THE OFFICIAL JOURNAL OF THE BRITISH DIETETIC ASSOCIATION
Journal of Human Nutrition and Dietetics

NUTRITIONAL SCIENCE

A Mediterranean diet improves HbA1c but not fasting blood glucose compared to alternative dietary strategies: a network meta-analysis

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Keywords
glucose management, Mediterranean diet, nutrition therapy, type 2 diabetes.

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How to cite this article
Carter P., Achana F., Troughton J., Gray L.J., Khunti K. & Davies M.J. (2014) A Mediterranean diet improves HbA1c but not fasting blood glucose compared to alternative dietary strategies: a network meta-analysis. *J Hum Nutr Diet*. **27**, 280–297
doi:10.1111/jhn.12138

Abstract

Background: Overweight or obese individuals with type 2 diabetes are encouraged to lose weight for optimal glucose management, yet many find this difficult. Determining whether alterations in dietary patterns irrespective of weight loss can aid glucose control has not been fully investigated.
Methods: We conducted a systematic review and meta-analysis aiming to determine the effects of a Mediterranean diet compared to other dietary interventions on glycaemic control irrespective of weight loss. Electronic databases were searched for controlled trials that included a Mediterranean diet intervention. The interventions included all major components of the Mediterranean diet and were carried out in free-living individuals at high risk or diagnosed with type 2 diabetes. Network meta-analysis compared all interventions with one another at the same time as maintaining randomisation. Analyses were conducted within a Bayesian framework.
Results: Eight studies met the inclusion criteria, seven examined fasting blood glucose (n = 972), six examined fasting insulin (n = 1330) and three examined HbA1c (n = 487). None of the interventions were significantly better than the others in lowering glucose parameters. The Mediterranean diet reduced HbA1c significantly compared to usual care but not compared to the Palaeolithic diet.
Conclusions: The effect of alterations in dietary practice irrespective of weight loss on glycaemic control cannot be concluded from the present review. The need for further research in this area is apparent because no firm conclusions about relative effectiveness of interventions could be drawn as a result of the paucity of the evidence.

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is currently estimated to be 8.3% worldwide and its diagnosis has been increasing rapidly over the past two decades, showing strong correlations with sedentary behaviour and obesity (Stumvoll *et al.*, 2005; The International Diabetes Federation, 2011). Weight reduction is strongly encouraged for overweight and obese individuals with T2DM for glucose management; however, many patients fail to meet weight loss goals. Indeed, evidence exists suggesting that it may be harder for those with T2DM to lose weight than those with normal glucose regulation (Khan *et al.*, 2000). The American Diabetes Association state that medical nutritional therapy is imperative in those with T2DM to manage blood glucose and delay the progression of diabetes complications; however, determining whether alterations in dietary patterns irrespective of weight loss can influence glucose management has not been fully investigated (Bantle *et al.*, 2008; Dyson *et al.*, 2011).

Foods are rarely eaten in isolation but, instead, in combination with other food groups; thus, the combined effect of food groups may create an additive effect on health (Jacobs & Steffen, 2003). Analysis of dietary intake patterns rather than of individual food groups takes this potential food synergy into account (Jinlin *et al.*, 2007). Dietary patterns based on a high consumption of fruits, vegetables and whole grains, as well as a low consumption of red meat and saturated fatty acids, have been associated with reduced risk of T2DM in a number of observational studies (Van Dam *et al.*, 2002; Montonen *et al.*, 2005; Liese *et al.*, 2009). The traditional Mediterranean diet is one such diet that incorporates all of these food groups. The Mediterranean diet is also characterised by the regular intake of legumes, nuts and fish, as well as a moderate intake of wine, generally consumed with meals. The Mediterranean diet is distinguishable from other dietary patterns, however, by a high intake of monounsaturated fatty acids, mostly from olive oil. The health benefits of the Mediterranean diet were recognised some years ago in the Seven Countries Study (Keys *et al.*, 1986). The study demonstrated that populations from Mediterranean regions of Europe such as Crete had significantly lower all-cause mortality than those from other regions of Europe and the USA (Keys *et al.*, 1986). A high adherence to the Mediterranean diet has additionally been implicated in reducing the risk of T2DM. A large prospective study carried out in Spain found that those individuals who had a high adherence to the Mediterranean diet had an 83% reduced risk of developing diabetes compared to those with low adherence (Martinez-Gonzalez *et al.*, 2008).

A number of components of the Mediterranean diet may be beneficial for managing glucose regulation. Fruits, vegetables and whole grains provide both antioxidants and fibre, both of which have been implicated in improvements in glucose regulation and the progression of complications associated with diabetes (Hallfrisch & Behall, 2000; Miller *et al.*, 2000). In addition, a high intake of monounsaturated fatty acids from olive oil and polyunsaturated fatty acids from fatty fish may influence insulin resistance by altering the phospholipid bilayer of skeletal and adipose tissue (Borkman *et al.*, 1993).

T2DM is a chronic progressive disease characterised by the body's inability to regulate blood glucose levels. It is well documented that weight loss will improve glucose regulation; however, the effect that altering dietary intake without weight loss remains to be determined. Furthermore, evidence for the recommendation of the Mediterranean diet over other healthy diets for glucose regulation remains to be demonstrated; therefore, our aim was to systematically review controlled clinical trials that compared the Mediterranean diet with any other dietary intervention in those with or at high risk of diabetes, irrespective of weight loss. Accordingly, we examined the change in fasting blood glucose, fasting insulin or HbA1c (i.e. glycosylated haemoglobin).

Materials and methods

Search strategy

We followed the recommendations of the Cochrane handbook (Higgins & Green, 2008) and the guide to systematic reviews from the Centre for Reviews and Dissemination (2009), aiming to develop a systematic review protocol. To ensure a broad search, the search strategy included the medical subject headings, T2DM, prediabetes, blood glucose, insulin resistance, metabolic syndrome, cardiovascular disease, coronary disease, Mediterranean diet and randomised controlled trials. Text word, title word, abstract and subject headings were also searched for the above terms plus any non-medical subject headings to cover the Mediterranean diet, blood glucose and insulin.

We searched OVID Medline(R) from 1946 to April 2012; Embase from 1974 to May 2012; the Cumulative Index to Nursing and Allied Health Literature (CINHAL) and the British Nursing Index (BNI) from inception (1981 and 1985, respectively) until May 2012 via NLH Search 2.0; and the Cochrane Library (CENTRAL) from inception until May 2012. We sought expert opinion and checked references in any articles that met the inclusion criteria. We did not limit our search to any language restrictions.

Study selection

Only controlled clinical trials were included in the review. The intervention had to include all major components of the Mediterranean diet (i.e. a high intake of fruit, vegetables, whole grains and monounsaturated fatty acids, regular fish and nut intake, moderate poultry and alcohol consumption and a low intake of red meat and saturated fatty acids) (Fig. 1) (Willett *et al.*, 1995; Champagne, 2009). Studies that only investigated one aspect of the Mediterranean diet were excluded, as were those that restricted calorie intake or aimed to reduce body weight. The studies were also required to at least provide a measure of fasting blood glucose, fasting insulin or HbA1c. The populations under investigation were to be free-living individuals at high risk (i.e. cardiovascular risk factors present) or have diabetes.

One reviewer (PC) carried out the electronic search and the initial review of the results; studies that did not

Mediterranean diet
High intake fruits, vegetables and legumes
High intake of whole grains
High monounsaturated fat intake
Regular fish intake
Regular nut intake
Moderate alcohol consumption (generally red wine)
Low saturated fat intake
Low red meat intake

Figure 1 Components considered part of a Mediterranean diet (Willett *et al.*, 1995; Champagne, 2009).

meet the inclusion criteria were discarded during the initial assessment. Where uncertainty existed, the full text article was retrieved and assessed. Two reviewers (PC and JT) independently assessed all potentially relevant studies and resolved any uncertainty through discussion.

Data abstraction and validity assessment

Two of the authors (PC and JT) independently extracted the data from each study. Information required for retrieval included population demographics, details of the dietary interventions, number of treatment arms and outcome variables. Mean fasting blood glucose concentrations were extracted and converted (to mM) if necessary. If available, HbA1c and fasting insulin levels were also extracted. All selected studies were assessed for the risk of bias using the Jadad scoring system (Jadad *et al.*, 1996).

Diet categories

To be included in the meta-analysis, the studies were required to have a Mediterranean diet arm that included the majority of dietary components generally associated with a Mediterranean diet. However, the studies differed in their specific Mediterranean diets; indeed, some studies split participants between two different versions of the Mediterranean diet. Furthermore, the comparator diet was not the same across studies; thus, to pool data, we created specific categories of the dietary interventions (Fig. 2).

Statistical analysis

Three continuous outcomes (fasting glucose, fasting insulin and HbA1c levels) were considered separately in the analyses. Paired arm-specific outcome data (i.e. sample size, mean value and SD per intervention arm) measured at baseline and at a prespecified follow-up point or one of these measures together with a change from baseline statistics were obtained for each outcome. We used the final outcome scores because SDs for change from baseline scores were not reported for majority of the studies included in the analyses, as recommended in the Cochrane handbook of systematic reviews (Higgins & Green, 2008). Two papers compared two versions of the Mediterranean diet and education with low fat and education (Elhayany *et al.*, 2010; Salas-Salvado *et al.*, 2011). We considered the two versions of Mediterranean diet with education intervention to be similar and thus pooled these arms together using the method described in Cochrane handbook of systematic reviews (Higgins & Green, 2008).

Network meta-analysis

The effect of dietary interventions on glycaemic outcomes (fasting blood glucose, fasting insulin and HbA1c levels) were pooled across studies using both pairwise and network meta-analyses. As a result of difficulty in conducting random effects analysis with a small number of studies, an arbitrary cut-off was used to fit a fixed effect model when there were less than five studies and a random effects model if there were five or more studies in the analysis.

Separate pairwise meta-analyses were first used to compare all interventions on which there was direct head-to-head trial data. Network meta-analysis (Lumley, 2002; Lu & Ades, 2004; Ades *et al.*, 2007) was then used to synthesise all the available evidence. Network meta-analysis methods are extensions of the standard pairwise meta-analysis model and enable simultaneous comparison of multiple interventions at the same time as preserving the internal randomisation of individual trial studies. The method is particularly useful in this context because it enables all interventions to be compared with one another, including interventions that have not directly been compared in any one of the included randomised controlled trials, without breaking the within-study randomised comparisons of individual studies. Pooled effect sizes are presented as weighted mean difference (WMD) and 95% credible intervals (CrI) (i.e. Bayesian equivalent of confidence intervals) in the appropriate units.

Sensitivity analyses were carried out to investigate the impact of including: (i) the study by Djuric *et al.* (2009), which recruited only healthy participants and (ii) studies of Mediterranean diet that had reported specifically restricting calorie intake (Esposito *et al.*, 2003, 2004, 2009; Tuttle *et al.*, 2008). We conducted the second sensitivity analysis to ensure that excluding studies encouraging weight loss did not bias the results.

(1) Written advice on a healthy diet

Participants were only provided with written materials on a healthy diet. Participants met with the dietician once at the start of the study. This was considered as the control diet.

(2) Written advice on the Mediterranean diet

Participants were only provided with written materials on a Mediterranean diet. Participants met with the dietician once at the start of the study.

(3) Mediterranean diet and education

To be included in this category, the intervention given had to provide advice on how to increase components of the Mediterranean diet into daily eating habits. In addition, the participants received regular sessions with a dietician, as either phone calls or face to face appointments. Studies that gave group education sessions were also included in this category.

(4) Low fat diet and education

Participants in this category received the same level of advice as in group (3); however, the advice was aimed at achieving a low fat diet, such as that recommended by the American Heart Association (Vincent-Baudry *et al.*, 2005)

(5) Palaeolithic diet and education

This group was required as the Lindeberg *et al.* (2007) study specifically compared a Mediterranean diet to a Palaeolithic diet. [A Palaeolithic diet is based on lean meat, fish, fruits, leafy and cruciferous vegetables, root vegetables (with restricted potato intake), eggs and nuts]. The participants in this group received a similar amount of advice and time for dietary advice as groups (3) and (4).

(6) Mediterranean diet and behaviour change retreat

Participants in this group went on a weekend retreat to be educated about the Mediterranean diet but also to learn about stress management and were given education on lifestyle modification and behaviour change.

(7) Usual care

This group was included for the Toobert *et al.* (2003) paper; no detail of what was classed as usual care was provided.

Figure 2 Dietary categories included in the review.

Heterogeneity was assessed using the between-study variance parameter, τ^2. Publication bias was not assessed because of the small number of studies available for each outcome (Sterne *et al.*, 2011). Pairwise meta-analyses were conducted in STATA, version 11 (StataCorp, College Station, TX, USA). Network meta-analyses were conducted using Markov chain Monte Carlo simulation implemented through the freely available software WINBUGS, version 1.4.3 (Spiegelhalter *et al.*, 2007). The WINBUGS code used to fit the models is freely-available in an online NICE technical support document (http://www.nicedsu.org.uk) (Dias *et al.*, 2011).

Results

A total of 3001 articles were identified in the initial search (Fig. 3). The title and abstracts were assessed and the full articles of 196 potentially relevant studies were obtained. Eighty-two studies were discarded because they only

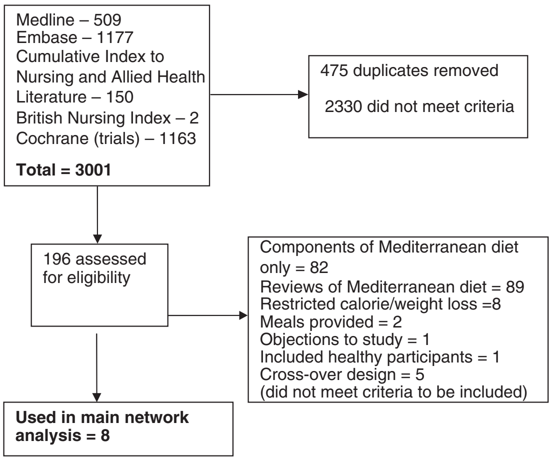

Figure 3 Process of study selection.

examined components of the Mediterranean diet and 89 articles reviewed the Mediterranean diet. Five studies were cross-over design studies (Pérez-Jiménez *et al.*, 2001; Jula *et al.*, 2002; Avellone *et al.*, 2003; Ambring *et al.*, 2004; De Natale *et al.*, 2009) but were excluded from analysis because they did not meet the inclusion criteria, and not as a result of study design. Two studies were excluded because they did not have a comparator diet and thus could not be included into the network analysis (De Lorenzo *et al.*, 2001; Andreoli *et al.*, 2008). A further study was excluded because we did not consider the diet to meet our criteria of a Mediterranean diet (Singh *et al.*, 2002); furthermore, an expression of concern with respect to this study has previously been raised (Horton, 2005) and the study is not generally included when considering the Mediterranean diet (Esposito *et al.*, 2010). Two studies were excluded because they provided meals to participants (Bos *et al.*, 2010; Itsiopoulos *et al.*, 2011) and one study was excluded because it was a work-based intervention (Ben-Avraham *et al.*, 2009).

Five studies were excluded because they specifically restricted calorie intake (Esposito *et al.*, 2003, 2004, 2009; Shai *et al.*, 2008; Tuttle *et al.*, 2008); sensitivity analysis was conducted to include these studies. The article by Shai *et al.* (2008) did not provide relevant data for the network meta-analysis. One study met all the inclusion criteria except that healthy participants were recruited (Djuric *et al.*, 2009); thus, sensitivity analysis was also carried out to include this study. Eight studies met all the inclusion criteria (Toobert *et al.*, 2003; Vincent-Baudry *et al.*, 2005; Michalsen *et al.*, 2006; Lindeberg *et al.*, 2007; Rallidis *et al.*, 2009; Elhayany *et al.*, 2010; Salas-Salvado *et al.*, 2011; Thomazella *et al.*, 2011).

Risk of bias assessment

The risk of bias was assessed by the Jadad score (Jadad *et al.*, 1996); as a result of the nature of the studies, double-blinding could not be achieved in any of them. Four of the studies (Michalsen *et al.*, 2006; Lindeberg *et al.*, 2007; Elhayany *et al.*, 2010; Salas-Salvado *et al.*, 2011) were considered higher quality than the remaining four (Toobert *et al.*, 2003; Vincent-Baudry *et al.*, 2005; Rallidis *et al.*, 2009; Thomazella *et al.*, 2011). These studies provided a reasonable description of the prescribed diets and advice received; they also assessed dietary compliance. Nonetheless, all papers could have been more explicit; only two papers gave detailed information regarding dietary education (Lindeberg *et al.*, 2007; Salas-Salvado *et al.*, 2011). Lack of overall transparency would make the studies difficult to reproduce.

Study characteristics

Eight controlled trials were included in the analyses (Toobert *et al.*, 2003; Vincent-Baudry *et al.*, 2005; Michalsen *et al.*, 2006; Lindeberg *et al.*, 2007; Rallidis *et al.*, 2009; Elhayany *et al.*, 2010; Salas-Salvado *et al.*, 2011; Thomazella *et al.*, 2011). The PREDIMED study data was obtained from two articles; fasting insulin was available in one paper (Estruch *et al.*, 2006) but fasting glucose was provided by personal correspondence with Professor J. Salas-Salvadó. Baseline characteristics of the trials are presented in Table 1. The combined population of the eight studies was 1352 study participants. The combined population included for analysis of fasting blood glucose, fasting insulin and HbA1c were 972, 1330 and 487 study participants, respectively. Mean age was 57 years (range 50–67 years), mean body mass index was 30 kg m^{-2} (range 26–35 kg m^{-2}) and median duration of follow-up was 3 months (range 2–12 months).

Random effects analysis

Table 2 presents the summary data of the individual studies. Table 3 presents the relative effectiveness of the dietary interventions in lowering glycaemic outcome from a random effects network meta-analysis (fixed effects in the case of HbA1c). The Mediterranean diet was not significantly different from other diets with respect to its effects on fasting blood glucose or fasting insulin. The Mediterranean diet reduced HbA1c significantly compared to usual care but not compared to the Palaeolithic diet.

Compared to written healthy dietary advice, a Mediterranean diet with education (WMD = 0.03 mM; 95% CrI: −2.78 to 2.88) and written Mediterranean diet advice (WMD = 0.07 mM; 95% CrI: −1.92 to 2.05) and a low-fat diet with education (WMD = 0.18 mM; 95% CI: −2.77 to 3.25) were associated with a nonsignificant increase in fasting blood glucose levels. These statistically nonsignificant differences would also not be considered clinically significant. A Palaeolithic diet with education (WMD = −1.07 mM; 95% CrI: −3.19 to 0.96) was associated with a nonsignificant reduction in fasting blood glucose levels compared to written healthy dietary advice.

Compared to written healthy dietary advice, a Mediterranean diet with education (WMD = −2.01; 95% CrI: −24.18 to 21.14), written Mediterranean diet advice (WMD = −0.55; 95% CrI: −18.83 to 18.29), a Palaeolithic diet with education (WMD = −4.09; 95% CrI: −32.89 to 26.05) and a low-fat diet with education (WMD = −0.32; 95% CrI: −25.74 to 26.55) were associated with a nonsignificant reduction in fasting insulin levels.

Compared to usual care, a Mediterranean diet with education (WMD = −0.31; 95% CrI: −0.61 to −0.03) and a Palaeolithic with education (WMD = −0.52; 95% CrI: −0.98 to −0.05) were associated with a significant reduction in HbA1c. The low-fat diet with education was associated with a nonsignificant reduction in HbA1c

Table 1 Study characteristics

Study	Study length	Total number	Participant information	Diet 1	Diet 2	Diet 3	Additional information	Jadad score
Thomazella *et al.* (2011) Brazil	3 months	40 men Mean age = 55 years Mean BMI = 26 kg m^{-2}	≥1 coronary event BMI 18.5–30 kg m^{-2}	*Mediterranean diet* (3) (n = 21) Given personalised dietary advice to increase unrefined cereals, fruits and vegetables, olive oil, nuts, fish and reduce red meat intake Given daily food plans, advice on portion size, food frequency intake Individually scheduled dietician access throughout	*Therapeutic lifestyle change diet* (4) (n = 19) Followed national cholesterol education programme advice, to reduce fat, increase fruit and vegetables, avoid alcohol Given daily food plans, advice on portion size, food frequency intake Individually scheduled dietician access throughout	–	Given personalised dietary advice No supplements allowed Exercise was unchanged Subjects were allocated diets	1
Salas-Salvado *et al.* (2011); Estruch *et al.* (2006) PREDIMED study Spain	12 months: Salas salvado 3 months: Estruch *et al.*, 2006;	418 men and women Mean age = 67 years Mean BMI = 30 kg m^{-2}	3 or more CHD risk factors: smoking, hypertension, dyslipidaemia, BMI ≥25 kg m^{-2} or family history of premature cardiovascular disease	*Mediterranean plus VOO* (3) (n = 137) Given advice to increase their Mediterranean diet score plus provided with olive oil Given personalised dietary advice at start of trail 1 h group session and free access to the dietitian throughout	*Mediterranean plus nuts* (3) (n = 144) Given advice to increase their Mediterranean diet score plus provided with walnuts, hazelnuts and almonds Given personalised dietary advice at start of trail 1 h group session and free access to the dietician throughout	*American Heart, low fat diet* (4) (n = 132) Given advice to reduce all fat intake Given personalised dietary advice at start of trail	–	3
Elhayany *et al.* (2010) Israel	12 months	179 men and women Mean age = 55 years Mean BMI = 31 kg m^{-2}	Type 2 diabetes for 1–10 years BMI 27–34 kg m^{-2} HbA1c 7–10% Plasma triglycerides 1.8–4.5 mM Serum creatinine <123.2 µM No change in diabetic medicine for 3 months	*Traditional Mediterranean* (3) (n = 63) 50–55% Low glycaemic index carbohydrates 30% fat (high monounsaturated) 15–20% protein Patients seen every 2 weeks for 1 year by the same dietician	*Low carb Mediterranean* (3) (n = 61) 35% Low glycaemic index carbohydrates 45% fat (high monounsaturated) 15–20% protein Patients seen every 2 weeks for 1 year by the same dietician	*ADA* (4) (n = 55) 50–55% carbohydrate 30% fat 15–20% protein Patients seen every 2 weeks for a 1 year by the same dietician	All advised to engage in 30–45 min aerobic activity 3 days per week	3

Table 1. *(Continued)*

Study	Study length	Total number	Participant information	Diet 1	Diet 2	Diet 3	Additional information	Jadad score
Rallidis *et al.* (2009) Greece	2 months	82 men and women Mean age = 50 years Mean BMI = 32 kg m^{-2}	Presence of abdominal obesity (>102 cm men >88 cm women)	*Mediterranean intervention* (3) (n = 41) Participants were provided with a copy of the Greek Mediterranean diet and were counselled on this eating pattern Received counselling on food groups, frequency and portions and followed weekly food plans Received weekly phone calls and appointments with a dietician	*Mediterranean control* (2) (n = 41) Participants were provided with a copy of the Greek Mediterranean diet and initially counselled on this eating pattern	–	–	2
Lindeberg *et al.* (2007) Sweden	3 months	30 men Mean age = 61 years Mean BMI = 30 kg m^{-2}	Ischemic heart disease patients with increased glucose levels. Or diabetes Waist circumference >94 cm	*Mediterranean/Consensus* (3) (n = 15) Diet based on whole grains, low fat dairy, fruit, vegetables, potatoes fatty fish, fats rich in monounsaturated and alpha linolenic acid Given two 1 h sessions, written advice and recipes. Also attended a group education session	*Palaeolithic* (5) (n = 14) Diet based on lean meat, fish, fruits, root leafy, and cruciferous vegetables, eggs and nuts Given two 1 h sessions, written dietary advice and recipes. Also attended a group education session	–	Given advice about the benefits of regular physical activity Advised not to consume more than one glass of wine per day	3
Michalsen *et al.* (2006) Germany	12 months	101 men and women Mean age = 59 years Mean BMI = 27 kg m^{-2}	Coronary artery disease present BMI <33 kg m^{-2}	*Lifestyle modification group* (6) (n = 48) Intensive 100 h per year programme. Given extensive instructions on how to adopt a Mediterranean diet	*Advice group* (2) (n = 53) Provided with written advice on dietary principles of a Mediterranean diet	–	Advice on stress management provided	3

Table 1. *(Continued)*

Study	Study length	Total number	Participant information	Diet 1	Diet 2	Diet 3	Additional information	Jadad score
Vincent-Baudry *et al.* (2005) Medi-RIVAGE Study France	3 months	169 men and women Mean age = 51 years Mean BMI = 29 kg m^{-2}	Have at least 1 of the following: Cholesterol: 6.5–7.7 mM Triglycerides: 2.1–4.6 mM Fasting glucose: 6.1–6.9 mM Systolic blood pressure: 140–180 mmHg or Diastolic blood pressure: 90–105 mmHg BMI >27 kg m^{-2} Smoker, sedentary or family history of cardiovascular disease	*Mediterranean* (2) (*n* = 88) Total fat 35–38% with 50% monounsaturated 25 g fibre per day Maximum calcium 800 mg per day Avoid offal and saturated fat rich animal products Fish 4 × per week Red meat 1 × per week Recommend nuts, wholemeal bread and cereals. Raw, cooked, fresh or dried fruit and vegetables and legumes received an advice booklet	*Low fat American* (2) (*n* = 81) Recommend more poultry than red meat, avoid offal and SFA rich meat Eat fish 2–3 × per week Fat <30%, 33% from mono/saturated/poly fatty acids Avoid alcohol Were provided with nutritional advice from physicians and dieticians and received a booklet with advice	–	–	2
Toobert *et al.* (2003)	6 months	279 women Mean age not provided Mean BMI = 35 kg m^{-2}	Post-menopausal women with T2DM	*Mediterranean lifestyle* (6) (*n* = 163) Educated about fats and carbohydrates, increase bread, root vegetables, legumes and fish. Reduce meat, avoid butter. Use olive or canola oil every day and eat fruit every day The intervention began with a 3-day retreat, followed by weekly meetings	*Usual care* (7) (*n* = 116) No information provided	–	Those in the intervention arm received information on physical activity and stress management	1
Djuric *et al.* (2009)* USA	6 months	60 women Mean age = 44 years Mean BMI = 24 kg m^{-2}	General good health BMI 18.5–30 Women included had fat intake of ≥23%, ≤48% fat from monounsaturated fats and fruit and vegetable intake <5.5 servings per day	*Mediterranean* (3) (*n* = 27) Received exchange goals to help achieve: poly/saturated/mono ratio of 1 : 2 : 5 7–9 servings fruit and vegetables depending on energy intake from specified varieties Length of counselling time was not documented	*Nonintervention* (1) (*n* = 33) Given written material to correct any nutritional deficiency Given National Cancers Institutes Action Guide To Healthy Eating Did not receive dietary counselling	–	–	1

Table 1. *(Continued)*

Study	Study length	Total number	Participant information	Diet 1	Diet 2	Diet 3	Additional information	Jadad score
Esposito *et al.* (2009)* Italy	48 months	215 men and women Mean age = 52 years Mean BMI = 30 kg m^{-2}	Newly diagnosed with T2DM BMI >25 kg m^{-2} Sedentary (<1 h activity per week) Weight stable (±2 kg in past 6 months)	*Mediterranean* (3) (*n* = 108) Low carb Mediterranean diet Rich in vegetables and whole grains, low in red meat, poultry and fish encouraged Maximum 50% energy from complex carbohydrate No <30% fat Restricted energy to 6276 kJ (1500 kcal) for women and 7531 kJ (1800 kcal) for men Monthly sessions with dieticians for the first year then bimonthly	*American Heart Association* (5) (*n* = 107) Rich in whole grains, restricted added fat, sweets and high fat snacks Maximum 30% fat, maximum 10% SFA Restricted energy to 6276 kJ (1500 kcal) for women and 7531 kJ (1800 kcal) for men Monthly sessions with dieticians for the first year then bimonthly	–	Both intervention arms received guidance on increasing physical activity	3
Tuttle *et al.* (2008)* The Heart Institute of Spokane Diet Intervention and Evaluation Trial USA	24 months	101 men and women Mean age = 58 years Mean BMI = 30 kg m^{-2}	<6 weeks post myocardial infarction	*Mediterranean* (3) (*n* = 51) Reduced SFA to ≤7% Cholesterol ≤200 mg per day Increase intake of omega3 fatty acids Increase MUFA Increase intake fresh fruits, vegetables and whole grains Those with BMI 26–30 kg m^{-2} encouraged to lose weight Received 2 individual and group dietary counselling sessions	*American Heart Association* (5) (*n* = 50) Reduced SFA to ≤7% Cholesterol ≤200 mg per day Increase intake fresh fruits, vegetables and whole grains Those with BMI 26–30 kg m^{-2} encouraged to lose weight Received 2 individual and group dietary counselling sessions	*Community matched controls* Provided with dietary advice from the medical centre This group were not included in the meta-analysis	Exercise encouraged Smoking cessation encouraged	3
Esposito *et al.* (2004)* Italy	24 months	180 men and women Mean age = 44 years Mean BMI = 28 kg m^{-2}	Met criteria for metabolic syndrome as defined by Adult Treatment Panel III Sedentary (<1 h activity per week) Weight stable (±1 kg in past 6 months)	*Mediterranean* (3) (*n* = 90) Carbs 50–60% Total fat <30%, <10% SFA, Cholesterol <300 mg per day Consume 250–300 g fruits, 125–150 g vegetables, 25–50 g walnuts, 400 g whole grains Increase olive oil Series of monthly small group sessions Received tailored dietary advice Received education in reducing calories	*Control* (1) (*n* = 90) Given oral and written information on healthy food choices	–	Those in the Mediterranean arm also received behavioural and psychological counselling if desired	3

Table 1. *(Continued)*

Study	Study length	Total number	Participant information	Diet 1	Diet 2	Diet 3	Additional information	Jadad score
Esposito *et al.* (2003)* Italy	24 months	120 women Mean age = 35 years Mean BMI = 35 kg m^{-2}	Obese premenopausal women 20–46 years Sedentary (<1 h activity per week) No evidence of participation in weight loss programme in past 6 months	*Mediterranean* (3) (*n* = 60) Given detailed advice on how to lose at least 10% of weight Mean calorie intake set to 5439 kJ (1300 kcal) for first year and 6276 kJ (1500 kcal) in second year 50–60% carbs, 15–20% protein, <30% total fat, <10% SFA, 10–15% MUFA, 18 g fibre per 4184 kJ (1000 kcal) Given individual guidance and monthly group sessions	*Control* (1) (*n* = 60) Given oral and written information on healthy food choices and exercise	–	Those in the Mediterranean arm also received behavioural and psychological counselling if desired Individuals encouraged to increase activity	3

(1): Written advice on a healthy diet, (2): Written advice on the Mediterranean diet, (3): Mediterranean diet plus education, (4): Low fat diet plus education, (5): Palaeolithic diet and education, (6): Mediterranean diet plus behaviour change, (7): usual care.

*Study only included in sensitivity analysis.

BMI, body mass index; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid; T2DM, type 2 diabetes mellitus.

compared to usual care (WMD = −0.02; 95% CrI: −0.44 to 0.41). The between-study variance was 0.73 for fasting glucose and 16.97 for fasting insulin. The between study variance was assumed to be zero in the fixed effect analysis for HbA1c.

Sensitivity analysis

Table 4 displays the results of the sensitivity analysis. Including the additional studies increased the precision of effect estimates (i.e. estimates have narrow credible intervals). Overall, the increase in precision of estimates only had the effect of changing the relative effect of a Palaeolithic diet with education compared to the other diets on fasting glucose levels from a nonsignificant association in the main analysis (Table 3) to a significant association in the sensitivity analysis (Table 4).

Discussion

No significant benefits in fasting blood glucose or fasting insulin levels were observed between the different dietary treatments provided. The results suggest that, in terms of fasting blood glucose or insulin levels, providing written healthy dietary advice is as beneficial as providing group or individual education. Compared to usual care, both the Mediterranean diet with education and the Palaeolithic diet with education were associated with a significant reduction in HbA1c. However, this outcome must be regarded with caution; as a result of the small number of studies included, the results are imprecise. Furthermore, the lack of closed loops of evidence in the networks of evidence means that there was no pooling of direct and indirect evidence on any of the pairwise contrasts. Relative effect estimates were therefore based only on direct trial evidence for intervention comparisons on which there is information for one or more trial, as well as on indirect evidence for interventions not directly compared in any of the included trials.

For the analysis of both fasting blood glucose and fasting insulin, no authentic control group existed. All diets were compared with a group given written advice or a healthy diet in which they were provided with nutritional recommendations and received a booklet recommending a low-fat diet. Alcohol avoidance was also encouraged, particularly to those identified with hypertriglyceridaemia. Thus, these participants received nutritional guidance above normal clinical practice. The lack of an authentic control group may mask a benefit of intervention. The analysis of HbA1c included a group given usual care; however, no description of this was provided (Toobert *et al.*, 2003). It may be assumed that this group is a more realistic control arm, which may explain the significant

Table 2 Summary data of included studies

Study	Intervention 1 versus intervention 2	Intervention arm 1 Baseline score *n*/mean (SD)	Intervention arm 1 Final score *n*/mean (SD)	Intervention arm 1 Change score Mean (SD)	Intervention arm 2 Baseline score *n*/mean (SD)	Intervention arm 2 Final score *n*/mean (SD)	Intervention arm 2 Change score Mean (SD)
Fasting blood glucose (mM)	Mediterranean diet + education versus	21/5.05 (0.45)	21/5.16 (0.45)	–	19/4.94 (0.5)	19/4.88 (0.5)	–
Thomazella *et al.* (2011)	Low fat diet + education			–			
Elhayany *et al.* (2010)‡	Mediterranean diet + education versus Low fat diet + education	124/10.59 (1.9)	124/6.38 (1.13)	–	55/10.26 (1.69)	55/7.19 (1.85)	–
Rallidis *et al.* (2009)	Mediterranean diet + education versus Mediterranean diet only	41/5.41 (0.89)	41/5.28 (0.77)	–	41/5.36 (0.67)	41/5.31 (0.55)	–
Lindeberg *et al.* (2007)	Mediterranean diet + education versus Palaeolithic diet + education	15/7.1 (1.80)	15/6.20 (1.40)	−0.9 (1.8)	14/6.80 (1.30)	14/5.10 (1.00)	−1.7 (1.7)
Vincent-Baudry *et al.* (2005)	Mediterranean diet only versus Written healthy dietary advice	88/5.30 (0.60)	88/5.10 (0.6)	−0.2	81/5.20 (0.70)	81/5.00 (0.60)	−0.2
Salas-Salvado *et al.* (2011)	Mediterranean diet + education versus Low fat diet + education	281/5.51 (0.87)	281/5.52	–	132/5.52 (0.86)	132/5.58 (0.90)	–
Djuric *et al.* (2009)*	Mediterranean diet + education versus Healthy dietary advice	35/5.05 (0.39)	27/5.11 (0.28)	–	34/5.00 (0.33)	33/5.11 (0.44)	–
Esposito *et al.* (2009)*	Mediterranean diet + education versus Low fat diet + education	108/9/ (1.9)	108/7.3 (1.9)	−1.7 (1.1)	107/8.8 (1.8)	107/8 (1.8)	−0.8 (0.8)
Tuttle *et al.* (2008) (nondiabetic)*	Mediterranean diet + education versus Low fat diet + education	41/4.50 (0.50)	41/4.60 (0.50)		40/4.72 (1.00)	34/4.88 (1.30)	–
Tuttle *et al.* (2008) (diabetic)*	Mediterranean diet + education versus Low fat diet + education	10/7.66 (4.72)	10/6.55 (1.39)		10/7.38 (3.11)	10/6.22 (2.05)	–
Esposito *et al.* (2004)*	Mediterranean diet + education versus Written healthy dietary	90/6.27 (0.56)	90/5.83 (0.50)	−0.44 (0.17)	90/6.33 (0.56)	90/6.22 (0.50)	−0.11 (0.08)
Esposito *et al.* (2003)*	Mediterranean diet + education versus Written healthy dietary	60/5.89 (0.78)	60/5.38 (0.72)	−0.5 (0.01)	60/5.83 (0.7)	60/5.72 (0.61)	0.11 (0.001)
Fasting insulin (μU mL^{-1})							
Elhayany *et al.* (2010)‡	Mediterranean diet + education versus Low fat diet + education	124/11.89 (7.54)	124/13.63 (6.07)	–	55/12.80 (6.70)	55/13.70 (5.30)	–
Rallidis *et al.* (2009)	Mediterranean diet + education versus Written Mediterranean diet	41/14.90 (7.80)	41/11.8 (7.10)	–	41/14.10 (5.80)	41/15.30 (8.60)	–
Lindeberg *et al.* (2007)	Mediterranean diet + education versus Palaeolithic + education	15/17.70 (9.79)	15/14.54 (7.63)	−3.17 (7.78)	14.00/14.69 (5.18)	14/12.38 (5.18)	−2.3 (3.89)
Estruch *et al.* (2006)	Mediterranean diet + education versus Low fat diet + education	515/5.60 (3.41)	515/4.20 (3.41)	−1.40 (0.7)†	258/6.20 (4.40)	255/7.14 (4.40)	0.94 (0.75)†
Michalsen *et al.* (2006)	Mediterranean diet + education versus Written Mediterranean diet	48/10.50 (4.80)	48/11.30 (9.30)	–	53/14.30 (19.60)	53/10.60 (7.60)	–
Vincent-Baudry *et al.* (2005)	Mediterranean diet only versus Written dietary advice	88/10.60/5.80	88/8.30/4.40	−2.6/–	81/10.60/7.80	81/8.90/5.90	−1.7/–
Esposito *et al.* (2009)*	Mediterranean diet + education versus Low fat diet + education	108/15.55 (6.19)	108/14.15 (6.19)	−1.4 (1.25)	107/16.56 (7.2)	107/15.75 (7.2)	−0.81 (0.62)
Tuttle *et al.* (2008) (nondiabetic)*	Mediterranean diet + education versus Low fat diet + education	41/10 (5)	37/10 (9)		40/13 (8)	34/17 (32)	–

Table 2. *(Continued)*

Study	Intervention 1 versus intervention 2	Intervention arm 1 Baseline score *n*/mean (SD)	Intervention arm 1 Final score *n*/mean (SD)	Intervention arm 1 Change score Mean (SD)	Intervention arm 2 Baseline score *n*/mean (SD)	Intervention arm 2 Final score *n*/mean (SD)	Intervention arm 2 Change score Mean (SD)
Tuttle *et al.* (2008) (diabetic)*	Mediterranean diet + education versus Low fat diet + education	10/15 (9)	10/20 (16)		10/32 (32)	10/16 (6)	–
Esposito *et al.* (2004)*	Mediterranean diet + education versus Written healthy dietary advice	90/15 (6)	90/11 (5)	−4 (1.9)	90/16 (7)	90/15.5 (7)	−0.5 (1)
Esposito *et al.* (2003)*	Mediterranean diet + education versus Written healthy dietary advice	60/14 (4)	60/9 (3)	−5 (0.02)	60/14 (4)	60/12 (3)	−2 (0.02)
HbA1c levels (%)							
Elhayany *et al.* (2010)‡	Mediterranean diet + education versus Low fat diet + education	124/8.30 (1.00)	124/6.40 (1.14)	–	55/8.30 (0.80)	55/6.70 (0.90)	–
Lindeberg *et al.* (2007)	Mediterranean diet + education versus Palaeolithic + education	15/4.89 (0.79)	15/4.85 (0.69)	−0.03 (0.39)	14/4.76 (0.26)	14/4.64 (0.22)	−0.13 (0.26)
Toobert *et al.* (2003)	Mediterranean diet + education versus Usual care	163/7.43 (1.30)	163/7.07 (1.11)	–	116/7.40 (1.48)	116/7.38 (1.33)	–

*Only included in the sensitivity analysis.
†SD calculated from the reported 95% confidence interval (hence the value is the SE).
‡Two groups combined to into one Mediterranean diet + education intervention group.

Table 3 Results from random effects (fasting blood glucose and fasting insulin) and fixed effects (HbA1c levels) network meta-analysis models

	Fasting blood glucose (mM)		Fasting insulin (μU mL^{-1})		HbA1c level (%)	
	Pairwise meta-analysis*	Network meta-analysis	Pairwise meta-analysis*	Network meta-analysis	Pairwise meta-analysis*	Network meta-analysis*
MD + education versus						
Written healthy diet		0.03 (−2.78, 2.88)		−2.01 (−24.18, 21.14)	−0.31 (−0.61, −0.01)	−0.31 (−0.61, −0.03)
Written MD versus						
Written healthy diet	0.10 (−0.08, 0.28)	0.07 (−1.92, 2.05)	−0.60 (−2.18, 0.98)	−0.55 (−15.83, 18.29)		
MD + education	0.03 (−0.26, 0.32)	0.03 (−1.95, 2.13)	1.35 (−1.04, 3.74)	1.43 (−12.57, 14.14)		
Palaeolithic diet + education versus						
Written healthy diet		−1.05 (−4.59, 2.62)		−4.09 (−32.89, 26.05)		−0.52 (−0.98, −0.05)
MD + education	−1.10 (−1.98, −0.22)	−1.08 (−3.24, 1.16)	−2.16 (−6.88, 2.56)	−2.10 (−20.48, 16.55)	−0.22 (−0.49, 0.05)	−0.21 (−0.58, 0.16)
Written MD		−1.13 (−4.19, 1.90)		−3.56 (−26.05, 19.96)		
Low fat diet + education versus						
Written healthy diet		0.18 (−2.77, 3.25)		−0.32 (−25.74, 26.55)		−0.02 (−0.44, 0.41)
MD + education	0.03 (−0.12 to 0.19)	0.14 (−1.03, 1.35)	2.63 (2.05, 3.21)	1.68 (−10.89, 14.47)	0.30 (−0.01, 0.61)	0.30 (−0.01, 0.60)
Written MD		0.11 (−2.23, 2.43		0.26 (−17.95, 19.11)		
Palaeolithic diet + education		1.23 (−1.29, 3.76)		3.73 (−19.31, 26.04)		0.51 (0.03, 0.99)

Relative intervention effectiveness is expressed as the weighted mean difference (95% credible intervals).
*Results are individual study estimate of fixed effect meta-analysis of two or more studies.
MD, Mediterranean diet.

Table 4 Sensitivity analysis results from random effects (fasting blood glucose and fasting insulin) network meta-analysis models

	Fasting blood glucose (mM)		Fasting insulin (μU mL^{-1})	
	Pairwise meta-analysis*	Network meta-analysis	Pairwise meta-analysis*	Network meta-analysis
Mediterranean diet + education versus				
Written healthy diet	−0.01 (−0.19, 0.17)	−0.20 (−0.56, 0.16)	−3.40 (−4.32, −2.48)	−3.31 (−5.15, −1.45)
Written MD versus				
Written healthy diet	0.10 (−0.08, 0.28)	−0.02 (−0.53, 0.47)	−0.60 (−2.18, 0.98)	−1.26 (−3.59, 0.99)
Mediterranean diet + education	0.03 (−0.26, 0.32)	0.19 (−0.34, 0.66)	1.35 (−1.04, 3.74)	0.186 (−0.34, 0.66)
Palaeolithic diet + education versus				
Written healthy diet		−1.28 (−2.37, −0.19)		−5.63 (−11.06, 0.07)
Mediterranean diet + education	−1.10 (−1.98, −0.22)	−1.08 (−2.12, −0.02)	−2.16 (−6.88, 2.56)	−2.32 (−7.55, 3.13)
Written MD		−1.27 (−2.42, −0.10)		−4.36 (−9.98, 1.40)
Low fat diet + education versus				
Written healthy diet		0.25 (−0.31, 0.75)		0.25 (−0.31, 0.75)
Mediterranean diet + education	0.26 (−0.14, 0.65)	0.45 (0.03, 0.82)	−0.08 (1.66, 3.40)	1.81 (0.01, 3.31)
Written MD		0.26 (−0.38, 0.90)		−0.27 (−3.10, 2.50)
Palaeolithic diet + education		1.53 (0.39, 2.62)		4.08 (−1.70, 9.57)

Relative intervention effectiveness is expressed as the weighted mean difference (95% credible intervals).
*Results are individual study estimate of fixed effect meta-analysis of two or more studies.
MD, Mediterranean diet.

reductions in HbA1c in those who received Mediterranean dietary advice with education, or Palaeolithic dietary advice with education, compared to the lack of observed significant difference in fasting glucose and insulin.

To compare the Mediterranean diet with other types of diets, we specifically created diet categories. These were determined according to similarities between diets in the various studies. We grouped diets according to the type of diet described. In addition, we tried to account for contact time and created written groups, education groups and behaviour change groups. This may have introduced errors, both as a result of lack of explicit descriptions of the diets and because it was difficult to determine how much advice and or contact time was provided by the different studies. The possibility exists that the participants in the written groups received more contact time than individuals would normally receive in routine care.

We specifically selected articles that included participants at high risk or with T2DM; however, mean baseline fasting blood glucose was in the normal range for all studies except that by Elhayany *et al.* (2010), and this may have resulted in a lesser observed effect on fasting glucose than if all participants had raised blood glucose concentrations at baseline.

Another potential explanation for the lack of difference in effect between diets is that all the diets included were healthy diets. The Mediterranean, Palaeolithic and low-fat diets all share common elements of a healthy diet; all encourage a high intake of fruit and vegetables, as well as reductions in saturated fats and the replacement of red meat by fish or lean meat. Furthermore, refined carbohydrates are reduced and whole grains are encouraged in all diets. Previous reviews of dietary patterns that have included these components have shown the benefits for reducing risk of T2DM (Heidemann *et al.*, 2005; Erber *et al.*, 2010). Regardless of name, each diet encourages specific healthy elements supporting the current dietary recommendations with respect to glucose maintenance for those with diabetes (Bantle *et al.*, 2008; Dyson *et al.*, 2011).

A possible explanation for the lack of a difference between diets may also be explained by intervention effects. By virtue of being in a study, participants may be willing to change. The Hawthorne effect is a phenomenon suggesting that, regardless of the change introduced, simply being in a trial increases responses (McCarney *et al.*, 2007). Client characteristics are also important; those who enter the study may have positive expectations for improvement (Grencavage & Norcross, 1990). Furthermore, individuals who participate in studies have likely considered such behaviour changes as that in an intervention (Bergmann & Boeing, 2002). The intensity of follow-up is also considered to impact on patient's response; those in the control arm received the same amount of clinic time for data collection and therefore were more likely to consider eating habits than they would routinely do so (McCarney *et al.*, 2007).

The inclusion of studies that specifically restricted calorie intake increased the precision of estimate effects. The only change in outcome was the increased effect size of the Palaeolithic diet compared to other dietary interventions. A potential beneficial effect of this diet is the lower carbohydrate content of the diet. It is well accepted that the carbohydrate load in a diet exerts the greatest effect on post-prandial blood glucose (Kirk *et al.*, 2008). Recommendations for high carbohydrate intake have been questioned multiple times (Garg, 1994), yet low carbohydrate diets remain controversial. A meta-analysis of high-fat, low carbohydrate versus low-fat high carbohydrate diets in those with T2DM demonstrated a greater 2-h glucose in those on the high carbohydrate diet but found no difference in fasting blood glucose or HbA1c (Kodama *et al.*, 2009). Mixed effects on cardiovascular risk factors were also seen in a further meta-analysis on low carbohydrate diets for weight loss (Nordmann *et al.*, 2011). Thus, it is still accepted that there is insufficient evidence to recommend carbohydrate-restricted diets to those individuals with T2DM (Kirk *et al.*, 2008). The plethora of conflicting data suggests that the debate may continue for some time.

Independently, none of the studies examined showed significantly detrimental effects of dietary modification on fasting blood glucose, fasting insulin or HbA1c. The Palaeolithic diet in the study by Lindeberg *et al.* (2007) demonstrated the most positive effect on fasting blood glucose of all of the studies included in the analysis. We considered this study to be of higher quality; the article provided explicit details about the different dietary interventions, as well as details of contact time and the education received. This elegant study is well reported, which likely reflects the rigorous study procedures. However, caution should be taken with regard to recommending this diet, in that the results are only obtained from one study, which only included a small number of participants, and standards may be difficult to reproduce in a real-life setting. Furthermore, the diet may not be complete in all nutrients; a limitation of dairy products could increase the risk of calcium or other mineral deficiencies. In addition, if lean meats are not specifically selected, cardiovascular risk may be increased.

It should also be noted that the markers under investigation (fasting blood glucose, fasting insulin and HbA1c) are only surrogate markers for insulin sensitivity. A number of studies have used the gold standard measure of insulin sensitivity (i.e. the euglycaemic hyperinsulinaemic clamp) to measure insulin sensitivity directly. A high cereal fibre diet significantly improved whole body insulin sensitivity over 6 weeks, yet no differences were observed in fasting glucose or HbA1c (Weickert *et al.*, 2011). Furthermore, a study in older men showed that the fatty acid composition of both serum and skeletal muscle was affected by the level of saturated fatty acids in the diet and that di-homo-δ-linolenic acid explained 18% of variation in insulin sensitivity (Vessby *et al.*, 1994). As a result of the demonstration that changes in dietary content can influence insulin sensitivity, the surrogate markers in the studies included in this review may not have been sufficiently sensitive to detect small yet important changes.

We specifically included studies that did not restrict calorie intake; nonetheless, the majority of studies reported weight loss as an outcome. The inclusion of studies that encouraged weight loss did not change the overall findings about the Mediterranean diet but did increase precision. A review of the Mediterranean diet found greater reductions in body mass index and weight in those who followed the Mediterranean diet compared to other control diets (Esposito *et al.*, 2011). Our review is unique in that it examines dietary patterns in free-living individuals who are not specifically reducing calorie intake. The data suggest that, in overweight individuals, the provision of dietary information of any type or by any method (either one to one or within in a group setting) can result in weight loss and potentially aid glucose management (Resnick *et al.*, 2000). The results support a recent review of macronutrient and food group intake in the management of diabetes, which concluded that different approaches for medical nutritional therapy and eating patterns are effective for glycaemic control (Wheeler *et al.*, 2012). As previously observed, weight loss may be the key factor; however, finding a healthy dietary pattern (regardless of the name) that an individual can adhere to with respect to achieving successful weight loss is perhaps the most important aspect of nutritional therapy. As researchers and healthcare providers, we often try to find the 'best' diet, and perhaps avoiding labels and concentrating on healthy components within these different diets should be our focus.

Strengths and limitations

We conducted a broad, robust search over multiple databases, resulting in an extensive search strategy. We had strict inclusion and exclusion criteria and two independent reviews carried out the study selection procedure. Rigorous statistical analysis was carried out on the extracted data. However, as with all meta-analysis, a number of limitations must be considered. Publication bias is a concern; no formal method is available to assess publication bias in network meta-analysis. A significant benefit on HbA1c with the provision of either a Mediterranean diet with education or Palaeolithic diet with education compared to usual care was observed. However, this outcome was derived using fixed effects modelling, which gives narrower confidence intervals than random effects modelling; therefore, a significant result may more likely be observed.

The studies included ranged in follow-up length from 2–12 months, with a mean follow-up of just 3 months.

Longer-term adherence to any of the dietary patterns may demonstrate a greater difference between diets. A US observational study showed that a greater adherence to the Mediterranean diet was associated with a significantly lower homeostasis model assessment–insulin resistance index and fasting blood glucose, as well as a lower cumulative incidence of the metabolic syndrome, over a 7-year follow-up period (Rumawas *et al.*, 2009).

The studies included were not explicit in their diet descriptions or their explanation of contact time; this made grouping of dietary regimes difficult and potentially imprecise. Justification for conducting meta-analyses on differing dietary studies has previously been questioned (Mann & Morenga, 2013) and significant heterogeneity existed; however, the inclusion of the additional studies in the sensitivity analysis increased precision and the results remained, which suggests that the data are consistent. Furthermore, we excluded studies that specifically provided all foods to participants; yet we included the study by Salas-Salvado *et al.* (2011), which gave either oil or nuts to participants. We considered that the bulk of dietary intake was self-selected and therefore more authentic to free-living individuals than studies that were conducted in nutritional units. We cannot exclude other factors that may have impacted on the outcome of each study. A number of the interventions also encouraged exercise and stress management; thus, any changes in these behaviours may have impacted upon the overall results.

The benefits of the Mediterranean diet will continue to be debated. The landmark Lyon Study published over 10 years ago (de Lorgeril *et al.*, 1999) demonstrated strong benefits on cardiovascular risk factors. In addition, recently published results from the PREDIMED trial show a decreased incidence of cardiovascular events over 4.8 years in those who were randomised to the Mediterranean diet (Estruch *et al.*, 2013).

Conclusions

The Mediterranean diet with education does not appear to significantly improve fasting glucose but the data indicate beneficial improvements in HbA1c compared to other healthy dietary interventions in those at risk of (or diagnosed with) diabetes. Insufficient evidence has been demonstrated to encourage any change in current recommendations for the management or prevention of T2DM (Bantle *et al.*, 2008; Dyson *et al.*, 2011). Robust nutritional studies in real-life clinical settings are required and an urgent need for an improvement in the reporting of dietary interventions is needed. Explicit explanations of the diets provided, contact time and compliance should all be reported.

Acknowledgments

We would like to thank Jordi Salas-Salvadó, Professor of Nutrition for providing 1-year glucose data for the PREDIMED study. We also thank Sarah Sutton, Clinical Librarian for her help with the search strategy. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interests, source of funding and authorship

PC, FA, JT and LJG declare that they have no conflicts of interest.

The research was funded by The Cardiovascular Research Department of The University of Leicester. The project was supported by The NIHR Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit, which is a partnership between University Hospitals of Leicester NHS Trust, Loughborough University and the University of Leicester. We acknowledge on-going support from NIHR-CLAHRC. KK and MJD have received grants from the National Institute of Health Research (NIHR) for studies on the prevention of type 2 diabetes.

PC, KK and MJD had the original idea for the review. KK and MJD developed the protocol for the review with PC. PC performed the literature review and extracted and analysed data. JT also reviewed extracted and analysed data. FA and LJG performed the statistical analysis. PC and FA wrote the first draft of the article. All of the authors contributed to the writing of the paper, gave input at all stages of the study and approved the final version submitted for publication.

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