Chapter 3: Dietary Carbohydrate and Markers of Inflammation

Contents

Background

In the past decade, evidence has grown that implicates systemic inflammation in the development of cardiometabolic disease. Indeed, it is a popular area of research and a wide variety of biomarkers have been identified to reflect extent of inflammation.

Systemic inflammation and atherosclerosis

Atherosclerosis is a chronic inflammatory condition in which the components of an artery wall thicken (Ross, 1999) due to the deposition of lipids (atheroma) such as cholesterol (Lusis, 2000). Plaques are formed on the luminal surface of arteries which may limit the blood flow over time giving rise to chronic stable angina, peripheral vascular disease and cerebrovascular disease. Plaques may rupture acutely and block or severely limit the arterial supply downstream (Finn *et al.*, 2010) – typically this results in an acute coronary syndrome, acutely ischaemic limb and stroke respectively.

In addition to its association with atherosclerosis, systemic inflammation is also implicated in the development of diabetes (Kolb and Mandrup-Poulsen, 2005). That is, diabetes and cardiovascular disease demonstrate evidence of low-grade inflammation. Dietary components may impact upon systematic inflammation and therefore atherosclerosis and diabetes by influencing inflammatory markers (Basu *et al.*, 2006).

Markers of inflammation and their role in atherosclerosis

Systemic inflammation is not confined to a particular tissue but involves the endothelium and other organ systems.

There is evidence to support the mechanism of systemic inflammation in the process of accelerated atherosclerosis (Libby *et al.*, 2002). Elevated inflammatory markers are associated with a higher risk of adverse outcomes in patients with acute coronary syndromes, independent of the degree of myocardial (heart muscle) damage. Moreover, patients who demonstrate long-term (chronic) low-grade inflammation are at a higher risk of atherosclerotic complications such as an acute coronary syndrome, ischaemic limb and stroke. Some medication (such as lipid lowering drugs) may reduce cardiovascular risk and inflammation. A previous report (Committee on Medical Aspects of Food Policy, 1994) suggested that some diets (such as those low in glycaemic load and high in whole grains) may have a protective effect against systemic inflammation.

There are many blood-borne biomarkers of inflammation (Basu *et al.*, 2006). They can be classified as acute phase proteins, cytokines, chemokines, adhesion molecules and those concerned with the clotting cascade. The table below summarises their properties and their possible role in atherosclerosis. Typically, although not the case for interleukin-10 which is an anti-inflammatory cytokine, the higher the marker indicates the greater the extent of inflammation. For example, C-reactive protein (CRP) levels are elevated in infection and inflammation (Gotto, Jr., 2007).

The underlying assumption is that atherosclerosis and ‘active’ cardiovascular disease is underpinned by an inflammatory process, which can therefore be quantified using markers such

as CRP. However, because CRP, for example is influenced by a number of other pathological processes, elevated levels may not necessarily reflect cardiovascular disease nor therefore be a good proxy for cardiovascular risk. Additionally, there remains doubt concerning whether inflammatory markers such as CRP are part of the causal pathway for CVD or whether changes in their concentration are a consequence of the disease process.

Table 3.1 Markers of inflammation and their possible role in atherosclerosis

Markers of inflammation	**Examples**	**Sources**	**Action**
Acute phase proteins	1) C-reactive protein (CRP) 2) Serum amyloid A (SAA) 3) Complement 4) Clotting cascade proteins 5) Ferritin 6) α1 antitrypsin	Liver, adipose tissue, macrophages, smooth muscle cells, endothelial cells	1) Production of inflammatory cytokines, chemokines, tissue factor expression, chemotaxis of monocytes. Down-regulation of endothelial nitric oxide synthase (eNOS) and prostacyclin 2) Hypercoagulable state (through increased PAI-1, and decreased tPA) 3) Opsonization, lysis and clumping of target cells. Chemotaxis 4) see clotting cascade 5) Binding iron 6) down regulates inflammation
Cytokines	1) Interleukin-1 (IL-1) 2) IL-6, hsIL-6 3) Tissue necrosis factor-α (TNFα) 4) Interferon	Endothelial cells, macrophages, adipose tissue	1) Increase monocyte-endothelial adhesion 2) Activation of monocytes 3) Enhance production of inflammatory cytokines 4) Cell communication, trigger immune system
Chemokines	1) Monocyte chemotactic protein-1 (MCP-1) 2) Interleukin 8 (IL-8)	Endothelial cells, macrophages	1) Stimulate chemotaxis
Soluble cell adhesion molecules	1) Inter-Cellular Adhesion Molecule (ICAM) 2) Vascular-Cellular Adhesion Molecule-1 (VCAM-1) 3) P-selectin 4) E-selectin	Endothelial cells	1) Promote monocyte–endothelial adhesion
Clotting cascade	1) Plasminogen activator inhibitor-1 (PAI-1), 2) fibrinogen 3) Factor VII (proconventin) 4) Tissue plasminogen activator (tPA)	Endothelial cells, adipose tissue, macrophages	1) Reduce fibrinolysis 2) Promote thrombosis

- *Acute phase proteins* are a group of proteins such as CRP and serum amyloid A (SAA) whose concentrations in the blood increase in response to inflammation. In turn, they can increase inflammation and promote coagulation. Some studies provide data on high sensitivity CRP (hs-CRP) and others CRP. Both tests are designed to quantify CRP, but the hs-CRP test measures CRP in the range from 0.5 to 10mg/L. The CRP test measures in the range from 10 to 1000mg/L and tends to be used with patients at risk of infection. In this review they will be treated synonymously.

- *Cytokines* are a group of proteins such as interleukin-1 (IL-1) and tissue necrosis factor-α (TNFα) that are implicated in cell signalling (communication). When activated, they increase the inflammatory response. Other cytokines such as IL-10 are anti-inflammatory in action.

- *Chemokines* are a group of proteins such as monocyte chemotactic protein-1 (MCP-1) that are secreted by cells and once released, attract other cells. For example, MCP-1 is a pro-inflammatory chemokine which attracts cells from the immune system to promote and maintain the inflammatory response.

- *Soluble cell adhesion molecules* are a group of proteins such as Inter-Cellular Adhesion Molecule (ICAM), Vascular-Cellular Adhesion Molecule-1 (VCAM-1) and P-selectin. They bind to the surface of cells. They promote the adhesion of inflammatory cells to the blood vessel wall and may be responsible for atherosclerotic plaque formation (Miller *et al.*, 2011).

- *The clotting cascade* is a complex process involving many proteins (Mosca *et al.*, 2004). It is closely linked with the immune (defence) system. There are many clotting cascade proteins which can act to promote or reduce blood coagulation. Some clotting cascade proteins can increase vascular permeability and act as chemotactic agents - to attract other cells. Also, many acute phase proteins are involved in the clotting cascade. Tissue plasminogen activator (tPA) is an enzyme which breaks down blood clots. Plasminogen activator inhibitor-1 (PAI-1) inhibits tPA, thus preventing blood clot breakdown. Fibrinogen is a protein converted by thrombin into fibrin during blood coagulation. Factor VII (formerly known as proconventin) starts the coagulation cascade in conjunction with tissue factor (factor III).

Markers of inflammation and diet

It is well recognised that obesity is associated with elevations in CRP concentration (Ford, 2003). Analyses of the relationship between weight loss and CRP concentrations from 6 weight loss trials indicated that the extent of weight loss was strongly correlated with %CRP reduction (Dietrich and Jialal, 2005). Jialal *et al.* suggest that the reduction in fat mass through weight loss would reduce IL-6 production which in turn would decrease CRP production by the liver (Jialal *et al.*, 2004). Dietary interventions that promote weight loss are therefore likely to bring about reductions in inflammatory markers. What is less clear is whether variations in the nature of the diet, over and above its capacity to generate weight loss are capable of influencing markers of inflammation.

The observational epidemiological literature on the relationship between diet and markers of inflammation is not large and mostly consists of cross-sectional studies and short-term intervention trials, which have not been included in this review due to their recognised weaknesses in determining causal associations between diet and disease. The results of a recent review of clinical trials with duration greater than 2 weeks, and which included study participants with metabolic disorders reported that 6 of the 7 studies reviewed found greater reductions in CRP concentration (-25 to -54%) with high fibre consumption (3.3-7.8 g/MJ) (North *et al.*, 2009).

A number of cross-sectional analyses of cohort studies have been conducted which have explored the relationship between dietary patterns and markers of inflammation. Ford *et al.* (Ford *et al.*, 2005) explored cross-sectional associations between the Healthy Eating Index (HEI) score and serum CRP concentration in 13,811 adult participants of the US Third National Health and Nutrition Examination Survey (1988-1994). A clear dose-response trend was observed, with improving dietary quality (reflected in a high HEI score) being associated with decreasing serum CRP concentration (odds ratio per 10 unit change: 0.92; 95% confidence interval (CI): 0.86-0.99). Similarly, an analysis of 732 disease-free women from the Nurses' Health Study I cohort noted that the prudent (healthy) dietary pattern, as determined by factor analysis, was inversely associated with plasma concentrations of CRP (p=0.02) and E-selectin (p= 0.001) (Lopez-Garcia *et al.*, 2004).

The reduced rank regression approach was used on a nested case-control analysis of 656 cases of type 2 diabetes and 694 controls from the Nurses' Health Study II (Schulze *et al.*, 2005). This method identified a dietary pattern that was strongly related to a range of inflammatory markers. The pattern represented a diet relatively high in sugar-sweetened soft drinks, refined grains, diet soft drinks, processed meat, and certain vegetables. The correlation between inflammatory markers and pattern-derived food groups identified through the use of stepwise regression indicated high correlations in particular between sugar-sweetened soft drinks, CRP, E-selectin and IL-6.

Few cohort studies have employed a prospective study design to specifically explore the relationship between dietary carbohydrate and markers of inflammation. Some cross-sectional analyses of cohort studies however, have explored the association between dietary fibre and whole grains on markers of inflammation (Qi and Hu, 2007). In one cross-sectional analysis of healthy participants of the Health Professionals' Follow-up Study (HPFS) and Nurses' Health Study II no association was observed between daily intakes of whole grains, bran, and germ with plasma concentrations of the inflammatory markers CRP, IL-6 and fibrinogen (Jensen *et al.*, 2006). However, the US Multi-Ethnic Study of Atherosclerosis reported significantly decreasing blood concentrations of both CRP and IL-6 with increasing consumption of whole grain foods as assessed using the Block food frequency questionnaire (FFQ) (Lutsey *et al.*, 2007). This was apparent even after adjustment for lifestyle factors such as smoking and physical activity, but not after additional adjustment for BMI.

Other European studies have demonstrated an inverse association between dietary fibre and markers of inflammation. The British Regional Heart Study is a follow-up study of 7,735 men (initially aged 40-59 years) recruited through 24 general practices (Wannamethee *et al.*, 2009). The cohort has been followed up from an initial screening in 1978-1980 through a 20th year follow-up examination. At this examination, 3,428 diabetes-free men provided a blood sample which was used in a cross-sectional analysis to explore the association between dietary fibre intake assessed through 7-day recall FFQ, and the markers of inflammation CRP, IL-6 and tissue plasminogen

activator (tPA). Each of these markers tended to decrease with each increasing dietary fibre intake quartile (all p<0.0001), and this association persisted with adjustment for age, waist circumference and other covariates. Bo *et al.* also reported an inverse association between dietary fibre intake and high sensitivity CRP (hsCRP), in a cohort of 1,653 Italian adults and also in a healthy subgroup with normal body mass index (n = 205) (Bo *et al.*, 2006).

A similar inverse association between dietary fibre (but not total carbohydrate) and CRP and IL-6 concentrations was observed in a 1year follow-up of a subsample of participants of the Finnish Diabetes Prevention Study even after adjustment for BMI (Herder *et al.*, 2009). Although these studies are not entirely consistent, most large cross-sectional analyses appear to demonstrate lower levels of biomarkers of inflammation with increasing intakes of either dietary fibre or foods rich in whole grain. As with all observational studies, these results should be interpreted cautiously. It is not possible to determine the direction of causality in cross-sectional studies and the data are potentially highly subject to the influence of confounding.

Suggested mechanisms for the role of dietary fibre or whole grains in the modulation of inflammatory markers include reductions in release of proinflammatory cytokines through decreased hyperglyacaemia and the effects of co-ingested phytochemicals such as antioxidants and phenolic compounds (Qi and Hu, 2007).

Previous studies in COMA reports

The table below lists 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, 1994;Committee on Medical Aspects of Food Policy, 1991) that concerned the relationship between dietary carbohydrates and markers of inflammation. Studies were initially scanned by title and abstract for relevance to the current review. Those deemed non-relevant were omitted and those of relevance were passed through the inclusion/ exclusion criteria applied to this review.

Papers from COMA reports that did not meet inclusion criteria used in this review

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

Table 3.2 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
(Miller *et al.*, 1986)	1) Usual diet 2) Usual diet + fat 3) Usual diet + carbohydrate	15 days	11	The intervention was less than 6 weeks.
(Renaud *et al.*, 1986)	Not applicable	Not applicable	2	The study was a cross-sectional survey.

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

Summary of the evidence base

Cohort studies

Only one cohort study reported outcomes concerning inflammation: fibrinogen with total carbohydrate and dietary fibre (Ludwig *et al.*, 1999). The US-based CARDIA Study is a multi-centre population-based study designed to explore longitudinal CVD risk factor development in black and white participants aged 18-30 years at baseline. Data on 2,909 participants who were initially healthy at baseline were included in the paper. Adjusted mean fibrinogen levels were presented from the 5 year follow up. Diet was assessed at baseline (1985-6) in this cohort using a detailed interviewer-administered 700-item FFQ.

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. Data from such studies should therefore be interpreted cautiously.

Trial design

Details concerning the design, participants, duration and nature of the interventions in this chapter are included in Table 3.4. Thirty three publications from 30 studies provided information on the relationship between carbohydrate interventions and markers of inflammation. Three of these employed a cross-over design, with washout period of 2 weeks, 0 days, and 6 weeks respectively (Landin *et al.*, 1992;Sharman and Volek, 2004;Andersson *et al.*, 2007). One study used adolescent participants (age 12 – 18 year) (Demol *et al.*, 2009), but the remainder studied adults. Most studies used men and women, but 5 included only women (Howard *et al.*, 2006;Jensen *et al.*, 2008;Mahon *et al.*, 2007;Noakes *et al.*, 2005;O'Brien *et al.*, 2005), and 4 only men (Landin *et al.*, 1992;Lovejoy *et al.*, 2003;Sharman and Volek, 2004;Wood *et al.*, 2006).

Critically, the trials evidence base consists almost entirely of studies using overweight or obese participants. The exception to this is the Swedish study published by Landin *et al.* which specified healthy, non-obese males (Landin *et al.*, 1992). The primary aim of most of these studies was to explore weight or fat loss and consequently, the majority are also energy restricted. CRP is strongly associated with measures of adiposity such as body mass index, waist circumference, and waist:hip ratio and is also known to decrease in response to weight loss (Selvin *et al.*, 2007). Differences in extent of weight loss between intervention groups therefore need to be taken into consideration when interpreting the impact of the dietary carbohydrate interventions reported here. Whether each dietary group decreased, increased or experienced no change in body weight is reported within the results tables.

Trials were conducted in the USA (17), Denmark (4), Australia (4), Spain (1), Sweden (2), Canada (1), and Israel (1).

The duration of interventions ranged from 6 weeks to a maximum of 6 years in the Women's Health Initiative Dietary Modification Trial (Howard *et al.*, 2006). The majority were less than 3 months in duration (23/30 less than 3 months). However, the trials inclusion criterion of 6 weeks duration should be more than adequate to detect changes in inflammatory markers such as CRP, as it is recognised that significant changes may occur even with acute, single meal interventions (Esposito *et al.*, 2003).

Stewart *et al.* (Stewart *et al.*, 2010) provide an estimate of the degree of variability in CRP levels that might be observed in intervention trials (this one of postmenopausal women). The high degree of variability in CRP levels within and between individuals they observed has implications for the required sample size for intervention trials. In terms of power to detect meaningful changes in inflammatory markers, Stewart *et al.* (Stewart *et al.*, 2010) estimated that with 90 participants they had a power of 99% to detect differences in CRP between intervention groups of the order of 30%. This is a large difference and smaller differences may still be important in terms of population health (but would require even larger sample sizes). King *et al.* (King *et al.*, 2008) also undertook a pre-study power calculation and estimated that they had 80% power to detect standardized mean differences in CRP concentrations between groups in the region of 0.6mg/L using 43 subjects per group. Half of the parallel groups trials included here had fewer than 30 participants in each intervention group which suggests that they may have been insufficiently powered to detect changes of the magnitude suggested by Stewart *et al.* or King *et al*., and so, in isolation should be interpreted cautiously.

Risk of bias

A summary of the risk of bias assessment is provided in Table 3.5. 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 or allocation concealment. None were judged to be 'biased' in these aspects of trial design. Blinding of participants and researchers to the various dietary approaches was more difficult to achieve, as might be anticipated with dietary intervention trials. There was evidence of 'no bias' in respect of participants in five trials (Landin *et al.*, 1992;Lovejoy *et al.*, 2003;Salas-Salvado *et al.*, 2008;Smith *et al.*, 2008;Wood *et al.*, 2006) and in eight trials in respect of researchers (Howard *et al.*, 2006;King *et al.*, 2008;Landin *et al.*, 1992;Lovejoy *et al.*, 2003;Pittas *et al.*, 2006;Smith *et al.*, 2008;Wood *et al.*, 2006). Three of the studies that reported successful blinding of the intervention utilised dietary fibre isolates, for which an acceptable control product was available (Landin *et al.*, 1992;Salas-Salvado *et al.*, 2008;Wood *et al.*, 2006).

Eight of the 33 papers included in this review were considered to have limitations with regard to incomplete or selective outcome reporting (Due *et al.*, 2008;Keogh *et al.*, 2008;Noakes *et al.*, 2006;Noakes *et al.*, 2005;Pereira *et al.*, 2004;Seshadri *et al.*, 2005;Stoernell *et al.*, 2008;Smith *et al.*, 2008).

Table 3.3 Characteristics of cohort studies

Cohort Name	Authors/ Reference	Population characteristics	Recruitment of participants	Dietary assessment methods	Length of follow up (years)	Initial cohort size	Losses to follow-up (%)
The CARDIA Study	(Ludwig *et al.*, 1999)	Young Black and White Adults Mean age: 18-30 %Male: 45.9 Country: USA Ethnicity: Multi-ethnic	Community cohort (4 sites: Alabama, Illinois, Minnesota, California)	Diet was assessed at study entry using a 700-item FFQ for intake over the previous month. The FFQ was reported to be validated.	10	5115	Not reported

Table 3.4 Markers of Inflammation - Trial characteristics (n.b. grey shading indicates a trial involving children or adolescents)

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Andersson *et al.*, 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
(Dansinger *et al.*, 2005)	≥1 cardiac risk factor BMI 27-42 Free of chronic disease No insulin therapy No medications which influence outcomes	USA 49% Male Age: (49) BMI: (35)	Parallel Group	12 months	Free living diet plan	160	1. Atkins 2. Zone 3. Weight watchers 4. Ornish	1. Carbohydrate restriction. 2. Macronutrient balance. 3. Calorie restriction. 4. Fat restriction. For all participants dietary advice was strictly followed for the first 2 months. Participants then selected their own adherence levels.	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 Energy 1755 kcal/d Fibre g/d:14 4. g/d: C 237 P 74 F 54.5 Energy 1711 kcal/d Fibre g/d:14.5	Yes	NIH

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(de Luis *et al.*, 2007) Spanish Hypocaloric Diet Study	BMI >30 No CHD, T2DM or HTN	Spain 30% Male Age: (43) BMI: (36)	Parallel Group	3 months	Free living diet plan	90	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. %E: F 25.4 Energy: 1630kJ/d 2. %E: C 30.9 Energy: 1574kJ/d	Yes	Not reported
(de Luis *et al.*, 2008) Spanish Hypocaloric Diet Study	BMI >30 No CHD, T2DM or HTN	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. %E: C 52 P 20 F 27 Energy 1500 kcal/d 2. %E: C 38 P 26 F 36 Energy 1507 kcal/d	Intended diet	Not reported
(de Luis *et al.*, 2009a) Spanish Hypocaloric Diet Study	BMI >30 No CHD or T2DM No medications which influence outcomes Not hyperlipidaemic / hypercholesterolaemic	Spain 22% Male Age: (46) BMI: (35)	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. %E: C 53 P 20 F 27 Energy 1500 kcal/d 2. %E: C 38 P 26 F 36 Energy 1507 kcal/d	Intended diet	Not reported
(Demol *et al.*, 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 mo 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. %E: C 20 P 50 F 30 g/d: C 60 2. %E: C 20 P 20 F 60 g/d: C 60 3. %E: C 50 P 20 F 30	Intended diet	Not reported
(Due *et al.*, 2008) MonoUnsaturated Fatty acids in Obesity trial	<3kg Δ weight in previous 2m Age 18-35y BMI 28-36 Non smokers No T2DM Pre-	Denmark 42% Male Age: (28) BMI: (31)	Parallel Group	6 months	Free living diet plan	154	1. High MUFA 2. Low fat	1. Dietary counselling and food provided from study supermarket. Prescribed 35-45%FAT, >20%MUFA This diet also included more whole-grains, legumes and nuts. SFA:MUFA:PUFA% 7:20:8 2. Dietary counselling. Food provided	1. %E: C 43.3 P 15.3 F 38.4 Energy: 11500kJ/d 2. %E: C 57.6 P 15.8 F 23.6	Yes	HA Foundation, The Danish Heart Association, The Danish Diabetes Association, The Danish Pork Council and

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	menopausal Recently involved in weight loss trial						3. Control	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.	Energy: 10500kJ/d 3. %E: C 49.8 P 15.9 F 32.1 Energy: 10900kJ/d		research institute funding
(Due *et al.*, 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. %E: C 48.9 P 21.2 F 30 Energy: 8400kJ/d 2. %E: 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
(Ebbeling *et al.*, 2005)	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. %E: C 47.2 P 21.1 F 33 Energy 1391 kcal/d Fibre g/d:20.7 2. %E: 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
(Howard *et al.*, 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	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. %E: C 53.9 P 17.7 F 28.8 Energy 1432 kcal/d Fibre g/d:19.6 2. %E: C 45.9 P 17.1 F 37 Energy 1546 kcal/d Fibre g/d:14.4	Yes	National Heart, Lung, and Blood Institute

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Jensen *et al.*, 2008) The Danish GI study	Age 20-40y BMI 25-30 Generally healthy Moderate alcohol No HTN 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. %E: C 81.2 P 12.8 F 5.9 Energy: 4860kJ/d Fibre g/d:29.3 2. %E: C 81.7 P 12.6 F 5.7 Energy: 4886kJ/d Fibre g/d:32.2	Yes	Research institute funding
(Johnston *et al.*, 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. %E: C 42 P 31 F 30 g/d: C 157 P 117 F 50 Energy: 6250kJ/d Fibre g/d:30 2. %E: 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 *et al.*, 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, 24%PRO, 30%FAT	1. %E: C 5 P 35 F 59 g/d: C 20 P 133 F 103 Energy: 6608kJ/d Fibre g/d:13 2. %E: 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
(King *et al.*, 2008) TRIM (The Trial to Reduce Inflammatory markers)	Age 40-65y BMI >25 Elevated CRP levels No CVD or untreated HTN No fibre supplement use Weight stable	USA 27% Male Age: (50) BMI: (34)	Parallel Group	3 months	Supplement	171	1. Low dose fibre supplement 2. High dose fibre supplement 3. Control	1. 7g/d psyllium 2. 14g/d psyllium 3. No supplementation		Yes	NIH and research Institute funding

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Landin *et al.*, 1992)	Generally healthy Middle-aged adults Not extremely athletic/active Not obese WHR of 0.91	Sweden 100% Male Age: (52) BMI: (25)	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 and the Swedish Nutrition Foundation & Goteborg Medical Society.
(Lovejoy *et al.*, 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. %E: C 52 P 15 F 33 2. %E: C 58 P 17 F 25	Intended diet	Government funding and Procter & Gamble Co.
(Mahon *et al.*, 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 restriction + carbohydrate /fat	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 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)	1. %E: C 47 P 20 F 33 Energy: 1570 kcal/d 2. %E: C 46 P 24 F 30 Energy: 1114 kcal/d 3. %E: C 51 P 25 F 24 Energy: 1098 kcal/d 4. %E: C 59 P 17 F 24 Energy: 1158 kcal/d	Yes	Cattlemen's Beef Board and the National Cattlemen's Beef Association, Research and University funding
(McMillan-Price *et al.*, 2006)	<150 kg <5kg Δ weight in the previous 2m Age 18-40y BMI >25 Maintain current PA levels No chronic illness No medication	Australia 24% Male Age: (32) BMI: (31)	Parallel Group	12 weeks	All food provided	129	1. High CHO, high GI diet 2. High CHO, low GI diet 3. High protein, high GI diet 4. High protein, low	All groups: 1400 kcal/d women and 1900 kcal/d men. 1. 55% CHO, 15% PRO, <30% FAT, fibre 30g/d. Diet based on high-GI whole grains, fiber-rich cereals/breads. GI 70, GL 127g 2. 55% CHO, 15% PRO, <30% FAT, fibre 30g/d. Diet based on low-GI food. GI 45, GL 89g 3. 45% CHO, 25% PRO, <30%FAT, fibre 30g/d. Diet based on lean red meat and high-GI CHO whole grains. GI 59, GL 75g 4. 45% CHO, 25% PRO, <30%FAT,	1. %E: C 60 P 18 F 19 Energy: 9630kJ/d Fibre g/d:23 2. %E: C 56 P 19 F 22 Energy: 9030kJ/d Fibre g/d:20 3. %E: C 42 P 28 F 27 Energy: 9220kJ/d Fibre g/d:19 4. %E: C 40 P 26 F 29 Energy: 8890kJ/d	Yes	National Heart Foundation of Australia and Meat and Livestock Australia

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
							GI diet	fibre 30g/d. Diet based on lean red meat/low-GI CHO foods.GI 54, GL 59g	Fibre g/d:21		
(Meckling *et al.*, 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. %E: C 61.9 P 19.5 F 17.8 Energy: 6077kJ/d Fibre g/d:20.3 2. %E: C 15.4 P 26.2 F 55.5 Energy: 6421kJ/d Fibre g/d:8.9	Yes	Research institute funding
(Noakes *et al.*, 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 isocaloric with 30% energy restriction during weeks 1-8, weight maintenance weeks 9-12. 36% of key foods provided to aid compliance	1. %E: C 12.4 P 30.5 F 54.3 Energy: 7706kJ/d 2. %E: C 66 P 20.3 F 12.5 Energy: 7000kJ/d 3. %E: C 48.7 P 21.4 F 28 Energy: 7659kJ/d	Yes	The National Heart Foundation of Australia
(Noakes *et al.*, 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. %E: C 44.2 P 31.3 F 22.1 Energy: 5310kJ/d Fibre g/d:27.6 2. %E: C 60.8 P 17.8 F 20.1 Energy: 5219kJ/d Fibre g/d:26.1	Yes	Meat and Livestock Australia
(O'Brien *et al.*, 2005) American LC study IV	Age >18y BMI 30-35 No CHD, T2DM or HTN No weight Δ >10% in past 6m	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.		Yes	NIH, University funding and American Heart Association Grant-in-Aid
(Pereira *et al.*, 2004)	Age 18-35y BMI >25 Generally healthy No medications which influence outcomes No recent weight loss program Non smokers Not extremely	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. %E: C 43 P 27 F 30 Energy: 1500 kcal/d Fibre g/d:32 2. %E: 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

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	athletic/active Weight stable										
(Phillips *et al.*, 2008)	Age 18-50y BMI 29-39 Generally healthy No CHD, T2DM or HTN 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. Isocaloric 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.%E: F 30	Intended diet	NIH and the Medical College of Wisconsin Cardiovascular Center
(Pittas *et al.*, 2006) CALERIE	<15 lb Δ weight in previous 12m Age 24-42y Age 5-10y BMI 25-30 Fasting plasma glucose <5.6mmol/l Generally healthy No chronic illness No familial diabetes No strong family history of CVD/CHD	USA 21.8% Male Age: 24 - 42(35) BMI: (28)	Parallel Group	6 months	All food provided	34	1. Energy restricted high GL diet 2. Energy restricted low GL diet	1. 30% calorie restriction. fiber 15 g/1000kcal. Estimated GI=86, GL=116 g/1000 kcal 2. 30% calorie restriction. fiber 15 g/1000 kcal. Estimated GI=53, GL=45 g/1000kcal	1. %E: C 60 P 20 F 20 2. %E: C 40 P 30 F 30	Yes	Research institute funding and U.S. Department of Agriculture cooperative
(Salas-Salvado *et al.*, 2008)	Age 18-70y BMI >25 Generally healthy Highly motivated to	Spain 22% Male Age: 18 - 70(48)	Parallel Group	16 weeks		200	1. Mixed soluble fibre twice a day 2. Mixed soluble fibre	1. Mixed fibre dose (3g Plantago ovata husk and 1g glucomannan) added to hypoenergetic diet (-2.5MJ/d) twice a day. 2. Mixed fibre dose (3g Plantago ovata husk and 1g glucomannan)	1. %E: C 45 P 25 F 35 2. %E: C 45 P 25 F 35	Intended diet	MADAUS, S.A. and the Carlos III Health Institute funding

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
	lose weight No medication No recent weight loss program	BMI: (31)					3 times a day 3. Placebo	added to hypoenergetic diet (-2.5MJ/d) three times a day. 3. 3g microcrystalline cellulose added to an energy restricted diet (reduced by 2.5MJ/d)	3. %E: C 45 P 25 F 35		
(Seshadri *et al.*, 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. %E: C 31 P 25 F 44 Energy: 1343 kcal/d 2. %E: C 51 P 16 F 32 Energy: 1590 kcal/d	Yes	Veteran Affairs Healthcare Network Competitive Pilot Project Grant
(Sharman and Volek, 2004) American VLC study	Generally healthy No medications which influence outcomes No supplement use Non smokers Not extremely athletic/active Overweight/ Obese Weight stable	USA 100% Male Age: (33) BMI: (34)	Crossover (washout 0 days)	6 weeks	Free living diet plan	15	1. Very low carbohydrate 2. Low fat	1. <10%CHO, hypoenergetic (-500 kcal/d) 2. <30%FAT, hypoenergetic (-500 kcal/d) <10% SAFA, <300mg cholesterol	1. %E: C 8 P 28 F 63 Energy: 7770kJ/d Fibre g/d:16 2. %E: C 56 P 20 F 23 Energy: 6540kJ/d Fibre g/d:17	Yes	The Robert C. Atkins Foundation
(Smith *et al.*, 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 2. Beta glucan, high molecular weight	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. 2. High molecular weight barley B-glucan. 6g B-glucan per day was given as a dietary supplement		Yes	NIH

Authors, Study Name	Subject inclusion criteria	Characteristics of participants	Trial Design (washout duration)	Length of Inter-vention	Intervention Style	Total n	Intervention Group Names	Intervention Description	Diet/Supplement nutritional characteristics	Actual diet consumed reported?	Funding source
(Sorensen *et al.*, 2005) Danish Sweetened Beverage Study	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 2. Sweetener	1. Sucrose-containing food and drinks provided ~2g/kg/day (~23% total energy). 80% of sucrose within drinks and 20% within food. 2. Food and drinks provided matched sucrose intervention but contained artificial sweeteners	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
(Stoernell *et al.*, 2008)	Mild to moderate lipidaemias No recent weight loss program No T2DM Not hyperlipidaemic / hypercholesterolaemic	USA 46-50% Male Age: Low fat group 57, Low CHO group 48 BMI: Low fat group 30, low CHO group 35	Parallel Group	8 weeks	Free living diet plan	28	1. Low carbohydrate diet 2. Low fat diet	1. Similar to Atkins but not as restrictive on quantity of carbohydrates. Goal 15% E CHO 2. Low fat diet was based on the standard dietary approach to lower elevated triglycerides (including weight loss)	1. %E: C 20 P 25 F 55 Energy: 5475kJ/d 2. %E: C 48 P 20 F 33 Energy: 6898kJ/d	Yes	No funding: Master of Science thesis
(Thompson *et al.*, 2005)	BMI 30-40 No medications which influence outcomes No supplement use Weight stable	USA 14% Male Age: mean not reported BMI: mean not reported	Parallel Group	48 weeks	Free living diet plan	90	1. Energy restricted diet 2. Energy restriction + dairy 3. Energy restriction + dairy + fibre	1. Calorie deficit of 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	1. %E: C 54.5 P 18.8 F 26.3 Energy: 1437.1 kcal/d Fibre g/d:18.8 2. %E: C 53.6 P 21.5 F 24.6 Energy: 1490.1 kcal/d Fibre g/d:17.6 3. %E: C 58.1 P 20.9 F 20.6 Energy: 1510.2 kcal/d Fibre g/d:28.9	Yes	National Dairy Council and research institute funding
(Wood *et al.*, 2006) American Soluble Fibre Study	DBP <90mmHg Weight loss <2.5kg in the past 6m No CHD or T2DM Not on CHO restricted diet 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 + Soluble fibre 2. Low carbohydrate diet + placebo	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. %E: C 12.5 P 28.4 F 60.7 Energy: 1632 kcal/d Fibre g/d:12.7 2. %E: C 13.3 P 27.1 F 59.6 Energy: 1632 kcal/d Fibre g/d:9.6	Yes	Not reported

Table 3.5 Markers of Inflammation - RCT bias information

Authors	Allocation sequence generation	Allocation concealment	Participant blinding	Researcher Blinding	Incomplete outcome reporting	Selective outcome reporting	Any other bias
(Andersson *et al.*, 2007)	Unclear	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Dansinger *et al.*, 2005)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(de Luis *et al.*, 2007)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(de Luis *et al.*, 2008)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(de Luis *et al.*, 2009a)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Demol *et al.*, 2009)	Unclear	Unclear	Bias	Bias	No Bias	Bias	No Bias
(Due *et al.*, 2008)	No Bias	No Bias	Bias	Bias	Bias	No Bias	No Bias
(Due *et al.*, 2005)	No Bias	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
(Ebbeling *et al.*, 2005)	Unclear	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Howard *et al.*, 2006)	No Bias	Unclear	Bias	No Bias	No Bias	No Bias	No Bias
(Jensen *et al.*, 2008)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Johnston *et al.*, 2006)	No Bias	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Keogh *et al.*, 2008)	No Bias	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(King *et al.*, 2008)	No Bias	No Bias	Bias	No Bias	No Bias	No Bias	No Bias
(Landin *et al.*, 1992)	Unclear	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Lovejoy *et al.*, 2003)	No Bias	Unclear	No Bias	No Bias	No Bias	No Bias	No Bias
(Mahon *et al.*, 2007)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(McMillan-Price *et al.*, 2006)	No Bias	Unclear	Bias	Bias	No Bias	No Bias	No Bias
(Meckling *et al.*, 2004)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Noakes *et al.*, 2006)	No Bias	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Noakes *et al.*, 2005)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(O'Brien *et al.*, 2005)	Unclear	Unclear	Bias	Unclear	Unclear	No Bias	No Bias
(Pereira *et al.*, 2004)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Phillips *et al.*, 2008)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Pittas *et al.*, 2006)	No Bias	Unclear	Bias	No Bias	Unclear	Unclear	Unclear
(Salas-Salvado *et al.*, 2008)	No Bias	No Bias	No Bias	No Bias	No Bias	No Bias	No Bias
(Seshadri *et al.*, 2005)	Unclear	Unclear	Unclear	Unclear	Bias	No Bias	No Bias
(Sharman and Volek, 2004)	Unclear	Unclear	Bias	Unclear	No Bias	No Bias	No Bias
(Smith *et al.*, 2008)	No Bias	Unclear	No Bias	No Bias	No Bias	Bias	No Bias
(Sorensen *et al.*, 2005)	No Bias	Unclear	Unclear	Unclear	No Bias	No Bias	No Bias
(Stoernell *et al.*, 2008)	Unclear	Unclear	Bias	Unclear	Bias	No Bias	No Bias
(Thompson *et al.*, 2005)	No Bias	No Bias	Bias	Bias	No Bias	No Bias	No Bias
(Wood *et al.*, 2006)	No Bias	Unclear	No Bias	No Bias	Unclear	No Bias	No Bias

Results - Inflammatory markers

Inflammatory markers, total carbohydrate and high carbohydrate diets

Summary of cohort results

Data were extracted from one study: The CARDIA Study (Ludwig *et al.*, 1999). This study of black and white participants aged 18-30 years at baseline, reported adjusted mean fibrinogen levels at 5 year follow up by quintile of carbohydrate intake as assessed at study entry. Mean fibrinogen of participants in the lowest quintile of carbohydrate intake was not significantly different from those in the highest quintile of intake (p=0.32). Whilst diet was assessed at multiple time points (0, 7, 10 years) during the 10 year follow-up phase of the study, fibrinogen was only assessed at the 5-year follow-up.

Carbohydrate intake was measured using a 700 item FFQ and was presented as the percentage total energy from carbohydrate.

This study adjusted for an appropriate number of different variables including age, sex, physical activity and energy intake.

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

Summary of RCT data

Randomised controlled trials that assessed the effect of high carbohydrate, low fat, low protein diets compared with low carbohydrate, higher protein/fat diets on markers of systemic inflammation are included here. It should be noted that some of these trials were designed to assess other aspects of diet including the nature of the carbohydrate (high or low GI, or whole grain content). However, if the difference in percentage carbohydrate from energy was greater than 5% between diet groups and all other inclusion criteria were met, the study was eligible for inclusion.

The most common marker of inflammation studied was CRP, with 17 trials providing data (see Table 3.6). Five studies provided data on cytokine concentrations (IL-6, TNFα) (de Luis *et al.*, 2007;de Luis *et al.*, 2008;de Luis *et al.*, 2009a;Seshadri *et al.*, 2005;Sharman and Volek, 2004). Four studies provided data on adhesion molecules (E-selectin , P-selectin, ICAM-1, VCAM-1, PAI-1 activity, tPA) (Keogh *et al.*, 2008;Meckling *et al.*, 2004;Sharman and Volek, 2004;Ebbeling *et al.*, 2005). Two studies reported clotting associated markers (fibrinogen and factor VII/proconvertin) (Lovejoy *et al.*, 2003;Howard *et al.*, 2006). One study provided data on amyloid A in relation to variation in the proportion of carbohydrate consumed (O'Brien *et al.*, 2005). Sufficient trials data were available to undertake meta-analyses for two inflammatory markers, CRP and TNF-α.

C-Reactive Protein

Seventeen studies were eligible to be included in the meta-analysis reporting associations between CRP and dietary differences in carbohydrate and fat and/or protein between groups in adults. Definitions of different levels of carbohydrate and fat are reported in the trial characteristics table (Table 3.4). The standard method of reporting CRP is in mg per litre. Some studies reported CRP results as mg/dL that were of the same order of magnitude as would be expected if expressed as mg/L. These were (de Luis *et al.*, 2007;de Luis *et al.*, 2008;de Luis *et al.*, 2009a;de Luis *et al.*, 2009b). These papers are thought to relate to the same study and so results from only one were included in the meta-analysis (de Luis *et al.*, 2007). The CRP data were included unaltered (assumed to be mg/L).

It was not possible to include three studies in the meta-analysis due to lack of data on variance within the outcome and because the study reported by Demol *et al.* was on adolescents rather than adults (Demol *et al.*, 2009;Stoernell *et al.*, 2008;O'Brien *et al.*, 2005). Data from the studies of Stoernell *et al.* in adults (Stoernell *et al.*, 2008) and Demol *et al.* in adolescents (Demol *et al.*, 2009) found no difference in CRP response between low and high carbohydrate diets. Similarly, the study by O'Brien *et al.* which compared a very low carbohydrate diet with a high carbohydrate, low fat diet over three months in obese women, found that the macronutrient composition of the diet had little independent effect on CRP concentrations (O'Brien *et al.*, 2005). Both study groups lost weight and this was reflected in similar decreases in CRP. These three studies not included in the meta-analysis appear to have a similar outcome to the pooled estimate from the meta-analysis.

Results from the first follow up point after completion of the intervention for each study were used in the meta-analysis. This ranged from 6 weeks to 12 months. Five studies had more than two groups (Mahon *et al.*, 2007;Due *et al.*, 2008;Dansinger *et al.*, 2005;McMillan-Price *et al.*, 2006;Noakes *et al.*, 2006). In four studies the group with the lowest carbohydrate level was compared with the group with the highest carbohydrate level. In one study with four groups, the subjects were split into 2 groups; namely high GI diet and low GI diet (McMillan-Price *et al.*, 2006). Two studies had data from different genetic subgroups (Ala54Thr polymorphism of fatty acid-binding protein 2, and -55CT polymorphism of the UCP3 gene) (de Luis *et al.*, 2008;de Luis *et al.*, 2009a). Mutant and wild-type participants did not differ in their CRP response to dietary type (de Luis *et al.*, 2008) and polymorphisms of the UCP3 gene did not differentially affect CRP response to high and low carbohydrate diets (de Luis *et al.*, 2009a).

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 difference in percentage of energy between groups of 5% or more was required. This was on the basis of reported consumption rather than the intended or prescribed diet unless otherwise stated – see trial characteristics table.

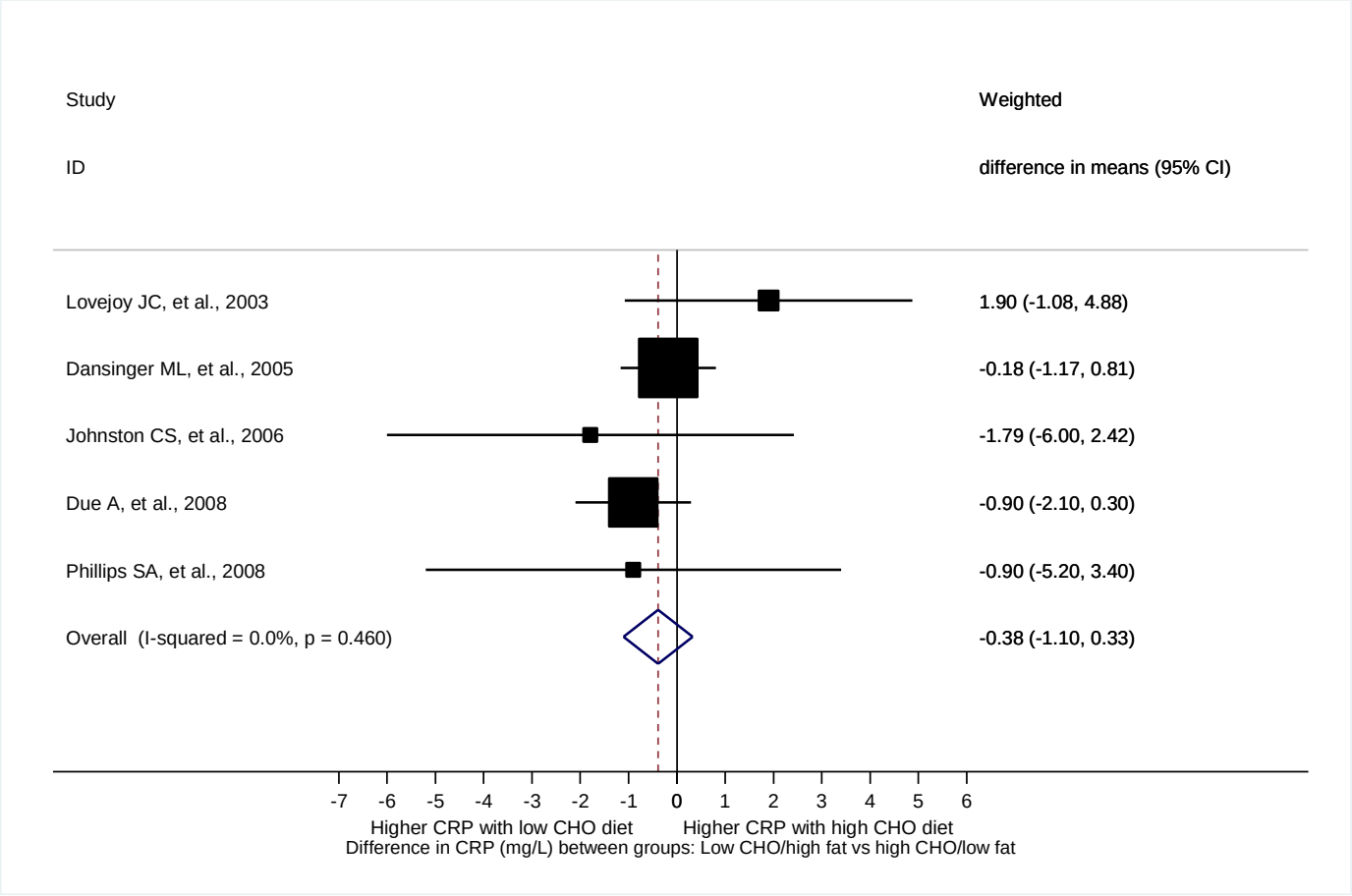
Higher carbohydrate, lower fat diets were differentiated from lower carbohydrate, higher fat diets where percentage of energy from fat differed by 2% or more. Higher carbohydrate, lower protein diets were differentiated from lower carbohydrate, higher protein diets where percentage of energy from fat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

Higher carbohydrate, lower fat diets vs. lower carbohydrate, higher fat diets

The data from five studies were pooled in a meta-analysis that compared CRP results after high carbohydrate diets with diets that were lower in carbohydrate by at least 5% of energy and which were different in fat content by at least 2% of energy. The pooled estimate indicated that fasting blood CRP was 0.38mg/L (95% CI -0.33 to 1.10) lower with consumption of a high carbohydrate diet compared with a low carbohydrate diet. This was not statistically significant from zero (p=0.29). Heterogeneity denoted by I^2 was 0% (95% CI 0 to 77%). Statistically, there was no evidence that a diet higher in carbohydrate and lower in fat is associated with differences in CRP levels. A funnel plot was not carried out due to the small number of studies included in the analysis.

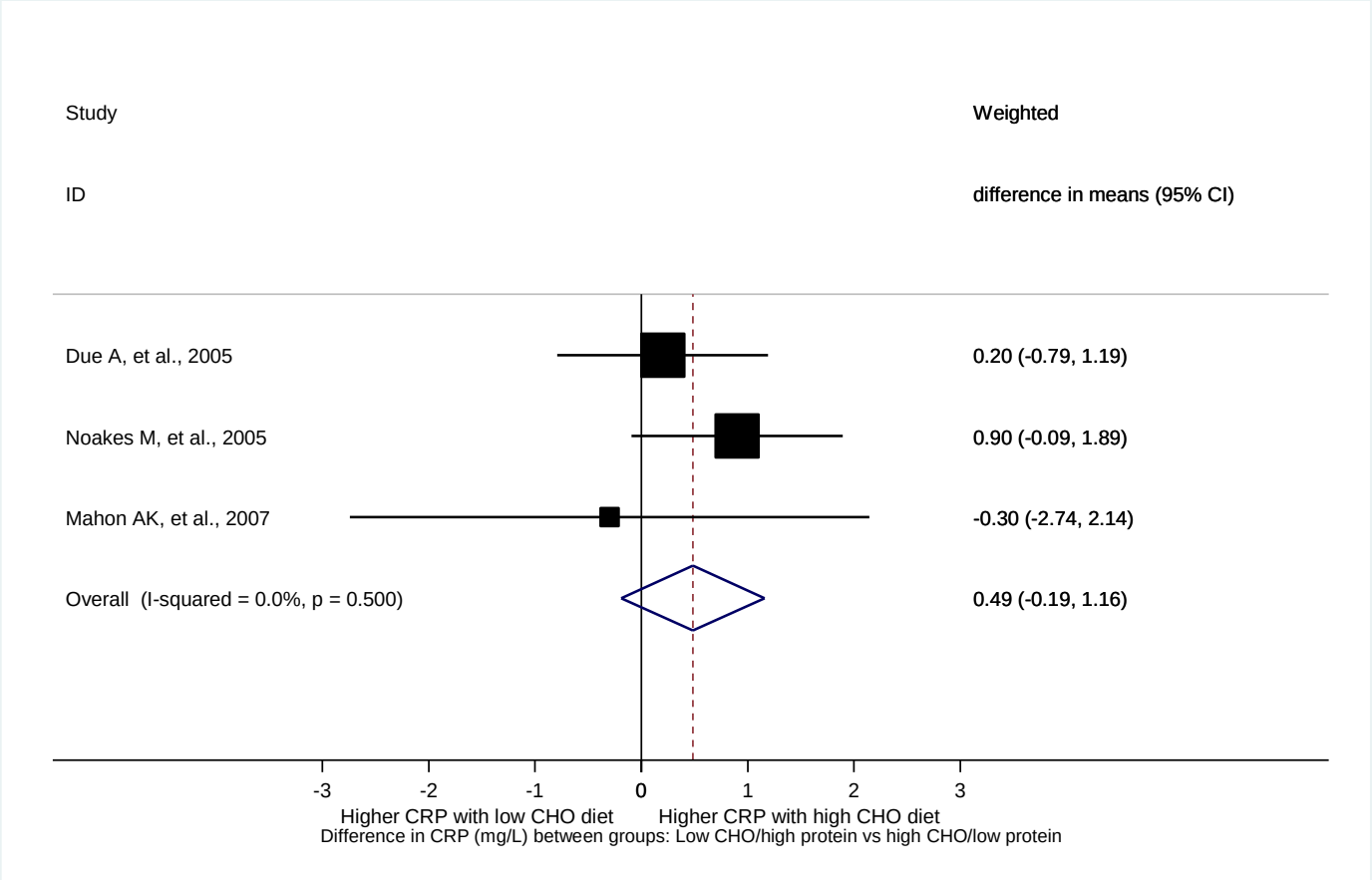
Figure 3.1 Forest plot for higher carbohydrate, lower fat diets and lower carbohydrate, higher fat diets and CRP (mg/L)



Higher carbohydrate, lower protein diets vs. lower carbohydrate, higher protein diets

The data from three studies were pooled in a meta-analysis that compared CRP results after high carbohydrate diets with diets that were lower in carbohydrate by at least 5% of energy and which were different in protein content by at least 2% of energy. The pooled estimate indicated that fasting blood CRP was 0.49mg/L (95% CI -0.19 to 1.16) higher with consumption of a high carbohydrate, low protein diet compared with a low carbohydrate, high protein diet. This was not statistically significantly different from zero (p=0.16). Heterogeneity denoted by I^2 was 0% (95% CI 0 to 85%). Statistically, there was no evidence that a diet higher in carbohydrate and lower in protein is associated with differences in CRP levels. A funnel plot was not carried out due to the small number of studies included in the analysis.

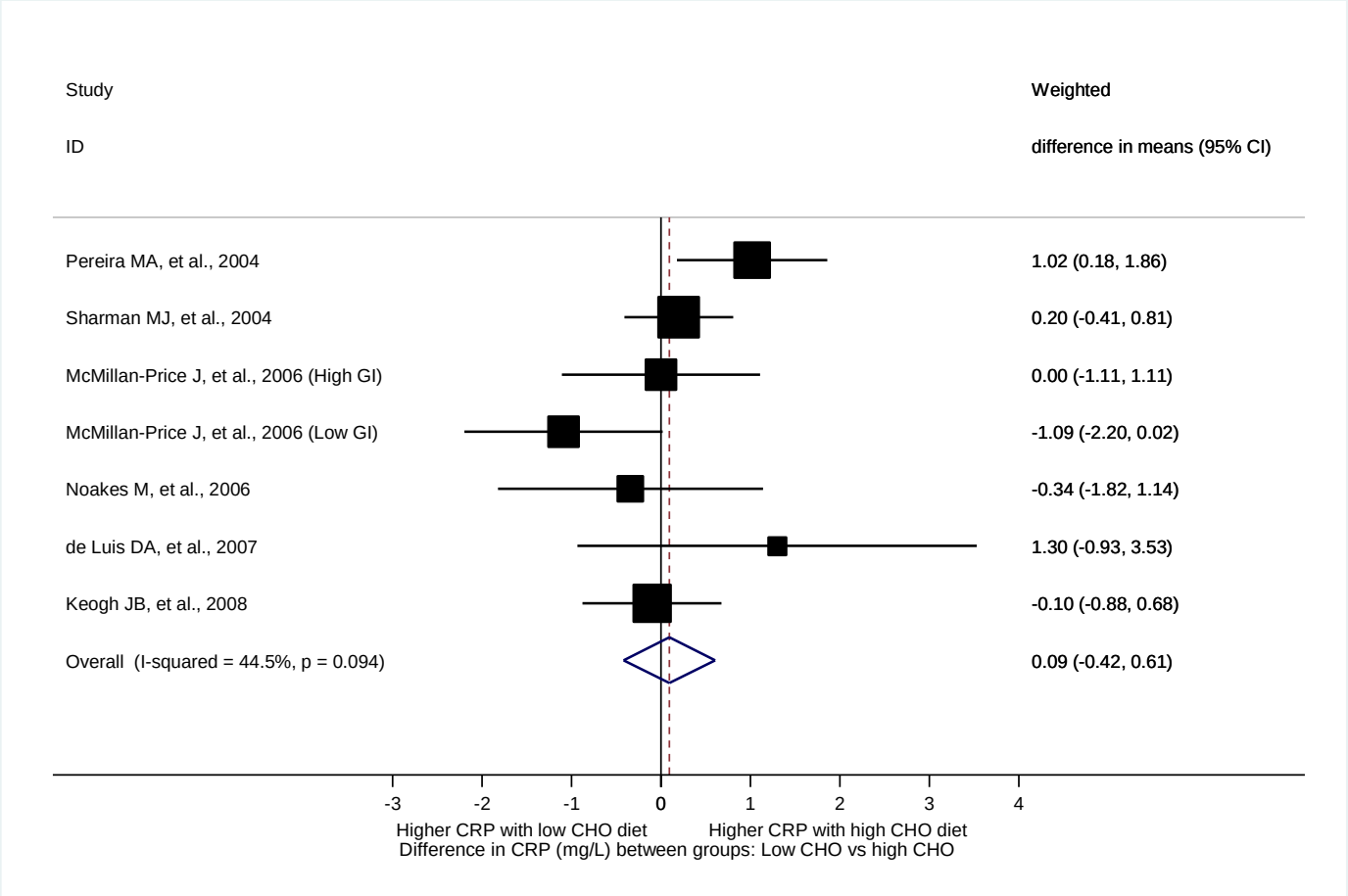
Figure 3.2 Forest plot for higher carbohydrate, lower protein diets and lower carbohydrate, higher protein diets and CRP (mg/L)



Higher carbohydrate, lower protein, low fat diets vs. lower carbohydrate, higher protein and higher fat diets

The data from six studies were pooled in a meta-analysis that compared CRP results after high carbohydrate diets with diets that were lower in carbohydrate by at least 5% of energy and which were different in fat and protein content by at least 2% of energy. The pooled estimate indicated that fasting blood CRP was 0.09mg/L (95% CI -0.42 to 0.61) higher with consumption of a high carbohydrate diet compared with a low carbohydrate diet. This was not statistically significant from zero (p=0.72). Heterogeneity denoted by I^2 was 45% (95% CI 0 to 77%). Statistically, there was no evidence that a diet higher in carbohydrate is associated with differences in CRP levels. A funnel plot was not carried out due to the small number of studies included in the analysis.

Figure 3.3 Forest plot for higher carbohydrate, lower protein and fat diets and lower carbohydrate, higher protein and fat diets and CRP (mg/L)



In each of these studies, blood concentrations of the various adhesion molecules tended to decrease in line with weight losses experienced (see results tables for indication of weight status in each intervention group). These data indicate that weight loss is primarily the driving force underlying the reductions in CRP, rather than the macronutrient content of the diets.

Cytokines

Data from five studies reporting IL-6 or TNF-α are included here (see Table 3.7).

Interleukin 6

Four papers provided results concerning the effects of high versus low carbohydrate diets on interleukin 6 (IL-6). However, the papers published by de Luis *et al.* are thought to be from the same study (not confirmed by the author) and so there were two remaining studies, which meant there were insufficient to include in a meta-analysis. Definitions of different levels of carbohydrate are reported in the trial characteristics table (Table 3.4).

The first follow up point after completion of the intervention for each study ranged from 6 weeks to 3 months. Two papers had 4 intervention groups (de Luis *et al.*, 2008;de Luis *et al.*, 2009a) which compared high and low carbohydrate in participants with different genetic profiles.

In the study by Sharman and Volek (Sharman and Volek, 2004), a very-low-carbohydrate diet (<10% energy from carbohydrate) was compared with a conventional low-fat weight-loss diet in 15 overweight men -using a cross-over design. After 6 weeks, the decrease in IL-6 was similar in both groups when expressed as the direct comparison between groups, and also when expressed as the change in inflammatory biomarkers per 1kg reduction in body mass.

In the three papers published by de Luis and colleagues, two hypoenergetic diets were compared: a low carbohydrate diet (higher fat and protein) and a higher carbohydrate (lower fat and protein) diet, with results reported at either 2 or 3 months after randomisation (see Trial Characteristics table for details). Changes in IL-6 were similar in both diet groups overall (de Luis *et al.*, 2007), in individuals with different polymorphisms of the fatty acid (FA) binding protein 2 (FABP2) gene (de Luis *et al.*, 2008) and 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).

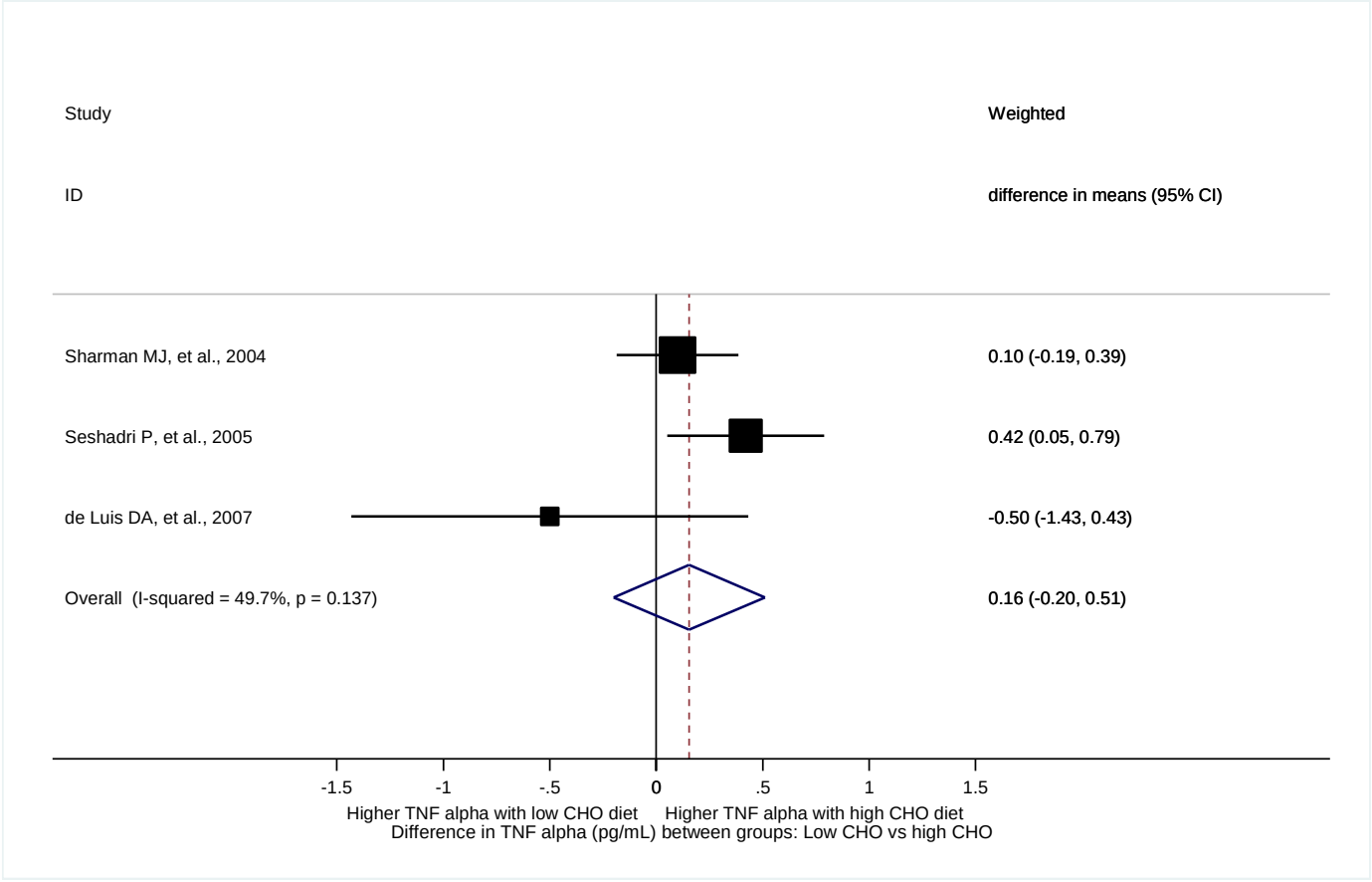
Tumour necrosis factor-α

Three studies were eligible to be included in the meta-analysis reporting associations between Tumour Necrosis Factor-α (TNF-α) and dietary differences in carbohydrate in adults. Definitions of different levels of carbohydrate are reported in the trial characteristics table. There were insufficient studies to stratify on other macronutrients; namely fat and protein. The standard method of reporting TNF-α is in pg per millilitre.

The first follow up period after completion of the intervention for each study was used in the meta-analysis. This ranged from 6 weeks to 6 months. Data from two papers (de Luis *et al.*, 2009a;de Luis *et al.*, 2008) 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.*, 2007). Changes in TNF-α were similar in both diet groups overall (de Luis *et al.*, 2007), in individuals with different polymorphisms of the fatty acid (FA) binding protein 2 (FABP2) gene (de Luis *et al.*, 2008) and 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).

The pooled estimate of three studies indicated that fasting blood TNF-α was 0.16pg/mL (95% CI -0.20 to 0.51) higher with consumption of a high carbohydrate diet compared with a low carbohydrate diet. This was not statistically significantly different from zero (p=0.39). Heterogeneity denoted by I^2 was 50% (95% CI 0 to 85%). Statistically, there was no evidence that a high carbohydrate diet is associated with differences in TNF-α levels. A funnel plot was not carried out due to the small number of studies included in the analysis.

Figure 3.4 Forest plot for high carbohydrate diets and TNF-α (pg/mL)



Adhesion molecules

Four studies provided data on adhesion molecules (E-selectin, P-selectin, ICAM-1, VCAM-1, PAI-1 activity, tPA) (Keogh *et al.*, 2008;Meckling *et al.*, 2004;Ebbeling *et al.*, 2005;Sharman and Volek, 2004). Three studies were eligible to be included in the meta-analysis reporting associations between plasminogen activator inhibitor 1(PAI-1) and dietary differences in carbohydrate in adults (Keogh *et al.*, 2008;Meckling *et al.*, 2004;Ebbeling *et al.*, 2005). Definitions of different levels of carbohydrate are reported in the trial characteristics table. Upon inspection, the results were too heterogeneous to obtain a pooled estimate.

In the study reported by Ebbling *et al.* both diet groups lost similar amounts of weight, but at the interim follow-up (6 months), PAI-1 activity had decreased by 58% in the low carbohydrate/low GI dietary group and increased by 30% in the high carbohydrate/high GI group (Ebbeling *et al.*, 2005). At 12 months, the extent of change in the low carbohydrate/low GI group had diminished somewhat (-39%) but was still significantly different from the change in the high carbohydrate /high GI group (+33%) (p=0.004). Energy and dietary fibre intakes were similar in both groups. The studies by Keogh *et al.* and Meckling *et al.* did not find any difference in PAI-1 activity between the high carbohydrate and low carbohydrate diets tested (Keogh *et al.*, 2008;Meckling *et al.*, 2004).

ICAM -1 and sICAM-1 (soluble intercellular cell-adhesion molecule-1) levels were not affected by the carbohydrate content of the diets tested by Keogh *et al.* (Keogh *et al.*, 2008) and Sharman and Volek (Sharman and Volek, 2004), although levels decreased in all diet groups in both studies.

VCAM-1 levels were not affected by the carbohydrate content of the diets tested by Keogh *et al.* (Keogh *et al.*, 2008).

P-selectin levels were not affected by the carbohydrate content of the diets tested by Keogh *et al.* (Keogh *et al.*, 2008), but there was a greater reduction in soluble P-selectin with the very low carbohydrate diet in the study reported by Sharman and Volek (Sharman and Volek, 2004) when the sP-selectin values were normalised and expressed as delta change per 1kg reduction in body mass (3.13 vs. 0.78, p=0.03). These data are not included in table 3.7.

E-selectin levels were not differentially affected by the carbohydrate content of the diets tested by Keogh *et al.* (Keogh *et al.*, 2008).

In each of these studies, blood concentrations of the various adhesion molecules tended to decrease in line with weight losses experienced. These data indicate that weight loss is primarily the driving force underlying the reductions in most of the inflammatory biomarkers, rather than the macronutrient content of the diets.

Clotting-associated factors

Two studies provided data on fibrinogen and factor VII (Lovejoy *et al.*, 2003;Howard *et al.*, 2006). Lovejoy *et al.* conducted a 9 month trial designed to compare the standard control diet (52% carbohydrate, 33% fat) with a high carbohydrate, low fat diet (58% carbohydrate, 25% fat) in healthy overweight men (Lovejoy *et al.*, 2003). A third comparison group was also studied, where one third of the dietary fat was replaced with the non-absorbable fat Olestra. However, data from that group were not eligible for inclusion in this review. Both groups lost weight (4±1.25 kg in the control group, and 1.79±0.81kg in the high carbohydrate diet group), but there were no significant differences in fibrinogen or Factor VII between the diet groups at 9 months.

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). 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. Results concerning blood fibrinogen levels are reported here at three years from baseline randomisation. Both groups experienced a decrease in fibrinogen (by -10.2 and -11.1 mg/dL in control and low fat groups respectively), but the difference between these means was not statistically significant.

Serum Amyloid A

One study provided data on serum amyloid A levels in relation to dietary carbohydrate manipulation. O'Brien *et al.* compared the effects of the American Heart Association Step 1 diet (55% carbohydrate, 30% fat) with an *ad libitum* very low carbohydrate (<20g/d, rising to 60g/d) diet in 44 obese women (O'Brien *et al.*, 2005). At the end of the intervention period (3 months), there was a greater decrease in serum amyloid A in the group following the very low carbohydrate diet ($p=0.04$), however, weight losses in this group were also greater (-7.6±3.2 kg vs. -4.3±3.5kg, $p<0.01$).

Table 3.6 Inflammatory markers and total carbohydrate: cohort study

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 (SD)	P trend	Adjustments
13704 (Ludwig *et al.*, 1999) The CARDIA Study	USA, Multi-ethnic, Generally healthy, No hypertension, No T2DM	18-30 %M 45.9	5115	10 years	FFQ (700)	Carbohydrate, total (% energy)	Fibrinogen Fasting, mg/dL	Race - White	(51.9) vs (33.5)	% Energy	253 vs. 257	0.32	Age, Alcohol, Centre, Education, Energy Intake, Physical Activity, Gender, Smoking, Vitamin intake
13705 The CARDIA Study								Race - Black	(51.9) vs (33.5)	% Energy	268 vs. 275	0.17	As above

Table 3.7 Inflammatory markers and high carbohydrate diets: RCT data

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
C-reactive protein														
Adolescent study														
(Demol *et al.*, 2009) 15413		High carbohydrate, low fat	20/20	0.56 (SD 0.29)	0.56 (SD 0.37)					CRP	Fasting (mg/dL)	12 weeks	Decrease	unclear
		Low carbohydrate, high fat	17/17	1.52 (SD 0.32)	0.61 (SD 0.38)			NS		CRP	Fasting (mg/dL)	12 weeks	Decrease	unclear
		Low carbohydrate, high protein	18/18	0.64 (SD 0.29)	0.43 (SD 0.32)			NS		CRP	Fasting (mg/dL)	12 weeks	Decrease	unclear
Adult studies														
(de Luis *et al.*, 2008) 16150	Genetics - wild-type Ala54/Ala54	Low carbohydrate	55/105	3.2 (SD 2.3)	2.6 (SD 2.2)					CRP	Fasting	2 months	Decrease	unclear
		Low fat	55/99	5.5 (SD 5.4)	3.9 (SD 4.4)					CRP	Fasting	2 months	Decrease	unclear
(de Luis *et al.*, 2008)	Genetics - mutant-type	Low carbohydrate	50/105	6.1 (SD 5.8)	6.3 (SD 5.8)					CRP	Fasting (mg/dL)	2 months	Decrease	unclear

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
16167	Ala54/Thr54 or Thr54/Thr54	Low fat	44/99	4.7 (SD 5.3)	3.4 (SD 3.1)					CRP	Fasting (mg/dL)	2 months	Decrease	unclear
(de Luis *et al.*, 2007) *14020		Low carbohydrate	47/47	5.6 (SD 6)	4.1 (SD 4)		<0.05	NS		CRP	Serum (mg/dL)	3 months	Decrease	unclear
		Low fat	43/43	5.5 (SD 6.7)	5.4 (SD 6.6)		NS			CRP	Serum (mg/dL)	3 months	Decrease	unclear
(Keogh *et al.*, 2008) *16738		High carbohydrate, low SFA	completers not reported/50	3.9 (SD 2.8)	2.8 (SD 2.1)			NS		CRP	(mg/L)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	completers not reported/57	3.2 (SD 1.8)	2.9 (SD 2.0)					CRP	(mg/L)	8 weeks	Decrease	unclear
(de Luis *et al.*, 2009a) 16709	Genetics - UCP3 Gene -55CC polymorphism	Low carbohydrate	54/67	5.1 (SD 2.3)	4.7 (SD 2.2)		NS			CRP	(mg/dL)	2 months	Decrease	unclear
		Low fat	40/64	4.2 (SD 5.5)	4.6 (SD 6.6)		NS			CRP	(mg/dL)	2 months	Decrease	unclear
(de Luis *et al.*, 2009a) 16710	Genetics - UCP3 Gene -55CT/TT polymorphism	Low carbohydrate	13/67	5.9 (SD 5.8)	5.3 (SD 5.8)		NS			CRP	(mg/dL)	2 months	Decrease	unclear
		Low fat	24/64	5.5 (SD 5.3)	5.1 (SD 3.1)		NS			CRP	(mg/dL)	2 months	Decrease	unclear
(Mahon *et al.*, 2007) *15075		Control	11/11	3.5 (SD 3.7)	3.2 (SD 3.3)	-0.3 (SD 1.1)	NS			CRP	Fasting Plasma (mg/L)	9 weeks	No change	unclear
		Energy restriction + beef	14/14	2.4 (SD 2.1)	2.4 (SD 2.4)	0 (SD 1.5)	NS	NS		CRP	Fasting Plasma (mg/L)	9 weeks	Decrease	unclear
		Energy restriction + carbohydrate /fat	14/14	3.8 (SD 6.1)	3.2 (SD 3.6)	-0.6 (SD 4.0)	NS	NS		CRP	Fasting Plasma (mg/L)	9 weeks	Decrease	unclear
		Energy restriction + chicken	15/15	2.6 (SD 3.6)	3.0 (SD 4.6)	-0.4 (SD 2.1)	NS	NS		CRP	Fasting Plasma (mg/L)	9 weeks	Decrease	unclear
(Noakes *et al.*, 2006) *16592		High unsaturated fat	21/27	4.52 (SE 0.7)	4.17 (SE 0.71)	-0.35 (SE 0.71)				CRP	(mg/L)	12 weeks	Decrease	unclear
		Very low carbohydrate	24/28	5.27 (SE 0.71)	4.51 (SE 0.6)	-0.76 (SE 0.56)				CRP	(mg/L)	12 weeks	Decrease	unclear
		Very low fat	22/28	4.52 (SE 0.78)	3.42 (SE 0.7)	-1.10 (SE 0.5)				CRP	(mg/L)	12 weeks	Decrease	unclear
(Sharman and Volek, 2004) *16040		Low fat	15/15	2.9 (SD 1.5)	1.5 (SD 0.8)		0.00001			hsCRP	(mg/L)	6 weeks	Decrease	unclear
		Very low carbohydrate	15/15	2.9 (SD 1.5)	1.3 (SD 0.9)		0.00005			hsCRP	(mg/L)	6 weeks	Decrease	unclear

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
(Stoernell *et al.*, 2008) 16533		Low carbohydrate diet	10/14	3.7 (1.1, 10.3)	1.5 (0.8, 6.7)			NS		hsCRP	Fasting (mg/L)	8 weeks	Decrease	unclear
		Low fat diet	13/14	1.3 (0.8, 6.7)	1.9 (1.0, 3.4)					hsCRP	Fasting (mg/L)	8 weeks	Decrease	unclear
(McMillan-Price *et al.*, 2006) *16230		High CHO, high GI diet	32/32	3.6 (SE 0.8)		-0.8 (SE 0.4)				CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	4.3 (SE 0.7)		-1.1 (SE 0.4)				CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High protein, high GI diet	32/32	3.1 (SE 0.6)		-0.8 (SE 0.4)		NS		CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High protein, low GI diet	33/33	4.3 (SE 0.9)		-0.01 (SE 0.4)		NS		CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
(O'Brien *et al.*, 2005) 16960		Low carbohydrate	22/22			-0.16		0.20		LogCRP	Fasting (mg/L)	3 months	Decrease	unclear
		Moderate fat	19/19			-0.02				LogCRP	Fasting (mg/L)	3 months	Decrease	unclear
(Dansinger *et al.*, 2005) 15831		Atkins	40/40			-0.33 (SD 1.6)	NS			CRP	Fasting Serum (mg/L)	2 months	Decrease	No bias
		Ornish	40/40			-0.61 (SD 2.6)	NS			CRP	Fasting Serum (mg/L)	2 months	Decrease	No bias
		Weight watchers	40/40			-0.04 (SD 1.2)	NS			CRP	Fasting Serum (mg/L)	2 months	Decrease	No bias
		Zone	40/40			-0.22 (SD 1.9)	NS			CRP	Fasting Serum (mg/L)	2 months	Decrease	No bias
15832		Atkins	40/40			-0.71 (SD 2)	0.05			CRP	Fasting Serum (mg/L)	6 months	Decrease	No bias
		Ornish	40/40			-0.7 (SD 2.8)	NS			CRP	Fasting Serum (mg/L)	6 months	Decrease	No bias
		Weight watchers	40/40			-0.5 (SD 1.5)	0.05			CRP	Fasting Serum (mg/L)	6 months	Decrease	No bias
		Zone	40/40			-0.42 (SD 1.9)	NS			CRP	Fasting Serum (mg/L)	6 months	Decrease	No bias
		Atkins	40/40			-0.7 (SD 2.1)	0.05			CRP	Fasting	1 year	Decrease	No bias

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
*15833											Serum (mg/L)			
		Ornish	40/40			-0.88 (SD 2.4)	0.05			CRP	Fasting Serum (mg/L)	1 year	Decrease	No bias
		Weight watchers	40/40			-0.58 (SD 1.3)	0.01			CRP	Fasting Serum (mg/L)	1 year	Decrease	No bias
		Zone	40/40			-0.58 (SD 2.1)	NS			CRP	Fasting Serum (mg/L)	1 year	Decrease	No bias
(Due *et al.*, 2008) *15303		Control	24/25	3.18 (CI 2.1, 4.3)	2.25 (CI 1.4, 3.1)	-1.2(CI -2.1, -0.3)				hsCRP	(mg/L)	6 months	Increase	unclear
		High MUFA	39/52	2.11 (CI 1.5, 2.7)	1.39 (CI 0.9, 1.9)	-0.8 (CI -1.4, -0.2)		NS		hsCRP	(mg/L)	6 months	Increase	unclear
		Low fat	43/48	3.42 (CI 2.5, 4.4)	1.76 (CI 1.1, 2.4)	-1.7 (CI -2.7, -0.7)		NS		hsCRP	(mg/L)	6 months	Increase	unclear
(Johnston *et al.*, 2006) 17522		Low carbohydrate diet	10/10	4.12 (SE 0.78)	4.48 (SE 1.27)					CRP	Fasting (mmol/L)	2 weeks	Decrease	unclear
		Very low-carbohydrate diet	9/9	7.50 (SE 2.07)	6.93 (SE 2.06)			NS		CRP	Fasting (mmol/L)	2 weeks	Decrease	unclear
*17523		Low carbohydrate diet	10/10	4.12 (SE 0.78)	4.60 (SE 1.40)					CRP	Fasting (mmol/L)	6 weeks	Decrease	unclear
		Very low-carbohydrate diet	9/9	7.50 (SE 2.07)	6.39 (SE 1.65)			NS		CRP	Fasting (mmol/L)	6 weeks	Decrease	unclear
(Lovejoy *et al.*, 2003) 15005		Control	13/15	0.26 (SE 0.09)		0.09 (SE 0.17)				CRP	Fasting (mg/dL)	3 months	Decrease	unclear
		Fat reduced	13/15	0.2 (SE 0.04)		0.03 (SE 0.06)				CRP	Fasting (mg/dL)	3 months	Decrease	unclear
15006		Control	13/15	0.26 (SE 0.09)		-0.08 (SE 0.09)				CRP	Fasting (mg/dL)	6 months	Decrease	unclear
		Fat reduced	13/15	0.2 (SE 0.04)		0.19 (SE 0.18)				CRP	Fasting (mg/dL)	6 months	Decrease	unclear
*15007		Control	13/15	0.26 (SE 0.09)		-0.11 (SE 0.08)				CRP	Fasting (mg/dL)	9 months	Decrease	unclear
		Fat reduced	13/15	0.2 (SE 0.04)		0.08 (SE 0.13)				CRP	Fasting (mg/dL)	9 months	Decrease	unclear
(Phillips *et*		Low	10/~14	5.7 (SE 1.3)	6.2 (SE 1.1)		NS	NS		CRP		6 weeks	Decrease	unclear

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
al., 2008) *17429		carbohydrate diet									Fasting (mg/L)			
		Low fat diet	10/~14	4.9 (SE 1.5)	5.3 (SE 1.9)		NS			CRP	Fasting (mg/L)	6 weeks	Decrease	unclear
(Pereira *et al.*, 2004) *17032		Hypoenergetic low fat diet	17/23	0.19 (SE 0.06)	0.13 (SE 0.04)	-5.1% (SE 13.61%)				CRP	Fasting (mg/dL)	67 days	Decrease	unclear
		Hypoenergetic low GL diet	22/23	0.28 (SE 0.06)	0.1 (SE 0.03)	-47.7% (SE 11.94%)		0.03		CRP	Fasting (mg/dL)	67 days	Decrease	unclear
(Due *et al.*, 2005) *17544		High protein	23/23	2.4 (CI 1.5, 3.3)	1.9 (CI 1.2, 2.7)					CRP	Fasting (mg/L)	6 months	Decrease	unclear
		Moderate protein	23/18	2.9 (CI 1.9, 3.9)	2.1 (CI 1.5, 2.8)					CRP	Fasting (mg/L)	6 months	Decrease	unclear
(Noakes *et al.*, 2005) *17007		High carbohydrate diet	48/48	4.8 (SE 0.5)	4.0 (SE 0.4)	-0.8 (SE 0.3)				CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High protein diet	52/52	6.6 (SE 0.7)	4.9 (SE 0.6)	-1.7 (SE 0.4)		0.447		CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
Cytokines														
(de Luis *et al.*, 2007) 16316		Low carbohydrate	47/47	1.6 (SD 1.2)	2.1 (SD 2.6)		NS	NS		IL-6	Serum (pg/ml)	3 months	Decrease	No bias
		Low fat	43/43	1.7 (SD 1.9)	2 (SD 2.1)		NS			IL-6	Serum (pg/ml)	3 months	Decrease	No bias
*16318		Low carbohydrate	47/47	3.5 (SD 4.3)	3.1 (SD 2.3)		NS	NS		TNFα	Serum (pg/ml)	3 months	Decrease	unclear
		Low fat	43/43	2.7 (SD 2.5	2.6 (SD 2.2)		NS			TNFα	Serum (pg/ml)	3 months	Decrease	unclear
(de Luis *et al.*, 2008) 17127	Genetics - wild-type Ala54/Ala54	Low carbohydrate	55/105	2.9 (SD 3.1)	2.6 (SD 2.2)					IL-6	Fasting (pg/ml)	2 months	Decrease	unclear
		Low fat	55/99	4.1 (SD 4.2)	3.1 (SD 3.1)					IL-6	Fasting (pg/ml)	2 months	Decrease	unclear
17128	Genetics - mutant-type Ala54/Thr54 or Thr54/Thr54	Low carbohydrate	50/105	2.7 (SD 2.2)	2.9 (SD 2.4)					IL-6	Fasting (pg/ml)	2 months	Decrease	unclear
		Low fat	44/99	2.8 (SD 2.7)	3.3 (SD 3.4)					IL-6	Fasting (pg/ml)	2 months	Decrease	unclear
17129	Genetics - wild-type Ala54/Ala54	Low fat	55/99	4.4 (SD 4.5)	4.1 (SD 2.6)					TNFα	Fasting (pg/ml)	2 months	Decrease	unclear
		Low carbohydrate	55/105	3.88 (SD 2.8)	3.9 (SD 2.5)					TNFα	Fasting (pg/ml)	2 months	Decrease	unclear
17130	Genetics - mutant-type Ala54/Thr54 or Thr54/Thr54	Low carbohydrate	50/105	3.8 (SD 2.9)	4.4 (SD 2.7)					TNFα	Fasting (pg/ml)	2 months	Decrease	unclear
		Low fat	44/99	3.6 (SD 2.7)	2.9 (SD 2.4)					TNFα	Fasting (pg/ml)	2 months	Decrease	unclear

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
(de Luis *et al.*, 2009a) 16713	Genetics - UCP3 Gene -55CC polymorphism	Low carbohydrate	54/67	2.3 (SD 3.1)	2.6 (SD 2.2)		NS			IL-6	(pg/ml)	2 months	Decrease	unclear
		Low fat	40/64	2.1 (SD 4.2)	2.2 (SD 3.1)		NS			IL-6	(pg/ml)	2 months	Decrease	unclear
16714	Genetics - UCP3 Gene -55CT/TT polymorphism	Low carbohydrate	13/67	3.1 (SD 2.2)	3.3 (SD 2.4)		NS			IL-6	(pg/ml)	2 months	Decrease	unclear
		Low fat	24/64	2.9 (SD 2.7)	3.2 (SD 3.4)		NS			IL-6	(pg/ml)	2 months	Decrease	unclear
16715	Genetics - UCP3 Gene -55CC polymorphism	Low carbohydrate	54/67	4.3 (SD 2.8)	4.4 (SD 2.5)		NS			TNFα	(pg/ml)	2 months	Decrease	unclear
		Low fat	40/64	3.9 (SD 2.7)	3.1 (SD 2.4)		<0.05			TNFα	(pg/ml)	2 months	Decrease	unclear
16716	Genetics - UCP3 Gene -55CT/TT polymorphism	Low carbohydrate	13/67	4.2 (SD 2.9)	4.3 (SD 2.7)		NS			TNFα	(pg/ml)	2 months	Decrease	unclear
		Low fat	24/64	2.3 (SD 2.7)	3.1 (SD 2.4)		NS			TNFα	(pg/ml)	2 months	Decrease	unclear
(Seshadri *et al.*, 2005) 16119		Low carbohydrate diet	40/allocated unclear			-0.01 (SD 1.62)	NS			TNFα	Fasting (pg/ml)	6 months	Decrease	unclear
		Standard diet, energy restricted	35/allocated unclear			0.23 (SD 0.73)	NS			TNFα	Fasting (pg/ml)	6 months	Decrease	unclear
*16121	No diabetes	Low carbohydrate diet	23/allocated unclear			-0.14 (SD 0.6)	NS			TNFα	Fasting (pg/ml)	6 months	Decrease	unclear
		Standard diet, energy restricted	22/allocated unclear			0.28 (SD 0.66)	NS			TNFα	Fasting (pg/ml)	6 months	Decrease	unclear
16123		Low carbohydrate diet	40/allocated unclear			-0.45 (SD 175)	NS			TNFα SR1	Fasting (pg/ml)	6 months	Decrease	unclear
		Standard diet, energy restricted	35/allocated unclear			27.65 (SD 211)	NS			TNFα SR1	Fasting (pg/ml)	6 months	Decrease	unclear
16124	No diabetes	Low carbohydrate diet	23/allocated unclear			-17.27 (SD 165)	0.001			TNFα SR1	Fasting (pg/ml)	6 months	Decrease	unclear
		Standard diet, energy restricted	22/allocated unclear			22.86 (SD 204)	0.01			TNFα SR1	Fasting (pg/ml)	6 months	Decrease	unclear
(Sharman and Volek, 2004) *16042		Low fat	15/15	3.3 (SD 1.0)	1.9 (SD 0.4)		0.00001			hsTNFα	(pg/ml)	6 weeks	Decrease	unclear
		Very low carbohydrate	15/15	3.3 (SD 1.0)	1.8 (SD 0.4)		0.00001			hsTNFα	(pg/ml)		Decrease	
16043		Low fat	15/15	3.9 (SD 1.4)	2.1 (SD 0.6)		0.0000			hsIL-6	(pg/ml)	6 weeks	Decrease	unclear
		Very low	15/15	3.9 (SD 1.4)	1.9 (SD 0.6)		0.0000			hsIL-6	(pg/ml)		Decrease	

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
		carbohydrate												
Adhesion Molecules														
(Keogh *et al.*, 2008) 16732		High carbohydrate, low SFA	29/50	46.6 (SD 23.7)	32.6 (SD 12.0)			NS		E Selectin	(ng/ml)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	30/57	47.0 (SD 19.7)	31.3 (SD 11.8)					E Selectin	(ng/ml)		Decrease	
16733		High carbohydrate, low SFA	29/50	91.4 (SD 33.9)	82.9 (SD 31.9)			NS		P Selectin	(ng/ml)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	30/57	94.5 (SD 36.9)	90.4 (SD 32.5)					P Selectin	(ng/ml)		Decrease	
16734		High carbohydrate, low SFA	completers not reported/50	467 (SD 122)	410 (SD 96)			NS		ICAM-1	(ng/ml)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	completers not reported/57	455 (SD 86)	375 (SD 72)					ICAM-1	(ng/ml)		Decrease	
16735		High carbohydrate, low SFA	completers not reported/50	685 (SD 160)	714 (SD 140)			NS		VCAM-1	(ng/ml)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	completers not reported/57	685 (SD 112)	714 (SD 136)					VCAM-1	(ng/ml)		Decrease	
16736		High carbohydrate, low SFA	29/50	9.9 (SD 7.1)	6.0 (SD 3.9)			NS		PAI-1 activity	(ng/ml)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	30/57	8.9 (SD 7.1)	4.9 (SD 3.4)					PAI-1 activity	(ng/ml)		Decrease	
16737		High carbohydrate, low SFA	29/50	2.6 (SD 2.0)	2.0 (SD 1.7)			NS		tPA (tissue-type plasminogen activator)	(ng/ml)	8 weeks	Decrease	unclear
		Low carbohydrate, high SFA	30/57	3.0 (SD 2.3)	2.1 (SD 2.4)					tPA (tissue-type plasminogen activator)	(ng/ml)		Decrease	
(Meckling		Low	15/10	30.1 (SE	16.2 (SE		0.05	NS		PAI-1 activity	Fasting	10 weeks	Decrease	No bias

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
et al., 2004) 14938		carbohydrate		8.5)	7.9)						(IU/ml)			
		Low fat	16/10	27.7 (SE 10)	8.2 (SE 3.9)		0.05						Decrease	
(Sharman and Volek, 2004) 16044		Low fat	15/15	337.2 (SD 60.1)	270.2 (SD 18.4)		0.00002	NS		sICAM-I	(ng/ml)	6 weeks	Decrease	unclear
		Very low carbohydrate	15/15	337.2 (SD 60.1)	275.9 (SD 13.9)		0.00007						Decrease	
16045		Low fat	15/15	105.4 (SD 37.5)	99.8 (SD 50.8)		0.470	NS		sP-selectin	(ng/ml)	6 weeks	Decrease	unclear
		Very low carbohydrate	15/15	105.4 (SD 37.5)	94.8 (SD 40.5)		0.176						Decrease	
(Ebbeling *et al.*, 2005) 15511		Low fat diet	12/17	47.5 (SE 7.8)		30.4% (CI -19.2, 110.4)				PAI-1 activity	Fasting (ng/ml)	6 months	Decrease	unclear
		Low GI diet	11/17	58.4 (SE 4.9)		-58.3% (CI -74.7, -31.3)							Decrease	
(Ebbeling *et al.*, 2005) 15512		Low fat diet	12/17	47.5 (SE 7.8)		33.1% (CI -32.9, 164.3)				PAI-1 activity	Fasting (ng/ml)	1 year	Decrease	unclear
		Low GI diet	11/17	58.4 (SE 4.9)		-39% (CI -70.2, 24.9)							Decrease	
Clotting-associated markers														
(Lovejoy *et al.*, 2003) 14996		Control	13/15	302.57 (SE 16.18)		21.68 (SE 21.44)		NS		Fibrinogen	Fasting (mg/dL)	3 months	Decrease	unclear
		Fat reduced	13/15	317.4 (SE 16.42)		-14.29 (SE 14.52)							Decrease	
14997		Control	13/15	302.57 (SE 16.18)		2.42 (SE 20.27)		NS		Fibrinogen	Fasting (mg/dL)	6 months	Decrease	unclear
		Fat reduced	13/15	317.4 (SE 16.42)		-13.5 (SE 20.43)							Decrease	
14998		Control	13/15	302.57 (SE 16.18)		11.85 (SE 15.82)		NS		Fibrinogen	Fasting (mg/dL)	9 months	Decrease	unclear
		Fat reduced	13/15	317.4 (SE 16.42)		-14.46 (SE 15.68)							Decrease	
(Howard *et al.*, 2006) 16256		Control	approx 1699 participants included as a 5.8% sub-sample of 29294 in group	298.7 (SD 61.7)	290.2 (SD 60.0)	-10.2 (SD 54.0)		NS		Fibrinogen	Fasting (mg/dL)	3 years	No change	No bias
		Low fat	approx 1132 participants	301.5 (SD 59.3)	288.0 (SD 58.1)	-11.1 (SD 49.9)							Decrease	

Results Number	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	Difference between groups in Δ from baseline	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assess-ment Bias
			included as a 5.8% sub-sample of 19541 in group											
17621		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						-0.97 (CI -6.41, 4.47)	Fibrinogen	Fasting (mg/dL)	3 years	No change in control group, decrease in low fat group	No bias
(Lovejoy *et al.*, 2003) 16965		Control	13/15	85.7 (SE 3.02)		-2.68 (SE 3.78)		NS		Factor VII/proconvertin	Fasting (%)	3 months	Decrease	unclear
		Fat reduced	13/15	81.8 (SE 4.23)		-0.39 (SE 2.81)							Decrease	
16966		Control	13/15	85.7 (SE 3.02)		-0.12 (SE 3.37)		NS		Factor VII/proconvertin	Fasting (%)	6 months	Decrease	unclear
		Fat reduced	13/15	81.8 (SE 4.23)		5.73 (SE 2.59)							Decrease	
16967		Control	13/15	85.7 (SE 3.02)		1.08 (SE 2.72)		NS		Factor VII/proconvertin	Fasting (%)	9 months	Decrease	unclear
		Fat reduced	13/15	81.8 (SE 4.23)		3.19 (SE 2.5)							Decrease	
Amyloid A														
(O'Brien *et al.*, 2005) 16964		Low carbohydrate	22/22			-0.1		0.04		Log Serum amyloid A	Fasting (mg/L)	3 months	Decrease	unclear
		Moderate fat	19/19			-0.02				Log Serum amyloid A	Fasting (mg/L)	3 months	Decrease	unclear

*This result was used in the meta-analysis for high carbohydrate diets and CRP/ TNFα

Inflammatory markers and sugars

No cohort studies provided data on sugars consumption and markers of inflammation.

Summary of RCT data

One study (Table 3.8) provided information concerning the effects of high and low sucrose diets on markers of inflammation (CRP, haptoglobin and transferrin) in overweight men and women (Sorensen *et al.*, 2005). The intervention was achieved through provision of food and drinks high in sucrose or sweetened with artificial sweeteners, with the majority of the additional sucrose being derived from sweetened beverages (70% of sucrose). The intervention resulted in an average increase in sucrose intake of 151% in the sucrose group and a corresponding 42% decrease in the artificial sweetener group. This resulted in weight gain in the sucrose group (1.6kg gain) and weight reduction (1.2kg loss) in the latter group. Each of the three markers of inflammation increased in the sucrose group and decreased in the artificial sweetener group, although the differences between groups were not statistically significant for CRP. Adjustment through analysis of covariance for baseline values, changes in energy intake and body weight change did not markedly alter this outcome, and the differences in transferrin and haptoglobin between groups remained statistically significant (data not in table).

Table 3.8 Inflammatory markers and sugars: RCT data

Results Number	Intervention group	Completers/ Allocated	Baseline	Follow-up	p-value difference between groups at wk 10	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Sorensen *et al.*, 2005) 17445	Sucrose	19/21	1.8	2.2	0.10	CRP	(mg/L)	10 weeks	Increase	unclear
	Sweetener	18/20	1.8	1.3			(mg/L)		Decrease	
17448	Sucrose	19/21	296	312	0.01	Transferrin	(mg/dL)	10 weeks	Increase	unclear
	Sweetener	18/20	288	280			(mg/dL)		Decrease	
17449	Sucrose	19/21	138	156	0.006	Haptoglobin	(mg/dL)	10 weeks	Increase	unclear
	Sweetener	18/20	156	132			(mg/dL)		Decrease	

Inflammatory markers and diets high in dietary fibre and dietary fibre isolate studies

Summary of cohort results

Data were extracted from one study: The CARDIA Study (Ludwig *et al.*, 1999). See Table 3.9. This study presented evidence on the association between fibre density and fibrinogen. This study of black and white participants aged 18-30 years at baseline, reported adjusted mean fibrinogen levels at 5 year follow up by quintile of dietary fibre intake. Mean fibrinogen level of participants in the lowest quintile of dietary fibre intake (expressed as g/4184 kJ/d) was not significantly different than for those in the highest quintile of intake ($p=0.32$) in the black participants, but was significantly lower in the white participants ($p<0.005$). Further adjustment for baseline fasting insulin levels attenuated the association (difference between lowest and highest fibre quintile: −0.21 µmol/L [7.2 mg/dL], $p=0.38$).

Exposure definition and assessment

Fibre density was measured using a 700 item FFQ and was calculated using the AOAC method.

Adjustment for appropriate confounders

This study adjusted for an appropriate number of different variables including age, sex, physical activity and energy intake, but not BMI. Inclusion of fasting baseline insulin in the model attenuated the inverse association between dietary fibre and fibrinogen concentration.

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

Summary of RCT data

Seven studies provided data on the relationship between dietary fibre and markers of inflammation including CRP, IL-6, PAI-1 activity, fibrinogen and TNF-α. Two intervention studies explored the impact of diets high in total dietary fibre (Thompson *et al.*, 2005;Andersson *et al.*, 2007). Other trials assessed the impact of dietary fibre supplements composed of Plantago ovata husk and glucomannan (Salas-Salvado *et al.*, 2008), konjac-mannan (Wood *et al.*, 2006), guar gum (Landin *et al.*, 1992), psyllium (King *et al.*, 2008), and the effects of high or low molecular weight barley beta-glucan (Smith *et al.*, 2008). Due to the heterogeneity in types and mode of fibre delivery the data were inappropriate for pooling in a meta-analysis.

Two studies investigated the effects of high fibre diets achieved through consumption of foods naturally high in dietary fibre, rather than through the use of dietary isolates (Thompson *et al.*, 2005;Andersson *et al.*, 2007). The results of these trials are included in Table 3.10. In the study reported by Thompson *et al.* obese subjects were randomly assigned to one of three hypoenergetic regimens designed to test the effects of a high dairy food diet with high or low dietary fibre content compared with a standard diet (Thompson *et al.*, 2005). 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±9 g/d (AOAC fibre) was reported in the high fibre/high dairy adherents, compared with an average of 18±5 g/d in the high dairy/low fibre adherents, which are the comparison groups of interest here. The greatest decrease in CRP was observed in the high fibre group. However, the extent of change from baseline to 48 weeks between the three groups was not statistically significant overall. This study indicates no improvement in this marker of inflammation with consumption of high fibre foods within the context of an energy restricted diet. This finding was not altered in analyses using the intention-to-treat approach or when using protocol adherents only.

Andersson *et al.* (Andersson *et al.*, 2007) conducted a 6-week cross-over trial of the effects of diets high in either wholegrain or refined grain cereal foods (whole or refined grain versions of bread, crisp bread, muesli and pasta). The fibre content of the wholegrain and refined grain food products supplied to the participants was 18g/d and 6g/d respectively (by AOAC method). Total dietary fibre intake was 30g/d and 17g/d during the whole grain and refined grain phases respectively. The aim of the study was to compare the substitution of refined grain for whole grain foods, however, there was some evidence of an increase in energy intake during both interventions relative to usual pre-intervention intakes (although differences were not statistically significant). Despite apparent high compliance to the diets, no differential effect on markers of inflammation (CRP, IL-6 and PAI-1 activity) was observed. This was a relatively small study (n=30) of middle-aged and older men and women with moderate overweight. With duration of just 6 weeks on each diet, the study may have been too short to detect subtle changes in markers of inflammation. A small increase in BMI was observed during the whole grain phase, however, the lack of impact on inflammation remained after adjustment for BMI.

These 2 trials provide evidence that a diet rich in high fibre foods does not impact on markers of inflammation compared with low fibre diets.

Five other studies explored the effects of fibre isolates derived from a variety of sources (see Table 3.11). Using a 3-group design, Salas-Salvado *et al.* (Salas-Salvado *et al.*, 2008), tested the effects of a mixed soluble fibre dose (3g Plantago ovata husk and 1g glucomannan) added to hypoenergetic diet (-2.5MJ/d) either twice or three times daily compared with the addition of a control product (microcrystalline cellulose). After 16 weeks, the participants in the fibre-supplemented groups experienced a small decrease in serum CRP while the placebo group remained unchanged. However any changes observed were not statistically significant and the authors concluded that there was no overall difference between groups. All groups experienced weight loss, and although there was a trend for greater losses in the fibre-supplemented groups the difference in weight loss between the groups was not statistically significant (p=0.43). This

study therefore indicates no improvement in CRP with additional fibre consumption within the context of a hypoenergetic regimen.

The Trial of Inflammatory Markers (TRIM) conducted by King *et al.* (King *et al.*, 2008) tested the effects of psyllium supplementation at either 7 or 14g/d compared with no supplement for a period of 3 months. The 171 eligible participants provided data on a range of markers of inflammation including CRP, IL-6, and fibrinogen levels. Overall, supplementation with psyllium at either dose did not consistently decrease levels of the inflammatory markers tested compared with the no-supplement condition. Overall, this was the case in analyses based on the intention to treat method or protocol completers only, although there was some evidence of lower fibrinogen levels in the highest psyllium group compared with the control group using the latter analytical approach.

Landin *et al.* (Landin *et al.*, 1992) employed a 6-week cross-over design to determine the effect of guar gum compared with placebo on fasting fibrinogen. The guar gum was administered as 10g granulated guar given in a glass of water, 3 times a day before meals. This was compared with granulated swelling starch in 25 healthy non-obese males, with a 2-week washout period between phases. Compared with the placebo phase, plasminogen activator inhibitor activity decreased 2.9±4.9 mU/L ($p<0.01$) during the guar gum phase. Conversely, fibrinogen levels were unaffected by treatment with guar gum compared with placebo.

Wood *et al.* explored the effects of a low carbohydrate diet (30% energy) with a soluble fibre supplement (Konjac mannan 3 g/d) or placebo (maltodextrin) in 29 overweight or obese men (Wood *et al.*, 2006). CRP and TNF-α measured after 12 weeks were found to have decreased (by -8.1% and -9.3% respectively, $p<0.05$), but IL-6 concentrations remained unaltered. No differences between the fibre-supplemented and placebo groups were observed. The addition of dietary fibre to a low carbohydrate dietary regimen therefore did not improve markers of inflammation.

Smith *et al.* explored the effects of high or low molecular weight barley beta-glucan (6 grams beta-glucan per day) administered over 6 weeks to 90 individuals with mild hypercholesterolaemia (mean total cholesterol in the region of 227mmol/L) (Smith *et al.*, 2008). The barley fibre supplement was consumed in the form of a powder added to beverages twice per day. The authors reported minor changes in cardiovascular disease markers overall, although the high molecular weight group experienced some weight loss, whilst the low molecular group tended to increase in weight. C-reactive protein decreased in both groups, significantly so in the low molecular weight group (-11±5 mg/L, $p<0.05$). However, the change from baseline was not significantly different between groups ($p=0.48$).

These five trials of fibre isolates collectively indicate that markers of inflammation are unaffected by consumption of dietary fibre delivered as a dietary supplement.

Table 3.9 Inflammatory markers and dietary fibre: cohort study

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 (SD)	P trend	Adjustments
13702 (Ludwig *et al.*, 1999) The CARDIA Study	USA, Multi-ethnic, Generally healthy, No hypertension, No T2DM	18-30 %M 45.9	5115	10 years	FFQ (700)	Fibre density (g/unit energy. AOAC method)	Fibrinogen Fasting, mg/dL	Race - White	(12.3) vs (5.2)	g/4184kJ/ day	248: vs. 264	0.005	Age, Alcohol, Centre, Education, Energy Intake, Physical Activity, Sex, Smoking, Vitamin intake
13703 The CARDIA Study								Race - Black	(12.3) vs (5.2)	g/4184kJ/ day	269 vs. 274	0.8	As above

Table 3.10 Inflammatory markers and diets high in dietary fibre: RCT data

Results 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	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Thompson *et al.*, 2005) 17084	Energy restriction + dairy	22/30			-0.8 (SD 2.7)			hsCRP	Fasting (mg/L)	48 weeks	Decrease	bias
	Energy restriction + dairy + fibre	24/31			-1.6 (SD 4)			hsCRP	Fasting (mg/L)	48 weeks	Decrease	bias
(Andersson *et al.*, 2007) 16307	Refined grain products	30/30	2.86 (SD 2.96)	2.34 (SD 1.57)		NS		hsCRP	Fasting (mg/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	2.03 (SD 1.62)	2.38 (SD 2.29)		NS	0.55	hsCRP	Fasting (mg/L)	6 weeks	Small increase	unclear
16308	Refined grain products	30/30	15.9 (SD 32.4)	15.8 (SD 30.9)		NS		IL-6	Fasting (ng/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	14.8 (SD 32.2)	15.2 (SD 33.2)		NS	0.79	IL-6	Fasting (ng/L)	6 weeks	Small increase	unclear
16602	Refined grain products	30/30	24.8 (SD 19.9)	22.1 (SD 19.5)		NS		PAI-1 activity	(kU/l)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	24.7 (SD 15.8)	26.9 (SD 20.3)		NS	0.26	PAI-1 activity	(kU/l)	6 weeks	Small increase	unclear

Table 3.11 Inflammatory markers and fibre isolates, gums and extracts: RCT data

Results 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	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Salas-Salvado *et al.*, 2008) 14512	Mixed soluble fibre 3 times a day	58/68			-0.08 (SD 0.10)		vs placebo NS	hsCRP	Fasting (mg/L)	16 weeks	Decrease	No bias
	Mixed soluble fibre twice a day	53/66			-0.10 (SD 0.15)		vs placebo NS	hsCRP	Fasting (mg/L)	16 weeks	Decrease	No bias
	Placebo	55/66			0.02 (SD 0.05)			hsCRP	Fasting (mg/L)	16 weeks	Decrease	No bias
(King *et al.*, 2008) 16809	Control	57/59			0.05 (SD 7.87)			CRP	(mg/L)	3 months	Not reported	No bias
	High-dose fibre supplement	48/55			0.98 (SD 4.57)		NS	CRP	(mg/L)	3 months	Not reported	No bias
	Low-dose fibre supplement	53/57			-0.96 (SD 4.45)		NS	CRP	(mg/L)	3 months	Not reported	No bias
16810	Control	57/55			10.32 (SD 48.92)			Fibrinogen	(mg/dL)	3 months	Not reported	No bias
	High-dose fibre supplement	48/55			-2.44 (SD 32.69)		NS	Fibrinogen	(mg/dL)	3 months	Not reported	No bias
	Low-dose fibre supplement	53/57			-2.29 (SD 35.34)		NS	Fibrinogen	(mg/dL)	3 months	Not reported	No bias
16812	Control	57/59		57.1				IL-6 >2.5 pg/mL	(%)	3 months	Not reported	No bias
	High-dose fibre supplement	48/55		51.2			NS	IL-6 >2.5 pg/mL	(%)	3 months	Not reported	No bias
	Low-dose fibre supplement	53/57		68.6			NS	IL-6 >2.5 pg/mL	(%)	3 months	Not reported	No bias
(Landin *et al.*, 1992) 17120	Guar gum	25/25		2.3 (0.6)				Fibrinogen	Fasting (g/L)	6 weeks	No change	No bias
	Placebo	25/25		2.4 (0.5)			NS	Fibrinogen	Fasting (g/L)	6 weeks	No change	No bias
	Guar gum	25/25		12.1 (6.1)				PAI-1 activity	Fasting (U/mL)	6 weeks	No change	No bias
	Placebo	25/25		14.5 (8.2)			<0.01	PAI-1 activity	Fasting (U/mL)	6 weeks	No change	No bias
(Wood *et al.*, 2006) 16400	Low carbohydrate diet + placebo	14/15	1.86 (SD 1.29)	1.55 (SD 1.23)		NS		hsCRP	Fasting Plasma (mg/dL)	12 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre	14/14	1.68 (SD 1.50)	1.35 (SD 0.95)		NS	NS	hsCRP	Fasting Plasma (mg/dL)	12 weeks	Decrease	No bias
16401	Low carbohydrate diet + placebo	14/15	2.00 (SD 1.62)	1.88 (SD 1.07)		NS		hsIL-6	Fasting Plasma (mg/dL)	12 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre	14/14	1.31 (SD 0.39)	1.39 (SD 0.5)		NS	NS	hsIL-6	Fasting Plasma (mg/dL)	12 weeks	Decrease	No bias
16946	Low carbohydrate diet + placebo	14/15	1.18 (SD 0.27)	1.03 (SD 0.27)		<0.05		TNFα	(pg/ml)	12 weeks	Decrease	No bias
	Low carbohydrate diet + Soluble fibre	14/14	1.29 (SD 0.26)	1.25 (SD 0.3)		<0.05	NS	TNFα	(pg/ml)	12 weeks	Decrease	No bias
(Smith *et al.*, 2008) 16556	High molecular weight Beta glucan	45/45			-6.7 (SE 4)	NS	0.48	CRP	Fasting (mg/ml)	6 weeks	Decrease	No bias
	Low molecular	45/45			-11	0.05		CRP	Fasting (mg/ml)	6 weeks	Increase	No bias

Results 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	Outcome	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
	weight Beta glucan				(SE 5)							

Inflammatory markers and whole grains

No cohort studies provided data on wholegrain consumption and markers of inflammation.

Summary of RCT data

Two studies provided data on the effects of wholegrain consumption on the markers of inflammation, CRP, IL-6, fibrinogen and PAI-1 activity (Andersson *et al.*, 2007;Howard *et al.*, 2006). See Table 3.12.

Andersson *et al.* (Andersson *et al.*, 2007) conducted a cross-over trial of the effects of diets high or low in wholegrain or refined grain cereal foods (whole or refined grain versions of bread, crispbread, muesli and pasta). The whole grain products used, provided 112g/d of whole grain, and the whole grain products used were defined on the basis of supplying at least 50% whole grain on a dry weight basis. The aim was to compare the substitution of refined grain for whole grain foods, however, there was some evidence of an increase in energy intake during both interventions relative to usual pre-intervention intakes (although differences were not statistically significant). Despite apparent high compliance to the regimes, no differential effect on markers of inflammation (CRP, IL-6 and PAI-1 activity) was observed. This was a relatively small study (n=30) of middle-aged and older men and women with moderate overweight. The authors did report a robust power calculation to determine sample size, based on the primary outcome which was insulin sensitivity, however, there may have been insufficient power to detect a meaningful difference in CRP or the study may have been too short to detect subtle changes in markers of inflammation. A small increase in BMI was observed during the whole grain phase; however, the lack of impact on inflammation remained after adjustment for BMI.

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). 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. At the year 1 assessment, wholegrain consumption in the intervention group had increased by one third of a serving, whilst the comparison group remained unchanged. Results concerning blood fibrinogen levels are reported here at three years from baseline randomisation. Both groups experienced a decrease in fibrinogen (by -10.2 and -11.1mg/dL in control and low fat groups respectively), but the difference between these means was not statistically significant.

Neither study provides evidence of an impact of whole grain foods on markers of inflammation, although the Swedish study implemented a large dietary change in a well controlled, small number of subjects and the US Women's Health Initiative Trial was extremely large, with modest changes in diet followed up for a long duration.

Table 3.12 Inflammatory markers and whole grains: RCT data

Results 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	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
(Andersson *et al.*, 2007) 16307	Refined grain products	30/30	2.86 (SD 2.96)	2.34 (SD 1.57)		NS			hsCRP	Fasting (mg/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	2.03 (SD 1.62)	2.38 (SD 2.29)		NS	0.55					Small increase	
16308	Refined grain products	30/30	15.9 (SD 32.4)	15.8 (SD 30.9)		NS			IL-6	Fasting (ng/L)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	14.8 (SD 32.2)	15.2 (SD 33.2)		NS	0.79					Small increase	
16602	Refined grain products	30/30	24.8 (SD 19.9)	22.1 (SD 19.5)		NS			PAI-1 activity	(kU/l)	6 weeks	Small increase	unclear
	Wholegrain products	30/30	24.7 (SD 15.8)	26.9 (SD 20.3)		NS	0.26					Small increase	unclear
(Howard *et al.*, 2006) 16256	Control	approx 1699 participants included as a 5.8% sub-sample of 29294 in group	298.7 (SD 61.7)	290.2 (SD 60.0)	-10.2 (SD 54.0)				Fibrinogen	Fasting (mg/dL)	3 years	No change	No bias
	Low fat + whole grain	approx 1132 participants included as a 5.8% sub-sample of 19541 in group	301.5 (SD 59.3)	288.0 (SD 58.1)	-11.1 (SD 49.9)		NS					Decrease	
17621	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						-0.97 (CI -6.41, 4.47)	Fibrinogen	Fasting (mg/dL)	3 years	No change in control group, decrease in low fat group	No bias

Inflammatory markers and glycaemic index or load

No cohort studies provided data on glycaemic index or load and markers of inflammation.

Summary of RCT data

Five randomised controlled trials explored the impact of high or low glycaemic index diets on markers of inflammation, which included adhesion molecules (PAI-1 activity) and CRP (Jensen *et al.*, 2008;Ebbeling *et al.*, 2005;Pittas *et al.*, 2006;Pereira *et al.*, 2004;McMillan-Price *et al.*, 2006).

Adhesion molecules

Two trials conducted in Denmark and the USA provided data on the effects of high or low GI diets on adhesion molecules (Jensen *et al.*, 2008;Ebbeling *et al.*, 2005). There were too few studies to undertake a meta-analysis. One study (Jensen *et al.*, 2008) was conducted using 44 healthy, overweight females, who were randomly allocated to *ad libitum* high carbohydrate, low fat diets that were composed of either lower or higher GI foods for 10 weeks. Some of these high/low GI foods were provided by the experimenters. The weighted average GI of the provided foods was 72 and 95 for low and high GI diets respectively (determined in 10 subjects according to the in vivo method described by the United Nations Food and Agriculture Organisation and World Health Organisation) (FAO/WHO, 1998). The fibre content of the high and low GI foods did not differ markedly. Both groups lost weight during the trial, and fasting PAI-1 antigen was not differentially affected by the 2 dietary regimes (p=0.49). However, PAI-1 activity was significantly reduced (by 1.8 U/mL) in the lower GI group compared to the higher GI group (p=0.01).

The trial reported by Ebbeling and co-workers, used participants that were markedly more overweight than Jensen *et al.* and during the 12 months that they were monitored, lost considerably more weight (Ebbeling *et al.*, 2005). The high and low GI groups in this trial lost similar amounts of weight, but at the interim follow-up (6 months), PAI-1 activity had decreased by 58% in the lower GI dietary group and increased by 30% in the higher GI group. At 12 months, the extent of change in the lower GI group had diminished somewhat (-39%) but was still significantly different from the change in the higher GI group (+33%) (p=0.004). Energy and dietary fibre intakes were similar in both groups, but the authors reported that the glycaemic load of the lower and higher GI diets was 53 and 77 respectively.

While there may be differences in the approach used and extent of difference in GI between the diet groups in these two trials, both studies found a greater reduction in PAI-1 activity with consumption of a hypoenergetic lower glycaemic index diet when compared with a similarly hypoenergetic higher glycaemic index diet.

C-reactive protein

Three studies were included in a meta-analysis of CRP and dietary differences in glycaemic index (GI) or load (GL) in adults (Pittas *et al.*, 2006;Pereira *et al.*, 2004;McMillan-Price *et al.*, 2006). Definitions of different levels of glycaemic index and load are reported in the trial characteristics table, but range from an average GI of 45-54 for the lower GI groups and 53-86 for the higher GI groups. 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.

All studies used a parallel group design, with overweight or obese men and women following a hypoenergetic diet (generally in the region of 1500kcal/d).

The first follow up period after completion of the intervention for each study was used in the meta-analysis. These were 67 days, 9 weeks and 6 months respectively (Pittas *et al.*, 2006;Pereira *et al.*, 2004;McMillan-Price *et al.*, 2006). One study had four groups (McMillan-Price *et al.*, 2006) which compared high and low GI in participants consuming moderate and high carbohydrate diets. The differences between each of these two GI comparisons were both included in the meta-analysis. Overall there was no statistically significant difference between these four groups in terms of the extent of change in CRP concentration.

The study by Pereira *et al.* found that the reduction in CRP concentration was significantly greater in the lower GI group compared with the higher GI group (mean change -48% vs. -5%, p=0.03). This study had a relatively small number of participants (n=39), short duration (67 days), but all test food was provided and was therefore well controlled in terms of the dietary intervention. Similarly, all food was provided in the CALERIE study reported by Pittas *et al.*, the participants were similar (overweight, aged 24-42 years), but the duration was longer (6 months) (Pittas *et al.*, 2006). CRP concentration decreased by 35% in the lower GI group and remained essentially unchanged in the higher GI group, despite similar weight losses at 3 and 6 months in the 2 groups (approx. 7 kg). The difference of the change in CRP within each group was not statistically significant after adjustment for baseline differences and change in body weight.
The pooled estimate indicated that fasting blood CRP was 0.11mg/L (95% CI -0.50 to 0.72) higher with consumption of a higher GI/GL diet compared with a lower GI/GL diet. This was not statistically significant. Heterogeneity denoted by I^2 was 46% (95% CI 0 to 82%). Statistically, there was no evidence that a higher glycaemic index diet is associated with differences in CRP levels when compared with a lower GI diet. A funnel plot was not prepared due to the small number of studies included in the analysis.

Figure 3.5 Forest plot for glycaemic index or glycaemic load diets and CRP (mg/L)

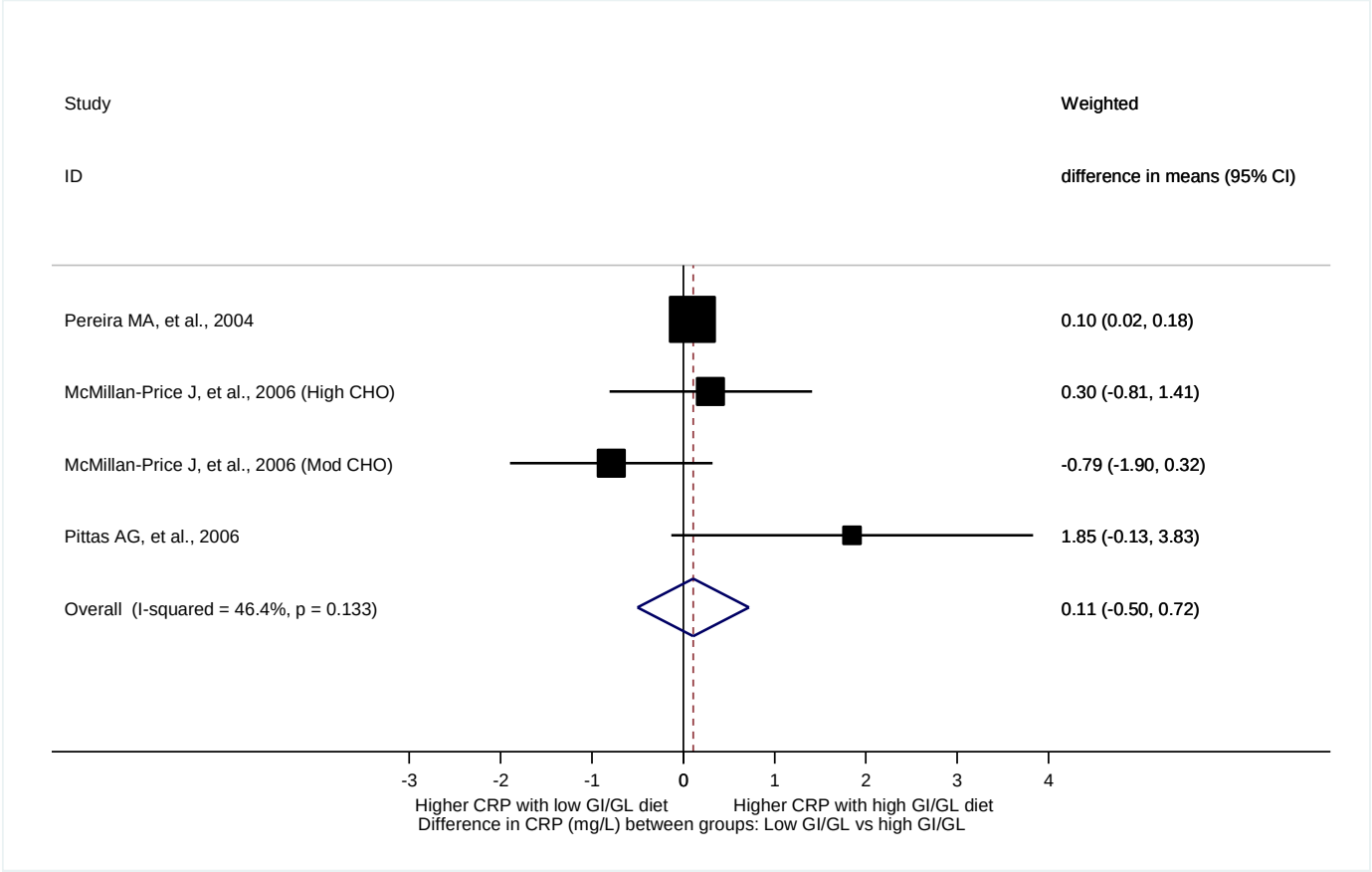


Table 3.13 Inflammatory markers and high and low glycaemic index diets: RCT data

Results Number	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	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
Adhesion molecules													
(Jensen *et al.*, 2008) 15041		High GI diet	22/26	10.3 (SE 0.8)	11.1 (SE 0.8)	0.8 (SE 0.4)	NS		PAI-1 activity	Fasting Plasma (U/ml)	10 weeks	Decrease	unclear
		Low GI diet	22/29	12 (SE 0.8)	10.2 (SE 0.7)	-1.8 (SE 0.6)	0.05	0.01	PAI-1 activity	Fasting Plasma (U/ml)	10 weeks	Decrease	unclear
15043		High GI diet	22/26	19.8 (SE 3)	20.1 (SE 3.1)	-0.0 (SE 1.4)	NS		PAI-1 antigen	Fasting Plasma (ng/ml)	10 weeks	Decrease	unclear
		Low GI diet	22/29	17.9 (SE 2.6)	16.3 (SE 2)	-1.3 (SE 2.4)	NS	0.49	PAI-1 antigen	Fasting Plasma (ng/ml)	10 weeks	Decrease	unclear
16961	subjects participating in the meal test study	High GI diet	15/26		9.3 (SE 0.4)				PAI-1 activity 4 hour post meal response	Plasma (U/ml)	10 weeks	Decrease	unclear
	subjects participating in the meal test study	Low GI diet	14/29		10.7 (SE 0.7)				PAI-1 activity 4 hour post meal response	Plasma (U/ml)	10 weeks	Decrease	unclear
16962	subjects participating in the meal test study	High GI diet	15/26		11.8 (SE 2.4)				PAI-1 antigen 4 hour post meal response	Plasma (ng/ml)	10 weeks	Decrease	unclear
	subjects participating in the meal test study	Low GI diet	14/29		12.4 (SE 2.6)				PAI-1 antigen 4 hour post meal response	Plasma (ng/ml)	10 weeks	Decrease	unclear
(Ebbeling *et al.*, 2005) 15511		Low fat diet	12/17	47.5 (SE 7.8)		30.4% (CI -19.2, 110.4)			PAI-1 activity	Fasting (ng/ml)	6 months	Decrease	unclear
		Low GI diet	11/17	58.4 (SE 4.9)		-58.3% (CI -74.7, -31.3)			PAI-1 activity	Fasting (ng/ml)	6 months	Decrease	unclear
15512		Low fat diet	12/17	47.5 (SE 7.8)		33.1% (CI -32.9, 164.3)		0.004	PAI-1 activity	Fasting (ng/ml)	1 year	Decrease	unclear
		Low GI diet	11/17	58.4 (SE 4.9)		-39% (CI -70.2, 24.9)			PAI-1 activity	Fasting (ng/ml)	1 year	Decrease	unclear

Results Number	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	Outcome details	Result-specific follow-up	Weight Change	Outcome Assessment Bias
C-reactive protein													
(Pittas *et al.*, 2006) *16597		Energy restricted high GI/GL diet	16/16	2.2 (SE 0.6)		0.41 (SE 0.91)	0.13	NS	CRP	Fasting (mg/L)	6 months	Decrease	No bias
		Energy restricted low GI/GL diet	16/16	3.1 (SE 0.7)		-1.44 (SE 0.44)	<0.01		CRP	Fasting (mg/L)	6 months	Decrease	No bias
(Pereira *et al.*, 2004) *17032		Hypoenergetic low fat diet	17/23	0.19 (SE 0.06)	0.13 (SE 0.04)	-5.1% (SE 13.61%)			CRP	Fasting, serum (mg/dL)	67 days	Decrease	unclear
		Hypoenergetic low GL diet	22/23	0.28 (SE 0.06)	0.1 (SE 0.03)	-47.7% (SE 11.94%)		0.03	CRP	Fasting, serum (mg/dL)	67 days	Decrease	unclear
(McMillan-Price *et al.*, 2006) *16230		High CHO, high GI diet	32/32	3.6 (SE 0.8)		-0.8 (SE 0.4)			CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High CHO, low GI diet	32/32	4.3 (SE 0.7)		-1.1 (SE 0.4)			CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High protein, high GI diet	32/32	3.1 (SE 0.6)		-0.8 (SE 0.4)			CRP	Fasting (mg/L)	12 weeks	Decrease	unclear
		High protein, low GI diet	33/33	4.3 (SE 0.9)		-0.01 (SE 0.4)		0.18	CRP	Fasting (mg/L)	12 weeks	Decrease	unclear

*This result was used in the meta-analysis for glycaemic index or glycaemic load diets and CRP

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