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Systematic Review with Meta-analysis

Very-low-carbohydrate ketogenic diet *v.* low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials

Nassib Bezerra Bueno*, Ingrid Sofia Vieira de Melo, Suzana Lima de Oliveira and Terezinha da Rocha Ataide

Laboratório de Nutrição Experimental, Faculdade de Nutrição, Universidade Federal de Alagoas, Campus A. C. Simões, BR 104 Norte, Km 97, 57.072-970 Tabuleiro do Martins, Maceió, AL, Brazil

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Abstract

The role of very-low-carbohydrate ketogenic diets (VLCKD) in the long-term management of obesity is not well established. The present meta-analysis aimed to investigate whether individuals assigned to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d) achieve better long-term body weight and cardiovascular risk factor management when compared with individuals assigned to a conventional low-fat diet (LFD; i.e. a restricted-energy diet with less than 30 % of energy from fat). Through August 2012, MEDLINE, CENTRAL, ScienceDirect, Scopus, LILACS, SciELO, ClinicalTrials.gov and grey literature databases were searched, using no date or language restrictions, for randomised controlled trials that assigned adults to a VLCKD or a LFD, with 12 months or more of follow-up. The primary outcome was body weight. The secondary outcomes were TAG, HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), systolic and diastolic blood pressure, glucose, insulin, HbA_{1c} and C-reactive protein levels. A total of thirteen studies met the inclusion/exclusion criteria. In the overall analysis, five outcomes revealed significant results. Individuals assigned to a VLCKD showed decreased body weight (weighted mean difference −0·91 (95 % CI −1·65, −0·17) kg, 1415 patients), TAG (weighted mean difference −0·18 (95 % CI −0·27, −0·08) mmol/l, 1258 patients) and diastolic blood pressure (weighted mean difference −1·43 (95 % CI −2·49, −0·37) mmHg, 1298 patients) while increased HDL-C (weighted mean difference 0·09 (95 % CI 0·06, 0·12) mmol/l, 1257 patients) and LDL-C (weighted mean difference 0·12 (95 % CI 0·04, 0·2) mmol/l, 1255 patients). Individuals assigned to a VLCKD achieve a greater weight loss than those assigned to a LFD in the long term; hence, a VLCKD may be an alternative tool against obesity.

Key words: Cardiovascular risk factors: Low-carbohydrate diets: Meta-analysis: Obesity: Weight loss

Obesity continues to be a major worldwide health problem, despite the efforts of the medical community. At least 2·8 million adults die from obesity-related causes each year, and 65 % of the worldwide population lives in countries where obesity causes more deaths than underweight[1]. Although it is a difficult task, intensive lifestyle interventions can achieve weight loss that is sustained over the long term, as shown by the findings of a recent large clinical trial[2].

Diet is a cornerstone of any lifestyle intervention programme. The dietary plan that restricts energy and fat is the most common strategy, and based on it, several other dietary strategies have been proposed[3–5]. The very-low-carbohydrate ketogenic diet (VLCKD) differs from these approaches. According to Accurso *et al.*[6], in the early phases of this therapy, individuals must have approximately 50 g carbohydrates/d or 10 % of energy from a nominal 8400 kJ (approximately 2000 kcal) diet, unlike low-carbohydrate diets, which may have up to 130 g carbohydrates/d or 26 % of energy from a nominal diet. A major concern regarding the prescription of the VLCKD is the adherence of the individuals assigned to it, since it promotes important lifestyle changes[7].

Given the importance of dietary counselling in weight loss, it is useful to investigate the effectiveness of different dietary therapies. A recent large randomised clinical trial, which assigned individuals to diets ranging from 35 to 65 % of dietary carbohydrate content, showed that, at this level of carbohydrate intake, there is no difference in weight loss between interventions[8]. Nonetheless, evidence suggests

Abbreviations: DBP, diastolic blood pressure; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; LFD, low-fat diet; SBP, systolic blood pressure; VLCKD, very-low-carbohydrate ketogenic diet; WMD, weighted mean differences.

* **Corresponding author:** N. B. Bueno, email nassibbb@hotmail.com

that greater dietary carbohydrate restrictions lead to greater weight loss[9]. Indeed, previous meta-analyses have shown that carbohydrate-restricted diets promote greater weight loss than conventional energy-restricted low-fat diets (LFD)[10,11]. However, these analyses did not exclusively focus on VLCKD studies[10], or included mostly trials with 6 months of follow-up[11]; hence, these analyses do not guarantee the long-term effectiveness of the VLCKD.

A recent meta-analysis by Santos *et al.*[12] reported that low-carbohydrate diets lead to significantly favourable changes in body weight and major cardiovascular risk factors. Nevertheless, this analysis was based only on the individuals who had adopted a low-carbohydrate diet, comparing final values against baseline values. Although it was an important investigation, the question of whether an abrupt change to an individual's lifestyle, such as the adoption of a VLCKD, leads to relevant long-term clinical improvements remains unanswered.

Thus, the present meta-analysis evaluated randomised controlled trials to determine whether overweight and obese individuals assigned to a VLCKD achieve greater weight loss and manage cardiovascular risk factors more effectively than those assigned to a LFD over the long term (defined as 12 months or more post-intervention).

Methods

The present meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[13]. The protocol was previously published in the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO), under registration no. CRD42012002408.

Search strategy

The following databases were searched until August 2012: MEDLINE, CENTRAL, ScienceDirect, Scopus, LILACS, SciELO and ClinicalTrials.gov. In addition, the following grey literature databases were searched: OpenGrey.eu, DissOnline.de, NYAM.org and ClinicalEvidence.com. There was no manual search of the included articles, and no specialists in the field were contacted to avoid the risk of citation bias[14]. The search strategy included terms related to the intervention (VLCKD), the primary outcome (weight loss) and the secondary outcomes (cardiovascular risk factors), as well as related terms designed to improve the sensitivity of a search for randomised controlled trials[15]. The search was not restricted to any particular years of publication or languages. The complete search strategy is shown in the Supplementary material (available online).

Eligibility criteria

Only randomised controlled trials that met the following criteria were included: (1) the study participants were individuals older than 18 years old who were assigned to a LFD (i.e. a restricted-energy diet with less than 30 % of energy from fat) or to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d or 10 % of daily energy from carbohydrates); (2) the follow-up period was 12 months or more; (3) the participants had a mean BMI greater than 27·5 kg/m^2. The third criterion allowed the inclusion of studies of populations who are already at high risk beyond this BMI threshold[16].

The present analysis aimed to evaluate the differences in the outcomes of the prescribed diets, without addressing individual adherence to the diets. There were no restrictions based on sex, race or co-morbidities. At a minimum, the studies must have assessed weight loss as an outcome and must have reported mean values or the differences between the mean values. The exclusion criteria were as follows: (1) studies with a concomitant pharmacological intervention and (2) duplicate publications of the included trials.

Data extraction

The titles and abstracts of the retrieved articles were evaluated independently by two investigators who were not blinded to the authors or the journal titles. The full-text versions of potentially eligible articles were retrieved for further evaluation.

The primary outcome sought in the studies was the mean change between the baseline body weight and the final body weight (in kg), with the associated measure of dispersion. The secondary outcomes were the mean changes between the baseline and final values (with the associated measures of dispersion) for TAG (in mg/dl (to convert to mmol/l, multiply by 0·0113)), HDL-cholesterol (HDL-C) and LDL-cholesterol (LDL-C) (in mg/dl (to convert to mmol/l, multiply by 0·0259)), fasting blood glucose (in mg/dl (to convert to mmol/l, multiply by 0·0555)), insulin (in mU/ml (to convert to pmol/l, multiply by 6·945)), C-reactive protein (in mg/l (to convert to nmol/l, multiply by 9·524)), HbA_{1c} (percentage), and systolic and diastolic blood pressure (SBP and DBP, respectively, in mmHg).

All the necessary information was extracted from the published articles, protocols and commentaries related to each study, and when necessary, the authors were contacted to obtain additional information. For the studies that had more than two experimental groups, the most suitable one was chosen. Any disagreements were resolved by consensus. A standard form for storing data was created based on the Cochrane Collaboration model[17].

Assessment of risk of bias

Risk of bias was evaluated according to the Cochrane Handbook recommendations[18], at the primary outcome level. The quality of the studies were assessed by two investigators independently in five categories: adequate sequence generation; allocation concealment; blinding of the outcome assessors; handling of missing data (intention-to-treat or per-protocol analysis); selective outcome reporting. The nature of the trials required an open intervention with no blinding of the trial participants or the investigators.

Data analysis

The absolute changes for each outcome, reported as the differences between the final and baseline mean values,

were analysed. The treatment effects across the trials were pooled, and weighted mean differences (WMD) for the outcome measures were calculated. The study weights were assigned by using the inverse variance method[19], and the calculations were performed using a random-effects model[20]. An α value of 0·05 was considered to be statistically significant. When it was not possible to retrieve adequate data, imputations were performed[21]. These imputations are shown in the Supplementary material (available online).

Statistical heterogeneity among the studies was tested using the Cochran Q test, and inconsistency was tested using the I^2 test. A P value less than 0·10 was considered to be statistically significant. Whenever a result showed heterogeneity, it was explored in three different ways. First, each analysis was repeated, removing each study one at a time in order to assess whether a particular study explained the heterogeneity. Second, univariate meta-regressions were performed to analyse whether methodological covariates were influencing the results[22]. The covariates included the risk of bias in the study, adequate nutritional counselling of the individuals (studies that included individual or group meetings with a dietitian at least bimonthly until the end of the follow-up period were considered as adequate), the use of an intention-to-treat analysis, the study follow-up length in months and the presence of co-morbidities in the inclusion criteria for the participants in each study. Thereafter, it was planned to perform a multivariate meta-regression including all covariates that had a P value less than 0·10 in the univariate analysis. Finally, subgroup analyses were performed on studies that shared certain methodological features, including studies with a low risk of bias, studies using an intention-to-treat analysis and studies with 24 months of follow-up. Subgroup analyses were conducted regardless of heterogeneity.

Contour-enhanced funnel plots[23] were created and Egger's test[24] was performed to evaluate publication bias; P values less than 0·10 were considered to be statistically significant. All analyses were conducted using Stata software 9.0 (StataCorp). Graphs were plotted using RevMan 5.4 (Cochrane Collaboration).

Results

Included studies

From 3123 potentially relevant records identified by searching the databases, twenty-five full-text publications met the inclusion criteria and were retrieved for further assessment. From these, eleven were excluded after the full-text analysis, leaving fourteen full texts included in the qualitative and quantitative analysis (Table 1). The flow diagram illustrating the search and selection of studies is shown in Fig. 1. Reasons for exclusion are shown in the Supplementary material (available online).

From the fourteen full-text articles included, the report by Vetter *et al.*[25] had characteristics that were unexpected and not mentioned in the inclusion or exclusion criteria for the review. This report describes a body weight analysis of the individuals included in the study by Stern *et al.*[26], conducted 36 months after randomisation. Nevertheless, follow-up ceased after 12 months; thus, it was not possible to assess whether the individuals continued with the intervention in the period after follow-up, so the data from this full-text article were included in a sensitivity analysis.

In total, thirteen studies were included in the quantitative analysis, with a total of 1577 individuals randomised to a condition (787 to a LFD group and 790 to a VLCKD group). From these, six studies had more than two intervention groups, and it was determined by consensus which groups fit best in the analysis. Intervention groups of all studies are shown in the Supplementary material (available online).

Assessment of risk of bias

The risk of bias in the studies at the primary outcome level is shown in Table 2. In the final result, nine from the thirteen included studies were assessed as having a low risk of bias.

Of these nine studies, two did not report the sequence generation method used, while seven did not report using any measure to conceal the allocation. All the nine studies did not report blinding of the outcome assessors, but as all

Table 1. Characteristics of the included studies

Source	Duration (months)	Dietary counselling	Dropouts (*n*/*N*)	Females (%)	Country	Risk factor	Mean age (years)	Mean BMI (kg/m^2)	CHO intake/d (VLCKD)*
Brinkworth *et al.*[28]	12	Adequate	38/107	70	Australia	CV risk factor	50·6	33·6	36 g
Dansinger *et al.*[50]	12	Inadequate	41/80	47	USA	CV risk factor	47	35	190 g
Davis *et al.*[51]	12	Adequate	14/105	78	USA	T2D	53·5	35·9	33 %
Dyson *et al.*[52]	24	Inadequate	4/26	73	UK	T2D	52	35·1	Unreported
Foster *et al.*[53]	12	Inadequate	37/63	68	USA	None	44·9	34·1	Unreported
Foster *et al.*[27]	24	Adequate	113/307	68	USA	None	45·5	36·1	Unreported
Gardner *et al.*[30]	12	Inadequate	26/153	100	USA	None	42	32	34 %
Iqbal *et al.*[29]	24	Adequate	76/144	10	USA	T2D	60	37·4	47 %
Lim *et al.*[54]	15	Inadequate	25/60	80	Australia	CV risk factor	48·4	31·4	36 %
McAuley *et al.*[55]	12	Inadequate	15/63	100	NZ	None	45	36·1	33 %
Shai *et al.*[49]	24	Adequate	44/213	16	Israel	CV risk factor	51·5	30·7	40 %
Stern *et al.*[26]	12	Adequate	45/132	17	USA	None	53·5	42·9	120 g
Truby *et al.*[56]	12†	Inadequate	98/116	72	UK	None	39·8	32	Unreported

CHO, carbohydrate; VLCKD, very-low-carbohydrate ketogenic diet; CV, cardiovascular; T2D, type 2 diabetes mellitus; NZ, New Zealand.
* Mean carbohydrate intake in the VLCKD group at the end of the follow-up, measured by dietary assessment, shown as g/d or percentage of energy from carbohydrates per d.
† Truby *et al.*[56] assessed only the body weight at 12 months.

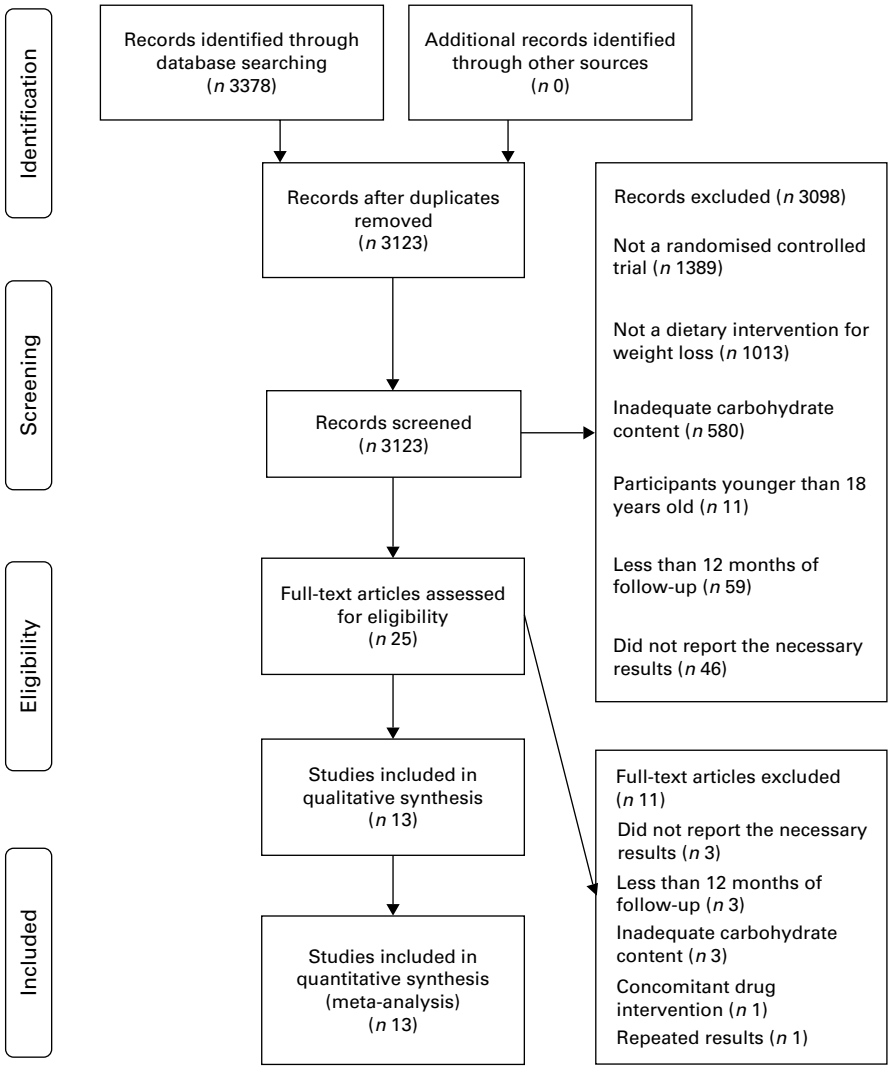


Fig. 1. Flow diagram of the study selection.

the outcomes are objective, it is unlikely that this domain affected the results of the trials. Regarding the handling of missing data, five studies were categorised as having a high risk of bias because they utilised a per-protocol analysis. There was no evidence of selective outcome reporting.

Data analysis

Body weight. All the thirteen included studies (1415 patients) were assessed (Fig. 2(a)). The individuals assigned to a VLCKD achieved a significantly greater weight loss compared with the individuals assigned to a LFD (WMD −0·91 (95 % CI −1·65, −0·17) kg, P=0·02; I^2 = 0 %, P=0·47). This result was consistent across all subgroup analyses, except for the subgroup of studies with 24 months of follow-up (data not shown). The substitution of the data from Stern *et al.*[26] for the data from Vetter *et al.*[25] changed the results (WMD −0·73 (95 % CI −1·52, 0·06) kg, P=0·07; I^2 = 5 %, P=0·39). There was no evidence of publication bias (P=0·34). The contour-enhanced funnel plots for body weight and all other outcomes are shown in the Supplementary material (available online).

TAG. In total, twelve studies (1258 patients) were assessed (Fig. 2(b)). The individuals assigned to a VLCKD showed a significantly greater reduction in TAG than the individuals assigned to a LFD (WMD −0·18 (95 % CI −0·27, −0·08) mmol/l, P<0·001; I^2 = 12 %, P=0·33). This result was consistent across all subgroup analyses, except for the subgroup of studies with 24 months of follow-up (data not shown). Heterogeneity was reversed when the study by Foster *et al.*[27] was excluded, and also when the study by Stern *et al.*[26] was excluded, but there were no statistically significant changes in the results. The evidence of publication bias (P=0·04) was also reversed with the exclusion of both aforementioned studies. The meta-regression analysis showed that the covariate 'study follow-up length' affected the results significantly (r^2 87·19 %, P=0·09; Table 3).

HDL-cholesterol. Overall, twelve studies (1257 patients) were assessed (Fig. 2(c)). The individuals assigned to a VLCKD achieved a significantly greater increase in their

Table 2. Risk of bias of the included studies

Source	Sequence generation	Allocation concealment	Blinding	Missing data	Selective report	Overall
Brinkworth *et al.*[28]	Low	High	Unclear	Low	Low	High
Dansinger *et al.*[50]	Low	Low	Low	Low	Low	Low
Davis *et al.*[51]	Low	High	Unclear	Low	Low	High
Dyson *et al.*[52]	Low	Low	Low	High	Low	Low
Foster *et al.*[53]	Low	Unclear	Unclear	Low	Low	Low
Foster *et al.*[27]	Low	Unclear	Unclear	Low	Low	Low
Gardner *et al.*[30]	Low	Low	Low	Low	Low	Low
Iqbal *et al.*[29]	Low	Unclear	Unclear	Low	Low	Low
Lim *et al.*[54]	Unclear	Unclear	Unclear	High	Low	High
McAuley *et al.*[55]	Low	Low	Unclear	High	Low	Low
Shai *et al.*[49]	Low	Unclear	Low	Low	Low	Low
Stern *et al.*[26]	Low	Unclear	Unclear	Low	Low	Low
Truby *et al.*[56]	Low	Unclear	High	High	Low	High

HDL-C levels compared with the individuals assigned to a LFD (WMD 0·09 (95% CI 0·06, 0·12) mmol/l, $P<0·001$; $I^2=9\%$, $P=0·36$). All the subgroups showed the same result (data not shown). The study by Brinkworth *et al.*[28] and the study by Iqbal *et al.*[29] were each individually responsible for the heterogeneity in the overall analysis, and the stepwise exclusion of both studies did not change the main result (data not shown). In the meta-regression analysis, only the covariate 'study follow-up length' significantly affected the results ($r^2=100\%$, $P=0·03$; Table 3). There was no evidence of publication bias ($P=0·53$).

LDL-cholesterol. A total of twelve studies (1255 patients) were assessed (Fig. 2(d)). The individuals assigned to a VLCKD achieved a significantly greater increase in their LDL-C levels compared with the individuals assigned to a LFD (WMD 0·12 (95% CI 0·04, 0·2) mmol/l, $P=0·002$; $I^2=0\%$, $P=0·7$). The subgroup of studies with 24 months of follow-up was the only subgroup that showed different results (data not shown). There was no evidence of publication bias ($P=0·42$).

Systolic and diastolic blood pressure. Overall, eleven studies (1298 patients) were included in the SBP (Fig. 3(A)) and DBP analyses (Fig. 3(B)). There were no differences in SBP between the groups (WMD in favour of the VLCKD −1·47 (95% CI −3·44, 0·50) mmHg, $P=0·14$; $I^2=33\%$, $P=0·13$), a result that held in the subgroup analyses. However, individuals assigned to a VLCKD had a significantly greater reduction in DBP than the individuals assigned to a LFD (WMD −1·43 (95% CI −2·49, −0·37) mmHg, $P=0·008$; $I^2=3\%$, $P=0·41$).

The sensitivity analysis for SBP showed that the study by Gardner *et al.*[30] was responsible for the heterogeneity, and its exclusion did not change the results (data not shown). The covariate 'adequate nutritional counselling' significantly affected the SBP results ($r^2=79·7\%$, $P=0·05$; Table 3). Due to the extremely low heterogeneity, neither a sensitivity analysis nor a meta-regression analysis was undertaken for DBP, and only the subgroup of studies with 24 months of follow-up showed different results (data not shown). There was no evidence of publication bias for SBP ($P=0·79$), but the DBP analysis showed statistically significant publication bias ($P=0·04$), which was not reversed by the exclusion of any study.

Fasting blood glucose, insulin, HbA_{1c} and C-reactive protein. These analyses were performed in less than ten studies; thus, no sensitivity, subgroup, meta-regression and publication bias analyses were conducted. None of these analyses showed statistically significant results. The forest plots for these analyses are shown in the Supplementary material (available online). For the fasting blood glucose analysis, eight studies (770 patients) were assessed (WMD in favour of the VLCKD −0·08 (95% CI −0·18, 0·02) mmol/l, $P=0·11$; $I^2=0\%$, $P=0·88$). For the insulin analysis, six studies (584 patients) were assessed (WMD in favour of the VLCKD −5·52 (95% CI −13·62, 2·57) pmol/l, $P=0·18$; $I^2=26\%$, $P=0·24$). For the HbA_{1c} analysis, four studies (319 patients) were assessed (WMD in favour of the VLCKD −0·24 (95% CI −0·55, 0·06)%, $P=0·12$; $I^2=0\%$, $P=0·59$). Finally, for the C-reactive protein analysis, four studies (355 patients) were also assessed (WMD in favour of the VLCKD −1·85 (95% CI −6·66, 2·96) nmol/l, $P=0·45$; $I^2=0\%$, $P=0·55$).

Discussion

The present meta-analysis showed that individuals assigned to a VLCKD achieve greater reductions in body weight, TAG and DBP, but they also demonstrate a greater increase in LDL-C and HDL-C levels over a treatment follow-up period of 12 months or more, compared with individuals assigned to a LFD. Only the change in HDL-C levels retained statistical significance in the subgroup analysis of studies with 24 months of follow-up; however, it is important to note that this analysis included only four studies. Low risk of bias was not unanimous, although this characteristic did not influence any of the results, since potential bias was explored by conducting subgroup and meta-regression analyses. Also, studies that included individuals with co-morbidities were not sources of heterogeneity. Furthermore, only the TAG and the DBP analyses revealed evidence of publication bias.

With regard to the primary outcome, the present findings are similar to the findings of previous meta-analyses[10,11]. The supposed beneficial effect of a VLCKD on body weight may be due to the modulation of resting energy expenditure.

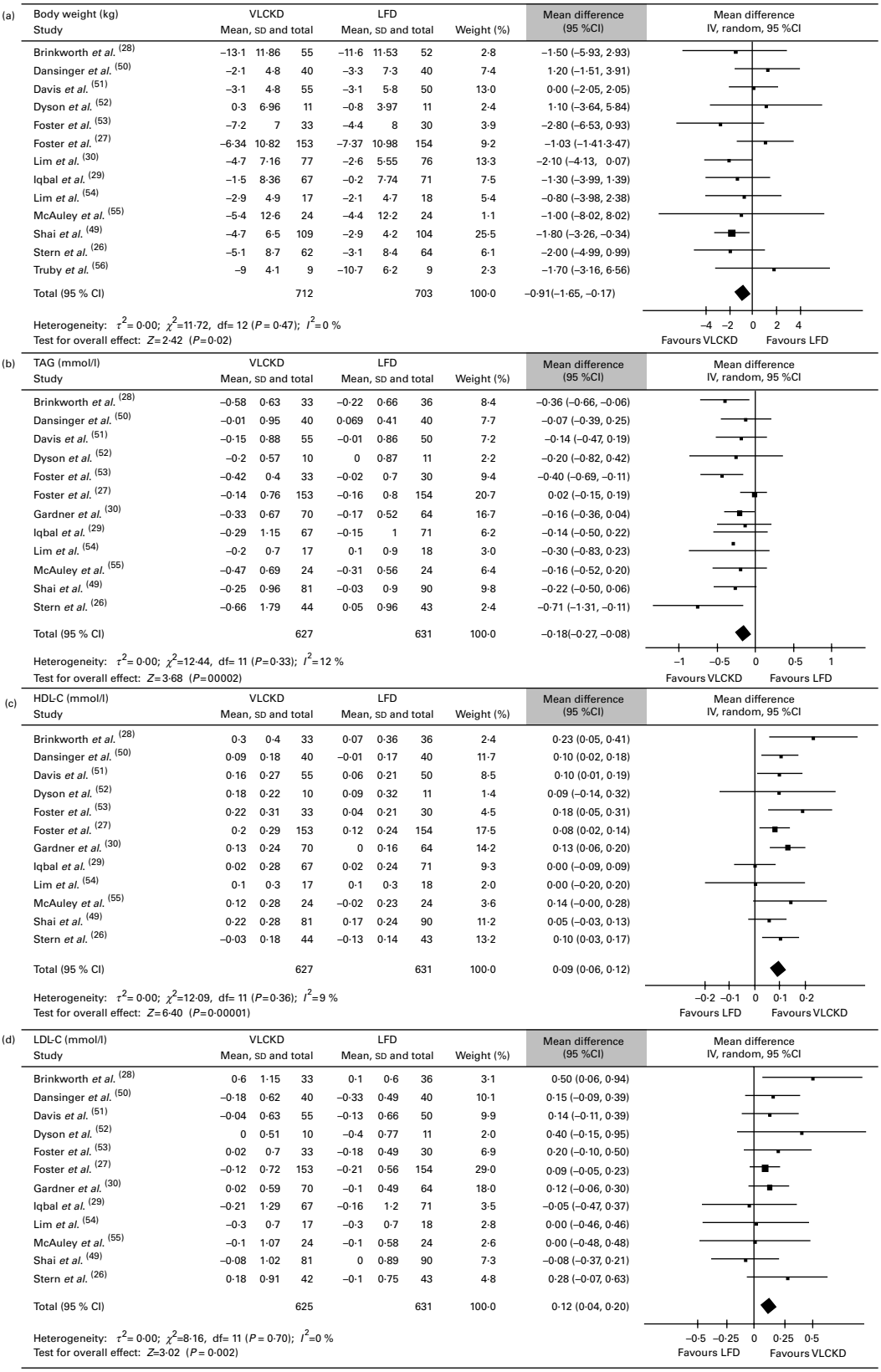


Fig. 2. Absolute changes in (a) body weight, (b) TAG, (c) HDL-cholesterol (HDL-C) and (d) LDL-cholesterol (LDL-C). VLCKD, very-low-carbohydrate ketogenic diet; LFD, energy-restricted low-fat diet.

Table 3. Meta-regression analysis
(Coefficients and 95 % confidence intervals)

Covariates	Coefficient	95 % CI	Adj r^2 (%)	*P*
Adequate nutritional counselling				
TAG (mmol/l)	4·051	−17·008, 25·110	−9·67	0·677
HDL-C (mmol/l)	−1·645	−4·030, 0·740	100·00	0·155
Systolic blood pressure (mmHg)	3·582	−0·167, 7·333	79·79	0·059
Co-morbidities				
TAG (mmol/l)	−2·498	−23·740, 18·742	−17·52	0·799
HDL-C (mmol/l)	−1·542	−3·852, 0·768	100·00	0·168
Systolic blood pressure (mmHg)	2·309	−2·063, 6·682	28·18	0·263
Intention-to-treat analysis				
TAG (mmol/l)	13·173	−8·286, 34·632	34·23	0·201
HDL-C (mmol/l)	−0·406	−3·233, 2·421	−644·4	0·755
Systolic blood pressure (mmHg)	−0·946	−6·441, 4·548	−13·25	0·706
Length of the follow-up				
TAG (mmol/l)	1·259	−0·261, 2·781	87·19	0·095
HDL-C (mmol/l)	−0·208	−0·404, −0·013	100·00	0·039
Systolic blood pressure (mmHg)	0·094	−0·318, 0·506	−1·55	0·619
Low risk of bias				
TAG (mmol/l)	13·494	−7·667, 34·656	33·87	0·186
HDL-C (mmol/l)	0·117	−2·610, 2·845	−510·1	0·925
Systolic blood pressure (mmHg)	−1·821	−7·270, 3·627	−6·98	0·469

Adj r^2, adjusted r^2; HDL-C, HDL-cholesterol.

Under isoenergetic conditions, Ebbeling *et al.*[31] found that a carbohydrate-restricted diet is better than a LFD for retaining an individual's BMR. In addition, Westman *et al.*[32] hypothesised that a VLCKD reduces insulin levels, which would explain the satietogenic effects of this diet. This hypoinsulinaemic effect of the VLCKD was not evidenced in this analysis.

TAG decreased significantly in individuals assigned to a VLCKD. The heterogeneity in the analysis and the evidence of publication bias were entirely attributable to the study by Foster *et al.*[27], which was the only study to present neutral results in this analysis. On the other hand, individuals assigned to a VLCKD showed significantly increased levels of both LDL-C and HDL-C levels. As discussed by Volek *et al.*[33], the preservation of the circulating HDL-C and the hypotriacylglycerolaemic effect of a VLCKD might be explained by the reduction in the dieting individuals' postprandial lipaemia. Conversely, the increase in LDL-C concentration associated with the VLCKD is an expected finding that is attributable to the increase in saturated fat intake. However, this finding warrants further investigation. Krauss *et al.*[34] showed that high fat intake, combined with carbohydrate restriction, raises the levels of larger-sized LDL-C, which are known to be less atherogenic than the small, dense LDL-C[35].

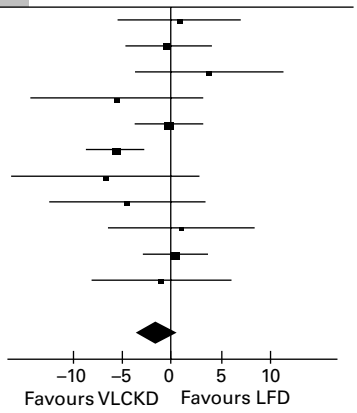
There was also evidence that individuals assigned to a VLCKD showed a significantly greater reduction in DBP. Hession *et al.*[10] analysed five studies and found that carbohydrate-restricted diets only influenced SBP. Usually, hypertension is attributable to obesity and Na intake, but Appel *et al.*[36] showed that substituting carbohydrates for proteins and monounsaturated fats may decrease blood pressure beyond the decrease expected with Na restriction alone.

It is remarkable to note that although five outcomes demonstrated statistical significance, these findings must be carefully interpreted regarding its clinical significance[37]. For example, a typical 1·70 m-tall adult with a BMI of 30 kg/m^2 weighs 87 kg; hence, a weight loss of 0·91 kg, as observed here, would represent only 1·04 % of the initial body weight. However, large randomised clinical trials with long-term dietary interventions aiming weight loss showed that individuals under intensive lifestyle interventions lose about 4·8 kg[2,38]. Hence, the further reduction of 0·9 kg in the individuals assigned to a VLCKD would represent almost 20 % of the awaited weight loss achieved with long-term dietary interventions. Additionally, if we assume the cut-off points of the metabolic syndrome[39], similar percentages would be found regarding the other outcomes. The extra reduction of 1·43 mmHg in DBP achieved by individuals assigned to a VLCKD is similar to the reductions promoted by other dietary interventions, such as Mg supplementation[40] or consumption of flavonol-rich products[41].

Undoubtedly, the present findings demonstrate that a VLCKD has favourable effects on body weight and some cardiovascular risk factors, as stated by Santos *et al.*[12]; however, in the long term and when compared with conventional therapy, the differences appear to be of little clinical significance, although statistically significant. Healthcare professionals should weigh the advantages and disadvantages of recommending a VLCKD and consider their patients' will power, since this therapy prominently alters an individual's daily habits.

The present meta-analysis has several limitations. First, it used aggregated data from the studies instead of individual patient data. Second, only blood risk factors were assessed, neglecting important pathological markers such as hepatic lipid infiltration[42], endothelial function[43], general cardiovascular events[44] and renal function[45], which are important in assessing the safety of dietary therapies. Third, the adherence to the VLCKD in the included studies was low (Table 1). At the end of the follow-up period in most studies, carbohydrate intake was higher than the protocol allowed. However, in most cases, there was good adherence in the

(a) SBP (mmHg)	VLCKD			LFD				Mean difference	Mean difference
Study	Mean, SD and total			Mean, SD and total			Weight (%)	(95 % CI)	IV, random, 95 % CI
Brinkworth *et al.* [28]	−13·8	14·36	33	−14·6	12	36	7·5	0·80 (−5·47, 7·07)	
Dansinger *et al.* [50]	0·2	12	40	0·5	7·7	40	12·0	−0·30 (−4·72, 4·12)	
Davis *et al.* [51]	0·2	15·6	55	−1·8	22·6	50	5·6	3·80 (−3·70, 11·30)	
Foster *et al.* [53]	−1·9	15	33	3·6	20	30	4·3	−5·50 (−14·30 3·30)	
Foster *et al.* [27]	−2·8	15·17	153	−2·59	15·67	154	15·8	−0·21 (−3·66, 3·24)	
Gardner *et al.* [30]	−7·6	11	77	−1·9	7·7	76	17·8	−5·70 (−8·71 −2·69)	
Iqbal *et al.* [29]	−11·2	30·28	67	−4·5	26·96	71	3·7	−6·70 (−16·29 −2·89)	
Lim *et al.* [54]	−10·6	10·6	17	−6	13·3	18	5·1	−4·60 (−12·55 3·35)	
McAuley *et al.* [55]	−5	15·9	24	−6	9·89	24	5·6	1·00 (−6·49, 8·49)	
Shai *et al.* [49]	−3·9	12·8	109	−4·3	11·8	104	16·4	1·40 (−2·90, 3·70)	
Stern *et al.* [26]	1	19	44	2	15	43	6·0	−1·00 (−8·18, 6·18)	
Total (95 % CI)			652			646	100·0%	−1·47 (−3·44, 0·50)	
Heterogeneity: τ^2= 3·33; χ^2 = 14·94, df = 10 (P=0·13); I^2 = 33 %									
Test for overall effect: Z=1·46 (P=0·14)									



(b) DBP (mmHg)	VLCKD			LFD				Mean difference	Mean difference
Study	Mean, SD and total			Mean, SD and total			Weight (%)	(95 % CI)	IV, random, 95 % CI
Brinkworth *et al.* [28]	−6·3	19·9	33	−7·9	9·6	36	2·0	1·60 (−5·88, 9·08)	
Dansinger *et al.* [50]	−1·4	7·5	40	0·2	4·6	40	14·3	1·60 (−5·33, 1·13)	
Davis *et al.* [51]	−2·9	9·4	55	−2·2	11·6	50	6·7	1·70 (−5·76, 3·36)	
Foster *et al.* [53]	−4·6	12	33	−5·2	13	30	2·9	1·60 (−5·60, 6·80)	
Foster *et al.* [27]	−3·19	9·24	153	−0·5	10·32	154	21·6	−2· 69 (−4·88, −0·50)	
Gardner *et al.* [30]	−4·4	8·4	77	−0·7	6	76	19·6	−3·70(−6·01, −1·39)	
Iqbal *et al.* [29]	−3·8	19·64	67	−4·3	16·85	71	3·0	0·50 (−5·62, 6 62)	
Lim *et al.* [54]	−6·6	12·1	17	−7·5	8·7	18	2·3	0·90 (−6·12, 7 92)	
McAuley *et al.* [55]	−4	9·81	24	−3	10·43	24	3·4	−1·00 (−6·73, 4·73)	
Shai *et al.* [49]	−0·8	8·7	109	−0·9	8·1	104	20·4	0·10 (−2·16, 2·36)	
Stern *et al.* [26]	3	15	44	1	10	43	3·9	2·00 (−3·35, 7·35)	
Total (95 % CI)			652			646	100·0	−1·43 (−2·49, −0·37)	
Heterogeneity: τ^2= 0·11; χ^2 = 10·33, df = 10 (P=0·41); I^2=3 %									
Test for overall effect: Z=2·64 (P=0·008)									

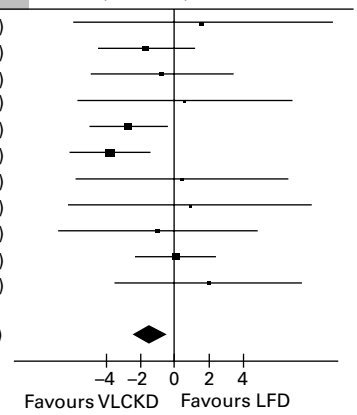


Fig. 3. Absolute changes in (a) systolic blood pressure (SBP) and (b) diastolic blood pressure (DBP). LFD, energy-restricted low-fat diet; VLCKD, very-low-carbohydrate ketogenic diet.

short term, which may explain why meta-analyses of 6-month studies show more impressive results than meta-analyses of longer-term studies, like the present analysis. Greenberg *et al.*[46] found that among dieters, the initial weight reduction in the first 6 months is the main predictor of both long-term retention and success in weight loss, which may explain the statistically significant differences observed here.

The Cochrane risk of bias tool was used in the present meta-analysis. Despite being the most recommended tool to assess the risk of bias in randomised controlled trials, it may face some limitations when assessing behavioural or lifestyle interventions, such as dietary ones[47]. These interventions are usually complex, i.e. have multiple components, which deem its fidelity (the extent to which the intervention has been delivered as planned) an important issue to be assessed[48]. Since the risk of bias tool does not directly address fidelity, it may be difficult to distinguish between an ineffective intervention and a failed implementation[47].

Upcoming trials should focus on dietary adherence, implementing measures to ensure that individuals adhere to the protocol, as was done by some of the included studies[28,49], permitting better investigation of the long-term effects of a VLCKD. Nevertheless, it is necessary to consider the feasibility of such measures, like those applied by Shai *et al.*[49], where the investigators managed the lunches of all individuals, in a real-life scenario.

In conclusion, the present meta-analysis demonstrates that individuals assigned to a VLCKD achieve significantly greater long-term reductions in body weight, diastolic blood pressure and TAG, as well as greater LDL and HDL increases when compared with individuals assigned to a LFD; hence, the VLCKD may be an alternative tool against obesity. Investigations beyond that of blood cardiovascular risk factors merit further study.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S0007114513000548

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References

1. World Health Organization (2012) Obesity and overweight. http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 10 May 2012).
2. Gögebakan O, Kohl A, Osterhoff MA, *et al.* (2011) Effects of weight loss and long-term weight maintenance with diets varying in protein and glycemic index on cardiovascular risk factors: the diet, obesity, and genes (DiOGenes) study: a randomized, controlled trial. *Circulation* **124**, 2829–2838.
3. Ornish D (1997) *Every Day Cooking With Dean Ornish*. New York: Harper Collins.
4. Sears B & Lawren W (1995) *Enter the Zone*. New York: Harper Collins.
5. Weight Watchers Publishing Group (1997) *Weight Watchers New Complete Cookbook*. New York: Macmill.
6. Accurso A, Bernstein R, Dahlqvist A, *et al.* (2008) Dietary carbohydrate restriction in type 2 diabetes mellitus and metabolic syndrome: time for a critical appraisal. *Nutr Metab (Lond)* **5**, 9.
7. Alhassan S, Kim S, Bersamin A, *et al.* (2008) Dietary adherence and weight loss success among overweight women: results from the A to Z weight loss study. *Int J Obes (Lond)* **32**, 985–991.
8. Sacks FM, Bray GA, Carey VJ, *et al.* (2009) Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. *N Engl J Med* **360**, 859–873.
9. Krieger JW, Sitren HS, Daniels MJ, *et al.* (2006) Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression. *Am J Clin Nutr* **83**, 260–274.
10. Hession M, Rolland C, Kulkarni U, *et al.* (2009) Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. *Obes Rev* **10**, 36–50.
11. Nordmann AJ, Nordmann A, Briel M, *et al.* (2006) Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Arch Intern Med* **166**, 285–293.
12. Santos FL, Esteves SS, da Costa Pereira A, *et al.* (2012) Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors. *Obes Rev* **13**, 1048–1066.
13. Moher D, Liberati A, Tetzlaff J, *et al.* (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* **151**, 264–269.
14. Sterne JAC, Egger M & Moher D (2011) Addressing reporting biases. In Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0* [updated March 2011]. http://www.cochrane-handbook.org (accessed 10 March 2012).
15. Robinson KA & Dickersin K (2002) Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *Int J Epidemiol* **31**, 150–153.
16. World Health Organization Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* **363**, 157–163.
17. Higgins JPT & Deeks JJ (2011) Selecting studies and collecting data. In Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0* [updated March 2011]. http://www.cochrane-handbook.org (accessed 22 March 2012).
18. Higgins JPT, Altman DG & Sterne JAC (2011) Assessing risk of bias in included studies. In Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0* [updated March 2011]. http://www.cochrane-handbook.org (accessed 21 March 2012).
19. Deeks JJ, Higgins JPT & Altman DG (2011) Analysing data and undertaking meta-analyses. In Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0* [updated March 2011]. http://www.cochrane-handbook.org (accessed 01 April 2012).
20. DerSimonian R & Laird N (1986) Meta-analysis in clinical trials. *Control Clin Trials* **7**, 177–188.
21. Higgins JPT, Deeks JJ & Altman DG (2011) Special topics in statistics. In Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0* [updated March 2011]. http://www.cochrane-handbook.org (accessed 01 April 2012).
22. Harbord RM & Higgins JPT (2008) Meta-regression in stata. *Stata J* **8**, 493–519.
23. Peters JL, Sutton AJ, Jones DR, *et al.* (2008) Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol* **61**, 991–996.
24. Egger M, Smith GD, Schneider M, *et al.* (1997) Bias in meta-analysis detected by a simple, graphical test. *BMJ* **315**, 629–634.
25. Vetter ML, Iqbal N, Volger S, *et al.* (2010) Long-term effects of low-carbohydrate versus low-fat diets in obese persons. *Ann Int Med* **152**, 334–335.
26. Stern L, Iqbal N, Seshadri P, *et al.* (2004) The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med* **140**, 778–785.
27. Foster GD, Wyatt HR, Hill JO, *et al.* (2010) Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* **153**, 147–157.
28. Brinkworth GD, Noakes M, Buckley JD, *et al.* (2009) Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr* **90**, 23–32.
29. Iqbal N, Vetter ML, Moore RH, *et al.* (2010) Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. *Obesity (Silver Spring)* **18**, 1733–1738.
30. Gardner CD, Kiazand A, Alhassan S, *et al.* (2007) Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: the A to Z Weight Loss Study: a randomized trial. *JAMA* **297**, 969–977.
31. Ebbeling CB, Swain JF, Feldman HA, *et al.* (2012) Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* **307**, 2627–2634.
32. Westman EC, Feinman RD, Mavropoulos JC, *et al.* (2007) Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr* **86**, 276–284.
33. Volek JS, Sharman MJ & Forsythe CE (2005) Modification of lipoproteins by very low-carbohydrate diets. *J Nutr* **135**, 1339–1342.
34. Krauss RM, Blanche PJ, Rawlings RS, *et al.* (2006) Separate effects of reduced carbohydrate intake and weight

loss on atherogenic dyslipidemia. *Am J Clin Nutr* **83**, 1025–1031.
35. Berneis KK & Krauss RM (2002) Metabolic origins and clinical significance of LDL heterogeneity. *J Lipid Res* **43**, 1363–1379.
36. Appel LJ, Sacks FM, Carey VJ, *et al.* (2005) Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the omniheart randomized trial. *JAMA* **294**, 2455–2464.
37. Anonymous (2001) Primer on statistical significance and *P* values. *Eff Clin Pract* **4**, 183–184.
38. Wadden TA, Volger S, Sarwer DB, *et al.* (2011) A two-year randomized trial of obesity treatment in primary care practice. *N Engl J Med* **365**, 1969–1979.
39. Alberti KG, Zimmet P, Shaw J, *et al.* (2005) The metabolic syndrome – a new worldwide definition. *Lancet* **366**, 1059–1062.
40. Kass L, Weekes J & Carpenter L (2012) Effect of magnesium supplementation on blood pressure: a meta-analysis. *Eur J Clin Nutr* **66**, 411–418.
41. Ried K, Sullivan TR, Fakler P, *et al.* (2012) Effect of cocoa on blood pressure. *The Cochrane Database of Systematic Reviews,* issue 8 CD008893.
42. Haufe S, Engeli S, Kast P, *et al.* (2011) Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology* **53**, 1504–1514.
43. Phillips SA, Jurva JW, Syed AQ, *et al.* (2008) Benefit of low-fat over low-carbohydrate diet on endothelial health in obesity. *Hypertension* **51**, 376–382.
44. Lagiou P, Sandin S, Lof M, *et al.* (2012) Low carbohydrate-high protein diet and incidence of cardiovascular diseases in Swedish women: prospective cohort study. *BMJ* **344**, e4026–e4037.
45. Friedman AN, Ogden LG, Foster GD, *et al.* (2012) Comparative effects of low-carbohydrate high-protein versus low-fat diets on the kidney. *Clin J Am Soc Nephrol* **7**, 1103–1111.
46. Greenberg I, Stampfer MJ, Schwarzfuchs D, *et al.* (2009) Adherence and success in long-term weight loss diets: the dietary intervention randomized controlled trial (DIRECT). *J Am Coll Nutr* **28**, 159–168.
47. Institute of Medicine (2011) *Finding What Works in Health Care: Standards for Systematic Reviews*. Washington, DC: The National Academy Press.
48. Centre for Reviews and Dissemination (2009) *Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care*. York: York Publishing Services.
49. Shai I, Schwarzfuchs D, Henkin Y, *et al.* (2008) Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. *N Engl J Med* **359**, 229–241.
50. Dansinger ML, Gleason JA, Griffith JL, *et al.* (2005) Comparison of the atkins, ornish, weight watchers, and zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA* **293**, 43–53.
51. Davis NJ, Tomuta N, Schetcher C, *et al.* (2009) Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. *Diabetes Care* **32**, 1147–1152.
52. Dyson PA, Beatty S & Matthews DR (2010) An assessment of low-carbohydrate or low-fat diets for weight loss at 2 year's follow-up. *Diabet Med* **27**, 363–368.
53. Foster GD, Wyatt HR, Hill JO, *et al.* (2003) A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med* **348**, 2082–2090.
54. Lim SS, Noakes M, Keogh JB, *et al.* (2010) Long-term effects of a low carbohydrate, low fat or high unsaturated fat diet compared to a no-intervention control. *Nutr Metab Cardiovasc Dis* **20**, 599–607.
55. McAuley KA, Smith KJ, Taylor RW, *et al.* (2006) Long-term effects of popular dietary approaches on weight loss and features of insulin resistance. *Int J Obes (Lond)* **30**, 342–349.
56. Truby H, Baic S, deLooy A, *et al.* (2006) Randomised controlled trial of four commercial weight loss programmes in the UK: initial findings from the BBC "diet trials". *BMJ* **332**, 1309–1314.