was no evidence that diets lower in carbohydrate and higher in fat and protein increase the risk of DM, and that replacing carbohydrate with protein or fat of vegetable, rather than animal origin may reduce risk.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning nutrient-based dietary patterns and incident DM 2.

Table 4.23 Incident diabetes mellitus type 2 and nutrient-based dietary patterns: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
16982 (Halton <i>et al.</i> , 2008) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4670) /121700	20 years	FFQ (127)	Low carbohydrate diet score (estimated by total carbohydrate, animal protein and animal fat)	Multiple diagnosis methods American diabetes association Criteria, Multiple methods of diagnosis	(27) vs. (4.3)	units	0.99 (0.85, 1.16)	1.0	age, alcohol, BMI, family history of DM, hormone replacement therapy, physical activity, smoking
16981 NHS						Low carbohydrate diet score (estimated by total carbohydrate, protein and fat)		23.5-30 (26) vs. 0-7 (5)	units	0.9 (0.78, 1.04)	0.26	As above
16983 NHS						Low carbohydrate diet score (estimated by total carbohydrate, vegetable protein and vegetable fat)		(21.8) vs. (8)	units	0.82 (0.71, 0.94)	0.001	As above

## **Incident diabetes mellitus type 2 and foods rich in added sugars**

### **Summary of cohort results**

Two cohort studies conducted in Finland and Australia reported risk of DM in association with consumption of sugary foods, table sugar and preserves (Hodge *et al.*, 2004; Montonen *et al.*, 2007). The Finnish Mobile Clinic Health Surveys study reported a weak increase in risk associated with increasing consumption of preserves in one publication after 12 years follow-up (Montonen *et al.*, 2007). No association with this dietary exposure was found however, in a later analysis after 23 years follow-up (Montonen *et al.*, 2005). The Melbourne Collaborative Cohort Study reported no association with consumption of sweet snack foods, which included fruit bread, crackers, biscuits, cakes and puddings (Hodge *et al.*, 2004).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning added sugar and incident DM 2.

Table 4.24 Incident diabetes mellitus type 2 and added sugar: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14225 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Sweet snack foods (Fruit bread, crackers or crisp breads, sweet biscuits, cakes/sweet pastries, puddings)	Fasting serum/blood glucose, Glucose (random) Clinic tested	Continuous risk estimate	1 serving/week	0.98 (0.96, 1)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13243 (Montonen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(177) /10054	12 years	Dietary history	Jam and marmalade	Diagnosis criteria not reported Registry data	(32) vs. (0)	g/day	1.39 (0.89, 2.18)	0.06	age, BMI, diet pattern- conservative, diet pattern- prudent, energy intake, family history of DM, region, physical activity, gender, smoking
13244						Extrinsic sugar syrups- Honey and other syrup		Consumers (2) vs. non consumers (0)	g/day	0.8 (0.56, 1.14)	0.21	As above
13245						Table sugar		(48) vs. (5)	g/day	0.59 (0.34, 1.02)	0.08	As above
13255 (Montonen <i>et al.</i> , 2005) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(383) /10054	23 years	Dietary history	Jam and sugar rich condiments	Diagnosis criteria not reported Registry data	>70 vs. <31	g/day	0.97 (0.69, 1.36)	0.88	age, BMI, energy intake, family history of DM, region, gender, smoking

## **Incident diabetes mellitus type 2 and starchy foods**

### **Summary of cohort results**

Two cohort studies conducted in China and Australia reported risk of DM in association with consumption of starchy foods (Hodge *et al.*, 2004; Villegas *et al.*, 2007). In the Shanghai Women's Health Study, increasing consumption of starchy roots and cereals was associated with a reduction in risk of DM, whereas an increased risk was observed for starchy cereal-based foods excluding vegetable roots (Villegas *et al.*, 2007). The Melbourne Collaborative Cohort Study reported an increased risk of DM with increasing consumption of starchy snacks, which included pizza, dim sum, pies and savoury pastries (Hodge *et al.*, 2004).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning starchy foods and incident DM 2.

Table 4.25 Incident diabetes mellitus type 2 and starchy foods: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	Adjustments
14223 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Starchy snacks, Savoury starch-based snacks (Pizza, dim sum/spring rolls, pies/savoury pastries)	Fasting serum/blood glucose, Glucose (random) Clinic tested	Continuous risk estimate	1 serving/week	1.23 (1, 1.51)	age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13069 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle-aged adults, No CHD, Normal glucose tolerance	40-70 %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Starchy foods (rice, noodles, steamed bread and bread)	Fasting serum/blood glucose American diabetes association criteria, Confirmed self report	Q5 vs. Q1		1.37 (1.11, 1.69)	age, alcohol, BMI, energy intake, income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13071 Shanghai Women's Health Study						Starchy roots (tubers, plantain, total rice, noodles, steamed bread and bread)		Q5 vs. Q1		0.67 (0.58, 0.78)	As above



## **Incident diabetes mellitus type 2 and total cereals/grains**

### **Summary of cohort results**

Four cohort studies conducted in Finland, Australia and the USA reported risk of DM in association with consumption of total cereal and/or total grains (refined and wholegrain combined) (Hodge *et al.*, 2004; Montonen *et al.*, 2007; Liu *et al.*, 2000a; Meyer *et al.*, 2000). The Finnish Mobile Clinic Health Surveys study reported a strong decrease in risk associated with increasing consumption of total grains (whole and refined) (Montonen *et al.*, 2003), but no association with grains excluding wheat and rye in a later publication after 23 years follow-up (Montonen *et al.*, 2005). The Iowa Women's Health Study (Meyer *et al.*, 2000) also reported a reduced risk of DM in women with a high consumption of total grains (whole and refined) (RR for extreme categories 0.68, 95% CI: 0.54, 0.87,  $p < 0.001$ ), and a similar finding was reported from the Nurse's Health Study (RR for extreme quintiles 0.75, 95% CI: 0.63, 0.89) (Liu *et al.*, 2000a).

The Melbourne Collaborative Cohort Study reported no association with DM and total cereal food consumption, which included bread, breakfast cereals, pasta, rice, biscuits, cakes and puddings (Hodge *et al.*, 2004).

Meta-analysis for total cereals and DM was not undertaken as the exposures varied excessively between cohorts.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning total cereals and grains and incident DM 2.

Table 4.26 Incident diabetes mellitus type 2 and total cereals/grains: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14206 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Total cereals: Wheat germ; breakfast cereal; rice; all bread; crackers; sweet biscuits; cakes/sweet pastries; puddings; pasta/noodles; pizza; dim sum/spring rolls; pies/savoury pastries	Fasting serum/blood glucose, Glucose (random) Clinic tested	Continuous risk estimate	1 serving/week	1 (0.99, 1.01)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13416 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Total Grains, whole and refined (dark bread, whole- grain breakfast cereal, popcorn, cooked oatmeal, wheat germ. Brown rice, bran, other grains (bulgur, kasha, couscous and refined grain))	Self reported, and confirmed by the National Diabetes Data Group	Q5 vs. Q1		0.75 (0.63, 0.89)	0.005	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, Vitamin intake
13772 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Total Grains (whole and refined)	Self-reported	>33 (41.5) vs. <13 (9.5)	g/day	0.68 (0.54, 0.87)	0.0011	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
13253 (Montonen <i>et al.</i> , 2005) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(383) /10054	23 years	Dietary history	Grains, (except wheat and rye)	Diagnosis criteria not reported Registry data	>29 vs. <10	g/day	1.2 (0.86, 1.66)	0.56	age, BMI, energy intake, family history of DM, region, gender, smoking
13146 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle- aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Total Grains (whole and refined)	Diagnosis criteria not reported Registry data, WHO criteria	340-1535 vs. 10-181	g/day	0.38 (0.19, 0.77)	0.001	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake

## Incident diabetes mellitus type 2 and bread

### Summary of cohort results

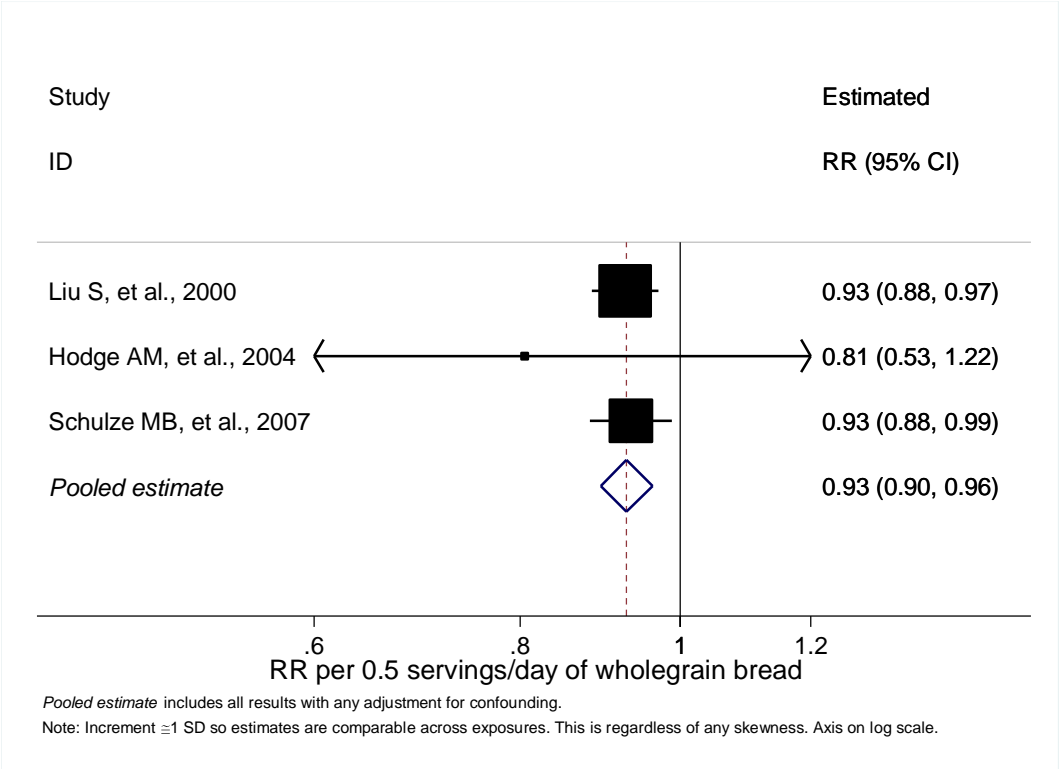
Four cohort studies, namely EPIC Norfolk (Simmons *et al.*, 2007), EPIC Potsdam (Schulze *et al.*, 2007a), the Melbourne Collaborative Cohort Study (Hodge *et al.*, 2004) and NHS (Liu *et al.*, 2000a), provided data on bread consumption in relation to risk of DM. These studies were conducted in the UK, the USA, Germany and Australia. The Australian Study (Hodge *et al.*, 2004) provided risk estimates associated with all bread types combined (no association), white bread or rolls (increased risk with consumption) and wholemeal bread (wheat or rye – no association). The other cohort studies provided data on wholegrain or dark bread (USA), wholegrain bread (Germany) and wholegrain bread (wholemeal and brown bread in the UK), so there was some variation in types of bread collectively categorised as wholegrain. These latter cohort studies consistently provided evidence of decreased risk of DM with increasing consumption.

Results from three of four cohorts were included in the meta-analysis of wholegrain bread and diabetes

The EPIC Norfolk study could not be included because the exposure was dichotomised, so could not provide a dose-response trend (Simmons *et al.*, 2007). This study, which was an analysis of UK data from EPIC Norfolk, found that participants consuming one or more portions of wholegrain bread per day had a 30% lower risk of DM than those consuming less than one portion per day. The remaining studies all contributed towards the dose-response meta-analysis. For EPIC Potsdam, we assumed a serving of bread was one slice weighing 40 grams (Schulze *et al.*, 2007a).

The pooled estimate of relative risk from the cohort studies was 0.93 (95% CI: 0.90 to 0.96) per half serving of wholegrain bread per day ( $p < 0.001$ ).

Figure 4.16 Forest plot for wholegrain bread and incident diabetes mellitus type 2



There was no excess heterogeneity between the cohort studies ( $I^2=0\%$  [95% CI: 0% to 59%],  $Q=0.5$ ,  $df=2$ ,  $p=0.8$ ).

There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. There were insufficient studies to explore small-study bias such as publication bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

**Summary of RCT results**

No RCTs reported outcomes concerning bread and incident DM 2.

Table 4.27 Incident diabetes mellitus type 2 and bread: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	p	P trend	Adjustments
14220 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Bread, total (White bread, rolls, or toast; whole-wheat or rye bread, rolls, or toast)	Fasting serum/blood glucose, Glucose (random) Clinic tested	Continuous risk estimate	1 serving /week	1.02 (1, 1.03)			age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
14221						White bread (White rolls or toast)		Continuous risk estimate	1 serving /week	1.18 (1.07, 1.29)			As above
*14222						Wholemeal bread (Whole- wheat or rye bread)		Continuous risk estimate	1 serving /week	0.94 (0.83, 1.05)			As above
*13424 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Wholewheat bread (Dark bread)	Self reported, and confirmed by the National Diabetes Data Group	≥1 vs. 0	times/ day	0.77 (0.66, 0.9)		0.002	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, Vitamin intake
*13613 (Schulze <i>et al.</i> , 2007a) EPIC Potsdam	Germany, Primarily White, Not diabetic	35-65 %M 40	(849) /27548	7 years (9)	FFQ (148)	Wholegrain bread	Multiple diagnosis methods Confirmed self report	Continuous risk estimate	50 g/day	0.918 (0.855, 0.986)		0.02	age, alcohol, waist, smoking, Coffee, Height, hypertension, Meat, physical activity, Whole- grain bread
13660 (Simmons <i>et al.</i> , 2007) EPIC Norfolk	UK, Primarily White, Not diabetic	40-79 %M 45	(199) /25633	4.6 years (41)	FFQ (130)	Wholewheat bread (Wholemeal and brown bread)	Health checks, registry data, use of hyperglycaemic medication, HbA1c >7% at baseline or follow-up.	<1 vs. ≥1	portio n/day	0.72 (0.53, 0.97)			

\*This result was used in the meta-analysis of wholegrain bread and Incident DM 2

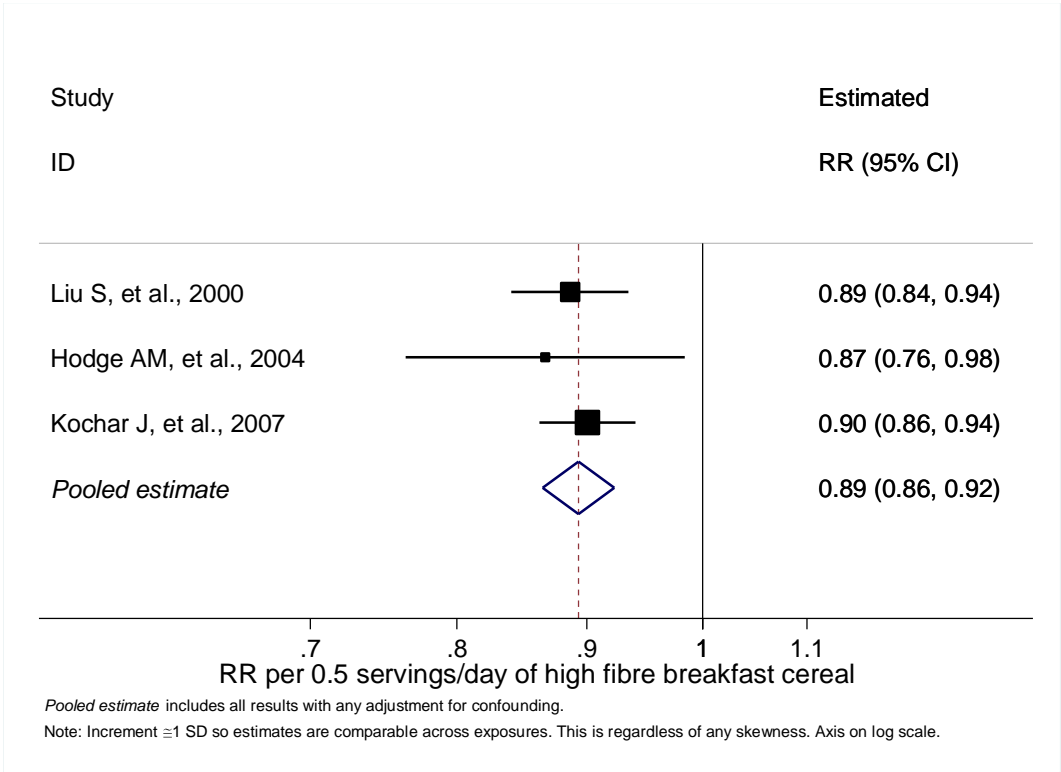
# Incident diabetes mellitus type 2 and breakfast cereals

## Summary of cohort results

Data were extracted from three publications presenting results from three cohort studies: Physicians Health Study (PHS) I (Kochar *et al.*, 2007), Melbourne Collaborative Cohort Study (Hodge *et al.*, 2004) and NHS (Liu *et al.*, 2000a) conducted in the USA and Australia. All three papers were included in the meta-analysis of high fibre cereals and incident DM. For two studies, we had to assume that the mean of the highest exposure category was 1.5 times the lower limit of that category (Kochar *et al.*, 2007;Liu *et al.*, 2000a).

The pooled estimate of relative risk from the cohort studies was 0.89 (95% CI: 0.86 to 0.92) per half serving of high fibre breakfast cereal per day (p<0.001).

Figure 4.17 Forest plot for high fibre breakfast cereals and incident diabetes mellitus type 2



There was no excess heterogeneity between the cohort studies ( $I^2=0\%$  [95% CI: 0% to 52%],  $Q=0.4$   $df=2$ ,  $p=0.8$ ).

There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. There were insufficient studies to explore small-study bias such as publication bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning breakfast cereals and incident DM 2.

Table 4.28 Incident diabetes mellitus type 2 and breakfast cereals: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
*14218 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54)  %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Breakfast cereals, (Wheatgerm, muesli and other breakfast cereal)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	1 serving/week	0.96 (0.93, 1)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13152 (Kochar <i>et al.</i> , 2007) PHS I	USA	40-84 (54)  %M 100	(1395) /22071	19.1 years	FFQ (61)	Breakfast cereals, high fibre (Cold wholegrain types)	Self-reported		≥7 vs. 0	servings/week	0.6 (0.5, 0.71)	0.0001	age, alcohol, BMI, vegetable intake, vitamin intake
13159 PHS I			(463) /22071					BMI <25	≥7 vs. 0	servings/week	0.65 (0.5, 0.84)	0.0001	age, alcohol, vegetable intake, vitamin intake
13161 PHS I			(758) /22071					BMI 25-30	≥7 vs. 0	servings/week	0.57 (0.45, 0.73)	0.0001	age, alcohol, physical activity, vegetable intake, vitamin intake
13163 PHS I			(174) /22071					BMI >30	≥7 vs. 0	servings/week	0.75 (0.41, 1.4)	0.31	age, alcohol, physical activity, vegetable intake, vitamin intake
13158 PHS I			(968) /22071			Breakfast cereals, low fibre (Cold refined-grain types)	Self-reported		≥7 vs. 0	servings/week	0.95 (0.73, 1.3)	0.05	age, alcohol, BMI, vegetable intake, vitamin intake
*13145 PHS I			(1958) /22071			Breakfast cereals, (All cold types)	Self-reported		≥7 vs. 0	servings/week	0.69 (0.6, 0.79)	0.0001	age, alcohol, BMI, vegetable intake, vitamin intake
*13425 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55  %M 0	(1879) /121700	10 years	FFQ (126)	Breakfast cereals, high fibre (>25% whole grain or bran by weight)	Self reported, and confirmed by the National Diabetes Data Group		≥1 vs. 0	times/day	0.66 (0.55, 0.8)	0.0001	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake
13427 NHS						Oatmeal, Cooked			≥1 vs. 0	times/day	0.73 (0.35, 1.54)	0.08	As above

\*This result was used in the meta-analysis of high fibre breakfast cereals and Incident DM 2



## **Incident diabetes mellitus type 2 and rice**

### **Summary of cohort results**

Data were extracted from three publications presenting results from the Shanghai Women's Health Study (Villegas *et al.*, 2007), the Melbourne Collaborative Cohort Study (Hodge *et al.*, 2004) and NHS (Villegas *et al.*, 2007;Hodge *et al.*, 2004;Liu *et al.*, 2000a) conducted in China, Australia and the USA respectively.

Liu *et al.* reported on intake of brown rice in the US (Liu *et al.*, 2000a) suggesting clear protective associations over four categories of intake, adjusted for important confounders, whilst Hodge *et al.* reported from Australia that for total rice (mostly white rice,) there was no evidence of any such association (Hodge *et al.*, 2004).

Villegas *et al.* studied intake of white rice in China, reporting that this was strongly associated with increased risk of DM (Villegas *et al.*, 2007). To include this study with the others in a meta-analysis, we would need to assume that standard servings of rice were comparable across the countries, which is unlikely. In addition, the inclusion of both brown and white rice together in a meta-analysis is not sensible, given the different types of carbohydrate, as this would introduce substantial heterogeneity. No meta-analysis for this exposure is therefore presented.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning rice and incident DM 2.

Table 4.29 Incident diabetes mellitus type 2 and rice: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14219 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Rice, total Boiled (including brown, fried rice, mixed dishes with rice)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	1 serving/ week	1.00 (0.92, 1.08)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13428 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Rice, Brown	Self reported, and confirmed by the National Diabetes Data Group		5-6 vs. 0	times/ week	0.47 (0.15,1.45)	0.0001	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake
13070 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70 %M 0	(1608) /74942	4.6 years (0.2)	FFQ (77)	Rice, total raw (Energy adjusted raw rice intake. Raw rice (100 g of raw=250g cooked rice=1 cup rice))	Fasting serum/blood glucose. American diabetes association Criteria, Confirmed self report		>300 vs. <200	g/day	1.78 (1.48, 2.15)		age, alcohol, BMI, energy intake, Income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13079			(Subgroup cases not reported) /74942					WHR >0.85 (F) >0.90(M)	>300 vs. <200	g/day	2.04 (1.51, 2.1)	<0.001	age, alcohol, BMI, energy intake, Income, smoking, occupation, physical activity, hypertension, education
13078								WHR <0.85 (F) <0.90(M)	>300 vs. <200	g/day	1.64 (1.28, 2.1)	<0.001	As above
13086								BMI <25	>300 vs. <200	g/day	1.39 (1.02, 1.9)	0.001	age, alcohol, energy intake, Income, occupation, physical activity, hypertension, waist: hip ratio smoking, education
13087								BMI >25	>300 vs. <200	g/day	2.05 (1.61, 2.61)	<0.001	As above
13107								Sedentary/ Low physical activity	>300 vs. <200	g/day	2.44 (1.69, 3.52)	<0.001	age, alcohol, BMI, energy intake, Income, occupation, hypertension, smoking, waist:hip ratio, education
13108								Med/High physical activity	>300 vs. <200	g/day	1.59 (1.28, 1.98)	<0.001	As above
13120								Insulin Resistance- Low Risk	>300 vs. <200	g/day	1.95 (1.6, 2.37)	0.001	age, alcohol, energy intake, Income, occupation, smoking hypertension, education
13121								Insulin Resistance- High Risk	>300 vs. <200	g/day	2.6 (1.34, 5.06)	<.0001	As above

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

## **Incident diabetes mellitus type 2 and other cereal foods**

### **Summary of cohort results**

Three cohort studies presented data on a heterogeneous mixture of cereal foods which we have collated here (Hodge *et al.*, 2004; Montonen *et al.*, 2005; Liu *et al.*, 2000a). The Melbourne Collaborative Cohort Study (Hodge *et al.*, 2004), the Finnish Mobile Clinic Health Surveys (Montonen *et al.*, 2005) and NHS (Liu *et al.*, 2000a) were conducted in Finland, the USA and Australia respectively. The individual results are presented in the table below.

No meta-analysis was conducted due the wide range of cereal foods included in this section.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning other cereal foods and incident DM 2.

Table 4.30 Incident diabetes mellitus type 2 and other cereal foods: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14224 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Pasta and noodles	Fasting serum/blood glucose, Glucose (random)  Clinic tested	Continuous risk estimate	1 serving/week	0.88 (0.42, 1.84)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13251 (Montonen <i>et al.</i> , 2005) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(383) /10054	23 years	Dietary history	Rye and rye products, total	Diagnosis criteria not reported Registry data	181- vs. -58	g/day	0.8 (0.57, 1.11)	0.24	age, BMI, energy intake, family history of DM, region, gender, smoking
13252						Wheat	Diagnosis criteria not reported Registry data	>158 vs. <57	g/day	0.84 (0.62, 1.15)	0.17	age, BMI, energy intake, family history of DM, region, gender, smoking
13426 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Popcorn	Self reported, and confirmed by the National Diabetes Data Group	≥1 vs. 0	times/day	0.88 (0.59, 1.31)	0.47	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake

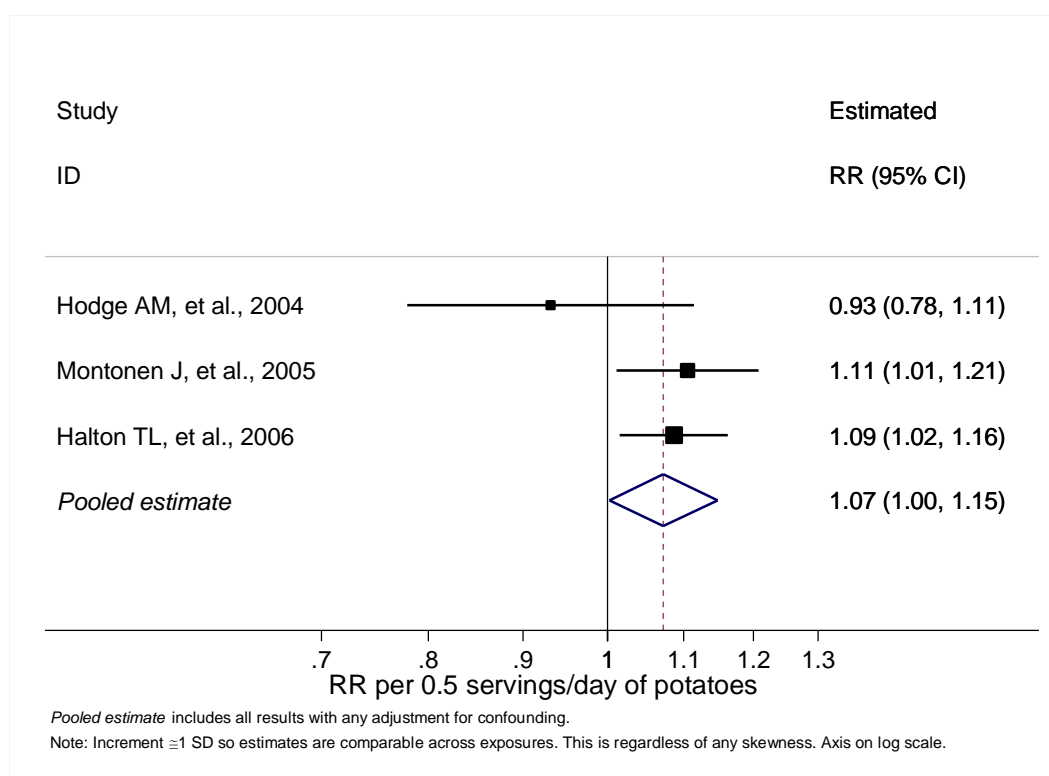
## Incident diabetes mellitus type 2 and potatoes

### Summary of cohort results

Data were extracted from four publications presenting results from four cohort studies conducted in the USA, Australia, Finland and China (Villegas *et al.*, 2007; Halton *et al.*, 2006; Montonen *et al.*, 2005; Hodge *et al.*, 2004). The Shanghai Women's Health Study paper was excluded from the meta-analysis because it did not present any information by which the intake of potatoes could be inferred, so no dose-response trend could be estimated (Villegas *et al.*, 2007). That particular study combined sweet potatoes and potatoes into one exposure and so also differed from the other cohort studies. A reduction in risk was observed with increasing consumption in this study. The remaining three papers all contributed towards the meta-analysis, with both the NHS and Finnish Mobile Clinic Health Surveys study showing an elevation of risk with increasing consumption (Halton *et al.*, 2006; Montonen *et al.*, 2005), and the Melbourne Collaborative Cohort Study showing no association (Hodge *et al.*, 2004). So that one paper could be included in the meta-analysis, we assumed that the median intake of the lowest exposure category was half the upper limit of that category, and that the median intake of the upper exposure category was 1.5 times the lower limit of that category (Montonen *et al.*, 2005). To combine studies presenting results in units of grams/day (Montonen *et al.*, 2005) with those using servings/day or /week, we assumed a serving size of 200 grams.

The pooled estimate of relative risk from the cohort studies was 1.07 (95% CI: 1.00 to 1.15) per half serving of potatoes per day ( $p=0.04$ ).

Figure 4.18 Forest plot for potatoes and incident diabetes mellitus type 2



There was a little heterogeneity between the cohort studies ( $I^2=31\%$  [95% CI: 0% to 93%],  $Q=2.9$   $df=2$ ,  $p=0.2$ ).

There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. There were insufficient studies to explore small-study bias such as publication bias through funnel plots or hypothesis tests. No one study had a dominant influence on the pooled estimate from the random effects analysis.

### **Exposure definition and assessment**

The Nurse's Health Study reported information on both potatoes generally, and French fries separately, whereas the Melbourne study grouped potatoes together regardless of cooking method and addition of fats. These studies assessed diet through FFQ, whereas the Finnish cohort study used the dietary history approach.

### **Adjustment for appropriate confounders**

All adjusted for age, gender (where appropriate) and BMI/weight change

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning potatoes and incident DM 2.





Table 4.31 Incident diabetes mellitus type 2 and potatoes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub- group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13529 (Halton <i>et al.</i> , 2006) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4496) /121700	20 years	FFQ (120)	French fries	Self reported, and confirmed by the National Diabetes Data Group		Continuous risk estimate	113 g/week	1.16 (1.05, 1.29)		age, cereal fibre, energy from trans fat, energy intake, family history of DM, physical activity, PUFA:SFA, smoking, postmenopausal hormone replacement therapy
13532 NHS			(1950) /121700					BMI <30	Q5 vs. Q1		1.34 (1.15, 1.55)	0.0003	As above
13533 NHS			(2540) /121700					BMI >30	Q5 vs. Q1		1.19 (1.04, 1.36)	0.003	As above
*13528 (Halton <i>et al.</i> , 2006) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4496) /121700	20 years	FFQ (120)	Potatoes	Self reported, and confirmed by the National Diabetes Data Group		Continuous risk estimate	1 Cup/day	1.18 (1.03, 1.35)		age, cereal fibre, energy from trans fat, energy intake, family history of DM, physical activity, PUFA:SFA, smoking, postmenopausal hormone replacement therapy
13530 NHS			(1958) /121700					BMI <30	Q5 vs. Q1		0.95 (0.82, 1.11)	0.58	As above
13531 NHS			(2538) /121700					BMI >30	Q5 vs. Q1		1.22 (1.06, 1.41)	0.007	As above
*14227 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54) %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Potatoes (fried or roasted and cooked without fat)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	1 serving/ week	0.98 (0.93, 1.03)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13254 (Montonen <i>et al.</i> , 2005) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(383) /10054	23 years	Dietary history	Potatoes	Diagnosis criteria not reported Registry data		<283 vs. >132	g/day	1.42 (1.02, 1.98)	0.58	age, cereal fibre, energy from trans fat, energy intake, family history of DM, physical activity, PUFA:SFA, smoking, postmenopausal hormone replacement therapy
17567 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70 %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Potatoes and sweet potatoes	Fasting serum/blood glucose American diabetes association criteria, Confirmed self report		Q5 vs. Q1		0.67 (0.58, 0.78)		age, alcohol, BMI, blood pressure, education, energy intake, Income, occupation, physical activity, smoking, waist:hip ratio

\*This result was used in the meta-analysis of potatoes and Incident DM 2.

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

## **Incident diabetes mellitus type 2 and legumes**

### **Summary of cohort results**

Two cohort studies conducted in Australia and China provided data on non-soya legume intakes in relation to risk of DM (Hodge *et al.*, 2004; Villegas *et al.*, 2008). The Shanghai Women's Health Study (Villegas *et al.*, 2008) found evidence of reduction in risk associated with increasing intakes of legumes, but the Melbourne Collaborative Cohort Study found no evidence of an association.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning legumes and incident DM 2.

Table 4.32 Incident diabetes mellitus type 2 and legumes: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14228 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi-ethnic, Not diabetic, Without angina or heart attack	27-75 (54)  %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Legumes (Bean, pea, or lentil soup; green beans or peas; cooked dried bean, chickpea, or lentil dish (including baked beans))	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	1 serving /week	1.01 (0.96, 1.06)		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
13060 (Villegas <i>et al.</i> , 2008) Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70  %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Legumes (All legumes excluding peanuts and soybeans)	Multiple diagnosis methods Confirmed self report		(37.1) vs. (5.6)	g/day	0.76 (0.64, 0.9)	<0.0001	age, alcohol, BMI, energy intake, Fibre, Income, occupation, physical activity, hypertension, smoking, vegetable intake, waist:hip ratio, education
13064			(Subgroup cases not reported) /74942					BMI <25	(37.1) vs. (5.6)	g/day			age, alcohol, energy intake, Fibre, Income, occupation, physical activity, hypertension, smoking, vegetable intake, waist:hip ratio, education
13065								BMI >25	(37.1) vs. (5.6)	g/day			As above
13066								WHR <0.85 (F) <0.90(M)	(37.1) vs. (5.6)	g/day			age, alcohol, BMI, energy intake, Fibre, Income, occupation, physical activity, hypertension, smoking, vegetable intake, education
13123								WHR >0.85 (F) >0.90(M)	(37.1) vs. (5.6)	g/day			As above
13062								Pre- menopausal	(37.1) vs. (5.6)	g/day			age, alcohol, BMI, energy intake, Fibre, Income, occupation, physical activity, hypertension, smoking, vegetable intake, waist:hip ratio, education
13061								Post- menopausal	(37.1) vs. (5.6)	g/day			As above

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

# Incident diabetes mellitus type 2 and sweetened beverages

## Summary of cohort results

Six cohort studies provided data on sweetened beverages in relation to risk of developing DM, which include the Finnish Mobile Clinic Health Surveys, ARIC, NHS II, Multi-Ethnic Study of Atherosclerosis (MESA), the Black Women's Health Study and the Framingham Heart Study (Montonen *et al.*, 2007;Paynter *et al.*, 2006;Schulze *et al.*, 2004b;Nettleton *et al.*, 2009;Palmer *et al.*, 2008;Dhingra *et al.*, 2007). All but one of the studies had been conducted in the USA. The Multi-Ethnic Study of Atherosclerosis (MESA) (Nettleton *et al.*, 2009) reported within the text of the paper that no association was observed between intakes of full calorie sugar sweetened beverages and risk of DM. However, no risk estimates or consumption data were provided. The Atherosclerosis Risk in Communities study (ARIC) reported no consistent association with incidence of type 2 DM, with hazard ratios for men and women both close to one (Paynter *et al.*, 2006). The four remaining studies all provided some evidence of increased risk of DM with increasing intakes of the various sweetened beverages reported.

There was considerable inconsistency in whether studies combined soft drinks and fruit juices, and in serving sizes, so there was little confidence that the studies could be combined in meta-analysis without a very large amount of heterogeneity.

## Exposure definition and assessment

Beverage consumption was generally assessed by questionnaire or food frequency questionnaire, other than in the Finnish Mobile Health Clinic cohort study (Montonen *et al.*, 2007), which employed the dietary history technique. There is a marked lack of consistency between studies in terms of the beverage types variously described by authors as "sugar-sweetened beverages". Different types of beverage are grouped together in each of the cohort studies, with some including fruit juice within the category of "fruit drinks" and others not (Palmer *et al.*, 2008;Schulze *et al.*, 2004b).

The Nurse's Health Study provided data on fruit punches and carbonated non-diet drinks (Cola) both separately and combined as 'all sugar-sweetened soft drinks'. Fruit punches described in the Nurse's Health Study II contain only small amounts of fruit juice, but large amounts of added high-fructose corn syrup. Data on diet (artificially sweetened) soft drinks and fruit juices are reported separately. The Framingham Study however, combined artificially sweetened and sugar-sweetened beverages into one category called 'soft drinks' (Dhingra *et al.*, 2007).

### ***Adjustment for appropriate confounders***

Most studies included here, that were conducted in the USA, report that high consumers of sugar-sweetened beverages differ from non- or low-consumers in many aspects of lifestyle. Consumers are more likely to smoke, to be sedentary and to have a higher energy intake (Schulze *et al.*, 2004b). These are lifestyle attributes that could potentially confound the association between sugar-sweetened beverage consumption and risk of DM. The Nurse's Health Study result for total sugar-sweetened beverages included in the tables below was not adjusted for energy intake (Schulze *et al.*, 2004b). Including both BMI *and* energy intake in the model attenuated the association, although an increased risk of DM remained (RR for extreme categories, 1.32; 95% CI 1.01, 1.73;  $p=0.04$  for trend).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning sweetened beverages and incident DM 2.

Table 4.33 Incident Diabetes Mellitus type 2 and sweetened beverages: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14262 (Dhingra <i>et al.</i> , 2007) The Framingham Heart Study	USA, No CHD, Without metabolic syndrome	(53) %M 43	(1426) /8997	4 years	Questionnaire (general)	Mixed sugar and artificial sweetener beverages (soft drink - number of 12oz cans of fizzy drinks sugar or sweetener)	Fasting serum/blood glucose Clinic tested		≥1 vs. 0	servings/day	1.25 (1.05, 1.48)		age, smoking, SFA, energy intake, Fibre, GI, magnesium Intake, physical activity, gender, trans fat
13242 (Mntononen <i>et al.</i> , 2007) Finnish Mobile Clinic Health Surveys	Finland, Not diabetic	40-69 %M 53	(177) /10054	12 years	Dietary history	Full-calorie sugar sweetened beverages (Soft Drinks)	Diagnosis criteria not reported  Registry data		(143) vs. (0)	g/day	1.67 (0.98, 2.87)	0.01	age, BMI, diet pattern- conservative, diet pattern- prudent, energy intake, family history of DM, region, physical activity, gender, smoking
13241 Finnish Mobile Clinic Health Surveys						Full-calorie sugar sweetened beverages (Sweetened berry juice)	Diagnosis criteria not reported Registry data		(51) vs. (0)	g/day	1.69 (1.17, 2.43)	0.001	age, BMI, diet pattern- conservative, diet pattern- prudent, energy intake, family history of DM, region, physical activity, gender, smoking
14160 (Nettleton <i>et al.</i> , 2009) Multi- Ethnic Study of Atherosclerosis (MESA)	USA, Multi- ethnic, No CHD	45-84 %M 47	(413) /6841	7 years	FFQ (114)	Full-calorie sugar sweetened beverages	Fasting serum/blood glucose  Clinic tested		Q2 vs. Q1		No significant association, no detail presented in paper		
13287 (Palmer <i>et al.</i> , 2008) Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69 %M 0	(2713) /59000	10 years (20)	FFQ (68)	Full-calorie sugar sweetened beverages (soft drinks)	Diagnosis criteria not reported  Self- reported		≥2/day vs. <1/month	servings/day	1.24 (1.06, 1.45)	0.002	age, cereal fibre, Coffee, education, family history of DM, GI, Fruit juice, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages
13292 Black Women's Health Study			(904) /59000					Age <40	>1/d vs. <1/mo	servings/day	1.28 (1.02, 1.59)		age, cereal fibre, Coffee, Completion of dietary questionnaire, education, family history of DM, GI, Fruit juice, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13293 Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69 %M 0	(1809) /59000	10 years (20)	FFQ (68)	Full-calorie sugar sweetened fruit flavour drinks (fruit drinks, including fortified fruit drinks, kool- aid and fruit juice other than orange and grapefruit)	Diagnosis criteria not reported Self- reported	Age >40	>1/d vs. <1/mo	servings/day	1.11 (0.95, 1.29)	0.001	As above
13294 Black Women's Health Study			(278) /59000					BMI <25	>1/d vs. <1/mo	servings/day	1.07 (0.72, 1.58)		age, cereal fibre, Coffee, Completion of dietary questionnaire, education, family history of DM, GI, Fruit juice, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages
13295 Black Women's Health Study			(813) /59000					BMI 25-30	>1/d vs. <1/mo	servings/day	1.08 (0.85, 1.36)		As above
13296 Black Women's Health Study			(1622) /59000					BMI >30	>1/d vs. <1/mo	servings/day	1.05 (0.9, 1.23)		As above
13297 Black Women's Health Study			(1142) /59000					family history of Diabetes	>1/d vs. <1/mo	servings/day	1.17 (0.99, 1.37)		age, cereal fibre, Coffee, Completion of dietary questionnaire, education, GI, Fruit juice, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages
13298 Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69 %M 0	(1518) /59000	10 years (20)	FFQ (68)	Full-calorie sugar sweetened fruit flavour drinks (fruit drinks, including fortified fruit drinks, kool- aid and fruit juice other than orange and grapefruit)	Diagnosis criteria not reported Self- reported	No family history of diabetes	>1/d vs. <1/mo	servings/day	1.16 (0.96, 1.4)	0.001	As above
13288 (Palmer <i>et al.</i> , 2008) Black Women's Health Study			(2713) /59000						≥2/day vs. <1/month	servings/day	1.31 (1.13, 1.52)		age, Carbonated drink/juice, cereal fibre, Coffee, education, family history of DM, GI, Fruit juice, physical activity, Processed Meat, Red Meat, smoking
13299 Black Women's Health Study			(893) /59000					Age <40	>1/d vs. <1/mo	servings/day	1.13 (0.91, 1.41)		age, Carbonated drink/juice, cereal fibre, Coffee, Completion of dietary questionnaire, education, family history of DM, GI,

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13300 Black Women's Health Study			(1761) /59000					Age >40	>1/d vs. <1/mo	servings/day	1.25 (1.08, 1.44)		physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages As above
13301 Black Women's Health Study			(273) /59000					BMI <25	>1/d vs. <1/mo	servings/day	0.84 (0.56, 1.25)		age, Carbonated drink/juice, cereal fibre, Coffee, Completion of dietary questionnaire, education, family history of DM, GI, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages
13302 Black Women's Health Study			(791) /59000					BMI 25-30	>1/d vs. <1/mo	servings/day	1.28 (1.02, 1.6)		As above
13303 Black Women's Health Study			(1590) /59000					BMI >30	>1/d vs. <1/mo	servings/day	1.3 (1.11, 1.52)		As above
13304 Black Women's Health Study			(1119) /59000					family history of Diabetes	>1/d vs. <1/mo	servings/day	1.18 (1, 1.38)		age, Carbonated drink/juice, cereal fibre, Coffee, Completion of dietary questionnaire, education, GI, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages
13305 Black Women's Health Study			(1484) /59000					No family history of diabetes	>1/d vs. <1/mo	servings/day	1.29 (1.01, 1.56)		As above
17598 Black Women's Health Study			(2713) /59000			Fruit juice (Orange and grapefruit juices only)			≥2/day vs. <1/month	servings/day	1.11 (0.92, 1.35)	0.28	age, Carbonated drink/juice, cereal fibre, Coffee, education, family history of DM, GI, Fruit juice, physical activity, Processed Meat, Red Meat, smoking
13268 (Paynter <i>et al.</i> , 2006) ARIC	USA, Multi-ethnic	45-64 (54)  %M 44	(719) /15792	9 years	FFQ (61)	Sugar-sweetened beverages (total fruit punch, non-diet soda and orange or grapefruit	Diagnosis criteria not reported Multiple diagnosis methods	Women	≥2 vs. <1	Cups/day	1.01 (0.79, 1.29)	0.58	age, alcohol, education, energy intake, ethnicity, family history of DM, Fibre, hypertension, physical activity, smoking

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13273 ARIC			(718) /15792			juice)		Men	≥2 vs. <1	Cups/day	1.03 (0.82, 1.28)	0.94	age, alcohol, education, energy intake, ethnicity, family history of DM, Fibre, hypertension, physical activity, smoking
13580 ARIC			(Subgroup cases not reported; total cohort cases 1437) /15792					Age <50	≥2 vs. <1	Cups/day		NS	age, alcohol, education, energy intake, ethnicity, family history of DM, Fibre, hypertension, physical activity, smoking
13583 ARIC								Age >50	≥2 vs. <1	Cups/day		NS	
13585 ARIC								BMI <median	≥2 vs. <1	Cups/day		NS	
13586 ARIC								BMI ≥median	≥2 vs. <1	Cups/day		NS	
13587 ARIC								Light physical activity	≥2 vs. <1	Cups/day		NS	
13588 ARIC								Moderate/ heavy physical activity	≥2 vs. <1	Cups/day		NS	
14565 (Schulze <i>et al.</i> , 2004b) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) /116671	8 years(<10)	FFQ (133)	Full-calorie sugar sweetened beverages (fruit flavour drinks)	Multiple diagnosis methods  Confirmed self report		≥1/day vs. <1/month	Time/day or time/week	2 (1.33, 3.03)	0.001	age, alcohol, BMI, cereal fibre, family history of DM, energy from fat, hormone replacement therapy, Fruit juice, magnesium Intake, oral contraceptive pill, physical activity, PUFA:SFA, smoking, SSB intake at measurement age, trans fat
14564 NHS II						Full-calorie sugar sweetened beverages (cola)	Multiple diagnosis methods  Confirmed self report		≥1/day vs. <1/month	Time/day or time/week	1.87 (1.43, 2.45)	<0.001	age, alcohol, BMI, cereal fibre, family history of DM, energy from fat, hormone replacement therapy, Fruit juice, magnesium Intake, oral contraceptive pill, physical activity, PUFA:SFA, smoking, SSB intake at measurement age, SSB, trans fat
14562	USA,	24-44	(741)	8	FFQ (133)	Sugar-	Multiple		≥1/day	Time/day or	1.83 (1.42, 2.36)	<0.001	age, alcohol, BMI, cereal

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
(Schulze <i>et al.</i> , 2004b) NHS II	Primarily White, Cancer free, No CHD, Not diabetic	%M 0	/116671	years(<10)		sweetened beverages, total	diagnosis methods Confirmed self report		vs. <1/month	time/week			fibre, family history of DM, energy from fat, hormone replacement therapy, Fruit juice, magnesium Intake, oral contraceptive pill, physical activity, PUFA:SFA, smoking, SSB, trans fat
14566 NHS II			(143) /116671					BMI <30	≥1/day vs. <1/month	Time/day or time/week	1.78 (0.97, 3.26)	0.06	age, alcohol, BMI, cereal fibre, family history of DM, hormone replacement therapy, magnesium Intake, oral contraceptive pill, physical activity, PUFA:SFA, smoking, trans fat
14567 NHS II			(579) /116671					BMI >30	≥1/day vs. <1/month	Time/day or time/week	1.35 (1.01, 1.8)	0.4	As above
14568 NHS II			(308) /116671					Med/High physical activity	≥1/day vs. <1/month	Time/day or time/week	1.54 (1.01, 2.33)	0.02	As above
14569 NHS II			(433) /116671					Sedentary/ Low physical activity	≥1/day vs. <1/month	Time/day or time/week	1.68 (1.21, 2.32)	0.001	As above
14570 NHS II			(459) /116671					No family history of diabetes	≥1/day vs. <1/month	Time/day or time/week	1.86 (1.34, 2.56)	<0.001	As above
14571 NHS II			(282) /116671					family history of Diabetes	≥1/day vs. <1/month	Time/day or time/week	1.3 (0.85, 1.99)	0.12	As above
14572 NHS II			(319) /116671					High cereal fibre intake	≥1/day vs. <1/month	Time/day or time/week	1.44 (0.86, 2.42)	0.08	As above
14573 NHS II			(422) /116671					Low cereal fibre intake	≥1/day vs. <1/month	Time/day or time/week	1.79 (1.31, 2.43)	<0.001	As above
14574 NHS II			(356) /116671					High PUFA:SFA intake	≥1/day vs. <1/month	Time/day or time/week	1.64 (1.11, 2.43)	0.005	As above
14575 NHS II			(385) /116671					Low PUFA:SFA	≥1/day vs. <1/month	Time/day or time/week	1.53 (1.09, 2.15)	0.1	As above
14576 NHS II			(280) /116671					High trans fat intake	≥1/day vs. <1/month	Time/day or time/week	1.59 (1.03, 2.44)	0.02	As above

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
14577 NHS II			(461) /116671					Low trans fat intake	≥1/day vs. <1/month	Time/day or time/week	1.66 (1.21, 2.27)	0.001	As above

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

## Incident Diabetes Mellitus type 2 and glycaemic index

### Summary of cohort results

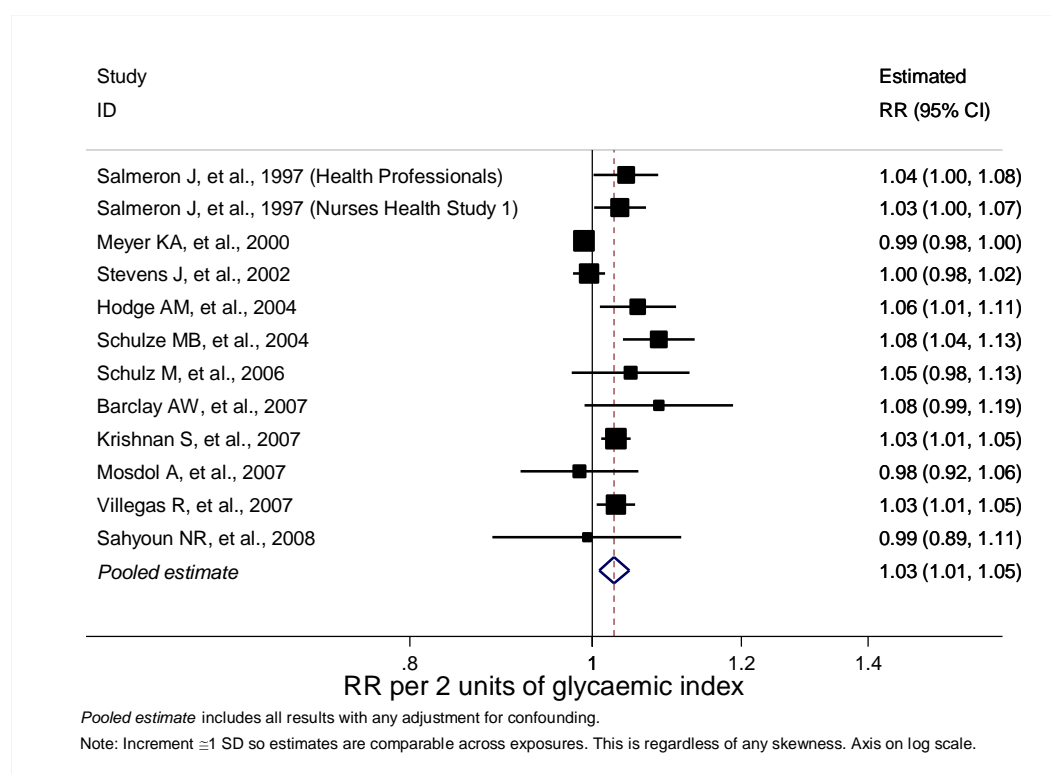
Data were extracted from 12 publications presenting results from the following 12 cohort studies: the Blue Mountains Eye Study, the Melbourne Collaborative Cohort Study, the Black Women's Health Study, the Iowa Women's Health Study, the Whitehall II study, the Health, Aging, and Body Composition Study, HPFS, NHS, the Insulin Resistance Atherosclerosis Study, NHS II, ARIC and the Shanghai Women's Cohort Study (Sahyoun *et al.*, 2008;Schulz *et al.*, 2006;Villegas *et al.*, 2007;Krishnan *et al.*, 2007;Barclay *et al.*, 2007;Mosdol *et al.*, 2007;Hodge *et al.*, 2004;Schulze *et al.*, 2004a;Meyer *et al.*, 2000;Salmeron *et al.*, 1997a;Salmeron *et al.*, 1997b;Stevens *et al.*, 2002). These studies were conducted predominantly in the USA (8/12).

In the Insulin Resistance Atherosclerosis Study (Schulz *et al.*, 2006), no overall association between dietary glycaemic index (GI) and risk of incident type 2 DM was observed. Dietary GI increased the risk of type 2 DM among non-abdominally obese subjects and among subjects with increases in waist circumference in excess of 2 cm over the 5 yr period of follow-up. Numbers in these subgroups were small, however. In the ARIC study no statistically significant association with incident DM was observed for dietary glycaemic index, either overall, or by racial subgroup (Stevens *et al.*, 2002). Three other cohort studies, including the UK-based Whitehall II study also reported no association between dietary GI and risk of incident DM (Meyer *et al.*, 2000;Mosdol *et al.*, 2007;Sahyoun *et al.*, 2008). The remaining 7 cohort studies did all indicate some degree of increased risk associated with increasing GI of the diet, particularly in obese subgroups (see table below).

All 12 studies contributed sufficient information for inclusion in the dose-response meta-analysis. So that one paper could be included, we assumed GI followed an approximate normal distribution with a mean of 55, with standard deviation 5 (Villegas *et al.*, 2007).

The pooled estimate of relative risk from the cohort studies was 1.03 (95% CI: 1.01 to 1.05) per 2 units of glycaemic index ( $p=0.005$ ).

Figure 4.19 Forest plot for glycaemic index and incident diabetes mellitus type 2



There was considerable heterogeneity between the cohort studies ( $I^2=75\%$  [95% CI: 56% to 86%],  $Q=44.4$ ,  $df=11$ ,  $p<0.001$ ), so the pooled estimate needs to be interpreted cautiously.

There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups, though adjusting for family history appeared to be associated with higher estimates ( $p=0.01$ ), and this improved heterogeneity within each subgroup. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 4.34: Subgroup analyses of glycaemic index and incidence of diabetes. Relative risks are per 2 units/day.

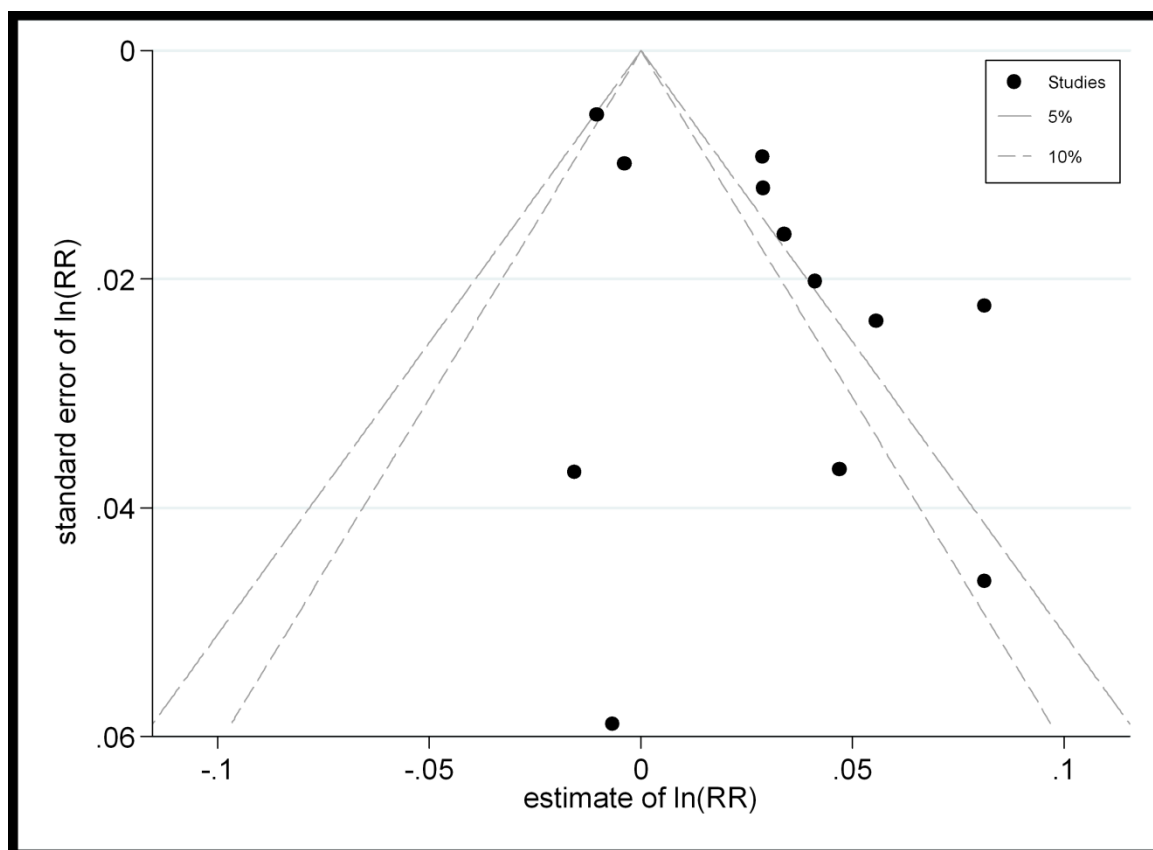
Subgroup	subgroup	RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> *	P <sub>het</sub> **
subjects' gender	Male	1.04 (1.00, 1.08)		1		.9
	Mixed	1.02 (0.99, 1.06)	48%	6	.09	
	Female	1.03 (1.00, 1.06)	88%	5	<0.001	
standard used to derive GI values	glucose	1.03 (1.02, 1.05)	0%	4	.7	
	white bread	1.00 (0.98, 1.02)		1		
	not stated	1.03 (1.00, 1.06)	80%	7	<0.001	.5
median glycaemic index	<=60	1.03 (1.02, 1.04)	0%	6	.6	.7
	>60	1.02 (1.00, 1.05)	84%	5	<0.001	
length of follow-up	<10 years	1.03 (1.01, 1.05)	78%	10	<0.001	
	>=10 years	1.03 (0.94, 1.13)	63%	2	.1	.5
geographic location	Americas	1.02 (1.00, 1.05)	80%	8	<0.001	
	EU	0.98 (0.92, 1.06)		1		
	Other	1.04 (1.02, 1.06)	0%	3	.4	.4
adjusted for age	yes	1.03 (1.01, 1.05)	75%	12	<0.001	
	no			0		
adjusted for alcohol	yes	1.03 (1.00, 1.06)	80%	8	<0.001	
	no	1.02 (0.99, 1.05)	65%	4	.03	.8
adjusted for anthropometry	yes	1.03 (1.01, 1.04)	76%	11	<0.001	
	no	1.08 (0.99, 1.19)		1		.3
adjusted for energy intake	yes	1.03 (1.01, 1.06)	81%	8	<0.001	
	no	1.02 (0.99, 1.05)	55%	4	.08	.6
adjusted for family history	yes	1.04 (1.03, 1.06)	19%	6	.3	
	no	1.00 (0.99, 1.02)	54%	6	.05	.01
adjusted for physical activity	yes	1.03 (1.01, 1.05)	77%	11	<0.001	
	no	1.05 (0.98, 1.13)		1		.6
adjusted for gender	yes	1.03 (1.01, 1.05)	77%	11	<0.001	
	no	1.05 (0.98, 1.13)		1		.6
adjusted for smoking	yes	1.02 (1.01, 1.04)	75%	11	<0.001	
	no	1.06 (1.01, 1.11)		1		.4
adjusted for age and anthropometry	yes	1.03 (1.01, 1.04)	76%	11	<0.001	
	no	1.08 (0.99, 1.19)		1		.3

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup

There was a little evidence of possible small-study effect from the contour-enhanced funnel plot, though half the studies did not suggest any evidence of a protective association.

Figure 4.20 Contour-enhanced funnel plot for publications presenting incident diabetes mellitus type 2 and glycaemic index



### Exposure definition and assessment

The glycaemic index (GI) is a relative measure of the plasma glucose response induced by a specific food, as compared to the response induced by the same amount of available carbohydrate from a reference source, such as white bread or pure glucose (Liu *et al.*, 2000c).

All studies used previously published glycaemic index values, from a variety of sources. For the majority, the reference food used to calculate GI values was not listed, but one paper cites that values were derived using white bread (Stevens *et al.*, 2002), and four using glucose (Barclay *et al.*, 2007; Villegas *et al.*, 2007; Krishnan *et al.*, 2007; Schulz *et al.*, 2006).

Most studies used a similar method to calculate dietary GI and GL: namely, summing the products of the GI for each food, multiplied by its carbohydrate content per serving, multiplied by the average number of servings of that food per day (to give dietary GL), then dividing by the average daily carbohydrate intake to give dietary GI:

Dietary GI =  $\{\sum[(\text{servings of food per day}) \times (\text{CHO content}) \times \text{GI}]\} / \text{total CHO}$  (Meyer *et al.*, 2000).



One study, however, calculated dietary GI by summing the products of each food's GI multiplied by its percent contribution to total carbohydrate intake (Barclay *et al.*, 2007).

Barclay *et al.* (Barclay *et al.*, 2007) used a FFQ which was validated against another method for assessing the GI of the diet. They suggest that their questionnaire reliably ranks individuals for GI, with a correct classification of 74% of their validation study participants within one quintile for GI. However, given the limited nature of databases of GI values for foods it is apparent that ascribing a GI to an individual's diet as captured via a FFQ is potentially problematic. Typically, GI values for each food item in a questionnaire are taken from the 2002 international table of GI values of foods (Foster-Powell *et al.*, 2002). Further issues concern, whether ascribing an overall GI to a diet is meaningful, when it is recognised that foods consumed together impact on each other to alter the GI of the whole meal. The glycaemic index (and thus also GL) is determined not only by the nature of the carbohydrate component of a food or diet, but also by the types and amounts of protein, fat and dietary fibre, as well food processing and storage (Venn and Green, 2007). Unless tightly controlled in an experimental situation, in most cases high and low GI/GL diets differ in many ways other than the carbohydrate fraction, including dietary fibre content, energy density and sensory quality. This particular exposure is therefore potentially highly prone to measurement error and misclassification of study participants.

### ***Adjustment for appropriate confounders***

All studies included age and gender (where appropriate) in their models. The impact of adjustment for a range of potential confounders is described by the data in the table outlining sources of heterogeneity.

Some studies additionally adjusted for dietary fibre. In the Nurse's Health Study (Salmeron *et al.*, 1997b), adjustment for cereal fibre increased the risk estimate for DM comparing the highest vs. lowest quantiles to 1.37 [95% CI:1.09-1.71] (data not extracted).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning glycaemic index and incident Diabetes Mellitus type 2.

Table 4.35 Incident Diabetes Mellitus type 2 and glycaemic index: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
*13345 (Barclay <i>et al.</i> , 2007) Blue Mountains Eye Study	Australia, Primarily White, Age >49y	49- (65)  %M 44	(138) /3654	10 years (29)	FFQ (145)	Glycaemic index	Self-reported diabetes and current use of insulin/oral hypoglycaemic medication, or fasting glucose $\geq 126$ mg/dL (WHO criteria)		Continuous risk estimate	10 units	1.5 (0.95, 2.36)		0.082		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglyceride, vegetable fibre
13346 Blue Mountains Eye Study			(Subgroup cases not reported; total cohort cases 138) /3654					Age <70	Continuous risk estimate	10 units	1.75 (1.05, 2.92)		0.031		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglyceride, vegetable fibre
13347 Blue Mountains Eye Study								Age >70	Continuous risk estimate	10 units	0.8 (0.29, 2.24)		0.671		age, family history of DM, HDL-C, physical activity, gender, smoking, blood triglyceride, vegetable fibre
*14244 (Hodge <i>et al.</i> , 2004) Melbourne Collaborative Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54)  %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Glycaemic index (values from Foster- Powell tables 2002)	Fasting serum/blood glucose, Glucose (random) Clinic tested		Continuous risk estimate	10 units	1.32 (1.05, 1.67)		0.02		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13275 (Krishnan <i>et al.</i> , 2007) Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69  %M 0	(1938) /59000	8 years (20)	FFQ (68)	Glycaemic index	Diagnosis criteria not reported Self-reported		(58.8) vs. (42.7)	Units	1.23 (1.05, 1.44)			0.001	age, BMI, cereal fibre, energy intake, family history of DM, energy from fat, physical activity, energy from protein, smoking
13279 Black Women's Health Study			(166) /59000					BMI <25	Q5 vs. Q1		1.91 (1.16, 3.16)			0.002	As above
13280 Black Women's Health Study			(1772) /59000					BMI >25	Q5 vs. Q1		1.19 (1.01, 1.4)			0.01	As above
*13763 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not	55-69 (61)  %M 0	(1141) /41836	6 years (21)	FFQ (127)	Glycaemic index	Self-reported		>80 (89) vs. <58 (53)	g/day	0.89 (0.72, 1.1)			0.0507	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio, fibre intake

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
	diabetic, Post- menopausal														
*14085 (Mosdol <i>et al.</i> , 2007) Whitehall II Study	England, White, Not diabetic	(50) %M 71	(329) /10308	13 years	FFQ (127)	Glycaemic index	Whole Blood Glucose OGTT (75g/120mins) Clinic tested		(59.3) vs. (51.7)	units	0.94 (0.72, 1.22)			0.64	age, Ratio: reported energy intake to estimated energy expenditure, Gender
*13397 (Sahyoun <i>et al.</i> , 2008) Health, Aging, and Body Composition Study	USA, Multi-ethnic	(75) %M 46	(99) /3075	6 years	FFQ (108)	Glycaemic index (Energy adjusted)	GP reports, use of insulin/oral hypoglycaemic medication, or fasting serum glucose ≥126mg/dL(American diabetes association criteria)		(61.8) vs. (50.5)	units	1 (0.5, 2)			0.8628	age, alcohol, Blood glucose, BMI, centre, education, ethnicity, physical activity, gender, smoking
*13473 (Salmeron <i>et al.</i> , 1997a) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(523) /51529	6 years	FFQ (131)	Glycaemic index	Multiple diagnosis methods Confirmed self report		(79) vs. (65)	g/day	1.37 (1.02, 1.83)			0.03	age, alcohol, BMI, family history of DM, physical activity, smoking, cereal fibre
*13574 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(915) /121700	6 years	FFQ (134)	Glycaemic index	Multiple diagnosis methods Confirmed self report		(77) vs. (64)	g/day	1.25 (0.99, 1.54)			0.04	age, alcohol, BMI, family history of DM, physical activity, smoking
*13811 (Schulz <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi- ethnic, Impaired glucose tolerance, Normal glucose tolerance	40-69 (55) %M 46	(146) /1625	5 years	FFQ (114)	Glycaemic index (Glucose=100 scale)	Plasma glucose OGTT (75g/120mins) Clinic tested			1 Unit		0.0234	0.2		age, BMI, education, energy intake, ethnicity, impaired glucose tolerance, DM, smoking
14205 Insulin Resistance Atherosclerosis Study			(74) /1625					Abdominal obesity		1 Unit		- 0.0035	0.9		As above
14257 Insulin Resistance			(72) /1625					No abdominal obesity		1 Unit		0.0517	0.06		As above

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
Atherosclerosis Study															
15088 Insulin Resistance Atherosclerosis Study			(23) /1625					Waist decrease >2cm		1 Unit		0.0404	0.4		As above
15089 Insulin Resistance Atherosclerosis Study			(36) /1625					Waist stable +/- 2cm		1 Unit		- 0.0678	0.14		As above
15090 Insulin Resistance Atherosclerosis Study			(87) /1625					Waist increase >2cm		1 Unit		0.0571	0.04		As above
*13534 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44 %M 0	(741) /116671	8 years (<10)	FFQ (133)	Glycaemic index	Multiple diagnosis methods Confirmed self report		>80.2 (82.1) vs. <73.1 (71.1)	Units	1.59 (1.21, 2.1)			0.001	age, alcohol, BMI, caffeine, cereal fibre, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, Hypercholesterolaemia, hypertension, magnesium Intake, oral contraceptive pill, physical activity, smoking, postmenopausal hormone replacement therapy
13541 NHS II			(114) /116671					BMI <27	Q5 vs. Q1		1.69 (0.84, 3.4)				As above
13542 NHS II			(608) /116671					BMI >27	Q5 vs. Q1		1.5 (1.1, 2.05)				As above
13543 NHS II			(421) /116671					Sedentary/ Low physical activity	Q5 vs. Q1		2.01 (1.38, 2.93)				As above
13544 NHS II			(320) /116671					High physical	Q5 vs. Q1		1.08 (0.7,				As above

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
13545 NHS II			(459) /116671					activity No family history of diabetes	Q5 vs. Q1		1.66) 1.69 (1.18, 2.43)				As above
13546 NHS II			(282) /116671					family history of Diabetes	Q5 vs. Q1		1.5 (0.97, 2.32)				As above
*13263 (Stevens <i>et al.</i> , 2002) ARIC	USA, Multi-ethnic	45-64 (54)  %M 44	(Subgroup cases not reported; total cohort cases 1447) /15792	9 years	FFQ (66)	Glycaemic index	Physician reports, use of diabetic medication, fasting glucose level ≥126 mg/dL or non-fasting glucose level ≥200 mg/dL.	Race - White	Continuous risk estimate	1 SD increase of exposure	1.01 (0.999, 1.003)		0.355		age, BMI, centre, education, physical activity, gender, smoking
*13264 ARIC								African- American	Continuous risk estimate	1 SD increase of exposure	0.998 (0.982, 1.015)		0.848		age, BMI, centre, education, physical activity, gender, smoking
*13067 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle-aged adults, No CHD, Normal glucose tolerance	40-70  %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Glycaemic index (Energy adjusted. Glucose as reference value)	Fasting serum/blood glucose American diabetes association Criteria, Confirmed self report		Q5 vs. Q1		1.21 (1.03, 1.43)				age, alcohol, BMI, energy intake, Income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13075 Shanghai Women's Health Study			(Subgroup cases not reported; total cohort cases 1608) /74942					WHR >0.85 (F) >0.90(M)	Q5 vs. Q1		1.35 (1.05, 1.75)			0.06	age, alcohol, BMI, energy intake, Income, occupation, physical activity, hypertension, smoking, education
13074 Shanghai Women's Health Study								WHR <0.85 (F) <0.90(M)	Q5 vs. Q1		1.17 (0.94, 1.45)			0.08	As above
13082 Shanghai Women's Health Study								BMI <25	Q5 vs. Q1		1.08 (0.82, 1.43)			0.62	age, alcohol, energy intake, Income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
13083 Shanghai Women's Health Study								BMI >25	Q5 vs. Q1		1.3 (1.06, 1.6)			<0.1	As above
13101 Shanghai Women's Health Study								Sedentary/ Low physical activity	Q5 vs. Q1		1.45 (1.04, 2.01)			0.01	age, alcohol, BMI, energy intake, Income, occupation, hypertension, smoking, waist:hip ratio, education
13104 Shanghai Women's Health Study								Med/High physical activity	Q5 vs. Q1		1.15 (0.96, 1.39)			0.11	As above
13116 Shanghai Women's Health Study								Insulin Resistance- Low Risk	Q5 vs. Q1		1.32 (1.11, 1.57)			<0.001	age, alcohol, energy intake, Income, occupation, hypertension, smoking, education
13117 Shanghai Women's Health Study								Insulin Resistance- High Risk	Q5 vs. Q1		1.32 (0.73, 2.36)			0.2	As above

\*This result was used in the meta-analysis of glycaemic index and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

## Incident Diabetes Mellitus type 2 and glycaemic load

### Summary of cohort results

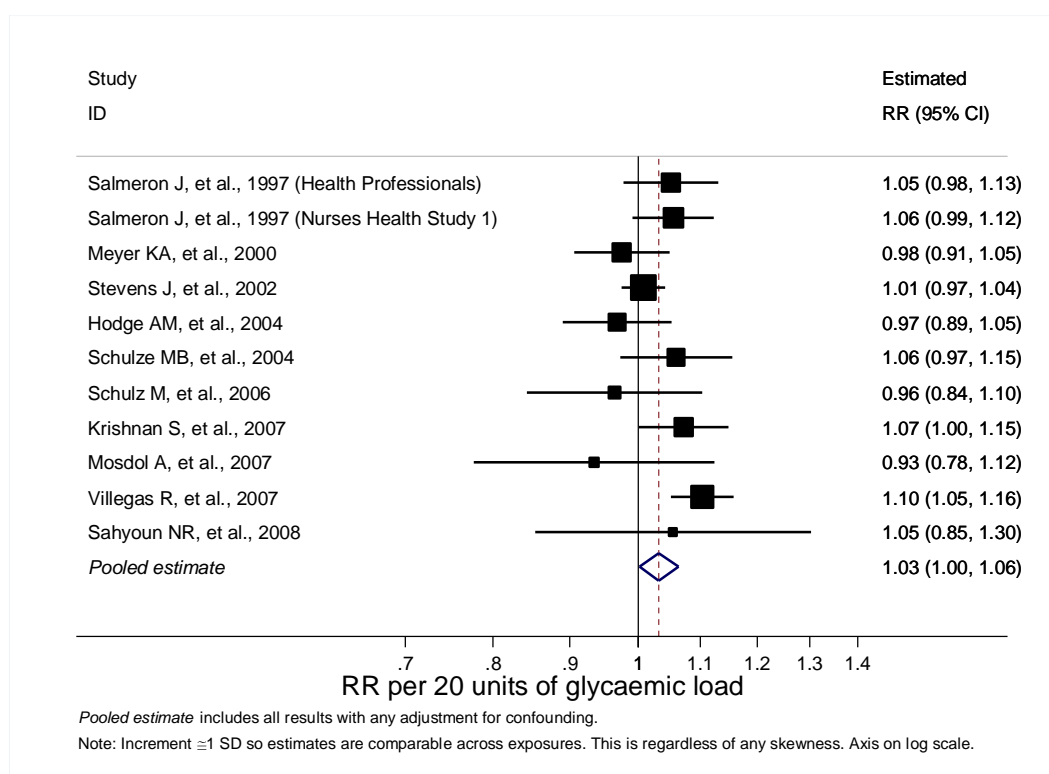
Eleven cohort studies: NHS (Halton *et al.*, 2008; Salmeron *et al.*, 1997b); the Melbourne Collaborative Cohort Study (Hodge *et al.*, 2004); the Black Women's Health Study (Krishnan *et al.*, 2007); Iowa Women's Health Study (Meyer *et al.*, 2000); the Whitehall II Study (Mosdol *et al.*, 2007); the Health, Aging, and Body Composition Study (Sahyoun *et al.*, 2008); HPFS (Salmeron *et al.*, 1997a); Insulin Resistance Atherosclerosis Study (Schulz *et al.*, 2006); NHS II (Schulze *et al.*, 2004a); ARIC (Stevens *et al.*, 2002); and the Shanghai Women's Health Study (Villegas *et al.*, 2007) contributed data on glycaemic load (GL) and risk of incident DM. These studies were conducted predominantly in the USA (8/11) (see table below).

Compared to the data on dietary GI, the evidence base for GL is more inconsistent in terms of direction of association. Four cohort studies provided some evidence of increased risk with increasing GL (although the point estimates are not always statistically significant) (Krishnan *et al.*, 2007; Schulze *et al.*, 2004a; Salmeron *et al.*, 1997b; Villegas *et al.*, 2007), but 6 studies found no evidence of an association (Stevens *et al.*, 2002; Meyer *et al.*, 2000; Salmeron *et al.*, 1997a; Sahyoun *et al.*, 2008; Schulz *et al.*, 2006; Hodge *et al.*, 2004). In the UK-based Whitehall II Study, high-dietary GL was associated with *decreased* risk of DM (Mosdol *et al.*, 2007). In this study, participants with a high GL tended to have a lower BMI, although the authors concluded that this was not masking the potential impact of GL on risk of DM.

For the meta-analysis, data were extracted from 11 of 12 publications presenting results from the 11 cohort studies (Halton *et al.*, 2008; Sahyoun *et al.*, 2008; Schulz *et al.*, 2006; Villegas *et al.*, 2007; Krishnan *et al.*, 2007; Mosdol *et al.*, 2007; Hodge *et al.*, 2004; Schulze *et al.*, 2004a; Stevens *et al.*, 2002; Meyer *et al.*, 2000; Salmeron *et al.*, 1997a; Salmeron *et al.*, 1997b). So that one paper could be included, we assumed that glycaemic load followed an approximate normal distribution with a mean of 130, and with standard deviation of 25 (Villegas *et al.*, 2007). One study (Halton *et al.*, 2008) was a later publication presenting results already published previously (Salmeron *et al.*, 1997b), and was excluded to avoid double-counting and because the later study did not present category exposure estimates. All remaining publications contributed information to the dose-response meta-analysis.

The pooled estimate of relative risk from the cohort studies was 1.03 (95% CI: 1.00 to 1.06) per 20 units of glycaemic load ( $p=0.04$ ).

Figure 4.21 Forest plot for glycaemic load and incident diabetes mellitus type 2



There was moderate heterogeneity between the cohort studies ( $I^2=45\%$  [95% CI: 0% to 73%],  $Q=18.2$ ,  $df=10$ ,  $p=0.05$ ).

There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups, though, as with glycaemic index, adjusting for family history appeared to be associated with higher estimates, though in this case this could easily be a chance finding. No one study had a dominant influence on the pooled estimate from the random effects analysis.



Table 4.36: Subgroup analyses of glycaemic load and incidence of diabetes. Relative risks are per 20 units/day.

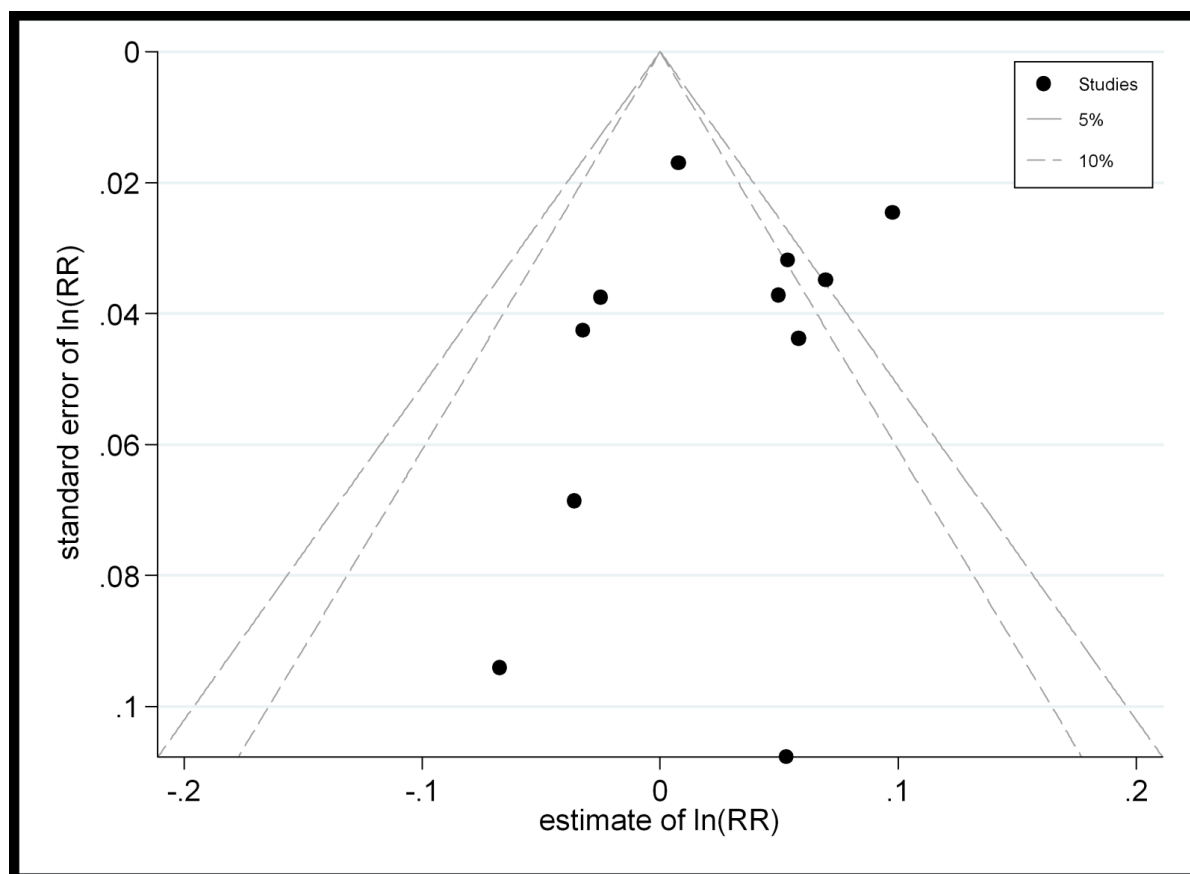
Subgroup	subgroup	RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> *	P <sub>het</sub> **
Subjects' gender	Male	1.05 (0.98, 1.13)		1		.1
	Mixed	1.00 (0.97, 1.03)	0%	5	.8	
	Female	1.06 (1.01, 1.10)	48%	5	.1	
Subjects' gender in same study	Male			0		
	Female			0		
standard used to derive GL values	glucose	1.07 (1.01, 1.13)	42%	3	.2	
	white bread	1.01 (0.97, 1.04)		1		
	not stated	1.02 (0.99, 1.06)	7%	7	.4	.2
median glycaemic load	<=130	1.03 (0.97, 1.09)	62%	6	.02	1
	>130	1.02 (0.99, 1.05)	4%	4	.4	
length of follow-up	<10 years	1.03 (1.00, 1.07)	47%	10	.05	
	>=10 years	0.93 (0.78, 1.12)		1		.6
geographic location	Americas	1.02 (1.00, 1.05)	2%	8	.4	
	EU	0.93 (0.78, 1.12)		1		
	Other	1.04 (0.91, 1.18)	86%	2	.008	.1
adjusted for age	yes	1.03 (1.00, 1.06)	45%	11	.05	
	no			0		
adjusted for alcohol	yes	1.04 (1.00, 1.08)	46%	8	.07	
	no	1.02 (0.97, 1.07)	37%	3	.2	.7
adjusted for anthropometry	yes	1.03 (1.00, 1.06)	45%	11	.05	
	no		45%	0		
adjusted for energy intake	yes	1.03 (0.98, 1.08)	59%	7	.02	
	no	1.02 (1.00, 1.05)	0%	4	.5	.9
adjusted for family history	yes	1.04 (1.01, 1.08)	0%	5	.4	
	no	1.02 (0.96, 1.07)	63%	6	.02	.5
adjusted for physical activity	yes	1.04 (1.00, 1.07)	47%	10	.05	
	no	0.96 (0.84, 1.10)		1		.4
adjusted for gender	yes	1.04 (1.00, 1.07)	47%	10	.05	
	no	0.96 (0.84, 1.10)		1		.4
adjusted for smoking	yes	1.04 (1.01, 1.07)	43%	10	.07	
	no	0.97 (0.89, 1.05)		1		.2
adjusted for age and anthropometry	yes	1.03 (1.00, 1.06)	45%	11	.05	
	no		45%	0		

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup

There was no evidence of any small-study bias such as publication bias identified through the contour-enhanced funnel plot.

Figure 4.22 Contour-enhanced funnel plot for publications presenting incident diabetes mellitus type 2 and glycaemic load



### Exposure definition and assessment

The glycaemic load (GL) is the product of a specific food's GI and its available carbohydrate content (Liu *et al.*, 2000c), therefore taking into account both the quality and quantity of carbohydrate consumed. This may be interpreted as a measure of diet-induced insulin demand (Stevens *et al.*, 2002).

All studies used previously published glycaemic index values, from a variety of sources to derive GL. For the majority, the reference food used to calculate GI values was not listed, but one source derived values using white bread (Stevens *et al.*, 2002), and three using glucose (Villegas *et al.*, 2007; Krishnan *et al.*, 2007; Schulz *et al.*, 2006).

Most studies used a similar method to calculate dietary GI and GL: namely, summing the products of the GI for each food multiplied by its carbohydrate content per serving multiplied by the average number of servings of that food per day (to give dietary GL), then dividing by the average daily carbohydrate intake to give dietary GI:

Dietary GI =  $\{\sum[(\text{servings of food per day}) \times (\text{CHO content}) \times \text{GI}]\} / \text{total CHO}$  (Meyer *et al.*, 2000).

One study, however, calculated dietary GI by summing the products of each food's GI multiplied by its percent contribution to total carbohydrate intake (Barclay *et al.*, 2007).

Two studies performed these calculations using 'digestible' (versus total) carbohydrate, which was derived by subtracting dietary fibre from total carbohydrate (Schulz *et al.*, 2006; Sahyoun *et al.*, 2008).

### ***Adjustment for appropriate confounders***

The impact of adjustment for a range of potential confounders is described by the data in Table 4.37. Since many foods with a low glycaemic index tend to be high in dietary fibre, in general the glycaemic load of a diet is likely to be strongly related to the dietary fibre content, and this means that it is difficult to dissociate the effects of GL from the fibre content. Some studies provided risk estimates adjusted for dietary fibre, although the majority did not. In the Nurse's Health Study (Salmeron *et al.*, 1997b), adjustment for cereal fibre increased the risk estimate for DM comparing the highest vs. lowest quantiles to 1.47 [95% CI: 1.16-1.86] (data not extracted). Similarly, in the Black Women's Health Study, the risk estimates were diminished in the model that did *not* include adjustment for cereal fibre intake (RR 1.01 [95% CI: 0.88-1.16, p trend 0.75] data not extracted) (Krishnan *et al.*, 2007). In the analysis of data from the Health Professionals Follow Up Study, the combination of high glycaemic load diet and a low cereal fibre intake was associated with a further increased risk of DM (RR 2.17 [95% CI: 1.04-4.54]) compared with a low GL diet and high fibre intake. The Iowa Women's Health Study provided risk estimates adjusted for dietary fibre intake (Meyer *et al.*, 2000). Glycaemic load was non-significantly inversely related to DM. Without adjustment, the point estimates were similar, and the authors concluded that 'the findings did not appear to have been due to confounding or effect modification by dietary fibre intake'.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning glycaemic load and incident DM 2.



Table 4.37 Incident Diabetes Mellitus type 2 and glycaemic load: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
14247 (Halton <i>et al.</i> , 2008) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55  %M 0	(4670) /121700	20 years	FFQ (127)	Glycaemic load (Each GL unit = 1g carbohydra te from white bread or glucose)	Multiple diagnosis methods American diabetes association Criteria, Multiple methods of diagnosis		Q10 vs. Q1		2.47 (1.75, 3.47)			<0.0001	age, alcohol, BMI, family history of DM, hormone replacement therapy, physical activity, smoking
*14245 (Hodge <i>et al.</i> , 2004) Melbourne Collaborati ve Cohort Study	Australia, Multi- ethnic, Not diabetic, Without angina or heart attack	27-75 (54)  %M 41.1	(365) /41528	4 years (14)	FFQ (121)	Glycaemic load (GI values from Foster- Powell tables 2002) Fasting serum/bloo d glucose, Glucose (random)	Clinic tested		Continuous risk estimate	100 units/day	0.85 (0.56, 1.29)		0.45		age, alcohol, country of birth, education, energy intake, family history of DM, physical activity, gender, weight change
*13274 (Krishnan <i>et al.</i> , 2007) Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69  %M 0	(1938) /59000	8 years (20)	FFQ (68)	Glycaemic load	Diagnosis criteria not reported Self-reported		(141.6) vs. (81.7)	Units	1.22 (0.98, 1.51)			0.06	age, BMI, cereal fibre, energy intake, family history of DM, energy from fat, physical activity, energy from protein, smoking
13277 Black Women's Health Study			(166) /59000					BMI <25	Q5 vs. Q1		1.54 (0.74, 3.19)			0.21	As above
13278 Black Women's Health Study			(1772) /59000					BMI >25	Q5 vs. Q1		1.19 (0.95, 1.49)			0.1	As above
*13764 (Meyer <i>et al.</i> , 2000)	USA, Primarily White,	55-69 (61)	(1141) /41836	6 years (21)	FFQ (127)	Glycaemic load	Self-reported		>136 (145) vs. <103 (94)		0.95 (0.78, 1.16)			0.53	age, alcohol, BMI, education, energy intake, smoking,

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
Iowa Women's Health Study	Middle- aged adults, Not diabetic, Post- menopausal	%M 0													physical activity, waist:hip ratio , dietary fibre intake
*14099 (Mosdol <i>et al.</i> , 2007) Whitehall II Study	England, White, Not diabetic	(50) %M 71	(329) /10308	13 years	FFQ (127)	Glycaemic load	Whole Blood Glucose OGTT (75g/120mins) Clinic tested		(168.8) vs. (121.3)	units	0.7 (0.54, 0.92)			0.011	age, Ratio: reported energy intake to estimated energy expenditure, Gender
*13412 (Sahyoun <i>et al.</i> , 2008) Health, and Aging, and Body Compositio n Study	USA, Multi- ethnic	(75) %M 46	(99) /3075	6 years	FFQ (108)	Glycaemic load (Energy adjusted)	GP report, use of insulin/oral hyperglycaemic medication, fasting serum glucose ≥126mg/dL (American diabetes association criteria)		(161.6) vs. (94.6)	units	1.3 (0.6, 2.7)			0.1147	age, alcohol, Blood glucose, BMI, centre, education, ethnicity, physical activity, gender, smoking
*13474 (Salmeron <i>et al.</i> , 1997a) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(523) /51529	6 years	FFQ (131)	Glycaemic load	Multiple diagnosis methods Confirmed self report		(203) vs. (119)		1.25 (0.9, 1.73)			0.17	age, alcohol, BMI, family history of DM, physical activity, smoking, cereal fibre
*13575 (Salmeron <i>et al.</i> , 1997b) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-65 %M 0	(915) /121700	6 years	FFQ (134)	Glycaemic load	Multiple diagnosis methods Confirmed self report		(178) vs. (111)		1.26 (1.0, 1.57)			0.09	age, alcohol, BMI, family history of DM, physical activity, smoking
*14204 (Schulz <i>et al.</i> , 2006) Insulin Resistance Atheroscle rosis Study	USA, Multi- ethnic, Impaired glucose tolerance, Normal glucose	40-69 (55) %M 46	(146) /1625	5 years	FFQ (114)	Glycaemic load (GI assessed using glucose=10 0 scale) Plasma	Clinic tested			1 Unit		-0.0018	0.6		age, waist, education, energy intake, ethnicity, impaired glucose tolerance, DM, smoking

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Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
						tolerance									
						glucose OGTT (75g/120mins)									
14269			(74) /1625					Abdominal obesity		1 Unit		-0.0017	0.74		As above
14270			(72) /1625					No abdominal obesity		1 Unit		-0.0019	0.7		As above
15091			(23) /1625					Waist decrease >2cm		1 Unit		-0.0007	0.94		As above
15092			(36) /1625					Waist stable +/- 2cm		1 Unit		-0.0131	0.1		As above
15093			(87) /1625					Waist increase >2cm		1 Unit		-0.0006	0.9		As above
*13535 (Schulze <i>et al.</i> , 2004a) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	24-44  %M 0	(741) /116671	8 years (<10)	FFQ (133)	Glycaemic load	Multiple diagnosis methods Confirmed self report		>196 (211) vs. <150 (139)	Units	1.33 (0.92, 1.91)			0.21	age, alcohol, BMI, caffeine, cereal fibre, MUFA, PUFA, SFA, energy from trans fat, energy intake, family history of DM, Hypercholesterolaemia , hypertension, magnesium Intake, oral contraceptive pill, physical activity, smoking, postmenopausal hormone replacement therapy
13547 NHS II			(114) /116671					BMI <27	Q5 vs. Q1		1.38 (0.55, 3.48)				As above
13548 NHS II			(608) /116671					BMI >27	Q5 vs. Q1		1.29 (0.86, 1.93)				As above
13549 NHS II			(421) /116671					Sedentary/ Low physical	Q5 vs. Q1		0.65 (1.01, 2.7)				As above

This document was prepared for consideration by the Scientific Advisory Committee on Nutrition. It does not necessarily represent the final views of SACN or the advice/policy of Public Health England and Health Departments.

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
activity															
13550 NHS II			(320) /116671					High physical activity	Q5 vs. Q1		1.01 (0.58, 1.75)				As above
13551 NHS II			(459) /116671					No family history of diabetes	Q5 vs. Q1		1.02 (0.64, 1.63)				As above
13552 NHS II			(282) /116671					family history of Diabetes	Q5 vs. Q1		2.04 (1.13, 3.66)				As above
*13265 (Stevens <i>et al.</i> , 2002) ARIC	USA, Multi- ethnic	45-64 (54)  %M 44	(Subgroup cases not reported; total cohort cases 1447) /15792	9 years	FFQ (66)	Glycaemic load	Physician reports, use of diabetic medication, fasting glucose level ≥126 mg/dL or non- fasting glucose level ≥200 mg/dL.	Race - White	Continuous risk estimate	1 SD increase of exposure	1.01 (0.999, 1.003)		0.35 5		age, BMI, centre, education, physical activity, gender, smoking
*13266 ARIC								African- American	Continuous risk estimate	1 SD increase of exposure	0.999 (0.996, 1.002)		0.41 4		As above
*13068 (Villegas <i>et al.</i> , 2007) Shanghai Women's Health Study	China, Middle- aged adults, No CHD, Normal glucose tolerance	40-70  %M 0	(1605) /74942	4.6 years (0.2)	FFQ (77)	Glycaemic load (Energy adjusted)	Fasting serum/blood glucose American diabetes association Criteria, Confirmed self report		Q5 vs. Q1		1.34 (1.13, 1.58)				age, alcohol, BMI, energy intake, Income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13076 Shanghai Women's Health Study			(Subgroup cases not reported) /74942					WHR <0.85 (F) <0.90(M)	Q5 vs. Q1		1.26 (1.02, 1.56)			<0.001	age, alcohol, BMI, energy intake, Income, occupation, physical activity, hypertension, smoking, education
13077 Shanghai Women's Health Study								WHR >0.85 (F) >0.90(M)	High vs. Low		1.54 (1.17, 2.02)			<0.001	As above



Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Beta	p	P trend	Adjustments
13084 Shanghai Women's Health Study								BMI <25	Q5 vs. Q1		1.18 (0.91, 1.55)			0.2	age, alcohol, energy intake, Income, occupation, physical activity, hypertension, smoking, waist:hip ratio, education
13085 Shanghai Women's Health Study								BMI >25	Q5 vs. Q1		1.52 (1.22, 1.89)			<0.001	As above
13105 Shanghai Women's Health Study								Sedentary/ Low physical activity	Q5 vs. Q1		1.66 (1.2, 2.29)			<0.001	age, alcohol, BMI, energy intake, Income, occupation, hypertension, smoking, waist:hip ratio, education
13106 Shanghai Women's Health Study								Med/High physical activity	Q5 vs. Q1		1.24 (1.02, 1.51)			0.02	As above
13118 Shanghai Women's Health Study								Insulin Resistance- Low Risk	Q5 vs. Q1		1.49 (1.25, 1.76)			<0.001	age, alcohol, energy intake, Income, occupation, hypertension, smoking, education
13119 Shanghai Women's Health Study								Insulin Resistance- High Risk	Q5 vs. Q1		1.93 (1.03, 3.63)			<0.01	As above

\*This result was used in the meta-analysis of glycaemic load and Incident DM 2

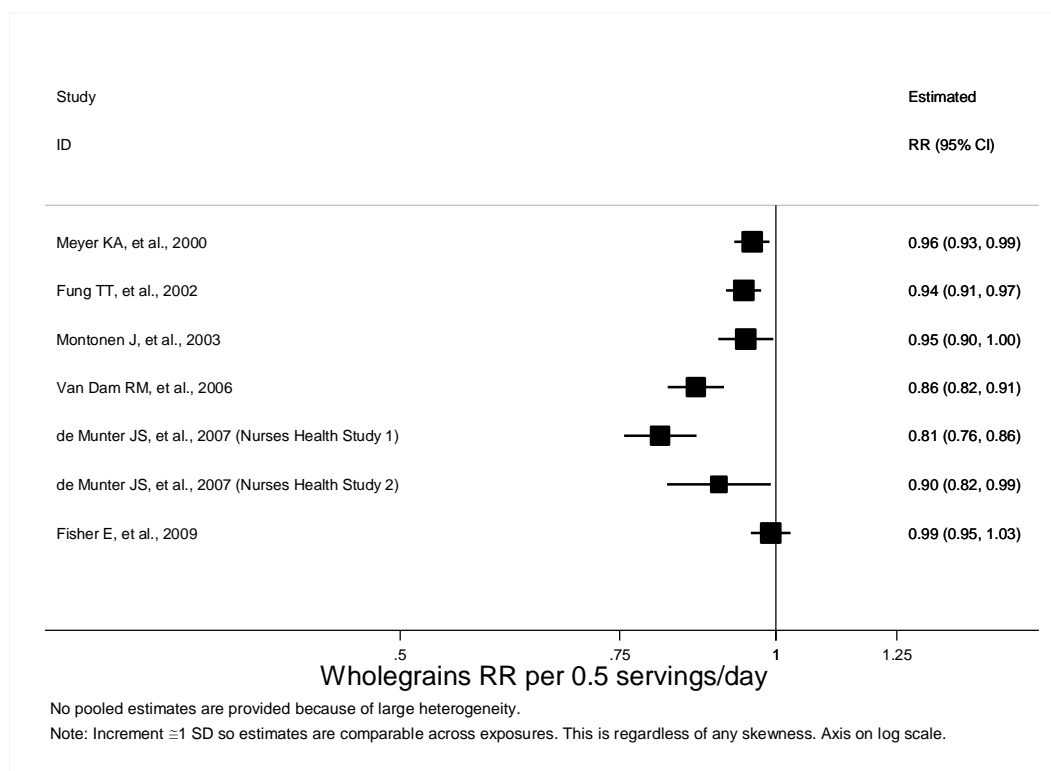
NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

# Incident Diabetes Mellitus type 2 and wholegrain

## Summary of cohort results

Data were extracted from seven publications presenting results from the following eight cohort studies: NHS, NHS II, EPIC Potsdam, HPFS, the Iowa Women's Health Study, the Finnish Mobile Clinic Health Surveys and the Black Women's Health Study (de Munter *et al.*, 2007;Fisher *et al.*, 2009;Van Dam *et al.*, 2006;Montonen *et al.*, 2003;Fung *et al.*, 2002;Liu *et al.*, 2000a;Meyer *et al.*, 2000). Of these, one publication (Liu *et al.*, 2000a) was an early analysis of data presented more fully in a later publication (de Munter *et al.*, 2007) and six publications from seven cohort studies contributed information to the dose-response meta-analysis (Fisher *et al.*, 2009;Van Dam *et al.*, 2006;Montonen *et al.*, 2003;Fung *et al.*, 2002;Liu *et al.*, 2000a;Meyer *et al.*, 2000). The German arm of EPIC presented results for two subgroups which were first combined into one estimate for that study using a fixed effects meta-analysis, before combining with the other studies (Fisher *et al.*, 2009).

Figure 4.23 Forest plot for wholegrain and incident diabetes mellitus type 2



There was excess heterogeneity between the cohort studies ( $I^2=85\%$  [95% CI: 71% to 92%],  $Q=39.8$ ,  $df=6$ ,  $p<0.001$ ). This level of heterogeneity means that a pooled estimate holds little meaning and could be misleading, so this has not been presented.

There were sufficient studies to further explore the sources of heterogeneity by subgroup analysis and meta-regression (see table below). Estimates were largely consistent across subgroups,

though use of the US Food and Drug Administration (FDA) definition of wholegrains was associated with lower estimates ( $p=0.01$ ). Stratifying by the definition of wholegrains lead to substantially improved measures of heterogeneity within each stratum. No one study had a dominant influence on the pooled estimate from the random effects analysis.

Table 4.38: Subgroup analyses of wholegrains and incidence of diabetes. Relative risks are per half serving/day.

Subgroup	subgroup	RR (95% CI)	I <sup>2</sup>	n	P <sub>het</sub> *	P <sub>het</sub> **
Subjects' gender	Male	0.94 (0.91, 0.97)		1		.3
	Mixed	0.97 (0.93, 1.02)	51%	2	.2	
	Female	0.88 (0.81, 0.96)	88%	4	<0.001	
Subjects' gender in same study	Male			0		
	Female			0		
definition of wholegrain	FDA	0.85 (0.81, 0.90)	49%	3	.1	
	Jacobs	0.95 (0.93, 0.97)	0%	3	.8	
	not stated	0.99 (0.95, 1.03)		1		.01
length of follow-up	<10 years	0.94 (0.87, 1.00)	89%	3	<0.001	
	≥10 years	0.90 (0.84, 0.96)	83%	4	<0.001	.08
geographic location	Americas	0.90 (0.85, 0.95)	86%	5	<0.001	
	EU	0.97 (0.93, 1.02)	51%	2	.2	
	Other			0		.2
adjusted for age	yes	0.92 (0.88, 0.96)	85%	7	<0.001	
	no			0		
adjusted for alcohol	yes	0.91 (0.87, 0.96)	87%	6	<0.001	
	no	0.95 (0.90, 1.00)		1		.7
adjusted for anthropometry	yes	0.92 (0.88, 0.96)	85%	7	<0.001	
	no			0		
adjusted for energy intake	yes	0.92 (0.88, 0.96)	85%	7	<0.001	
	no			0		
adjusted for family history	yes	0.90 (0.83, 0.99)	87%	2	.005	
	no	0.92 (0.87, 0.98)	86%	5	<0.001	.7
adjusted for physical activity	yes	0.91 (0.87, 0.96)	87%	6	<0.001	
	no	0.95 (0.90, 1.00)		1		.7
adjusted for gender	yes	0.92 (0.88, 0.96)	85%	7	<0.001	
	no			0		
adjusted for smoking	yes	0.92 (0.88, 0.96)	85%	7	<0.001	
	no			0		
adjusted for age and anthropometry	yes	0.92 (0.88, 0.96)	85%	7	<0.001	
	no			0		

\* P for heterogeneity within each subgroup

\*\* P for heterogeneity between each subgroup

There were insufficient studies to explore small-study bias such as publication bias through funnel plots or hypothesis tests.

### **Exposure definition and assessment**

Wholegrain intake was assessed using FFQs in six cohort studies and a dietary history in one (Montonen *et al.*, 2003). Number of food items generally ranged from 126 to 148, bar the Black Women's Health Study which used 68 items (Van Dam *et al.*, 2006). Given the limited number of items used in this latter cohort, it is questionable whether this estimate of wholegrain intake is wholly valid.

The American Association of Cereal Chemists International and the FDA define whole grains as "intact, ground, cracked or flaked fruit of the grain whose principal components, the starchy endosperm, germ and bran, are present in the same relative proportions as they exist in the intact grain" (United States FDA, 2006; American Association of Cereal Chemists International, 1999). This approach therefore includes all foods with more than 51% whole-grain content. Three cohorts (in 2 publications) applied the FDA definition for wholegrains (de Munter *et al.*, 2007; Van Dam *et al.*, 2006).

More than half of the cohorts (Liu *et al.*, 2000a; Fung *et al.*, 2002; Montonen *et al.*, 2003; Meyer *et al.*, 2000) defined wholegrain intake using classifications outlined by Jacobs and colleagues (Jacobs, Jr. *et al.*, 1998). This definition classifies the following foods as wholegrain: "dark bread", breakfast cereals with  $\geq 25\%$  wholegrain or bran by weight, brown rice, popcorn, wheatgerm, bran, cooked oatmeal and other grains including bulgar, kasha and couscous (Jacobs, Jr. *et al.*, 1998).

The remaining cohort study: the EPIC Potsdam classed the following foods as wholegrain: (whole-grain) bread, (whole-grain) rolls and (whole-grain) cereals (Fisher *et al.*, 2009). However, it should be noted that the paper does not explicitly state the wholegrain definition for these foods (Fisher *et al.*, 2009).

Ranges of wholegrain intakes were somewhat different between studies. Wholegrain intake in the Iowa Women's Health Study (Meyer *et al.*, 2000), for example, varied from less than 3 servings per week in the lowest quintile to more than 7.5 servings in the highest. Ranges of intake were also similar in the Nurses' Health Study with 10 years of follow-up (Liu *et al.*, 2000a). One US cohort: the HPFS reported an average intake of 0.4 servings per day in the lowest quintile and 3.2 servings per day in the highest quintile whereas another: the Black Women's Health Study compared less than one wholegrain serving per week to more than one daily serving (Fung *et al.*, 2002; Van Dam *et al.*, 2006). Intakes of wholegrain in a US and German cohort also showed differences – the Nurses' Health Study and Nurses' Health Study II ranged from 3.7-6.2g in the lowest quintile and 31.2-39.9g in the highest whilst the EPIC Potsdam cohort used a continuous risk estimate per 50g/day portion (de Munter *et al.*, 2007; Fisher *et al.*, 2009).

Compared to the US cohort studies, the Finnish Mobile Clinic Health Surveys study had a considerably higher wholegrain intake (de Munter *et al.*, 2007; Montonen *et al.*, 2003). Daily intakes in this cohort ranged from 0-109g in the lowest quintile to 1238-1321g in the highest. According to Montonen *et al.* (Montonen *et al.*, 2003) wholegrain intakes in the Finnish Mobile Clinic Health Surveys cohort primarily consisted of rye bread whereas breakfast cereals and yeast breads were found to be more typical contributors to wholegrain intake in the US (Cleveland *et al.*, 2000).

Such variation in wholegrain intake and range of intakes must therefore be considered with regard to the findings.

It is recommended that Americans eat at least three portions (around 85g) of whole grains per day, yet the UK, Finland and Germany do not currently have any specific recommendations other than the respective recommendations “to choose whole-grain varieties whenever you can”, “increase consumption of whole-grain cereal products” and “[consume] bread, pasta, rice, grain flakes, preferably from whole grain” (USDA, 2010; Food Standards Agency, 2010; National Nutrition Council of Finland, 2011; The German Nutrition Society (DGE), 2011).

### ***Adjustment for appropriate confounders***

In the Iowa Women’s Health Study, the inverse association observed between wholegrains and risk of DM was attenuated after the models were adjusted for cereal fibre (Zaveri and Drummond, 2009). Comparing the highest against the lowest quintile the relative risk was 0.93 (p for trend: 0.46) which suggests that some of the association between wholegrains and reduced risk may be attributable to the fibre content. Given that the other six studies also did not adjust for fibre content in the wholegrain models, it is possible that such relationships may be confounded by dietary fibre.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

One trial provided data on the effect of higher wholegrain intakes on incident DM. In the study by Tinker *et al.* (Tinker *et al.*, 2008), participants were randomised to either an intensive intervention group which included individual sessions designed to reduce fat intake to 20% of total energy and increase consumption of fruits, vegetables and grains or a comparison group which received diet-related education materials only.

The percentage of participants in each group experiencing incident DM 2 events was very similar and the hazard ratios which compared the low-fat, higher wholegrain intervention group with the comparison group did not show any clear direction of association or a statistically significant result for incident DM.

Results from this trial should be interpreted with caution as dietary components were altered other than wholegrain content, the absolute difference between groups in terms of wholegrain intake was very small (0.3 servings/day) and the low fat, wholegrain diet group experienced weight loss but the comparison group did not.

Table 4.39 Incident Diabetes Mellitus type 2 and wholegrain: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
*14104 (de Munter <i>et al.</i> , 2007) NHS	USA, Primarily White, Cancer free, No CHD, Not diabetic	30-55 %M 0	(4747) /121700	18 years	FFQ (126)	Wholegrains, FDA definition (Food and Drug Administration (US), 2006) (Whole wheat and whole wheat flour, whole oats and flour, whole cornmeal and flour, brown rice, whole rye and flour, whole barley, bulgar, buckwheat, popcorn, amaranth and psyllium)	Diagnosis criteria not reported Confirmed self report		(31.2) vs. (3.7)	g/day	0.63 (0.57, 0.69)	<0.001	age, alcohol, Coffee, energy intake, DM, hormone replacement therapy, oral contraceptive pill, physical activity, PUFA:SFA, Processed Meat, smoking, SSB
*14107 (de Munter <i>et al.</i> , 2007) NHS II	USA, Primarily White, Cancer free, No CHD, Not diabetic	26-44 %M 0	(1739) /116671	12 years	FFQ (133)	As above	Diagnosis criteria not reported Confirmed self report		(39.9) vs. (6.2)	g/day	0.68 (0.57, 0.81)	<0.001	As above
*13648 (Fisher <i>et al.</i> , 2009) EPIC Potsdam	Germany, primarily white, Not diabetic, genetic rs7903146 CC	35-65 %M 40	(375)/1249	7 years	FFQ (148)	Wholegrains: definition unclear (Sum of whole-grain bread, whole-grain rolls and whole-grain cereals)	Confirmed self report		Continuous risk estimate	50g/day	0.86 (0.75, 0.99)		age, gender, BMI, waist, education, physical activity, smoking, alcohol, meat, low-fat dairy, butter, margarine and vegetable fat, coffee, EI
*13649 EPIC Potsdam	Germany, primarily white, Not diabetic,  transcription factor-7-like 2 (TCF7L2) rs7903146 genotype – CT+TT	35-65 %M 40	(397)/976	7 years	FFQ (148)	As above	Confirmed self report		Continuous risk estimate	50g/day	1.08 (0.96, 1.23)		As above

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
*13461 (Fung <i>et al.</i> , 2002) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(1197) /51529	12 years (6)	FFQ (131)	Wholegrains, non- FDA definition (as described in (Jacobs, Jr. <i>et al.</i> , 1998) (Wholegrains included brown rice, dark breads, whole- grain ready to eat cereals (>25% whole- grain content by weight), cooked cereal, popcorn, wheat germ, bran and other grains)	Multiple diagnosis methods Confirmed self report		(3.2) vs. (0.4)	servings/day	0.58 (0.47, 0.7)	<0.0001	age, alcohol, energy intake, family history of DM, fruit, Missing dietary data, Assessment period, Period of exposure, physical activity, smoking, vegetable intake
13420 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Wholegrain Ratio (Refined:whole grain), non-FDA definition (as described in (Jacobs, Jr. <i>et al.</i> , 1998)	Self reported, and confirmed by the National Diabetes Data Group		Q5 vs. Q1		1.26 (1.08, 1.46)	0.01	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake
13430 NHS						Wholegrains, non- FDA definition (Jacobs, Jr. <i>et al.</i> , 1998) (Other whole grains excluding: dark bread, whole-grain breakfast cereal, popcorn, cooked oatmeal, brown rice, wheat germ and bran)	Self reported, and confirmed by the National Diabetes Data Group		≥1 vs. 0	times/week	0.77 (0.63, 0.94)	0.02	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake
*13725 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle- aged adults, Not diabetic, Post- menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Wholegrains, as defined by Jacobs <i>et al.</i> 1998 (Jacobs, Jr. <i>et al.</i> , 1998)	Self-reported		>7.15 (20.5) vs. <3 (1)	servings/week	0.79 (0.65, 0.96)	0.008	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13149 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle-aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Wholegrain (excluding Rye) Non- FDA definition, as defined by Jacobs <i>et al.</i> 1998 approach (Jacobs, Jr. <i>et al.</i> , 1998)	Diagnosis criteria not reported Registry data, WHO criteria		76-632 vs. 0-5	g/day	1.14 (0.69, 1.87)	0.69	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
*13147 Finnish Mobile Clinic Health Surveys			(156) /4316			Total wholegrain foods (including rye products) Non-FDA definition, classified using a modified Jacobs <i>et al.</i> 1998 approach (Jacobs, Jr. <i>et al.</i> , 1998)			238-1321 (302) vs. 0- 109 (79)	g/day	0.65 (0.36, 1.18)	0.02	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
13198			(32) /4316					Smokers	Q4 vs. Q1		0.41 (0.12, 1.41)		age, BMI, energy intake, fruit, region, gender, vegetable intake
13199			(84) /4316					No hypertensives	Q4 vs. Q1		0.9 (0.44, 1.85)		age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
13200			(72) /4316					Hypertensives	Q4 vs. Q1		0.35 (0.13, 0.94)		As above
13201			(68) /4316					No hypercholesterolaemia	Q4 vs. Q1		0.52 (0.24, 1.13)		As above
13202			(88) /4316					With hypercholesterolaemia	Q4 vs. Q1		0.81 (0.37, 1.74)		As above
13203			(Cases not reported)/4316					Lowest tertile of Refined Grain	Q3 vs. Q1		0.6 (0.3, 1.19)		As above
13204			(Cases not reported)/4316					Highest tertile of Refined Grain	Q3 vs. Q1		0.73 (0.27, 1.97)		As above
13180			(24) /4316					Age <50	Q4 vs. Q1	g/day	0.52 (0.13, 2.09)		BMI, energy intake, fruit, region, gender, smoking, vegetable intake



Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
13184			(132) /4316					Age >50	Q4 vs. Q1	g/day	0.74 (0.4, 1.38)		As above
13191			(54) /4316					Men	Q4 vs. Q1	g/day	0.43 (0.18, 1)		age, BMI, energy intake, fruit, region, smoking, vegetable intake
13192			(102) /4316					Women	Q4 vs. Q1	g/day	0.91 (0.44, 1.86)		As above
13194			(33) /4316					BMI <27	Q4 vs. Q1	g/day	0.93 (0.36, 2.41)		age, energy intake, fruit, region, gender, smoking, vegetable intake
13196			(123) /4316					BMI >27	Q4 vs. Q1	g/day	0.57 (0.28, 1.14)		As above
13197			(124) /4316					Non-smokers	Q4 vs. Q1	g/day	0.76 (0.4, 1.42)		age, BMI, energy intake, fruit, region, gender, vegetable intake
*13272 (Van Dam <i>et al.</i> , 2006) Black Women's Health Study	USA, Black, Cancer free, No CHD, Not diabetic	21-69 %M 0	(1964) /59000	8 years (20)	FFQ (68)	Wholegrains, FDA definition (Food and Drug Administration (US), 2006) (Dark breads such as wheat, rye, pumpernickel. High fibre, bran or granola cereals and shredded wheat)	Diagnosis criteria not reported Self-reported	≥daily (1.29) vs. <1 serv/week (0.03)	servings/day	0.69 (0.6, 0.79)	<0.0001		age, alcohol, BMI, Coffee, education, energy intake, family history of DM, Low fat dairy, physical activity, Processed Meat, Red Meat, smoking, sugar sweetened beverages

\*This result was used in the meta-analysis of wholegrain and Incident DM 2

NB – Duplicate cohort characteristic data are not presented for subgroups within cohorts, but the subgroup data are presented directly underneath data from the total cohort.

Table 4.40 Incident Diabetes Mellitus type 2 and wholegrain: RCT data

Result ID/Author	Intervention group	Completers/ Allocated	% of group experiencing event	Outcome/ Assessment method	Contrast	RR (95% CI)	p	Result- specific follow-up	Weight Change	Outcome Assessment Bias
17625 (Tinker <i>et al.</i> , 2008) The women's	Low fat Control	18376/19541 27511/29294	7.1 7.4	Incident diabetes mellitus	Control	0.96 (0.90, 1.03)	0.25	8.1 years	Decrease No change	No bias

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health initiative dietary modification trial	type 2 Self-reported and use of insulin/oral hypoglycaemic medication	(reference) vs. Low fat
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# Incident Diabetes Mellitus type 2 and refined grains

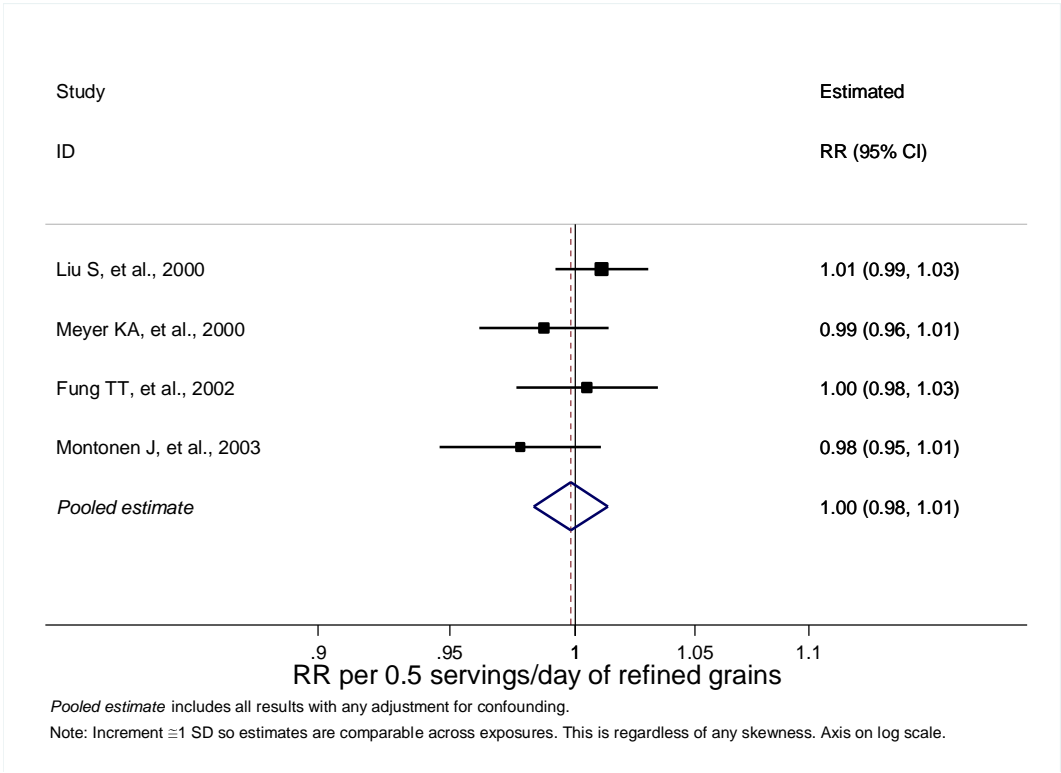
## Summary of cohort results

Data were extracted from four publications presenting results from four cohort studies: Finnish Mobile Clinic Health Surveys, HPFS, NHS and the Iowa Women’s Health Study (Montonen *et al.*, 2003;Fung *et al.*, 2002;Liu *et al.*, 2000a;Meyer *et al.*, 2000). One study was conducted in Finland, and 3 in the USA. These studies do not provide evidence of a clear direction of association between refined grain consumption and risk of DM.

For the meta-analysis, one publication (Liu *et al.*, 2000a) could only be included because a form of quantification of the dietary exposure could be derived from a separate paper from the same cohort (Liu *et al.*, 2000b). So that two studies could be included, a standard serving of refined grains was assumed to be approximately 40 grams (Montonen *et al.*, 2003;Meyer *et al.*, 2000).

The pooled estimate of relative risk from the cohort studies was 1.00 (95% CI: 0.98 to 1.01) per half serving of refined grains per day (p=0.7).

Figure 4.24 Forest plot for refined grains and incident diabetes mellitus type 2



There was a little heterogeneity between the cohort studies ( $I^2=26\%$  [95% CI: 0% to 72%],  $Q=4.1$   $df=3$ ,  $p=0.3$ ).

There were insufficient studies to explore the heterogeneity further through stratified forest plots or meta-regression. There were insufficient studies to explore small-study bias such as publication bias through funnel plots or hypothesis tests. No single study dominated the results.

### ***Exposure definition and assessment***

The refined grain exposures reported in these 4 cohorts varied in terms of the foods listed, but generally included wheat-based sweet and savoury foods based on refined flours rather than the wholegrain versions.

### ***Adjustment for appropriate confounders***

The cohort results were all adjusted for age, energy intake and smoking. Other than the Health Professionals Follow-Up Study (Fung *et al.*, 2002), the results extracted were also adjusted for BMI. In the HPFS, further inclusion of BMI in the model did not influence the point estimates or significance of the test for trend across the quantiles (data not in tables). None provided results adjusted for dietary fibre. In the Nurses' Health Study, exploration of the ratio of refined grain to whole grain intake in relation to risk of DM was undertaken (Liu *et al.*, 2000a). Compared with women in the quintile with the lowest ratio (high wholegrain and low refined grain consumers), women in the highest quintile had a 26% increase in risk of DM (RR=1.26; 95% CI=1.08, 1.46;  $p=.01$  for trend), reflecting the beneficial association observed for wholegrains and positive association for refined grains in this cohort.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning refined grains and incident DM 2.

Table 4.41 Incident Diabetes Mellitus type 2 and refined grains: cohort studies in adults

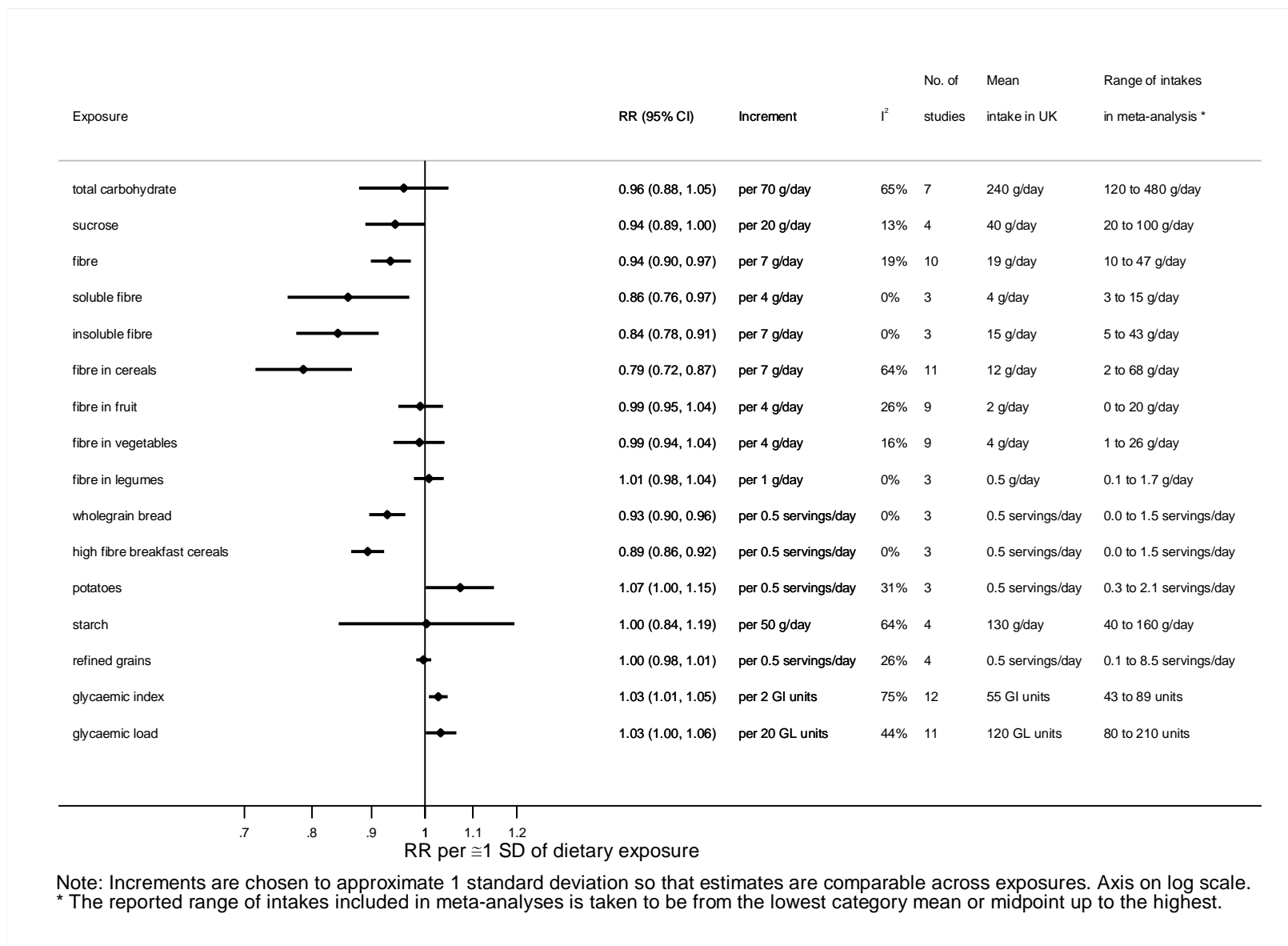
Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment Details	Contrast (mean)	Units	RR (CI)	P trend	Adjustments
*13462 (Fung <i>et al.</i> , 2002) HPFS	USA, Primarily White, Cancer free, No CHD, Not diabetic	40-75 %M 100	(1197) /51529	12 years (6)	FFQ (131)	Refined grains (white bread, white rice, English muffins, pancakes, waffles, cakes, sweet rolls, refined grain ready-to-eat cereal, muffins, biscuits and pizza)	Multiple diagnosis methods Confirmed self report	(4.1) vs. (0.8)	servings/day	1.01 (0.82, 1.25)	0.78	age, alcohol, energy intake, family history of DM, physical activity, smoking, fruit, vegetable intake
*13419 (Liu <i>et al.</i> , 2000a) NHS	USA, Primarily White, No CHD, Not diabetic	30-55 %M 0	(1879) /121700	10 years	FFQ (126)	Refined grain foods, total (sweet rolls, cakes, desserts, white bread, pasta, English muffin, muffins or biscuits, refined-grain breakfast cereal, white rice, pancakes, waffles and pizza)	Self reported, and confirmed by the National Diabetes Data Group	Q5 vs. Q1	servings/day	1.11 (0.94, 1.3)	0.26	age, alcohol, BMI, energy intake, family history of DM, physical activity, smoking, vitamin intake
*13773 (Meyer <i>et al.</i> , 2000) Iowa Women's Health Study	USA, Primarily White, Middle-aged adults, Not diabetic, Post-menopausal	55-69 (61) %M 0	(1141) /41836	6 years (21)	FFQ (127)	Refined grains	Self-reported	>22 (29.5) vs. <6 (3.5)	servings/week	0.87 (0.7, 1.08)	0.36	age, alcohol, BMI, education, energy intake, smoking, physical activity, waist:hip ratio
13151 (Montonen <i>et al.</i> , 2003) Finnish Mobile Clinic Health Surveys	Finland, Middle- aged adults, Not diabetic	40-69 %M 53	(156) /4316	10 years	Dietary history	Refined grains from wheat only	Diagnosis criteria not reported Registry data, WHO criteria	91-389 vs. 0-33	g/day	0.69 (0.41, 1.17)	0.11	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake
*13150 Finnish Mobile Clinic Health Surveys						Refined grain foods, total (White bread, wheat rusk, cream crackers, refined breakfast cereal, polished rice, pasta, white wheat flour)	Diagnosis criteria not reported Registry data, WHO criteria	111-567 vs. 0-45	g/day	0.62 (0.36, 1.06)	0.05	age, BMI, energy intake, fruit, region, gender, smoking, vegetable intake

\*This result was used in the meta-analysis of refined grains and Incident DM 2

## Pooled estimate plot for Diabetes Mellitus Type 2

The following plot includes all the calculated pooled risk estimates from previous sections on the relationship between carbohydrate and incident DM derived from cohort studies. These have been plotted together to give an over-arching picture of the relationship of various carbohydrate exposures for incident DM. Please refer back to previous sections for further detail on each point estimate to aid interpretation of these pooled results. Please also refer back to the review methods for justification of the size of increments used, approximating one standard deviation for each exposure, so that the point estimates for each exposure are on comparable scales.

Figure 4.25 Pooled estimate plot for all exposures and incident type 2 diabetes mellitus





# **Glycaemia, impaired glucose tolerance, insulinaemia, insulin resistance and glycated haemoglobin**

This section of the report documents evidence concerning aspects of dietary carbohydrate and markers of carbohydrate metabolism, including fasting blood glucose, responses to an oral glucose tolerance test (OGTT), fasting blood insulin, insulin response to OGTT, incident impaired glucose tolerance (IGT), glycated haemoglobin (predominantly HbA1c, the product of a chemical reaction between haemoglobin and blood glucose, which represents an average blood glucose level during the preceding 10-12 weeks) and direct and surrogate markers of insulin resistance and sensitivity.

## **Total carbohydrate and carbohydrate density**

### **Incidence of impaired glucose tolerance and total carbohydrate/ carbohydrate density**

#### **Summary of cohort results**

Two studies, reported in 3 papers provided data on total carbohydrate intake expressed as grams per day or percentage of energy and incidence of impaired glucose tolerance (Feskens *et al.*, 1991; Feskens *et al.*, 1995; Leonetti *et al.*, 1996). In the Zutphen Elderly Study, the Dutch contribution to the Seven Countries Study, with 4 years of follow-up, there was evidence of increased risk of impaired glucose tolerance with increasing carbohydrate intake after adjustment for covariates (Feskens *et al.*, 1991). However, in the study of Japanese American men, carbohydrate consumption did not differ greatly between the cases and non-cases of impaired glucose tolerance (Leonetti *et al.*, 1996). In both the Zutphen Elderly Study and the Seven Countries Study, the percentage of energy from carbohydrate was similar in cases and non-cases (Feskens *et al.*, 1991; Feskens *et al.*, 1995). Overall, these studies do not provide evidence of a consistent direction of association between carbohydrate intake and development of impaired glucose tolerance.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

#### ***Exposure definition and assessment***

Total carbohydrate was assessed by dietary history or by FFQ in these cohort studies.

### ***Adjustment for appropriate confounders***

The Zutphen Elderly Study included important covariates in their model exploring total carbohydrate and impaired glucose tolerance (Feskens *et al.*, 1991). All other data were unadjusted or relatively unadjusted and should therefore be interpreted cautiously.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

No RCTs reported outcomes concerning total carbohydrate and incidence of impaired glucose tolerance.

### **Carbohydrate density**

#### **Summary of cohort results**

In the Seven Countries Study with both 4 and 20 years of follow-up (Feskens *et al.*, 1991; Feskens *et al.*, 1995), and in a study of Japanese-American Men (Leonetti *et al.*, 1996) carbohydrate intakes were similar in cases and non-cases of impaired glucose tolerance. In the Seven Countries Study, however, the risk estimate for the development of impaired glucose tolerance was indicative of increasing risk with increasing carbohydrate intake after adjustment for age, alcohol intake, BMI, energy intake, gender and smoking (RR for highest vs. lowest intake categories 2.97, 95% CI: 1.3, 6.79).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

#### **Summary of RCT results**

One trial reported by Swinburn *et al.* (Swinburn *et al.*, 2001) published impaired glucose tolerance events in relation to high carbohydrate diets (Tinker *et al.*, 2008; Swinburn *et al.*, 2001). The authors randomly allocated participants (n=176) to a low fat group, which consisted of a 1-year structured program which aimed to reduce total fat in participants' habitual diets, or a control group, in which participants received general healthy eating advice. At 1 year follow-up, there were a statistically significantly smaller number of participants who had either incident DM or impaired glucose tolerance in the low fat group compared to those in the control group (Swinburn *et al.*, 2001). No statistically significant differences were observed at the 2, 3 of 5 year time-points.

It is important to note however that participants in the low fat group lost weight throughout the trial, whereas the control group did not.

Table 4.42 Impaired glucose tolerance and total carbohydrate: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Sub-group Detail	Contrast (mean)	Units	RR (CI)	Mean exposure (SD)	Adjustments
13874 (Feskens <i>et al.</i> , 1991) Zutphen Elderly Study	The Netherlands	(70) %M 100	(59) /175	4 years	Dietary history	Carbohydrate, total (% energy)	Impaired glucose tolerance Clinic tested			% Energy		Cases: (n: 59) 42.1 (5.4) Non-cases: (n: 116) 40.2 (7.1)	
13894 Zutphen Elderly Study						Carbohydrate, total (grams/day)	Impaired glucose tolerance Clinic tested		>228.8 vs. <205	g/day	2.97 (1.3, 6.79)		age, alcohol, BMI, energy intake, gender, smoking
13269 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	(71) /338	20 years	Dietary history	Carbohydrate, total (% energy)	Impaired glucose tolerance  Fasting			% Energy		Cases: (n: 71) 48.4 Non-cases: (n: 241) 48.8	age, Cohort
14615 (Leonetti <i>et al.</i> , 1996) Japanese- American Men Diabetes Study	USA, Asian, Not diabetic	45-74 %M 100	(27) /229	5 years (5.6)	FFQ Interview (89)	Carbohydrate, total (grams/day)	Impaired glucose tolerance Confirmed self report	Normal glucose tolerance at baseline		g/day		Cases: (n: 27) 275.1 (89.7) Non-cases: (n: 42) 275.6 (77.9)	
14620 Japanese-American Men Diabetes Study			(9) /229					IGT at baseline		g/day		Cases: (n: 23) 246.8 (74.3) Non-cases: (n: 23) 238.8 (72.2)	

Table 4.43 Impaired glucose tolerance and carbohydrate type: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Mean exposure (SD)	Adjustments
14640 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	(71) /338	20 years	Dietary history	Mono and disaccharides	Impaired glucose tolerance  Fasting	% Energy	Cases: (n: 71) 25 Non-cases: (n: 241) 24.7	age, Cohort
14642 Seven Countries Study						Polysaccharides (>10), unspecified	Impaired glucose tolerance  Fasting	% Energy	Cases: (n: 71) 23.4 Non-cases: (n: 241) 24.1	age, Cohort
14644 Seven Countries Study								g/1000kcal	Cases: (n: 71) 10.2 Non-cases: (n: 241) 10.1	age, Cohort

Table 4.44 Impaired glucose tolerance and high carbohydrate diets: RCT data

Result ID/Author	Intervention group	Completers/Allocated	% of group experiencing event	Outcome/ Assessment method	p value difference between groups	Result-specific follow-up	Weight Change	Outcome Assessment Bias
17630 (Swinburn <i>et al.</i> , 2001) New Zealand Diabetic Workforce Study	Low fat diet	70/70	47%	Incident diabetes type II or Impaired glucose tolerance	<0.05	1 year	Decrease	unclear
	Control diet	66/66	67%	Plasma glucose OGTT (75g/ 120 mins) WHO criteria			No change	
17631	Low fat diet	70/70	Data were presented in a figure and could not be extracted		NS	2 years	Decrease	
	Control diet	66/66	As above				No change	
17632	Low fat diet	70/70	As above		NS	3 years	Decrease	
	Control diet	66/66	As above				No change	
17633	Low fat diet	70/70	As above		NS	5 years	Decrease	
	Control diet	66/66	As above				No change	

## **Glycaemia and total carbohydrate/carbohydrate density and high carbohydrate diets**

### **Total carbohydrate**

#### **Summary of cohort results**

Four studies provided data on total carbohydrate expressed as grams per day; percentage of energy or change in intake and glycaemia (Leonetti *et al.*, 1996; Feskens *et al.*, 1995; Schroeder *et al.*, 2007; Mayer-Davis *et al.*, 2006). The outcome was defined as either blood glucose level or area under the curve following a 2-hour glucose tolerance test. One study also presented results according to fasting glucose levels (Mayer-Davis *et al.*, 2006). None of the results showed evidence of a statistically significant relationship between total carbohydrate intake and glycaemia.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

#### ***Exposure definition and assessment***

Total carbohydrate was assessed by dietary history or by FFQ in these cohort studies.

#### ***Adjustment for appropriate confounders***

Age was adjusted for in all studies. The Middle Aged Runners Study (Schroeder *et al.*, 2007) only adjusted for age and should be interpreted cautiously. The other analyses all also adjusted for BMI and energy intake plus other potential confounders. The Insulin Resistance Atherosclerosis Study was most fully adjusted (Mayer-Davis *et al.*, 2006).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Carbohydrate density**

#### **Summary of cohort results**

Two studies provided data on carbohydrate density and glycaemia (Feskens *et al.*, 1995; Mayer-Davis *et al.*, 2006). Carbohydrate density was expressed as density of sugars from food at baseline as a percentage of energy or as density of the change in intake of sugars from food over follow up as a percentage of energy. The outcome was expressed as either blood glucose level or area under the curve following a 2-hour oral glucose tolerance test or fasting blood glucose. The Seven Countries Study (Feskens *et al.*, 1995) showed no evidence of a statistically significant association between carbohydrate density and blood glucose levels. The Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006) found evidence of an inverse relationship between glucose response to an oral glucose tolerance test expressed as area under the curve

and dietary density of both fructose and glucose. However, when fasting-blood glucose levels were the outcome, there was no significant relationship and the direction of effect was reversed. Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

### ***Exposure definition and assessment***

Carbohydrate density was only expressed as density of specific (mono or di-saccharides) or total sugars. It was assessed by diet history or FFQ.

### ***Adjustment for appropriate confounders***

The Insulin Resistance Atherosclerosis Study was more fully adjusted than the Seven Countries Study, although both included a number of confounding factors in analyses.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

Forty seven studies, reported in 53 papers, explored the effects of dietary variation in carbohydrate proportion of diets – replacing carbohydrate with fat and/ or protein – on blood glucose. Of these studies, four also reported blood glucose during the first 120 minutes following an oral glucose tolerance test (Due *et al.*, 2008a; Foster *et al.*, 2003; Swinburn *et al.*, 2001; Lasker *et al.*, 2008).

All studies, bar four, implemented a parallel group design. The exceptions were Sharman *et al.* (Sharman *et al.*, 2004) and Segal-Isaacson *et al.* (Segal-Isaacson *et al.*, 2004) which opted for a crossover approach and Dale *et al.* (Dale *et al.*, 2009) and Racette *et al.* (Racette *et al.*, 1995) which used a factorial design. Most studies did not indicate the extent of blinding, however nine were reported as open, three as single blind and two as double blind.

Studies were carried out in a variety of countries, such as the USA (22), Australia (6), Canada (3), Denmark (1), Switzerland (2), New Zealand (2), Spain (1), Israel (1), the UK (1), France (1), Germany (1), Scotland (1), Sweden (1), the Netherlands (1) and Europe as a whole (1).

The majority of trials used adults as participants, although one trial by (Demol *et al.*, 2009) recruited adolescents aged 12-18 years. Thirteen studies recruited females only (Brehm *et al.*, 2003; Leidy *et al.*, 2007; Mahon *et al.*, 2007; Meckling and Sherfey, 2007; Clifton *et al.*, 2004; Dale *et al.*, 2009; Gardner *et al.*, 2007; Kirkwood *et al.*, 2007; Lofgren *et al.*, 2005; Racette *et al.*, 1995; Segal-Isaacson *et al.*, 2004; Howard *et al.*, 2006; Tinker *et al.*, 2008; Clifton *et al.*, 2008; Noakes *et al.*, 2005) and four studied males (Sharman *et al.*, 2004; Helge, 2002; Landry *et al.*, 2003; Lovejoy *et al.*, 2003).

Average BMI of study participants was  $\geq 25 \text{ kg/m}^2$  in those trials reporting this and trials were mainly conducted on overweight or obese individuals. Other than one particularly large study (The Women's Health Initiative Dietary Modification Trial of 48,835 participants), final sample sizes ranged from 4 (Segal-Isaacson *et al.*, 2004) to 811 (Sacks *et al.*, 2009) participants (mean=130; median=63).

Forty three studies were included in the meta-analyses comparing different carbohydrate intakes and blood glucose levels. There were seven studies that reported results from three groups. For each of these studies the group with the lowest carbohydrate intake was compared with the highest carbohydrate intake. There were five studies that reported results for four groups. For two studies the groups with lowest carbohydrate were compared with the highest carbohydrate (Morgan *et al.*, 2009; Dansinger *et al.*, 2005). The remaining three studies were separated into two groups of participants; lower and higher body fat (Bowden *et al.*, 2007), moderate and high protein (Sacks *et al.*, 2009) or low and high GI (McMillan-Price *et al.*, 2006).

Forty seven studies measured fasting blood glucose, but three also provided data arising from oral glucose tolerance tests; either the area under the curve, or glucose levels at 2 hours post-load (Due *et al.*, 2008a; Foster *et al.*, 2003; Swinburn *et al.*, 2001). Those that measured AUC glucose did not observe statistically significant changes within or between groups. These data were not included in a meta-analysis due to an insufficient number of studies.

The studies measuring fasting blood glucose were analysed according to which macronutrients changed as a result of a change in carbohydrate. Trials were separated into 3 main types on the basis of the proportion of energy derived from the macronutrients. For inclusion in a meta-analysis a 5% difference in energy from carbohydrate was taken as meaningful. Actual consumption was used rather than the intended diet unless otherwise stated – see trial characteristics table.

If a trial tested the effects of diets which differed by 5% or more of energy from carbohydrate it was then further categorised into one of 3 categories. Higher carbohydrate, lower fat diets were differentiated from lower carbohydrate, higher fat diets where percentage of energy from fat also differed by 2% or more. Higher carbohydrate, lower protein diets were differentiated from lower carbohydrate, higher protein diets where percentage of energy from protein differed by 2% or more and higher carbohydrate, lower protein and fat diets were differentiated from lower carbohydrate, higher protein and fat diets where percentage of energy from fat was 2% or more, but protein intakes were also different by more than 2%.

Two studies were not included in the meta-analysis as the between group difference in carbohydrate was less than 5% (Dale *et al.*, 2009; Clifton *et al.*, 2008). Neither Dale *et al.* (Dale *et al.*, 2009) nor Clifton *et al.* (Clifton *et al.*, 2008) showed significant between group differences in fasting blood glucose.

One study was excluded as there were no data for one of the groups (Kirkwood *et al.*, 2007). This randomised control trial reported by Kirkwood *et al.* (Kirkwood *et al.*, 2007) compared the effects of a conventional weight loss diet to a 'no advice' group and an exercise group to a conventional weight loss diet plus exercise group. Fasting blood glucose, measured at 12 weeks, had increased from baseline in the conventional weight loss diet group ( $p=0.01$ ) but not in the remaining groups. This outcome also differed between conditions as the conventional weight loss diet group experienced a statistically significant increase compared with the 'no advice' group ( $p=0.05$ ). No differences between the exercise group and the conventional weight loss diet plus exercise group were observed.

Similarly, in the study by Mahon *et al.* (Mahon *et al.*, 2007) which compared a control diet with an energy restricted diet plus 250kcal/day from beef, an energy restricted diet plus 250kcal/d from chicken and an energy restricted diet plus 250kcal/d from carbohydrate/ fat foods, the authors did not report differences in fasting glucose either within or between groups. This study could not be incorporated into the meta-analysis as insufficient data were available (Mahon *et al.*, 2007).

One further study was not included in the meta-analysis as participants used were adolescents aged 12-18 years (Demol *et al.*, 2009). This study compared the effects of a high carbohydrate, low fat diet with lower carbohydrate diets that varied in the proportion of energy derived from fat or protein (Demol *et al.*, 2009). Fasting blood glucose, measured at 12 weeks and 1 year, was not significantly different between diet groups.

Data from two papers (de Luis *et al.*, 2008; de Luis *et al.*, 2009a) which explored the dietary impact of high compared with low carbohydrate diets in individuals with different genetic profiles were not included in the meta-analysis as it was considered that these were from the same study as de Luis *et al.* (de Luis *et al.*, 2009b). In one paper that divided individuals by polymorphisms of the fatty acid (FA) binding protein 2 (FABP2) gene (de Luis *et al.*, 2008) and also by wild type, differences in blood glucose were not observed.

Likewise, separating participants according to different polymorphisms of the uncoupling protein-3 gene (a gene with influence on energy expenditure and fat storage) (de Luis *et al.*, 2009a) did not indicate differences in blood glucose response.



Finally, papers by Howard *et al.* (Howard *et al.*, 2006) and Tinker *et al.* (Tinker *et al.*, 2008) are from the same study. Results from Howard *et al.* (Howard *et al.*, 2006) only are included in the meta-analysis.

*Nb. As there has been no evidence from the authors to suggest otherwise, it is assumed that (de Luis et al., 2009b; de Luis et al., 2009a; de Luis et al., 2008) are the same study given the identical diets, same ethical submission dates (for two out of the four studies) and use of similar participants and sample sizes.*

### **Fasting blood glucose (mmol/L) and lower carbohydrate/higher fat diets vs. higher carbohydrate/lower fat diets**

Twenty five studies were included in the meta-analysis concerning group differences in both carbohydrate and fat content of diets but where there was no great difference in protein intake between the groups. All studies included adults as participants. Definitions of different levels of carbohydrate and fat are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were converted appropriately. The first follow up reported at the end of the intervention was used. This varied from six weeks to six years. The pooled estimate indicated that fasting blood glucose was 0.01mmol/L (95% CI, -0.04 to 0.06) higher with consumption of a low carbohydrate and high fat diet compared with a high carbohydrate and low fat diet but this was not significantly different from zero ( $p=0.75$ ). Heterogeneity denoted by  $I^2$  was 39% (95% CI, 5 to 61). A funnel plot indicated low risk of publication bias. Statistically, there was no evidence that diets higher in carbohydrate and lower in fat were associated with differences in fasting blood glucose levels compared to lower carbohydrate, higher fat diets.

**Figure 4.26 Forest plot for lower carbohydrate, higher fat diets and higher carbohydrate, lower fat diets and fasting blood glucose (mmol/L)**

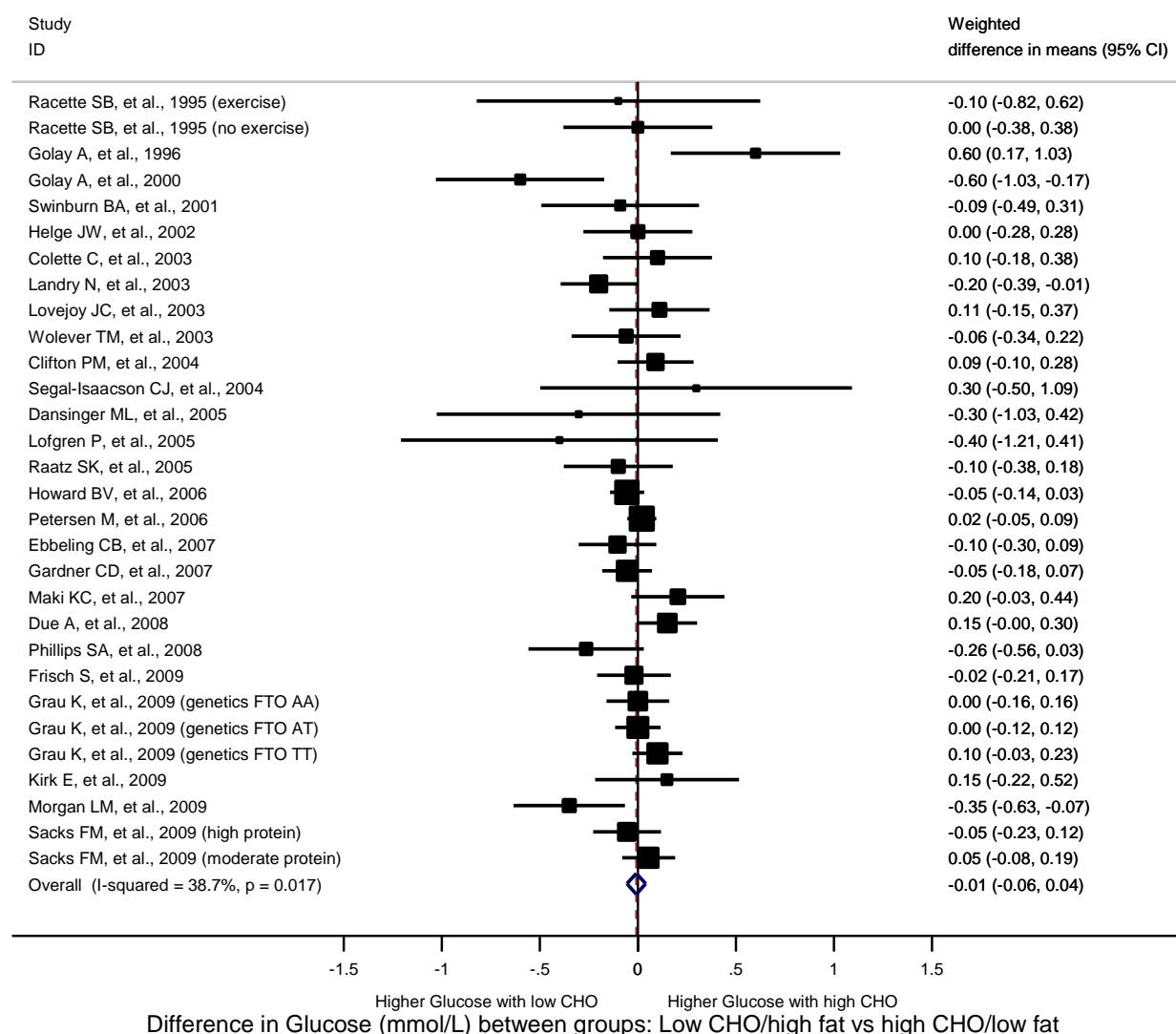
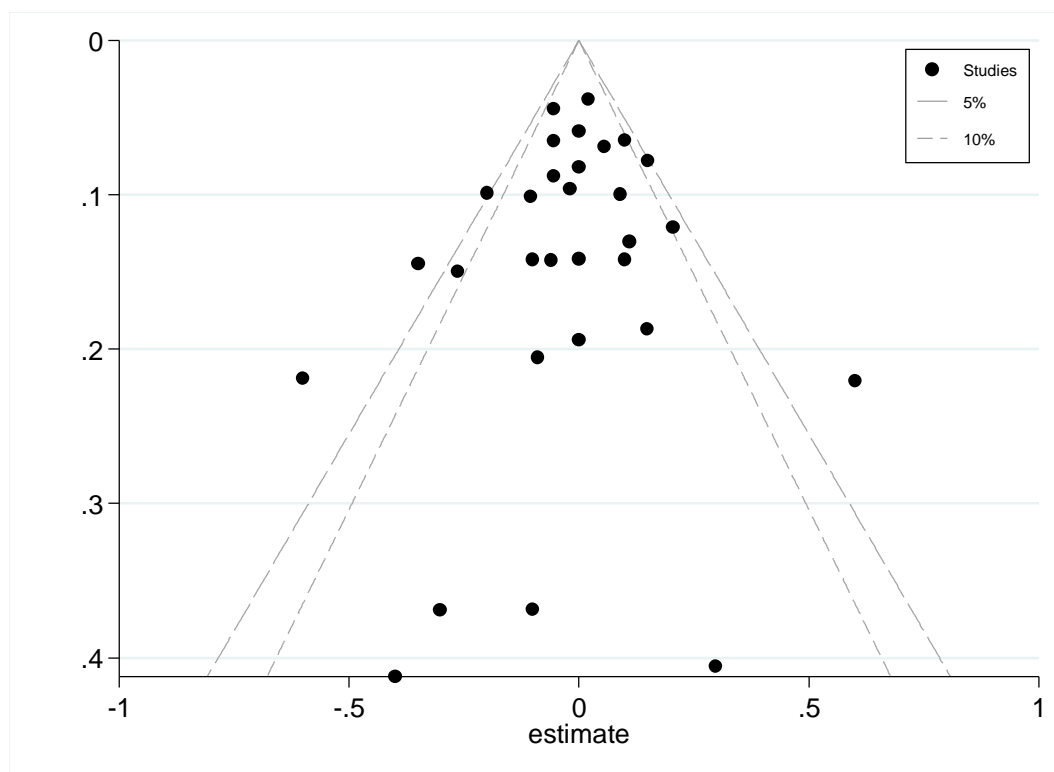


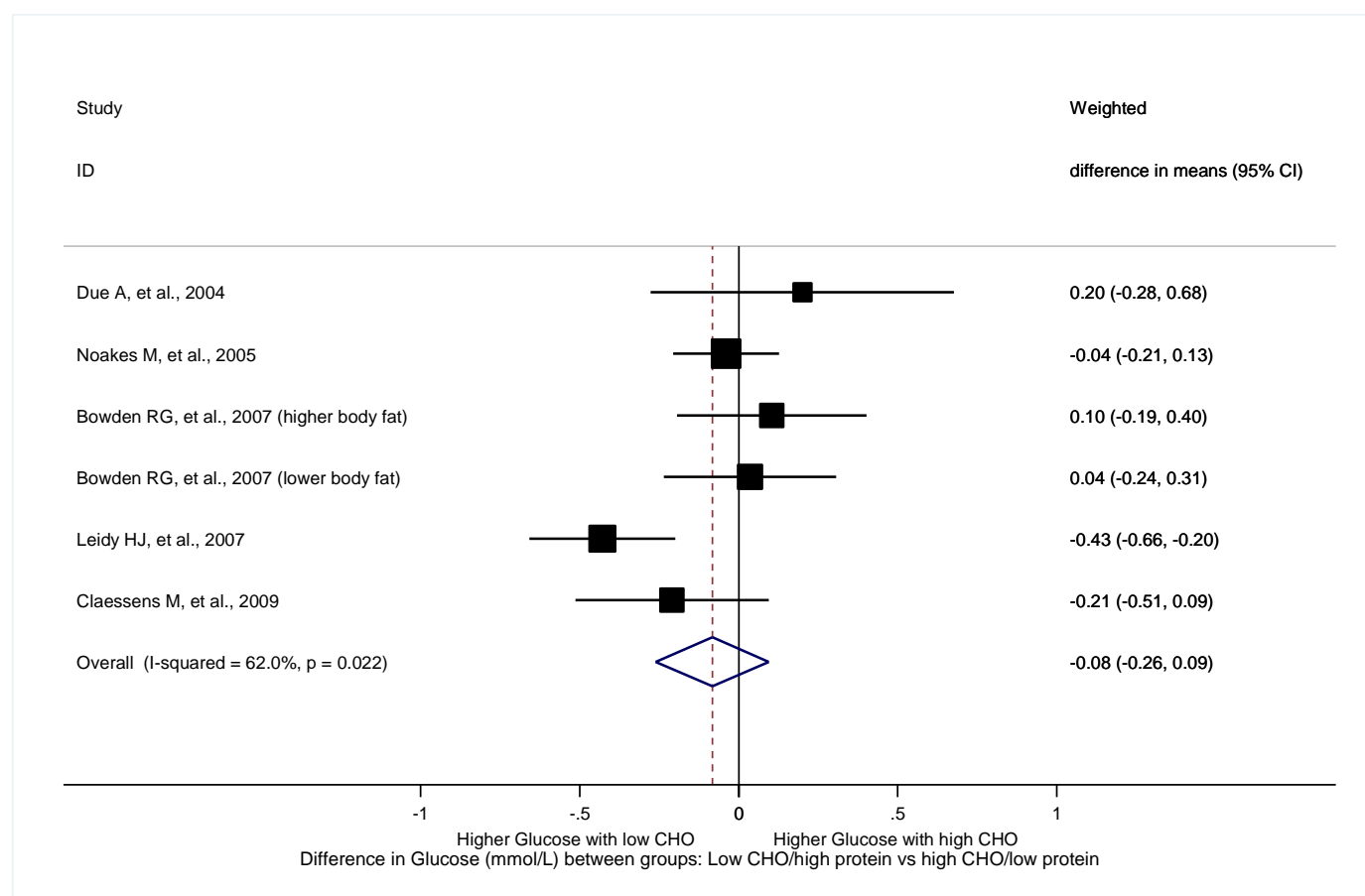
Figure 4.27 Contour-enhanced funnel plot for publications presenting fasting blood glucose (mmol/L) and lower carbohydrate, higher fat diets and higher carbohydrate, lower fat diets



## Fasting blood glucose (mmol/L) and lower carbohydrate, higher protein diets vs. higher carbohydrate, lower protein diets

Five studies providing dietary differences in carbohydrate and protein, but with no reported major changes in dietary fat between groups were included in the meta-analysis. All studies included adults as participants. Definitions of different levels of carbohydrate and protein are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were appropriately converted. The first follow up reported at the end of the intervention was used. This varied from 12 weeks to 1 year. The pooled estimate indicated that fasting blood glucose was 0.08mmol/L (95% CI, 0.26 to -0.09) higher with consumption of a lower carbohydrate, higher protein diet compared with a higher carbohydrate, lower protein diet but this was not significantly different from zero ( $p=0.36$ ). Heterogeneity denoted by  $I^2$  was 62% (95% CI, 7 to 84). There were too few studies to carry out a funnel plot to explore publication bias. Statistically, there was no evidence that a diet higher in carbohydrate and lower in protein was associated with differences in fasting blood glucose levels.

*Figure 4.28 Forest plot for lower carbohydrate, higher protein diets and higher carbohydrate, lower protein diets and fasting blood glucose (mmol/L)*



## Fasting blood glucose (mmol/L) and lower carbohydrate, higher fat and protein diet vs. higher carbohydrate, lower protein and fat diet

Twelve studies were included in the meta-analysis reporting differences in dietary carbohydrate, fat and protein between trial groups. Low carbohydrate diets higher in fat and protein were compared with higher carbohydrate diets which were lower in both fat and protein. This differs from the previous two analyses where fat or protein was reduced with an increase in carbohydrate. Definitions of different levels of carbohydrate and fat are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were converted appropriately. The first follow up reported at the end of the intervention was used. This varied from 6 weeks to 2 years. The pooled estimate indicated that fasting blood glucose was 0.02mmol/L (95% CI -0.14 to 0.17) higher with consumption of a higher carbohydrate diet compared with a low carbohydrate diet but this was not significantly different from zero ( $p=0.84$ ). Heterogeneity denoted by  $I^2$  was 64% (95% CI, 37 to 79). A funnel plot indicated low risk of publication bias. Statistically, there was no evidence that a diet higher in carbohydrate and lower in fat and protein was associated with differences in fasting blood glucose levels.

Figure 4.29 Forest plot for lower carbohydrate, higher fat and protein diets vs. higher carbohydrate, lower protein and fat diets and fasting blood glucose (mmol/L)

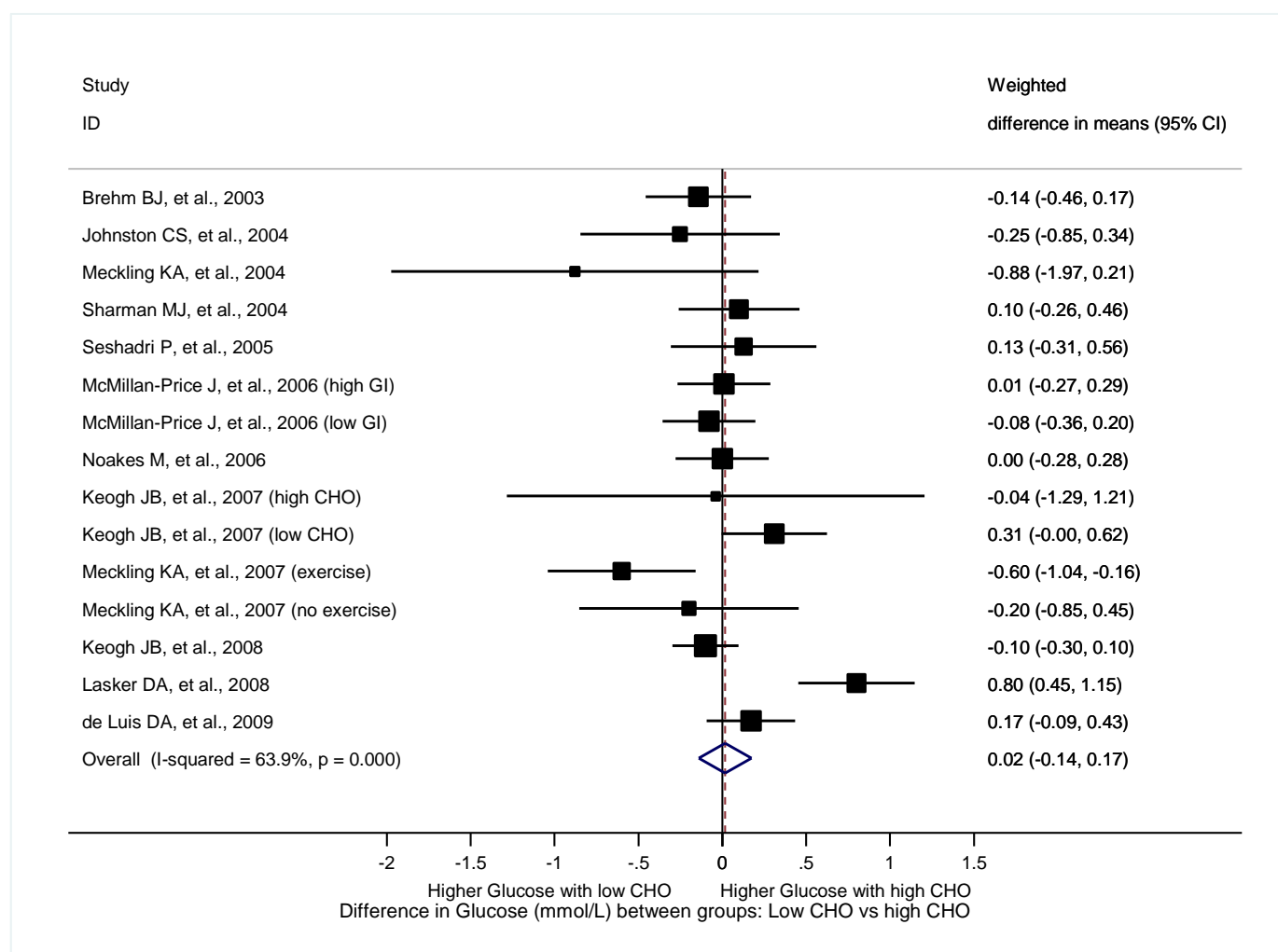


Figure 4.30 Contour-enhanced funnel plot for publications presenting fasting blood glucose (mmol/L) and lower carbohydrate, higher fat and protein diets higher carbohydrate, lower protein and fat diets

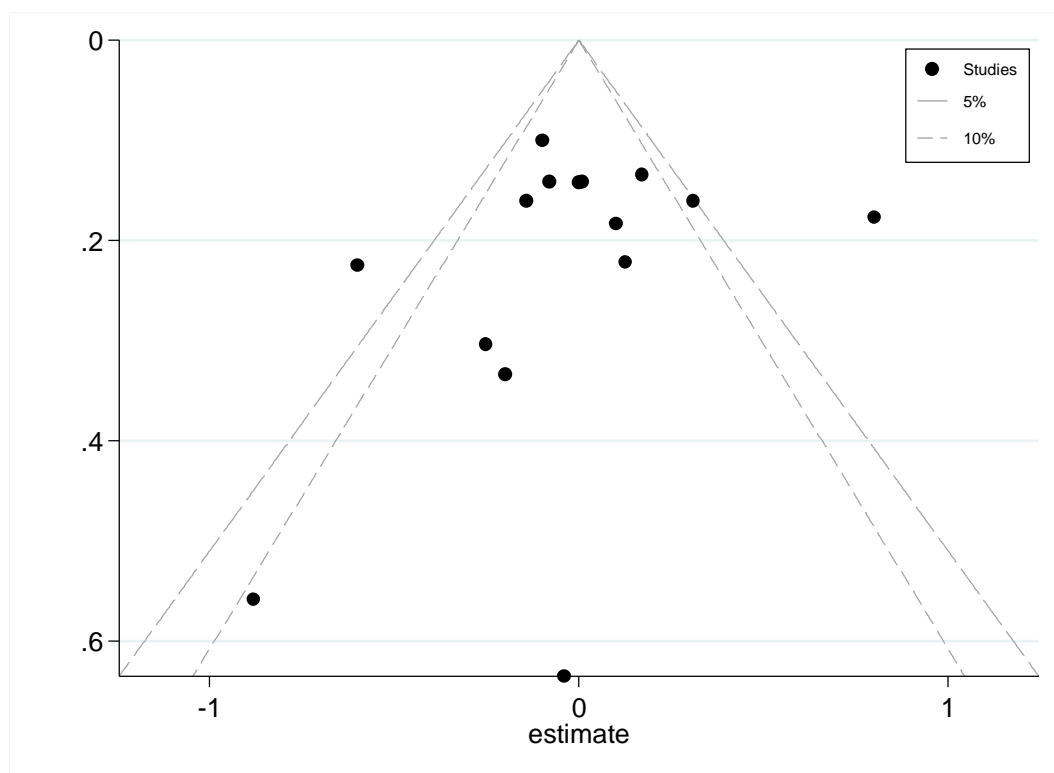


Table 4.45 Glycaemia and total carbohydrate: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14646 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	338	20 years	Dietary history	Carbohydrate, total (% energy)	Blood glucose (OGTT 120 min)	1 % Energy	-0.027 (0.03)	NS	age, BMI, Cohort, Energy intake
14692 Seven Countries Study						Carbohydrate, total (Change in intake)	Blood glucose (OGTT 120 min)	1 % Energy	0.004 (0.022)	NS	age, BMI, Baseline Exposure, Cohort, Energy intake
14626 (Leonetti <i>et al.</i> , 1996) Japanese-American Men Diabetes Study	USA, Asian, Not diabetic	45-74 %M 100	229	5 years (5.6)	FFQ Interview (89)	Carbohydrate, total (% energy)	Blood glucose (OGTT 120 min)	1 % Energy	-0.1	NS	age, BMI, energy intake, impaired glucose tolerance, DM
13868 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi-ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Carbohydrate, total (grams/day)	Blood glucose  Fasting	1 SD of Mean exposure	-1.03 (2.06)	NS	age, alcohol, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13877 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response	1 SD of Mean exposure	1.28 (4.11)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
14179 (Schroeder <i>et al.</i> , 2007) Middle-aged Runners Study	USA, Active people only, No heart disease, No hypertension	(51) %M 62	91	10 years	Food diary	Carbohydrate, total (grams/day)	Blood glucose  Fasting	1 g/day	No effect on regression direction		Age

Table 4.46 Glycaemia and carbohydrate density: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14698 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	338	20 years	Dietary history	Sugars (as food) density g/unit energy (change in intake)	Blood glucose (OGTT 120 min)  Fasting	1 g/1000 kcal	-0.112 (0.108)	NS	age, BMI, Baseline Exposure, Cohort, EI
14652 Seven Countries Study						Sugars, (as food) total (% energy)		1 g/1000 kcal	0.056 (0.176)	NS	age, BMI, Cohort, EI
14647 Seven Countries Study						Mono and disaccharides		1 % Total energy	-0.014 (0.032)	NS	age, BMI, Cohort, EI
14693 Seven Countries Study						Mono and disaccharides-Change in intake		1 % Total energy	0.014 (0.025)	NS	age, BMI, Baseline Exposure, Cohort, EI
13871 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi-ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Fructose	Blood glucose  Fasting	1 SD of Mean exposure	0.5 (0.83)	NS	age, alcohol, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13880 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response  Plasma	1 SD of Mean exposure	-3.83 (1.67)	<0.05	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13872 Insulin Resistance Atherosclerosis Study						Glucose	Blood glucose  Fasting	1 SD of Mean exposure	0.61 (0.77)	NS	age, alcohol, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13881 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response  Plasma	1 SD of Mean exposure	-4.76 (1.69)	<0.05	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking



Table 4.47 Glycaemia and high carbohydrate diets: RCT data

Author/ Results Number	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups in $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>														
(Demol <i>et al.</i> , 2009) 15399		High carbohydrate, low fat	20/20	87.4 (SD 1.7)	81.1 (SD 2.2)					Glucose	Fasting plasma, (mg/dL)	12 weeks	Decrease	unclear
		Low carbohydrate, high fat	17/17	85.0 (SD 1.9)	81.0 (SD 2.2)			NS					Decrease	
		Low carbohydrate, high protein	18/18	85.4 (SD 1.8)	81.3 (SD 2.0)			NS					Decrease	
15400		High carbohydrate, low fat	20/20	87.4 (SD 1.7)	81.9 (SD 2.5)					Glucose	Fasting plasma, (mg/dL)	1 year	Decrease	unclear
		Low carbohydrate, high fat	17/17	85.0 (SD 1.9)	76.4 (SD 2.9)			NS					Decrease	
		Low carbohydrate, high protein	18/18	85.4 (SD 1.8)	80.1 (SD 2.3)			NS					Decrease	
<b>Adult studies</b>														
(Bowden <i>et al.</i> , 2007) *14723		High protein diet, higher body fat participants	7/7	92.71 (SD 12.33)	87.71 (SD 8.04)	-5	0.208	NS		Blood glucose	Fasting (mg/dL)	12 weeks	Not reported	unclear
		High protein diet, lower body fat participants	15/15	91.6 (SD 6.49)	86.4 (SD 6.24)	-5.2	0.001	NS					Not reported	
		Standard diet, higher body fat participants	34/38	89.24 (SD 6.98)	89.59 (SD 6.38)	0.75	0.786	NS					Not reported	
		Standard diet, lower body fat participants	38/34	88.53 (SD 8.4)	87.05 (SD 8.89)	-1.48	0.446						Not reported	
(Brehm <i>et al.</i> , 2003) 15731		Low carbohydrate	22/22	99.1 (SE 2.6)	99.1 (SE 2.6)		<0.001	NS		Glucose	Fasting (mg/dL)	3 months	Decrease	unclear
		Moderate fat	20/20	91.9 (SE 2.1)	91.1 (SE 2.1)		<0.001						Decrease	
*15734		Low carbohydrate	22/22	99.1 (SE 2.6)	90.1 (SE 2.1)		<0.001	NS		Glucose	Fasting (mg/dL)	6 months	Decrease	unclear
		Moderate fat	20/20	91.9 (SE 2.1)	87.5 (SE 2)		<0.001						Decrease	

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(Claessens <i>et al.</i> , 2009) *16816		High carbohydrate supplement	16/allocated not reported	5.13 (SE 0.12)	5.26 (SE 0.08)	0.13 (SE 0.1)	NS			Glucose	Fasting (mmol/L)	12 weeks	Increase	unclear
		High protein supplement - casein	14/allocated not reported	5.01 (SE 0.16)	5.35 (SE 0.12)	0.34 (SE 0.12)	NS						Decrease	
		High protein supplement - whey	18/allocated not reported	4.93 (SE 0.08)	5.40 (SE 0.11)	0.47 (SE 0.06)	NS						Decrease	
(Clifton <i>et al.</i> , 2008) 16009		High carbohydrate diet	38/38			-0.57 (SD 0.82)				Glucose	Fasting (mmol/L)	1.25 years	Decrease	unclear
		High protein diet	40/41			-0.7 (SD 0.39)							Decrease	
(Clifton <i>et al.</i> , 2004) 16752		High MUFA	31/35	5.02 (SD 0.57)	4.99 (SD 0.52)					Glucose	Fasting plasma, (mmol/L)	4 weeks	Decrease	unclear
		Very low fat	31/35	5.07 (SD 0.51)	4.96 (SD 0.41)								Decrease	
16753		High MUFA	31/35	5.02 (SD 0.57)	4.92 (SD 0.47)					Glucose	Fasting plasma, (mmol/L)	8 weeks	Decrease	unclear
		Very low fat	31/35	5.07 (SD 0.51)	4.97 (SD 0.36)								Decrease	
*16754		High MUFA	31/35	5.02 (SD 0.57)	4.91 (SD 0.42)		<0.01			Glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	unclear
		Very low fat	31/35	5.07 (SD 0.51)	5.0 (SD 0.36)		<0.01						Decrease	
(Colette <i>et al.</i> , 2003) *17408		High carbohydrate diet	15/15	4.7 (SE 0.1)	4.7 (SE 0.1)		NS			Glucose	Fasting plasma, (mmol/L)	8 weeks	Decrease	unclear
		High MUFA diet	17/17	5.2 (SE 0.2)	4.6 (SE 0.1)		0.003	NS					Decrease	
(Dale <i>et al.</i> , 2009) 15986		High MUFA diet minus high carbohydrate diet	High MUFA: 85/100 High CHO: 89/100						-0.06 (CI - 0.14, 0.03)	Glucose	Fasting (mmol/L)	2 years	Decrease in both	unclear
17381		High carbohydrate diet	89/100	4.8 (SD 0.5)	4.62 (SD 0.44)					Glucose	Fasting (mmol/L)	2 years	Decrease	unclear
		High MUFA diet	85/100	4.8 (SD 0.5)	4.53 (SD 0.52)								Decrease	
17402		High carbohydrate	89/100	4.8 (SD 0.5)	4.58 (SD 0.49)					Glucose	Fasting (mmol/L)	1 year	Decrease	unclear

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		diet												
		High MUFA diet	85/100	4.8 (SD 0.5)	4.58 (SD 0.46)								Decrease	
(Dansinger <i>et al.</i> , 2005) 15825		Atkins	40/40			-9.8 (SD 30)	0.05			Glucose	Fasting serum, (mg/dL)	2 months	Decrease	No bias
		Ornish	40/40			-3.1 (SD 23)	NS						Decrease	
		Weight watchers	40/40			-5.5 (SD 24)	NS						Decrease	
		Zone	40/40			-9 (SD 29)	NS						Decrease	
15826		Atkins	40/40			-7.8 (SD 26)	NS			Glucose	Fasting serum, (mg/dL)	6 months	Decrease	No bias
		Ornish	40/40			-5.1 (SD 25)	NS						Decrease	
		Weight watchers	40/40			-3.8 (SD 22)	NS						Decrease	
		Zone	40/40			-8.2 (SD 33)	NS						Decrease	
*15827		Atkins	40/40			1.4 (SD 30)	NS			Glucose	Fasting serum, (mg/dL)	1 year	Decrease	No bias
		Ornish	40/40			-4.1 (SD 30)	NS						Decrease	
		Weight watchers	40/40			-4.7 (SD 19)	NS						Decrease	
		Zone	40/40			-4.2 (SD 18)	NS						Decrease	
(de Luis <i>et al.</i> , 2008) 16142	Genetics - wild-type Ala54/Ala54	Low carbohydrate	55/105	99.3 (SD 20.8)	93.5 (SD 13.8)					Glucose	Fasting (mg/dL)	2 months	Decrease	unclear
		Low fat	55/99	96.3 (SD 20.8)	95.3 (SD 18.8)								Decrease	
16160	Genetics - mutant-type Ala54/Thr54 or Thr54/Thr54	Low carbohydrate	50/105	99.2 (SD 22)	94.8 (SD 18.6)					Glucose	Fasting (mg/dL)	2 months	Decrease	unclear
		Low fat	44/99	102.6 (SD 18)	98.6 (SD 18.6)								Decrease	
(de Luis <i>et al.</i> , 2009b) *16081		Low carbohydrate	52/52	99.7 (SD 20)	91.2 (SD 12)					Glucose	Fasting (mg/dL)	3 months	Decrease	unclear
		Low fat	66/66	99.1 (SD 18)	94.3 (SD 14)								Decrease	
(de Luis <i>et al.</i> , 2009a) 16693	Genetics - UCP3 Gene - 55CC polymorphism	Low carbohydrate	54/67	98.3 (SD 20.8)	96.7 (SD 13.8)		NS			Glucose	Plasma (mg/dL)	2 months	Decrease	unclear
	Genetics -	Low fat	40/64	97.4 (SD 13.0)	94.7 (SD 8.8)		NS						Decrease	

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16694	UCP3 Gene - 55CC polymorphism													
	Genetics - UCP3 Gene - 55CT/TT polymorphism	Low carbohydrate	13/67	102.2 (SD 22)	98.8 (SD 18.6)		NS			Glucose	Plasma (mg/dL)	2 months	Decrease	unclear
	Genetics - UCP3 Gene - 55CT/TT polymorphism	Low fat	24/64	94.6 (SD 13)	98.6 (SD 18.6)		NS						Decrease	
(Due <i>et al.</i> , 2008a) 16395		Control diet	12/12	613 (CI 532, 694)	667 (CI 605, 730)					Glucose AUC OGTT (120min)	Serum	6 months	Increase	unclear
		High MUFA	16/16	713 (CI 671, 754)	735 (CI 679, 791)								Increase	
		Low fat diet	18/18	732 (CI 680, 783)	736 (CI 682, 789)								Increase	
(Due <i>et al.</i> , 2008b) *15295		Control	24/25	4.78 (CI 4.6, 5.0)	4.90 (CI 4.7, 5.1)	0.11 (CI -0.05, 0.27)				Glucose	Fasting serum, (pmol/L)	6 months	Increase	unclear
		High MUFA	39/52	4.98 (CI 4.8, 5.1)	4.91 (CI 4.8, 5.0)	-0.06 (CI -0.19, 0.07)		NS					Increase	
		Low fat	43/48	4.82 (CI 4.7, 4.9)	4.91 (CI 4.8, 5.0)	0.09 (CI 0.01, 0.18)		NS					Increase	
(Due <i>et al.</i> , 2004) 17532		High protein	23/23	4.9 (CI 4.6, 5.4)	4.9 (CI 4.6, 5.1)					Glucose	Fasting (mmol/L)	6 months	Decrease	unclear
		Moderate protein	23/18	4.9 (CI 4.6, 5.4)	4.9 (CI 4.7, 5.3)								Decrease	
*17533		High protein	23/23	4.9 (CI 4.6, 5.2)	5.0 (CI 4.6, 5.3)					Glucose	(mmol/L)	1 year	Decrease	unclear
		Moderate protein	18/18	4.9 (CI 4.6, 5.4)	5.2 (CI 4.9, 5.5)								Decrease	
(Ebbeling <i>et al.</i> , 2007) *15459		Low fat diet	37/37			-0.3 (SE 1.3)				Glucose	Fasting plasma, (mg/dL)	6 months	Decrease	No bias
		Low GL diet	ITT: 36/36			1.6 (SE 1.3)		0.31					Decrease	
15460		Low fat diet	37/37			1.4 (SE 1.3)				Glucose	Fasting plasma, (mg/dL)	18 months	Decrease	No bias
		Low GL diet	ITT:			2.1 (SE 1.3)		0.73					Decrease	

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36/36														
(Foster <i>et al.</i> , 2003) 15230		Conventional diet plan	30/30			1.6 (SD 16.6)	NS			Change in Glucose AUC OGTT (120min)	Plasma (%)	3 months	Decrease	unclear
		Low carbohydrate diet	33/33			6.7 (SD 20.7)	NS	0.27					Decrease	
15231		Conventional diet plan	30/30			-0.8 (SD 12.2)	NS			Change in Glucose AUC OGTT (120min)	Plasma (%)	6 months	Decrease	unclear
		Low carbohydrate diet	33/33			1 (SD 15.9)	NS	0.8					Decrease	
*15232		Conventional diet plan	30/30			1.2 (SD 10.1)	NS			Change in Glucose AUC OGTT (120min)	Plasma (%)	1 year	Decrease	unclear
		Low carbohydrate diet	33/33			3.2 (SD 16.2)	NS	0.8					Decrease	
(Frisch <i>et al.</i> , 2009) *15172		High carbohydrate diet	100/100			-0.28 (SD 0.59)	0.05			Glucose	Fasting serum, (mmol/L)	6 months	Decrease	unclear
		Moderate carbohydrate diet	100/100			-0.26 (SD 0.76)	0.05	0.475					Decrease	
15173		High carbohydrate diet	100/100			-0.14 (SD 0.46)	0.05			Glucose	Fasting serum, (mmol/L)	1 year	Decrease	unclear
		Moderate carbohydrate diet	100/100			-0.25 (SD 0.75)	0.05	0.235					Decrease	
(Gardner <i>et al.</i> , 2007) *15123		Atkins: low carbohydrate	70/77			-0.4 (SD 6.8)		NS		Glucose	Whole blood (mg/dL)	2 months	Decrease	No bias
		Ornish: high carbohydrate	64/76			-1.4 (SD 6.9)		NS					Decrease	
		Zone: moderate carbohydrate	65/79			-1.6 (SD 10.6)							Decrease	

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15124		Atkins: low carbohydrate	70/77			0.2 (SD 7.6)		NS		Glucose	Whole blood (mg/dL)	6 months	Decrease	No bias
		Ornish: high carbohydrate	64/76			-0.6 (SD 7.3)		NS					Decrease	
		Zone: moderate carbohydrate	65/79			-1.7 (SD 9.6)							Decrease	
15125		Atkins: low carbohydrate	70/77			-1.8 (SD 13.4)		NS		Glucose	Whole blood (mg/dL)	1 year	Decrease	No bias
		Ornish: high carbohydrate	64/76			-0.8 (SD 7.9)		NS					Decrease	
		Zone: moderate carbohydrate	65/79			-1.6 (SD 6.5)							Decrease	
(Golay <i>et al.</i> , 1996) *16623		Moderate carbohydrate diet	completers not reported/21	5.4 (SE 0.3)	5.0 (SE 0.2)		<0.01			Glucose	Fasting plasma, (mmol/L)	6 weeks	Decrease	unclear
		Low carbohydrate diet	completers not reported/22	5.3 (SE 0.2)	4.4 (SE 0.1)		<0.001						Decrease	
(Golay <i>et al.</i> , 2000) *14850		Dissociated low energy diet	26/26	5.1 (SE 0.3)	4.4 (SE 0.2)		<0.01			Blood glucose	Fasting plasma, (mmol/L)	6 weeks	Decrease	unclear
		Lower carbohydrate, macronutrients eaten simultaneously	28/28	5.6 (SE 0.3)	5 (SE 0.1)		<0.01						Decrease	
(Grau <i>et al.</i> , 2009) *17451	Genetics - FTO rs9939609 TT	High carbohydrate, low fat diet	88/320	5.2 (SD 0.5)		-0.1 (SD 0.4)				Glucose	Fasting plasma, (mM)	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 TT	Low CHO, high fat diet	117/298	5.5 (SD 0.9)		-0.2 (SD 0.5)							Decrease	
*17455	Genetics - FTO rs9939609 AT	High carbohydrate, low fat diet	168/320	5.5 (SD 1.4)		-0.1 (SD 0.6)				Glucose	Fasting plasma, (mM)	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 AT	Low CHO, high fat diet	143/298	5.4 (SD 0.5)		-0.1 (SD 0.4)							Decrease	
*17459	Genetics - FTO rs9939609 AA	High carbohydrate,	64/320	5.3 (SD 0.5)		-0.1 (SD 0.4)				Glucose	Fasting plasma,	10 weeks	Decrease	bias

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		low fat diet									(mM)			
	Genetics - FTO rs9939609 AA	Low CHO, high fat diet	38/298	5.3 (SD 0.6)		-0.1 (SD 0.4)							Decrease	
(Helge, 2002) *15914		High carbohydrate + exercise	16/16	4.7 (SE 0.1)	4.5 (SE 0.1)					Glucose	Fasting plasma, (mmol/L)	7 weeks	Decrease	unclear
		High fat + exercise	17/17	4.5 (SE 0.1)	4.5 (SE 0.1)			NS					Decrease	
(Howard <i>et al.</i> , 2006) *16252		Control	approx 1699 participants included as a 5.8% sub- sample of 29294 in group	100.0 (SD 26.9)	99.5 (SD 27.3)	-0.7 (SD 21.6)				Glucose	Fasting (mg/dL)	3 years	No change	No bias
		Low fat	approx 1132 participants included as a 5.8% sub- sample of 19541 in group	100.4 (SD 26.6)	98.8 (SD 25.6)	-1.7 (SD 19.9)		NS					Decrease	
17619		Low fat minus control	Low fat: approx 1132 participants included as a 5.8% sub-sample of 19541 in group Control: approx 1699 participants included as a 5.8% sub-sample of 29294 in group						-1.06 (CI - 3.06, 0.93)	Glucose	Fasting (mg/dL)	3 years	No change in control group, decrease in low fat group	No bias
(Johnston <i>et al.</i> , 2004) *14866		High carbohydrate, low fat	7/10	5.2 (SE 0.1)		-3.9% (SE 3.7%)	NS			Blood glucose	Fasting (mmol/L)	6 weeks	Decrease	unclear
		High protein, low fat	9/10	5.3 (SE 0.2)		0.9% (SE 4.2%)	NS	0.388					Decrease	
(Keogh <i>et al.</i> , 2007) 15610		High carbohydrate diet	12/12	5.83 (SE 0.41)	5.5 (SE 0.52)		0.05			Glucose	Fasting plasma, (mmol/L)	6 weeks	Decrease	unclear
		Low carbohydrate diet	13/13	5.9 (SE 0.81)	5.44 (SE 0.45)		0.05						Decrease	
*15611		High carbohydrate diet	12/12	5.83 (SE 0.41)	5.48 (SE 0.48)		NS			Glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	unclear

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15612		Low carbohydrate diet	13/13	5.9 (SE 0.81)	5.52 (SE 0.42)		NS						Decrease	
		High carbohydrate diet	completers not reported/12	5.57 (SE 0.09)	5.5 (SE 0.09)		NS			Glucose	Fasting plasma, (mmol/L)	1 year	Decrease	unclear
		Low carbohydrate diet	completers not reported/13	5.37 (SE 0.07)	5.19 (SE 0.13)		NS						Decrease	
(Keogh <i>et al.</i> , 2008) *16718		High carbohydrate, low SFA	47/50	5.6 (SD 0.5)	5.4 (SD 0.5)		<0.001			Glucose	(mmol/L)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	52/57	5.7 (SD 0.6)	5.5 (SD 0.5)		<0.001	NS					Decrease	
(Kirk <i>et al.</i> , 2009) *17554		High carbohydrate	completers not reported/11	96.8 (SE 2.7)		-6.2 (SE 1.6)	<0.05			Glucose	Fasting plasma, (mg/dL)	11 week	Decrease	unclear
		Very low carbohydrate	completers not reported/11	101.5 (SE 4.5)		-8.9 (SE 3.0)	<0.05	>0.05					Decrease	
(Kirkwood <i>et al.</i> , 2007) 15676		Group 1: No advice	18/allocated not reported				NS			Glucose	Fasting Whole blood, (mmol/L)	12 weeks	No change	unclear
		Group 2: Conventional weight loss diet	16/allocated not reported		5.07 (SE 0.22)	0.92	0.01	0.05					Decrease	
15677		Group 3: Exercise	19/allocated not reported				NS	NS		Glucose	Fasting Whole blood, (mmol/L)	12 weeks	Decrease	unclear
		Group 4: Conventional weight loss diet + exercise	16/allocated not reported				NS						Decrease	
(Landry <i>et al.</i> , 2003) *15995		High carbohydrate	19/19	5.3 (SD 0.4)		-0.2 (SD 0.3)	<0.05			Glucose	Fasting plasma, (mmol/L)	7 weeks	Decrease	unclear
		Low carbohydrate, high fat diet	18/18	5.1 (SD 0.5)		0.0 (SD 0.3)	NS						Decrease	

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(Lasker <i>et al.</i> , 2008) *15897		high carbohydrate	25/33			0.52 (SE 0.12)				Glucose	Fasting plasma, (mmol/L)	4 months	Decrease	unclear
		High protein	25/32			-0.28 (SE 0.13)		0.19					Decrease	
15900		high carbohydrate	25/33							Glucose (OGTT 60 min)	Plasma (mmol/L)	4 months	Decrease	unclear
		High protein	25/32					0.39					Decrease	
15901		high carbohydrate	25/33							Glucose (OGTT 120 min)	Plasma (mmol/L)	4 months	Decrease	unclear
		High protein	25/32					0.59					Decrease	
(Leidy <i>et al.</i> , 2007) *16838		High protein, energy restricted	21/27	86 (SE 2)	87 (SE 1)	0.8 (SE 2)		0.05		Glucose	Fasting (mg/dL)	12 weeks	Decrease	unclear
		Moderate protein, energy restricted	25/27	96 (SE 2)	89 (SE 2)	-7 (SE 1)							Decrease	
(Lofgren <i>et al.</i> , 2005) *17255		High carbohydrate, low fat	20/20	5.2 (SE 0.10)	5 (SE 0.1)			NS		Glucose	Fasting plasma, (mmol/L)	10 weeks	Decrease	unclear
		High fat, moderate carbohydrate	20/20	5.5 (SE 0.3)	5.4 (SE 0.4)								Decrease	
(Lovejoy <i>et al.</i> , 2003) 15008		Control	13/15	5.42 (SE 0.1)		-0.11 (SE 0.05)				Glucose	Fasting (mmol/L)	3 months	Decrease	unclear
		Fat reduced	13/15	5.45 (SE 0.1)		-0.02 (SE 0.08)							Decrease	
15009		Control	13/15	5.42 (SE 0.1)		-0.17 (SE 0.08)				Glucose	Fasting (mmol/L)	6 months	Decrease	unclear
		Fat reduced	13/15	5.45 (SE 0.1)		-0.09 (SE 0.11)							Decrease	
*15010		Control	13/15	5.42 (SE 0.1)		-0.01 (SE 0.07)				Glucose	Fasting (mmol/L)	9 months	Decrease	unclear
		Fat reduced	13/15	5.45 (SE 0.1)		0.1 (SE 0.11)							Decrease	
(McMillan-Price <i>et al.</i> , 2006) *16224		High CHO, high GI diet	32/32	5.04 (SE 0.11)		-0.04 (SE 0.10)				Change in glucose	Fasting (mmol/L)	12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	4.95 (SE 0.07)		-0.06 (SE 0.10)							Decrease	
		High protein, high GI diet	32/32	4.92 (SE 0.14)		-0.05 (SE 0.10)		NS					Decrease	
		High protein, low GI diet	33/33	5.04 (SE 0.09)		0.02 (SE 0.10)		NS					Decrease	
(Mahon <i>et al.</i>		Control	11/11	100	No change		NS			Glucose	Fasting	9 weeks	No	unclear

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<i>al.</i> , 2007) 15076				(SD 13)							plasma (mg/dL)		change	
		Energy restriction + beef	14/14		No change		NS	NS					Decrease	
		Energy restriction + carbohydrate/f at	14/14		No change		NS	NS					Decrease	
		Energy restriction + chicken	15/15		No change		NS	NS					Decrease	
(Maki <i>et al.</i> , 2007b) 17288		Low fat	39/43	95.2 (SE 1.7)		-0.3 (SE 1.1)				Glucose	Fasting serum, (mg/dL)	12 weeks	Decrease	unclear
		Low GL	39/43	95.3 (SE 1.3)		-2.9 (SE 1.3)							Decrease	
*17289		Low fat	39/43	95.2 (SE 1.7)		2.6 (SE 1.4)				Glucose	Fasting serum, (mg/dL)	36 weeks	Decrease	unclear
		Low GL	39/43	95.3 (SE 1.3)		-1.1 (SE 1.7)							Decrease	
(Meckling <i>et al.</i> , 2004) *14879		Low carbohydrate	15/10	113 (SE 12)	104 (SE 10)		NS	NS		Blood glucose	Serum (mg/dL)	10 weeks	Decrease	No bias
		Low fat	16/10	98 (SE 8)	88 (SE 3)		NS						Decrease	
14880		Low carbohydrate	15/10	3.76	2.91		0.05	0.5		Glucose: Insulin ratio		10 weeks	Decrease	No bias
		Low fat	16/10	3.85	4.12		NS						Decrease	
(Meckling and Sherfey, 2007) *16371		Hypocaloric control diet	8/15	4.9 (SD 0.4)	4.8 (SD 0.3)		NS			Glucose	Fasting (mmol/L)	12 weeks	Decrease	unclear
		Hypocaloric protein rich diet	10/15	5.0 (SD 0.6)	5.0 (SD 0.9)		NS						Decrease	
*16372		Hypocaloric control diet + exercise	11/15	5.5 (SD 0.8)	5.1 (SD 0.5)		NS			Glucose	Fasting (mmol/L)	12 weeks	Decrease	unclear
		Hypocaloric protein rich diet + exercise	14/15	5.9 (SD 0.7)	5.7 (SD 0.6)		NS						Decrease	
(Morgan <i>et al.</i> , 2009) 14711		Atkins	33/57	5.59 (SD 0.45)	5.52 (SD 0.43)		NS			Blood glucose	Fasting Whole blood, (mmol/L)	8 weeks	Decrease	unclear

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		Control	37/61	5.44 (SD 0.37)	5.42 (SD 0.43)		NS						No change	
		Slim Fast	44/59	5.5 (SD 0.52)	5.41 (SD 0.49)		NS						Decrease	
		Weight Watchers	46/58	5.54 (SD 0.49)	5.36 (SD 0.51)		NS						Decrease	
*14712		Atkins	33/57	5.59 (SD 0.45)	5.3 (SD 0.61)		0.05			Blood glucose	Fasting Whole blood, (mmol/L)	24 weeks	Decrease	unclear
		Control	37/61	5.44 (SD 0.37)	5.18 (SD 0.51)		0.05						No change	
		Slim Fast	44/59	5.5 (SD 0.52)	5.23 (SD 0.6)		0.05						Decrease	
		Weight Watchers	46/58	5.54 (SD 0.49)	4.95 (SD 0.65)		0.01						Decrease	
(Noakes <i>et al.</i> , 2006) 16587		High unsaturated fat	21/27	5.4 (SE 0.1)	5.2 (SE 0.1)					Glucose	Fasting plasma, (mmol/L)	8 weeks	Decrease	unclear
		Very low carbohydrate	24/28	5.3 (SE 0.1)	5.3 (SE 0.1)								Decrease	
		Very low fat	22/28	5.3 (SE 0.1)	5.2 (SE 0.1)								Decrease	
*16588		High unsaturated fat	21/27	5.4 (SE 0.1)	5.2 (SE 0.1)	-0.2 (SE 0.1)				Glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	unclear
		Very low carbohydrate	24/28	5.3 (SE 0.1)	5.3 (SE 0.1)	-0.1 (SE 0.1)							Decrease	
		Very low fat	22/28	5.3 (SE 0.1)	5.3 (SE 0.1)	-0.1 (SE 0.1)							Decrease	
(Noakes <i>et al.</i> , 2005) 16996		High carbohydrate diet	48/48	6.08 (SE 0.58)	6.00 (SE 0.54)					Glucose	Fasting plasma, (mmol/L)	8 weeks	Decrease	unclear
		High protein diet	52/52	6.16 (SE 0.65)	6.13 (SE 0.66)								Decrease	
*16997		High carbohydrate diet	48/48	6.08 (SE 0.58)	5.83 (SE 0.62)	-0.25 (SE 0.07)				Glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	unclear
		High protein diet	52/52	6.16 (SE 0.65)	5.93 (SE 0.61)	-0.21 (SE 0.05)		0.589					Decrease	
(Petersen <i>et al.</i> , 2006) 17211	Women	High carbohydrate, low fat diet	251/389	5.29 (SD 1.0)		-0.11 (SD 0.47)				Glucose	Fasting plasma, (mmol/L)	10 weeks	Decrease	bias
	Women	Low CHO, high fat diet	235/382	5.32 (SD 0.67)		-0.07 (SD 0.44)							Decrease	
	Men	High	85/389	5.71 (SD 1.21)		-0.17 (SD 0.54)				Glucose	Fasting	10 weeks	Decrease	bias

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17212		carbohydrate, low fat diet									plasma, (mmol/L)			
	Men	Low CHO, high fat diet	77/382	5.74 (SD 0.62)		-0.37 (SD 0.51)							Decrease	
*17213		High carbohydrate, low fat diet	336/389	5.39 (SD 1.07)		-0.12 (SD 0.49)				Glucose	Fasting plasma, (mmol/L)	10 weeks	Decrease	bias
		Low CHO, high fat diet	312/382	5.43 (SD 0.68)		-0.14 (SD 0.48)							Decrease	
(Phillips <i>et al.</i> , 2008) *17428		Low carbohydrate diet	10/~14	91.7 (SE 1.1)	96 (SE 2.2)		NS	NS		Glucose	Fasting plasma, (mg/dL)	6 weeks	Decrease	unclear
		Low fat diet	10/~14	89.65 (SE 1.9)	91.2 (SE 1.6)		NS						Decrease	
(Raatz <i>et al.</i> , 2005) *17233		High fat diet	10/8	4.7 (SE 0.1)		-0.2 (SE 0.1)		NS		Change in glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	unclear
		High GI diet	9/8	4.9 (SE 0.2)		-0.3 (SE 0.1)							Decrease	
		Low GI diet	10/6	4.8 (SE 0.1)		-0.2 (SE 0.1)		NS					Decrease	
(Racette <i>et al.</i> , 1995) 16027		Low carbohydrate diet	6/allocated not reported	5.2 (SD 0.2)	5.1 (SD 0.2)					Glucose	Fasting (mmol/L)	10 weeks	Decrease	unclear
		Low fat diet	7/allocated not reported	5.0 (SD 0.3)	4.8 (SD 0.6)								Decrease	
*16031		Low carbohydrate diet	6/allocated not reported	5.2 (SD 0.2)	5.0 (SD 0.4)					Glucose	Fasting (mmol/L)	16 weeks	Decrease	unclear
		Low fat diet	7/allocated not reported	5.0 (SD 0.3)	5.0 (SD 0.3)								Decrease	
16032		Low carbohydrate diet + exercise	5/allocated not reported	5.0 (SD 0.4)	4.7 (SD 0.2)					Glucose	Fasting (mmol/L)	10 weeks	Decrease	unclear
		Low fat diet + exercise	5/allocated not reported	4.9 (SD 0.3)	5.1 (SD 0.4)								Decrease	
*16033		Low carbohydrate diet + exercise	5/allocated not reported	5.0 (SD 0.4)	4.8 (SD 0.2)					Glucose	Fasting (mmol/L)	16 weeks	Decrease	unclear
		Low fat diet + exercise	5/allocated not reported	4.9 (SD 0.3)	4.7 (SD 0.8)								Decrease	
(Sacks <i>et al.</i> , 2009) 15591		High-fat, average- protein	ITT: /204		90 (SD 12)	-1.9%				Glucose	Fasting serum, (mg/dL)	6 months	Decrease	No bias
		High-fat, high-	ITT:		91 (SD 12)	-1.2%							Decrease	

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*15592		protein	/201											
		Low-fat, average- protein	ITT: /204		90 (SD 11)	-3%							Decrease	
		Low-fat, high- protein	ITT: /202		90 (SD 16)	-2.6%							Decrease	
		High-fat, average- protein	ITT: /204	92 (SD 12)	93 (SD 13)	1.6%				Glucose	Fasting serum, (mg/dL)	2 years	Decrease	No bias
		High-fat, high- protein	ITT: /201	92 (SD 13)	94 (SD 15)	2.8%							Decrease	
		Low-fat, average- protein	ITT: /204	93 (SD 12)	94 (SD 12)	1.1%							Decrease	
(Segal- Isaacson <i>et al.</i> , 2004) *14989		Low fat diet	4/4	95.4 (SD 10.2)	84.0 (SD 9.1)		<0.05			Glucose	Fasting serum, (g/dL)	6 weeks	Decrease	unclear
		Very low carbohydrate	4/4	95.4 (SD 10.2)	78.6 (SD 11.6)		<0.05	0.206					Decrease	
(Seshadri <i>et al.</i> , 2005) 16102		Low carbohydrate diet	40/40			-16.47 (SD 29.05)	0.01			Glucose	Fasting (mg/dL)	6 months	Decrease	unclear
		Standard diet, energy restricted	35/35			-4.05 (SD 30.11)	NS						Decrease	
*16103	No diabetes	Low carbohydrate diet	23/23			-1.48 (SD 14.11)	NS			Glucose	Fasting (mg/dL)	6 months	Decrease	unclear
	No diabetes	Standard diet, energy restricted	22/22			0.82 (SD 12.84)	NS						Decrease	
(Sharman <i>et al.</i> , 2004) *14758		Low fat	15/15	5.23 (SD 0.35)	5.03 (SD 0.58)		NS			Blood glucose	Fasting serum, (mmol/L)	6 weeks	Decrease	unclear
		Very low carbohydrate	15/15	5.23 (SD 0.35)	4.93 (SD 0.41)		0.05	0.05					Decrease	
(Swinburn <i>et al.</i> , 2001) 15863		Control diet	70/70			0.11 (SE 0.16)				Glucose	Fasting (mmol/L)	6 months	No change	unclear
		Low fat	66/66			0.04 (SE 0.17)							Decrease	

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*15864		Control diet	70/70			0.17 (SE 0.13)				Glucose	Fasting (mmol/L)	1 year	No change	unclear
		Low fat	66/66			0.08 (SE 0.16)							Decrease	
15865		Control diet	57/70			0.05 (SE 0.24)				Glucose	Fasting (mmol/L)	2 years	No change	unclear
		Low fat	47/66			-0.17 (SE 0.26)							Decrease	
15866		Control diet	51/70			0.09 (SE 0.22)				Glucose	Fasting (mmol/L)	3 years	No change	unclear
		Low fat	48/66			-0.04 (SE 0.18)							Decrease	
15867		Control diet	52/70			0.29 (SE 0.3)				Glucose	Fasting (mmol/L)	5 years	No change	unclear
		Low fat	51/66			0.02 (SE 0.18)							Decrease	
15868		Control diet	70/70			0.13 (SE 0.37)				Glucose (OGTT 120 min)	(mmol/L)	6 months	No change	unclear
		Low fat	66/66			-0.36 (SE 0.36)							Decrease	
15869		Control diet	70/70			0.74 (SE 0.35)				Glucose (OGTT 120 min)	(mmol/L)	1 year	No change	unclear
		Low fat	66/66			0.01 (SE 0.33)							Decrease	
15870		Control diet	57/70			0.01 (SE 0.49)				Glucose (OGTT 120 min)	(mmol/L)	2 years	No change	unclear
		Low fat	47/66			-0.76 (SE 0.42)							Decrease	
15872		Control diet	51/70			0.48 (SE 0.45)				Glucose (OGTT 120 min)	(mmol/L)	3 years	No change	unclear
		Low fat	48/66			0.2 (SE 0.37)							Decrease	
15875		Control diet	52/70			2.3 (SE 0.54)				Glucose (OGTT 120 min)	(mmol/L)	5 years	No change	unclear
		Low fat	51/66			1.02 (SE 0.4)							Decrease	
(Tinker <i>et al.</i> , 2008) 15372		Control	1366/29294	94.6 (SD 12.5)	94.3 (SD 13.4)					Glucose	Fasting serum, (mg/dL)	1 year	No change	unclear
		Low fat diet	915/19541	94.4 (SD 14.9)	92.4 (SD 10.9)			0.001					Decrease	
15373		Control	1165/29294	94.6 (SD 12.5)	96.2 (SD 15.6)					Glucose	Fasting serum, (mg/dL)	6 years	No change	unclear
		Low fat diet	760/19541	94.4 (SD 14.9)	96.6 (SD 15.5)			NS					Decrease	
(Wolever and		High carbohydrate,	11/13	6.01 (SE 0.28)		0.16 (SE 0.09)				Glucose	Fasting (mmol/L)	4 months	Decrease	unclear

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Mehling, 2003) *17133		high GI												
		High carbohydrate, low GI	13/13	5.79 (SE 0.22)		0.05 (SE 0.12)							Decrease	
		High carbohydrate, Low carbohydrate, high MUFA	11/12	5.42 (SE 0.24)		0.22 (SE 0.11)							Increase	

\*This result was used in the meta-analysis of high carbohydrate diets and glycaemia

# Insulinaemia and total carbohydrate and high carbohydrate diets

## Summary of cohort results

Two cohort studies provided evidence on total carbohydrate and insulinaemia (Ludwig *et al.*, 1999; Marshall *et al.*, 1997). Total carbohydrate was expressed as either percentage of energy (Ludwig *et al.*, 1999) or total in grams (Marshall *et al.*, 1997). The CARDIA study from the USA, a multi-ethnic, generally healthy cohort (Ludwig *et al.*, 1999), compared the top and bottom quintiles of baseline-assessed carbohydrate density against levels of fasting or 2hour insulin following a glucose tolerance test. No differences in follow-up insulin response were observed between the highest and lowest baseline carbohydrate consumers. The San Luis Valley Diabetes Study (Marshall *et al.*, 1997) was also conducted in the USA, and included a multi-ethnic cohort with baseline normal glucose tolerance. This study assessed the effect of variation in baseline total carbohydrate intake (per 45g/day) against fasting plasma insulin levels at follow-up. After adjusting for age, gender, ethnicity, vigorous activity, BMI, waist circumference and total energy, there was no evidence of a association between total carbohydrate intake and blood insulin levels in this study.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

## ***Exposure definition and assessment***

Total carbohydrate was presented in these studies as either total carbohydrate intake or carbohydrate density. The CARDIA study assessed diet using an FFQ (Ludwig *et al.*, 1999) and the San Luis Valley Diabetes Study assessed diet using a dietary recall (Marshall *et al.*, 1997).

## ***Adjustment for appropriate confounders***

Both studies adjusted for age, BMI and energy intake.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## Summary of RCT results

Fifty six papers provided data on the effects of variation in dietary carbohydrate on fasting blood insulin. Some papers presented data from the same study in multiple publications therefore the total number of studies was 49.

Of those studies that reported mean BMI, participants were generally overweight (BMI 25-30kg/m<sup>2</sup>) or obese (BMI >30). Only one study of adolescents aged 12-18 years was identified; the



remaining studies were of adults. Sixteen studies included females only and four included males only. The average age of participants in each trial was 43 years and the median was 44 years.

Trials were conducted in a range of countries that included the USA (22), Australia (7), Denmark (3), Canada (3), Switzerland (2), New Zealand (2), Spain (1), Israel (1), France (1), the UK (1), Germany (1), Scotland (1), Sweden (1), the Netherlands (1), Europe (1) and the UK and the USA collectively.

Forty five of the 49 studies used a parallel group design as described in the Trial Characteristics Table and the others used a crossover approach (2) or a factorial design (2).

Twenty two papers were relatively large, with more than 100 participants in each. Excluding the Women's Health Initiative Trial which included 48,835 participants, the mean number of participants in each trial was 166 (median=60).

Due to variation in methodologies used to measure fasting blood insulin levels, it was not possible to combine these studies using meta-analysis.

For discussion, trials were separated into three main types where carbohydrate content of the diets in different groups differed by 5% or more. Higher carbohydrate, lower fat diets were differentiated from lower carbohydrate, higher fat diets where percentage of energy from fat differed by 2% or more. Higher carbohydrate, lower protein diets were differentiated from lower carbohydrate, higher protein diets where percentage of energy from protein differed by 2% or more and higher carbohydrate, lower protein and fat diets were differentiated from lower carbohydrate, higher protein and fat diets where percentage of energy from fat differed by 2% or more and protein also differed by more than 2%.

### **Fasting blood insulin and lower carbohydrate, higher fat diets vs. higher carbohydrate, lower fat diets**

Thirty studies reported on blood insulin and dietary differences in carbohydrate and fat, but less than 2% dietary differences in protein between groups. Collectively, most studies tended to indicate an increase in fasting blood insulin in participants consuming a higher carbohydrate, lower fat diet compared to lower carbohydrate, higher fat diet.

Twenty four studies in total did not indicate statistically significant differences in fasting blood insulin comparing diets differing in carbohydrate and fat composition. Those that did are described in detail here.

The Monounsaturated Fatty acids in Obesity trial, reported in Due *et al.* (Due *et al.*, 2008b), investigated the long-term weight loss maintenance effects (6 months) of a high mono-unsaturated fatty acid (MUFA) diet (43.3% energy from carbohydrate, 38.4% energy from fat), a low fat diet (57.6% energy from carbohydrate, 23.6% energy from fat) and a control diet (49.8% energy from carbohydrate, 32.1% energy from fat) in young overweight adults. Despite weight re-gain, fasting blood insulin assessed at 6 months was statistically significantly lower in the high MUFA diet group ( $p<0.001$ ) when compared to the control; but was statistically significantly higher in the low fat intervention group ( $p<0.01$ ). This study therefore provides some evidence that replacement of

some dietary carbohydrate with energy from monounsaturated fat may reduce fasting blood insulin.

One other trial also assessed the effect of high MUFA/ lower carbohydrate and lower fat/ high carbohydrate diets. In the study by Clifton *et al.* (Clifton *et al.*, 2004) 70 healthy females with BMI <27kg/m<sup>2</sup> were instructed to consume a very low fat diet (65% energy from carbohydrate; 11.6% energy from fat) or a high MUFA diet (43.7% energy from carbohydrate; 35.5% energy from fat) as part of a free living diet plan. Change in fasting blood insulin from baseline was statistically significant in both groups ( $p < 0.01$  for both), and there was a significant diet by time interaction. In spite of these findings, it must be considered that weight loss was apparent in both groups.

In individuals with different polymorphisms of the uncoupling protein-3 gene (a gene with influence on energy expenditure and fat storage) (de Luis *et al.*, 2009a), separating participants according to genetic subgroups showed differences from baseline in fasting insulin levels. A significant improvement in insulin – that is, a decrease in insulin from baseline - in probands with the wild type allele of the UCP-3 gene treated with both the low carbohydrate diet and low fat diet ( $p < 0.05$  for both) was reported. In carriers of the T variant, insulin was unaffected by either diet.

Finally, Kirk *et al.* (Kirk *et al.*, 2009) conducted an 11-week parallel group trial designed to compare a high carbohydrate diet and very low carbohydrate diet. At follow-up, statistically significant reductions in insulin were observed in both the high carbohydrate diet group and the very low carbohydrate diet group ( $p < 0.05$  and  $p < 0.001$  respectively). In addition, there appeared to be a greater decrease in the very low carbohydrate diet compared to the high carbohydrate diet ( $p < 0.05$ ). All food was provided which suggests that dietary compliance was high, however it must also be recognised that the final sample only contained 22 participants and the number of completers in each group was not reported.

In contrast to the other studies, which found greater reductions in insulin levels with lower carbohydrate intakes, Swinburn *et al.* found a greater benefit from higher carbohydrate intakes. Swinburn *et al.* (Swinburn *et al.*, 2001) tested the effects of a control diet and a high carbohydrate, low fat diet in 176 males and females and found that high carbohydrate diet compliers had significantly lower fasting insulin levels at 1 year ( $p = 0.023$ ) compared with the control diet group.

In the majority of these trials, participants lost weight in each diet group and generally insulin levels decreased. Weight loss is recognised to influence fasting insulin levels. Dansinger *et al.* found that extent of weight change predicted the decrease in insulin levels regardless of dietary type ( $r = -0.39$ ) (Dansinger *et al.*, 2005). Against a background of decreasing weight, the effect of dietary composition generally appears to have had minimal influence in these studies.

### **Area under the curve of blood insulin (µIU/L) and lower carbohydrate, higher fat diets vs. higher carbohydrate, lower fat diets**

Five studies recorded differences in the area under the curve (AUC) of blood insulin during the first 120 minutes following an oral glucose tolerance test (OGTT).

Raatz *et al.* (Raatz *et al.*, 2005) found no statistically significant effect of a high fat diet, a low GI diet or high GI diet on change in insulin after 12 weeks using a parallel group design. One further study which compared a high MUFA diet, a low fat diet and a control diet did not observe an effect on AUC blood insulin (Due *et al.*, 2008a).

Foster *et al.* (Foster *et al.*, 2003) investigated the effects of a low carbohydrate diet and a conventional diet in 63 obese males and females. AUC blood insulin, measured at 3 months, 6 months and 1 year was statistically significantly lower in both diet groups, excluding the conventional diet group at 6 months only, which witnessed a minor non-significant decrease. There was no between-group difference in the extent of this decrease. Foster *et al.* (Foster *et al.*, 2003) however highlight the high attrition rate (41%) reported in this study.

A diet high in carbohydrate compared to a diet with moderate carbohydrate content was also assessed by Frisch *et al.* (Frisch *et al.*, 2009). In this study of 200 overweight males and females, participants in both dietary groups witnessed a reduction in proinsulin at 1 year follow-up. There was no between-group difference in the extent of this decrease.

Swinburn *et al.* (Swinburn *et al.*, 2001) also tested the effects of control diet and a low fat diet in 176 males and females and found that compliers had significantly lower 2-hour insulin levels at 1 year ( $p=0.018$ ) compared with the control diet group.

In summary, four trials did not find an improvement in insulin response to an OGTT with higher carbohydrate diets, over and above the general improvements that were observed as a consequence of weight loss. Just one trial indicated a beneficial effect of high carbohydrate, low fat diets (Swinburn *et al.*, 2001).

### **Fasting blood insulin and lower carbohydrate, higher protein diet vs. higher carbohydrate, lower protein diets**

Five studies provided data on dietary differences in carbohydrate and protein where minimal changes in dietary fat between groups were reported. None showed a statistically significant difference between dietary groups at follow-up.

One study by Claessens *et al.* (Claessens *et al.*, 2009) explored the effects of a carbohydrate supplement, rather than a carbohydrate diet. Sixty participants with BMI  $>27\text{kg/m}^2$  were randomly assigned to a high carbohydrate supplement, a high protein supplement (casein) or one other high protein supplement (whey) for a period of 12 weeks. At follow-up, no statistically significant differences in fasting insulin within groups were observed (data not provided for between groups).

Using parallel group designs, Clifton *et al.* (Clifton *et al.*, 2008) and Noakes *et al.* (Noakes *et al.*, 2005) tested the effects of high carbohydrate diets and high protein diets. Measurements of fasting insulin were made at 12 weeks in one study (Clifton *et al.*, 2008) and 6 months and 1 year in another (Noakes *et al.*, 2005). No differential effect of a high carbohydrate or low carbohydrate diet on blood insulin in either study was shown.

Finally, in the randomised controlled trial conducted by Due *et al.* (Due *et al.*, 2004) the effects of a high protein diet and a moderate protein diet were investigated using previously overweight and obese participants (n=50). Fasting insulin was not statistically significantly different within or between groups at 6 months and 1 year. In a comparable study by Sacks *et al.* (Sacks *et al.*, 2009), adults from the US were instructed to consume one of four diets: i) a high-fat average-protein diet; ii) a high-fat high-protein diet; iii) a low-fat average-protein diet; or iv) a low-fat high-protein diet. Fasting insulin at 6 months and 2 years decreased, but not statistically significantly so, in all dietary groups.

### **Fasting blood insulin and lower carbohydrate, higher protein and fat diets vs. higher carbohydrate, lower protein and fat diets**

Data from seventeen studies providing dietary differences in carbohydrate, protein and fat between groups were extracted. Most studies reported decreases in fasting insulin in the trial overall. Only 2 studies reported a statistically significant difference with group differences in dietary carbohydrate intake (Noakes *et al.*, 2006; Seshadri *et al.*, 2005). These two studies suggest beneficial decreases with lower carbohydrate diets.

Noakes (Noakes *et al.*, 2006) compared 3 different iso-caloric diets over 8 weeks in overweight and obese men and women with at least one coronary heart disease risk factor. Between weeks 8 and 12 of the trial the goal was weight maintenance. All groups, which differed in carbohydrate intake (12 to 66% of energy from carbohydrate) lost weight and experienced a decrease in fasting insulin at 8 weeks. At the 12 week assessment, the greatest decrease in insulin was observed in the lowest carbohydrate group (-3.6 mU/L) and there was a small increase in the highest carbohydrate group (+1.3 mU/L). There was a significant overall effect of diet in this study despite similar losses in body fat mass in each dietary group.

Seshadri *et al.* (Seshadri *et al.*, 2005) similarly found a greater decrease in fasting insulin levels with a low carbohydrate (31% energy) diet compared with a standard, energy restricted diet (51% energy from carbohydrate) in a 6 month, parallel group trial of 132 obese men and women which was conducted in the USA (p=0.006).

### **Area under the curve of blood insulin and lower carbohydrate, higher protein and fat diets vs. higher carbohydrate, lower protein and fat diets**

One study recorded differences in the area under the curve of blood insulin during the first 120 minutes following an oral glucose tolerance test (OGTT). Lasker *et al.* (Lasker *et al.*, 2008) found that dietary treatment with a high protein, energy restricted diet resulted in lower AUC blood insulin compared to a high carbohydrate diet at 4 months ( $p=0.011$ ). Differences over time however were not reported.

There were no data that reported AUC of insulin and changes in carbohydrate and protein.

*Nb. As there has been no evidence from the authors to suggest otherwise, it is assumed that (de Luis et al., 2009b; de Luis et al., 2009a; de Luis et al., 2008) are the same study given the identical diets, same ethical submission dates (for two out of the four studies) and use of similar participants and sample sizes.*

Table 4.48 Insulinaemia and total carbohydrate: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assess ment	Exposure	Outcome/ Assessment details	Sub- group Detail	Contrast (mean)	Units	Mean Outcome	Beta coefficient (SE)/(CI)	P Trend	Adjustments
13676 (Ludwig <i>et al.</i> , 1999) The CARDIA Study	USA, Multi-ethnic, Generally healthy, No hypertension, Not diabetic	18-30 %M 45.9	5115	10 years	FFQ (700)	Carbohydrate, total (% energy)	Blood insulin Fasting, uU/mL	Race - White	Q5 vs. Q1 (51.9) vs. (33.5)	% Energy	10.4 vs. 10.5		0.93	age, alcohol, BMI, centre, education, energy intake, physical activity, gender, smoking, vitamin intake
13677 The CARDIA Study								Race - Black	Q5 vs. Q1 (51.9) vs. (33.5)	% Energy	13.1 vs. 12.7		0.72	As above
13680 The CARDIA Study							Blood insulin 2-Hour Insulin, uU/mL	Race - White	Q5 vs. Q1 (51.9) vs. (33.5)	% Energy	33.4 vs. 36.3		0.39	As above
13681 The CARDIA Study								Race - Black	Q5 vs. Q1 (51.9) vs. (33.5)	% Energy	47.1 vs. 47.6		0.65	As above
13089 (Marshall <i>et al.</i> , 1997) San Luis Valley Diabetes Study	USA, Multi-ethnic, Normal glucose tolerance	20-74 (52) %M 46.8	1069	4.3 years (26)	Dietary recall	Carbohydrate, total (grams/day)	Blood insulin Fasting, Plasma			45 g/day		Regression direction negative, beta coefficient not reported	0.14	age, waist, BMI, energy intake, ethnicity, physical activity, Gender

Table 4.49 Insulinaemia and high carbohydrate diets: RCT data

Result number	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Diff- erence between groups in $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>														
15409 (Demol <i>et al.</i> , 2009)		High carbohydrate, low fat	20/20	20.0 (SD 2.1)	18.7 (SD 2.4)					Insulin	Fasting Serum, ( $\mu$ U/ml)	12 weeks	Decrease	unclear
		Low carbohydrate, high fat	17/17	19.5 (SD 2.4)	12.9 (SD 2.8)			NS					Decrease	
		Low carbohydrate, high protein	18/18	20.3 (SD 2.3)	15.0 (SD 2.5)			NS					Decrease	
15410		High carbohydrate, low fat	20/20	20 (SD 2.1)	15.1 (SD 2.9)					Insulin	Fasting Serum, ( $\mu$ U/ml)	1 year	Decrease	unclear
		Low carbohydrate, high fat	17/17	19.5 (SD 2.4)	12.0 (SD 3.3)			NS					Decrease	
		Low carbohydrate, high protein	18/18	20.3 (SD 2.3)	13.1 (SD 2.7)			NS					Decrease	
<b>Adult studies</b>														
16868 (Bhargava, 2006)		Control	379/allocated not reported	76.95 (SD 46.25)	74.31 (SD 57.23)			NS		Insulin	Fasting Serum, (pmol/L)	1 year	Decrease	unclear
		Low fat	615/allocated not reported	76.33 (SD 41.88)	69.23 (SD 56.46)			0.05	NS				Decrease	
15741 (Brehm <i>et al.</i> , 2003)		Low carbohydrate	22/22	16.9 (SE 1.8)	11.6 (SE 1.2)			<0.0001	NS	Insulin	Fasting ( $\mu$ U/ml)	3 months	Decrease	unclear
		Moderate fat	20/20	23.9 (SE 2.34)	18.1 (SE 2.5)			<0.0001					Decrease	
15749		Low carbohydrate	22/22	16.9 (SE 1.8)	14.4 (SE 1.4)			<0.0001	NS	Insulin	Fasting ( $\mu$ U/ml)	6 months	Decrease	unclear
		Moderate fat	20/20	23.9 (SE 2.34)	18.4 (SE 2.1)			<0.0001					Decrease	
16818 (Claessens <i>et al.</i> , 2009)		High carbohydrate supplement	16/allocated not reported	15.75 (SE 2.39)	18.28 (SE 3.67)	2.53 (SE 2.11)	NS	NS		Insulin	Fasting ( $\mu$ U/ml)	12 weeks	Increase	unclear
		High protein supplement - casein	14/allocated not reported	12.56 (SE 1.23)	11.26 (SE 0.88)	-1.29 (SE 0.73)	NS						Decrease	

Result number	Subgroup detail	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Diff-erence between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
		High protein supplement - whey	18/allocated not reported	14.91 (SE 2.16)	14.13 (SE 1.26)	-0.78 (SE 1.84)	NS						Decrease	
16820		High carbohydrate supplement	16/allocated not reported	51.02 (SE 4.15)	63.4 (SE 6.18)	12.38 (SE 3.57)	<0.05	NS		Glucagon	Fasting (pg/ml)	12 weeks	Increase	unclear
		High protein supplement - casein	14/allocated not reported	55.52 (SE 3.26)	58.6 (SE 3.61)	3.08 (SE 2.73)	NS						Decrease	
		High protein supplement - whey	18/allocated not reported	57.84 (SE 5.76)	60.35 (SE 5.36)	2.52 (SE 3.42)	NS						Decrease	
16010 (Clifton <i>et al.</i> , 2008)		High carbohydrate diet	38/38			-1.23 (SD 6.88)			NS	Insulin	Fasting (mIU/L)	1.25 years	Decrease	unclear
		High protein diet	40/41			-2.92 (SD 3.50)						1.25 years	Decrease	
16755 (Clifton <i>et al.</i> , 2004)		High MUFA	31/35	85 (SD 29)	50 (SD 20)	-35	<0.01	DietXTime, p<0.05		Insulin	Fasting (pmol/L)	12 weeks	Decrease	unclear
		Very low fat	31/35	117 (SD 58)	87 (SD 65)	-30	<0.01						Decrease	
17409 (Colette <i>et al.</i> , 2003)		High carbohydrate diet	15/15	12 (SE 2)	9.1 (SE 1.4)		0.009			Insulin	Fasting Plasma, (mU/L)	8 weeks	Decrease	unclear
		High MUFA diet	17/17	11 (SE 2)	7.1 (SE 1.3)		0.020	NS		Insulin		8 weeks	Decrease	unclear
17176 (Cornier <i>et al.</i> , 2005)	Insulin resistant	High carbohydrate, low fat	4/10	20.8 (SE 1.3)	10.4 (SE 1.4)			NS		Insulin	Fasting ( $\mu$ U/ml)	16 weeks	Decrease	unclear
		Low carbohydrate, high fat	5/11	18.4 (SE 1.2)	7.2 (SE 1.3)								Decrease	
16341	Insulin sensitive	High carbohydrate, low fat	6/10	7.2 (SE 1.1)	4.2 (SE 1.2)			NS		Insulin	Fasting ( $\mu$ U/ml)	16 weeks	Decrease	unclear
		Low carbohydrate, high fat	6/11	7 (SE 1.1)	6.6 (SE 1.2)								Decrease	
15987 (Dale <i>et al.</i> , 2009)		High MUFA diet minus high carbohydrate diet	High MUFA: 85/100 High CHO: 89/100						0.97 (CI 0.87, 1.09), p=0.62	Insulin	Fasting (mIU/L)	2 years	Decrease in both	unclear



Result number	Subgroup detail	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Diff-erence between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
17382		High carbohydrate diet	89/100	9.1 (SD 5.9)	7.24 (SD 5.61)					Insulin	Fasting (mIU/L)	2 years	Decrease	unclear
		High MUFA diet	85/100	9.4 (SD 7.9)	6.41 (SD 5.16)								Decrease	
17403		High carbohydrate diet	89/100	9.1 (SD 5.9)	7.32 (SD 4.41)					Insulin	Fasting (mIU/L)	1 year	Decrease	unclear
		High MUFA diet	85/100	9.4 (SD 7.9)	7.65 (SD 4.15)								Decrease	
15828 (Dansinger <i>et al.</i> , 2005)		Atkins	40/40			-5.1 (SD 13)	0.01		0.06	Insulin	Fasting Serum, ( $\mu$ IU/ml)	2 months	Decrease	No bias
		Ornish	40/40			-1.7 (SD 12)	NS						Decrease	
		Weight watchers	40/40			-1.8 (SD 6)	NS						Decrease	
		Zone	40/40			-7.1 (SD 12)	0.01						Decrease	
15829		Atkins	40/40			-2.1 (SD 11)	NS		0.60	Insulin	Fasting Serum, ( $\mu$ IU/ml)	6 months	Decrease	No bias
		Ornish	40/40			-0.4 (SD 18)	NS						Decrease	
		Weight watchers	40/40			-2.5 (SD 7.1)	NS						Decrease	
		Zone	40/40			-1.9 (SD 16)	NS						Decrease	
15830		Atkins	40/40			-1.2 (SD 6.7)	NS		0.70	Insulin	Fasting Serum, ( $\mu$ IU/ml)	1 year	Decrease	No bias
		Ornish	40/40			-3 (SD 6.3)	0.05						Decrease	
		Weight watchers	40/40			-2.6 (SD 6.1)	0.01						Decrease	
		Zone	40/40			-5.4 (SD 14)	0.01						Decrease	
16148 (de Luis <i>et al.</i> , 2008)	Genetics - wild-type Ala54/Ala54	Low carbohydrate	55/105	19.9(SD 8.2)	14.3 (SD 9.8)				Not reported	Insulin	Fasting	2 months	Decrease	unclear
		Low fat	55/99	15.9 (SD 7.7)	11.6 (SD 5.1)								Decrease	
16165	Genetics - mutant-type Ala54/Thr54 or Thr54/Thr54	Low carbohydrate	50/105	23.5 (SD 18.2)	17.5 (SD 7.6)				Not reported				Decrease	
		Low fat	44/99	13.5 (SD 6.2)	13.7 (SD 8.6)								Decrease	

Result number	Subgroup detail	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Diff-erence between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
16086 (de Luis <i>et al.</i> , 2009b)		Low carbohydrate	52/52	22.5 (SD 10)	15.3 (SD 6)			NS		Insulin	Fasting (mIU/L)	3 months	Decrease	unclear
		Low fat	66/66	16.9 (SD 13)	11.5 (SD 4.9)								Decrease	
16705 (de Luis <i>et al.</i> , 2009a)	Genetics - UCP3 Gene -55CC polymorphism	Low carbohydrate	54/67	15.9 (SD 7.7)	11.6 (SD 9.8)		<0.05	NS		Insulin	(mUI/L)	2 months	Decrease	unclear
		Low fat	40/64	21.1 (SD 12)	16.2 (SD 10)		<0.05						Decrease	
16706	Genetics - UCP3 Gene -55CT/TT polymorphism	Low carbohydrate	13/67	11.8 (SD 18.2)	11.2 (SD 7.6)		NS						Decrease	
		Low fat	24/64	23.2 (SD 6.2)	24.7 (SD 8.6)		NS						Decrease	
17534 (Due <i>et al.</i> , 2004)		High protein	23/23	42 (CI 32, 78)	34 (CI 25, 62)					Insulin	Fasting (pmol/L)	6 months	Decrease	unclear
		Moderate protein	23/18	50 (CI 28, 61)	43 (CI 37, 54)								Decrease	
17535		High protein	23/23	42 (CI 32, 78)	47 (CI 27, 92)					Insulin	Fasting (pmol/L)	1 year	Decrease	unclear
		Moderate protein	18/18	50 (CI 28, 61)	61 (CI 34, 76)								Decrease	
16397 (Due <i>et al.</i> , 2008a)		Control diet	12/12	35811 (CI 23246, 48375)	33922 (CI 25499, 42344)			NS		Insulin AUC OGTT (120min)	Serum	6 months	Increase	unclear
		High MUFA	16/16	26332 (CI 19889, 32775)	27359 (CI 21493, 33225)								Increase	
		Low fat diet	18/18	31355 (CI 24458, 38253)	32727 (CI 25492, 39962)								Increase	
15296 (Due <i>et al.</i> , 2008b)		Control	24/25	43.2 (CI 34.5, 51.8)	57.2 (CI 44.6, 69.8)	14.0 (CI 5.1, 23)				Insulin	Fasting Serum, (pmol/L)	6 months	Increase	unclear
		High MUFA	39/52	40.9 (CI 33.6, 48.1)	38.3 (CI 33.5, 43.1)	-2.6 (CI -9.6, 4.5)		<0.001					Increase	
		Low fat	43/48	41.4 (CI 36.7, 46.1)	45.7 (CI 39.9, 51.5)	4.3 (CI -1.8, 10.3)		<0.01					Increase	
15461 (Ebbeling <i>et al.</i> , 2007)		Low fat diet	37/37			-0.9 (SE 0.8)				Insulin	Fasting Serum, (μUI/ml)	6 months	Decrease	No bias
		Low GL diet	ITT: 36/36			-2.1 (SE 0.8)		0.28					Decrease	

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Result number	Subgroup detail	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Diff-erence between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
15462		Low fat diet	37/37			0 (SE 0.8)				Insulin	Fasting Serum, ( $\mu$ U/ml)	18 months	Decrease	No bias
		Low GL diet	ITT: 36/36			-0.8 (SE 0.8)		0.49					Decrease	
15235 (Foster <i>et al.</i> , 2003)		Conventional diet plan	30/30			-11.2 (SD 40.5)	<0.05			Change in Insulin AUC OGTT (120min)	Plasma (%)	3 months	Decrease	unclear
		Low carbohydrate diet	33/33			-14.1 (SD 27.6)	<0.05	0.48					Decrease	
15237		Conventional diet plan	30/30			-5.1 (SD 35.8)	NS			Change in Insulin AUC OGTT (120min)	Plasma (%)	6 months	Decrease	unclear
		Low carbohydrate diet	33/33			-14.7 (SD 25.7)	<0.05	0.19					Decrease	
15238		Conventional diet plan	30/30			-8.2 (SD 28.4)	<0.05			Change in Insulin AUC OGTT (120min)	Plasma (%)	1 year	Decrease	unclear
		Low carbohydrate diet	33/33			-11.2 (SD 24.7)	<0.05	0.6					Decrease	
15177 (Frisch <i>et al.</i> , 2009)		High carbohydrate diet	100/100			-1.4 (SD 11.4)	NS			Proinsulin	Fasting (pmol/L)	6 months	Decrease	unclear
		Moderate carbohydrate diet	100/100			-3.7 (SD 14.8)	NS	0.676					Decrease	
15178		High carbohydrate diet	100/100			-2.2 (SD 8.2)	0.05			Proinsulin	Fasting (pmol/L)	1 year	Decrease	unclear
		Moderate carbohydrate diet	100/100			-5 (SD 14)	0.05	0.148					Decrease	
15120 (Gardner <i>et al.</i> , 2007)		Atkins: low carbohydrate	70/77			-3 (SD 3.9)		NS		Insulin	Plasma ( $\mu$ U/ml)	2 months	Decrease	No bias
		Ornish: high carbohydrate	64/76			-1.1 (SD 3.3)		NS					Decrease	
		Zone: moderate carbohydrate	65/79			1 (SD 6)							Decrease	
15121		Atkins: low carbohydrate	70/77			-2.8 (SD 4.1)		NS		Insulin	Plasma ( $\mu$ U/ml)	6 months	Decrease	No bias

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Result number	Subgroup detail	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Diff-erence between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
15122		Ornish: high carbohydrate	64/76			-0.1 (SD 3.6)		NS					Decrease	
		Zone: moderate carbohydrate	65/79			0.1 (SD 8.9)							Decrease	
		Atkins: low carbohydrate	70/77			-1.8 (SD 4.8)		NS		Insulin	Plasma ( $\mu$ U/ml)	1 year	Decrease	No bias
		Ornish: high carbohydrate	64/76			-0.2 (SD 3.8)		NS					Decrease	
		Zone: moderate carbohydrate	65/79			-1.5 (SD 4.9)							Decrease	
16624 (Golay <i>et al.</i> , 1996)		Low carbohydrate diet	completers not reported/22	106.8 (SE 15.6)	96.0 (SE 13.2)		<0.001	Not reported		Insulin	Fasting Plasma, (pmol/L)	6 weeks	Decrease	unclear
		Moderate carbohydrate diet	completers not reported/21	57.6 (SE 6.6)	88.2 (SE 9.6)		NS						Decrease	
14851 (Golay <i>et al.</i> , 2000)		Higher carbohydrate, macronutrient s not eaten simultaneously	26/26	14.2 (SE 2.8)	10.6 (SE 1.5)			NS		Blood insulin	Fasting Plasma, (mU/L)	6 weeks	Decrease	unclear
		Lower carbohydrate, macronutrient s eaten simultaneously	28/28	16.3 (SE 1.7)	14.2 (SE 1.3)								Decrease	
17452 (Grau <i>et al.</i> , 2009)	Genetics - FTO rs9939609 TT	High carbohydrate, low fat diet	88/320	9.7 (SD 5.4)		-2.4 (SD 4.6)		No diet x gene interaction		Insulin	Fasting Serum, ( $\mu$ U/ml <sup>-1</sup> )	10 weeks	Decrease	bias
		Low CHO, high fat diet	117/298	10.6 (SD 6.6)		-1.1 (SD 5.2)							Decrease	
17456	Genetics - FTO rs9939609 AT	High carbohydrate, low fat diet	168/320	9.9 (SD 6)		-0.6 (SD 5.3)				Insulin	Fasting Serum, ( $\mu$ U/ baseline value)	10 weeks	Decrease	bias
		Low CHO, high fat diet	143/298	10.5 (SD 6.3)		-1.5 (SD 5.8)							Decrease	
17460	Genetics - FTO rs9939609 AA	High carbohydrate, low fat diet	64/320	9.7 (SD 5.6)		-0.8 (SD 4.7)				Insulin	Fasting Serum, ( $\mu$ U/ml <sup>-1</sup> )	10 weeks	Decrease	bias
		Low CHO, high	38/298	10.7 (SD 7.7)		-1.2 (SD							Decrease	

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		fat diet				5.1)								
15915 (Helge, 2002)		High carbohydrate + exercise	16/16	9.3 (SE 0.9)	7.8 (SE 1.1)			0.06		Insulin	Fasting Plasma, ( $\mu$ U/l)	7 weeks	Decrease	unclear
		High fat + exercise	17/17	7.4 (SE 0.8)	7.7 (SE 1.0)								Decrease	
16253 (Howard <i>et al.</i> , 2006)		Control	approx 1699 participants included as a 5.8% sub-sample of 29294 in group	10.2 (SD 5.3)	11.2 (SD 5.9)	1.1 (SD 0.5)				Insulin	Fasting ( $\mu$ U/ml)	3 years	No change	No bias
		Low fat	approx 1132 participants included as a 5.8% sub-sample of 19541 in group	9.9 (SD 4.9)	10.5 (SD 5.3)	1.1 (SD 0.5)		NS					Decrease	
17620		Low fat minus control	Low fat: approx 1132 participants included as a 5.8% sub-sample of 19541 in group Control: approx 1699 participants included as a 5.8% sub-sample of 29294 in group						-0.03 (CI - 0.07, 0.02)	Insulin	Fasting ( $\mu$ U/ml)	3 years	No change in control group, decrease in low fat group	No bias
14865 (Johnston <i>et al.</i> , 2004)		High carbohydrate, low fat	7/10	152 (SE 13)		-24.1% (SE 6.6%)	0.05			Blood insulin	Fasting (pmol/L)	6 weeks	Decrease	unclear
		High protein, low fat	9/10	156 (SE 22)		-24.2% (SE 8.2%)	0.05	0.889					Decrease	
15613 (Keogh <i>et al.</i> , 2007)		High carbohydrate diet	12/12	11.84 (SE 6.08)	6.73 (SE 3.09)		0.001	NS		Insulin	Fasting Plasma, (mIU/l)	6 weeks	Decrease	unclear
		Low carbohydrate diet	13/13	16.88 (SE 13.89)	9.53 (SE 6.08)		0.001						Decrease	
15614		High carbohydrate diet	12/12	11.84 (SE 6.08)	8.96 (SE 5.44)		0.001			Insulin	Fasting Plasma, (mIU/l)	12 weeks	Decrease	unclear

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15615		Low carbohydrate diet	13/13	16.88 (SE 13.89)	7.97 (SE 5.12)		0.001						Decrease	
		High carbohydrate diet	completers not reported/12	9.09 (SE 0.78)	5.22 (SE 0.49)		0.001			Insulin	Fasting Plasma, (mIU/l)	1 year	Decrease	unclear
		Low carbohydrate diet	completers not reported/13	11.06 (SE 2.64)	7.28 (SE 1.5)		0.001						Decrease	
16719 (Keogh <i>et al.</i> , 2008)		High carbohydrate, low SFA	47/50	11.3 (SD 6.0)	7.8 (SD 3.1)		<0.001			Insulin	(mIU/L)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	52/57	9.6 (SD 4.8)	6.9 (SD 5.0)		<0.001	NS					Decrease	
17556 (Kirk <i>et al.</i> , 2009)		High carbohydrate	completers not reported/11	15.5 (SE 2.8)		-22.0 (SE 5.7)	<0.05			Insulin	Fasting Plasma, ( $\mu$ U/ml)	11 week	Decrease	unclear
		Very low carbohydrate	completers not reported/11	18.7 (SE 2.4)		-38.4 (SE 5.2)	<0.001	<0.05					Decrease	
15678 (Kirkwood <i>et al.</i> , 2007)		Group 1: No advice	18/allocated not reported				NS			Insulin	Fasting (mU/L)	12 weeks	No change	unclear
		Group 2: Conventional weight loss diet	16/allocated not reported				NS	NS					Decrease	
15679		Group 3: Exercise	19/allocated not reported			-1.88	0.06	NS		Insulin	Fasting (mU/L)	12 weeks	Decrease	unclear
		Group 4: Conventional weight loss diet + exercise	16/allocated not reported				NS						Decrease	
15898 (Lasker <i>et al.</i> , 2008)		high carbohydrate	25/33	119.2 (SD13.7)		~ +21 units				Insulin	Fasting Plasma, (pmol/L)	4 months	Decrease	unclear
		High protein	25/32	169.7 (SD19.7)		~ -20 units		0.07					Decrease	
15902		high carbohydrate	25/33			-1				Insulin OGTT (60min)	Plasma (%)	4 months	Decrease	unclear
		High protein	25/32			-34.3		0.005					Decrease	
15903		high carbohydrate	25/33			46.2				Insulin OGTT (120min)	Plasma (%)	4 months	Decrease	unclear

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		High protein	25/32			-9.2		0.011					Decrease	
15996 (Landry <i>et al.</i> , 2003)		High carbohydrate	19/19	60 (SD 22)		-6.0 (SD 21.7)	NS	Not reported		Insulin	Fasting Plasma, (pmol/L)	7 weeks	Decrease	unclear
		Low carbohydrate, high fat diet	18/18	64 (SD 28)		6.5 (SD 29.7)	NS						Decrease	
16171 (Layman <i>et al.</i> , 2005)		High carbohydrate diet	9/12	153.5 (SD 27.9)	141.3 (SD 9.3)		NS			Insulin	Fasting (pmol/L)	16 weeks	Decrease	unclear
		High protein diet	9/12	150.6 (SD 26.5)	125.5 (SD 10.8)		NS	0.78					Decrease	
16172		High carbohydrate diet + exercise	10/12	184.4 (SD 15.8)	133.4 (SD 8.6)		<0.05			Insulin	Fasting (pmol/L)	16 weeks	Decrease	unclear
		High protein diet + exercise	9/12	189.4 (SD 17.2)	138.8 (SD 7.9)		<0.05	0.16					Decrease	
17269 (Lofgren <i>et al.</i> , 2005)		High carbohydrate, low fat	20/20	14.5 (SE 2)	10.7 (SE 1.1)			NS		Insulin	Fasting Plasma, (pmol/L)	10 weeks	Decrease	unclear
		High fat, moderate carbohydrate	20/20	13.1 (SE 1.4)	10.1 (SE 1.2)								Decrease	
15011 (Lovejoy <i>et al.</i> , 2003)		Control	13/15	75.6 (SE 10.5)		-11.9 (SE 7.9)			NS	Insulin	Fasting (pmol/L)	3 months	Decrease	unclear
		Fat reduced	13/15	57 (SE 5.7)		1.9 (SE 3.2)							Decrease	
15012		Control	13/15	75.6 (SE 10.5)		-5.8 (SE 6.9)			NS	Insulin	Fasting (pmol/L)	6 months	Decrease	unclear
		Fat reduced	13/15	57 (SE 5.7)		0.5 (SE 4.5)							Decrease	
15013		Control	13/15	75.6 (SE 10.5)		6.6 (SE 9.9)			NS	Insulin	Fasting (pmol/L)	9 months	Decrease	unclear
		Fat reduced	13/15	57 (SE 5.7)		12.6 (SE 4.7)							Decrease	
15077 (Mahon <i>et al.</i> , 2007)		Control	11/11	14 (SD 9)		No change	NS			Insulin	Fasting Plasma ( $\mu$ U/mL)	9 weeks	No change	unclear
		Energy restriction + beef	14/14			No change	NS	NS					Decrease	
		Energy restriction + carbohydrate/fat	14/14			No change	NS	NS					Decrease	

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		Energy restriction + chicken	15/15				NS	NS					Decrease	
17290 (Maki <i>et al.</i> , 2007b)		Low fat, energy restricted	39/43	9 (SE 1.2)		0.9 (SE 1.1)			NS	Insulin	Fasting (mU/L)	12 weeks	Decrease	unclear
		Ad libitum low GL diet	39/43	10.4 (SE 1)		-0.4 (SE 1.1)							Decrease	
17291		Low fat, energy restricted	39/43	9 (SE 1.2)		2.4 (SE 0.7)			NS	Insulin	Fasting (mU/L)	36 weeks	Decrease	unclear
		Ad libitum low GL diet	38/43	10.4 (SE 1)		1.1 (SE 1)							Decrease	
16225 (McMillan-Price <i>et al.</i> , 2006)		High CHO, high GI diet	32/32	79 (SE 7)		-8.1 (SE 6.9)				Change in insulin	Fasting (pmol/L)	12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	83 (SE 10)		-13.3 (SE 6.9)							Decrease	
		High protein, high GI diet	32/32	101 (SE 12)		-17.1 (SE 7)		NS					Decrease	
		High protein, low GI diet	33/33	81 (SE 8)		-10.4 (SE 6.8)		NS					Decrease	
14878 (Meckling <i>et al.</i> , 2004)		Low carbohydrate	15/10	23.7 (SE 2.7)	16.9 (SE 1.9)		0.05	NS		Blood insulin	Fasting ( $\mu$ U/ml)	10 weeks	Decrease	No bias
		Low fat	16/10	20.9 (SE 1.3)	20.2 (SE 1.5)		NS						Decrease	
16373 (Meckling and Sherfey, 2007)		Hypocaloric control diet	8/15	20.1 (SD 7.6)	18.8 (SD 7.1)		NS	NS		Insulin	Fasting Plasma, ( $\mu$ U/ml)	12 weeks	Decrease	unclear
		Hypocaloric protein rich diet	10/15	19.0 (SD 5.7)	15.9 (SD 4.6)		NS						Decrease	
		Hypocaloric control diet + exercise	11/15	18.6 (SD 11.5)	16.7 (SD 6.7)		NS						Decrease	
		Hypocaloric protein rich diet + exercise	14/15	15.8 (SD 4.3)	14.7 (SD 5.0)		NS						Decrease	
14713 (Morgan <i>et al.</i> , 2009)		Atkins	33/57	73.2 (SD 35.1)	75.2 (SD 83.6)		NS	NS		Blood insulin	Fasting Whole blood, (pmol/L)	8 weeks	Decrease	unclear
		Control	37/61	68.1 (SD 35.6)	69.2 (SD 41)		NS						No change	
		Slim Fast	44/59	72.3 (SD 39.1)	80.1 (SD 67.1)		NS						Decrease	



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14714		Weight Watchers	46/58	62.2 (SD 32.4)	57.2 (SD 35.9)		NS						Decrease	
		Atkins	33/57	73.2 (SD 35.1)	54.8 (SD 32.4)		NS	NS		Blood insulin	Fasting Whole blood, (pmol/L)	24 weeks	Decrease	unclear
		Control	37/61	68.1 (SD 35.6)	75.9 (SD 45)		NS						No change	
		Slim Fast	44/59	72.3 (SD 39.1)	64.6 (SD 39.6)		0.01						Decrease	
		Weight Watchers	46/58	62.2 (SD 32.4)	52.9 (SD 30.2)		NS						Decrease	
(Noakes <i>et al.</i> , 2006) 16590		High unsaturated fat	21/27	9.1 (SE 0.6)	7.9 (SE 0.6)					Insulin	Fasting Plasma, (mU/L)	8 weeks	Decrease	unclear
		Very low carbohydrate	24/28	10.7 (SE 1.1)	8.1 (SE 1.0)								Decrease	
		Very low fat	22/28	8.6 (SE 0.7)	7.8 (SE 0.8)								Decrease	
16591		High unsaturated fat	21/27	9.1 (SE 0.6)	7.4 (SE 0.7)	-1.7 (SE 0.5)			0.05	Insulin	Fasting Plasma, (mU/L)	12 weeks	Decrease	unclear
		Very low carbohydrate	24/28	10.7 (SE 1.1)	7.1 (SE 0.8)	-3.6 (SE 0.5)							Decrease	
		Very low fat	22/28	8.6 (SE 0.7)	9.9 (SE 1.9)	1.3 (SE 1.7)							Decrease	
(Noakes <i>et al.</i> , 2005) 17002		High carbohydrate diet	48/48	10 (SE 0.07)	7.9 (SE 0.8)			NS		Insulin	Fasting (mU/L)	8 weeks	Decrease	unclear
		High protein diet	52/52	10 (SE 0.09)	7.4 (SE 0.7)								Decrease	
17003		High carbohydrate diet	48/48	10 (SE 0.07)	8.4 (SE 1.2)	-1.6 (SE 0.9)				Insulin	Fasting (mU/L)	12 weeks	Decrease	unclear
		High protein diet	52/52	10 (SE 0.09)	7.3 (SE 0.5)	-2.7 (SE 0.5)		0.278					Decrease	
17489 (Peterson and Jovanovic-Peterson, 1995)	BMI - Obese (130-200% ideal BW)	40% CHO supplement bar 1st	4/13	11 (SD 8)	13 (SD 4)	NS				Insulin	Fasting Serum, (mU/L)	6 weeks	Decrease	bias
		55% CHO supplement bar 1st	6/12	12 (SD 4)	13 (SD 3)	NS							Decrease	
17491	BMI - Obese (130-200%)	40% CHO supplement bar 2nd	4/12	12 (SD 4)	15 (SD 6)	NS				Insulin	Fasting Serum, (mU/L)	6 weeks	No change	bias

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	ideal BW)	55% CHO supplement bar 2nd	4/13	11 (SD 8)	27 (SD 10)	NS							No change	
17492	Previous gestational DM in last pregnancy	40% CHO supplement bar 1st	5/13	17 (SD 6)	12 (SD 7)	NS				Insulin	Fasting Serum, (mU/L)	6 weeks	Decrease	bias
		55% CHO supplement bar 1st	4/12	24 (SD 13)	22 (SD 6)	NS							Decrease	
17493	Previous gestational DM in last pregnancy	40% CHO supplement bar 2nd	2/12	24 (SD 13)	26 (SD 10)	NS				Insulin	Fasting Serum, (mg/dL)	6 weeks	No change	bias
		55% CHO supplement bar 2nd	5/13	17 (SD 6)	15 (SD 12)	NS							No change	
17218 (Petersen <i>et al.</i> , 2006)		Hypoenergetic low carbohydrate, high fat diet minus hypoenergetic high carbohydrate, low fat diet	Low CHO: 312/383 High CHO: 336/389					NS	0.3 (CI - 0.5, 1) (low carb – high carb)	Insulin	Fasting Plasma, ( $\mu$ U/ml)	10 weeks	Decrease in both	bias
17208	Women	Hypoenergetic high carbohydrate, low fat diet	251/389	9.5 (SD 5.0)		-1.1 (SD 4.1)				Insulin	Fasting Plasma, ( $\mu$ U/ml)	10 weeks	Decrease	bias
		Hypoenergetic low carbohydrate, high fat diet	235/382	10.2 (SD 6.8)		-0.74 (SD 6.1)							Decrease	
17209	Men	Hypoenergetic high carbohydrate, low fat diet	85/389	10.9 (SD 7.2)		-1.5 (SD 6.7)				Insulin	Fasting Plasma, ( $\mu$ U/ml)	10 weeks	Decrease	bias
		Hypoenergetic low carbohydrate, high fat diet	77/382	12.0 (SD 5.7)		-2.7 (SD 5.1)							Decrease	
17210		Hypoenergetic high	336/389	9.9 (SD 5.7)		-1.2 (SD 4.9)		NS		Insulin	Fasting Plasma,	10 weeks	Decrease	bias

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		carbohydrate, low fat diet									( $\mu$ U/ml)			
		Hypoenergetic low carbohydrate, high fat diet	312/382	10.7 (SD 6.6)		-1.2 (SD 5.9)							Decrease	
17426 (Phillips <i>et al.</i> , 2008)		Low carbohydrate diet	10/~14	18.2 (SE 3)	12.6 (SE 1.2)		0.05	NS		Insulin	Fasting Serum, (mg/dL)	6 weeks	Decrease	unclear
		Low fat diet	10/~14	17.05 (SE 3.92)	14.46 (SE 2.09)		NS						Decrease	
17234 (Raatz <i>et al.</i> , 2005)		High fat diet	10/8	56.3 (SE 9.7)		-6.3 (SE 4.8)		NS		Change in insulin	Fasting Serum, (pmol/L)	12 weeks	Decrease	unclear
		High GI diet	9/8	54.9 (SE 9)		-20.1 (SE 6.9)							Decrease	
		Low GI diet	10/6	67.4 (SE 11.8)		-28.5 (SE 6.3)		NS					Decrease	
16034 (Racette <i>et al.</i> , 1995)		Low carbohydrate diet	2/allocated not reported	79 (SD 36)	86 (SD 29)			NS		Insulin	Fasting (pmol/L)	10 weeks	Decrease	unclear
		Low fat diet	7/allocated not reported	93 (SD 14)	57 (SD 29)								Decrease	
16035		Low carbohydrate diet	2/allocated not reported	79 (SD 36)	64 (SD 7)			NS		Insulin	Fasting (pmol/L)	16 weeks	Decrease	unclear
		Low fat diet	7/allocated not reported	93 (SD 14)	72 (SD 36)								Decrease	
16036		Low carbohydrate diet + exercise	5/allocated not reported	86 (SD 36)	57 (SD 22)			NS		Insulin	Fasting (pmol/L)	10 weeks	Decrease	unclear
		Low fat diet + exercise	5/allocated not reported	72 (SD 22)	72 (SD 21)								Decrease	
16037		Low carbohydrate diet + exercise	5/allocated not reported	86 (SD 36)	79 (SD 36)			NS		Insulin	Fasting (pmol/L)	16 weeks	Decrease	unclear
		Low fat diet + exercise	3/allocated not reported	72 (SD 22)	43 (SD 22)								Decrease	
15593 (Sacks <i>et al.</i> , 2009)		High-fat, average- protein	ITT: /204		10 (SD 7)	-18.2%			NS	Insulin	Fasting Serum, ( $\mu$ U/ml)	6 months	Decrease	No bias
		High-fat, high- protein	ITT: /201		10 (SD 9)	-14.4%							Decrease	

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15594		Low-fat, average-protein	ITT: /204		10 (SD 7)	-16.2%							Decrease	
		Low-fat, high-protein	ITT: /202		10 (SD 6)	-19.9%							Decrease	
		High-fat, average-protein	ITT: /204	12 (SD 7.5)	12 (SD 8)	-6.4%			NS	Insulin	Fasting Serum, ( $\mu$ U/ml)	2 years	Decrease	No bias
		High-fat, high-protein	ITT: /201	12 (SD 8)	11 (SD 7)	-9.2%							Decrease	
		Low-fat, average-protein	ITT: /204	12 (SD 7)	12 (SD 10)	-2.4%							Decrease	
		Low-fat, high-protein	ITT: /202	12 (SD 8)	11 (SD 8)	-11.5%							Decrease	
14991 (Segal-Isaacson <i>et al.</i> , 2004)		Low fat diet	4/4	4.8 (SD 2.4)	4.0 (SD 1.5)		NS			Insulin	Fasting Serum, ( $\mu$ g/dL)	6 weeks	Decrease	unclear
		Very low carbohydrate	4/4	4.8 (SD 2.4)	1.8 (SD 1.29)		NS	0.141					Decrease	
16105 (Seshadri <i>et al.</i> , 2005)		Low carbohydrate diet	40/75			-7.84 (SD 21.01)	0.01		0.006	Insulin	Fasting Serum, ( $\mu$ U/ml)	6 months	Decrease	unclear
		Standard diet, energy restricted	35/75			6.14 (SD 34.96)	NS						Decrease	
16106	No diabetes	Low carbohydrate diet	23/75			-9.24 (SD 19.52)	0.01		0.003	Insulin	Fasting Serum, ( $\mu$ U/ml)	6 months	Decrease	unclear
		Standard diet, energy restricted	22/75			11 (SD 37.79)	NS						Decrease	
14759 (Sharman <i>et al.</i> , 2004)		Low fat	15/15	77.1 (SD 32.7)	55.4 (SD 26.8)		0.05			Blood insulin	Fasting Plasma, (pmol/L)	6 weeks	Decrease	unclear
		Very low carbohydrate	15/15	77.1 (SD 32.7)	45.1 (SD 27.5)		0.05	NS					Decrease	
17123 (Sloth <i>et al.</i> , 2009)		Control	9/9			19 (10)			0.05	Insulin	Fasting (pmol/L)	6 months	Increase	bias
		High MUFA	15/15			3 (5)							Increase	
		Low fat	18/18			6 (5)							Increase	
15888		Control diet	70/70			-4.31 (SE			Main	Insulin	Fasting	6 months	No change	unclear

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(Swinburn <i>et al.</i> , 2001)		Low fat	66/66			0.86)			effect of diet p<0.001		(mIU/L)		Decrease	
15889		Control diet	70/70			-3.71 (SE 1.58)				Insulin	Fasting (mIU/L)	1 year	No change	unclear
		Low fat	66/66			-4.87 (SE 1.09)							Decrease	
15893		Control diet	70/70			-6.2 (SE 3.64)			Main effect of diet p<0.01	Insulin OGTT (120min)	(mIU/L)	6 months	No change	unclear
		Low fat	66/66			-12.01 (SE 6.16)							Decrease	
15894		Control diet	70/70			-1.9 (SE 3.75)				Insulin OGTT (120min)	(mIU/L)	1 year	No change	unclear
		Low fat	66/66			-14.94 (SE 4.2)							Decrease	
15374 (Tinker <i>et al.</i> , 2008)		Control	1339/29294	9.9 (SD 4.9)	9.6 (SD 4.9)			NS		Insulin	Fasting Serum, ( $\mu$ IU/ml)	1 year	No change	unclear
		Low fat diet	883/19541	9.7 (SD 4.6)	8.9 (SD 4.3)								Decrease	
15375		Control	1164/29294	9.9 (SD 4.9)	7.9 (SD 5.3)			NS		Insulin	Fasting Serum, ( $\mu$ IU/ml)	6 years	No change	unclear
		Low fat diet	759/19541	9.7 (SD 4.6)	7.6 (SD 5)								Decrease	
17134 (Wolever and Mehling, 2003)		High carbohydrate, high GI	11/13			1.5 (SE 5.6)			NS	Insulin	Fasting (pmol/L)	4 months	Decrease	unclear
		High carbohydrate, low GI	13/13			-0.8 (SE 7.7)							Decrease	
		High carbohydrate, Low carbohydrate, high MUFA	11/12			-1.0 (SE 8.2)							Increase	

## Insulin resistance/sensitivity and high carbohydrate diets

No cohort studies provided data on high carbohydrate diets and insulin resistance/ sensitivity.

### Summary of RCT results

Twenty five studies, reported in 29 papers, explored the effects of dietary variation in the carbohydrate proportion of diets – replacing carbohydrate with fat and/ or protein – on insulin resistance/ sensitivity.

All studies, apart from one, implemented a parallel group design. The exception was Sharman *et al.* (Sharman *et al.*, 2004), which adopted a crossover approach. Most studies did not indicate the extent of blinding, however six were reported as open and one as double blind.

Studies were carried out in a variety of countries, such as the USA (16), Denmark (3), Australia (1), Spain (1), Israel (1), Sweden (1), the Netherlands (1) and Europe as a whole (1).

The majority of trials used adults as participants, although two trials (Demol *et al.*, 2009;Ebbeling *et al.*, 2003) recruited adolescents aged 12-18 years and 13-21 years respectively. Four studies recruited females only (Mahon *et al.*, 2007;Gray *et al.*, 2008;O'Brien *et al.*, 2005;Lofgren *et al.*, 2005) and two studied males only (Sharman *et al.*, 2004;Helge, 2002).

In the trials that reported an average BMI of the participants this was consistently  $\geq 25\text{kg/m}^2$ . Final sample sizes ranged from 15 to 811 participants (mean=117; median=48), other than the very large Women's Health Initiative Study which measured insulin resistance on a proportion of the 48,557 participants (n=1448).

Due to variation in methodologies used to measure insulin resistance, it was not appropriate to combine these studies using meta-analysis.

For discussion, trials were separated into 3 main types on the basis of proportion of energy derived from percentage macronutrients if there was a difference of energy from carbohydrate between trial groups of 5% or more. Actual consumption was used rather than intended diet unless otherwise stated – see trial characteristics table.

Higher carbohydrate, lower fat diets were differentiated from lower carbohydrate, higher fat diets where percentage of energy from fat differed by 2% or more. Higher carbohydrate, lower protein diets were differentiated from lower carbohydrate, higher protein diets where percentage of energy from protein differed by 2% or more and higher carbohydrate, lower protein and fat diets were differentiated from lower carbohydrate, higher protein and fat diets where percentage of energy from fat differed by 2% or more and percent energy from protein also differed by 2% or more

## **Insulin resistance/ sensitivity and lower carbohydrate/higher fat diet vs. higher carbohydrate/lower fat diet**

Nine studies that manipulated the percentage of carbohydrate and fat experimentally provided data on markers of insulin resistance or sensitivity. Four studies suggest some improvement in terms of insulin resistance with diets that are lower in carbohydrate and higher in fat.

Ebbeling *et al.* (Ebbeling *et al.*, 2003) compared a low fat diet (55% energy derived from carbohydrate, 28% energy derived from fat) and a low GL diet (51% energy derived from carbohydrate, 31% energy derived from fat), consumed as part of a free living diet plan, in 16 adolescents. Despite the carbohydrate content of the diets differing by only 4% here, after 6 months, insulin resistance assessed by HOMA, had statistically significantly decreased in the low GL (low carbohydrate) group compared to the higher carbohydrate, low fat group ( $p=0.02$ ). Body weights decreased in the former group, but remained unchanged in the higher carbohydrate group. Ebbeling *et al.* urge caution when considering the results, given the limited sample size and possible underreporting of dietary intakes. Comparison of the high carbohydrate, low fat and low carbohydrate, higher fat groups in the adolescent study by Demol *et al.* (Demol *et al.*, 2009) did not reveal a different HOMA response at either the 12 week, or 1 year assessments. All diet groups experienced an improvement in markers of insulin resistance in this study.

One study conducted by Kirk *et al.* (Kirk *et al.*, 2009), which also measured fasting insulin, provided evidence of an association between a very low carbohydrate diet and HOMA-IR. After 11 weeks, HOMA-IR had improved in both diet groups ( $p<0.001$ ) although the decrease was statistically significantly greater in the very low carbohydrate diet group compared to the high carbohydrate group ( $p<0.05$ ).

The NUGENOB study reported similar beneficial effects of higher and lower carbohydrate diets on fasting insulin levels (Petersen *et al.*, 2006). Grau *et al.* further examined whether there was a differential insulin response to these diets in participants stratified by variants of the FTO gene (Grau *et al.*, 2009). In this study, a significant diet by genotype interaction was observed, which indicates that FTO rs9939609 may interact with the macronutrient composition of weight loss diets to influence insulin resistance differently. Grau *et al.* found that participants with the genotype TT in a high carbohydrate, low fat diet group had a statistically significantly greater decrease in HOMA-beta (insulin release) at 10 weeks compared to those with the same genotype consuming a low carbohydrate, higher fat diet ( $p=0.006$ ). HOMA-IR (surrogate marker of insulin resistance) also decreased more with a higher carbohydrate diet, but this change was not significantly different to the low carbohydrate diet. There were no differences in HOMA-IR or HOMA-beta for the genotypes AT and AA. It is of note that allocated and not actual diets were analysed which may also have masked associations (Grau *et al.*, 2009).

The weight maintenance trial reported by Due *et al.* (Due *et al.*, 2008b), tested the effects of a high MUFA diet, a low fat diet and a control diet in young overweight adults after 8% weight loss. There was a general trend towards weight regain in the subjects over the 6 month study period in all diet groups. The authors reported that HOMA-IR was statistically significantly reduced in the high MUFA, lower carbohydrate diet group ( $p < 0.001$ ). The increase in HOMA-IR was smaller in the low fat, high carbohydrate diet group when compared to the control group ( $p < 0.01$ ).

Collectively, the data reported here are inconsistent and do not provide clear evidence that replacement of some dietary carbohydrate with energy from fat may affect insulin resistance/ sensitivity.

### **Insulin resistance/ sensitivity and lower carbohydrate/higher protein diet vs. higher carbohydrate/lower protein diet**

Two studies investigated the effects of diets that varied in carbohydrate and protein composition on insulin resistance/ sensitivity.

Due *et al.* (Due *et al.*, 2005) conducted a randomised controlled trial to compare a high protein diet (25% energy from protein, <30% energy from fat) and a moderate protein diet (12% energy from protein, <30% energy from fat) in 50 participants. No differences in HOMA-IR within or between groups were observed at the end of the intervention.

Whilst Due *et al.* (Due *et al.*, 2005) explored diets, Claessens *et al.* (Claessens *et al.*, 2009) tested the effects of a carbohydrate supplement on insulin resistance/ sensitivity. Sixty participants with BMI  $> 27 \text{ kg/m}^2$  were randomly assigned to a high carbohydrate supplement, a high protein supplement (casein) or one other high protein supplement (whey) for a period of 12 weeks. At follow-up, no statistically significant differences in HOMA-IR within or between groups were observed.

Overall the findings from these two trials suggest no effect of a low carbohydrate/ higher protein diet or a higher carbohydrate/ lower protein diet on insulin resistance/ sensitivity.

### **Insulin resistance/ sensitivity and lower carbohydrate/higher protein and fat diet vs. higher carbohydrate/lower protein and fat diet**

Sixteen studies, reported in 18 papers, were extracted that investigated diets with differences in carbohydrate, protein and fat between groups. Of these studies, four recorded statistically significant differences between high and low carbohydrate diets which are described in detail here. Improvements in markers of insulin resistance with lower carbohydrate intakes reflected in lower HOMA-IR were apparent in 3 of these studies



In Pereira *et al.* (Pereira *et al.*, 2004), insulin resistance as measured by HOMA score, was statistically significantly lower (improved) in the low GL (lower carbohydrate) diet group compared to the low fat (higher carbohydrate) diet group at 67 days ( $p=0.01$ ). All food was provided and participants recorded non-adherence to diet, however as mentioned previously, only a small number of participants were studied and the intervention duration was fairly short (Pereira *et al.*, 2004).

Seshadri *et al.* (Seshadri *et al.*, 2005) investigated the effects of a low carbohydrate diet (carbohydrate intake limited to  $<30\text{g/day}$ ) and a standard, energy restricted diet on insulin resistance/ sensitivity in 132 adults. A decrease in the HOMA index was reported in the low carbohydrate group at 6 months ( $p=0.01$ ), with the difference between groups being statistically significant ( $p=0.008$ ). Similarly, when separating participants further into those with DM and those without, the authors found a decrease in HOMA from baseline in those without DM in the low carbohydrate diet group ( $p=0.01$ ). This difference between the two intervention groups for participants without DM was also statistically significant ( $p=0.002$ ).

Wolever *et al.* (Wolever and Mehling, 2002) fed 37 participants, in a parallel group design, diets high in carbohydrate, high in GI or high in carbohydrate, low in GI or low in carbohydrate, high in MUFA. After adjusting for baseline values, the authors concluded that mean disposition index had statistically significantly increased in the high carbohydrate, low GI group compared to the other two treatment groups ( $p<0.05$ ). However, findings should be treated with caution given the small final sample size and the fact that the intervention– a free-living diet plan – did not permit researcher control over foods consumed.

In exercising individuals, a different response to high carbohydrate diets was observed. Helge *et al.* (Helge, 2002) compared markers of insulin sensitivity in individuals following an exercise training regime, whilst consuming either high carbohydrate or high fat, lower carbohydrate diets. The insulin resistance index (HOMA-R<sub>mod</sub>) was significantly decreased by 19% in the high carbohydrate group, but was unaffected in the high fat group, whereas the calculated insulin secretion index HOMA- $\beta$ <sub>mod</sub> was unchanged in both groups.

Overall, findings from the 16 trials tend to show improvements in insulin resistance in both dietary groups studied, which is likely to be a reflection of decreasing weights in the majority of the studies. Few demonstrated different responses between diets that differed in carbohydrate content.

*N.b. As there has been no evidence from the authors to suggest otherwise, it is assumed that three papers (de Luis *et al.*, 2009b; de Luis *et al.*, 2009a; de Luis *et al.*, 2008) are the same study given the identical diets, same ethical submission dates (for two out of the four studies) and use of similar participants and sample sizes.*

Table 4.50 Insulin resistance/sensitivity and high carbohydrate diets: RCT data

Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>													
(Demol <i>et al.</i> , 2009) 15411		High carbohydrate, low fat	20/20	4.2 (SD 0.5)	3.8 (SD 0.5)				Basal state method		12 weeks	Decrease	unclear
		Low carbohydrate, high fat	17/17	4.1 (SD 0.5)	2.6 (SD 0.6)			NS		HOMA-IR (glucose)* (insulin)/22.5 (mg/dL)		Decrease	
		Low carbohydrate, high protein	18/18	4.3 (SD 0.5)	3.1 (SD 0.5)			NS				Decrease	
15412		High carbohydrate, low fat	20/20	4.2 (SD 0.5)	3.1 (SD 0.6)				Basal state method		1 year	Decrease	unclear
		Low carbohydrate, high fat	17/17	4.1 (SD 0.5)	2.3 (SD 0.7)			NS		HOMA-IR (glucose)* (insulin)/22.5 (mg/dL)		Decrease	
		Low carbohydrate, high protein	18/18	4.3 (SD 0.5)	2.7 (SD 0.6)			NS				Decrease	
15021 (Ebbeling <i>et al.</i> , 2003)		Low fat diet	7/8			2.6 (SE 1.5)			Basal state method (change)	HOMA-R	6 months	No change	unclear
		Low GL diet	7/8			-0.4 (SE 0.9)		0.02				Decrease	
<b>Adult studies</b>													
(Claessens <i>et al.</i> , 2009) 16819		High carbohydrate supplement	16/allocated not reported	3.68 (SE 0.64)	4.31 (SE 0.87)	0.62 (SE 0.47)	NS		Basal state method		12 weeks	Increase	unclear
		High protein supplement - casein	14/allocated not reported	2.83 (SE 0.31)	2.69 (SE 0.23)	-0.14 (SE 0.19)	NS	NS		HOMA-IR (glucose)* (insulin)/22.5		Decrease	
		High protein supplement - whey	18/allocated not reported	3.31 (SE 0.49)	3.45 (SE 0.35)	0.15 (SE 0.4)	NS					Decrease	
(de Luis <i>et al.</i> , 2008) 16149	Genetics - wild-type Ala54/Ala54	Low carbohydrate	55/105	3.1 (SD 2.1)	2.4 (SD 1.9)				Basal state method	HOMA	2 months	Decrease	unclear
		Low fat	55/99	1.7 (SD 0.4)	1.6 (SD 0.7)							Decrease	
16166	Genetics - mutant-type Ala54/Thr54 or	Low carbohydrate	50/105	2.7 (SD 1.6)	3.1 (SD 1.5)				Basal state method	HOMA	2 months	Decrease	unclear
		Low fat	44/99	2.1 (SD 1.6)	1.9 (SD 1.3)							Decrease	

Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
Thr54/Thr54													
(de Luis <i>et al.</i> , 2009b) 16087		Low carbohydrate	52/52	3.9 (SD 4.9)	2.2 (SD 1.1)				Basal state method	HOMA	3 months	Decrease	unclear
		Low fat	66/66	2.83 (SD 3.1)	1.8 (SD 0.7)							Decrease	
16707 (de Luis <i>et al.</i> , 2009a)	Genetics - UCP3 Gene - 55CC polymorphism	Low carbohydrate	54/67	2.8 (SD 2.1)	2.7 (SD 1.9)		NS		Basal state method	HOMA-S	2 months	Decrease	unclear
	Genetics - UCP3 Gene - 55CC polymorphism	Low fat	40/64	2.5 (SD 2.1)	2.4 (SD 1.9)		NS					Decrease	
16708	Genetics - UCP3 Gene - 55CT/TT polymorphism	Low carbohydrate	13/67	2.2 (SD 1.6)	2.7 (SD 1.5)		NS		Basal state method	HOMA-S	2 months	Decrease	unclear
	Genetics - UCP3 Gene - 55CT/TT polymorphism	Low fat	24/64	3.1 (SD 1.6)	2.8 (SD 1.3)		NS					Decrease	
(Due <i>et al.</i> , 2005) 17546		High protein	23/23	2.3 (CI 1.2, 3.3)	1.8 (CI 1.2, 2.4)	NS		NS	Steady state method	HOMA-IR (glucose)* (insulin)/22.5	6 months	Decrease	unclear
		Moderate protein	23/18	2.2 (CI 1.4, 2.9)	1.9 (CI 1.4, 2.4)	NS						Decrease	
(Due <i>et al.</i> , 2008a) 16398		Control diet	12/12	1.19 (CI 0.74, 1.65)	1.47 (CI 1.00, 1.94)				Dynamic/Basal state methods	HOMA-IR (glucose)* (insulin)/22.5	6 months	Increase	unclear
		High MUFA	16/16	1.4 (CI 1.03, 1.76)	1.23 (CI 0.92, 1.54)*			0.02 *diff from other groups				Increase	
		Low fat diet	18/18	1.42 (CI 1.21, 1.62)	1.64 (CI 1.36, 1.91)							Increase	
(Due <i>et al.</i> , 2008b) 15297		Control	24/25	1.3 (CI 1.0, 1.6)	1.76 (CI 1.3, 2.2)	0.47 (CI 0.17, 0.76)			Basal state method	HOMA-IR (glucose)* (insulin)/22.5	6 months	Increase	unclear
		High MUFA	39/52	1.28 (CI 1.0, 1.5)	1.17 (CI 1.0, 1.3)	-0.11 (CI -0.34, 0.13)		<0.001				Increase	
		Low fat	43/48	1.24 (CI 1.1, 1.4)	1.4 (CI 1.2, 1.6)	0.16 (CI -0.03, 0.36)		<0.01				Increase	
(Ebbeling <i>et al.</i> , 2005) 15517		Low fat, high carb diet	12/17	0.35 (SE 0.01)		5.8% (CI 1.1, 10.7)		NS	Basal state method	Insulin sensitivity index I/(insulin + log glucose)	6 months	Decrease	unclear
		Low carb, low GI diet	11/17	0.34 (SE 0.01)		6.4% (CI 1.5, 11.5)						Decrease	
15518		Low fat, high	12/17	0.35 (SE 0.01)		8.7% (CI 2.3,		NS	Basal state	Insulin	1 year	Decrease	unclear

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Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
(Foster <i>et al.</i> , 2003) 15247		carb diet				15.5)			method	sensitivity index 1/(insulin + log glucose)		Decrease	
		Low carb, low GI diet	11/17	0.34 (SE 0.01)		10.4% (CI 3.6, 17.6)							
		Conventional diet plan	30/30			4.1 (SD 10.7)	NS		Basal state method (change)	Insulin sensitivity index 1/(log insulin + log glucose) (%)	3 months	Decrease	unclear
		Low carbohydrate diet	33/33			6.7 (SD 11.6)	<0.05	0.37				Decrease	
15249		Conventional diet plan	30/30			5.2 (SD 10.3)	<0.05		Basal state method (change)	Insulin sensitivity index (%)	6 months	Decrease	unclear
		Low carbohydrate diet	33/33			5.8 (SD 12.0)	<0.05	0.79				Decrease	
15250		Conventional diet plan	30/30			2.9 (SD 9.5)	NS		Basal state method (change)	Insulin sensitivity index, (%)	1 year	Decrease	unclear
		Low carbohydrate diet	33/33			2.9 (SD 9.5)	NS	0.92				Decrease	
(Grau <i>et al.</i> , 2009) 17453	Genetics - FTO rs9939609 TT	High carbohydrate, low fat diet	88/320	115 (SD 64.4)		-25.6 (SD 56.2)			Basal state method	Fasting HOMA-beta	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 TT	Low CHO, high fat diet	117/298	110 (SD 65.2)		-2.4 (SD 55.8)		0.006				Decrease	
17454	Genetics - FTO rs9939609 TT	High carbohydrate, low fat diet	88/320	2.3 (SD 1.4)		-0.6 (SD 1.1)			Basal state method	Fasting HOMA-IR (mm)	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 TT	Low CHO, high fat diet	117/298	2.7 (SD 2)		-0.3 (SD 1.4)		0.14				Decrease	
17457	Genetics - FTO rs9939609 AT	High carbohydrate, low fat diet	168/320	110 (SD 64.1)		-6.2 (SD 51.5)			Basal state method	Fasting HOMA-beta	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 AT	Low CHO, high fat diet	143/298	115 (SD 59.1)		-11.6 (SD 52.6)		NS				Decrease	
17458	Genetics - FTO rs9939609 AT	High carbohydrate, low fat diet	168/320	2.5 (SD 2.1)		-0.1 (SD 1.8)			Basal state method	HOMA-IR	10 weeks	Decrease	bias
	Genetics - FTO	Low CHO, high	143/298	2.5 (SD 1.7)		-0.4 (SD 1.6)		NS				Decrease	

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Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
	rs9939609 AT	fat diet											
17461	Genetics - FTO rs9939609 AA	High carbohydrate, low fat diet	64/320	112 (SD 66.8)		-1.1 (SD 64.3)			Basal state method	Fasting HOMA-beta	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 AA	Low CHO, high fat diet	38/298	117 (SD 89.5)		-11 (SD 54.7)		NS				Decrease	
17462	Genetics - FTO rs9939609 AA	High carbohydrate, low fat diet	64/320	2.3 (SD 1.4)		-0.3 (SD 1.2)			Basal state method	Fasting HOMA-IR	10 weeks	Decrease	bias
	Genetics - FTO rs9939609 AA	Low CHO, high fat diet	38/298	2.6 (SD 1.9)		-0.4 (SD 1.4)		NS				Decrease	
(Gray <i>et al.</i> , 2008) 13134		Low carbohydrate	22/22	4.5 (SD 2.1)	2.9 (SD 1.9)		<0.03		Basal state method	HOMA-IR [fasting plasma glucose (mmol/L) x fasting serum insulin (mU/L)/25]	3 months	Decrease	unclear
		Moderate fat	20/20	5.3 (SD 2.2)	4.1 (SD 2.8)		<0.03	NS				Decrease	
(Helge, 2002) 15916		High carbohydrate + exercise	16/16			14	<0.05	<0.05	Basal state method (change)	HOMA-R (%)	7 weeks	Decrease	unclear
		High fat + exercise	17/17			no change						Decrease	
15919		High carbohydrate + exercise	16/16			no change			Basal state method (change)	HOMA-beta (%)	7 weeks	Decrease	unclear
		High fat + exercise	17/17			no change						Decrease	
14867 (Johnston <i>et al.</i> , 2004)		High carbohydrate, low fat	7/10	0.305 (SE 0.004)		4.8% (SE 1.6%)	NS		Basal state method	Insulin sensitivity index (index)	6 weeks	Decrease	unclear
		High protein, low fat	9/10	0.305 (SE 0.004)		4.8% (SE 2.0%)	NS	0.974				Decrease	
(Johnston <i>et al.</i> , 2006) 17521		Low carbohydrate diet	10/10	6.50 (SE 0.91)	4.32 (SE 0.37)				Basal state method	Fasting HOMA (mmol/L)	6 weeks	Decrease	unclear
		Very low- carbohydrate diet	9/9	6.24 (SE 0.65)	4.38 (SE 0.39)			NS				Decrease	
(Kirk <i>et al.</i> , 2009)		High carbohydrate	completers not			-27.1 (SE 5.1)	<0.001		Basal state method	HOMA-IR	11 week	Decrease	unclear

Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
17558		Very low carbohydrate	reported/11 completers not reported/11			-44.0 (SE 4.7)	<0.001	<0.05				Decrease	
15899 (Lasker <i>et al.</i> , 2008)		high carbohydrate	25/33			0.4 (SE 0.4)			Basal state method	HOMA-IR (mmol/L)	4 months	Decrease	unclear
		High protein	25/32			-1.1 (SE 0.7)		0.08				Decrease	
(Lofgren <i>et al.</i> , 2005) 17271		High carbohydrate, low fat	20/20	3.5 (SE 0.6)	2.9 (SE 0.3)			NS	Basal state method	HOMA	10 weeks	Decrease	unclear
		High fat, moderate carbohydrate	20/20	3.5 (SE 0.6 SD)	3.1 (SE 0.7)							Decrease	
		Control	11/11		No change		NS	NS	Basal state method		9 weeks	No change	unclear
(Mahon <i>et al.</i> , 2007) 15078		Energy restriction + beef	14/14	0.41 (SD 0.28)	No change		NS			HOMA-S		Decrease	
		Energy restriction + carbohydrate/fat	14/14		No change		NS					Decrease	
		Energy restriction + chicken	15/15		No change		NS					Decrease	
(Maki <i>et al.</i> , 2007b) 17292		Low fat	39/43	2.1 (SE 0.3)		0.2 (SE 0.3)		NS	Basal state method	HOMA (fasting plasma glucose x fasting plasma insulin)	12 weeks	Decrease	unclear
		Low GL	39/43	2.4 (SE 0.2)		-0.1 (SE 0.3)						Decrease	
		Low fat	39/43	2.1 (SE 0.3)		0.7 (SE 0.2)		NS	Basal state method	HOMA (fasting plasma glucose x fasting plasma insulin)	36 weeks	Decrease	unclear
17293		Low GL	39/43	2.4 (SE 0.2)		0.3 (SE 0.3)						Decrease	
(McMillan- Price <i>et al.</i> , 2006) 16226		High CHO, high GI diet	32/32	2.6 (SE 0.2)		-0.3 (SE 0.2)		0.72	Basal state method (change)	Fasting HOMA-IR (original model)	12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	2.7 (SE 0.4)		-0.5 (SE 0.2)						Decrease	

Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
16227		High protein, high GI diet	32/32	3.1 (SE 0.3)		-0.6 (SE 0.2)						Decrease	
		High protein, low GI diet	33/33	2.7 (SE 0.3)		-0.3 (SE 0.2)						Decrease	
		High CHO, high GI diet	32/32	81 (SE 8)		1.7 (SE 7.3)			Basal state method		12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	85 (SE 6)		9.3 (SE 7.4)				HOMA-insulin sensitivity computer model		Decrease	
		High protein, high GI diet	32/32	70 (SE 6)		25.7 (SE 7.4)		0.13				Decrease	
		High protein, low GI diet	33/33	82 (SE 6)		16.4 (SE 7.2)						Decrease	
16228		High CHO, high GI diet	32/32	123 (SE 6)		-11.3 (SE 17.8)			Basal state method		12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	122 (SE 8)		-15.0 (SE 17.8)				HOMA-beta cell function computer model		Decrease	
		High protein, high GI diet	32/32	164 (SE 24)		-16.5 (SE 18.1)		0.64				Decrease	
		High protein, low GI diet	33/33	125 (SE 10)		11.8 (SE 17.5)						Decrease	
17080		High CHO, low GI diet	32/32	1.5 (SE 0.2)		-0.2 (SE 0.1)			Basal state method		12 weeks	Decrease	unclear
		High protein, high GI diet	32/32	1.8 (SE 0.2)		0.3 (SE 0.1)				HOMA-IR (updated computer model)		Decrease	
		High protein, low GI diet	33/33	1.6 (SE 0.2)		-0.2 (SE 0.1)		0.77				Decrease	
		High CHO, high GI diet	32/32	1.5 (SE 0.1)		-0.1 (SE 0.1)						Decrease	
(O'Brien <i>et al.</i> , 2005) 16957		Low carbohydrate	19/22	4.5 (SD 2.1)	2.9 (SD 1.9)		<0.03	0.49	Basal state method (change)	Fasting HOMA	3 months	Decrease	unclear
		Moderate fat	22/19	5.3 (SD 2.2)	4.1 (SD 2.8)		<0.03					Decrease	
(Pereira <i>et al.</i> , 2004) 14578		Low fat	17/23	1.45 (SE 0.2)	1.1 (SE 0.13)	-15.8% (SE 5.3%)			Basal state method	HOMA-S (score)	67 days	Decrease	unclear
		Low GL	22/23	1.5 (SE 0.18)	0.97 (SE 0.11)	-33.9% (SE 4.51%)		0.01				Decrease	
(Raatz <i>et al.</i> , 2005) 17220		High fat diet	10/8	1.56 (SE 0.3)	1.32		<0.05	<0.05	Basal state method	HOMA (fasting plasma glucose x fasting plasma	12 weeks	Decrease	unclear
		High GI diet	9/8	1.61 (SE 0.3)	0.94		<0.05					Decrease	
		Low GI diet	10/6	1.90 (SE 0.3)	1.04		<0.05	NS				Decrease	

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Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
17246		High fat diet	8/8	1.56 (SE 0.3)		0.22 (SE 0.22)		NS	Basal state method	insulin)/25 HOMA (fasting plasma glucose x fasting plasma insulin) /25	36 weeks	Decrease	unclear
		High GI diet	8/8	1.61 (SE 0.3)		-0.06 (SE 0.16)						Decrease	
		Low GI diet	6/6	1.90 (SE 0.3)		0.09 (SE 0.33)						Decrease	
(Sacks <i>et al.</i> , 2009) 15595		High-fat, average-protein	ITT: /204	2.9 (SD 1.9)	2.4 (SD 1.8)	-18.6%		Highest vs. lowest carbohydrate diet comparison p=0.46	Basal state method	HOMA Insulin sensitivity	6 months	Decrease	No bias
		High-fat, high- protein	ITT: /201	2.8 (SD 1.9)	2.4 (SD 2.9)	-13.4%						Decrease	
		Low-fat, average-protein	ITT: /204	2.8 (SD 1.9)	2.3 (SD 1.6)	-18.7%						Decrease	
		Low-fat, high- protein	ITT: /202	2.8 (SD 2.2)	2.2 (SD 1.6)	-22.7%						Decrease	
15596		High-fat, average-protein	ITT: /204		2.8 (SD 2.1)	-3.5%		Highest vs. lowest carbohydrate diet comparison p=0.42	Basal state method	HOMA Insulin sensitivity	2 years	Decrease	No bias
		High-fat, high- protein	ITT: /201		2.6 (SD 1.9)	-6.3%						Decrease	
		Low-fat, average-protein	ITT: /204		2.8 (SD 2.3)	-1.4%						Decrease	
		Low-fat, high- protein	ITT: /202		2.5 (SD 2.2)	-10.4%						Decrease	
(Seshadri <i>et al.</i> , 2005) 16112		Low carbohydrate diet	40/40			-2.69 (SD 6.77)	0.01	0.008	Basal state method (change)	Fasting HOMA, (index)	6 months	Decrease	unclear
		Standard diet, energy restricted	35/35			0.29 (SD 9.34)	NS					Decrease	
16113	No diabetes	Low carbohydrate diet	23/23			-3.07 (SD 6.08)	0.01	0.002	Basal state method (change)	Fasting HOMA, (index)	6 months	Decrease	unclear
	No diabetes	Standard diet, energy restricted	22/22			2.34 (SD 6.31)	NS					Decrease	
16114	Diabetes	Low carbohydrate diet	17/17			-3.17 (SD 8.15)	NS	0.36	Basal state method (change)	Fasting HOMA, (index)	6 months	Decrease	unclear
	Diabetes	Standard diet, energy restricted	13/13			-2.33 (SD 13.11)	NS					Decrease	
(Sharman <i>et al.</i> , 2004) 14760		Low fat	15/15	2.49 (SD 1.05)	1.74 (SD 0.89)		0.05		Basal state method	HOMA-R	6 weeks	Decrease	unclear
		Very low	15/15	2.49 (SD 1.05)	1.41 (SD 0.97)		0.05	NS				Decrease	

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Result ID/ Author	Subgroup detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow- up	Weight Change	Outcome Assessment Bias
carbohydrate													
(Tinker <i>et al.</i> , 2008) Women's Health Initiative Study		Control	1490	2.3 (SD 1.2)	2.2 (SD 1.3)			NS		HOMA-IR	1 year	Decrease	unclear
		Low fat diet	948	2.3 (SD 1.3)	2.0 (SD 1.1)					insulin/{22.5 x exp[-ln (glucose/18)]}		No change	
(Wolever and Mehling, 2002) 17014		High carbohydrate, high GI	11/11			No change					16 weeks	Decrease	unclear
		High carbohydrate, low GI	13/13			+56%		P<0.05 vs. high GI and high MUFA		Glucose disposition index ** (%)		Decrease	
		Low carbohydrate, high MUFA	11/11			-16%						Increase	
(Wolever and Mehling, 2002)		High carbohydrate, high GI	11/11			Data presented in figure only				Insulin sensitivity (frequently sampled intravenous glucose tolerance test, plus MINMOD program)	16 weeks	Decrease	unclear
		High carbohydrate, low GI	13/13					NS				Decrease	
		Low carbohydrate, high MUFA	11/11									Increase	

\*\*Index of the ability of the beta-cell to compensate for changes in insulin sensitivity by increasing insulin secretion, with a low value indicating reduced beta-cell responsiveness

# Glycosylated blood proteins and total carbohydrate/ high carbohydrate diets

## Summary of cohort results

Two cohort studies provided data on follow-up HbA1c levels according to dietary carbohydrate consumption.

In the Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006), 813 adults underwent a baseline examination and then returned for a 5-year follow-up examination. Diet was assessed by FFQ at both time points (data are included here only for the prospective analysis). Total carbohydrate intake at baseline was not associated with HbA1c levels at follow-up in any of the models presented in the paper.

In the 1946 British Birth Cohort (Prynne *et al.*, 2009), some evidence of reduction in risk of an HbA1c level  $\geq 6.3\%$  was reported in association with increasing habitual carbohydrate intakes assessed using 5 day food diaries, although the confidence intervals around this estimate were wide, making it unreliable.

A meta-analysis was not undertaken due to the small number of studies providing data.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## Summary of RCT results

Six studies explored the effects of dietary variation in carbohydrate proportion of diets – replacing carbohydrate with fat and/ or protein – on glycosylated blood proteins.

All implemented a parallel group design and were either unclear regarding the extent of blinding or were open. Predominantly, studies were conducted in the USA (3), although some trials were also carried out in Germany (1), Denmark (1) and the Netherlands (1).

All participants used were adults and had a mean age of between 28 and 56 years. The included studies were all mixed gender. Of those trials that reported an average study BMI, participants were either overweight (BMI 25-30kg/m<sup>2</sup>) or obese (BMI >30).

Final sample sizes of participants ranged from relatively small (13) (Dyson *et al.*, 2007) to fairly large (200) (Frisch *et al.*, 2009). The mean and median sample size was 83 and 58 respectively.

One study which explored the effects of a high MUFA diet, a low fat diet and a control diet in 46 overweight and obese participants was excluded from meta-analysis as there were no measures of variation (Dyson *et al.*, 2007). Dyson *et al.* did not show changes in HbA1c in the treatment groups (Dyson *et al.*, 2007).

One additional study which compared a moderate carbohydrate diet (40% energy from carbohydrate, >35% energy from fat, 25% energy from protein) and a high carbohydrate diet (<55% energy from carbohydrate, >30% energy from fat, 15% energy from protein) in 200 overweight males and females provided data on the outcome, fructosamine (Frisch *et al.*, 2009). Changes in fructosamine, at 6 months were comparable between the two dietary intervention groups (0.4 and 1.1  $\mu\text{mol/L}$  in the moderate carbohydrate group and high carbohydrate group respectively) and as such, did not reach statistical significance. Also, no significant results in fructosamine between groups were evident at 1 year. The authors did report changes from baseline however as fructosamine statistically significantly decreased in both groups at this latter time point (Frisch *et al.*, 2009).

For inclusion in a meta-analysis a 5% difference in energy from carbohydrate between study groups was taken as meaningful. Actual consumption was used rather than the intended diet unless otherwise stated – see trial characteristics table.

Five studies were included in the meta-analysis comparing different carbohydrate intakes and blood HbA1c levels. There were three studies that reported results from three groups. One study reported results from three levels of carbohydrate and the middle level was excluded (Sloth *et al.*, 2009). In one study, the group with the whey supplement was excluded (Claessens *et al.*, 2009). In the third study, the groups with low glycaemic index were excluded (Wolever and Mehling, 2003).

Definitions of different levels of carbohydrate are reported in the trial characteristics table. The first follow up reported at the end of the intervention was used. This varied from 3 to 6 months. The overall pooled estimate indicated that fasting blood HbA1c was 0.01 percent (95% CI, -0.05 to 0.06) higher with consumption of a diet low in carbohydrate but this was not significantly different from zero ( $p=0.82$ ). Heterogeneity denoted by  $I^2$  was 0% (95% CI, 0 to 66). One study with over 100 participants (the remaining studies had fewer than 20 in each group) contributed 87% to the pooled estimate (Frisch *et al.*, 2009). No funnel plot was carried out due to the small number of studies. Statistically, there was no evidence of a difference in fasting blood HbA1c with differences in consumption of carbohydrate.

Figure 4.31 Forest plot for high carbohydrate diets and HbA1c

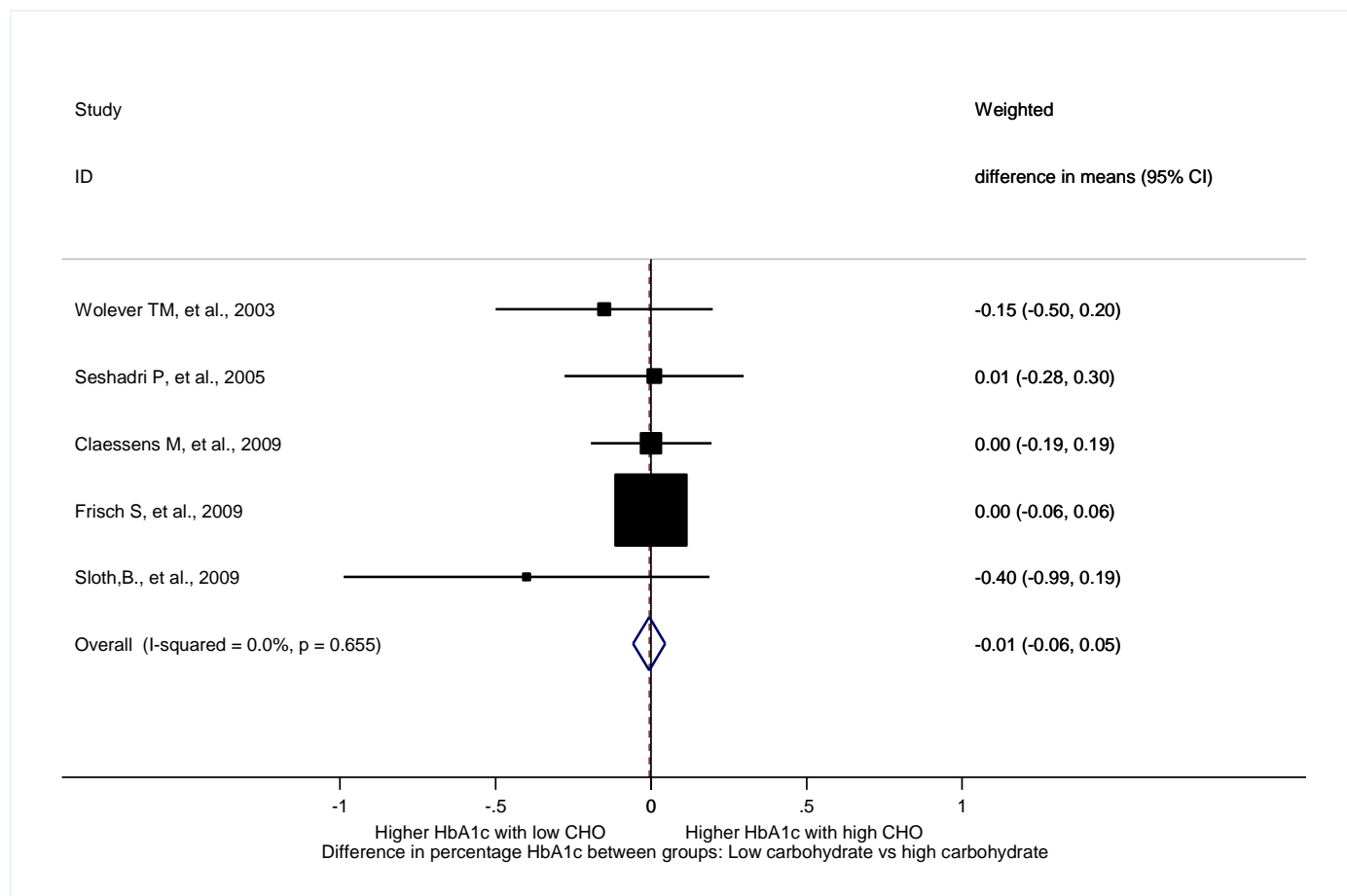


Table 4.51 Glycosylated blood proteins and total carbohydrate: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Contrast (mean)	Units	RR (95%CI)	Beta coefficient (SE)/(CI)	P	Adjustments
13884 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi- ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Carbohydrate, total (grams/day)	HbA1c Plasma		1 SD of mean exposure		0.03 (0.05)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13997 (Prynne <i>et al.</i> , 2009) 1946 British Birth Cohort	UK, Primarily White	(36) %M 46	(46) /5362	17 years	Food diary	Carbohydrate, total (grams/day) (past intake, mean of 1982 and 1989)	HbA1c ≥ 6.3% assessed in 1999 Non-fasting, Whole blood	Continuous risk estimate	1 g/day	0.81 (0.54, 1.2)		NS	BMI, socioeconomic status/class, smoking

Table 4.52 Glycosylated blood proteins and high carbohydrate diets: RCT data

Study ID/Authors	Subgroup detail	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Claessens <i>et al.</i> , 2009) *16817		High carbohydrate supplement	16/allocated not reported	5.58 (SE 0.12)	5.6 (SE 0.09)	0.09 (SE 0.07)	NS	NS	HbA1c		12 weeks	Increase	unclear
		High protein supplement - casein	14/allocated not reported	5.38 (SE 0.09)	5.58 (SE 0.11)	0.09 (SE 0.07)	NS			(%)		Decrease	
		High protein supplement - whey	18/allocated not reported	5.39 (SE 0.08)	5.49 (SE 0.07)	0.07 (SE 0.07)	NS					Decrease	
(Dyson <i>et al.</i> , 2007) *16351		Healthy eating diet	4/~6	6.0	5.8	-0.02			HbA1c	(%)	3 months	Decrease	bias
		Low carbohydrate diet	6/~6	6.1	5.9	-0.02		NS				Decrease	
(Frisch <i>et al.</i> , 2009) *15174		High carbohydrate diet	100/100			-0.2 (SD 0.2)	0.05		HbA1c		6 months	Decrease	unclear
		Moderate carbohydrate diet	100/100			-0.2 (SD 0.2)	0.05	0.84		Fasting (%)		Decrease	
15175		High carbohydrate diet	100/100			-0.2 (SD 0.2)	0.05		HbA1c		1 year	Decrease	unclear
		Moderate carbohydrate diet	100/100			-0.2 (SD 0.2)	0.05	0.314		Fasting (%)		Decrease	
15195		High carbohydrate diet	100/100			0.4 (SD 27.5)	NS		Fructosamine		6 months	Decrease	unclear
		Moderate carbohydrate diet	100/100			1.1 (SD 24.6)	NS	0.96		Fasting ( $\mu$ mol/L)		Decrease	
15196		High carbohydrate diet	100/100			-5.9 (SD 24.6)	0.05		Fructosamine		1 year	Decrease	unclear
		Moderate carbohydrate diet	100/100			-8.8 (SD 31.1)	0.05	0.58		Fasting ( $\mu$ mol/L)		Decrease	
(Seshadri <i>et al.</i> , 2005) 16098		Low carbohydrate diet	40/40			-0.49 (SD 1.04)	0.01	0.13	HbA1c		6 months	Decrease	unclear
		Standard diet, energy restricted	35/35			-0.11 (SD 0.91)	NS			Fasting (%)		Decrease	
*16100	No diabetes	Low carbohydrate diet	23/23			-0.17 (SD 0.58)	NS	0.96	HbA1c		6 months	Decrease	unclear
		Standard diet, energy restricted	22/22			-0.16 (SD 0.4)	NS			Fasting (%)		Decrease	
(Sloth <i>et al.</i> , 2009) *15928		Control	9/9	5.6 (SE 0.2)	5.8 (SE 0.1)	0.3 (SE 0.3)	<0.05 vs. other groups	0.03	HbA1c		6 months	Increase	bias
		High MUFA	15/15	5.8 (SE 0.2)	5.7 (SE 0.1)	-0.1 (SE 0.2)				Fasting (%)		Increase	
		Low fat	18/18	5.6 (SE 0.1)	5.6 (SE 0.1)	-0.1 (SE 0)						Increase	
(Wolever and Mehling, 2003) *17132		High carbohydrate, high GI	11/13	5.95 (SE 0.18)		-0.13 (SE 0.14)		0.006	HbA1c		4 months	Decrease	unclear
		High carbohydrate, low GI	13/13	5.67 (SE 0.17)		-0.19 (SE 0.08)				(%)		Decrease	
		Low carbohydrate, high MUFA	11/12	5.42 (SE 0.17)		0.02 (SE 0.11)	<0.05 vs. other groups					Increase	

# Carbohydrate supplements

## Glycaemia and carbohydrate supplements

No cohort studies provided data on carbohydrate supplements and glycaemia.

### Summary of RCT results

Data from one intervention, which tested the effects of carbohydrate supplements on plasma glucose levels, are tabulated in Table 4.53 (Pasman *et al.*, 1997b).

Pasman *et al.* (Pasman *et al.*, 1997b) randomly assigned obese female subjects (n=33) to three treatments designed to test the effects of a supplement containing carbohydrate, chromium, dietary fibre and caffeine, a supplement containing 50g plain carbohydrate (42% glucose and 58% maltodextrins) and a diet without supplementation. The latter two regimens are the comparison groups of interest. The 50g carbohydrate supplement was dissolved in water and consumed once daily in replacement of a habitual afternoon drink. Body weights increased in both groups because the intervention followed a very low calorie run-in period. There was no difference in fasting plasma glucose levels at 2, 8 and 14 months between the supplement and no-supplement condition.

Table 4.53 Glycaemia and carbohydrate supplements: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Pasman <i>et al.</i> , 1997b) 15485	Carbohydrate supplement	11/10	4.8 (SD 0.4)	5.0 (SD 0.4)	Glucose	Fasting Plasma, (mmol/L)	2 months	Increase	unclear
	Control	9/9	4.8 (SD 0.4)	4.9 (SD 0.5)	Glucose			Increase	
15486	Carbohydrate supplement	11/10	4.8 (SD 0.4)	4.9 (SD 0.3)	Glucose	Fasting Plasma, (mmol/L)	8 months	Increase	unclear
	Control	9/9	4.8 (SD 0.4)	4.9 (SD 0.3)	Glucose			Increase	
15487	Carbohydrate supplement	11/10	4.8 (SD 0.4)	4.7 (SD 0.3)	Glucose	Fasting Plasma, (mmol/L)	14 months	Increase	unclear
	Control	9/9	4.8 (SD 0.4)	4.7 (SD 0.5)	Glucose			Increase	

## Insulinaemia and carbohydrate supplements

No cohort studies provided data on carbohydrate supplements and insulinaemia.

### Summary of RCT results

One trial provided data on the effects of carbohydrate supplements on fasting blood insulin (Pasman *et al.*, 1997b). Pasman *et al.* randomly assigned obese female participants (n=33) to a supplement containing 50g plain carbohydrate or a diet without supplementation. There were no statistically significant differences in insulin values between the two groups at 2, 8 and 14 months.

Body weight increased in both diet groups since the intervention followed a run-in phase with a very low energy diet.

Table 4.54 Insulinaemia and carbohydrate supplements: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
15488 (Pasman <i>et al.</i> , 1997b)	Carbohydrate	11/10	10.1 (SD 3.9)	11.8 (SD 5.1)	Insulin	Fasting Plasma, (mmol/L)	2 months	Increase	unclear
	Control	9/9	8.8 (SD 2.7)	9.3 (SD 2.0)				Increase	
15489	Carbohydrate	11/10	10.1 (SD 3.9)	11.9 (SD 4.8)	Insulin	Fasting Plasma, (mmol/L)	8 months	Increase	unclear
	Control	9/9	8.8 (SD 2.7)	12.6 (SD 3.5)				Increase	
15490	Carbohydrate	11/10	10.1 (SD 3.9)	10.1 (SD 3.0)	Insulin	Fasting Plasma, (mmol/L)	14 months	Increase	unclear
	Control	9/9	8.8 (SD 2.7)	10.5 (SD 4.1)				Increase	



# Sugars and sugar-manipulation trials

## Impaired glucose tolerance and sugars intake

### Summary of cohort results

In the Zutphen Elderly Study, of 175 initially normoglycaemic individuals, there was no difference in baseline consumption of added sugars in participants who developed impaired glucose tolerance after 4 years of follow-up compared to those remained glucose tolerant (Feskens *et al.*, 1991). Similarly, in the Seven Countries Study (Feskens *et al.*, 1995) there was no difference in baseline age and cohort-adjusted mono- and disaccharide consumption in those who subsequently became glucose intolerant and those who remained healthy.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning sugars and impaired glucose tolerance.

Table 4.55 Impaired glucose tolerance, mono and disaccharides and added sugars: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	Cases/ Total	Follow Up	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Mean exposure (SD)	Adjust ments
13892 (Feskens <i>et al.</i> , 1991) Zutphen Elderly Study	The Netherlands	(70) %M 100	59 /175	4 years	Dietary history	Added sugars, Sugar products	Impaired glucose tolerance  Clinic tested	g/day	Cases: (n: 59) 47.4g (37.7) Non-cases: (n: 116) 46.7g (36.3)	
14640 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	71 /338	20 years	Dietary history	Mono and di- saccharid es	Impaired glucose tolerance  Fasting	% Energy	Cases: (n: 71) 25% Non-cases: (n: 241) 24.7%	age, cohort

# Glycaemia and sugars and sugar-manipulation trials

## Summary of cohort results

No cohort studies provided data on sugars and glycaemia.

## Summary of RCT results

Five studies in adults provided data on the effects of sugars on blood glucose (Bantle *et al.*, 2000;Black *et al.*, 2006;Surwit *et al.*, 1997;Ryle *et al.*, 1990;Saris *et al.*, 2000). One further study included overweight adolescents (Davis *et al.*, 2009).

Two out of the four trials were similar in design: Black *et al.* (Black *et al.*, 2006) and Surwit *et al.* (Surwit *et al.*, 1997) compared a high sucrose diet with a low sucrose diet using a crossover and a parallel group design respectively. Two studies implemented crossover designs to investigate the effects of a high glucose, low soluble fibre diet and a low glucose, high soluble fibre diet in the study by Ryle *et al.* (Ryle *et al.*, 1990) and a high fructose diet and a high glucose diet in Bantle *et al.* (Bantle *et al.*, 2000). Similarly, the remaining trials used parallel group approaches to compare a high fibre, low sugar diet with a control diet in one (Davis *et al.*, 2009) and a low-fat, high “complex carbohydrate” diet, a low-fat, high “simple carbohydrate” diet and a control diet in another (Saris *et al.*, 2000).

Trials lasted 6 weeks (Bantle *et al.*, 2000;Black *et al.*, 2006;Ryle *et al.*, 1990;Surwit *et al.*, 1997), 16 weeks (Davis *et al.*, 2009) or 6 months (Saris *et al.*, 2000). In those studies that reported BMI, participants tended to be overweight or obese. The mean BMI of the study participants in Ryle *et al.* (Ryle *et al.*, 1990), on the other hand, was indicative of a healthy weight (mean BMI=22kg/m<sup>2</sup>).

Body weights were unchanged, apart from the studies by Bantle *et al.* (Bantle *et al.*, 2000) and Surwit *et al.* (Surwit *et al.*, 1997) which reported weight loss in both groups and Saris *et al.* (Saris *et al.*, 2000) in which the authors reported that there was a decrease in the low-fat high-simple carbohydrate and low-fat high-complex carbohydrate diet groups.

In the study by Bantle *et al.*, participants (n=24) were randomly assigned to two isoenergetic diets: a high fructose diet (17% of total energy from fructose) or a high glucose diet (3% of total energy from fructose) which comprised popular foods and the addition of crystalline fructose or crystalline glucose, respectively (Bantle *et al.*, 2000). Overall, no differences in glucose AUC (daylong observation) between the high fructose diet group and the high glucose diet group were observed (p=0.446) (Table 4.56).

In the study conducted by Davis *et al.* (Davis *et al.*, 2009), the primary outcomes were insulin sensitivity and measures of adiposity. Subjects (overweight Latino adolescents, n=54) were randomised to one of three groups: a control (do nothing group), a reduced sugar, higher fibre diet group and a diet plus exercise group (data not extracted). The control group reported consuming 118g/d total sugars (84g added sugars) and the intervention group 10 g/d (58g/d added sugars) by the end of the trial. After 16 weeks, there were no statistically significant differences in fasting glucose levels or 2-hour blood glucose levels between groups. On the other hand, AUC glucose following an oral glucose tolerance test was statistically significantly lower in the reduced sugar, higher fibre diet group compared to the control group ( $p<0.05$ ). Davis *et al.* (Davis *et al.*, 2009) also highlight the small sample size which may have impacted on capacity to detect differences between dietary groups. This study was not included in the meta-analysis since the subjects were not adult.

Four other studies of adults explored the influence of diets which varied in either glucose or sucrose content (Table 4.57). The study by Surwit *et al.* (Surwit *et al.*, 1997) compared 6-week isocaloric, energy-reduced diets with high total carbohydrate and low fat content, which differed in percentage of energy from sucrose (43 vs. 4%). Foods were provided to the participants using a 7-day rotating menu. After 6 weeks, the authors reported that there were no significant changes in fasting glucose between dietary groups.

Ryle *et al.* (Ryle *et al.*, 1990) compared a high-glucose, low-soluble-fibre diet with a low-glucose, high-soluble-fibre diet over a period of 6 weeks. Diets were supplemented with 100g glucose/day and a guar preparation of 5g (initially once per day then three times per day) on the high-glucose, low-soluble-fibre diet and low-glucose, high-soluble-fibre diet, respectively. Participants (n=11) did not experience any statistically significant changes in fasting glucose, 1-hour or 2-hour glucose during the treatment period.

In the study by Black *et al.* (Black *et al.*, 2006), healthy male volunteers consumed a eucaloric high sucrose diet (25% of total energy intake) or low sucrose diet (10% of total energy intake), each diet lasting 6 weeks with a 4 week washout period between phases. The intervention was achieved through the provision of all appropriate foodstuffs. Fasting plasma glucose and mean glucose measured in tissue fluid (interstitial fluid) did not differ between groups.

The CARMEN study conducted by Saris *et al.* (Saris *et al.*, 2000) randomly allocated 398 moderately obese males and females to a seasonal control group or one of three experimental groups: low-fat high “simple carbohydrate” group, low-fat high “complex carbohydrate” group or a control diet group. All diets were *ad libitum*. Diets for the low-fat high “simple carbohydrate” group and low-fat high “complex carbohydrate” group were achieved using both a purpose-built shop with a recorded choice of food items and conventional supermarkets. At 6 months follow up, fasting glucose levels were not statistically different between diet groups.

None of these adult studies reported a significant difference in glycaemia when comparing higher and lower sugars diets after a 6 week to 6 month trial duration. Due to variation in the sugars

compared in these interventions (and inclusion of guar gum in the trial by Ryle *et al.*) it was inappropriate to pool these studies in a meta-analysis.

Table 4.56 Glycaemia and fructose vs. glucose: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Bantle <i>et al.</i> , 2000) 15261	High-fructose diet	12/12		139	0.446	Glucose AUC daylong observation	Plasma	6 weeks	Decrease	Unclear
	High-glucose diet	12/12		141			(mmol/hour/L)		Decrease	

Table 4.57 Glycaemia and sugars: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Black <i>et al.</i> , 2006) 16617	High sucrose diet	13/13	4.8 (SE 0.1)	5.6 (SE 0.1)		NS	Glucose	Fasting plasma, (mmol/L)	6 weeks	No change	unclear
	Low sucrose diet	13/13	4.8 (SE 0.1)	5.6 (SE 0.1)						No change	
17418	High sucrose diet	13/13		6.1 (SE 0.7)		NS	Glucose	Interstitial (mmol/L)	6 weeks	No change	unclear
	Low sucrose diet	13/13		5.9 (SE 0.2)						No change	
(Ryle <i>et al.</i> , 1990) 16193	High glucose low soluble fibre	11/11	5.7 (SD 1)	6.1 (SD 1.0)		NS	Glucose	Fasting (mmol/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet	11/11	5.7 (SD 1)	6.0 (SD 0.9)						No change	
16194	High glucose low soluble fibre	11/11	5.7 (SD 1.2)	5.5 (SD 1.8)		NS	Glucose (OGTT 60 min)	Plasma (mmol/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet	11/11	5.7 (SD 1.2)	7.2 (SD 2.5)						No change	
16195	High glucose low soluble fibre	11/11	5.9 (SD 1.4)	5.7 (SD 1.5)		NS	Glucose (OGTT 120 min)	Plasma (mmol/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet	11/11	5.9 (SD 1.4)	6.4 (SD 1.5)						No change	
(Surwit <i>et al.</i> , 1997) 15050	High sucrose diet	20/28	4.97 (SD 0.7)	4.87 (SD 0.31)		NS	Glucose	Fasting serum, (mmol/L)	6 weeks	Decrease	unclear
	Low sucrose diet	22/24	4.92 (SD 0.58)	4.65 (SD 0.03)						Decrease	
(Saris <i>et al.</i> , 2000) 15099	Control diet	77/77	5.36 (SD 0.77)		-0.01 (SD 0.52)		Glucose		6 months	No change	unclear
	Low-fat high-complex carbohydrate diet	83/83	5.36 (SD 0.77)		-0.17 (SD 0.53)	NS		Fasting plasma, (mmol/L)		Decrease	
	Low-fat, high-simple carbohydrate diet	76/76	5.36 (SD 0.77)		-0.05 (SD 0.47)	NS				Decrease	

Table 4.58 Glycaemia and sugars: RCT data - adolescents

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>										
(Davis <i>et al.</i> , 2009) 14721	Control	16/22	93.7 (SD 7.1)	88.7 (SD 8)	NS	Glucose	Fasting plasma, (mg/dL)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	92.2 (SD 6.1)	91.4 (SD 6.5)					No change	
14722	Control	16/22	120 (SD 25.3)	120.9 (SD 32.3)	NS	Blood glucose (OGTT 120 min)	Plasma (mg/dL)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	134.6 (SD 18.5)	117.6 (SD 24.6)					No change	
14731	Control	16/22	80.7 (SD 50.7)	103.9 (SD 60.4)	<0.05	Glucose AUC OGTT (180min)	Plasma (nmol/min/l)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	114.1 (SD 41.6)	94.8 (SD 49.4)					No change	

# Insulinaemia and sugars and sugar manipulation trials

## Summary of cohort results

One cohort study provided evidence on sugars intake and insulinaemia (Marshall *et al.*, 1997). The San Luis Valley Diabetes Study was conducted in the USA, and was a multi-ethnic cohort with participants of normal glucose tolerance. Changes in fasting insulin over the 4 year period of follow-up were expressed separately for fructose, glucose and sucrose intakes. Variation in baseline intakes of these nutrients was not associated with changes in fasting insulin over time – all changes were smaller than 1% of baseline insulin levels.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

## Exposure definition and assessment

Sugars intakes were assessed using a 24-hour recall administered by bi-lingual interviewers.

## Adjustment for appropriate confounders

Appropriate confounders were included in the adjustments.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## Summary of RCT results

Five studies, two of UK origin, two of USA origin and one European explored the effects of sugars on blood insulin (Ryle *et al.*, 1990;Black *et al.*, 2006;Bantle *et al.*, 2000;Davis *et al.*, 2009;Saris *et al.*, 2000).

Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

Three used the crossover design (Ryle *et al.*, 1990;Black *et al.*, 2006;Bantle *et al.*, 2000) and two took parallel group approaches (Davis *et al.*, 2009;Saris *et al.*, 2000). Trials were either open or unclear regarding blinding. Sample sizes stretched from 11 to 398 subjects and included normal weight and overweight participants. All participants were adults, bar the study by Davis *et al.* (Davis *et al.*, 2009), which recruited adolescents.

Body weights were unchanged in three out of five studies, although a decrease was observed in both dietary groups in the study by Bantle *et al.* (Bantle *et al.*, 2000) and in the low-fat high-simple carbohydrate and low-fat high-complex carbohydrate diet groups in one other study (Saris *et al.*, 2000).

One trial of overweight Latino adolescents explored the effect of a lower sugar, higher fibre diet compared with a control (usual) diet on insulin resistance/ sensitivity as assessed by an insulin-modified frequently sampled intravenous glucose tolerance test (Davis *et al.*, 2009). The control group reported consuming 118g/d total sugars (84g added sugars) and the intervention group 101 g/d (58g/d added sugars) by the end of the trial. In this study, a small reduction in fasting, 2-hour insulin and AUC insulin following an oral glucose tolerance test in both groups, bar one result, was observed at 16 weeks. The difference between the two groups however was not statistically significant.

Ryle *et al.* (Ryle *et al.*, 1990) compared a high-glucose, low-soluble-fibre diet with a low-glucose, high-soluble-fibre diet over a period of 6 weeks. Diets were supplemented with 100g glucose/day and a guar preparation of 5g (initially once per day then three times per day) on the high-glucose, low-soluble-fibre diet and low-glucose, high-soluble-fibre diet, respectively. Subjects (n=11) did not experience any statistically significant changes in fasting or 2-hour insulin levels during the treatment period.

In the study by Black *et al.* (Black *et al.*, 2006), healthy male volunteers consumed a eucaloric high sucrose diet (25% of total energy intake) or low sucrose diet (10% of total energy intake), each diet lasting 6 weeks with a 4 week washout period between phases. The intervention was achieved through the provision of all appropriate foodstuffs. Insulin levels marginally decreased in both diet groups. The change between groups was not statistically significant.

In the CARMEN study (Saris *et al.*, 2000), fasting insulin values in the low-fat high-complex carbohydrate diet group tended to decrease over the duration of the study, whilst insulin values marginally increased on the low-fat high-simple carbohydrate diet and control diet. No significant difference in insulin between diet groups was observed, however.

One final study found that the daylong value for serum insulin was statistically significantly lower in the high-fructose diet compared to the high-glucose diet ( $p=0.011$ ), although values at baseline were not reported (Bantle *et al.*, 2000).

Mean fasting insulin levels in the studies that compared higher and lower sugars diets were uniformly not statistically different from each other in either adults or in adolescents.



Table 4.59 Insulinaemia and sugars: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P Trend	Adjustments
13095 (Marshall <i>et al.</i> , 1997) San Luis Valley Diabetes Study	USA, Multi-ethnic, Normal glucose tolerance	20-74 (52) %M 46.8	1069	4.3 years (26)	Dietary recall	Fructose	Blood insulin Fasting, Plasma	10 g/day	Regression direction negative, beta coefficient not reported	0.74	age, waist, BMI, energy intake, ethnicity, physical activity, Gender
13094 San Luis Valley Diabetes Study						Glucose		10 g/day	Regression direction positive, beta coefficient not reported	0.75	As above
13093 San Luis Valley Diabetes Study						Sucrose		10 g/day	Regression direction positive, beta coefficient not reported	0.4	As above

Table 4.60 Insulinaemia and fructose vs. glucose: RCT data

Results Number	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
15262 (Bantle <i>et al.</i> , 2000)	High-fructose diet	12/12		3486	0.011	Insulin AUC day long observation	Serum (pmol/hour/L)	6 weeks	Decrease	unclear
	High-glucose diet	12/12		4243					Decrease	

Table 4.61 Insulinaemia and sugars: RCT data on adolescents

Results Number	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>										
14727 (Davis <i>et al.</i> , 2009)	Control	16/22	27.1 (SD 17.3)	26.1 (SD 19.7)		Insulin	Fasting Plasma, (μU/ml)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	26.1 (SD 16.3)	24.3 (SD 14.5)	NS				No change	
14730	Control	16/22	132.7 (SD 91.4)	164.5 (SD 183.5)		Insulin OGTT (120min)	Plasma (μU/ml)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	249.9 (SD 204.3)	169 (SD 259.6)	NS				No change	
14732	Control	16/22	309.4 (SD 178)	338.4 (SD 281.2)		Insulin AUC OGTT (180min)	Plasma (nmol/min/l)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	459.3 (SD 319.5)	368.3 (SD 386.6)	NS				No change	



Table 4.62 Insulinaemia and sugars: RCT data in adults

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
16618 (Black <i>et al.</i> , 2006)	High sucrose diet	13/13	10.2	9.6 (SE 1.4)		NS	Insulin	Fasting Serum, (mU/L)	6 weeks	No change	unclear
	Low sucrose diet	13/13	10.2	8.6 (SE 1.2)						No change	
16198 (Ryle <i>et al.</i> , 1990)	High glucose low soluble fibre	11/11	6 (SD 2)	7 (SD 2)		NS	Insulin	Fasting (mU/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet	11/11	6 (SD 2)	8 (SD 3)						No change	
16200	High glucose low soluble fibre	11/11	20 (SD 2)	22 (SD 2)		NS	Insulin OGTT (120min)	Plasma (mU/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet	11/11	20 (SD 2)	22 (SD 1)						No change	
15100 (Saris <i>et al.</i> , 2000)	Control diet	77/77	12.16 (SD 5.07)		0.32 (SD 6.02)		Insulin	Fasting Plasma, (mU/L)	6 months	No change	unclear
	Low-fat high-complex carbohydrate diet	83/83	12.16 (SD 5.07)		-1.33 (SD 4.81)	NS				Decrease	
	Low-fat, high-simple carbohydrate diet	76/76	12.16 (SD 5.07)		0.85 (SD 9.6)	NS				Decrease	

## Insulin resistance/sensitivity and sugars and sugar manipulation trials

### Summary of cohort results

No cohort studies provided data on sugars/ sugar reduction and insulin resistance/sensitivity.

### Summary of RCT results

Three trials provided data on dietary sugars manipulations and insulin resistance (Black *et al.*, 2006; Sorensen *et al.*, 2005; Davis *et al.*, 2009).

One trial of overweight Latino adolescents explored the effect of a lower sugar, higher fibre diet compared with a control (usual) diet on insulin resistance/ sensitivity as assessed by an insulin-modified, frequently sampled, intravenous glucose tolerance test (Davis *et al.*, 2009). The control group reported consuming 118g/d total sugars (84g added sugars) and the intervention group 101g/d (58g/d added sugars) by the end of the trial. Achieved dietary fibre differences between the groups were small. Whilst small changes were noticed in HOMA-S, the insulin sensitivity index, the acute insulin response to glucose and disposition index in the control group and reduced sugar, higher fibre diet group, the reported differences were not statistically significant and the authors concluded that there was no overall difference between diet groups.

One Danish study provided information concerning the effects of high and low sucrose diets on blood insulin in 41 overweight adult men and women (Sorensen *et al.*, 2005). The intervention was achieved through the daily provision of food and drinks high in sucrose for the sucrose group or foods and drinks sweetened with artificial sweeteners for the sweetener group. In the sucrose group the majority of the sucrose (70%) was derived from beverages; similarly in the sweetener group 80% by weight of the supplements were drinks. After 10 weeks, there was no difference in HOMA IR concentrations between the sucrose and sweetener groups.

In the study by Black *et al.* (Black *et al.*, 2006), healthy male volunteers consumed eucaloric high sucrose (25% of total energy intake) or low sucrose diets (10% of total energy intake), each diet lasting 6 weeks with a 4 week washout period between phases. The intervention was achieved through the provision of all appropriate foodstuffs. In this study, insulin resistance which was assessed using a two-step euglycemic clamp method, was not influenced by the consumption of a high sucrose diet.

Body weights were unchanged in one study (Davis *et al.*, 2009) and decreased in the artificial sweetener group in the other (Sorensen *et al.*, 2005). In the study by Black *et al.*, (Black *et al.*, 2006) every effort was made to maintain stable body weights in both dietary groups. Despite variation in participant characteristics, mode and extent of sugars manipulation and study duration, these three trials consistently found no effect of variation in sugars intake on measures of insulin resistance.

Table 4.63 Insulin resistance/sensitivity and high sugar trials: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
Adolescent study										
(Davis <i>et al.</i> , 2009) 15044	Control	16/22	6.2 (SD 3.8)	5.9 (SD 4.8)	NS	Basal state method	HOMA-S	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	6.1 (SD 4.2)	5.5 (SD 3.3)		No change				
16671	Control	16/22	1.8 (SD 1.2)	1.9 (SD 1.4)	NS	Basal state method	Insulin sensitivity index (10 <sup>-4</sup> /min/μU/ml)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	1.6 (SD 0.9)	1.8 (SD 0.8)		No change				
16672	Control	16/22	1308.5 (SD 930.9)	1404.8 (SD 1119.7)	NS	Dynamic method	Acute insulin response to glucose (μU/ml*10/min)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	1160.4 (SD 869.9)	1222.8 (SD 994.2)		No change				
16673	Control	16/22	1944.4 (SD 1071.3)	1797.4 (SD 1038.1)	NS	Dynamic/Basal state methods	Disposition index (10 <sup>-4</sup> /min)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	1297 (SD 596.7)	1723 (SD 898.3)		No change				
Adult studies										
(Sorensen <i>et al.</i> , 2005) 17447	Sucrose	19/21	1	1.3	NS	Basal state method	HOMA-IR	10 weeks	Increase	unclear
	Sweetener	18/20	1.1	1.2		Decrease				
(Black <i>et al.</i> , 2006) 17635	High sucrose diet	13/13			NS	Steady state method	Endogenous glucose production during euglycemic- hyperinsulinemic clamp (μmol/kg/min)	6 weeks	No change	unclear
	Low sucrose diet	13/13				No change				
17636	High sucrose diet	13/13			NS	Steady state method	Peripheral glucose uptake during euglycemic- hyperinsulinemic clamp (μmol/kg/min)	6 weeks	No change	unclear
	Low sucrose diet	13/13				No change				

# Glycosylated blood proteins and sugarars

## Summary of cohort results

In the Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006), 813 adults underwent a baseline examination and then returned for a 5-year follow-up examination. Diet was assessed by FFQ at both time points (data are included here only for the prospective analysis). Neither fructose nor glucose intake at baseline were associated with HbA1c levels at follow-up in any of the models presented in the paper.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## Summary of RCT results

One small study conducted by Ryle *et al.* compared a high-glucose, low-soluble-fibre diet (Lucozade supplement) with a low-glucose, high-soluble-fibre diet (guar gum supplement) in eleven subjects over a period of 6 weeks (Ryle *et al.*, 1990). Body weights were unchanged in both groups. Overall, marginal reductions in HbA1c for both intervention groups were observed and the authors concluded that such changes did not reach statistical significance. It is also important to note that follow-up was reported at 6 weeks only, which is regarded as an inadequate duration for erythrocyte turn over (Ryle *et al.*, 1990), therefore any possible associations may have been impossible to detect with such short study duration.

Table 4.64 Glycosylated blood proteins and sugars: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess- ment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
13887 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Athero- sclerosis Study	USA, Multi- ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Fructose	HbA1c Plasma	1 SD of mean exposure	0.01 (0.02)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13888						Glucose	HbA1c Plasma	1 SD of mean exposure	0.01 (0.02)	NS	As above

Table 4.65 Glycosylated blood proteins and sugars: RCT data

Study ID/ Authors	Intervention group	Completers/ Allocated	Baseline	Follow-up	Outcome/ Assessment method	Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Ryle <i>et al.</i> , 1990) 16196	High glucose low soluble fibre	11/11	6.1 (SD 0.4)	6.0 (SD 0.5)	HbA1c	Plasma (%)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet	11/11	6.1 (SD 0.4)	5.9 (SD 0.3)				No change	

N.b. HbA1c results which report follow up at <12 weeks are shaded in grey as such durations are too short to allow sufficient turn-over of erythrocytes



# Polysaccharides

## Glycaemia and polysaccharides

### Summary of cohort results

Two studies provided data on polysaccharide intake and glycaemia (Feskens *et al.*, 1995; Mayer-Davis *et al.*, 2006). The outcome was expressed as either blood glucose level or area under the curve following a 2-hour oral glucose tolerance test or fasting blood glucose. The Seven Countries Study (Feskens *et al.*, 1995) showed no evidence of a statistically significant association between polysaccharide density and blood glucose levels. The Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006) found evidence of a significant positive relationship between glucose response to an oral glucose tolerance test expressed as area under the curve and total starch intake. However, when fasting-blood glucose levels were the outcome, there was no significant relationship and the direction of effect was reversed.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

### ***Exposure definition and assessment***

Polysaccharides were expressed either as density or change in density over a 20 year follow up (Feskens *et al.*, 1995) or total starch intake (Mayer-Davis *et al.*, 2006).

### ***Adjustment for appropriate confounders***

The Insulin Resistance Atherosclerosis Study was more fully adjusted than the Seven Countries Study, although both included a number of confounding factors as adjustments.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning polysaccharides and glycaemia.

Table 4.66 Glycaemia and polysaccharides: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14694 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59  %M 100	338	20 years	Dietary history	Nutrient polysaccharides % energy (10+ chain length), (Change in intake)	Blood glucose (OGTT 120 min)  Plasma	1 % Total energy	-0.015 (0.033)	NS	age, BMI, Baseline Exposure, Cohort, energy intake
14648 Seven Countries Study						Polysaccharides % energy (>10 chain length)	Blood glucose (OGTT 120 min)  Plasma	1 % Total energy	-0.035 (0.042)	NS	age, BMI, Cohort, energy intake
13870 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi- ethnic, Not diabetic	40-69 (55)  %M 43.5	1625	5.2 years (19)	FFQ (114)	Starch, total	Blood glucose  Fasting	1 SD Mean exposure	-1.56 (1.04)	NS	age, alcohol, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13879 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response  Plasma	1 SD Mean exposure	7.3 (3.13)	<0.05	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking

## Glycosylated blood proteins and polysaccharides

### Summary of cohort results

In the Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006), 813 adults underwent a baseline examination and then returned for a 5-year follow-up examination. Diet was assessed by FFQ at both time points (data are included here only for the prospective analysis). Starch intake at baseline was not associated with HbA1c levels at follow-up in any of the models presented in the paper.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No trials provided data on glycosylated blood proteins and polysaccharides.

Table 4.67 Glycosylated blood proteins and polysaccharides: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess- ment	Exposure	Outcome / Assess- ment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
13886 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclero- sis Study	USA, Multi- ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Starch, total	HbA1c Plasma	1 SD of mean exposure	-0.01 (0.05)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking

# Refined and “complex” carbohydrates

Definitions of “complex” carbohydrates were not provided by authors of the included studies, although it is generally recognised that “complex” carbohydrates are composed of complex sugar chains, with these chains acting as an energy store or fibrous structure in plants (Committee on Medical Aspects of Food Policy, 1989). As such, rich food sources include grains, legumes, fruits and vegetables (Shah *et al.*, 1994; Shah *et al.*, 1996; Poppitt *et al.*, 2002). According to the World Health Organisation and as stated in Farchi *et al.* (Farchi *et al.*, 1995), intakes of “complex” carbohydrates should make up 50-70% of total carbohydrate intake.

## Impaired glucose tolerance and “complex” and refined carbohydrates

### Summary of cohort results

In the study of Japanese American men, 78 initially had DM, 74 impaired glucose tolerance (IGT) and 77 normal glucose tolerance (NGT) at study baseline. At follow-up after 5 years, participants were re-assessed using self reports, physician examination and a 2-hour 75g oral glucose tolerance test (OGTT) using World Health Organisation criteria to determine glucose tolerance status. Neither “complex” nor refined carbohydrate consumption assessed by FFQ interview, were significantly different between the cases and non-cases of impaired glucose tolerance at follow-up (Leonetti *et al.*, 1996).

### *Exposure definition and assessment*

Dietary intake data on “complex” and refined carbohydrates was assessed using a FFQ interview (Leonetti *et al.*, 1996).

### *Adjustment for appropriate confounders*

Appropriate adjustments were made to the results.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning “complex” and refined carbohydrates and impaired glucose tolerance.

Table 4.68 Impaired glucose tolerance and “complex” and refined carbohydrates: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Sub-group Detail	Units	Mean exposure (SD)
14616 (Leonetti <i>et al.</i> , 1996) Japanese- American Men Diabetes Study	USA, Asian, Not diabetic	45-74 %M 100	(1) /229	5 years (5.6)	FFQ Interview (89)	Complex carbohydrates	Impaired glucose tolerance  Confirmed self report	Normal glucose tolerance at baseline	g/day	Cases: (n: 27) 232.4 (69.8) Non-cases: (n: 42) 231.3 (61.1)
14621 Japanese- American Men Diabetes Study								IGT at baseline	g/day	Cases: (n: 23) 211.2 (56.7) Non-cases: (n: 23) 302 (62.6)
14617 Japanese- American Men Diabetes Study						Refined carbohydrates	Impaired glucose tolerance  Confirmed self report	Normal glucose tolerance at baseline	g/day	Cases: (n: 27) 42.7 (52.4) Non-cases: (n: 42) 44.3 (33.1)
14622 Japanese- American Men Diabetes Study								IGT at baseline	g/day	Cases: (n: 23) 35.6 (30) Non-cases: (n: 23) 35.9 (23.5)

## **Glycaemia and refined and “complex” carbohydrates**

### **Summary of cohort results**

One study of Japanese-American Men was included in this category (Leonetti *et al.*, 1996). Refined and “complex” carbohydrate in grams was assessed in relation to 2-hour plasma glucose. There was no evidence of a significant association between either of these measures of carbohydrate and blood glucose.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

### ***Exposure definition and assessment***

Diet was assessed by FFQ interview.

### ***Adjustment for appropriate confounders***

Appropriate adjustments were made to the results.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

One randomised controlled trial provided data on the effects of consuming a diet high or low in “complex” carbohydrates on glycaemia (Saris *et al.*, 2000). In this study, moderately obese men and women were randomly allocated to a seasonal control group or one of three experimental groups: low-fat high-simple carbohydrate group, low-fat high-complex carbohydrate group or a control (do nothing) diet group. Body weights were unchanged in the control group but tended to decrease in the low-fat high-simple carbohydrate and low-fat high-complex carbohydrate diet groups over the duration of the study. The trial lasted 6 months and all diets were *ad libitum*. Diets for the low-fat high-simple carbohydrate group and low-fat high-complex carbohydrate group were achieved using both a purpose-built shop with a recorded choice of food items and conventional supermarkets. Consumption of a low-fat high-complex carbohydrate diet did not affect glucose levels differentially when compared to low-fat high-simple carbohydrate and control diets.

Table 4.69 Glycaemia and refined and “complex” carbohydrates: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14627 (Leonetti <i>et al.</i> , 1996) Japanese- American Men Diabetes Study	USA, Asian, Not diabetic	45-74 %M 100	229	5 years (5.6)	FFQ Interview (89)	Complex carbohydrates	Blood glucose (OGTT 120 min) Plasma	1 g/d	-0.05	NS	age, BMI, energy intake, impaired glucose tolerance, DM
14628 Japanese- American Men Diabetes Study						Refined carbohydrates	Blood glucose (OGTT 120 min) Plasma	1 g/d	-0.07	NS	As above

Table 4.70 Glycaemia and “complex” carbohydrates: RCT data

Results Number	Intervention group	Completers/ Allocated	Baseline	Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Saris <i>et al.</i> , 2000) 15099	Control diet	77/77	5.36 (SD 0.77)	-0.01 (SD 0.52)		Glucose	Fasting plasma, (mmol/L)	6 months	No change	unclear
	Low-fat high- complex carbohydrate diet	83/83	5.36 (SD 0.77)	-0.17 (SD 0.53)	NS				Decrease	
	Low-fat, high- simple carbohydrate diet	76/76	5.36 (SD 0.77)	-0.05 (SD 0.47)	NS				Decrease	

## Insulinaemia and “complex” carbohydrate

No cohort studies provided data on “complex” carbohydrate and insulinaemia.

### Summary of RCT results

In one parallel group trial that also reported glucose levels (Saris *et al.*, 2000), fasting insulin in the low-fat high-complex carbohydrate diet group decreased over the duration of the study, whilst insulin values marginally increased on the low-fat high-simple carbohydrate diet and control diet (Saris *et al.*, 2000). These changes however were not statistically significant.

Table 4.71 Insulinaemia and “complex” carbohydrate: RCT data

Results Number	Intervention group	Completers / Allocated	Baseline	Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
15100 (Saris <i>et al.</i> , 2000)	Control diet	77/77	12.16 (SD 5.07)	0.32 (SD 6.02)	NS	Insulin	Fasting Plasma, (mU/L)	6 months	No change	unclear
	Low-fat high-complex carbohydrate diet	83/83	12.16 (SD 5.07)	-1.33 (SD 4.81)					Decrease	
	Low-fat, high-simple carbohydrate diet	76/76	12.16 (SD 5.07)	0.85 (SD 9.6)					Decrease	



# Dietary fibre, fibre density and high fibre diets

## Impaired glucose tolerance and dietary fibre

### Summary of cohort results

In the Zutphen Elderly Study, of 175 initially normoglycaemic individuals, there was no difference in baseline dietary fibre intakes in participants who developed impaired glucose tolerance after 4 years of follow-up compared to those remained glucose tolerant (Feskens *et al.*, 1991).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning dietary fibre and impaired glucose tolerance.

Table 4.72 Impaired glucose tolerance and dietary fibre: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Mean exposure (SD)
13866 (Feskens <i>et al.</i> , 1991) Zutphen Elderly Study	The Netherlands	(70)  %M 100	(59) /175	4 years	Dietary history	Dietary Fibre, g/d (AOAC method)	Impaired glucose tolerance Clinic tested	g/day	Cases: (n: 59) 21.7 (6.4) Non-cases: (n: 116) 21.5 (6.2)

# Glycaemia and dietary fibre

## Summary of cohort results

Two studies provided data on dietary fibre intake and glycaemia (Feskens *et al.*, 1995; Mayer-Davis *et al.*, 2006). The outcome was expressed as either blood glucose level or area under the curve following a 2-hour oral glucose tolerance test or fasting blood glucose. There was no evidence of a statistically significant association between fibre intake or fibre density and blood glucose levels at follow-up.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

## Exposure definition and assessment

Fibre values used in both studies were from the AOAC method. Total fibre and fibre density data were reported. Values were measured using a dietary history or FFQ.

## Adjustment for appropriate confounders

The Insulin Resistance Atherosclerosis Study was more fully adjusted than the Seven Countries Study, although both included a number of confounding factors as adjustments in models.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## Summary of RCT results

Five studies provided data on the effects of diets high in dietary fibre on blood glucose (Aller *et al.*, 2004; Olendzki *et al.*, 2009; Thompson *et al.*, 2005; Andersson *et al.*, 2007; Davis *et al.*, 2009). These studies achieved differences in dietary fibre through use of foods naturally higher or lower in fibre content, rather than through the use of fibre isolates. In the adult studies, the higher fibre diets ranged in fibre content from 26-30g/day, and the lower fibre diets from 9-18g/day. All studies were open regarding blinding (or unclear). One study used a cross-over design (Andersson *et al.*, 2007), and the others used parallel groups. The majority of studies were conducted on adults; however one study recruited adolescents aged 14-18 years (Davis *et al.*, 2009). Trials were carried out in Spain, Sweden, and the USA (3). Of those studies that reported BMI, mean BMI ranged between 25kg/m<sup>2</sup> and 31kg/m<sup>2</sup>, and average adult age in each trial ranged from 47 to 59 years. Two trials imposed an energy intake restriction as part of each intervention diet (Thompson *et al.*, 2005; Olendzki *et al.*, 2009), and body weight decreased in each intervention group accordingly. In the other trials, body weights were unchanged or were slightly increased.

Data from one study are not included in the tables due to convincing evidence of poor study quality (Singh *et al.*, 1992).

In one study of overweight Latino adolescents, participants were randomised to one of three groups: a control (do nothing group), a reduced sugar, higher fibre diet group and a diet plus exercise group (data not extracted) (Davis *et al.*, 2009). After 16 weeks, fasting blood glucose and blood glucose during the first 120 and 180 minutes following the oral glucose tolerance test did not statistically significantly differ between groups.

Andersson *et al.* (Andersson *et al.*, 2007) reported that wholegrain products over a 6-week period did not alter fasting blood glucose in a group of 34 overweight men and women relative to refined grain products. Similarly, the trial conducted by Olendzki *et al.* (Olendzki *et al.*, 2009) investigated the effects of a high fibre diet, a high fibre and low saturated fat diet and a low saturated fat diet. All diets were hypoenergetic. Fasting blood glucose, measured at 3 and 6 months, had marginally decreased in all groups, bar the low saturated fat group at the two time points. However, the authors concluded that the difference between groups was not statistically significant. The Forest plot below suggests that there was a difference between the high fibre, low saturated fat and the low saturated fat groups.

Thompson *et al.* (Thompson *et al.*, 2005) also reported the effects of three hypoenergetic regimes designed to test the effects of a high dairy food diet with high or low dietary fibre content compared with a standard diet on 90 obese participants. The high fibre content was achieved through consumption of whole grains, fruit and vegetables and reduction in high GI foods. A mean dietary fibre intake of 29 (SD 9) g/d (AOAC fibre) was reported in the high fibre/high dairy adherents, compared with an average of 18 (SD 5) g/d in the high dairy/low fibre adherents, which are the comparison groups of interest here. At follow-up, fasting blood glucose and 2-hour glucose were not statistically significantly different within or between groups.

Aller *et al.* (Aller *et al.*, 2004) explored the effects of fibre on blood glucose and lipids over a 3-month period. The healthy eligible subjects (n=53) were randomised to receive a diet with 10.4g fibre (1.97g soluble fibre; 8.13g insoluble fibre) or a diet with 30.5g fibre (4.11g soluble fibre; 25.08g insoluble fibre) for 3 months. Body weights did not alter, but a significant decrease in fasting blood glucose from baseline was observed in the high fibre group but not in the low fibre group, although the between group difference was not statistically significant.

Four studies of adults providing dietary differences in fibre between groups were included in a meta-analysis. One study was excluded (Singh *et al.*, 1992). One study compared 3 groups (Olendzki *et al.*, 2009), the low saturated fat, high fibre group was compared with the low saturated fat group. Definitions of different levels of fibre are reported in the trial characteristics table. The first follow up reported at the end of the intervention was used. This ranged from 6 weeks to 48 weeks. Heterogeneity was high at 82% and therefore the overall pooled estimate has little meaning and is not reported. High fibre diets (26-30g/day) produced lower fasting blood glucose in 2 studies, but no effect in 2 others compared to lower fibre diets (9-18g/day).



Figure 4.32 Forest plot for high fibre diets and fasting blood glucose (mmol/L)

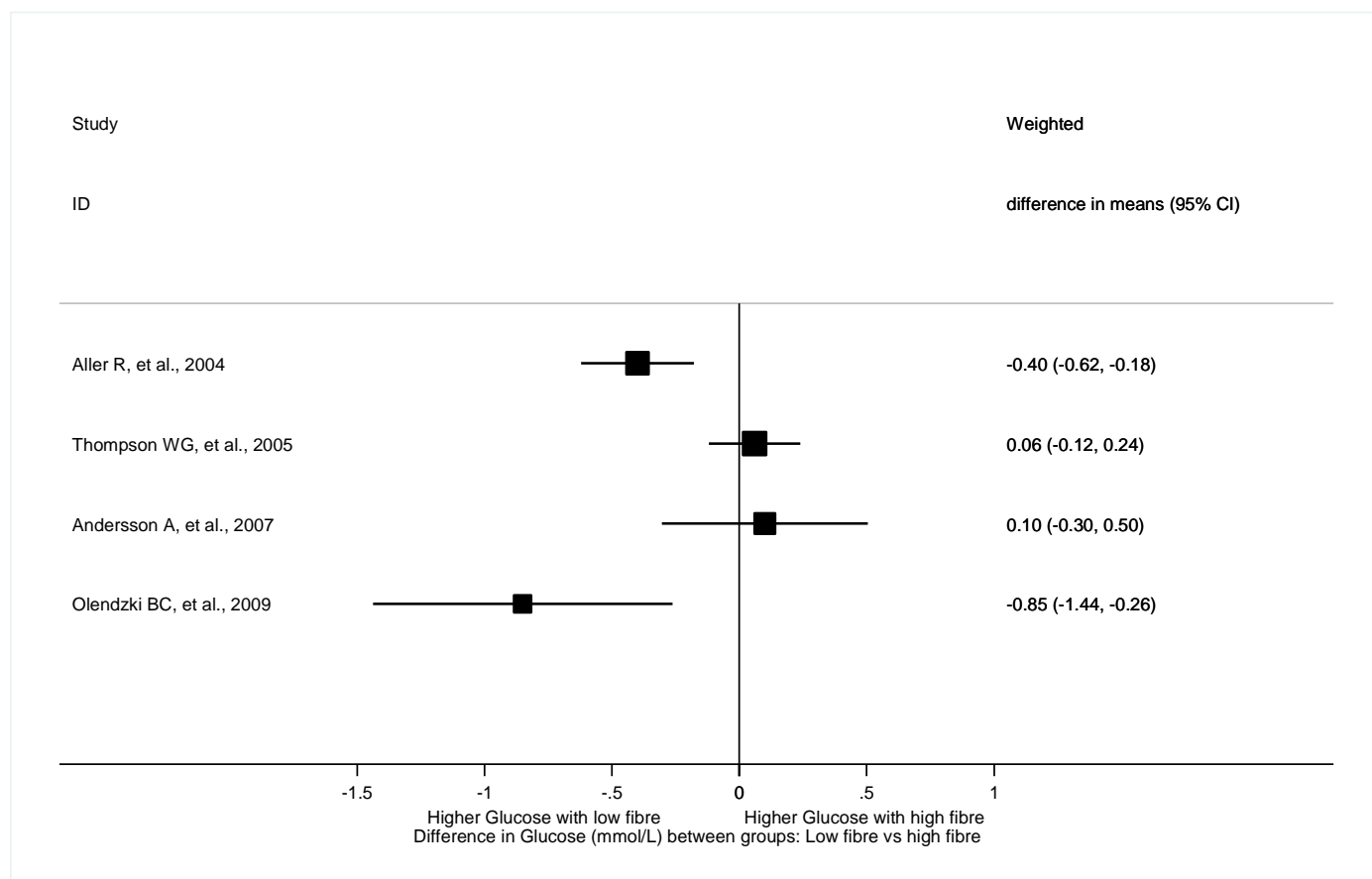


Table 4.73 Glycaemia and dietary fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14695 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	338	20 years	Dietary history	Fibre density - change in (g/energy unit) AOAC method	Blood glucose (OGTT 120 min)  Plasma	1 g/1000 kcal	-0.055 (0.048)	NS	age, BMI, Baseline Exposure, Cohort, EI
14649 Seven Countries Study						Fibre density (g/unit energy. AOAC method)	Blood glucose (OGTT 120 min)  Plasma	1 g/1000 kcal	-0.111 (0.069)	NS	age, BMI, Cohort, EI
13869 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi-ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Dietary Fibre, g/d (AOAC method)	Blood glucose  Fasting	1 SD Mean exposure	-1.72 (0.99)	NS	age, alcohol, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13878 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response  Plasma	1 SD Mean exposure	0.99 (2.22)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking

Table 4.74 Glycaemia and high fibre diets: RCT data

Results Number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>												
(Davis <i>et al.</i> , 2009) 14721	Control	16/22	93.7 (SD 7.1)	88.7 (SD 8)				Glucose	Fasting Plasma, (mg/dL)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	92.2 (SD 6.1)	91.4 (SD 6.5)			NS				No change	
14722	Control	16/22	120 (SD 25.3)	120.9 (SD 32.3)				Blood glucose (OGTT 120 min)	Plasma (mg/dL)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	134.6 (SD 18.5)	117.6 (SD 24.6)			NS				No change	
14731	Control	16/22	80.7 (SD 50.7)	103.9 (SD 60.4)				Glucose AUC OGTT (180min)	Plasma (nmol/min/l)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	114.1 (SD 41.6)	94.8 (SD 49.4)			NS				No change	
<b>Adult studies</b>												
(Aller <i>et al.</i> , 2004) 15580	High fibre	27/27	5.4 (SD 0.4)	4.7 (SD 0.3)	<0.05			Glucose	Fasting Plasma, (mmol/L)	3 months	No change	unclear
	Low fibre	26/26	5 (SD 0.5)	5.1 (SD 0.5)		NS					No change	
(Andersson <i>et al.</i> , 2007) 14021	Refined grain products	30/30	5.2 (SD 0.9)	5.2 (SD 0.8)		NS		Glucose	Fasting (mmol/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	5.2 (SD 0.8)	5.3 (SD 0.8)		NS	0.28				Small increase	
(Olendzki <i>et al.</i> , 2009) 14604	High fibre	12/12	90.4 (SE 4.8)		-0.7 (SE 3.7)			Blood glucose		3 months	Decrease	unclear
	high fibre and low saturated fat	9/9	106.6 (SE 5.5)		-8.6 (SE 4.3)				Fasting (mg/dL)		Decrease	
	low saturated fat	10/10	92.8 (SE 5.3)		6.8 (SE 4.1)						Decrease	
14605	High fibre	12/12	90.4 (SE 4.8)		-4.0 (SE 3.8)			Blood glucose		6 months	Decrease	unclear
	high fibre and low saturated fat	9/9	106.6 (SE 5.5)		-4.6 (SE 4.3)				Fasting		Decrease	
	low saturated fat	10/10	92.8 (SE 5.3)		9.1 (SE 4.2)						Decrease	
(Singh <i>et al.</i> , 1992) 16357												
(Thompson <i>et al.</i> , 2005) 17085	Energy restriction + dairy	22/30			-0.22 (SD 0.3)		0.27	Glucose	Fasting (mM)	48 weeks	Decrease	bias
	Energy restriction + dairy + fibre	24/31			-0.16 (SD 0.32)						Decrease	
17087	Energy restriction + dairy	22/30			-0.3 (SD 1.23)		0.67	Glucose	2 hour (mM)	48 weeks	Decrease	bias

Results Number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
	Energy restriction + diary + fibre	24/31			-0.49 (SD 1.59)						Decrease	



## **Insulinaemia and dietary fibre, fibre density and high fibre diets**

Two US cohort studies provided evidence on dietary fibre intake and insulinaemia (Ludwig *et al.*, 1999; Marshall *et al.*, 1997). Dietary fibre was expressed as either percentage of energy (Ludwig *et al.*, 1999) or total in grams/day (Marshall *et al.*, 1997). The CARDIA study (Ludwig *et al.*, 1999) compared levels of fasting or 2-hour insulin following a glucose tolerance test in the top and bottom quintiles of baseline fibre density. Results were presented by race: 'white' or 'black'. In both groups, insulin levels were significantly lower in the participants with the highest fibre intakes at baseline. The San Luis Valley Diabetes Study (Marshall *et al.*, 1997) was also a USA-based, multi-ethnic cohort of individuals with normal glucose tolerance at baseline. This study reported a significant negative association between baseline dietary fibre intakes and fasting insulin levels assessed after 4 years of follow-up. These studies collectively provide consistent evidence of lower fasting insulin levels in association with increasing dietary fibre intakes.

Meta-analysis of these data was not possible due to an insufficient number of studies presenting data in an appropriate way.

### ***Exposure definition and assessment***

Fibre was presented in these studies as either total intake or fibre density. The CARDIA study assessed diet using an FFQ (Ludwig *et al.*, 1999) and the San Luis Valley Diabetes Study assessed diet using a dietary recall (Marshall *et al.*, 1997).

### ***Adjustment for appropriate confounders***

Appropriate adjustments were included in both studies.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## **Summary of RCT results**

Four studies provided data concerning the relationship between dietary fibre intake and blood insulin (Davis *et al.*, 2009; Aller *et al.*, 2004; Andersson *et al.*, 2007; Thompson *et al.*, 2005). Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

One study by Davis *et al.* (Davis *et al.*, 2009) recruited adolescents aged 14-18 years, whereas the remaining three used adults as participants. Of the two trials that reported age, participants had an average age of between 47 and 59 years of age. All studies were mixed gender.

Three out of the four studies used a parallel group design and one employed a crossover approach. Studies were either open (Davis *et al.*, 2009;Thompson *et al.*, 2005;Andersson *et al.*, 2007) or did not state the extent of blinding (Aller *et al.*, 2004).

Two trials were conducted in the USA (Davis *et al.*, 2009;Thompson *et al.*, 2005), one was carried out in Sweden (Andersson *et al.*, 2007) and the other in Spain (Aller *et al.*, 2004).

All included studies were relatively small in size and ranged from 34 to 90 participants per trial. The mean sample size was 55 (median=49).

One trial imposed an energy intake restriction as part of the intervention diets (Thompson *et al.*, 2005) and body weight decreased in each intervention group accordingly. In the other trials, body weights were unchanged or were slightly increased.

One study by Davis *et al.* (Davis *et al.*, 2009) did not show statistically significant changes in fasting insulin, insulin 120 minutes after an oral glucose tolerance test or insulin 180 minutes following an oral glucose tolerance test between groups.

One Spanish study reported by Aller *et al.* (Aller *et al.*, 2004) explored the effects of fibre on blood glucose and lipids over a 3-month period. The healthy eligible subjects (n=53) were randomised to receive a diet with 10.4g fibre (1.97g soluble fibre; 8.13g insoluble fibre) or a diet with 30.5g fibre (4.11g soluble fibre; 25.08g insoluble fibre) for 3 months. Minor changes in fasting blood insulin and insulin/ glucose ratio from baseline to follow-up were observed; these changes did not reach statistical significance.

Andersson *et al.* (Andersson *et al.*, 2007) assessed the effect of whole grain (fibre 30g/d) or refined grain products (fibre 17g/d) on various aspects of health in a group of 34 overweight men and women. After 6 weeks, no statistically significant differences in insulin within or between groups were observed.

Finally, Thompson *et al.* (Thompson *et al.*, 2005) reported the effects of three hypoenergetic regimes designed to test the effects of a high dairy food diet with high or low dietary fibre content compared with a standard diet on 90 obese participants. The high fibre content was achieved through consumption of whole grains, fruit and vegetables and reduction in high GI foods. A mean dietary fibre intake of 29g/d (SD 9) (AOAC fibre) was reported in the high fibre/high dairy adherents, compared with an average of 18g/d (SD 5) in the high dairy/low fibre adherents. At follow-up, insulin and 2-hour insulin had, in both groups, statistically significantly reduced from baseline; however the extent of change between groups was not statistically significantly different.

Overall, the findings from the four trials suggest no difference in fasting or post load blood insulin with higher fibre diets.

Table 4.75 Insulinaemia and dietary fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Sub- group Detail	Contrast (mean)	Units	Mean Outcome	Beta coefficient (SE)/(CI)	P Trend	Adjustments
13674 (Ludwig <i>et al.</i> , 1999) The CARDIA Study	USA, Multi-ethnic, Generally healthy, No hypertension, Not diabetic	18-30 %M 45.9	5115	10 years	FFQ (700)	Fibre density (g/unit energy. AOAC method)	Blood insulin Fasting, uU/mL	Race - White	Q5 vs. Q1 (12.3) vs. (5.2)	g/4184kJ/ day	10.4 vs. 11.2		0.007	age, alcohol, BMI, centre, education, energy intake, physical activity, gender, smoking, vitamin intake
13675 The CARDIA Study								Race - Black	Q5 vs. Q1 (12.3) vs. (5.2)	g/4184kJ/ day	11.9 vs. 13.3		0.01	As above
13678 The CARDIA Study							Blood insulin 2-Hour Insulin, uU/mL	Race - White	Q5 vs. Q1 (12.3) vs. (5.2)	g/4184kJ/ day	33.8 vs. 37.6		0.03	As above
13679 The CARDIA Study								Race - Black	Q5 vs. Q1 (12.3) vs. (5.2)	g/4184kJ/ day	37.4 vs. 53.3		<0.001	As above
14619 (Marshall <i>et al.</i> , 1997) San Luis Valley Diabetes Study	USA, Multi-ethnic, Normal glucose tolerance	20-74 (52) %M 46.8	1069	4.3 years (26)	Dietary recall	Dietary Fibre, g/d	Blood insulin Fasting, Plasma			5 g/day		Regression direction negative, coefficient not reported. For each 5g/d increment at baseline, insulin decreased by approx. 1.3%	0.008	age, waist, BMI, energy intake, ethnicity, physical activity, gender

Table 4.76 Insulinaemia and high fibre diets: RCT data

Results Number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
Adolescent study												
14727 (Davis <i>et al.</i> , 2009)	Control	16/22	27.1 (SD 17.3)	26.1 (SD 19.7)				Insulin	Fasting Plasma, ( $\mu$ U/ml)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	26.1 (SD 16.3)	24.3 (SD 14.5)			NS			No change		
14730	Control	16/22	132.7 (SD 91.4)	164.5 (SD 183.5)				Insulin OGTT (120min)	Plasma ( $\mu$ U/ml)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	249.9 (SD 204.3)	169 (SD 259.6)			NS			No change		
14732	Control	16/22	309.4 (SD 178)	338.4 (SD 281.2)				Insulin AUC OGTT (180min)	Plasma (nmol/min/l)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	459.3 (SD 319.5)	368.3 (SD 386.6)			NS			No change		
Adult studies												
15581 (Aller <i>et al.</i> , 2004)	High fibre	27/27	65 (SD 3.4)	68.9 (SD 3.4)	NS			Insulin	Fasting , (pmol/L)	3 months	No change	unclear
	Low fibre	26/26	74.6 (SD 6.8)	76.7 (SD 6.8)	NS		NS			No change		
15582	High fibre	27/27	12.1 (SD 4.9)	13.6 (SD 5.2)	NS			Insulin/glucose ratio	Fasting	3 months	No change	unclear
	Low fibre	26/26	14.9 (SD 6)	15.1 (SD 5.9)	NS		NS			No change		
16298 (Andersson <i>et al.</i> , 2007)	Refined grain products	30/30	60.4 (SD 30.6)	57.6 (SD 25.7)		NS		Insulin	Fasting Plasma, (pmol/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	56.2 (SD 22.9)	57.6 (SD 24.3)		NS	0.47			Small increase		
17086 (Thompson <i>et al.</i> , 2005)	Energy restriction + dairy	22/30			-30.6 (SD 38.5)		0.67	Insulin	Fasting (pM)	48 weeks	Decrease	bias
	Energy restriction + dairy + fibre	24/31			-19.7 (SD 18.6)					Decrease		
17088	Energy restriction + dairy	22/30			-169 (SD 218)		0.55	Insulin	2-Hour Insulin (pM)	48 weeks	Decrease	bias
	Energy restriction + dairy + fibre	24/31			-127 (SD 159)					Decrease		

## Insulin resistance/sensitivity and high fibre diets

No cohort studies provided data on dietary fibre and insulin resistance/sensitivity.

### Summary of RCT results

Two studies conducted in the USA and Sweden provided data concerning the relationship between dietary fibre intake and insulin resistance/ sensitivity (Davis *et al.*, 2009; Andersson *et al.*, 2007). One study by Davis *et al.* (Davis *et al.*, 2009) recruited adolescents aged 14-18 years. The average age of the participants in the study by Anderson *et al.* was 59 years (Andersson *et al.*, 2007). Both studies were mixed gender.

Both studies were open with regard to blinding (Davis *et al.*, 2009; Andersson *et al.*, 2007). Both studies were relatively small in size and ranged from 34 to 44 participants per trial.

Body weight changes of participants differed between studies: one study by (Davis *et al.*, 2009) reported unaltered weights whereas Andersson *et al.* (Andersson *et al.*, 2007) recorded increased weight.

The randomised controlled trial of 54 overweight Latino adolescents conducted by Davis *et al.* (Davis *et al.*, 2009) reported no statistically significant between group effects for HOMA, insulin sensitivity, acute insulin response and disposition index (Davis *et al.*, 2009).

Using a crossover design, Andersson *et al.* (Andersson *et al.*, 2007) explored the effects of a diet rich in whole grains or a diet containing refined grains on fasting insulin. After 6 weeks, the authors concluded that the dietary intervention had not affected insulin sensitivity using the euglycemic hyperinsulinemic clamp method or reported as glucose disposal rate/ insulin sensitivity index within or between groups.

Overall the findings from these two studies do not indicate an effect of higher fibre diets on measures of insulin resistance.

Table 4.77 Insulin resistance/sensitivity and high fibre diets: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
<b>Adolescent study</b>											
(Davis <i>et al.</i> , 2009) 15044	Control	16/22	6.2 (SD 3.8)	5.9 (SD 4.8)			Basal state method	HOMA-S	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	6.1 (SD 4.2)	5.5 (SD 3.3)		NS				No change	
16671	Control	16/22	1.8 (SD 1.2)	1.9 (SD 1.4)			Basal state method	Insulin sensitivity index (10 <sup>-4</sup> /min/ $\mu$ U/ml)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	1.6 (SD 0.9)	1.8 (SD 0.8)		NS				No change	
16672	Control	16/22	1308.5 (SD 930.9)	1404.8 (SD 1119.7)			Dynamic method	Acute insulin response to glucose $\mu$ U/ml*10/min)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	1160.4 (SD 869.9)	1222.8 (SD 994.2)		NS				No change	
16673	Control	16/22	1944.4 (SD 1071.3)	1797.4 (SD 1038.1)			Dynamic/Basal state methods	Disposition index (10 <sup>-4</sup> /min)	16 weeks	No change	unclear
	High fibre, low sugar diet	21/22	1297 (SD 596.7)	1723 (SD 898.3)		NS				No change	
<b>Adult study</b>											
(Andersson <i>et al.</i> , 2007) 16299	Refined grain products	30/30	5.7 (SD 1.9)	6.0 (SD 2.0)	NS		Steady state method	Euglycemic hyperinsulinemic clamp (mg/kg/min)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	5.9 (SD 2.1)	5.5 (SD 1.7)	NS	0.24				Small increase	
16603	Refined grain products	30/30	6.4 (SD 2.9)	6.9 (SD 3.2)			Steady state method	Glucose disposal rate/Insulin sensitivity Insulin sensitivity index	6 weeks	Small increase	unclear
	Wholegrain products	30/30	6.8 (SD 3)	6.5 (SD 2.7)		0.79				Small increase	

## Glycosylated blood proteins and dietary fibre

### Summary of cohort results

Two cohort studies conducted in the US and the UK provided data. In the Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006), 813 adults underwent a baseline examination and then returned for a 5-year follow-up examination. Diet was assessed by FFQ at both time points (data are included here only for the prospective analysis). Dietary fibre intake at baseline was not associated with HbA1c levels at follow-up in any of the models presented in the paper.

In the 1946 British Birth Cohort (Prynne *et al.*, 2009), some evidence of reduction in risk of an HbA1c level  $\geq 6.3\%$  was reported in association with increasing habitual non-starch polysaccharide (NSP) intakes assessed using 5 day food diaries. For each gram of NSP consumed, the risk of an HbA1c level  $\geq 6.3\%$  was reduced by 11% (95% CI 0.82, 0.98,  $p=0.012$ ). In this small cohort study, participants with lower intakes of non-starch polysaccharides in 1982 and 1989 were at increased risk of high HbA1c status in 1999.

A meta-analysis was not undertaken due to the small number of studies providing data.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning dietary fibre and glycosylated blood proteins.

Table 4.78 Glycosylated blood proteins and dietary fibre: cohort studies in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Contrast (mean)	Units	RR (95%CI)	Beta coefficient (SE)/(CI)	P	Adjustments
13885 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi- ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Dietary Fibre, g/d (AOAC method)	HbA1c Plasma		1 SD of mean exposure		-0.02 (0.02)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13999 (Prynne <i>et al.</i> , 2009) 1946 British Birth Cohort	UK, Primarily White	(36) %M 46	(36) /5362	17 years	Food diary	Non starch polysaccharide	HbA1c $\geq$ 6.3% Non-fasting, Whole blood	Continuous risk estimate	1 g/day	0.89 (0.82, 0.98)		0.012	BMI, socioeconomic status/class, smoking



## Fibre isolates, fermentable oligosaccharides

Intakes of fermentable oligosaccharides in Western populations have been estimated to range between 2 to 12g per day (Roberfroid, 1993) certain plants being rich sources such as artichokes, onions, asparagus and chicory. Additionally, certain fermentable oligosaccharides are used as a food additive, either for gelling and/or thickening effects or as a pre-biotic. Various fructan preparations have been explored in studies with an intervention duration ranging from 2 weeks to 6 months. The range of different fermentable oligosaccharides here included mixed inulin-type fructans which are a mixture of low-, medium and high degree of polymerisation fructans, such as Synergy 1 or Synergy HP (Forcheron and Beylot, 2007), Yacon root syrup (Genta *et al.*, 2009), or inulin (Raftiline/ Raftilose) with an average degree of polymerisation of 10 to 25 (Parnell and Reimer, 2009; Jackson *et al.*, 1999; Letexier *et al.*, 2003). These were administered in doses ranging from 10 to 21g/day, and compared with placebo or control products such as maltodextrin. For a review of the chemistry, nomenclature and functional food properties of the inulin-type fructans see (Roberfroid, 2007).

Various methods of administration were employed to incorporate the fermentable oligosaccharide products into the diet. The majority of studies asked the participants to add the powdered product to either food or drinks, generally in 2-3 doses across the day (Forcheron and Beylot, 2007; Letexier *et al.*, 2003; Jackson *et al.*, 1999; Parnell and Reimer, 2009). Alternatively, the fermentable oligosaccharides were consumed as a naturally rich source e.g. Yacon root syrup (Genta *et al.*, 2009).

## Glycaemia and fibre isolates, fermentable oligosaccharides

No cohort studies provided data on fermentable oligosaccharides and glycaemia.

### Summary of RCT results

Five studies provided data on the effects of high fermentable oligosaccharide diets on blood glucose (Genta *et al.*, 2009; Parnell and Reimer, 2009; Jackson *et al.*, 1999; Letexier *et al.*, 2003; Forcheron and Beylot, 2007).

One study used a cross-over design (Letexier *et al.*, 2003), whilst the others used parallel groups. All were conducted on adults in France (2), Argentina, the UK and Canada. The studies were small with a median number of participants within the trials of 48. All were double blind. The study by Letexier *et al.* (Letexier *et al.*, 2003) included only participants with BMI <25kg/m<sup>2</sup>, but the other studies which reported BMI included lean and overweight, or mainly overweight or obese participants. The study by Genta *et al.* (Genta *et al.*, 2009) included only women, but the other studies were mixed gender. The study durations ranged from 6 weeks to 6 months.

Three studies compared 10g/day of inulin with a similar amount of maltodextrin (Jackson *et al.*, 1999; Letexier *et al.*, 2003; Forcheron and Beylot, 2007) and one study compared 21g/day with an equivalent amount of maltodextrin (Parnell and Reimer, 2009). The study by Genta *et al.* administered fermentable oligosaccharides in the form of yacon syrup, a naturally rich source (Genta *et al.*, 2009), and this was compared with a similar dose of placebo syrup.

Body weights were unchanged in all trials other than in Genta *et al.* in which the authors reported that there was a decrease in the low dose yacon syrup group (Genta *et al.*, 2009) and Parnell *et al.* (Parnell and Reimer, 2009) which reported a decrease and small increase in body weight in the intervention and control groups respectively.

Four studies providing dietary differences in fermentable oligosaccharide intake between groups were included in the meta-analysis. The study by Parnell and Reimer could not be included as follow-up data are presented in a figure only, from which it is not possible to accurately extract mean glucose values (Parnell and Reimer, 2009). Studies where fasting blood glucose was not presented as mmol/L were appropriately converted. The first follow up reported at the end of the intervention was used. This varied from 6 weeks to 6 months. The overall pooled estimate indicated that fasting blood glucose was 0.13mmol/L (95% CI, -0.2 to 0.46) higher with consumption of a low oligosaccharide diet but this was not significantly different from zero ( $p=0.79$ ). Heterogeneity denoted by  $I^2$  was 74% (95% CI, 27 to 91). No funnel plot was carried out due to the small number of studies. Statistically, there was no evidence of a difference in fasting blood glucose with differences in fermentable oligosaccharide intake.

Figure 4.33 Forest plot for fibre isolates, fermentable oligosaccharides (FOS) and fasting blood glucose (mmol/L)

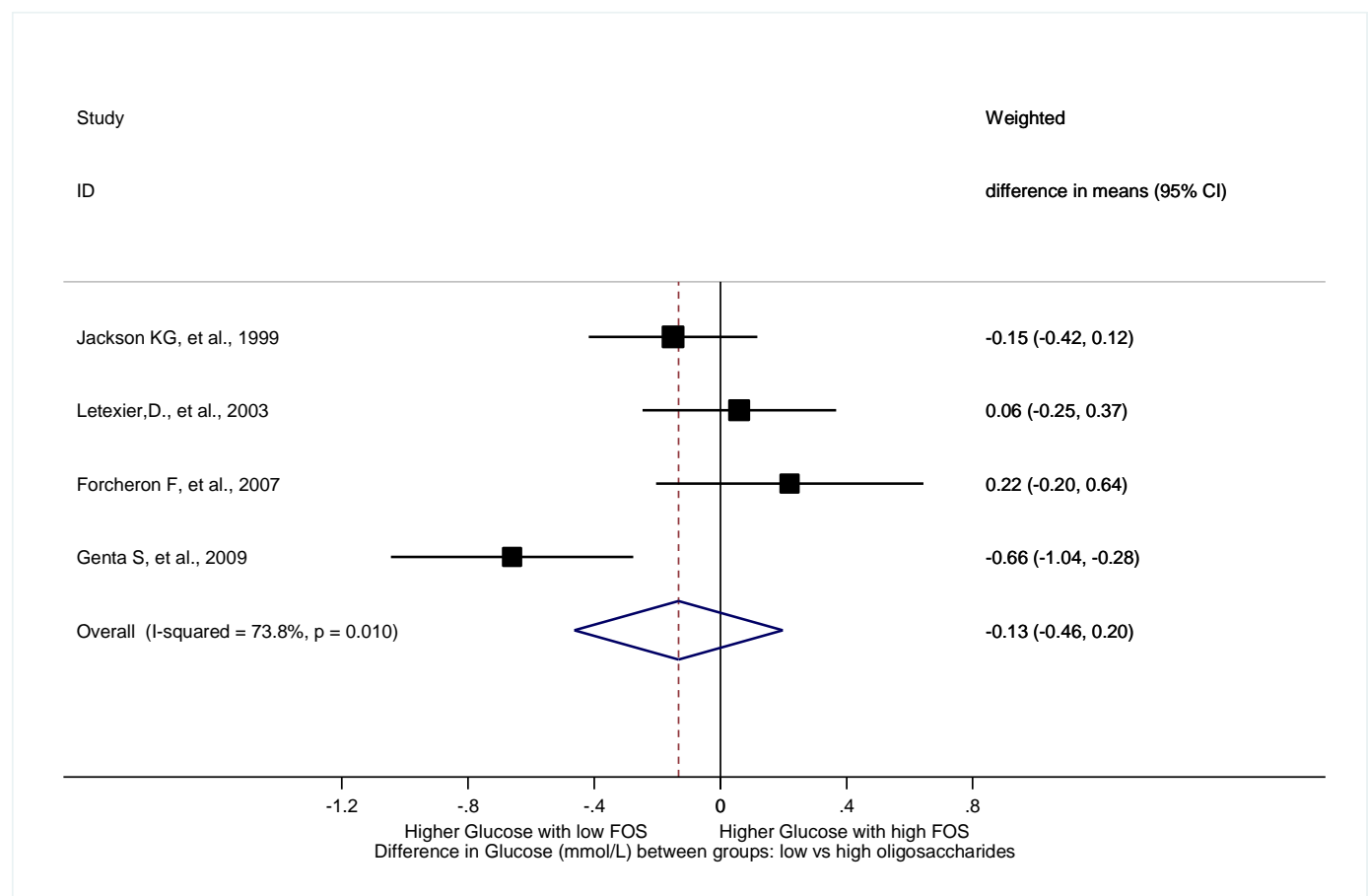


Table 4.79 Glycaemia and fibre isolates, fermentable oligosaccharides: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Forcheron and Beylot, 2007) *14792	Fructans	9/10	4.33 (SE 0.12)	4.03 (SE 0.1)	NS	NS	Blood glucose	Fasting plasma, (mmol/L)	6 months	No change	No bias
	Placebo	8/10	3.97 (SE 0.19)	3.81 (SE 0.2)						No change	
(Genta <i>et al.</i> , 2009) *14549	Low dose fructooligosaccharide syrup	completers not reported/20	12.6 (SD 1.7)	7.3 (SD 2.4)	NS	Not reported	Blood glucose	Fasting serum, ( $\mu$ UI/ml)	120 days	Decrease	No bias
	Placebo syrup	15/15	13.7 (SD 1.3)	14.2 (SD 1.5)	NS					No change	
(Jackson <i>et al.</i> , 1999) *14833	Inulin	27/27	4.73 (SD 0.51)	4.84 (SD 0.51)	NS	NS	Blood glucose	Fasting plasma, (mmol/L)	8 weeks	No change	No bias
	Placebo	27/27	4.92 (SD 0.39)	4.99 (SD 0.49)	NS					No change	
14834	Inulin	27/27	4.73 (SD 0.51)	4.73 (SD 0.45)	NS	NS	Blood glucose	Fasting plasma, (mmol/L)	12 weeks	No change	No bias
	Placebo	27/27	4.92 (SD 0.39)	4.77 (SD 0.53)	NS					No change	
14836	Inulin	27/27	151.5 (SD 72.5)	158.9 (SD 76.8)	NS	NS	Glucose: Insulin ratio	Fasting plasma	8 weeks	No change	No bias
	Placebo	27/27	155.7 (SD 65)	161.5 (SD 132.2)	NS					No change	
14837	Inulin	27/27	151.5 (SD 72.5)	177.8 (SD 184.6)	NS	NS	Glucose: Insulin ratio	Fasting plasma	12 weeks	No change	No bias
	Placebo	27/27	155.7 (SD 65.0)	148.2 (SD 99.9)	NS					No change	
(Letexier <i>et al.</i> , 2003) *14838	Inulin	8/8		4.68 (SE 0.14)	NS	NS	Blood glucose	Fasting plasma, (mmol/L)	6 weeks	No change	No bias
	Placebo	8/8		4.62 (SE 0.07)						No change	
(Parnell and Reimer, 2009) 17164	Oligofructose	21/21	1649.0 (SD 215.8)	Decreased at 6 hr vs. baseline Total AUC decreased by 5% on final day vs. initial day	Data in figures only <0.05	Glucose AUC post meal response	Post test meal (mmol/L/min)		12 weeks	Decrease	No bias
	Placebo	16/18	1627.6 (SD 138.8)	Increased at 4 and 6 hr vs. baseline						Small increase	

\*This result was used in the meta-analysis of fermentable oligosaccharides and glycaemia

## Insulinaemia and fibre isolates, fermentable oligosaccharides

No cohort studies provided data on fermentable oligosaccharides and insulinaemia.

### Summary of RCT results

Five studies provided data on the effects of fermentable oligosaccharide intake on blood insulin (Genta *et al.*, 2009;Parnell and Reimer, 2009;Jackson *et al.*, 1999;Letexier *et al.*, 2003;Forcheron and Beylot, 2007). These five also provided data on fasting glucose therefore trial summaries of these trials can be found in the section concerning glycaemia and fermentable oligosaccharides.

Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

Three studies – those conducted by Jackson *et al.*, Letexier *et al.* and Forcheron and Beylot - compared 10g/day of inulin with a similar amount of maltodextrin in healthy overweight and obese participants (Jackson *et al.*, 1999;Letexier *et al.*, 2003;Forcheron and Beylot, 2007). At follow-up, fasting blood insulin did not statistically significantly differ within or between intervention groups in any of the three trials. Additionally, two trials reported that such a dose of insulin did not differentially affect glucagon levels relative to the placebo product (Forcheron and Beylot, 2007;Letexier *et al.*, 2003).

The randomised, double blind study by Parnell and Reimer compared 21g/day oligofructose with an equivalent amount of maltodextrin in 48 participants (Parnell and Reimer, 2009). Insulin decreased in the oligofructose group and increased in the control group between initial and final tests ( $p<0.05$ ). Whether there was an overall effect of oligofructose compared to control is unclear.

Finally, the study by Genta *et al.* administered fermentable oligosaccharides in the form of yacon syrup, a naturally rich source (Genta *et al.*, 2009), which was compared with a similar dose of placebo syrup. Obese, mildly dyslipidaemic pre-menopausal female participants ( $n=55$ ) were required to consume half the syrup (at a level of 0.14g fructooligosaccharides/kg body weight) one hour before breakfast and the other half one hour before lunch. In the high dose fructooligosaccharides syrup group, fasting serum insulin statistically significantly decreased by approximately 50mmol/L from baseline ( $p=0.05$ ), yet there was no statistically significant change in the placebo group.

These data, therefore, generally indicate no effect of fermentable oligosaccharide intake on fasting blood insulin.

Table 4.80 Insulinaemia and fibre isolates, fermentable oligosaccharides: RCT data

Results Number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
14820 (Forcheron and Beylot, 2007)	Fructans	9/10	6.2 (SE 1.1)	6.8 (SE 1.1)			NS	Blood insulin	Fasting Plasma, (mU/L)	6 months	No change	No bias
	Placebo	8/10	6.6 (SE 0.7)	6.8 (SE 1.1)							No change	
14821	Fructans	9/10	164 (SE 26)	156 (SE 19)			NS	Glucagon	Fasting Plasma, (ng/L)	6 months	No change	No bias
	Placebo	8/10	175 (SE 23)	153 (SE 30)							No change	
14550 (Genta <i>et al.</i> , 2009)	Low dose fructooligosaccharide syrup	completers not reported/20	4.68 (SD 0.66)	4.18 (SD 0.5)		0.05	Not reported	Blood insulin	Fasting Serum, (mmol/L)	120 days	Decrease	No bias
	Placebo syrup	15/15	5.06 (SD 0.55)	4.84 (SD 0.66)		NS					No change	
(Jackson <i>et al.</i> , 1999)	Inulin	27/27	41.5 (SD 22.1)	37.5 (SD 18.3)		NS	NS	Blood insulin	Fasting Plasma, (pmol/L)	8 weeks	No change	No bias
14823	Placebo	27/27	41.3 (SD 24.4)	44.9 (SD 27.5)		NS					No change	
14824	Inulin	27/27	41.5 (SD 22.1)	39.6 (SD 21.5)		NS	NS	Blood insulin	Fasting Plasma, (pmol/L)	12 weeks	No change	No bias
	Placebo	27/27	41.3 (SD 24.4)	41.3 (SD 16.9)		NS					No change	
14842 (Letexier <i>et al.</i> , 2003)	Inulin	8/8		8.9 (SE 1.4)			NS	Blood insulin	Fasting Plasma, (mU/L)	6 weeks	No change	No bias
	Placebo	8/8		7.9 (SE 0.6)							No change	
14843	Inulin	8/8		163 (SE 34)			NS	Glucagon	Fasting Plasma, (ng/L)	6 weeks	No change	No bias
	Placebo	8/8		144 (SE 21)							No change	
17166 (Parnell and Reimer, 2009)	Oligofructose	21/21	274830.5 (SD 133797.7)		Total AUC decreased by 10% on final day vs. initial day		<0.05	Insulin AUC post meal response	Post test meal (pg/ml/min)	12 weeks	Decrease	No bias
	Maltodextrin placebo	16/18	232775.1 (SD 137934.8)		Total AUC increased by 23% on final day vs. initial day						Small increase	

## Insulin resistance/sensitivity and fibre isolates, fermentable oligosaccharides

No cohort studies provided data on fermentable oligosaccharides and insulin resistance/sensitivity.

### Summary of RCT results

One study provided data on fermentable oligosaccharide intake (yacon syrup) and insulin resistance/ sensitivity (Genta *et al.*, 2009). Genta *et al.* (Genta *et al.*, 2009) found that the intervention group in their study - the high dose fructooligosaccharides diet group - experienced a statistically significant reduction in HOMA-IR (fasting blood glucose (mmol/L) multiplied by insulin concentration (mU/ml) and divided by 22.5.2) compared to baseline ( $p=0.05$ ), whilst the placebo group remained unchanged. The statistical significance of the difference between groups was not reported.

Table 4.81 Insulin resistance/sensitivity and fibre isolates, fermentable oligosaccharides: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Genta <i>et al.</i> , 2009) 14552	Low dose fructooligosaccharide syrup	completers not reported/20	6.3 (SD 1.1)	2.07 (SD 0.91)	0.05	Basal state method	Fasting HOMA-IR	120 days	Decrease	No bias
	Placebo syrup	15/15	5.35 (SD 0.09)	5.66 (SD 1.01)	NS		fasting blood glucose (mmol/L) multiplied by insulin concentration (mU/ml) and divided by 22.5.2		No change	

# Fibre isolates, mixed soluble types

## Glycaemia and fibre isolates, mixed soluble types

No cohort studies provided data on soluble fibre and glycaemia.

### Summary of RCT results

Salas-Salvado *et al.* (Salas-Salvado *et al.*, 2008) reported data on the effects of a mixed soluble fibre supplement of 3g *Plantago ovata* husk and 1g glucomannan added to a hypoenergetic diet (-2.5MJ/d) either once or twice daily compared with a placebo product (microcrystalline 166 cellulose) which was similar in weight and presentation. Body weights decreased in both intervention groups. Findings from this study indicate a decrease in fasting glucose and blood glucose 2-hour following an oral glucose tolerance test from baseline in all three groups, but these reductions were not statistically significant. No statistically significant changes between diet groups were observed either.

Table 4.82 Glycaemia and fibre isolates, mixed soluble-types: RCT data

Results Number	Intervention group	Completers/ Allocated	Within group $\Delta$ from baseline	Difference between groups in $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Salas-Salvado <i>et al.</i> , 2008) 14497	Mixed fibre 3 times a day	58/68	-0.09 (SD 0.1)		Blood glucose	Fasting (mmol/L)	16 weeks	Decrease	No bias
	Mixed fibre twice a day	53/66	-0.12 (SD 0.11)					Decrease	
	Placebo	55/66	0.03 (SD 0.1)					Decrease	
14498	Mixed fibre 3 times a day	58/68	-0.17 (SD 0.26)		Blood glucose (OGTT 120 min)	(mmol/L)	16 weeks	Decrease	No bias
	Mixed fibre twice a day	53/66	-0.20 (SD 0.29)					Decrease	
	Placebo	55/66	0.24 (SD 0.27)					Decrease	
14782	Mixed fibre twice a day minus Placebo	Intervention: 53/66 Placebo: 55/66		0.04 (CI -0.64, 0.72)	Blood glucose (OGTT 120 min)	(mmol/L)	16 weeks	Decrease in both	No bias
14783	Mixed fibre 3 times a day minus Placebo	Intervention: 58/58 Placebo: 55/66		0.07 (CI -0.58, 0.72)	Blood glucose (OGTT 120 min)	(mmol/L)	16 weeks	Decrease in both	No bias
14784	Mixed fibre twice a day minus placebo	Intervention: 53/66 Placebo: 55/66		-0.15 (CI -0.42, 0.12)	Blood glucose	Fasting (mmol/L)	16 weeks	Decrease in both	No bias
14785	Mixed fibre 3 times a day minus Placebo	Intervention: 58/58 Placebo: 55/66		-0.12 (CI -0.38, 0.13)	Blood glucose	Fasting (mmol/L)	16 weeks	Decrease in both	No bias



## Insulinaemia and fibre isolates, mixed soluble-types

No cohort studies provided data on soluble fibre and insulinaemia.

### Summary of RCT results

Salas-Salvado *et al.* (Salas-Salvado *et al.*, 2008) reported data on the effects of a mixed soluble fibre supplement added to a hypoenergetic diet (-2.5MJ/d) either once or twice daily compared with a placebo product. After 16 weeks, insulin and blood insulin, following an oral glucose tolerance test for the mixed soluble fibre three times a day group and placebo group, indicated no significant differences from baseline or between the groups.

Table 4.83 Insulinaemia and fibre isolates, mixed soluble-types: RCT data

Results Number	Intervention group	Completers/Allocated	Within group $\Delta$ from baseline	Difference between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
14500 (Salas-Salvado <i>et al.</i> , 2008)	Mixed soluble fibre 3 times a day	58/68	-11.26 (SD 6.76)		Blood insulin	Fasting (pmol/L)	16 weeks	Decrease	No bias
	Mixed soluble fibre twice a day	53/66	-22.04 (SD 7.24)					Decrease	
	Placebo	55/66	-11.85 (SD 6.57)					Decrease	
14778	Mixed soluble fibre twice a day minus placebo	Intervention: 53/66 Placebo: 55/66		-28.37 (CI - 91.62, 34.87)	Insulin AUC OGTT response	2-Hour Insulin (pmol/L)	16 weeks	Decrease in both	No bias
14779	Mixed soluble fibre 3 times a day minus placebo	Intervention: 58/58 Placebo: 55/66		-3.10 (CI - 62.68, 56.47)	Insulin AUC OGTT response	2-Hour Insulin (pmol/L)	16 weeks	Decrease in both	No bias
14780	Mixed soluble fibre twice a day minus Placebo	Intervention: 53/66 Placebo: 55/66		-10.20 (CI - 27.13, 6.74)	Blood insulin	Fasting (pmol/L)	16 weeks	Decrease in both	No bias
14781	Mixed soluble fibre 3 times a day minus Placebo	Intervention: 58/58 Placebo: 55/66		0.59 (CI - 15.71, 16.89)	Blood insulin	Fasting (pmol/L)	16 weeks	Decrease in both	No bias

## Insulin resistance/sensitivity and fibre isolates, mixed soluble-types

No cohort studies provided data on soluble fibre and insulin resistance/sensitivity.

### Summary of RCT results

One study by Salas-Salvado *et al.* (Salas-Salvado *et al.*, 2008) noted reductions in insulin AUC OGTT response and HOMA-R from baseline, with the greatest reduction being seen in the mixed fibre twice a day diet group (-41.06pmol/L and -0.71 respectively). Changes from baseline, as well as changes between groups, however were not statistically significant.

Table 4.84 Insulin resistance/sensitivity and fibre isolates, mixed soluble-types: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Within group $\Delta$ from baseline	Difference between groups in $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Salas-Salvado <i>et al.</i> , 2008) 14503	Mixed fibre 3 times a day	58/68	-15.79 (SD 24.65)		Insulin AUC OGTT response	(pmol/L)	16 weeks	Decrease	No bias
	Mixed fibre twice a day	53/66	-41.06 (SD 26.37)					Decrease	
	Placebo	55/66	-12.69 (SD 24.65)					Decrease	
14504	Mixed fibre 3 times a day	58/68	-0.42 (SD 0.21)		Basal state method	HOMA-R (index)	16 weeks	Decrease	No bias
	Mixed fibre twice a day	53/66	-0.71 (SD 0.23)					Decrease	
	Placebo	55/66	-0.31 (SD 0.3)					Decrease	
14776	Mixed fibre twice a day minus Placebo	Intervention: 53/66 Placebo: 55/66		-0.4 (CI -0.93, 0.14)	Basal state method	HOMA-R (index)	16 weeks	Decrease in both	No bias
14777	Mixed fibre 3 times a day minus Placebo	Intervention: 58/58 Placebo: 55/66		-0.11 (CI -0.62, 0.4)	Basal state method	HOMA-R (index)	16 weeks	Decrease in both	No bias

## Glycosylated blood proteins and fibre isolates, mixed soluble-types

No cohort studies provided data on soluble fibre and glycosylated blood proteins.

### Summary of RCT results

After 16 weeks, Salas Salvado *et al.* (Salas-Salvado *et al.*, 2008) reported a decrease in HbA1c in all diet groups, yet these changes did not reach statistical significance.

Table 4.85 Glycosylated blood proteins and fibre isolates, mixed soluble-types: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Within group $\Delta$ from baseline	Difference between groups in $\Delta$ from baseline	Outcome/ Assessment method	Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Salas-Salvado <i>et al.</i> , 2008) 14496	Mixed fibre 3 times a day	58/68	-0.11 (SD 0.06)		HbA1c	Fasting (%)	16 weeks	Decrease	No bias
	Mixed fibre twice a day	53/66	-0.03 (SD 0.06)					Decrease	
	Placebo	55/66	-0.15 (SD 0.06)					Decrease	
14786	Mixed fibre twice a day minus Placebo	Intervention: 53/66 Placebo: 55/66		0.12 (CI -0.04, 0.28)	HbA1c	(%)	16 weeks	Decrease in both	No bias
14787	Mixed fibre 3 times a day minus Placebo	Intervention: 58/58 Placebo: 55/66		0.04 (CI -0.12, 0.19)	HbA1c	(%)	16 weeks	Decrease in both	No bias

# Fibre isolates, mixed insoluble types

## Glycaemia and fibre isolates, mixed insoluble types

No cohort studies provided data on insoluble fibre and glycaemia.

### Summary of RCT results

Two parallel-group studies provided data on the effects of mixed-insoluble sources of fibre isolates on glycaemia (Cairella *et al.*, 1995; Birketvedt *et al.*, 2000). Neither study found an effect of fibre tablets on glycaemia. There were insufficient studies to conduct a meta-analysis.

Body weights decreased in both studies (Cairella *et al.*, 1995); (Birketvedt *et al.*, 2000).

In Cairella *et al.* (Cairella *et al.*, 1995), 30 obese subjects (BMI range 30.9-47.0kg/m<sup>2</sup>) were randomised to a dietary fibre supplement or a placebo. An initial 15-day weight loss phase following a very low caloric diet was employed, after which participants in both the fibre supplement group and placebo group were encouraged to follow a balanced diet (with 17-22g fibre content) for the remaining 60 days of the study. Fibre was administered by tablets (fibre sourced from vegetables, citrus fruit and cereals), of which three tablets were taken six times daily. The identical placebo tablet followed similar administration and consumption patterns as the intervention. No statistically significant differences in blood glucose between the two groups were observed.

Birketvedt *et al.* (Birketvedt *et al.*, 2000) used 53 moderately overweight subjects on a reduced energy diet (1200kcal/day) to test a fibre supplement (mixture of fibre from grain and citrus; 15% soluble fibre and 85% insoluble fibre) compared to no supplement over a 24-week period. Fibre was initially administered in tablet form (6g) and prescribed three times a day for 8 weeks. The dosage was then reduced to five tablets per day for the rest of the study. Blood glucose levels statistically significantly decreased from baseline in both the fibre supplement and no supplement group ( $p < 0.05$ ). However, no differences in glucose between groups were reported.

Table 4.86 Glycaemia and fibre isolates, mixed insoluble-types: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assess- ment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessme nt Bias
(Birketvedt <i>et al.</i> , 2000) 14924	Energy restricted diet	25/25	5.6 (SE 0.1)	5.2 (SE 0.1)	<0.05		Blood glucose	Fasting	24 weeks	Decrease	No bias
	Energy restricted diet + Fibre supplement	28/28	5.3 (SE 0.1)	5.1 (SE 0.1)	<0.05			Whole blood, (mmol/L)		Decrease	
(Cairella <i>et al.</i> , 1995) 15689	Balanced diet	complete rs not reported /15				NS	Glucose	Not reported	60 days	Decrease	No bias
	Balanced diet with fibre supplement	complete rs not reported /15								Decrease	

# Psyllium

## Glycaemia and fibre isolates, psyllium

No cohort studies provided data on psyllium and glycaemia.

### Summary of RCT results

Only one trial provided data on the relationship between psyllium fibre and glycaemia (Bell *et al.*, 1990). Bell *et al.* (Bell *et al.*, 1990) compared glucose levels between three different groups in 58 males with mild to moderate hypercholesterolemia. In this study, body weights remained unchanged. A Step 1 diet was employed during the first 6 weeks of the trial, after which participants were randomised to receive pectin-enriched cereal (10.76% soluble fibre), psyllium-enriched cereal (10.2% soluble fibre) or a placebo (cornflakes) whilst continuing with the step 1 diet over a second 6-week period. Cereals were administered as 57g portions and were consumed as part of breakfast. Changes in glucose levels from baseline among the groups were marginal (1.8%, -3.6% and 0% in the pectin enriched cereal, the placebo and the psyllium enriched cereal, respectively) and as such, the authors concluded that no statistically significant differences were detected.

Table 4.87 Glycaemia and fibre isolates, psyllium: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow- up	Weight Change	Outcome Assessment Bias
(Bell <i>et al.</i> , 1990) 17163	Pectin enriched cereal	20/20	5.4 (SE 0.2)	5.5 (SE 0.1)	1.80%	Glucose		6 weeks	No change	No bias
	Placebo	19/20	5.6 (SE 0.1)	5.4 (SE 0.1)	-3.60%	Glucose	Fasting Serum, (mmol/L)		No change	
	Psyllium enriched cereal	19/20	5.3 (SE 0.1)	5.3 (SE 0.1)	0%	Glucose			No change	

# Fibre isolates, gums and extracts

## Glycaemia and fibre isolates, gums and extracts

No cohort studies provided data on gums and extracts and glycaemia.

### Summary of RCT results

Nine studies concerning the relationship between soluble fibre isolates in the form of gums and blood glucose were identified (Bell *et al.*, 1990;Landin *et al.*, 1992;Pasman *et al.*, 1997a;Ryle *et al.*, 1990;Wood *et al.*, 2007;Marett and Slavin, 2004;Garcia *et al.*, 2007;Schwab *et al.*, 2006;Lehtimaki *et al.*, 2005).

Five out of nine trials employed a parallel group design whereas the remaining four used a crossover design. For the most part, studies were double blind although one was single blind (Garcia *et al.*, 2007), one open (Pasman *et al.*, 1997a) and one unclear regarding blinding (Ryle *et al.*, 1990).

All trials used adults. Of these studies, three recruited male adults only (Bell *et al.*, 1990;Landin *et al.*, 1992;Wood *et al.*, 2007) and just one used females (Pasman *et al.*, 1997a). The majority however were mixed gender. Sample sizes ranged from 11 to 130 participants, with a mean size of 45 (median=35). In the studies that provided data on BMI, participants were generally overweight or obese. An exception to this is the study by Ryle *et al.* (Ryle *et al.*, 1990) in which, mean BMI was indicative of a healthy weight (mean BMI=22kg/m<sup>2</sup>).

Body weight change differed between studies. Most studies stated no difference in weight or simply did not report weight change during the intervention. The authors from two studies however did record a weight loss in both groups (Schwab *et al.*, 2006;Wood *et al.*, 2007) and one study showed an increase (following a very low energy diet phase) (Pasman *et al.*, 1997a).

One study could not be included in the meta-analysis since data were not provided. Pasman *et al.* (Pasman *et al.*, 1997a) compared a 20g water soluble fibre (guar gum) supplement with no treatment condition for 14 months, following a 2 month very low calorie diet weight loss. At follow-up, no statistically significant differences in glycaemia were reported in the text of the paper.

Eight studies provided data suitable for inclusion in a meta-analysis exploring the effects of gums and other fibre isolates on glycaemia. All studies included adults as participants. Definitions of different levels of gums and extracts are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were appropriately converted. The first follow up reported at the end of the intervention was used. This varied from 6 weeks to 6 months. The overall pooled estimate indicated that fasting blood glucose was 0.11mmol/L (95% CI, -0.05 to 0.26) higher with consumption of a diet low in gums or extracts but this was not significantly different from zero ( $p=0.18$ ). Heterogeneity denoted by  $I^2$  was 68% (95% CI, 35 to 84). No funnel plot was carried out due to the small number of studies. Statistically, there was no strong evidence of a difference in fasting blood glucose with differences in consumption of fibre isolates in the form of gums and extracts.

Figure 4.34 Forest plot for fibre isolates, gums and extracts and fasting blood glucose (mmol/L)

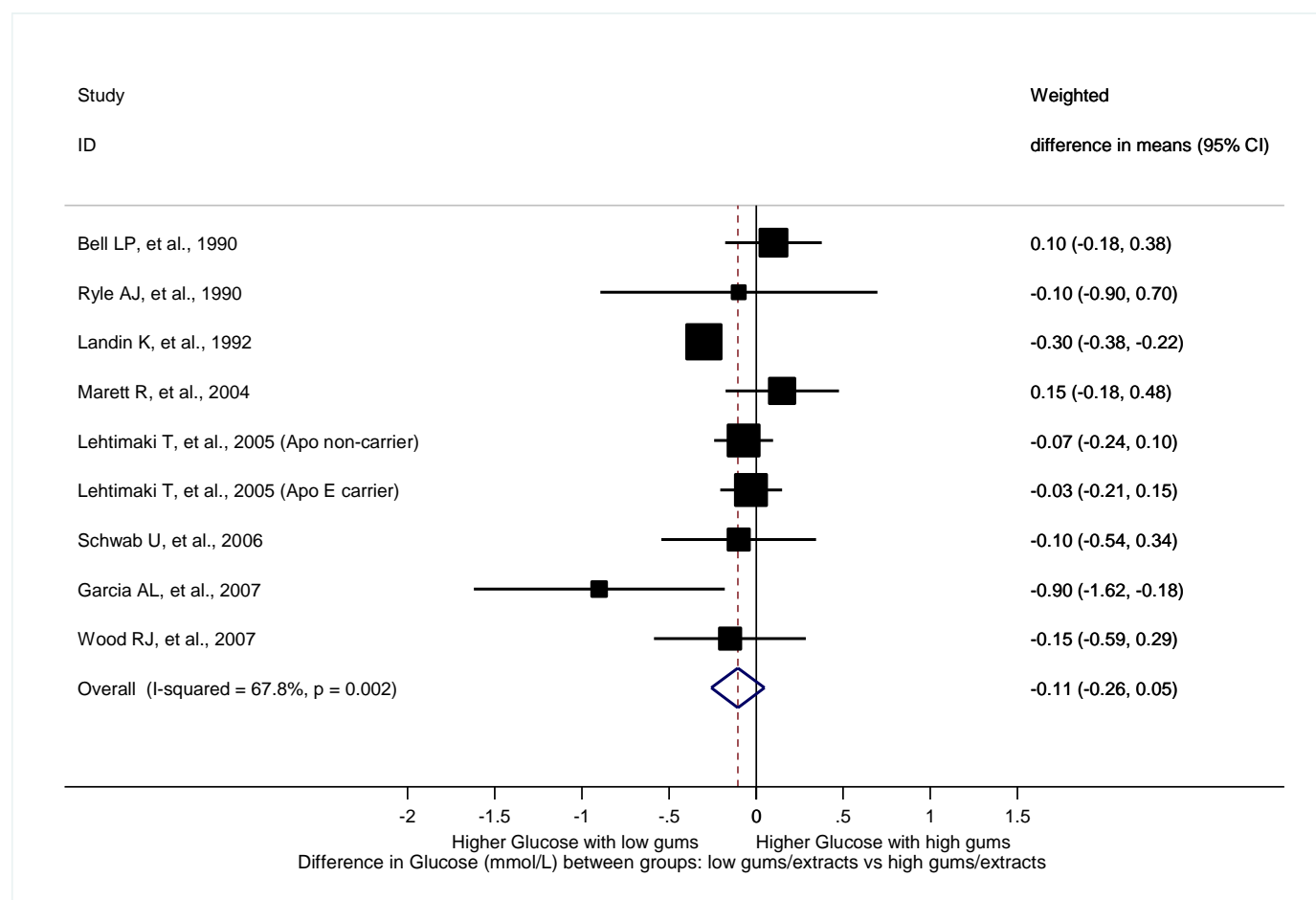




Table 4.88 Glycaemia and fibre isolates, gums and extracts: RCT data

Author/ result number	Sub- group detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups at follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Bell <i>et al.</i> , 1990) *17163		Pectin enriched cereal	20/20	5.4 (SE 0.2)	5.5 (SE 0.1)	-1.80%					Glucose		6 weeks	No change	No bias
		Placebo	19/20	5.6 (SE 0.1)	5.4 (SE 0.1)	-3.60%						Fasting serum, (mmol/L)		No change	
		Psyllium enriched cereal	19/20	5.3 (SE 0.1)	5.3 (SE 0.1)	0%								No change	
(Garcia <i>et al.</i> , 2007) *17393		Arabinosyran	11/11	5.4 (CI 4.9, 6.1)	5.4 (CI 4.9, 6.1)			0.029			Glucose	Fasting Geometric mean and standard error, Serum (mmol/L)	6 weeks	No change	unclear
		Placebo	11/11	6 (CI 5.7, 6.4)	6.3 (CI 5.9, 6.7)									No change	
17405		Arabinosyran	11/11		lower			0.005			Glucose AUC post meal response	4 hour AUC Serum, (pmol/L)	6 weeks	No change	unclear
		Placebo	11/11											No change	
(Landin <i>et al.</i> , 1992) *17116		Guar gum	25/25								Glucose		6 weeks	No change	No bias
		Placebo	25/25									Fasting Whole blood, (mmol/L)		No change	
		Guar gum minus placebo	Crossover: 25/25					-0.02 (CI - 0.11, 0.06)		<0.001				No change in both	
(Lehtimäki <i>et al.</i> , 2005) *17506	Genetics - Apo E genotype E4 carrier	Microcrystalline chitosan	86/96	4.82 (SD 0.6)	4.55 (SD 0.5)	-5.8 (SD 12.2)					Glucose	Fasting Whole blood, (mmol/L)	3 months	Not reported	No bias
		Placebo	85/96	4.82 (SD 0.6)	4.61 (SD 0.59)	-5.2 (SD 12.4)								Not reported	
*17507	Genetics - Apo E genotype E4 non-carrier	Microcrystalline chitosan	86/96	4.83 (SD 0.54)	4.51 (SD 0.43)	-6.5 (SD 11)					Glucose	Fasting Whole blood, (mmol/L)	3 months	Not reported	No bias
		Placebo	85/96	4.83 (SD 0.54)	4.56 (SD 0.46)	-5 (SD 12.3)								Not reported	
(Marett)		Larch	18/18	4.50 (SD)	4.23 (SD)		<0.05				Glucose	Fasting	2 months	No	No bias

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Author/ result number	Sub- group detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Difference between groups at follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
and Slavin, 2004) 16653		arabinogalactan		0.46)	0.51)							plasma, (mmol/L)		change	
		Placebo	17/17	4.58 (SD 0.24)	4.15 (SD 0.47)		NS							No change	
		Tamarack arabinogalactan	19/19	4.55 (SD 0.29)	4.33 (SD 0.41)		NS							No change	
16654		Larch arabinogalactan	18/18	4.50 (SD 0.46)	4.21 (SD 0.46)		<0.05				Glucose		3 months	No change	No bias
		Placebo	17/17	4.58 (SD 0.24)	4.16 (SD 0.32)		NS					Fasting plasma, (mmol/L)		No change	
		Tamarack arabinogalactan	19/19	4.55 (SD 0.29)	4.12 (SD 0.39)		<0.01							No change	
16655		Larch arabinogalactan	18/18	4.50 (SD 0.46)	4.33 (SD 0.54)		NS				Glucose		4 months	No change	No bias
		Placebo	17/17	4.58 (SD 0.24)	4.34 (SD 0.41)		NS					Fasting plasma, (mmol/L)		No change	
		Tamarack arabinogalactan	19/19	4.55 (SD 0.29)	4.18 (SD 0.43)		<0.01							No change	
16656		Larch arabinogalactan	18/18	4.50 (SD 0.46)	4.27 (SD 0.42)		NS				Glucose		5 months	No change	No bias
		Placebo	17/17	4.58 (SD 0.24)	4.24 (SD 0.54)		<0.05					Fasting plasma, (mmol/L)		No change	
		Tamarack arabinogalactan	19/19	4.55 (SD 0.29)	4.21 (SD 0.73)		<0.05							No change	
*16657		Larch arabinogalactan	18/18	4.50 (SD 0.46)	4.22 (SD 0.40)		<0.05				Glucose		6 months	No change	No bias
		Placebo	17/17	4.58 (SD 0.24)	4.07 (SD 0.58)		<0.01					Fasting plasma, (mmol/L)		No change	
		Tamarack arabinogalactan	19/19	4.55 (SD 0.29)	4.22 (SD 0.32)		<0.05							No change	
(Pasman <i>et al.</i> , 1997a) 15520		Control	11/14				NS				Glucose	Fasting plasma	14 months	Increase	unclear
		Guar gum - High compliance	10/10				NS	NS						Increase	

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Author/ result number	Sub- group detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Difference between groups at follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
		Guar Gum - Low compliance	10/10				NS	NS						Increase	
(Ryle <i>et al.</i> , 1990) *16193		High glucose low soluble fibre	11/11	5.7 (SD 1)	6.1 (SD 1.0)						Glucose	Fasting (mmol/L)	6 weeks	No change	unclear
		Low glucose high soluble fibre diet (guar)	11/11	5.7 (SD 1)	6.0 (SD 0.9)									No change	
16194		High glucose low soluble fibre	11/11	5.7 (SD 1.2)	5.5 (SD 1.8)						Glucose (OGTT 60 min)	Plasma (mmol/L)	6 weeks	No change	unclear
		Low glucose high soluble fibre diet (guar)	11/11	5.7 (SD 1.2)	7.2 (SD 2.5)									No change	
16195		High glucose low soluble fibre	11/11	5.9 (SD 1.4)	5.7 (SD 1.5)						Glucose (OGTT 120 min)	Plasma (mmol/L)	6 weeks	No change	unclear
		Low glucose high soluble fibre diet (guar)	11/11	5.9 (SD 1.4)	6.4 (SD 1.5)									No change	
(Schwab <i>et al.</i> , 2006) 16947		Pectin	22/22	2.2 (SD 0.9)	3.2 (SD 2.9)		NS				Glucose	2h AUC, Post test meal(mmol /L/ min)	12 weeks	Decrease	No bias
16477		Placebo	22/22	6.4 (SD 0.9)	6.5 (SD 1.1)						Glucose	Fasting plasma, (mmol/L)	8 weeks	Decrease	No bias
		Polydextrose	22/22	6.3 (SD 0.9)	6.6 (SD 0.9)									Decrease	
*16478		Pectin	22/22	6.4 (SD 0.5)	6.5 (SD 0.7)		NS				Glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	No bias
		Placebo	22/22	6.4 (SD 0.9)	6.6 (SD 0.8)		<0.05							Decrease	
		Polydextrose	22/22	6.3 (SD 0.9)	6.4 (SD 1.0)		NS							Decrease	
16947		Placebo	22/22	2.1 (SD 1.5)	2.6 (SD 1.6)						Glucose	2 hour AUC, Post test meal (mmol/L/ min)	12 weeks	Decrease	No bias
		Polydextrose	22/22	2.3 (SD 0.9)	2.9 (SD 2.6)		NS							Decrease	No bias
		Pectin	22/22	6.4 (SD 0.5)	6.2 (SD 0.7)									Decrease	
(Wood <i>et al.</i> , 2007) 17236		Low carbohydrate diet + placebo	15/15	5.15 (SD 0.63)	4.87 (SD 0.56)		NS				Glucose	Fasting serum, (mmol/L)	6 weeks	Decrease	No bias
		Low	14/15	5.09 (SD	4.55 (SD		NS	NS						Decrease	

Author/ result number	Sub- group detail	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups at follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
		carbohydrate diet + Soluble fibre (konjac mannan)		0.83)	0.7)										
*17237		Low carbohydrate diet + placebo	15/15	5.15 (SD 0.63)	5.01 (SD 0.56)	-0.14 (SD 0.47)	NS				Glucose		12 weeks	Decrease	No bias
		Low carbohydrate diet + Soluble fibre (konjac mannan)	14/15	5.09 (SD 0.83)	4.8 (SD 0.64)	-0.29 (SD 0.71)	NS	NS				Fasting serum, (mmol/L)		Decrease	

\*This result was used in the meta-analysis of gums and extracts and glycaemia

One paper (Garcia *et al.*, 2006) presented results for fasting blood glucose; however these have not been extracted as they are reported here in another paper (Garcia *et al.*, 2007).

## Insulinaemia and fibre isolates, gums and extracts

No cohort studies provided data on gums and extracts and insulinaemia.

### Summary of RCT results

Seven studies, reported in eight papers, provided data on the relationship between intake of gums and extracts and blood insulin. Three trials were similar in design: Landin *et al.* (Landin *et al.*, 1992), Ryle *et al.* (Ryle *et al.*, 1990) and Garcia *et al.* (Garcia *et al.*, 2007; Garcia *et al.*, 2006) employed a crossover design whereas the other four studies took a parallel group approach. Studies were double blind (4), single blind (1), open (1) or did not report the extent of blinding (1).

All participants were adults who had a mean age of between 26 and 52 years. Four trials were mixed gender, two were studies of males only (Landin *et al.*, 1992; Wood *et al.*, 2007) and one included females only (Pasman *et al.*, 1997a). Those trials that reported BMI generally included participants with BMI  $\geq 25 \text{ kg/m}^2$ . An exception was the study by Ryle *et al.* (Ryle *et al.*, 1990), which used those indicative of a healthy weight (mean BMI = 22  $\text{kg/m}^2$ ).

Sample sizes ranged from 11 to 70 participants, with a mean of 35 participants (median = 30).

Body weight was unaltered in the majority of all trials, yet two studies reported a decrease in weight (Wood *et al.*, 2007) and one a weight increase (Pasman *et al.*, 1997a).

Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

Three studies assessed the effect of guar gum compared to placebo (Landin *et al.*, 1992; Pasman *et al.*, 1997a) or a lower dose of guar gum (Ryle *et al.*, 1990). None of these studies showed changes in insulin between the intervention and control groups.

Pasman *et al.* (Pasman *et al.*, 1997a), for instance, compared a 20g water soluble fibre (guar gum) supplement with no treatment condition for 14 months, following a 2 month very low calorie diet weight loss. At follow-up, no statistically significant differences in insulin were reported.

Similarly, Landin *et al.* (Landin *et al.*, 1992) tested the effects of granulated guar, taken in a glass of water 3 times per day before meals, and a comparable placebo product administered in an identical fashion in 25 middle-aged males. Plasma insulin was not different between diets at follow-up. In addition, a study by Ryle *et al.* (Ryle *et al.*, 1990), which compared a high glucose, low soluble fibre diet (supplemented with 100g glucose/day) to a low glucose, high soluble fibre diet (supplemented with a guar gum preparation), indicated no statistically significant changes either in fasting insulin or insulin 120 minutes after an oral glucose tolerance test between or within groups.

Marett and Slavin (Marett and Slavin, 2004) conducted a 6-month randomised, double-blind, parallel group trial to explore the physiological effects of arabinogalactan (soluble fibre) supplementation from larch or tamarack. Fifty-four subjects were given 8.4g/day placebo (rice starch), 8.4g/day larch arabinogalactan supplement or 8.4g/day tamarack arabinogalactan supplement and instructed to consume this within a beverage or with food. At 2, 3, 4, 5 and 6 months, no statistically significant changes in fasting plasma insulin were observed.

Using a similar design, Schwab *et al.* investigated the effects of a pectin enriched beverage, a polydextrose enriched beverage or an identical placebo product in 70 healthy participants (Schwab *et al.*, 2006). Insulin AUC post test meal at 12 weeks was not statistically significantly different between groups.

The Arabinoxylan and Glucose Metabolism study reported by Garcia *et al.* (Garcia *et al.*, 2007) compared an arabinoxylan supplement with an identical placebo in overweight subjects with impaired glucose tolerance (n=14). Comparison of insulin AUC post meal response indicated a statistically significant decrease following arabinoxylan consumption but not with placebo (p=0.003). No differential effect in fasting insulin between the intervention and control groups was identified.

Finally, one small randomised trial reported fasting insulin at 6 and 12 weeks post-intervention for 30 men that had been randomly allocated to a low carbohydrate diet plus soluble fibre supplement or a low carbohydrate diet plus placebo (Wood *et al.*, 2007). At the 6-week follow-up, participants in both diet groups showed a minor decrease in insulin from baseline and after 12 weeks insulin had increased by 6.6pmol/L and 2.8pmol/L in the low carbohydrate diet plus placebo and low carbohydrate diet plus soluble fibre groups, respectively. These differences, however, did not reach statistical significance.

Collectively, these trials do not provide evidence of a change in blood insulin with an increase in dietary fibre derived from gums and extracts.

Table 4.89 Insulinaemia and fibre isolates, gums and extracts: RCT data

Author/ result number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups at follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
17346 (Garcia <i>et al.</i> , 2007)	Arabinoxylan	11/11	100 (CI 84, 119)	92 (CI 79, 107)			0.471			Insulin	Fasting Geometric mean and standard error, Serum (pmol/L)	6 weeks	No change	unclear
	Placebo	11/11	92 (CI 77, 109)	102 (CI 81, 124)									No change	
17404	Arabinoxylan	11/11		lower			0.003			Insulin AUC post meal response	4 hour AUC, Serum (pmol/L)	6 weeks	No change	unclear
	Placebo	11/11											No change	
17117 (Landin <i>et al.</i> , 1992)	Guar gum minus placebo	Crossover: 25/25						-0.02 (CI - 0.2, 0.17)	NS	Insulin	Fasting Plasma, (pmol/L)	6 weeks	No change in both	No bias
16659 (Marett and Slavin, 2004)	Larch arabinogalactan	18/18	2.45 (SD 1.21)	2.4 (SD 0.96)		NS				Insulin		2 months	No change	No bias
	Placebo	17/17	2.13 (SD 0.9)	2.09 (SD 0.9)		NS					Fasting Plasma, ( $\mu$ U/L)		No change	
	Tamarack arabinogalactan	19/19	2.23 (SD 0.88)	2.14 (SD 0.88)		NS							No change	
16660	Larch arabinogalactan	18/18	2.45 (SD 1.21)	2.37 (SD 0.88)		NS				Insulin		3 months	No change	No bias
	Placebo	17/17	2.13 (SD 0.9)	2.13 (SD 0.9)		NS					Fasting Plasma, ( $\mu$ U/L)		No change	
	Tamarack arabinogalactan	19/19	2.23 (SD 0.88)	2.19 (SD 0.9)		NS							No change	
16661	Larch arabinogalactan	18/18	2.45 (SD 1.21)	2.21 (SD 0.8)		NS				Insulin		4 months	No change	No bias
	Placebo	17/17	2.13 (SD 0.9)	2.23 (SD 1.13)		NS					Fasting Plasma, ( $\mu$ U/L)		No change	
	Tamarack arabinogalactan	19/19	2.23 (SD 0.88)	2.14 (SD 0.87)		NS							No change	
16662	Larch arabinogalactan	18/18	2.45 (SD 1.21)	2.27 (SD 0.81)		NS				Insulin		5 months	No change	No bias
	Placebo	17/17	2.13 (SD 0.9)	2.11 (SD 0.94)		NS					Fasting Plasma, ( $\mu$ U/L)		No change	
	Tamarack arabinogalactan	19/19	2.23 (SD 0.88)	2.28 (SD 1.1)		NS							No change	
16663	Larch arabinogalactan	18/18	2.45 (SD 1.21)	2.30 (SD 0.80)		NS				Insulin	Fasting Plasma, ( $\mu$ U/L)	6 months	No change	No bias
	Placebo	17/17	2.13 (SD 0.9)	2.02 (SD 0.68)		NS							No change	

Author/ result number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups at follow-up	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
	Tamarack arabinogalactan	19/19	2.23 (SD 0.88)	2.30 (SD 0.81)		NS							No change	
15521 (Pasman <i>et al.</i> , 1997a)	Control	11/14				NS				Insulin	Fasting Plasma	14 months	Increase	unclear
	Guar gum - High compliance	10/10				NS	NS						Increase	
	Guar Gum - Low compliance	10/10				NS	NS						Increase	
16198 (Ryle <i>et al.</i> , 1990)	High glucose low soluble fibre	11/11	6 (SD 2)	7 (SD 2)		NS				Insulin	Fasting (mU/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet (guar)	11/11	6 (SD 2)	8 (SD 3)		NS							No change	
16200	High glucose low soluble fibre	11/11	20 (SD 2)	22 (SD 2)		NS				Insulin OGTT (120min)	Plasma (mU/L)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet (guar)	11/11	20 (SD 2)	22 (SD 1)		NS							No change	
16948 (Schwab <i>et al.</i> , 2006)	Pectin	22/22					NS			Insulin	AUC Post test meal	12 weeks	Decrease	No bias
	Placebo	22/22											Decrease	
	Polydextrose	22/22					NS						Decrease	
17238 (Wood <i>et al.</i> , 2007)	Low carbohydrate diet + placebo	15/15	71.1 (SD 14.6)	64.8 (SD 11.8)		NS				Insulin	Fasting (pmol/L)	6 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre (Konjac mannan)	14/15	80.9 (SD 36.4)	79.3 (SD 24.9)		NS	NS						Decrease	
17239	Low carbohydrate diet + placebo	15/15	71.1 (SD 14.6)	77.7 (SD 32.9)	6.6 (SD 32)	NS				Insulin	Fasting (pmol/L)	12 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre (Konjac mannan)	14/15	80.9 (SD 36.4)	83.7 (SD 33)	2.8 (SD 38.2)	NS	NS						Decrease	

One paper (Garcia *et al.*, 2006) presented results for fasting serum insulin, however these have not been extracted as they are reported here in another paper (Garcia *et al.*, 2007).



## Insulin resistance/sensitivity and fibre isolates, gums and extracts

No cohort studies provided data on gums and extracts and insulin resistance/sensitivity.

### Summary of RCT results

One parallel group study conducted in the USA reported data on the effect of gums and extracts on insulin resistance/ sensitivity (Wood *et al.*, 2007). This study reported a decrease in weight in both diet groups. HOMA values measured at 6 weeks were found to have decreased in the low carbohydrate plus placebo and low carbohydrate plus soluble fibre diet groups ( $p=0.05$  for both), but no difference between groups was observed. Measurements of HOMA at 12 weeks also did not show a statistically significant effect within or between treatment groups.

Table 4.90 Insulin resistance/sensitivity and fibre isolates, gums and extracts: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Wood <i>et al.</i> , 2007) 17240	Low carbohydrate diet + placebo	15/15	2.6 (SD 1.2)	2.3 (SD 1)	0.05		Basal state method	HOMA	6 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre	14/15	2.3 (SD 1.1)	2 (SD 0.6)	0.05	NS				Decrease	
17241	Low carbohydrate diet + placebo	15/15	2.6 (SD 1.2)	2.6 (SD 1)	NS		Basal state method	HOMA	12 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre	14/15	2.3 (SD 1.1)	2.3 (SD 0.9)	NS	NS				Decrease	

## Glycosylated blood proteins and fibre isolates, gums and extracts

No cohort studies provided data on gums and extracts and glycosylated blood proteins.

### Summary of RCT results

Three studies explored the effects of gums and extracts on glycosylated blood protein values in adult participants (Ryle *et al.*, 1990; Garcia *et al.*, 2006; Schwab *et al.*, 2006). (Ryle *et al.*, 1990) and (Schwab *et al.*, 2006) were crossover designs: (Ryle *et al.*, 1990) compared a high glucose low soluble fibre diet against a low glucose high soluble fibre diet whereas (Schwab *et al.*, 2006) explored the effects of pectin and polydextrose drinks compared with a placebo drink. The study conducted by Garcia and colleagues (Garcia *et al.*, 2006), on the other hand, used a parallel group design to investigate arabinoxylan, supplied as two bread rolls and in a powder form, compared with a placebo product. The trials tended to have a 6-week (Ryle *et al.*, 1990; Garcia *et al.*, 2006) or 12-week duration (Schwab *et al.*, 2006).

Body weight was unaltered in two trials, yet decreased in the study by Schwab *et al.* (Schwab *et al.*, 2006).

It was not possible to combine these three studies using meta-analysis as follow-up was less than 12 weeks and therefore too short to allow sufficient turn-over of erythrocytes to demonstrate meaningful impact.

In Ryle *et al.* (Ryle *et al.*, 1990), participants (n=11) were randomly allocated to receive a high glucose, low soluble fibre diet or the low glucose, high soluble fibre diet. No statistically significant differences in HbA1c in either intervention group were observed.

Similarly, in Garcia *et al.* (Garcia *et al.*, 2006), comparison of HbA1c values indicated there were no statistically significant differences between the arabinoxylan and pectin diet groups when compared to the placebo group (p=0.962 for arabinoxylan).

Finally, the randomised, parallel double-blinded study by Schwab *et al.* (Schwab *et al.*, 2006) reported the effects of supplementation with either sugar beet pectin or polydextrose compared to a placebo. Log HbA1c, measured at 8 and 12 weeks, did not statistically significantly differ between diet groups. However, when comparing pre-treatment and post-treatment values of log HbA1c at 12 weeks, there was a small but statistically significant reduction in the pectin and polydextrose diet groups (p<0.05 for both).

Whilst these results do not provide evidence of a change in blood insulin with the addition of gums and extracts to the diet, it is worthwhile noting that follow-up in each study was generally less than 12 weeks, thus any possible longer term associations may not have been captured.



Table 4.91 Glycosylated blood proteins and fibre isolates, gums and extracts: RCT data

Study ID/Authors	Intervention group	Completers/Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Garcia <i>et al.</i> , 2006) 17374	Arabinoxylan	11/11	5.8 (CI 5.6, 6)	5.8 (CI 5.6, 5.9)		0.962	HbA1c	Fasting Geometric mean, (%)	6 weeks	No change	unclear
	Placebo	11/11	5.6 (CI 5.4, 5.8)	5.7 (CI 5.5, 5.9)						No change	
	Pectin	22/22	5.7 (SD 0.4)	5.8 (SD 0.3)		NS					
(Ryle <i>et al.</i> , 1990) 16196	High glucose low soluble fibre	11/11	6.1 (SD 0.4)	6.0 (SD 0.5)			HbA1c	Plasma (%)	6 weeks	No change	unclear
	Low glucose high soluble fibre diet (Guar)	11/11	6.1 (SD 0.4)	5.9 (SD 0.3)						No change	
(Schwab <i>et al.</i> , 2006) 16482	Pectin	22/22	5.7 (SD 0.4)	5.9 (SD 0.4)		NS	Log HbA1c	Fasting Whole blood, (%)	8 weeks	Decrease	No bias
	Placebo	22/22	6 (SD 0.6)	6.0 (SD 0.5)						Decrease	
	Polydextrose	22/22	5.9 (SD 0.5)	6.1 (SD 0.6)		NS				Decrease	
16483	Pectin	22/22	5.7 (SD 0.4)	5.8 (SD 0.4)	<0.05	NS	Log HbA1c	Fasting Whole blood, (%)	12 weeks	Decrease	No bias
	Placebo	22/22	6 (SD 0.6)	6.0 (SD 0.5)	NS					Decrease	
	Polydextrose	22/22	5.9 (SD 0.5)	6.1 (SD 0.7)	<0.05	NS				Decrease	

N.b. HbA1c results which report follow up at <12 weeks are shaded in grey as such durations are too short to allow sufficient turn-over of erythrocytes

# Starch

## Insulinaemia and starch

One cohort study provided evidence on starch intake and insulinaemia (Marshall *et al.*, 1997). The San Luis Valley Diabetes Study (Marshall *et al.*, 1997) was from the USA, and was a multi-ethnic cohort with participants of normal glucose tolerance. This study assessed the effect of changes in total starch intake against fasting plasma insulin levels. A significant inverse association was seen between starch intake and fasting insulin levels. For each 10g/d starch increment consumed at baseline, fasting insulin was lower by 1% at follow-up.

Meta-analysis of these data was not possible with just one study presenting data.

### Exposure definition and assessment

Starch intake was assessed using a 24-hour recall administered by bi-lingual interviewers.

### Adjustment for appropriate confounders

Appropriate confounders were included in the adjustments.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning starch and insulinaemia.

Table 4.92 Insulinaemia and starch: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	n	Follow Up (% loss)	Diet Assess ment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P Trend	Adjustments
13092 (Marshall <i>et al.</i> , 1997) San Luis Valley Diabetes Study	USA, Multi- ethnic, Normal glucose tolerance	20-74 (52) %M 46.8	1069	4.3 years (26)	Dietary recall	Starch, total	Blood insulin Fasting, Plasma	10 g/day	Regression direction negative, beta not reported. For each 10g/d, insulin was lower by 1% at follow-up	0.0007	age, waist, BMI, energy intake, ethnicity, physical activity, Gender

## Glycosylated blood proteins and starch

### Summary of cohort results

In the Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006), 813 adults underwent a baseline examination and then returned for a 5-year follow-up examination. Diet was assessed by FFQ at both time points (data are included here only for the prospective analysis). Starch intake at baseline was not associated with HbA1c levels at follow-up in any of the models presented in the paper.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning starch and glycosylated blood proteins.

Table 4.93 Glycosylated blood proteins and starch: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
13886 (Mayer- Davis <i>et al.</i> , 2006) Insulin Resistance Athero- sclerosis Study	USA, Multi- ethnic, Not diabetic	40-69 (55) %M: 43.5	1625	5.2 years (19)	FFQ (114)	Starch, total	HbA1c Plasma	1 SD of mean exposure	-0.01 (0.05)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking

## Fibre isolates, beta-glucan

Beta-glucan is a viscous soluble polysaccharide that occurs in the endosperm cell walls of grains. It is composed of glucose molecules with mixed  $\beta$ -(1→4) and  $\beta$ -(1→3) bonds. Oats and barley are recognised as particularly rich sources. Considerable variation in the amount of beta-glucans in oats and oat products exists which is due to varietal and processing influences. Commercial rolled oats may contain in the region of 3-5% beta-glucan and oat bran between 6-10% (Wursch and Pi-Sunyer, 1997). The majority of the studies explored the effects of whole oats, oat bran-supplemented foods or oat-based breakfast cereals compared with similar wheat-based test foods. However, Smith *et al.* (Smith *et al.*, 2008) used beta-glucans derived from barley and one study by Chen *et al.* (Chen *et al.*, 2006) compared wheat and corn.

## Glycaemia and fibre isolates, oat beta-glucan

No cohort studies provided data on oat beta-glucan and glycaemia.

### Summary of RCT results

Four trials provided data on oat beta-glucan consumption and blood glucose (Smith *et al.*, 2008;Chen *et al.*, 2006;Maki *et al.*, 2007a;Saltzman *et al.*, 2001). All implemented a parallel group design and were conducted in the USA.

Three trials were double blind. The remaining study by Saltzman *et al.* (Saltzman *et al.*, 2001) was unclear regarding the extent of blinding.

All studies used adults as participants and were mixed gender. Sample sizes of trials ranged from 43 to 110 participants, with a mean sample size across all trials of 85. The median number of participants was 94. In the studies that reported average BMI, participants were either overweight or obese.

Body weights remained unchanged in Maki *et al.* (Maki *et al.*, 2007a). The low fibre group in the study by Chen *et al.* (Chen *et al.*, 2006) and the low molecular weight beta-glucan group in Smith *et al.* (Smith *et al.*, 2008) experienced a weight increase. The authors in Saltzman *et al.* (Saltzman *et al.*, 2001) however reported weight loss in both study groups.

Four studies providing dietary differences in beta-glucans intake between groups were included in the meta-analysis. Definitions of different levels of beta-glucans are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were appropriately converted. The first follow up reported at the end of the intervention was used. This varied from 6 weeks to 12 weeks. The overall pooled estimate indicated that fasting blood glucose was 0.08mmol/L (95% CI, -0.06 to 0.21) higher with consumption of a diet low in beta-glucans but this was not significantly different from zero ( $p=0.25$ ). Heterogeneity denoted by  $I^2$  was 0% (95% CI, 0 to 60). No funnel plot was carried out due to the small number of studies. Statistically, there was no strong evidence of a difference in fasting blood glucose with differences in consumption of beta-glucans.



Figure 4.35 Forest plot for fibre isolates, beta glucan and fasting blood glucose (mmol/L)

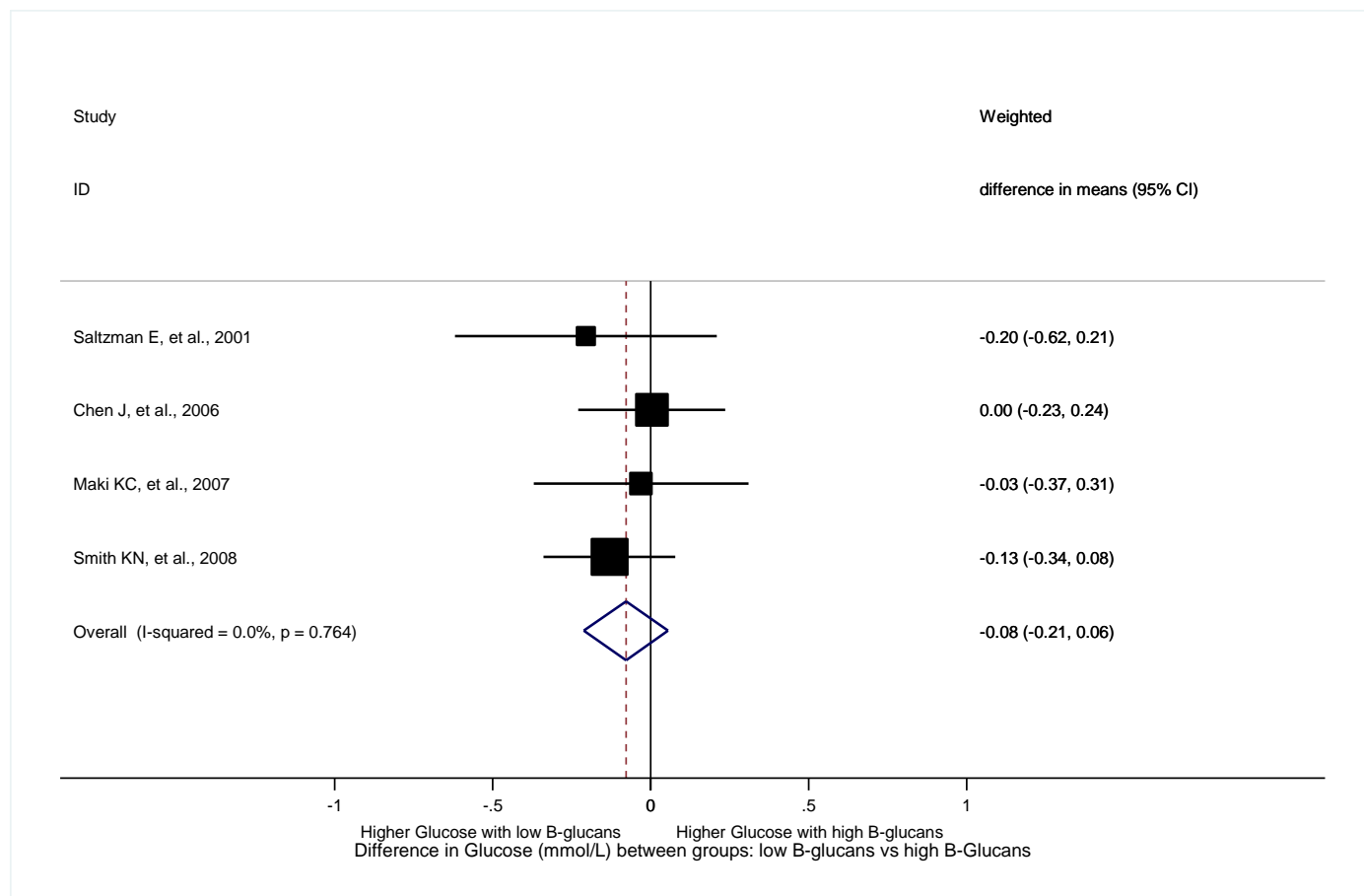


Table 4.94 Glycaemia and fibre isolates, beta-glucan: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Chen <i>et al.</i> , 2006) *17178	High fibre minus low fibre	ITT analysis: High fibre:56/56 Low fibre: 54/54						0.07 (CI - 4.16, 4.29)	Glucose	Fasting serum, (mg/dL)	12 weeks	No change in high fibre group, small increase in low fibre group (-0.7kg)	No bias
17185	High fibre	54/54			-0.74 (CI -3.43, 1.95)				Glucose	Fasting (mg/dL)	12 weeks	No change	No bias
	Low fibre	56/56			-0.81 (-4.11, 2.49)							Small increase	
(Maki <i>et al.</i> , 2007a) *15057	Oat beta-glucan cereal	26/26	5.48 (SE 0.13)	5.62 (SE 0.22)	0.08 (SE 0.16)		0.899		Glucose	Fasting plasma, (mmol/L)	12 weeks	No change	No bias
	Wheat cereal	34/34	5.43 (SE 0.09)	5.48 (SE 0.09)	0.11 (SE 0.09)							No change	
(Saltzman <i>et al.</i> , 2001) *16189	Control	21/21	4.82 (SD 0.38)		-0.005 (SD 0.9)				Glucose	Fasting plasma, (mmol/L)	6 weeks	Decrease	unclear
	Oats	20/22	4.82 (SD 0.38)		-0.21 (SD 0.29)	NS						Decrease	
(Smith <i>et al.</i> , 2008) *16560	High molecular weight Beta glucan	45/45			-0.21 (SE 0.08)	NS	0.2		Glucose	Fasting (mmol/L)	6 weeks	No change	No bias
	Low molecular weight Beta glucan	45/45			-0.08 (SE 0.07)	NS						Increase	

\*This result was used in the meta-analysis of oat beta-glucans and glycaemia

## Insulinaemia and fibre isolates, beta-glucan (oats and barley)

No cohort studies provided data on beta-glucan (oat and barley) and insulinaemia.

### Summary of RCT results

Four trials provided data concerning oat beta-glucan consumption and blood insulin (Smith *et al.*, 2008; Chen *et al.*, 2006; Maki *et al.*, 2007a; Saltzman *et al.*, 2001). All implemented a parallel group design and were conducted in the USA.

Three trials were double blind and one simply did not record the extent of blinding.

All studies used adults as participants and were mixed gender. Sample sizes of trials ranged from 14 to 110 participants. Of the studies that reported average BMI, participants fell into the overweight or obese categories.

Body weights were unchanged in one of the trials, although weight gain was evident in the low fibre group in the study by Chen *et al.* (Chen *et al.*, 2006) and the low molecular weight beta-glucan group in Smith *et al.* (Smith *et al.*, 2008). The authors in Saltzman *et al.* (Saltzman *et al.*, 2001) however reported weight loss.

Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

Maki *et al.* (Maki *et al.*, 2007a) and Saltzman *et al.* (Saltzman *et al.*, 2001) both investigated oats or oat-derived beta-glucans yet neither study showed statistically significant changes in fasting blood insulin. In the double blind, parallel group trial conducted by Maki *et al.* (Maki *et al.*, 2007a), 97 males and females with elevated blood pressure were randomly allocated to receive a ready-to-eat cold oatbran cereal (oatmeal and a powdered form of oat beta-glucan) or a low fibre cold wheat-based ready-to-eat cereal (a low fibre hot cereal and a control maltodextrin powder). Changes between baseline and follow-up did not differ markedly between groups and as such, these changes did not reach statistical significance. One other trial conducted by Saltzman *et al.* (Saltzman *et al.*, 2001) compared the effects of a hypocaloric diet that incorporated 45g dry weight of oats per day and a control hypocaloric diet in a sample of males and females (n=43). Similarly, the authors did not find a differential effect on plasma insulin in this trial.

Smith *et al.* (Smith *et al.*, 2008) compared the effect of high or low molecular weight beta-glucan supplements derived from barley on cardiovascular biomarkers and appetite for breakfast, lunch or dinner over a 6-week period (Smith *et al.*, 2008). There were no statistically significant differences in fasting insulin within or between groups following the intervention (Smith *et al.*, 2008). Likewise, the study which explored a high fibre diet composed of oats and a low fibre diet consisting of wheat and corn, did not find changes in insulin over the 12 week period (Chen *et al.*, 2006). These studies collectively show that high beta-glucan diets do not impact on blood insulin when compared to low beta-glucan diets.

Table 4.95 Insulinaemia and fibre isolates, beta-glucan (oats and barley): RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups in $\Delta$ from baseline	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
17179 (Chen <i>et al.</i> , 2006)	High fibre minus low fibre	ITT analysis: High fibre:56/56 Low fibre: 54/54						-2.19 (CI -5.84, 1.45)	Insulin	Fasting ( $\mu$ U/ml)	12 weeks	No change in high fibre group, small increase in low fibre group	No bias
17186	High fibre	54/54			-0.12 (CI -1.94, 1.7)				Insulin	Fasting ( $\mu$ U/ml)	12 weeks	No change	No bias
	Low fibre	56/56			2.08 (CI -1.07, 5.21)							Small increase	
15058 (Maki <i>et al.</i> , 2007a)	Oat beta-glucan cereal	26/26	70.2 (SE 6.3)	72.9 (SE 7)	2.8 (SE 4.9)		0.825		Insulin	Fasting Plasma, (pmol/L)	12 weeks	No change	No bias
	Wheat cereal	34/34	88.2 (SE 13.9)	86.1 (SE 19.5)	-1.4 (SE 12.5)							No change	
16190 (Saltzman <i>et al.</i> , 2001)	Control	21/21	115.5 (SD 48.1)		-9.3 (SD 46.7)				Insulin	Fasting Plasma, (pmol/L)	6 weeks	Decrease	unclear
	Oats	20/22	127.7 (SD 36.6)		-28.7 (SD 26.5)	NS						Decrease	
16561 (Smith <i>et al.</i> , 2008)	High molecular weight Beta glucan	45/45			-2.6 (SE 2.9)	NS	0.15		Insulin	Fasting (pmol/L)	6 weeks	No change	No bias
	Low molecular weight Beta glucan	45/45			3.4 (SE 2.8)	NS						Increase	

## Insulin resistance/sensitivity and fibre isolates, oat beta-glucan

No cohort studies provided data on oat beta-glucan and insulin resistance/sensitivity.

### Summary of RCT results

Consumption of an oat based diet did not statistically significantly alter HOMA-IR or insulin sensitivity index over a 6-week intervention period in one small USA randomised controlled trial (Saltzman *et al.*, 2001).

Table 4.96 Insulin resistance/sensitivity and beta-glucans (oat): RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Within group Δ from baseline	p-value Within group Δ from baseline	Outcome/ Assessment method	Result/ Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Saltzman <i>et al.</i> , 2001) 16191	Control	21/21	3.8 (SD 2.5)	-0.5 (SD 2.1)	NS	Basal state method	Fasting HOMA-IR (mmol/LμU/ml)	6 weeks	Decrease	unclear
	Oats	20/22	4.2 (SD 1.4)	-1.1 (SD 1.2)					Decrease	
16192	Control	21/21	3.5 (SD 1.3)	0.5 (SD 1.2)	NS	Dynamic/Basal state methods	Insulin sensitivity index (mg/dLμU/ml)	6 weeks	Decrease	unclear
	Oats	20/22	3.3 (SD 1.6)	0.6 (SD 1)					Decrease	

# Total cereals

## Impaired glucose tolerance and total cereals

### Summary of cohort results

In the Zutphen Elderly Study, of 175 initially normoglycaemic individuals, there was no difference in baseline consumption of total cereals in participants who developed impaired glucose tolerance after 4 years of follow-up compared to those remained glucose tolerant (Feskens et al., 1991).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning total cereals and impaired glucose tolerance.

Table 4.97 Impaired glucose tolerance and total cereals: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Mean exposure (SD)
13890 (Feskens <i>et al.</i> , 1991) Zutphen Elderly Study	The Netherlands	(70)  %M 100	(59) /175	4 years	Dietary history	Cereals, total	Impaired glucose tolerance  Clinic tested	g/day	Cases: (n: 59) 7.2 (9.2) Non-cases: (n: 116) 8 (11)

## Glycaemia and total cereals

### Summary of cohort results

One study, the Finnish and Dutch cohorts of the Seven Countries Study (Feskens *et al.*, 1995), provided evidence concerning total cereal intake and blood glucose levels following a 2-hour oral glucose tolerance test. Cereal intake was presented as total intake at baseline or change in intake, over 20 years follow up. There was no evidence of a statistically significant association between total cereal intake and glycaemia.

With just one study reporting data, meta-analysis was not possible.

### Exposure definition and assessment

Total and change in cereal intake was assessed using a dietary history.

### Adjustment for appropriate confounders

Some adjustments were included.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning total cereals and glycaemia.

Table 4.98 Glycaemia and total cereals: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assess- ment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14650 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59 %M 100	338	20 years	Dietary history	Cereals, total	Blood glucose (OGTT 120 min)  Fasting	1 g/ 1000 kcal	-0.004 (0.008)	NS	age, BMI, Cohort, energy intake
14696 Seven Countries Study						Cereals (change in consumption)	Blood glucose (OGTT 120 min)  Fasting	1 g/ 1000kcal	0.001 (0.006)	NS	age, BMI, Baseline Exposure, Cohort, energy intake



# Breakfast cereals

## Glycaemia and breakfast cereals

No cohort studies provided data on breakfast cereals and glycaemia.

### Summary of RCT results

One parallel group study (Zaveri and Drummond, 2009) compared the effects of a conventional cereal bar snack (30g weight; high in carbohydrate) or a control (no snack) on energy intake and other aspects of eating behaviour in 36 healthy males. The intervention was administered through the provision of two cereal bars per day, which could be consumed at any time. Body weight was unaltered throughout the trial. Overall, there were no statistically significant differences between or within groups in fasting glucose.

Table 4.99 Glycaemia and breakfast cereals: RCT data

Results Number	Intervention group	Completers/ Allocated	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Zaveri and Drummond, 2009) 16924	Cereal bar	13/14	NS	NS	Glucose	Fasting	12 weeks	No change	unclear
	Control	12/13	NS		Glucose			No change	

## Insulinaemia and breakfast cereals

No cohort studies provided data on breakfast cereals and insulinaemia.

### Summary of RCT results

One Scottish parallel group study (Zaveri and Drummond, 2009) did not show statistically significant differences within or between groups in fasting insulin.

Table 4.100 Insulinaemia and breakfast cereals: RCT data

Authors/ result number	Intervention group	Completers/ Allocated	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Results/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
16925 (Zaveri and Drummond, 2009)	Cereal bar	13/14	NS	NS	Insulin	Fasting	12 weeks	No change	unclear
	Control	12/13	NS					No change	

# Potatoes

## Impaired glucose tolerance and potatoes

### Summary of cohort results

In the Zutphen Elderly Study, of 175 initially normoglycaemic individuals, there was no difference in baseline consumption of potatoes in participants who developed impaired glucose tolerance after 4 years of follow-up compared to those remained glucose tolerant (Feskens et al., 1991).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning potatoes and impaired glucose tolerance.

Table 4.101 Impaired glucose tolerance and potatoes: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Mean exposure (SD)
13889 (Feskens <i>et al.</i> , 1991) Zutphen Elderly Study	The Netherlands	(70) %M 100	(59) /175	4 years	Dietary history	Potatoes	Impaired glucose tolerance  Clinic tested	g/day	Cases: (n: 59) 174.8 (97.7) Non-cases: (n: 116) 181.5 (97.9)

# Glycaemia and potatoes

## Summary of cohort results

One study, the Finnish and Dutch cohorts of the Seven Countries Study (Feskens *et al.*, 1995) provided evidence concerning potatoes intake and blood glucose levels following a 2-hour oral glucose tolerance test. Potato intake was presented as total at baseline or change in intake over 20 years of follow up. There was no evidence of a statistically significant association between potatoes intake at baseline and glycaemia. However, increasing potato intake over 20 years was statistically significantly associated with lower blood glucose levels.

With just one study presenting data, meta-analysis was not possible.

## Exposure definition and assessment

Total and change in potato intake was assessed using a dietary history.

## Adjustment for appropriate confounders

The model included age, BMI and energy intake.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

## Summary of RCT results

No RCTs reported outcomes concerning potatoes and glycaemia.

Table 4.102 Glycaemia and potatoes: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
14651 (Feskens <i>et al.</i> , 1995) Seven Countries Study	Holland & Finland, Primarily White	40-59  %M 100	338	20 years	Dietary history	Potatoes	Blood glucose (OGTT 120 min)  Fasting	1 g/1000 kcal	-0.005 (0.005)	NS	age, BMI, Cohort, energy intake
14697 Seven Countries Study						Potatoes, change in intake	Blood glucose (OGTT 120 min)  Fasting	1 g/1000 kcal	-0.008 (0.004)	<0.05	age, BMI, Baseline Exposure, Cohort, energy intake

# Legumes

## Impaired glucose tolerance and legumes

### Summary of cohort results

In the Zutphen Elderly Study, of 175 initially normoglycaemic individuals, the risk of becoming glucose intolerant was significantly reduced in the highest consumers of legumes compared to the lowest consumers (RR 0.4 95%CI: 0.18-0.9) (Feskens et al., 1991).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning legumes and impaired glucose tolerance.

Table 4.103 Impaired glucose tolerance and legumes: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	RR (95% CI)	Adjustme nts
13911 (Feskens <i>et al.</i> , 1991) Zutphen Elderly Study	The Netherlands	(70) %M 100	(59) /175	4 years	Dietary history	Legumes	Impaired glucose tolerance  Clinic tested	High vs. Low	0.4 (0.18, 0.9)	age, alcohol, BMI, energy intake, gender, smoking

## Glycaemia and legumes

No cohort studies provided data on legumes and glycaemia.

### Summary of RCT results

Two randomised controlled trials provided data concerning the effect of high legume diets on glucose levels (Crujeiras *et al.*, 2007; Nestel *et al.*, 2004). As there were insufficient studies, it was not possible to undertake a meta-analysis.

Body weights decreased or were not reported in the studies by (Crujeiras *et al.*, 2007) and (Nestel *et al.*, 2004) respectively.

In the study by Crujeiras *et al.* (Crujeiras *et al.*, 2007), 30 obese subjects were randomly allocated to receive a hypocaloric diet with consumption of non-soybean legumes 4 days/week or a hypocaloric diet without legumes (control). Both the hypocaloric diet with legumes and the hypocaloric diet without legumes aimed to supply 20% energy as proteins, 50% energy as carbohydrates and 30% energy as lipids. Consumption of legumes 4 days/week when incorporated into a hypocaloric diet did not influence glucose values as compared to a standard hypocaloric diet.

Nestel *et al.* (Nestel *et al.*, 2004) explored the effects of consumption of chickpea-based or wheat-based foods on glucose values of 21 subjects in this crossover trial. The trial lasted 6 weeks, during which all food was provided. No statistically significant differences in fasting values of glucose or 2-hour post-glucose-load values of glucose between diet groups were reported.

Table 4.104 Glycaemia and legumes: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Crujeiras <i>et al.</i> , 2007) 16944	Hypocaloric control diet	15/15	95 (SD 8)		NS		Glucose	Fasting (mg/dL)	8 weeks	Decrease	unclear
	Hypocaloric diet + legumes	15/15	95 (SD 8)		NS	NS				Decrease	
(Nestel <i>et al.</i> , 2004) 15329	Chickpea based foods	19/21	5.2 (SD 0.4)	4.9 (SD 0.4)			Glucose	Fasting plasma, (mmol/L)	6 weeks	Not reported	unclear
	Wheat based foods	19/21	5.2 (SD 0.4)	5.1 (SD 0.5)						Not reported	
15330	Chickpea based foods	19/21	5 (SD 2)	4.4 (SD 1.7)			Glucose (OGTT 120 min)	Plasma (mmol/L)	6 weeks	Not reported	unclear
	Wheat based foods	19/21	5 (SD 2)	4.4 (SD 1.5)						Not reported	



## Insulinaemia and legumes

No cohort studies provided data on legumes and insulinaemia.

### Summary of RCT results

Two trials provided data on the effect of legume intake on blood insulin in adults (Nestel *et al.*, 2004; Crujeiras *et al.*, 2007). In the study by Nestel *et al.* (Nestel *et al.*, 2004), the authors concluded that fasting insulin and blood insulin following OGTT did not statistically significantly differ between the two groups.

Similarly, in the parallel group trial conducted by Crujeiras *et al.* (Crujeiras *et al.*, 2007), no statistically significant differences in fasting insulin by the addition of legumes to a hypocaloric diet within or between diet groups were observed.

Table 4.105 Insulinaemia and legumes: RCT data

Authors/ result number	Intervention group	Completers / Allocated	Baseline	Follow- up	p-value Within group $\Delta$ from baseline	p-value differenc e between groups	Outcome/ Assessment method	Results/ Outcome details	Result- specific follow- up	Weight Change	Out- come Assessm ent Bias
16945 (Crujeiras <i>et al.</i> , 2007)	Hypocaloric control diet	15/15	9.42 (SD 7.9)		NS		Insulin	Fasting ( $\mu$ U/ml)	8 weeks	Decrease	unclear
	Hypocaloric diet + legumes	15/15	9.42 (SD 7.9)		NS	NS				Decrease	
15331 (Nestel <i>et al.</i> , 2004)	Chickpea based foods	19/21	6.6 (SD 3.6)	7.9 (SD 4.5)			Insulin	Fasting Plasma, (mU/L)	6 weeks	Not reported	unclear
	Wheat based foods	19/21	6.6 (SD 3.6)	8.2 (SD 4.7)						Not reported	
15332	Chickpea based foods	19/21	30.2 (SD 29)	30.6 (SD 29.9)			Insulin OGTT (120min)	Plasma (mU/L)	6 weeks	Not reported	unclear
	Wheat based foods	19/21	30.2 (SD 29)	27.6 (SD 18.4)						Not reported	

## Insulin resistance/sensitivity and legumes

No cohort studies provided data on legumes and insulin resistance/sensitivity.

### Summary of RCT results

Nestel *et al.* (Nestel *et al.*, 2004) explored the effects of consumption of chickpea-based or wheat-based foods on glucose values of 21 subjects in this trial. Overall, fasting values for HOMA and post-glucose-load values for HOMA were not statistically significant different between the two diet groups in this study.

Table 4.106 Insulin resistance/sensitivity and legumes: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow-up	Outcome/ Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Nestel <i>et al.</i> , 2004) 15333	Chickpea based foods	19/21	1.6 (SD 0.9)	1.8 (SD 1.2)	Basal state method	Fasting HOMA, (index)	6 weeks	Not reported	unclear
	Wheat based foods	19/21	1.6 (SD 0.9)	1.9 (SD 1.2)				Not reported	
15334	Chickpea based foods	19/21	7.8 (SD 9.4)	7.4 (SD 10.2)	Basal state method	HOMA Post glucose load, (index)	6 weeks	Not reported	unclear
	Wheat based foods	19/21	7.8 (SD 9.4)	5.9 (SD 4.9)				Not reported	



# Rice

## Glycaemia and rice

### Summary of cohort results

No cohort studies provided data on rice and glycaemia.

### Summary of RCT results

One Korean trial compared the effect of brown and black rice meal replacements against white rice meal replacements on fasting glucose (Kim *et al.*, 2008). Participants were randomised to receive either of the above treatments, with both groups following an energy-restricted diet (257.1-258.6 kJ/d). As such, body weights decreased accordingly. All food was provided. During the 6-week treatment period, no statistically significant differences in blood glucose values between the two groups were observed.

Table 4.107 Glycaemia and rice: RCT data

Results Number	Intervention group	Completers/Allocated	Baseline	Follow-up	p-value difference between groups	Outcome/Assessment method	Result/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Kim <i>et al.</i> , 2008) 16766	Brown & black rice meal replacement	20/23	84.93 (SD 2.76)	76.73 (SD 1.01)	NS	Glucose	Fasting (mg/dL)	6 weeks	Decrease	unclear
	White rice meal replacement	20/24	83.0 (SD 2.13)	77.28 (SD 0.9)					Decrease	

# Insulinaemia and rice

## Summary of cohort results

No cohort studies provided data on rice and insulinaemia.

## Summary of RCT results

One Korean trial (Kim *et al.*, 2008) reported no difference in fasting insulin between dietary groups.

Table 4.108 Insulinaemia and rice: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow- up	p-value difference between groups	Outcome	Results/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Kim <i>et al.</i> , 2008) 16768	Brown & black rice meal replacement	20/23	7.53 (SD 0.9)	6.45 (SD 0.57)	NS	Insulin	Fasting (µIU/ml)	6 weeks	Decrease	unclear
	White rice meal replacement	20/24	7.99 (SD 1.25)	6.73 (SD 0.92)					Decrease	

# Bread

## Impaired glucose tolerance and bread

### Summary of cohort results

In the Zutphen Elderly Study, of 175 initially normoglycaemic individuals, there was no difference in baseline consumption of bread in participants who developed impaired glucose tolerance after 4 years of follow-up compared to those who remained glucose tolerant (Feskens et al., 1991).

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

No RCTs reported outcomes concerning bread and impaired glucose tolerance.

Table 4.109 Impaired glucose tolerance and bread: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Mean exposure (SD)
13875 (Feskens et al., 1991) Zutphen Elderly Study	The Netherlands	(70)  %M 100	(59) /175	4 years	Dietary history	Bread, unspecified	Impaired glucose tolerance  Clinic tested	g/day	Cases: (n: 59) 136.9 (54.7) Non-cases: (n: 116) 143.1 (58.3)

# Wholegrain

## Glycaemia and wholegrain

### Summary of cohort results

No cohort studies provided data on wholegrain and glycaemia.

### Summary of RCT results

Four studies, reported in five papers, provided data on the effects of wholegrain intake on blood glucose (Andersson *et al.*, 2007;Kim *et al.*, 2008;Howard *et al.*, 2006;Tinker *et al.*, 2008;Saltzman *et al.*, 2001). Trials were conducted in the USA (2), Sweden (1) and Korea (1). All took parallel group approaches, except the study by Andersson *et al.* (Andersson *et al.*, 2007) which used a crossover design. One study was single blind (Howard *et al.*, 2006;Tinker *et al.*, 2008); the others either did not provide information regarding blinding or were open.

With the exception of the large Women's Health Initiative Dietary Modification Trial (sample size= 5.8% subsample of 48,835) (Howard *et al.*, 2006;Tinker *et al.*, 2008), sample sizes were relatively small with 34, 43 and 47 participants (Andersson *et al.*, 2007;Saltzman *et al.*, 2001;Kim *et al.*, 2008). Participants were all adults and mean BMI was less than 30kg/m<sup>2</sup>. Kim *et al.* (Kim *et al.*, 2008) did not provide mean BMI.

Interventions were somewhat mixed as they compared single wholegrain products such as oats with wheat or white vs. black rice (Kim *et al.*, 2008;Saltzman *et al.*, 2001) or diets consisting of a range of different grain-based products in whole or refined state (Andersson *et al.*, 2007;Howard *et al.*, 2006;Tinker *et al.*, 2008). It should be noted that the difference in wholegrain intake between the groups in the latter study was very small (difference of 0.3 servings per day at one year, and 0.2 at 6 years).

Studies differed considerably in terms of body weight changes. Body weight increased in one of the trials (Andersson *et al.*, 2007). Three studies, except a control group in one (Howard *et al.*, 2006;Tinker *et al.*, 2008), reported a weight decrease in participants.

Finally, papers by Howard (Howard *et al.*, 2006) and Tinker (Tinker *et al.*, 2008) are from the same study. Results from Howard *et al.* (Howard *et al.*, 2006) are included here in the meta-analysis.

Four studies providing dietary differences in wholegrain intake between groups were included in the meta-analysis. All studies included adults as participants. Definitions of different levels of wholegrain foods are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were appropriately converted. The first follow up reported at the end of the intervention was used. This varied from 6 weeks to 6 years. The overall pooled estimate indicated that fasting blood glucose was 0.05mmol/L (95% CI, -0.02 to 0.12) higher with consumption of a diet low in wholegrain but this was not significantly different from zero (p=0.14). Heterogeneity denoted by  $I^2$  was 0% (95% CI, 0 to 61). One study with over 1000 participants contributed 75% to the pooled estimate (Howard *et al.*, 2006). No funnel plot was carried out due to the small number of studies. Statistically, there was no evidence of a difference in fasting blood glucose with differences in consumption of wholegrain foods.

Figure 4.36 Forest plot for wholegrain and fasting blood glucose (mmol/L)

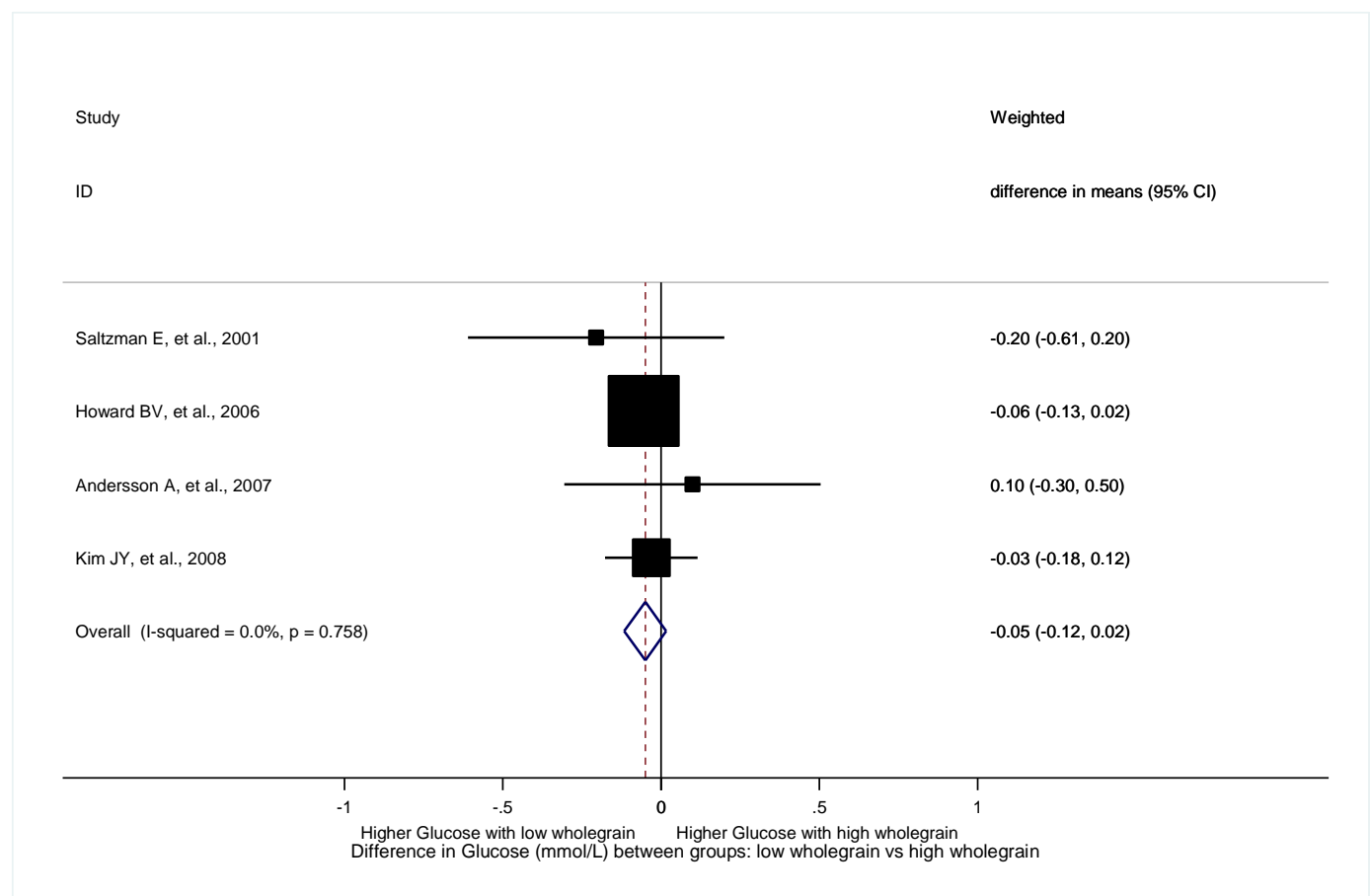


Table 4.110 Glycaemia and wholegrain: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups in $\Delta$ from baseline	Outcome/ Assessment method	Result/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Andersson <i>et al.</i> , 2007) *14021	Refined grain products	30/30	5.2 (SD 0.9)	5.2 (SD 0.8)		NS			Glucose	Fasting (mmol/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	5.2 (SD 0.8)	5.3 (SD 0.8)		NS	0.28					Small increase	
(Howard <i>et al.</i> , 2006) *16252	Control	approx 1699 participants included as a 5.8% sub- sample of 29294 in group	100.0 (SD 26.9)	99.5 (SD 27.3)	-0.7 (SD 21.6)				Glucose	Fasting (mg/dL)	3 years	No change	No bias
	Low fat	approx 1132 participants included as a 5.8% sub- sample of 19541 in group	100.4 (SD 26.6)	98.8 (SD 25.6)	-1.7 (SD 19.9)		NS					Decrease	
17619	Low fat minus control	Low fat: approx 1132 participants included as a 5.8% sub-sample of 19541 in group Control: approx 1699 participants included as a 5.8% sub-sample of 29294 in group						-1.06 (CI - 3.06, 0.93)	Glucose	Fasting (mg/dL)	3 years	No change in control group, decrease in low fat group	No bias
(Kim <i>et al.</i> , 2008) *16766	Brown & black rice meal replacement	20/23	84.93 (SD 2.76)	76.73 (SD 1.01)			NS		Glucose	Fasting (mg/dL)	6 weeks	Decrease	unclear
	White rice meal replacement	20/24	83.0 (SD 2.13)	77.28 (SD 0.9)								Decrease	
(Saltzman <i>et al.</i> , 2001) *16189	Control	21/21	4.82 (SD 0.38)		-0.005 (SD 0.9)				Glucose	Fasting plasma, (mmol/L)	6 weeks	Decrease	unclear
	Oats	20/22	4.82 (SD 0.38)		-0.21 (SD 0.29)	NS						Decrease	
(Tinker <i>et al.</i> , 2008) 15372	Control	1366/29294	94.6 (SD 12.5)	94.3 (SD 13.4)					Glucose	Fasting serum, (mg/dL)	1 year	No change	unclear
	Low fat diet	915/19541	94.4 (SD 14.9)	92.4 (SD 10.9)			0.001					Decrease	
15373	Control	1165/29294	94.6 (SD 12.5)	96.2 (SD 15.6)					Glucose	Fasting serum, (mg/dL)	6 years	No change	unclear
	Low fat diet	760/19541	94.4 (SD 14.9)	96.6 (SD 15.5)			NS					Decrease	

\*This result was used in the meta-analysis of wholegrain and glycaemia

## Insulinaemia and wholegrain

### Summary of cohort results

No cohort studies provided data on wholegrain and insulinaemia.

### Summary of RCT results

Four studies, reported in five papers, provided data on the effects of wholegrain intake on blood insulin (Andersson *et al.*, 2007; Kim *et al.*, 2008; Howard *et al.*, 2006; Tinker *et al.*, 2008; Saltzman *et al.*, 2001). These four also reported on fasting glucose; therefore a summary of the randomised controlled trials are not presented here but in the glycaemia and wholegrain section.

Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

The Women's Health Initiative Randomized Controlled Dietary Modification Trial was designed to test the hypothesis that a low fat, high fruit and vegetable, high grain diet would reduce the risk of cardiovascular disease in middle-aged and older women (Howard *et al.*, 2006; Tinker *et al.*, 2008). The goal of the dietary intervention was to decrease total fat to 20% of energy intake, to increase fruit and vegetable portions to 5 or more per day and to increase servings of grains to a minimum of 6 per day. This was implemented through a behavioural modification program that ran intensively throughout the first year of the trial and then less intensively thereafter. Fasting insulin results are reported here at three years from baseline randomisation. The low fat intervention did not statistically significantly alter insulin compared with the control group. However, it is important to note that compliance with the goal to increase wholegrain was only partially achieved. The difference in wholegrain intake between the groups in this study was very small (difference of 0.3 servings per day at one year, and 0.2 at 6 years).

In their study, Saltzman *et al.* (Saltzman *et al.*, 2001) compared the effects of a hypocaloric diet plus 45g dry weight of oats – which equated to approximately 1.5 servings of oatmeal - and a control hypocaloric diet in a sample of males and females (n=43). No statistically significant changes in insulin from baseline were recorded.

Using a crossover design, Andersson *et al.* (Andersson *et al.*, 2007) also explored the effects of a diet rich in whole grains or a diet containing refined grains on fasting insulin using 34 overweight and obese participants. Participants were instructed to consume the intervention food products as part of a free living diet plan. After 6 weeks, the authors concluded that the dietary intervention had not affected insulin within or between groups ( $p=0.47$ ).

Finally, Kim *et al.* (Kim *et al.*, 2008) fed 47 females, in a randomised parallel group design, diets containing white rice replacement meals or mixed rice replacement meals for 6 weeks. Both diets were energy restricted with all food being provided. Whilst insulin decreased in both groups, changes within and between groups were not statistically significant.

The studies reported here do not provide evidence to suggest that incorporation of wholegrains into the diet affects blood insulin levels.



Table 4.111 Insulinaemia and wholegrain: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Difference between groups in Δ from baseline	Outcome/ Assessment method	Results/ Outcome details	Result- specific follow-up	Weight Change	Outcome Assessment Bias
16298 (Andersson <i>et al.</i> , 2007)	Refined grain products	30/30	60.4 (SD 30.6)	57.6 (SD 25.7)		NS			Insulin	Fasting Plasma, (pmol/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	56.2 (SD 22.9)	57.6 (SD 24.3)		NS	0.47					Small increase	
16253 (Howard <i>et al.</i> , 2006)	Control	approx 1699 participants included as a 5.8% sub- sample of 29294 in group	10.2 (SD 5.3)	11.2 (SD 5.9)	1.1 (SD 0.5)				Insulin	Fasting (μIU/ml)	3 years	No change	No bias
	Low fat	approx 1132 participants included as a 5.8% sub- sample of 19541 in group	9.9 (SD 4.9)	10.5 (SD 5.3)	1.1 (SD 0.5)		NS					Decrease	
17620	Low fat minus control	Low fat: approx 1132 participants included as a 5.8% sub-sample of 19541 in group Control: approx 1699 participants included as a 5.8% sub-sample of 29294 in group						-0.03 (CI - 0.07, 0.02)	Insulin	Fasting (μIU/ml)	3 years	No change in control group, decrease in low fat group	No bias
								NS					
16768 (Kim <i>et al.</i> , 2008)	Brown & black rice meal replacement	20/23	7.53 (SD 0.9)	6.45 (SD 0.57)			NS		Insulin	Fasting (μIU/ml)	6 weeks	Decrease	unclear
	White rice meal replacement	20/24	7.99 (SD 1.25)	6.73 (SD 0.92)								Decrease	
16190 (Saltzman <i>et al.</i> , 2001)	Control	21/21	115.5 (SD 48.1)		-9.3 (SD 46.7)				Insulin	Fasting Plasma, (pmol/L)	6 weeks	Decrease	unclear
	Oats	20/22	127.7 (SD 36.6)		-28.7 (SD 26.5)		NS					Decrease	
15374 (Tinker <i>et al.</i> , 2008)	Control	1339/29294	9.9 (SD 4.9)	9.6 (SD 4.9)			NS		Insulin	Fasting Serum, (μIU/ml)	1 year	No change	unclear
	Low fat diet	883/19541	9.7 (SD 4.6)	8.9 (SD 4.3)		NS						Decrease	
15375	Control	1164/29294	9.9 (SD 4.9)	7.9 (SD 5.3)			NS		Insulin	Fasting Serum, (μIU/ml)	6 years	No change	unclear
	Low fat diet	759/19541	9.7 (SD 4.6)	7.6 (SD 5)		NS						Decrease	

# Insulin resistance/sensitivity and wholegrain

## Summary of cohort results

No cohort studies provided data on wholegrain and insulin resistance/sensitivity.

## Summary of RCT results

Three studies, reported in four papers, provided data on the effects of wholegrain intake on insulin resistance/ sensitivity (Howard *et al.*, 2006;Tinker *et al.*, 2008;Saltzman *et al.*, 2001). Three trials were conducted in the USA and one in Sweden (Andersson *et al.*, 2007). Three also took parallel group approaches, whereas the study by Andersson *et al.* used a crossover design (Andersson *et al.*, 2007). One study was single blind (Howard *et al.*, 2006;Tinker *et al.*, 2008) and the others did not provide information regarding blinding (Saltzman *et al.*, 2001) or were open (Andersson *et al.*, 2007).

The Women's Health Initiative Dietary Modification Trial had an extremely large sample size of 48,835 (5.8% subsample provided laboratory data) (Howard *et al.*, 2006;Tinker *et al.*, 2008) whereas the studies by Saltzman *et al.* and Andersson *et al.* had relatively small sample sizes of 43 and 34 participants respectively (Saltzman *et al.*, 2001;Andersson *et al.*, 2007). Participants were all adults and mean BMI was less than 30kg/m<sup>2</sup>.

Body weight decreased in both dietary groups in one of the trials (Saltzman *et al.*, 2001) but only in the low fat group in the other (Howard *et al.*, 2006;Tinker *et al.*, 2008). On the other hand, Andersson *et al.* reported an increase in body weight in both groups in the Uppsala Wholegrain Trial (Andersson *et al.*, 2007).

Due to variation in methodologies used to measure insulin sensitivity, it was not possible to combine these studies using meta-analysis.

The Women's Health Initiative Randomized Controlled Dietary Modification Trial, reported here in two publications, (Howard *et al.*, 2006;Tinker *et al.*, 2008) did not show statistically significant changes in HOMA-IR concentrations between the low fat intervention group and the control group. It is, once again, important to note that compliance with the goal to increase wholegrains was only partially achieved. Similarly, Andersson *et al.* (Andersson *et al.*, 2007) reported that wholegrain products over a 6-week period did not alter insulin sensitivity (as assessed by euglycaemic clamp and glucose disposal rate/ insulin sensitivity index) in a group of 34 overweight men and women compared to refined grain products.

In another randomised controlled trial which compared oats with wheat, no statistically significant changes in fasting HOMA-IR concentrations or insulin sensitivity index at 6 weeks were observed (Saltzman *et al.*, 2001).

These three studies collectively show that diets rich in whole grains do not improve insulin sensitivity when compared to low wholegrain diets. None of the studies demonstrated a differential improvement in insulin resistance, although deficiencies in dietary compliance in the larger studies may mean that an effect of whole grains cannot be ruled out.

Table 4.112 Insulin sensitivity and wholegrain: RCT data

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow- up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Difference between groups in $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
(Andersson <i>et al.</i> , 2007) 16299	Refined grain products	30/30	5.7 (SD 1.9)	6.0 (SD 2.0)		NS				Steady state method	Euglycemic hyperinsulinemic clamp (mg/kg/min)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	5.9 (SD 2.1)	5.5 (SD 1.7)		NS	0.24						Small increase	
16603	Refined grain products	30/30	6.4 (SD 2.9)	6.9 (SD 3.2)						Steady state method	Insulin sensitivity index [M/l <sup>5</sup> (mg glucose . kg body wt <sup>-1</sup> . Min <sup>-1</sup> per unit plasma insulin (mU/L) x100]	6 weeks	Small increase	unclear
	Wholegrain products	30/30	6.8 (SD 3)	6.5 (SD 2.7)			0.79						Small increase	
(Howard <i>et al.</i> , 2006) 16254	Control	approx 1699 participants included as a 5.8% sub- sample of 29294 in group	2.5 (SD 1.6)	1.1 (SD 0.5)	1.1 (SD 0.6)					Basal state method	HOMA-IR	3 years	No change	No bias
	Low fat	approx 1132 participants included as a 5.8% sub- sample of 19541 in group	2.4 (SD 1.4)	2.5 (SD 1.7)	1.1 (SD 0.5)		NS						Decrease	
17622	Low fat minus control	Low fat: approx 1132 participants included as a 5.8% sub-sample of 19541 in group Control: approx 1699 participants included as a 5.8% sub-sample of 29294 in group						-0.04 (CI - 0.09, 0.01)	NS	Basal state method	HOMA-IR	3 years	No change in control group, decrease in low fat group	No bias
(Saltzman <i>et al.</i> , 2001) 16191	Control	21/21	3.8 (SD 2.5)		-0.5 (SD 2.1)					Basal state method	HOMA-IR (mmol/L $\mu$ U/ml) (fasting glucose x fasting insulin)/22.5	6 weeks	Decrease	unclear
	Oats	20/22	4.2 (SD 1.4)		-1.1 (SD 1.2)		NS	NS					Decrease	
16192	Control	21/21	3.5 (SD 1.3)		0.5 (SD 1.2)					Dynamic/B asal state methods	Whole body Insulin sensitivity index (mg/dL $\mu$ U/ml) 10,000/ square root of [(fasting insulin x fasting glucose) x	6 weeks	Decrease	unclear
	Oats	20/22	3.3 (SD 1.6)		0.6 (SD 1)		NS	NS					Decrease	

Result ID/ Author	Intervention group	Completers/ Allocated	Baseline	Follow- up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Difference between groups in Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result- specific follow-up	Weight Change	Outcome Assessment Bias
											(mean glucose x mean insulin during oral glucose tolerance test)]			
(Tinker <i>et al.</i> , 2008) 15376	Control	1337/29294	2.3 (SD 1.3)	1.9 (SD 1.4)						Basal state method	HOMA-IR	1 year	No change	unclear
	Low fat diet	880/19541	2.3 (SD 1.2)	1.8 (SD 1.3)			NS						Decrease	
15377	Control	1163/29294	2.3 (SD 1.3)	1.9 (SD 1.4)						Basal state method	HOMA-IR	6 years	No change	unclear
	Low fat diet	759/19541	2.3 (SD 1.2)	1.8 (SD 1.3)			NS						Decrease	

## Glycaemic index and load

The glycaemic index (GI) is a relative measure of the plasma glucose response induced by a specific food, as compared to the response induced by the same amount of carbohydrate from a reference source, such as white bread or pure glucose (Liu *et al.*, 2000c). The glycaemic load (GL) is the product of a specific food's GI and its carbohydrate content (Liu *et al.*, 2000c), therefore taking into account both the quality and quantity of carbohydrate consumed. This may be interpreted as a measure of diet-induced insulin demand (Stevens *et al.*, 2002). The glycaemic index (and thus also GL) is determined not only by the nature of the carbohydrate component of a food or diet, but also by the types and amounts of protein, fat and dietary fibre, as well food processing and storage (Venn and Green, 2007). Unless tightly controlled in an experimental situation, in most cases high and low GI/GL diets differ in many ways other than the carbohydrate fraction, including dietary fibre content, energy density and sensory quality.

## Glycaemia and glycaemic index and load

### Summary of cohort results

One study, the Insulin Resistance Atherosclerosis Study, a multi-ethnic cohort from the USA provided evidence on glycaemic index and load in relation to glucose levels (Mayer-Davis *et al.*, 2006). Mayer-Davis and colleagues (Mayer-Davis *et al.*, 2006) reported glycaemic index and glycaemic load calculated from a 114 item FFQ using values from the International table of glycaemic index and glycaemic load values: 2002 (Foster-Powell *et al.*, 2002). The reference food used to calculate GI values was white bread. Where multiple foods were included on a line of the FFQ a weighted average value was calculated.

Participants were free of DM at cohort entry, and after an average follow-up of 5 years, fasting glucose and response to an oral glucose tolerance test were undertaken. There was no evidence of a consistent direction of association between baseline dietary glycaemic index or glycaemic load and glycaemia assessed at follow-up.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### Summary of RCT results

Fourteen papers, from 13 studies, provided data on high or low glycaemic index /glycaemic load diets and blood glucose.

All trials took a parallel group approach and tended to be unclear with regard to blinding. Two studies, however, were open (Philippou *et al.*, 2009a; Maki *et al.*, 2007b), two were single blind (Ebbeling *et al.*, 2007; Pittas *et al.*, 2006) and one was double blind (Jensen *et al.*, 2008). Studies were carried out in a range of countries, such as the USA (5), the UK (3), Spain (1), Australia (1), France (1), Denmark (1) and Brazil (1).

Participants in these 13 studies were aged 18 + and had mean ages of between 27 and 56 years (median= 35 years). Three studies of females only were identified (Bellisle *et al.*, 2007; Jensen *et al.*, 2008; Sichieri *et al.*, 2007) and one of males (Philippou *et al.*, 2009a). The remaining studies were mixed gender. Of studies that reported an average BMI, participants were either overweight (BMI 25-30kg/m<sup>2</sup>) or obese (BMI >30). Five studies did not record participant BMI (Ebbeling *et al.*, 2007; Bellisle *et al.*, 2007; Philippou *et al.*, 2008; Philippou *et al.*, 2009b; Philippou *et al.*, 2009a).

Final number of participants ranged from 18 to 203, with a mean sample size of 67 (median=49). Two of the trials were particularly large with more than 100 subjects (Sichieri *et al.*, 2007; McMillan-Price *et al.*, 2006).

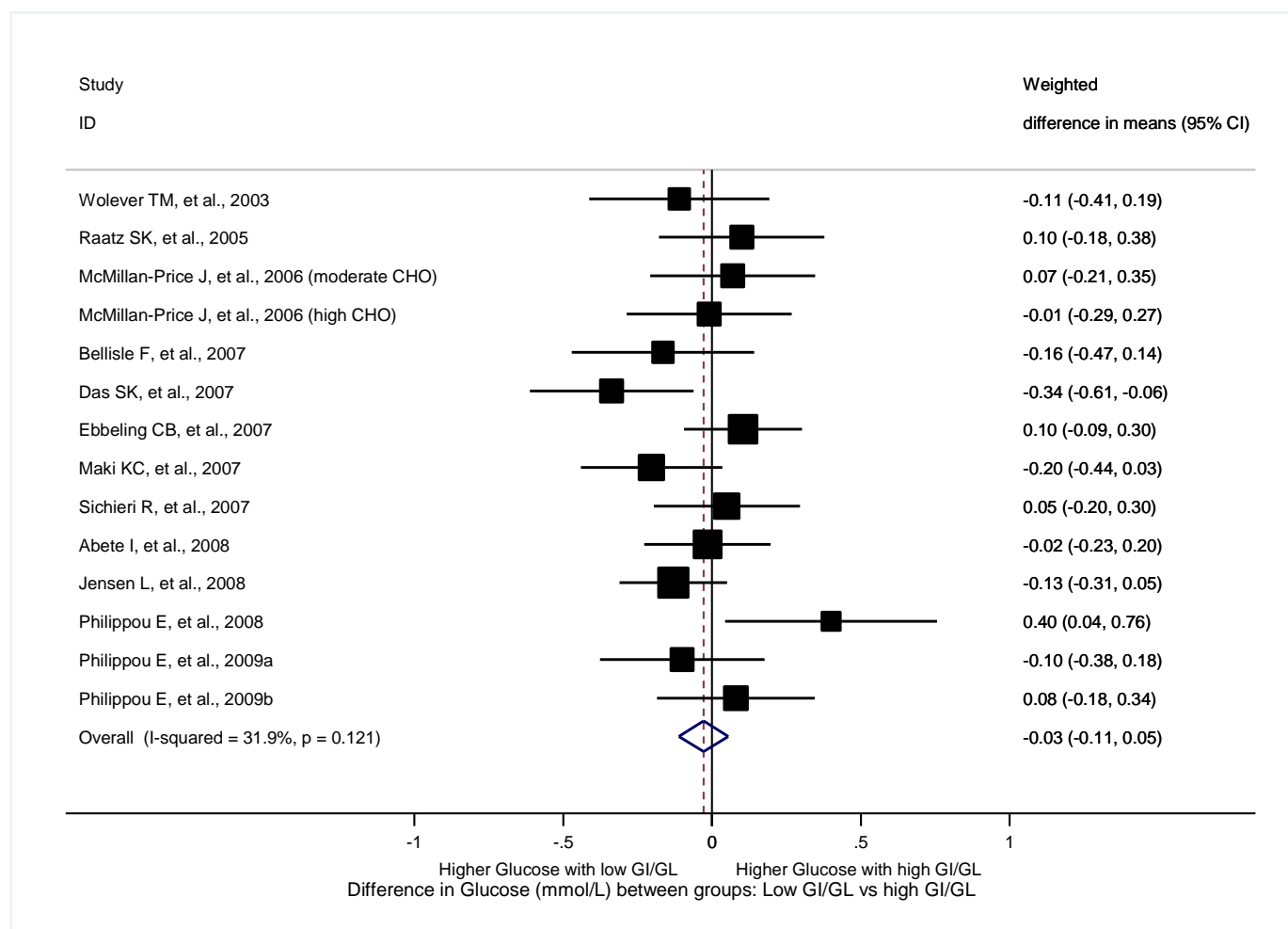
Body weight decreased in the majority of trials, but was unchanged in the studies by (Philippou *et al.*, 2009b; Philippou *et al.*, 2009a).

Papers from Pittas *et al.* (Pittas *et al.*, 2006) and Das *et al.* (Das *et al.*, 2007) are from same study. The results from Das *et al.* (Das *et al.*, 2007) are included in the meta-analysis.

All thirteen studies were included in the meta-analysis. All studies that were low glycaemic load also reported that the diets had a lower average glycaemic index than the high load comparison group. All studies included adults as participants. Definitions of different levels of GI and GL are reported in the trial characteristics table. Studies where fasting blood glucose was not presented as mmol/L were appropriately converted. The first follow up reported at the end of the intervention was used. This varied from 8 weeks to 1 year. The overall pooled estimate indicated that fasting blood glucose was 0.03mmol/L (95% CI, -0.05 to 0.11) higher with consumption of a lower GI or GL diet but this was not significantly different from zero (p=0.49). Heterogeneity denoted by I<sup>2</sup> was 31% (95% CI, 0 to 64). A funnel plot revealed that the risk of publication bias was low. Most trials reported an overall decrease or maintenance of plasma glucose level, with very few individual trials describing different responses between dietary groups.

Statistically, there was no evidence of a difference in fasting blood glucose with differences in dietary glycaemic index or glycaemic load.

**Figure 4.37 Forest plot for glycaemic index or glycaemic load diets and fasting blood glucose (mmol/L)**





*Figure 4.38 Contour-enhanced funnel plot for publications presenting fasting blood glucose and glycaemic index or glycaemic load diets*

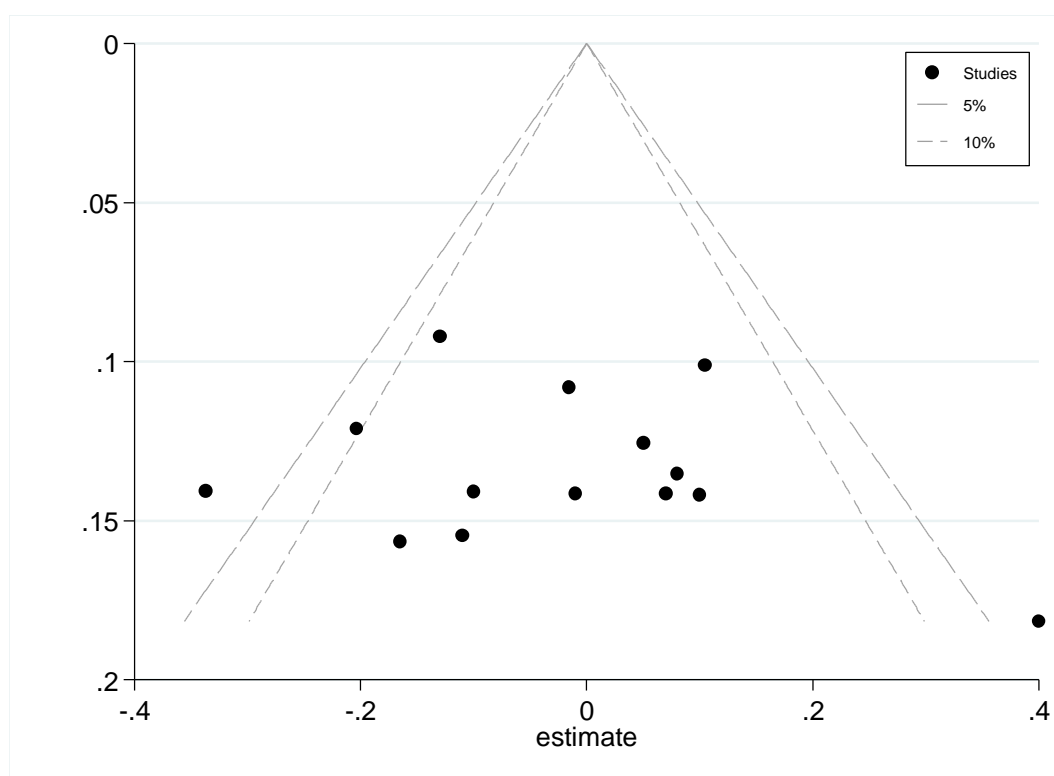


Table 4.113 Glycaemia and glycaemic index and load: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases)/ Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
13858 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi-ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Glycaemic index (mean GI values based on the white bread standard)	Blood glucose Fasting	1 SD of mean exposure	-0.27 (0.74)	NS	age, alcohol, BMI, centre, ethnicity, physical activity, gender, smoking
13873 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response Plasma	1 SD of Mean exposure	2.07 (1.59)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13867 Insulin Resistance Atherosclerosis Study						Glycaemic load	Blood glucose Fasting	1 SD of Mean exposure	-1.62 (1.62)	NS	age, alcohol, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13876 Insulin Resistance Atherosclerosis Study							Glucose AUC OGTT response Plasma	1 SD of Mean exposure	4.05 (4.05)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking

Table 4.114 Glycaemia and glycaemic index and load: RCT data

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Abete <i>et al.</i> , 2008) *15551	Higher GI diet	16/16	93 (SD 8)		-1.9% (SD 6.3%)	NS		Glucose	Fasting plasma, (mg/dL)	8 weeks	Decrease	unclear
	Lower GI diet	16/16	95 (SD 7)		-2.2% (SD 5.5%)	NS	0.897				Decrease	
(Bellisle <i>et al.</i> , 2007) *16049	Control	30/45	0.91 (SE 0.02)	0.9 (SE 0.02)				Glucose	Fasting plasma, (g/L)	12 weeks	Decrease	unclear
	Low GI	35/51	0.93 (SE 0.02)	0.93 (SE 0.02)							Decrease	
(Das <i>et al.</i> , 2007) 15242	High GL diet	15/17	83.5 (SD 6.1)		-2.5% (SD 6.1%)			Glucose	Fasting Whole blood, (mg/dL)	6 months	Decrease	No bias
	Low GL diet	14/17	84.4 (SD 5.8)		-1.8% (SD 7.8%)		NS				Decrease	
*15243	High GL diet	15/17	83.5 (SD 6.1)		-2.3% (SD 6.2%)			Glucose	Fasting Whole blood, (mg/dL)	1 year	Decrease	No bias
	Low GL diet	14/17	84.4 (SD 5.8)		5% (SD 9.9%)		NS				Decrease	
(Ebbeling <i>et al.</i> , 2007) *15459	Low fat diet	37/37			-0.3 (SE 1.3)			Glucose	Fasting plasma, (mg/dL)	6 months	Decrease	No bias
	Low GL diet	ITT: 36/36			1.6 (SE 1.3)		0.31				Decrease	

Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
15460	Low fat diet	37/37			1.4 (SE 1.3)			Glucose	Fasting plasma, (mg/dL)	18 months	Decrease	No bias
	Low GL diet	ITT: 36/36			2.1 (SE 1.3)		0.73				Decrease	
(Jensen <i>et al.</i> , 2008) *15035	High GI diet	22/26	4.75 (SE 0.1)	4.72 (SE 0.07)		NS		Glucose	Fasting plasma, (mmol/L)	10 weeks	Decrease	unclear
	Low GI diet	22/29	4.7 (SE 0.06)	4.85 (SE 0.06)		0.05	0.01				Decrease	
(McMillan-Price <i>et al.</i> , 2006) *16224	High CHO, high GI diet	32/32	5.04 (SE 0.11)		-0.04 (SE 0.10)			Change in glucose	Fasting (mmol/L)	12 weeks	Decrease	unclear
	High CHO, low GI diet	32/32	4.95 (SE 0.07)		-0.06 (SE 0.10)						Decrease	
	High protein, high GI diet	32/32	4.92 (SE 0.14)		-0.05 (SE 0.10)		NS				Decrease	
	High protein, low GI diet	33/33	5.04 (SE 0.09)		0.02 (SE 0.10)		NS				Decrease	
(Maki <i>et al.</i> , 2007b) 17288	Low fat	39/43	95.2 (SE 1.7)		-0.3 (SE 1.1)			Glucose	Fasting serum, (mg/dL)	12 weeks	Decrease	unclear
	Low GL	39/43	95.3 (SE 1.3)		-2.9 (SE 1.3)						Decrease	
*17289	Low fat	39/43	95.2 (SE 1.7)		2.6 (SE 1.4)			Glucose	Fasting serum, (mg/dL)	36 weeks	Decrease	unclear
	Low GL	39/43	95.3 (SE 1.3)		-1.1 (SE 1.7)						Decrease	unclear
(Philippou <i>et al.</i> , 2008) 16861	High GI	7/9	6.3	6.2	0.1 (CI -0.4, 0.1)	NS		Glucose	Mean 24-h (mmol/L)	12 weeks	Decrease	unclear
	Low GI	6/9	5.5	5.3	0.2 (CI -1.3, 0.4)	NS	<0.05				Decrease	
*16859	High GI	7/9	5.1	5.3	0.3 (CI -0.2, 0.3)	NS		Glucose	Fasting (mmol/L)	12 weeks	Decrease	unclear
	Low GI	6/9	5.2	5.3	-0.1 (CI -0.4, 0.1)	NS	NS				Decrease	
16862	High GI	7/9	8985	8841	-145 (CI -615, 195)	NS		Glucose	24 hour AUC, (mmol/ hour/l)	12 weeks	Decrease	unclear
	Low GI	6/9	7806	7559	336 (CI -1909, 505)	NS	<0.05				Decrease	
16863	High GI	7/9	7.1	6.3	-0.3 (CI -1.1, 0.1)	NS		Glucose	Overnight (8th hour) (mmol/L)	12 weeks	Decrease	unclear
	Low GI	6/9	5.5	5.1	0.1 (CI -2.3, 0.3)	NS	<0.01				Decrease	
16864	High GI	7/9	3386	3000	-155 (CI -537, 53)	NS		Glucose	AUC, Overnight (8 hour) (mmol/ hour/l)	12 weeks	Decrease	unclear
	Low GI	6/9	2569	2429	55 (CI -1080, 144)	NS	<0.01				Decrease	
(Philippou <i>et al.</i> , 2009b) 15157	High GI	19/19	4.92 (SD 0.47)	5.08 (SD 0.46)	0.17 (SD 0.47)			Glucose	Fasting plasma, (mmol/L)	2 months	No change	unclear
	Low GI	21/23	4.82 (SD 0.47)	5.07 (SD 0.58)	0.23 (SD 0.48)						No change	
*15158	High GI	19/19	4.92 (SD 0.47)	4.73 (SD 0.41)	-0.17 (SD 0.45)			Glucose	Fasting plasma, (mmol/L)	4 months	No change	unclear
	Low GI	21/23	4.82 (SD 0.47)	4.75 (SD 0.49)	-0.07 (SD 0.44)		0.8				No change	
	High GI	13/19		144			0.6	Glucose	2 hour	4 months	No	unclear

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Author/ result number	Intervention group	Completers/ Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Result/ Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
16847	Low GI	17/23		110.5					Post test meal, (mmol/L)		change No change	
(Philippou <i>et al.</i> , 2009a) *14663	High GI	16/28	5.14 (SD 0.36)	5.04 (SD 0.35)	-0.1 (SD 0.35)	NS		Blood glucose	Fasting (mmol/L)	6 months	Decrease	unclear
	Low GI	22/28	5.2 (SD 0.47)	4.99 (SD 0.47)	-0.18 (SD 0.45)	NS	NS				Decrease	
	High GI	15/28						Glucose	6 hour AUC, Post test meal	6 months	Decrease	unclear
14670	Low GI	18/28					NS				Decrease	
(Pittas <i>et al.</i> , 2006) 16563	High GI/GL diet	16/16	83.8 (SE 1.7)			NS	NS	Glucose	Fasting Plasma, (mg/dL)	3 months	Decrease	No bias
	Low GI/GL diet	16/16	83.8 (SE 1.6)			NS					Decrease	
16567	High GI/GL diet	16/16	83.8 (SE 1.7)			NS	NS	Glucose	Fasting plasma, (mg/dL)	6 months	Decrease	No bias
	Low GI/GL diet	16/16	83.8 (SE 1.6)			NS					Decrease	
16595	High GI/GL diet	16/16	585 (SE 28)			NS	NS	Glucose AUC OGTT response	Fasting (mg/dL)	6 months	Decrease	No bias
	Low GI/GL diet	16/16	609 (SE 25)			NS					Decrease	
(Raatz <i>et al.</i> , 2005) *17233	High fat diet	10/8	4.7 (SE 0.1)		-0.2 (SE 0.1)		NS	Change in glucose	Fasting plasma, (mmol/L)	12 weeks	Decrease	unclear
	High GI diet	9/8	4.9 (SE 0.2)		-0.3 (SE 0.1)						Decrease	
	Low GI diet	10/6	4.8 (SE 0.1)		-0.2 (SE 0.1)		NS				Decrease	
(Sichieri <i>et al.</i> , 2007) *15816	High GI/GL diet	56/102	4.80 (SD 0.9)	4.66 (SD 0.7)	-0.29			Glucose	Fasting serum, (mg/dL)	3 months	Decrease	unclear
	Low GI/GL diet	70/101	4.72 (SD 0.7)	4.71 (SD 0.7)	-0.01	0.13					Decrease	
(Wolever and Mehling, 2003) *17133	High carbohydrate, high GI	11/13	6.01 (SE 0.28)		0.16 (SE 0.09)			Glucose		4 months	Decrease	unclear
	High carbohydrate, low GI	13/13	5.79 (SE 0.22)		0.05 (SE 0.12)				Fasting (mmol/L)		Decrease	
	High carbohydrate, Low carbohydrate, high MUFA	11/12	5.42 (SE 0.24)		0.22 (SE 0.11)						Increase	

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\*This result was used in the meta-analysis of glycaemic index and load and glycaemia

## Insulinaemia and glycaemic index and load

### Summary of cohort results

No cohort studies provided data on glycaemic index or load and insulinaemia.

### Summary of RCT results

Thirteen papers, from 12 studies, investigated high or low glycaemic index /glycaemic load diets and blood insulin.

All trials took a parallel group approach and tended to be unclear with regard to blinding. Two studies, however, were open (Philippou *et al.*, 2009a;Maki *et al.*, 2007b), two were single blind (Ebbeling *et al.*, 2007;Pittas *et al.*, 2006) and one was double blind (Jensen *et al.*, 2008). Studies were carried out in a range of countries, such as the USA (5), the UK (2), Spain (1), Australia (1), France (1), Denmark (1) and Brazil (1).

Participants in these studies were aged 18 + and had mean ages of between 27 and 56 years (median= 36 years). Three studies of females only were identified (Bellisle *et al.*, 2007;Jensen *et al.*, 2008;Sichieri *et al.*, 2007) and one of males only (Philippou *et al.*, 2009a). The remaining studies were mixed gender. Of studies that reported BMI, participants were either overweight (BMI 25-30) or obese (BMI 30+). Four studies did not record mean participant BMI (Ebbeling *et al.*, 2007;Bellisle *et al.*, 2007;Philippou *et al.*, 2009b;Philippou *et al.*, 2009a).

Final number of participants ranged from 32 to 203, with a mean sample size of 74 (median=56). Two of the trials were particularly large with more than 100 subjects (Sichieri *et al.*, 2007;McMillan-Price *et al.*, 2006).

Body weight decreased in the majority of trials, but was also unchanged in the studies by (Philippou *et al.*, 2009b;Philippou *et al.*, 2009a).

Due to variation in methodologies used to measure insulin levels, it was not possible to combine these studies using meta-analysis.

Two studies provided some evidence that glycaemic index and load may impact on fasting insulin levels. Philippou *et al.* (Philippou *et al.*, 2009a) carried out a randomised, parallel group trial to test the effects of a high GI and a low GI diet on 56 eligible men over 6 months. Participants were instructed to consume at least one carbohydrate with meals and snacks, according to their intervention group. At 6 months, participants in both groups had experienced a decrease in fasting insulin and statistically significantly so in the low GI diet group ( $-11.7\text{pmol/L}$   $p<0.01$ ). Between groups there was also a difference that achieved statistical significance ( $p<0.01$ ). The attrition rate in this study was fairly high however resulting in a small number of participants completing the study.

One USA-based trial, CALERIE, conducted by Pittas *et al.* (Pittas *et al.*, 2006) on overweight adults found that energy restricted high GI/GL diets and low GI/GL diets tended to reduce fasting insulin and AUC blood insulin at 6 months ( $p<0.05$  for all) but not at 3 months (high GI/GL diet group only). No statistically significant effect between groups was observed.

Ten trials (Abete *et al.*, 2008;Bellisle *et al.*, 2007;Ebbeling *et al.*, 2007;Jensen *et al.*, 2008;Philippou *et al.*, 2009b;Raatz *et al.*, 2005;Sichieri *et al.*, 2007;Das *et al.*, 2007;Maki *et al.*, 2007b;Wolever and Mehling, 2003;McMillan-Price *et al.*, 2006) did not show an effect of dietary glycaemic index and/or load on fasting insulin. One additional paper that was published on the CALERIE study compared energy restricted high GL and low GL diets but did not show differences in fasting insulin at 6 months follow up (Das *et al.*, 2007).

One study by Maki *et al.* (Maki *et al.*, 2007b) reported the results of a parallel group trial with 86 generally healthy participants who had been randomised to an energy restricted, low fat diet or an *ad libitum* low GL diet. Comparison of fasting insulin did not show statistically significant differences within or between groups at 12 or 36 weeks.

Wolever *et al.* (Wolever and Mehling, 2003) also compared the effects of a high carbohydrate, high GI diet, a high carbohydrate, low GI diet and a low carbohydrate, high MUFA diet in participants with impaired glucose tolerance. Insulin was lower in the low carbohydrate, high MUFA diet following the intervention, however there was no statistically significant differences between the dietary groups.

In summary, the data reported here do not provide consistent evidence that differences in glycaemic index and load influence fasting blood insulin.

Table 4.115 Insulinaemia and glycaemic index and load: RCT data

Results Number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Results/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
15552 (Abete <i>et al.</i> , 2008)	Higher GI diet	16/16	6.5 (SD 2.2)		19.7% (SD 58.2%)	NS		Insulin	Fasting Plasma, ( $\mu$ UI/ml)	8 weeks	Decrease	unclear
	Lower GI diet	16/16	7.4 (SD 3.8)		-15.7% (SD 44.5%)	NS	0.085					
16050 (Bellisle <i>et al.</i> , 2007)	Control	30/45	5.9 (SE 0.53)	5.16 (SE 0.54)				Insulin	Fasting Plasma, ( $\mu$ U/ml)	12 weeks	Decrease	unclear
	Low GI	35/51	7.53 (SE 0.91)	6.16 (SE 0.56)			NS					
15245 (Das <i>et al.</i> , 2007)	Energy restricted high GL diet	15/17	10.5 (SD 3.6)		-14.9% (SD 20%)			Insulin	Fasting ( $\mu$ U/ml)	6 months	Decrease	No bias
	Energy restricted low GL diet	14/17	12.1 (SD 4.3)		25.4% (SD 24.2%)		NS					
15246	Energy restricted high GL diet	15/17	10.5 (SD 3.6)		-18% (SD 15%)			Insulin	Fasting ( $\mu$ U/ml)	1 year	Decrease	No bias
	Energy restricted low GL diet	14/17	12.1 (SD 4.3)		-21.2% (SD 16.7%)		NS					
15461 (Ebbeling <i>et al.</i> , 2007)	Low fat diet	37/37			-0.9 (SE 0.8)			Insulin	Fasting Serum, ( $\mu$ UI/ml)	6 months	Decrease	No bias
	Low GL diet	ITT: 36/36			-2.1 (SE 0.8)		0.28					
15462	Low fat diet	37/37			0 (SE 0.8)			Insulin	Fasting Serum, ( $\mu$ U/ml)	18 months	Decrease	No bias
	Low GL diet	ITT: 36/36			-0.8 (SE 0.8)		0.49					
15036 (Jensen <i>et al.</i> , 2008)	High GI diet	22/26	39.3 (SE 3.5)	34.1 (SE 2.6)		NS		Insulin	Fasting Serum, (pmol/L)	10 weeks	Decrease	unclear
	Low GI diet	22/29	36.1 (SE 3.3)	28.9 (SE 2.6)		NS	0.31					
17290 (Maki <i>et al.</i> , 2007b)	Low fat, energy restricted	39/43	9 (SE 1.2)		0.9 (SE 1.1)		NS	Insulin	Fasting (mU/L)	12 weeks	Decrease	unclear
	Ad libitum low GL diet	39/43	10.4 (SE 1)		-0.4 (SE 1.1)							
17291	Low fat, energy restricted	39/43	9 (SE 1.2)		2.4 (SE 0.7)			Insulin	Fasting (mU/L)	36 weeks	Decrease	unclear
	Ad libitum low GL diet	38/43	10.4 (SE 1)		1.1 (SE 1)		NS					



Results Number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Results/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
16225 (McMillan-Price <i>et al.</i> , 2006)	High CHO, high GI diet	32/32	79 (SE 7)		-8.1 (SE 6.9)			Change in insulin	Fasting (pmol/L)	12 weeks	Decrease	unclear
	High CHO, low GI diet	32/32	83 (SE 10)		-13.3 (SE 6.9)						Decrease	
	High protein, high GI diet	32/32	101 (SE 12)		-17.1 (SE 7)		NS				Decrease	
	High protein, low GI diet	33/33	81 (SE 8)		-10.4 (SE 6.8)		NS				Decrease	
16849 (Philippou <i>et al.</i> , 2009b)	High GI	13/19		38039.9			0.2	Insulin	2-Hour Insulin AUC, Post test meal (pmol/L)	4 months	No change	unclear
	Low GI	16/23		51980.9							No change	
15176	High GI	18/19	42.4	39.2	-2.6(-16.7, 12.8) (SE (SD			Insulin	Fasting Plasma, (pmol/L)	4 months	No change	unclear
	Low GI	22/23	47.2	53.1	8.3 (CI - 9.4, 21.9)		0.2				No change	
14664 (Philippou <i>et al.</i> , 2009a)	High GI	14/28	56.7 (SD 29.8)	48.9 (SD 21.8)	-7.8 (SD 28.3)	NS		Blood insulin	Fasting (pmol/L)	6 months	Decrease	unclear
	Low GI	19/28	44.3 (SD 19.2)	32.6 (SD 13.1)	-11.7 (SD 16.8)	<0.01	<0.01				Decrease	
14671	High GI	15/28						Insulin	6 hour AUC, Post test meal	6 months	Decrease	unclear
	Low GI	18/28					NS				Decrease	
16568 (Pittas <i>et al.</i> , 2006)	Energy restricted high GI/GL diet	16/16	11.1 (SE 1.0)			NS	NS	Insulin	Fasting (mU/L)	3 months	Decrease	No bias
	Energy restricted low GI/GL diet	16/16	12.2 (SE 1.2)		decrease	<0.05					Decrease	
16569	Energy restricted high GI/GL diet	16/16	11.1 (SE 1.0)		decrease	<0.05	NS	Insulin	Fasting (mU/L)	6 months	Decrease	No bias
	Energy restricted low GI/GL diet	16/16	12.2 (SE 1.2)		decrease	<0.05					Decrease	
16596	Energy restricted high GI/GL diet	16/16	338 (SE 35)		decrease	<0.05	NS	Insulin AUC OGTT response	Fasting (mU/L)	6 months	Decrease	No bias
	Energy restricted low GI/GL diet	16/16	335 (SE 27)		decrease	<0.05					Decrease	
17234 (Raatz <i>et al.</i> , 2005)	High fat diet	10/8	56.3 (SE 9.7)		-6.3 (SE 4.8)		NS	Change in insulin	Fasting Serum, (pmol/L)	12 weeks	Decrease	unclear

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Results Number	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Results/Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
	High GI diet	9/8	54.9 (SE 9)		-20.1 (SE 6.9)						Decrease	
	Low GI diet	10/6	67.4 (SE 11.8)		-28.5 (SE 6.3)		NS				Decrease	
15817 (Sichieri <i>et al.</i> , 2007)	High GI/GL diet	56/102	11.7 (SD 4.4)	11.3 (SD 3.3)	-0.2			Insulin	Fasting Serum, ( $\mu$ U/ml)	3 months	No change	unclear
	Low GI/GL diet	70/101	11.6 (SD 4.2)	12.4 (SD 4.5)	0.42	0.39					No change	
17134 (Wolever and Mehling, 2003)	High carbohydrate, high GI	11/13			1.5 (SE 5.6)			Insulin	Fasting (pmol/L)	4 months	Decrease	unclear
	High carbohydrate, low GI	13/13			-0.8 (SE 7.7)						Decrease	
	Low carbohydrate, high MUFA	11/12			-1.0 (SE 8.2)		NS				Increase	

# **Insulin resistance/sensitivity and glycaemic index and load**

## **Summary of cohort results**

No cohort studies provided data on glycaemic index and load and insulin resistance/sensitivity.

## **Summary of RCT results**

Twelve studies provided data on high or low glycaemic index /glycaemic load diets and insulin resistance/ sensitivity.

All trials took a parallel group approach and tended to be unclear with regards to blinding. One study, however, was open (Maki *et al.*, 2007b) and one was single blind (Pittas *et al.*, 2006). Studies were carried out in a range of countries, such as the USA (6), the UK (1), Spain (1), Australia (1), France (1), Denmark (1) and Brazil (1).

Participants in these studies were aged 18 + and had mean ages of between 31 and 57 years (median= 36 years). Three studies of females only were identified (Bellisle *et al.*, 2007;Sloth *et al.*, 2004;Sichieri *et al.*, 2007). The remaining studies were mixed gender. Of studies that reported BMI, participants were either overweight (BMI 25-30) or obese (BMI >30). Four studies did not record mean participant BMI (Bellisle *et al.*, 2007;Philippou *et al.*, 2009b;Pereira *et al.*, 2004;Ebbeling *et al.*, 2005).

Final number of participants ranged from 32 to 203, with a mean sample size of 70 (median=45). Two of the trials were particularly large with more than 100 subjects (Sichieri *et al.*, 2007;McMillan-Price *et al.*, 2006).

Body weight generally decreased in the majority of trials, but was unchanged in the study by (Philippou *et al.*, 2009b).

As methods of assessing insulin resistance/ sensitivity varied between studies, it was not possible to combine these in a meta-analysis.

Methods of assessing insulin resistance/ sensitivity varied between studies, although the most common approach was the assessment of HOMA-IR and HOMA-beta. Such an example of this method of estimation is the small study by Abete *et al.* (Abete *et al.*, 2008) which reported HOMA index at 8 weeks for 16 obese individuals that had been randomly allocated to either a high or low GI diet. Whilst the HOMA index increased by 20.6% and decreased by 16.5% on the higher GI diet and lower GI diets respectively, such differences did not achieve statistical significance within or between dietary groups.

Ten trials did not find a differential effect of high compared to low dietary glycaemic index or load diets on markers of insulin resistance (Abete *et al.*, 2008;Bellisle *et al.*, 2007;Ebbeling *et al.*, 2005;McMillan-Price *et al.*, 2006;Maki *et al.*, 2007b;Pittas *et al.*, 2006;Philippou *et al.*, 2009b;Sloth *et al.*, 2004;Sichieri *et al.*, 2007;Raatz *et al.*, 2005).

Pittas (Pittas *et al.*, 2006) employed a 6-month parallel-group design to determine the effect of a high-GL diet compared to a low-GL diet on insulin resistance/ sensitivity in 34 healthy overweight subjects. Diets were supplied at 30% caloric restriction and all food was provided. Fasting HOMA-IR was statistically significantly lower in the low GI/ GL diet group at 3 months ( $p<0.05$ ), whilst at 6 months HOMA-IR was significantly lower in both dietary groups ( $p<0.05$ ) when compared to baseline. After adjustments were made for baseline values and changes in weight, however, no statistically significant differences in insulin sensitivity, acute insulin response and disposition index between diet groups were observed (Pittas *et al.*, 2006).

Also using a similar parallel group design, Bellisle *et al.* (Bellisle *et al.*, 2007) compared a standard Weight Watchers energy restriction plan, with and without advice to preferentially adhere to low GI foods. Over 12 weeks, no statistically significant differences in HOMA index between groups were evident. It is of note, however, that the intervention and control group opted for similar food choices - that is those low in GI - and thus any potential associations may have been obscured (Bellisle *et al.*, 2007).

McMillan-Price *et al.* (McMillan-Price *et al.*, 2006) also conducted a parallel group trial, in which young and middle-aged adults were randomised to one of four dietary groups: a high carbohydrate, high GI diet; a high carbohydrate, low GI diet; high protein, high GI diet or a high protein, low GI diet. There were no changes in fasting HOMA-IR, HOMA-insulin sensitivity computer model, HOMA-beta cell function computer model and HOMA-IR computer model within or between groups.

Ebbeling *et al.* (Ebbeling *et al.*, 2005) compared a low GI diet (ad libitum GI food, 45-50% carbohydrate, 30-35% fat) and a low fat diet (energy deficit of 250-500 kcal/d) in 34 young adults but found no difference in insulin sensitivity index between the two groups. Similarly, Raatz *et al.* (Raatz *et al.*, 2005) reported lower (improved) HOMA scores following a high fat diet, a high GI diet and a low GI diet at 12 weeks ( $p<0.05$  for each) in their study. Minor changes in HOMA scores were observed, however, at 36 weeks follow-up. Under energy-restricted conditions, overweight

and obese males and females experienced an improvement in insulin sensitivity regardless of the dietary composition of the diet.

Just two trials reported a difference between dietary groups in terms of measures reflecting insulin resistance. In Pereira *et al.* (Pereira *et al.*, 2004), 46 participants with a BMI >25 were randomised to receive energy restricted diets either low in GL (GL 82) or low in fat (18% fat; GL 205). After 67 days, those in the low GL dietary group experienced a statistically significant reduction in HOMA score compared to the low fat group ( $p=0.01$ ).

Wolever *et al.* (Wolever and Mehling, 2002) fed 37 participants in a parallel group design diets high in carbohydrate, high in GI or high in carbohydrate, low in GI or low in carbohydrate, high in MUFA. After adjusting for baseline values, the authors concluded that mean disposition index had statistically significantly increased in the high carbohydrate, low GI group compared to the other two treatment groups ( $p<0.05$ ). However, findings should be treated with caution given the small final sample size and the fact that the intervention– a free-living diet plan – did not permit researcher control over foods consumed.

Collectively, these 12 trials do not provide clear and consistent evidence that diets high or low in GI/ GL differentially affect insulin resistance or sensitivity over and above the improvements that were observed through weight loss caused by energy restriction.

Table 4.116 Insulin resistance/sensitivity and glycaemic index and load: RCT data

Result ID/ Author	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Abete <i>et al.</i> , 2008) 15553	Higher GI diet	16/16	1.5 (SD 0.8)		20.6% (SD 65.8%)	NS		Basal state method	HOMA (index)	8 weeks	Decrease	unclear
	Lower GI diet	16/16	1.6 (SD 0.8)		-16.5% (SD 47.6%)	NS	0.102				Decrease	
(Bellisle <i>et al.</i> , 2007) 16056	Control	30/45	1.34 (SE 0.14)	1.22 (SE 0.13)				Basal state method	HOMA (index)	12 weeks	Decrease	unclear
	Low GI	35/51	1.75 (SE 0.24)	1.41 (SE 0.15)			NS				Decrease	
(Philippou <i>et al.</i> , 2009b) 15179	High GI	18/19	124.1	133	11.1 (CI -28.6, 40.5)			Basal state method	HOMA-S	4 months	No change	unclear
	Low GI	22/23	113.3	104.9	-16.3 (CI -40.3, 18.8)		0.3				No change	
15180	High GI	18/19	95.4	82.1	-1.1 (CI -11.5, 7.8)			Basal state method	HOMA-beta	4 months	No change	unclear
	Low GI	22/23	102.5	109.8	0.05 (CI -17.4, 25.3)		0.2				No change	
(Pittas <i>et al.</i> , 2006) 16563	Low GI/GL diet	16/16	83.8 (SE 1.6)			NS		Glucose	Fasting Plasma, (mg/dL)	3 months	Decrease	No bias
	High GI/GL diet	16/16	83.8 (SE 1.7)			NS	NS				Decrease	
16570	High GI/GL diet	16/16	2.3 (SE 0.2)			NS	NS	Basal state method	Fasting HOMA-IR	3 months	Decrease	No bias
	Low GI/GL diet	16/16	2.5 (SE 0.3)		decrease	<0.05					Decrease	
16571	High GI/GL diet	16/16	2.3 (SE 0.2)		decrease	<0.05	NS	Basal state method	Fasting HOMA-IR	6 months	Decrease	No bias
	Low GI/GL diet	16/16	2.5 (SE 0.3)		decrease	<0.05					Decrease	
16676	High GI/GL diet	16/16	448 (SE 80)				NS	Dynamic method	Acute insulin response to glucose (mU/L/min)	6 months	Decrease	No bias
	Low GI/GL diet	16/16	401 (SE 33)								Decrease	
16677	High GI/GL diet	16/16	1571 (SD 232)				NS	Dynamic/Basal state methods	Disposition index	6 months	Decrease	No bias
	Low GI/GL diet	16/16	1730 (SD)								Decrease	

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Result ID/ Author	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group Δ from baseline	p-value Within group Δ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
226)												
(Sichieri <i>et al.</i> , 2007) 15818	High GI/GL diet	56/102	2.5 (SD 1)	2.3 (SD 0.7)	-0.09			Basal state method	HOMA-IR	3 months	No change	unclear
	Low GI/GL diet	70/101	2.4 (SD 1)	2.6 (SD 1.1)	0.08		0.13				No change	
(Sloth <i>et al.</i> , 2004) 15028	High GI diet	22/26	1.39 (SE 0.13)	1.2 (SE 0.1)	-0.2 (SE 0.13)			Basal state method	HOMA-R (index)	10 weeks	Decrease	unclear
	Low GI diet	23/29	1.34 (SE 0.14)	1.17 (SE 0.15)	-0.18 (SE 0.09)		NS				Decrease	
15029	High GI diet	22/26	119 (SE 15)	100 (SE 11)	-21 (SE 12)			Basal state method	HOMA-beta (%)	10 weeks	Decrease	unclear
	Low GI diet	23/29	118 (SE 15)	95 (SE 22)	-22 (SE 12)						Decrease	
(Pereira <i>et al.</i> , 2004) 14578	Low fat	17/23	1.45 (SE 0.2)	1.1 (SE 0.13)	-15.8% (SE 5.3%)			Basal state method	HOMA-S (score)	67 days	Decrease	unclear
	Low GL	22/23	1.5 (SE 0.18)	0.97 (SE 0.11)	-33.9% (SE 4.51%)		0.01				Decrease	
(Ebbeling <i>et al.</i> , 2005) 15517	Low fat diet	12/17	0.35 (SE 0.01)		5.8% (CI 1.1, 10.7)			Basal state method	Insulin sensitivity index (index)	6 months	Decrease	unclear
	Low GI diet	11/17	0.34 (SE 0.01)		6.4% (CI 1.5, 11.5)		NS				Decrease	
15518	Low fat diet	12/17	0.35 (SE 0.01)		8.7% (CI 2.3, 15.5)			Basal state method	Insulin sensitivity index (index)	1 year	Decrease	unclear
	Low GI diet	11/17	0.34 (SE 0.01)		10.4% (CI 3.6, 17.6)						Decrease	
(Maki <i>et al.</i> , 2007b) 17292	Low fat	39/43	2.1 (SE 0.3)		0.2 (SE 0.3)		NS	Basal state method	HOMA	12 weeks	Decrease	unclear
	Low GL	39/43	2.4 (SE 0.2)		-0.1 (SE 0.3)						Decrease	
17293	Low fat	39/43	2.1 (SE 0.3)		0.7 (SE 0.2)		NS	Basal state method	HOMA	36 weeks	Decrease	unclear
	Low GL	39/43	2.4 (SE 0.2)		0.3 (SE 0.3)						Decrease	
(Wolever and Mehling, 2002) 17014	High carbohydrate, high GI	11/11			No change			Basal state method	Glucose disposition index* (%)	16 weeks	Decrease	unclear
	High carbohydrate, low GI	13/13			+56		P<0.05				Decrease	

Result ID/ Author	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
	Low carbohydrate, high MUFA	11/11			-16						Increase	
(McMillan- Price <i>et al.</i> , 2006) 16226	High CHO, high GI diet	32/32	2.6 (SE 0.2)		-0.3 (SE 0.2)			Basal state method (change)	Fasting HOMA-IR	12 weeks	Decrease	unclear
	High CHO, low GI diet	32/32	2.7 (SE 0.4)		-0.5 (SE 0.2)						Decrease	
	High protein, high GI diet	32/32	3.1 (SE 0.3)		-0.6 (SE 0.2)		NS				Decrease	
	High protein, low GI diet	33/33	2.7 (SE 0.3)		-0.3 (SE 0.2)		NS				Decrease	
16227	High CHO, high GI diet	32/32	81 (SE 8)		1.7 (SE 7.3)			Basal state method (change)	HOMA-insulin sensitivity computer model	12 weeks	Decrease	unclear
	High CHO, low GI diet	32/32	85 (SE 6)		9.3 (SE 7.4)						Decrease	
	High protein, high GI diet	32/32	70 (SE 6)		25.7 (SE 7.4)		NS				Decrease	
	High protein, low GI diet	33/33	82 (SE 6)		16.4 (SE 7.2)		NS				Decrease	
16228	High CHO, high GI diet	32/32	123 (SE 6)		-11.3 (SE 17.8)			Basal state method (change)	HOMA-beta cell function computer model	12 weeks	Decrease	unclear
	High CHO, low GI diet	32/32	122 (SE 8)		-15.0 (SE 17.8)						Decrease	
	High protein, high GI diet	32/32	164 (SE 24)		-16.5 (SE 18.1)		NS				Decrease	
	High protein, low GI diet	33/33	125 (SE 10)		11.8 (SE 17.5)		NS				Decrease	
17080	High CHO, low GI diet	32/32	1.5 (SE 0.2)		-0.2 (SE 0.1)			Basal state method	HOMA-IR computer model	12 weeks	Decrease	unclear
	High protein, high GI diet	32/32	1.8 (SE 0.2)		0.3 (SE 0.1)						Decrease	
	High protein, low GI diet	33/33	1.6 (SE 0.2)		-0.2 (SE 0.1)						Decrease	
	High CHO, high GI diet	32/32	1.5 (SE 0.1)		-0.1 (SE 0.1)						Decrease	



Result ID/ Author	Intervention group	Completers / Allocated	Baseline	Follow-up	Within group $\Delta$ from baseline	p-value Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Raatz <i>et al.</i> , 2005) 17246	High fat diet	8/8	1.56 (SE 0.3)		0.22 (SE 0.22)			Basal state method	HOMA	36 weeks	Decrease	unclear
	High GI diet	8/8	1.61 (SE 0.3)		-0.06 (SE 0.16)						Decrease	
	Low GI diet	6/6	1.90 (SE 0.3)		0.09 (SE 0.33)						Decrease	
17220	High fat diet	10/8	1.56 (SE 0.3)	1.32		<0.05	<0.05	Basal state method	Fasting HOMA	12 weeks	Decrease	unclear
	High GI diet	9/8	1.61 (SE 0.3)	0.94		<0.05	<0.05				Decrease	
	Low GI diet	10/6	1.90 (SE 0.3)	1.04		<0.05	NS				Decrease	

\*index of the ability of the b-cell to compensate for changes in insulin sensitivity by increasing insulin secretion, with a low value indicating reduced b-cell responsiveness

## **Glycosylated blood proteins and glycaemic index and load**

### **Summary of cohort results**

In the Insulin Resistance Atherosclerosis Study (Mayer-Davis *et al.*, 2006), 813 adults underwent a baseline examination and then returned for a 5-year follow-up examination. Diet was assessed by FFQ at both time points (data are included here only for the prospective analysis). Neither glycaemic index of the diet nor glycaemic load at baseline were associated with HbA1c levels at follow-up in any of the models presented in the paper.

*Please interpret observational data with caution: With observational studies there is substantial potential for biases.*

### **Summary of RCT results**

One trial provided data on the effects of a glycaemic index/ load diet on HbA1c (Wolever and Mehling, 2003). Body weights decreased in the high carbohydrate, high GI and high carbohydrate, low GI groups yet increased in the low carbohydrate, high MUFA group. Comparison of HbA1c values at 4 months in this study showed a small but statistically significant increase with the low carbohydrate, high MUFA diet compared to small decreases in both the high carbohydrate, high GI and low carbohydrate, low GI diets ( $p=0.006$ ) (Wolever and Mehling, 2003).

Table 4.117 Glycosylated blood proteins and glycaemic index and load: cohort study in adults

Result ID/ Reference/ Cohort Name	Country, Ethnicity, Inclusion criteria	Age range (mean) %Male	(Cases) / Total	Follow Up (% loss)	Diet Assessment	Exposure	Outcome/ Assessment details	Units	Beta coefficient (SE)/(CI)	P	Adjustments
13882 (Mayer-Davis <i>et al.</i> , 2006) Insulin Resistance Atherosclerosis Study	USA, Multi- ethnic, Not diabetic	40-69 (55) %M 43.5	1625	5.2 years (19)	FFQ (114)	Glycaemic index (mean GI values based on the white bread standard)	HbA1c Plasma	1 SD of mean exposure	0.01 (0.02)	NS	age, alcohol, Blood glucose, BMI, centre, energy intake, ethnicity, physical activity, gender, smoking
13883 Insulin Resistance Atherosclerosis Study						Glycaemic load	HbA1c Plasma	1 SD of mean exposure	0.05 (0.08)	NS	As above

Table 4.118 Glycosylated blood proteins and glycaemic index and load: RCT data

Study ID/Authors	Intervention group	Completers/ Allocated	Baseline	Within group $\Delta$ from baseline	p-value difference between groups	Outcome/ Assessment method	Outcome detail	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Wolever and Mehling, 2003) 17132	High carbohydrate, high GI	11/13	5.95 (SE 0.18)	-0.13 (SE 0.14)	0.006	HbA1c	(%)	4 months	Decrease	unclear
	High carbohydrate, low GI	13/13	5.67 (SE 0.17)	-0.19 (SE 0.08)					Decrease	
	Low carbohydrate, high MUFA	11/12	5.42 (SE 0.17)	0.02 (SE 0.11)					Increase	

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