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Systematic review and meta-analysis

Comparison of the long-term effects of high-fat *v.* low-fat diet consumption on cardiometabolic risk factors in subjects with abnormal glucose metabolism: a systematic review and meta-analysis

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Abstract

The aim of the present systematic review and meta-analysis was to examine the long-term effects (≥12 months) of high-fat (HF) *v.* low-fat (LF) diet consumption on the indicators of glycaemic control as well as cardiovascular risk factors in pre-diabetic and diabetic individuals. Literature search was carried out using the electronic databases MEDLINE, Embase and the Cochrane Trial Register until November 2013. Study-specific weighted mean differences (MD) were pooled using a random-effects model of the Cochrane software package Review Manager 5.1 and Stata 12.0 was used for meta-regressions. A total of fourteen trials met the inclusion criteria and a maximum of 1753 subjects were included in the meta-analysis. HF regimens were found to result in a significant decrease in TAG levels (MD −0·19 mmol/l, 95 % CI −0·23, −0·14, $P<0·001$; $I^2=0$ %, $P=0·58$) and diastolic blood pressure (MD −1·30 mmHg, 95 % CI −1·73, −0·87, $P<0·001$; $I^2=0$ %, $P=0·60$) and a significant increase in HDL-cholesterol levels (MD 0·05 mmol/l, 95 % CI 0·01, 0·08, $P=0·01$; $I^2=57$ %, $P=0·01$). In addition, MD in the reductions of fasting glucose levels (−0·41 mmol/l, 95 % CI −0·74, −0·08, $P=0·01$; $I^2=56$ %, $P=0·02$) were significantly high in patients with type 2 diabetes adhering to a HF diet. HF and LF diets might not be of equal value in the management of either pre-diabetes or type 2 diabetes, leading to emphasis being placed on the recommendations of HF diets.

Key words: **Low-fat diets: High-fat diets: Meta-analyses: Systematic review: Abnormal glucose metabolism**

With an estimated prevalence of 350 million cases worldwide, diabetes represents one of the most serious and pressing current health problems. Type 2 diabetes accounts for approximately 90–95 % of cases with manifested diabetes[1]. Due to the detrimental consequences and diabetes-associated disorders (e.g. retinopathy, neuropathy and CVD), it is necessary to use every available tool to prevent the onset as well the progression of the disease. Again, type 2 diabetes is of prime importance, as its pathogenesis can be prevented by lifestyle modifications. Increased physical activity and improved nutritional habits in the form of healthy balanced diets are of particular importance in the deceleration of type 2 diabetes manifestations. In 2003, the American Diabetes Association classified an intermediate group of individuals who did not meet the criteria for symptomatic diabetes with respect to their glucose levels. However, due to impaired fasting glucose (FG) levels (values of fasting plasma glucose in the range of 5·6–6·9 mmol/l) and impaired glucose tolerance (2 h values of plasma glucose in the range of 7·8–11 mmol/l following an oral glucose tolerance test) or permanently increased glycosylated Hb levels (5·7–6·4 % or 38·7–46·4 mmol/mol), these individuals are considered to be at an increased risk of type 2 diabetes and termed pre-diabetics. Impaired FG levels and impaired glucose tolerance are usually associated with obesity (especially increased abdominal and visceral fat mass), dyslipidaemia, increased plasma TAG levels, decreased plasma HDL-cholesterol (HDL-C) levels and hypertension, all representing established type 2 diabetes risk factors[2]. Numerous long-term intervention studies have shown that lifestyle improvements exert beneficial effects on the onset and progression of type 2 diabetes. Thus, both weight reduction and physical exercise have been shown to be significantly associated with a decreased incidence of diabetes[3,4].

Abbreviations: DBP, diastolic blood pressure; FG, fasting glucose; FI, fasting insulin; HDL-C, HDL-cholesterol; HF, high fat; LC, low carbohydrate; LF, low fat; MD, mean differences; RCT, randomised controlled trials; SBP, systolic blood pressure; TC, total cholesterol; TEC, total energy content.

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To accomplish the objective of weight reduction, the American Diabetes Association recommended energy-reduced dietary protocols without giving any preference to macronutrient composition. According to its position statement, both a low-carbohydrate (LC) regimen and a low-fat (LF) regimen are considered to be effective means for weight management[5]. In a meta-analysis published in 2009, Kodama *et al.*[6] investigated the short-term effects of LF *v.* LC diet consumption in patients with type 2 diabetes. They could observe significantly more pronounced changes in fasting insulin (FI), TAG and HDL-C levels, all in favour of the LC dietary protocol. With respect to their macronutrient distribution, it seems legitimate to put high-fat (HF) diets on a level with LC diets, assuming that a reduced carbohydrate content will most probably be accompanied by an increased amount of fat in the total energy content (TEC). The aim of the present systematic review was to examine the long-term effects (≥12 months) of HF *v.* LF diet consumption on the parameters of glycaemic control in both pre-diabetics and patients with established type 2 diabetes. Furthermore, cardiovascular risk factors (e.g. TAG, LDL-cholesterol and HDL-C) were included as outcome parameters. As has been described previously, a HF diet was defined to provide >30 % of TEC in the form of fat, whereas ≤30 % of TEC was taken up in the form of fat in the LF counterparts[7]. In this context, the data reported by Kodama *et al.*[6] would argue against the equivalent usefulness of LF (= high-carbohydrate) and LC (= HF) diets emphasising the value of the latter. However, the validity of this conclusion has to be substantiated by the analysis of long-term studies including the objectives of primary prevention, i.e. investigating the effects of different dietary protocols on risk parameters in pre-diabetic individuals.

Methods

Data sources and searches

Literature search restricted to randomised controlled trials (RCT) without any restrictions on language and calendar date was carried out using the electronic databases MEDLINE (until November 2013), Embase (until November 2013) and the Cochrane Trial Register (until November 2013) with the following search terms: low-fat diet; high-fat diet; low-carbohydrate diet; high-carbohydrate diet. Full details of the electronic search strategy are given in the online supplementary material. Furthermore, the reference lists from the retrieved articles were checked to search for further relevant studies. This systematic review was planned, conducted and reported in adherence to the standards of quality for reporting meta-analyses[8]. Literature search as well as article abstraction was conducted independently by both the authors, with disagreements being resolved by consensus.

Study selection

Studies were included in the meta-analysis if they met all the following criteria: (1) randomised controlled design; (2) minimum intervention period with a follow-up period of 12 months; (3) comparison of a HF dietary intervention (>30 % of TEC) with a LF dietary intervention (≤30 % of TEC), stated as the goal of intervention; (4) age of the subjects ≥18 years; (5) enrolment of subjects with either impaired FG levels (≥5·6 mmol/l) or insulin resistance[9] or type 2 diabetes[2]; (6) assessment of the 'outcome of interest' markers: body weight, total cholesterol (TC), LDL-cholesterol, HDL-C, TC:HDL-C ratio, TAG, systolic and diastolic blood pressure (SBP/DBP), C-reactive protein, FI, FG, glycosylated Hb, and adiponectin; (7) report of post-intervention mean or mean of values recorded at two time points with standard deviation (or basic data to calculate these parameters). If data of ongoing studies were published as updates, results of only those of the longest duration were included. Studies that enrolled patients with type 1 diabetes mellitus were excluded.

Data extraction and quality assessment – overall quality of evidence

The focus of this systematic review was the examination of the effects of LF *v.* HF diet consumption on the values of glycaemic control and cardiovascular risk factors in individuals at a high risk of type 2 diabetes or with manifested type 2 diabetes. The following types of dietary interventions were evaluated: in the primary analysis, LF diets were defined as those providing ≤ 30 % of TEC in the form of fat, approximately 15 % of TEC from protein and approximately 55 % of TEC from carbohydrates and HF diets were defined as those providing >30 % of TEC as fat. HF diets were further classified according to alternative macronutrient composition as follows:

(1) usual diet (total fat content >30 % of TEC and SFA content >10 % of TEC);
(2) LC diet (<50 g carbohydrates/daily);
(3) high-monounsaturated fat, MUFA diet (total fat content >30 % of TEC and total MUFA content >12 % of TEC).

The risk of bias assessment tool provided by the Cochrane Collaboration was applied specifying the following bias domains: selection bias (random sequence generation and allocation concealment); performance/detection bias (blinding of participants and personnel/blinding of outcome assessment); attrition bias (incomplete data outcome); reporting bias (selective reporting); other bias (see online supplementary Fig. S1)[10].

The following data were extracted for each study: the first author's last name; year of publication; study duration; sex distribution and age; BMI; percentage of diabetics; sample size; outcomes; post-intervention mean values or differences in the mean of values recorded at two time points with the corresponding standard deviation. The quality of evidence was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines[11].

Data synthesis and analysis

For each outcome measure of interest, a meta-analysis was carried out to determine the pooled effect of the intervention

in terms of weighted mean differences (MD) between the post-intervention (or differences in means) values of the HF group and those of the LF group. Combining both the post-intervention values and differences in means in one meta-analysis is a legitimate method described by the Cochrane Collaboration[12]. All data were analysed using the Review Manager 5.1 software, provided by the Cochrane Collaboration (http://ims.cochrane.org/revman). The random-effects model was used to estimate MD with 95 % CI. Forest plots were generated to illustrate the study-specific effect sizes along with 95 % CI. Heterogeneity between the trial results was tested with a standard χ^2 test. The I^2 parameter was used to quantify any inconsistency:

$$I^2 = ((Q - \mathrm{df}))/Q \times 100\,\%,$$

where Q is the χ^2 statistic. A cut-off point $\geq 50\,\%$ was chosen for I^2 to indicate substantial heterogeneity[12]. To evaluate substantial heterogeneity, several *post hoc* univariate random-effects meta-regressions were performed to examine the association between total fat, SFA, MUFA, PUFA, carbohydrate, protein, dietary cholesterol and fibre intake as independent variables and changes in FG, FI, TC and HDL-C levels (where substantial heterogeneity could be detected) as dependent variables. Furthermore, BMI, age, sex and study duration were used as covariates. The *P* values for differences in effects between the covariates were obtained using the *metareg* function of Stata 12.0 (Stata-Corporation). Two-sided *P* values $<0{\cdot}05$ were considered to be statistically significant. To increase the precision of the estimates of macronutrient intake (total fat, SFA, MUFA, PUFA, fibre, cholesterol, carbohydrate and protein (all in percentage of TEC)), data from FFQ, 24 h dietary recalls or 3–7 d dietary protocols (if available) were used instead of the theoretical macronutrient composition values of dietary intervention protocols. Funnel plots were sketched to indicate potential publication bias (e.g. the tendency for studies yielding statistically significant results to be more likely to be submitted and accepted for publication). To determine the presence of publication bias, the symmetry of the funnel plots in which MD were plotted against their corresponding standard errors was assessed. A primary analysis of all studies oriented towards the definition of HF and LF diets was carried out, followed by a subanalysis of the specific kind of dietary intervention as described in the selected studies. In addition, a sensitivity analysis including only subjects with type 2 diabetes as well as a sensitivity analysis to determine the risk of bias of the trials[13,14] was conducted.

Among the studies included in the review, two studies[15,16] used two types of LF diets, and these diets were combined into one group as described in the Cochrane Handbook[12]. In the study carried out by Shai *et al.*[17], the LF and LC branches were extracted for meta-analysis, while the MUFA group was discarded and re-analysed in the sensitivity analyses, as duplicate application of the LF dietary intervention data would not be legitimate. Data extraction was conducted independently by both the authors, with disagreements being resolved by consensus. Data processing for this review required the input of the mean and standard deviation of post-intervention values or differences in means. In case of missing data, the authors of the original article were asked for additional information and, if provided, the raw data were used for computations[16,17].

Results

Literature search

A total of fourteen studies extracted from 16 608 articles met the inclusion criteria and were analysed in the systematic review[15–30]. Detailed steps of the article selection process used for the present meta-analysis are shown as a flow chart in Fig. 1. In accordance with the overall inclusion criteria, five studies were excluded due to inconsistencies in the mean FG levels of the study populations ($\geq 5{\cdot}6$ mmol/l) and the corresponding standard deviations, thereby increasing the potential for selection bias (Fig. 1)[31–35].

Study and participant characteristics

All studies included in this systematic review were RCT with a duration ranging between 12 months and 6 years, published between 1978 and 2012, and enrolling a total of 2003 participants. All studies compared a HF regimen defined as a LC diet (six studies), a control/HF diet (four studies) or a MUFA-rich protocol (four studies) with a LF regimen. The reported BMI was $>25\,\mathrm{kg/m^2}$ in all the studies and the mean age of the participants varied between 52 and 62 years. The reported drop-out rates were 25 % for the HF group and 23 % for the LF group. The general study characteristics are given in Table 1. Results obtained using the risk of bias assessment tool are summarised in online supplementary Fig. S1.

Outcomes

The pooled estimates of weighted MD for the effects of HF diet consumption compared with those of LF diet consumption on body weight, blood lipids and parameters of glycaemic control are summarised in Table 2. Changes in body weight (see online supplementary Fig. S2), TC levels (see online supplementary Fig. S3), LDL-cholesterol levels (see online supplementary Fig. S4), SBP (see online supplementary Fig. S8), FI levels (see online supplementary Fig. S9), FG levels (see online supplementary Fig. S10), glycosylated Hb levels (see online supplementary Fig. S11), TC:HDL-C ratio and C-reactive protein levels in subjects following a HF diet were not significantly different from those in subjects following a LF diet.

The HF dietary protocols were found to lead to a significantly more pronounced decrease in TAG levels when compared with the LF dietary protocols (MD $-0{\cdot}19$ mmol/l, 95 % CI $-0{\cdot}23$, $-0{\cdot}14$, $P<0{\cdot}001$; $I^2 = 0\,\%$, $P=0{\cdot}58$). The subgroup analyses revealed that the decrease in TAG levels was significant in subjects following a MUFA-rich diet than in those following a LF diet (MD $-0{\cdot}20$ mmol/l, 95 % CI $-0{\cdot}25$, $-0{\cdot}15$, $P<0{\cdot}001$; $I^2 = 13\,\%$, $P=0{\cdot}33$; see online supplementary Fig. S6).

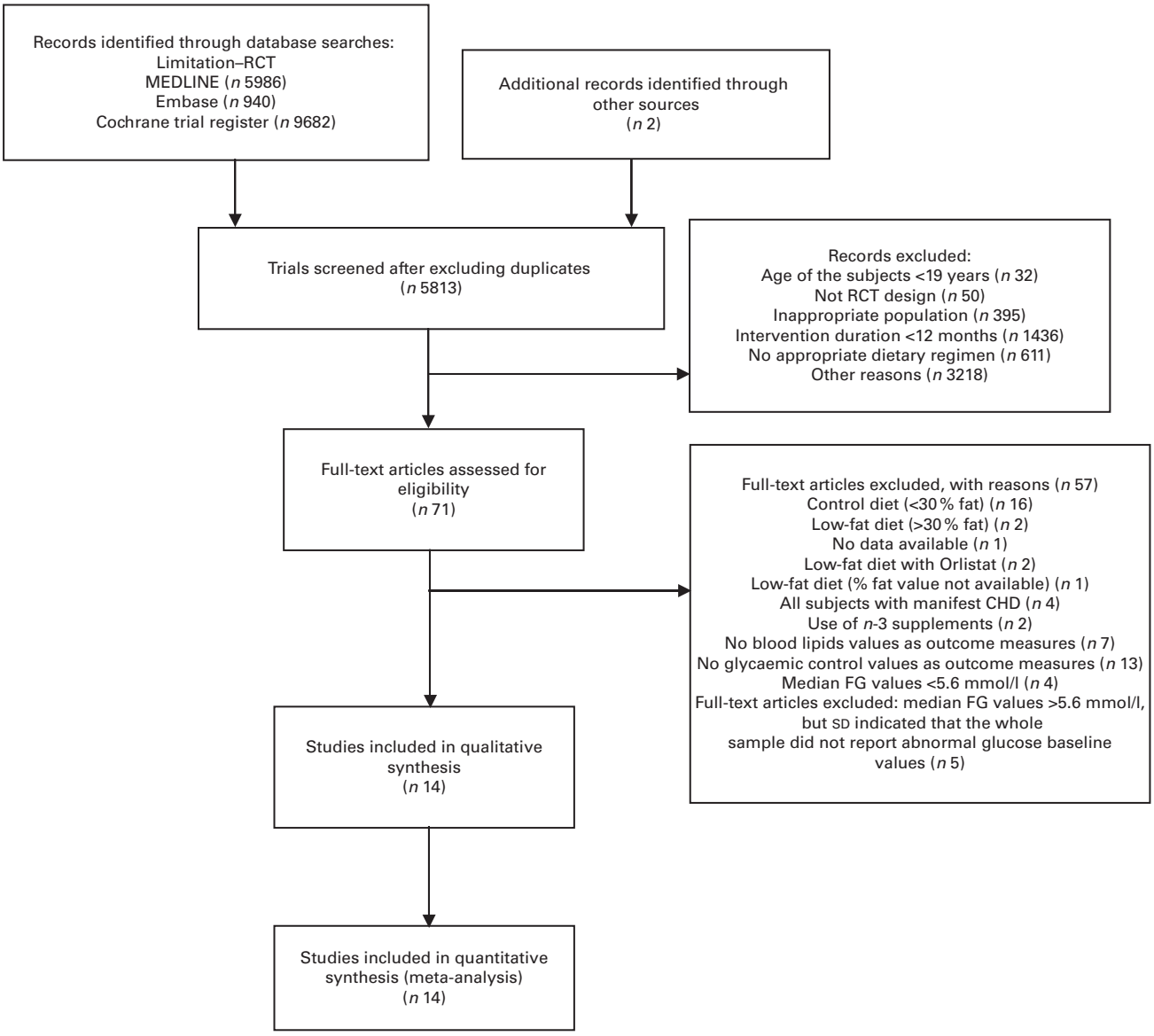

Fig. 1. Flow chart for the systematic review article selection process. RCT, randomised controlled trials; FG, fasting glucose.

HDL-C (see online supplementary Fig. S5; MD 0·05 mmol/l, 95 % CI 0·01, 0·08, $P=0·01$; $I^2=57\,\%$, $P=0·01$) and adiponectin (MD 1·10 μg/ml, 95 % CI 0·87, 1·33, $P<0·001$) levels were significantly more increased by the HF dietary interventions than by the LF dietary interventions. Subgroup analyses yielded non-significant results.

With respect to blood pressure values, reductions in DBP were significantly more explicit in subjects adhering to a HF diet than in those adhering to a LF diet (MD −1·30 mmHg, 95 % CI −1·73, −0·87, $P<0·001$; $I^2=0\,\%$, $P=0·60$; see online supplementary Fig. S7). Comparable results for both DBP (MD −1·38 mmHg, 95 % CI −1·82, −0·95, $P<0·001$; $I^2=0\,\%$, $P=0·79$) and SBP (MD −1·48 mmHg, 95 % CI −2·01, −0·96, $P<0·001$; $I^2=0\,\%$, $P=0·45$) were obtained when comparing high-MUFA groups with LF groups in subgroup analyses.

With regard to biomarkers of glycaemic control, changes in FI levels did not differ between the HF and LF groups. However, *post hoc* analysis of subgroups revealed that FI values were significantly more increased in subjects adhering to a usual/HF diet than in those adhering to a LF diet (MD 7·79 pmol/l, 95 % CI 3·24, 12·33, $P<0·001$; $I^2=0\,\%$, $P=0·95$).

Sensitivity/subgroup analyses

To investigate the effects of HF *v.* LF diet consumption in patients with manifested type 2 diabetes, a sensitivity analysis was carried out by excluding all RCT enrolling only subjects at a risk of type 2 diabetes (i.e. individuals with impaired FG levels or insulin resistance). A total of eleven studies remained for secondary analyses[15,17,19–23,26,29,30,36]. The results turned out to be not significantly different from those of the comprehensive

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Table 1. Characteristics of the randomised controlled intervention trials included in the present meta-analysis

Reference	Participants, BMI (kg/m^2), diabetics (%)	Age (years), female (%)	Diagnostic criteria for T2D, IFG and IR	Duration (years)	Dietary intervention	Dietary protocol: fat, protein, CH	Macronutrient intake at the end of the follow-up period: fat, protein, CH	Energy restricted		Dietary assessment	Dropout rate (%)	Hypoglycaemic agents (%)
								kcal	kJ			
Brehm *et al.*[19]	95	56·5	HbA1c*: 6·5–9 % (36·5–75 mmol/mol)	1	HF (MUFA) *v.*	40 %, 15 %, 45 %, 20 % MUFA (olive oil and canola oil)	38 %, 16 %, 46 %	−200 to −300	−837 to −1255	3 d food record	31	In thirty-two subjects, drug usage was tracked
	35·9	64			LF	25 %, 15 %, 60 %	28 %, 18 %, 54 %	−200 to −300	−837 to −1255		16	
	100											
Davis *et al.*[20]	105	53·5	HbA1c: 6–11 % (42–97 mmol/mol)	1	HF (LC) *v.*	20–25 g/d CH for 2 weeks, increase 5 g/week (CH)	44 %, 23 %, 33 %	No	No	24 h recall	19	78 Metformin 44 Sulphonylureas 35 Insulin
	36	75			LF	25 %	31 %, 19 %, 50 %	No	No		19	86 Metformin 52 Sulphonylureas 24 Insulin
	100											
Elhayany *et al.*[15]	179	56·3	HbA1c: 7–10 % (53–86 mmol/mol)	1	HF (MUFA) *v.*	45 %, 20 %, 35 %, 23 % MUFA	Not reported	1700	7113	24 h recall and FFQ	28	ND
	31·4	48			LF†	30 %, 20 %, 50 %	Not reported	1700	7113		32	
	100											
Esposito *et al.*[21]	215	52·2	HbA1c: >7 % (>53 mmol/mol)	4	HF (MUFA) *v.*	>30 %, 15 %, <50 %, 30–50 g/d olive oil	40 %, 17 %, 43 %	1500 women and 1800 men	6276 women and 7531 men	Diet diaries	9	Inclusion criteria: T2D subjects never been treated with antihyperglycaemic drugs
	29·6	51			LF	<30 %, 15 %, 55 %	29 %, 18 %, 53 %	1500 women and 1800 men	6276 women and 7531 men		9	
	100											
Guldbrand *et al.*[22]	61	62	Diagnosis of T2D treated with diet with or without additional glucose-lowering medication, incretin-based therapy or insulin	2	HF (LC) *v.*	50 %, 30 %, 20 %	44 %, 24 %, 31 %	1600 women and 1800 men	6694 women and 7531 men	3 d diet record	10	Metformin
	32·7	56			LF	<30 %, 10–15 %, 60 %	31 %, 20 %, 47 %	1600 women and 1800 men	6694 women and 7531 men		13	Insulin Glibenclamide
	100											
Hockaday *et al.*[23]	93	51·5	After 1 h 50 g glucose tolerance test: 10.6 mmol/l	1	HF (control) *v.*	40 %, 20 %, 40 %	Not reported	1500	6276	ND	ND	ND
	ND	56			LF	26 %, 20 %, 54 %	Not reported	1500	6276			
	100											
Howard *et al.*[24]/ Shikany *et al.*[25]	759	ND	IFG: 5.6–6.9 mmol/l Diabetes history or FG: >6.9 mmol/l	6	HF (control) *v.*	>30 %	37 %, 17 %, 46 %	No	No	FFQ	ND	Self-reported treatment of diabetes, 80 % were confirmed to use an anti-diabetic medication
	ND	100			LF	<20 %, <7 % (SFA)	29 %, 17 %, 54 %	No	No			
	29											
Iqbal *et al.*[26]	68	60	Diabetes defined as a pre-existing clinical diagnosis or use of insulin or oral anti-diabetic medications	2	HF (LC) *v.*	30 g/d CH	34 %, 17 %, 49 %	No	No	Self-reported dietary intake	54	57 Sulphonylureas 61 Metformin 9 Thiazolidinedione 23 Insulin
	37·5	11			LF	<30 %	34 %, 18 %, 48 %	−500	−2092		40	43 Sulphonylureas 53 Metformin 11 Thiazolidinedione 30 Insulin
	100											

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Table 1. *Continued*

Reference	Participants, BMI (kg/m^2), diabetics (%)	Age (years), female (%)	Diagnostic criteria for T2D, IFG and IR	Duration (years)	Dietary intervention	Dietary protocol: fat, protein, CH	Macronutrient intake at the end of the follow-up period: fat, protein, CH	Energy restricted		Dietary assessment	Dropout rate (%)	Hypoglycaemic agents (%)
								kcal	kJ			
Ley *et al.*[27]/ Swinburn *et al.*[28]	103 29·2 22	52·3 26	IGT: 2 h blood glucose 7–11 mmol/l; WHO 1985	5	HF (control) *v.* LF	>30 % <30 %	35 %, 18 %, 47 % 26 %, 19 %, 55 %	No No	No No	3 food diary	ND	ND
McAuley *et al.*[18]	48	ND	Reduced predicted insulin sensitivity (insulin sensitivity score ≤6·3 M × mμ per l)[9]	1	HF (LC) *v.*	20 g/d CH for 2 weeks, 50 g/d for 8 weeks	41 %, 21 %, 33 %	No	No	3 food diary	23	ND
	ND Insulin resistant	100			LF	<30 %, 15 %, 55 %	29 %, 22 %, 45 %	No	No		25	
Milne *et al.*[29]	43 29·5 100	59·5 53	Duration of diabetes: 5–5·6 years; HbA1c: 8·7–9·8 % (71·7–83·8 mmol/mol)	1·5	HF (control) *v.* LF	36 %, 19 %, 45 % 30 %, 15 %, 55 %	34 %, 20 %, 46 % 32 %, 21 %, 47 %	−500 −500	−2092 −2092	24 h recall	ND	50 57
Shai *et al.*[17]	19	ND	According to ADA 1997	2	HF (LC) *v.*	20 g/d CH; increase to max 120 g/d	39 %, 21 %, 40 % (whole sample size)	No	No	FFQ	ND	70 Oral agents 11 Insulin
	ND 100	ND ND			LF	<30 %	30 %, 19 %, 51 % (whole sample size)	1500 women and 1800 men	6276 women and 7531 men			50 Oral agents 17 Insulin
Stern *et al.*[30]	54	ND	Diabetes defined as a pre-existing clinical diagnosis or use of insulin or oral anti-diabetic medications	1	HF (LC) *v.*	<30 g/d CH	57 %, 20 %, 33 %	No	No	Dietary recall data	31	22 Sulphonylureas 44 Metformin 5 PPAR agonist 17 Insulin
	ND 100	ND ND			LF	<30 %	34 %, 16 %, 50 %	−500	−2092		37	43 Sulphonylureas 32 Metformin 5 PPAR agonist 14 Insulin
Wolever *et al.*[16]	156	59·86	FG: >7 mmol/l or >11 mmol/l after 2 h OGTT	1	HF (MUFA) *v.*	>35 %, ↑ % fat intake by about 10 % replacing CH (by nuts, olive oil and canola oil)	Not reported	−500‡	−2092‡	3 d food record	19	Exclusion criteria: use of insulin or any hypoglycaemic or antihyperglycaemic medication
	30·9 100	54			LF†	<30 %	Not reported	−500‡	−2092‡		20	

T2D, type 2 diabetes; IFG, impaired fasting glucose; IR, insulin resistance; CH, carbohydrates; HbA1c, glycosylated Hb; HF, high fat; LF, low fat; LC, low carbohydrate; ND, not determined; IGT, impaired glucose tolerance; ADA, American Diabetes Association; PPAR agonist, PPAR-γ agonist; OGTT, oral glucose tolerance test.

*To convert HbA1c to mmol/mol: 10·93 × HbA1c unit (%) − 23·50.

† Two kinds of LF diets (high-glycaemic index and low-glycaemic index; 10 and 30 % of total energy consumption).

‡ In case subjects wished to lose weight.

Table 2. Pooled estimates of effect size (95 % CI) expressed as weighted mean difference (MD) for the effects of high-fat *v.* low-fat diet consumption on cardiovascular and metabolic risk factors

Outcome parameters	No. of studies	No. of participants	MD	95 % CI	*P*	Inconsistency I^2 (%)	Quality of evidence (GRADE)
BW (kg)	11	1172	−0·11	−1·14, 0·91	0·83	0	Moderate*
BW (kg)†	8	928	−0·47	−1·85, 0·92	0·51	0	
TC (mmol/l)	11	1148	0·07	−0·10, 0·23	0·42	67	Moderate*‡
TC (mmol/l)†	9	997	0·08	−0·11, 0·27	0·41	73	
LDL-C (mmol/l)	9	836	0·05	−0·10, 0·20	0·53	49	Moderate*
LDL-C (mmol/l)†	7	685	0·04	−0·14, 0·23	0·64	60	
HDL-C (mmol/l)	11	1290	0·05	0·01, 0·08	0·01	57	Moderate*
HDL-C (mmol/l)†	9	1139	0·04	0·00, 0·08	0·03	65	
TAG (mmol/l)	12	1384	−0·19	−0·23, −0·14	<0·00001	0	Moderate*
TAG (mmol/l)†	10	1233	−0·18	−0·24, −0·13	<0·00001	4	
TC:HDL-C	2	240	0·06	−0·38, 0·50	0·80	34	Very low*
CRP (mg/l)	1	138	−1·31	−2·91, 0·29	0·11	/	Very low*
DBP (mmHg)	8	827	−1·30	−1·73, −0·87	<0·00001	0	Low*§
DBP (mmHg)†	6	676	−1·35	−1·79, −0·92	<0·00001	0	
SBP (mmHg)	7	695	0·59	−2·18, 3·36	0·68	40	Low*
SBP (mmHg)†	5	310	−1·35	0·35, 2·35	0·008	3	
FG (mmol/l)	11	1753	−0·18	−0·52, 0·15	0·28	82	Moderate*‡
FG (mmol/l)†	9	1062	−0·41	−0·74, −0·08	0·01	56	
FI (pmol/l)	10	1718	2·93	−3·30, 9·15	0·36	71	Moderate*‡
FI (pmol/l)†	8	994	0·61	−6·66, 7·89	0·87	58	
HbA1c (%)†	10	981	−0·17	−0·39, 0·06	0·14	46	Moderate*
HbA1c (mmol/mol)†	10	981	−1·055	−2·418, 0·372	0·14	46	Moderate*
Adiponectin (μg/ml)†	1	215	1·10	0·87, 1·33	<0·00001		Very low*§

GRADE, Grading of Recommendations Assessment, Development and Evaluation; BW, body weight; TC, total cholesterol; LDL-C, LDL-cholesterol; HDL-C, HDL-cholesterol; CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure; FG, fasting glucose; FI, fasting insulin; HbA1c, glycosylated Hb.
* Risk of bias in many studies.
† Sensitivity analysis: including studies with only subjects with type 2 diabetes.
‡ Heterogeneity was observed, but could not be explained.
§ Large study effects were observed; if studies excluded from the analysis, the MD became non-significant.

meta-analyses except for one parameter: detrimental effects on FI values were no longer valid when comparing usual *v.* LF protocols in the respective subgroup analysis.

Moreover, additional parameters were specifically altered by HF diet consumption in patients with type 2 diabetes. Both SBP (MD −1·35 mmHg, 95 % CI −2·35, −0·35, P=0·008; I^2 = 3 %, P=0·39) and FG (MD −0·41 mmol/l, 95 % CI −0·74, −0·08, P=0·01; I^2 = 56 %, P=0·02) levels were significantly more decreased in subjects following a HF diet than in those following a LF diet. In the Women's Health Initiative as well as the Workforce Diabetes Survey trials[24,25,27,28], the HF dietary intervention group was indicated as a control group receiving only 'usual care'. By implication, one might expect a bias due to the fact that the intervention (i.e. the LF) group received more attention from the investigators, e.g. in form of education, personal goal settings and regular meeting. However, the results of the primary analysis were not affected by the exclusion of these trials.

Subgroup analyses for change scores, hypoenergetic diets, *ad libitum* diets, study duration (long term and short term), high adherence and low risk of bias were carried out (see online supplementary Tables S1–S7). The majority of the results of the main analysis could be confirmed. Inclusion of only *ad libitum* diets significantly reduced heterogeneity. Information on the prescription of hypoglycaemic agents was extracted, and it is reported in Table 1. However, due to inconsistent reporting, the data did not allow carrying out further analyses.

Publication bias

The funnel plots (with respect to effect size changes for biomarkers of cardiovascular risk and glycaemic control in response to LF diet consumption) revealed very little asymmetry, suggesting low evidence of publication bias (see online supplementary Figs. S12–S21).

Heterogeneity

Substantial heterogeneity was found with respect to TC (I^2 = 67; 73 %), HDL-C (I^2 = 57; 65 %), FG (I^2 = 82; 56 %) and FI (I^2 = 71; 58 %) levels in both primary and secondary analyses (Table 2). It was assumed that substantial heterogeneity might be explained by non-uniform study characteristics of the HF groups such as variations in post-intervention macronutrient intake. To gain insight into these potential correlations, a random-effects meta-regression was performed to examine the associations between LF and HF group parameters and changes in TC, HDL-C, FG, and FI levels. Studies with a higher percentage of energy from carbohydrates were associated with slightly lower differences in TC levels between the two dietary intervention groups (0·026 mmol/l lower TC for every 1 % increase in energy from carbohydrates; 95 % CI 0·050, 0·002; P=0·036; Fig. 2(a)), those with a higher percentage of energy from fat were associated with slightly higher differences in FI levels between the two dietary intervention groups (2·67 pmol/l higher FI for every 1 % increase in

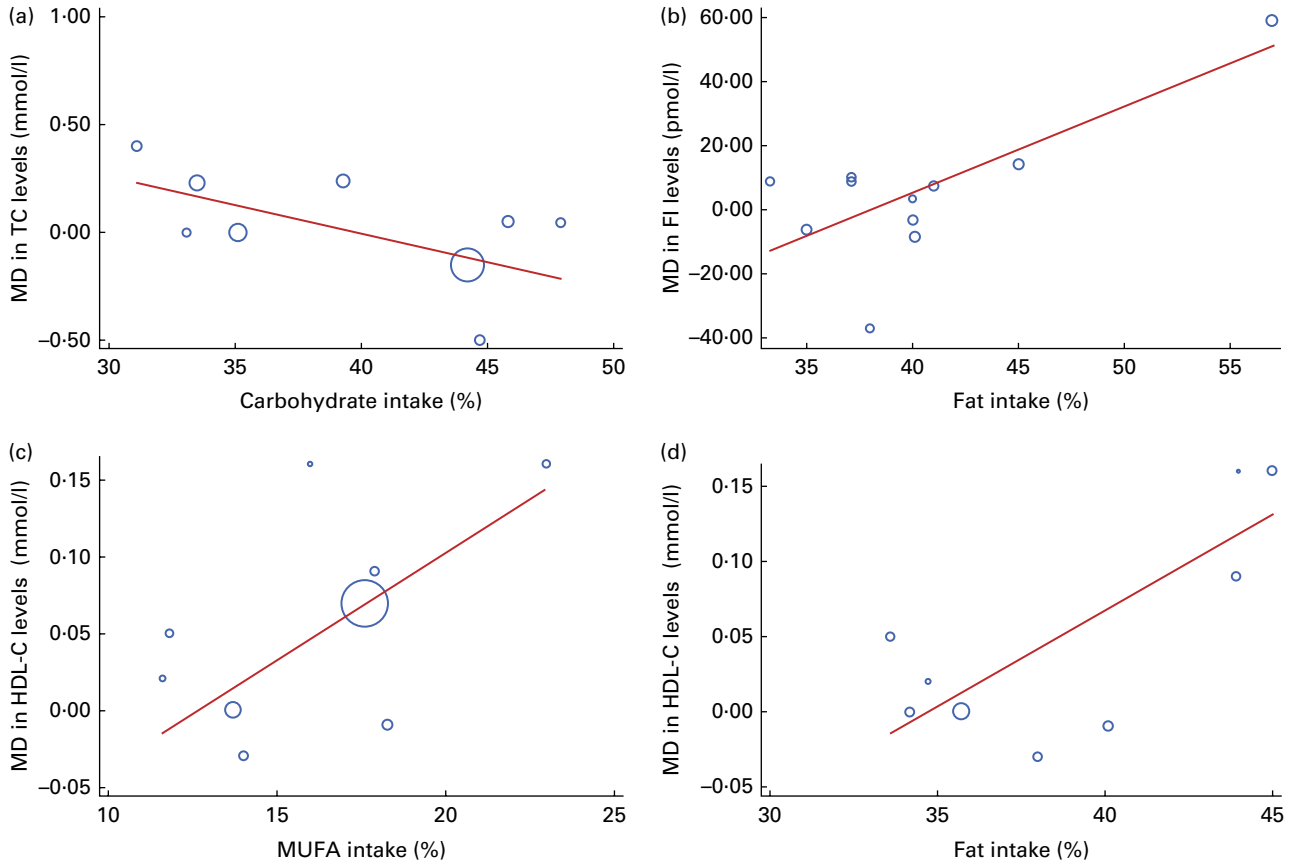

Fig. 2. Bubble plots showing the dose–response relationship between (a) carbohydrate intake and changes in total cholesterol (TC) levels (P=0·036), (b) fat intake (P=0·006) and changes in fasting insulin (FI) levels, (c) MUFA intake and changes in HDL-cholesterol (HDL-C) levels (P=0·015), and (d) total fat intake and changes in HDL-C levels (P=0·005). Macronutrient intake is given as the percentage of total energy consumption. The fitted regression lines together with the bubbles represent the estimates from each study, sized according to the precision of each estimate as calculated in the fitted random-effects meta-regression. MD, mean difference. (A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn).

energy from fat; 95 % CI 0·959, 4·38; P=0·006; Fig. 2(b)), and those with a higher percentage of energy from MUFA and total fat were associated with slightly higher differences in HDL-C levels between the two dietary intervention groups (0·014, 0·012 mmol/l higher HDL-C for every 1 % increase in energy from MUFA and total fat; 95 % CI 0·003, 0·024; P=0·015; 95 % CI 0·004, 0·020, P=0·005; Fig. 2(c) and (d)). No such correlations could be detected for the other parameters under investigation.

Overall quality of evidence

The overall quality of evidence rated according to the GRADE guidelines ranged from very low to moderate (Table 2). Moderate-quality evidence was found concerning the significant reduction in TAG levels as well as the significant increase in HDL-C levels in subjects following a HF diet. Similarly, moderate-quality evidence could be observed with respect to the non-significant effects of HF regimens on TC and LDL-cholesterol levels. Moderate-quality evidence was observed for the effects of HF diet consumption on the parameters of glycaemic control as outcomes as well. For the remaining outcome parameters (blood pressure, C-reactive protein and adiponectin), low-to-very-low-quality evidence was observed.

Discussion

Type 2 diabetes mellitus is one of the most pressing non-communicable chronic diseases with an estimated prevalence of approximately 235 million affected cases by the year 2030. In the pathogenesis of its manifestation, type 2 diabetes is preceded by a most often undetected phase of pre-diabetes with impaired glucose metabolism, which, however, is susceptible to the benefits of lifestyle changes[2]. Various biomarkers have been shown to be predictors of the detrimental consequences of diabetes-associated disorders resulting from micro- and macroangiopathies. In the present systematic review and meta-analysis, long-term intervention studies enrolling either patients with type 2 diabetes or subjects with pre-diabetes and comparing a HF dietary regimen with a LF dietary regimen were analysed. The primary analysis revealed a favourable effect of HF diet consumption with respect to TAG levels (decrease), DBP (decrease), HDL-C levels (increase) as well as adiponectin levels (increase), although the last-mentioned biomarker was measured in only one study including 215 diabetic volunteers[21]. By contrast, an advantage of a LF protocol could be observed when compared with its usual/HF counterpart with respect to FI values in the subgroup analyses. However, this benefit

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was no longer present following sensitivity analysis including studies with only patients with type 2 diabetes. Thus, a major finding of this meta-analysis is that HF diets exert beneficial effects – when compared with LF diets – on a number of biomarkers considered to be predictors of diabetes-associated complications.

CHD is a highly prevalent manifestation of microangiopathies associated with diabetes and has been reported to have caused 12 % of all premature deaths worldwide in 2004[37]. With respect to HDL-C levels, a previous epidemiological study has shown that an increase of approximately 0·025 mmol/l is associated with a decrease in CVD risk of 2 % in men and 3 % in women[38]. In the present meta-analysis, HF protocols were found to result in an average higher increase of 0·05 mmol/l in plasma HDL-C levels when compared with LF protocols, indicating a greater risk reduction in CHD by 3·75–5·5 %. Augmented plasma levels of TAG are considered to be univariate predictors of CVD as well[39]. An increase of 1 mmol/l in plasma levels is associated with a 2-fold increase in the relative risk of CHD[40]. On combining these data with the results of the present meta-analysis, it was found that the decline in TAG levels following HF diet consumption would be associated with a reduced CHD risk of approximately 10 %.

Increased blood pressure intensifies the risk of stroke and CHD in patients with type 2 diabetes and it could be shown that even minor reductions in blood pressure will reduce the incidence of CVD. Improvements in mean arterial pressure (−3 mmHg) were found to be correlated with a reduction in the risk of CVD (5–10 %), stroke (8–15 %) and all-cause mortality (5 %)[41]. Moreover, a single reduction of SBP (−3 %) was found to be associated with a decreased risk of fatal myocardial infarctions of approximately 8 %[42]. The present data suggest a beneficial effect of HF diet consumption on DBP in patients with type 2 diabetes and subjects with pre-diabetes, while the sensitivity analysis including only patients with manifested diabetes revealed a beneficial effect on SBP as well (when compared with LF diet consumption).

A significant decrease in FG values (−0·41 mmol/l) was found in patients with type 2 diabetes subjected to a HF diet challenge. According to the Asian Pacific Study, attenuations in FG levels of 180 mg/l are correlated with a 23 % diminished risk of CVD[43]. Moreover, the authors of the United Kingdom Prevention Study considered hyperglycaemia to be a more relevant predictor of coronary events in the course of type 2 diabetes when compared with increased insulin levels[44]. This hypothesis is supported by the findings of the Emerging Risk Factors Collaboration Study reporting a significant correlation between FG levels > 5·6 mmol/l and increased mortality risk[45].

Among the studies included in the present meta-analysis, one study reported that HF diets increased plasma adiponectin levels. Epidemiological data as well as experimental studies have indicated that decreased plasma adiponectin values are associated with a pronounced risk of insulin resistance and manifestation of type 2 diabetes[46].

When compared with the findings of the present meta-analysis, similar data have been reported in meta-analyses investigating short-term RCT. Thus, Kodama *et al.*[6] observed significant increases in TAG levels as well as decreases in HDL-C levels in patients with type 2 diabetes subjected to a LF diet challenge than in those of patients subjected to a HF diet challenge. Weighing moderate-fat diets against a regimen with LF intake, Cao *et al.*[47] found significant changes in TAG levels, HDL-C levels and TC:HDL-C ratio in favour of the moderate-fat protocol. Following a meta-regression analysis, the authors concluded that at least the changes observed in HDL-C levels were correlated with total fat as well as unsaturated fat intake, suggesting that a reduction in carbohydrate intake with simultaneous increase in unsaturated fat (MUFA and PUFA) intake would exert a beneficial effect on plasma lipoproteins. The adherence of individuals assigned to a LC dietary intervention might change over time. Usually, there is good adherence in the short term, but it gets poorer in the long term[48], which might explain the benefits of LC diet consumption observed by Kodama *et al.*[6]. In the present meta-analysis, macronutrient intakes in the included trials were found to be altered sometimes at the end of the follow-up period. However, in most studies, the dietary protocol at the end of the follow-up period was still distinguishable with respect to HF or LF intakes (Table 1). However, it should be noted that the HF and LF diets had roughly the same dietary macronutrient composition at the end of the follow-up period in the studies carried out by Iqbal *et al.*[26] and Milne *et al.*[29].

In this meta-analysis, a substantial heterogeneity ($I^2 > 50$ %) was found for TC, HDL-C, FG and FI levels (Table 2). Following meta-regressions to examine the associations between HF and LF diet consumption and changes in the outcome parameters, a statistically significant relationship was detected between carbohydrate intake and decreases in TC levels (probably caused by a reduction in SFA intake)[7], fat intake and increases in FI levels, and total fat and MUFA intake and increases in HDL-C levels. This is in accordance with the findings from other meta-analyses[49–54]. By comparing the results of four recent meta-analyses, Pagoto & Appelhans[55] suggested that investigations dealing with different dietary macronutrient approaches show only small differences between the diets. This statement could be confirmed by the results of the present meta-analysis.

Limitations of the present systematic review

The data of the present meta-analysis refer only to values obtained after an overnight fast and, as such, only represent part of the glycaemic control data; for example, there are no postprandial or post-glucose challenge data. Moreover, the present systematic review did not consider unpublished results, and it cannot be excluded that these results may have had at least a moderate impact on the effect size estimates. Examination of funnel plots revealed very little asymmetry, suggesting that the evidence for publication bias is of low quality. A major limitation of nutritional intervention trials is the heterogeneity of various aspects and characteristics of the study protocols. Therefore, it is not surprising that the RCT included in the present meta-analysis varied regarding the type(s) of diets used (energy restriction, isoenergetic), definitions of LF and HF diets, study population (i.e. age,

BMI, type 2 diabetics, abnormal glucose metabolism), intervention time and nutritional assessment as well as long-term follow-up periods (1–6 years.). Following sensitivity analysis including only studies enrolling patients with type 2 diabetes, the beneficial effects of HF diet consumption on TAG levels, HDL-C levels and DBP were found to remain the same as those observed in the conclusive analyses. Moreover, HF protocols were found to exert a more favourable effect than their LF counterparts with respect to SBP and FG levels in patients with manifested diabetes.

With respect to other potential modulating variables, sensitivity analyses and meta-regressions failed to reveal any correlations between the findings of the meta-analysis and age, sex, BMI and study duration (data not shown). These findings must be interpreted in a very conservative manner due to the low number of studies available for the meta-regressions. Not all the studies provided information on the quality of their respective set-up (e.g. method of randomisation and follow-up protocol with reasons for withdrawal; see online supplementary Fig. S1 for the risk of bias assessment according to the Cochrane Collaboration), demanding a conservative interpretation of results. In this context, it should be noted that the RCT varied with respect to dietary assessment methods to validate participant individual intakes. In addition, the drug regimen was not identical for all the participants in the included studies, and the diagnosis and classification of type 2 diabetes differed between the intervention trials. The pooled analysis of adiponectin values of only one study was disputable, but no more data were available. Part of the present meta-analysis was carried out using both post-intervention values and changes in MD; however, this was considered to be an acceptable procedure as described by the Cochrane Collaboration[12].

This systematic review has some strengths as well. The meta-analysis was conducted following a stringent protocol; for example, the participants were randomly assigned to the intervention groups in all trials. RCT are considered to be the gold standard for evaluating the effects of an intervention and are subject to fewer biases when compared with observational studies.

In conclusion, HF diet consumption was found to exert beneficial effects on TAG levels, DBP and SBP, and HDL-C levels as well as FG levels in subjects who either were pre-diabetic or had manifested type 2 diabetes when compared with LF diet consumption. Therefore, HF and LF diets might not be of equal value in the management of either pre-diabetes or type 2 diabetes, leading to emphasis being placed on the recommendations of HF diets. In this regard, one major issue is the qualitative composition of fat (i.e. higher amounts of MUFA and PUFA and lower amounts of SFA in the percentage of TEC). As a large number of individuals with pre-diabetes or type 2 diabetes are either overweight or obese, nutritional recommendations often include hypoenergetic diets for weight management. Thus, a successful HF strategy has to implement limitations on other nutrients with energetic value, most probably carbohydrates. However, with respect to the high heterogeneity of the RCT included in this systematic review, further long-term intervention trials with a standardised approach are necessary to elucidate the benefits and disadvantages of both dietary regimens.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114514000464

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