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REVIEW

Meta-analysis of studies of a specific delivery mode for a modified-carbohydrate diet

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Abstract

Background: Obesity is highly prevalent throughout the world. Although modified-carbohydrate diets (MCDs) comprise one popular approach, questions remain about their utility for weight loss. The objective of the present study was to conduct a meta-analysis of randomised controlled trials (RCTs) of a specific MCD compared with various control diets on weight loss.
Methods: Data from four RCTs (three obtained from the sponsor and one indentified through literature searches) were included. Intent-to-treat analyses were conducted using multiple imputation to handle missing data, where possible. Because inter-study heterogeneity was demonstrated with fixed-effects meta-analysis, a random-effects meta-analysis also was conducted.
Results: When considered separately, all four studies showed greater reduction in body weight with the MCD compared to control diets at 12-week follow-up; the results at 24 weeks (available for three of the studies) were not as consistent. Results for body mass index (BMI) were similar. Greater reductions in waist circumference with the MCD were seen at either time point in only one study. When fixed-effects meta-analysis was applied, significantly greater reductions in weight, BMI and waist circumference with the MCD at both 12 weeks (1.66 kg, 0.53 kg m^{-2} and 1.02 cm, respectively) and 24 weeks (1.20 kg, 0.43 kg m^{-2} and 0.69 cm, respectively) were evident. Random-effects meta-analysis revealed similar results; however, the 24-week difference for a reduction in waist circumference was no longer statistically significant.
Conclusions: Meta-analysis of individual RCT results demonstrated consistent benefits of this MCD compared to control diets on weight loss up to 24 weeks and waist circumference up to 12 weeks.

Introduction

Obesity is associated with reduced lifespan (Fontaine *et al.*, 2003) and many aspects of poor health (Klein *et al.*, 2004). Obesity is increasingly prevalent and widespread in the USA. In 2003–2004, approximately one-third of adults were obese and, by 2007, only one state had an obesity prevalence of <20% (Ogden *et al.*, 2006; Centers for Disease Control and Prevention, 2008). Although causes of obesity at both the individual and population levels are manifold and incompletely understood (Green, 1997; Astrup, 1999), many putative contributors to the obesity epidemic have been proposed, including the increased availability of inexpensive, highly palatable, high-density foods, ever increasing sedentary lifestyles, sleep debt, endocrine disruptors, reduction in variability in ambient temperature, decreased smoking, pharmaceutical iatrogenesis, increasing maternal age, and intrauterine and intergeneration effects (Keith *et al.*, 2006; McAllister *et al.*, 2009; Heber, 2010).

Countless dietary approaches for weight loss have been promoted over the years, with most previous approaches focused on reducing total energy intake, restricting dietary fat, and replacing dietary fat with carbohydrates (National Institutes of Health, 1998). Carbohydrate restriction as a means of weight loss has been another popular approach in the past decade, although carbohydrate-restricted diets were first described more than a century ago (Banting, 1863). Some proponents of carbohydrate-restricted diets claim that, when the intake of carbohydrate is sufficiently reduced, the body will convert from metabolising carbohydrate to metabolising stored fat as the primary energy source, resulting in rapid and dramatic weight loss (Atkins, 2002). High-protein, carbohydrate-restricted diets are further promoted as causing negligible elevations in serum glucose, resulting in smaller post-prandial increases in serum insulin than seen when higher carbohydrate diets are consumed. Because insulin inhibits the mobilisation of previously stored fat, reducing insulin concentration theoretically would allow more fat to be mobilised (Steward *et al.*, 1998).

One popular modified-carbohydrate diet (MCD) incorporates multiple phases and emphasises not only reduction in dietary carbohydrate, but also improvement in carbohydrate quality, utilising the concepts of glycaemic index and glycaemic load (Agatston, 2005). The objective of the present study was to provide the most precise estimates possible of the effects of this MCD (compared with the effects of standard energy-restricted and reduced-fat diets) on body weight and related measures. Data were obtained from three randomised controlled trials (RCTs) supplied by the sponsor and a fourth RCT identified through literature searches. A meta-analytic methodology was used to pool the evidence from the individual trials.

Materials and methods

Modified-carbohydrate diet

The MCD investigated, the South Beach Diet (Agatston, 2005), includes three phases. During the 2-week Phase 1, all carbohydrates are severely restricted. Lean high-protein foods (fish, skinless white-meat poultry and lean beef), high-fibre vegetables, reduced-fat cheeses, eggs, low-fat dairy, nuts and seeds, and high-monounsaturated-fat oils (such as olive and canola oils) are emphasised. Phase 2 is a long-term weight-loss phase of the diet. In this phase, selected carbohydrates, including whole grains, fruits and additional vegetables, are added to the foods consumed in Phase 1. The concept of glycaemic index is introduced, and low-glycaemic index carbohydrates, such as apples, high-fibre cereals, multigrain breads and reduced-fat milk, are reintroduced into the diet. Higher-glycaemic index carbohydrates, such as refined-grain breads and potatoes, are proscribed. Phase 3 is the maintenance phase of the diet, and is initiated once the desired weight is attained. The dietary recommendations of Phases 1 and 2 remain the foundation of Phase 3, although restricted amounts of additional foods and occasional indulgences are allowed (Agatston, 2005).

Search strategy for studies included in the meta-analysis

Data from three RCTs were obtained from the sponsor. The authors asked the sponsor for data from all of the trials that they conducted or sponsored of the MCD. The sponsor cofirmed in writing that all such trial data were provided to us. In addition, the investigators conducted extensive literature searches aiming to identify any other published RCTs of the effects of the MCD on body weight or related measures. Specifically, searches were conducted utilising the online databases of scientific publications PubMed and Web of Science, from the earliest date included in the databases (approximately 1950) up to April 2010, using the key words ‘south beach’. The abstracts of all citations identified by the literature searches were reviewed to determine whether the inclusion criteria were met and the full article should be obtained. Inclusion criteria for the meta-analysis included that the study was an RCT on weight loss, the intervention diet was identified as this specific MCD (or could be presumed to be this specific MCD based on a description of the diet) and that body weight or a related anthropometric measure was included as an outcome measure. Every article that appeared to meet the inclusion criteria (or that could not be ruled out by review of the abstract) was retrieved and assessed for possible inclusion in the meta-analysis. References from one of the studies provided by the sponsor that has been published (Maki *et al.*, 2007) were reviewed to identify potential articles for inclusion. Finally, review articles were examined to identify other possible RCTs.

Description of studies included in the meta-analysis

In addition to the data from three studies obtained from the sponsor, one RCT of this MCD was identified through the search process (Aude *et al.*, 2004) (Fig. 1). Two of the studies included have been published in peer-reviewed journals (Aude *et al.*, 2004; Maki *et al.*, 2007). Descriptions of the four studies included in the meta-analysis follow and are summarised in Table 1.

Study 1

The primary objective of this investigation was to examine the effectiveness of this MCD on body weight and cardiovascular disease risk markers in overweight and

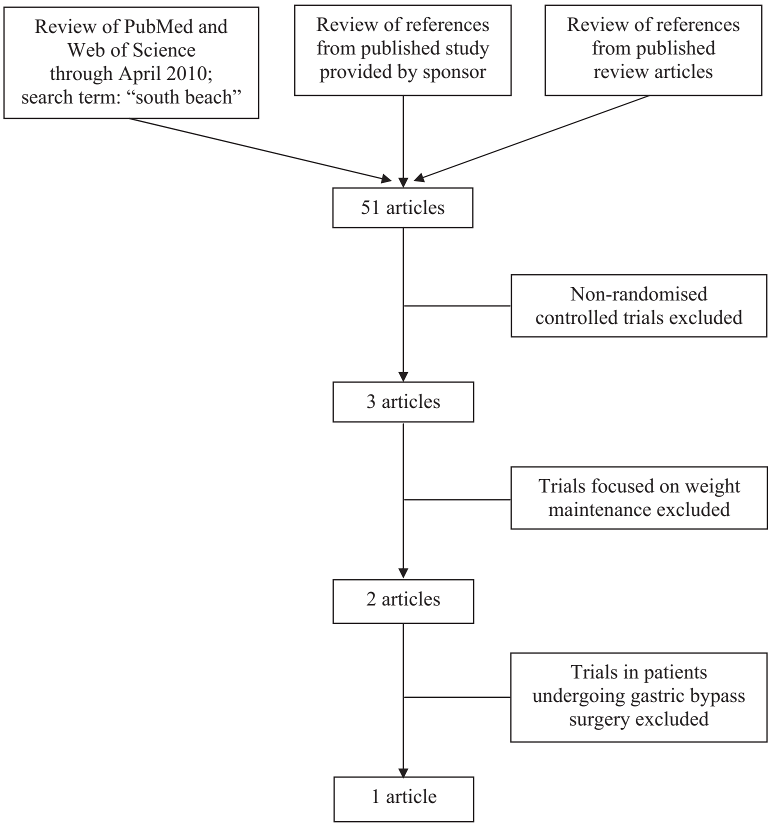

Figure 1 Flow diagram describing the search process for additional published articles of randomised controlled trials of the modified-carbohydrate diet.

obese adults (Aude *et al.*, 2004). This single-centre, two-arm, parallel-group RCT conducted in 1998–1999 compared this MCD with a reduced-fat, isocaloric diet, the National Cholesterol Education Program (NCEP) diet. Eligible subjects were men and women, 27–71 years of age, with body mass index (BMI) >27 kg m^{-2}. The interventions were 12 weeks in duration. Weeks 0–4 were a weight-loss treatment phase and weeks 5–12 were a weight maintenance phase. Outcome measures included body weight measured at multiple time points, including at baseline and 12 weeks. Drop-outs in this study from lost to follow-up and discontinued intervention (inappropriate enrollment, withdrew consent, noncompliance, adverse events and principal investigator discretion) were 3.3% in the intervention group and 16.7% in the control group.

Study 2

This study examined the effectiveness of this MCD on body weight, body composition and cardiovascular disease risk markers in overweight and obese adults (Maki *et al.*, 2007). This single-centre, two-arm, parallel-group RCT conducted in 2005 compared this MCD, consumed *ad libitum*, with a reduced-fat, portion-controlled (energy-restricted) diet. Men and women, aged 18–65 years of age, with waist circumference ≥90 cm for men and ≥87 cm for women, and no previous diagnosis of diabetes mellitus, were included. In this 36-week intervention, weeks 0–12 were weight-loss treatment. At some point between weeks 12 and 24, each subject transitioned to a weight-maintenance phase. From week 24 onward, all subjects were in the weight-maintenance phase. Body weight, BMI and waist circumference were measured at multiple time points, including at baseline, as well as 12 and 24 weeks. Drop-outs in this study from lost to follow-up and discontinued intervention were 46.5% in the intervention group and 30.2% in the control group.

Study 3

The goal of this investigation was to examine the effectiveness of this MCD and the use of commercially available meal and snack products (formulated to be consistent with the phases of this MCD) on body weight

Table 1 Characteristics of the studies included in the meta-analysis of randomised controlled trials of a specific modified-carbohydrate diet (MCD) compared with various control diets on weight loss

Years conducted	Number of centres	Number of subjects randomised	Baseline characteristics of subjects: Gender	Age (year)	Waist circumference (cm)	Diabetes status	Intervention/ control diets	Intervention duration (weeks)	Drop-outs* (%)
Study 1: comparison of the MCD with a reduced-fat, isocaloric diet									
1998–1999	1	60 (30 per group)	male, female	27–71	NR (BMI >27 kg m^{-2})	diabetic, nondiabetic	MCD/NCEP	12	I: 3.3 C: 16.7
Study 2: comparison of the MCD with a reduced-fat, portion-controlled (energy-restricted) diet									
2005	1	86 (43 per group)	male, female	21–67	≥90 (male) ≥87 (female)	nondiabetic	MCD/portion-controlled	36	I: 46.5 C: 30.2
Study 3: comparison of the MCD (with and without diet products) with an energy-restricted diet (with and without diet products)									
2007–2008	4	240 (60 per group)	female	18–55	≥87	nondiabetic	MCD + diet products/MCD + grocery store gift cards/ energy-restricted + diet products/energy-restricted + grocery store gift cards	24	I: 50.8 I: 38.1 C: 37.7 C: 44.3
Study 4: comparison of the MCD with diet products with an energy restricted diet with grocery store gift cards									
2007–2008	6	120 (60 per group)	female	24–69	≥87	diabetic	MCD + diet products/ADA exchange + grocery store gift cards	24	I: 38.3 C: 21.7

ADA, American Diabetes Association; BMI, body mass index; NCEP, National Cholesterol Education Program; NR, not reported; I, intervention; C, control.
*Includes lost to follow-up and discontinued intervention (inappropriate enrollment, withdrew consent, noncompliance, adverse events, and principal investigator discretion).

in overweight women. This was a multicentre (Northridge, CA; Bradenton, FL; Miami, FL; Virginia Beach, VA, USA), four-arm, parallel-group RCT conducted between March 2007 and April 2008. The four interventions included: (i) the MCD with commercially available products specific to this diet; (ii) the MCD without the diet products (replaced by grocery store gift cards of equal value); (iii) energy-restricted diet with the commercially available diet products; and (iv) energy-restricted diet without the diet products (replaced by grocery store gift cards of equal value). Women, aged 18–55 years of age, with waist circumference ≥87 cm, and no previous diagnosis of diabetes mellitus, were eligible. The interventions were 24 weeks in duration, with outcomes (including body weight, BMI and waist circumference) measured at multiple time points, including at baseline, as well as 12 and 24 weeks. Drop-outs in this study from lost to follow-up and discontinued intervention were 50.8% and 38.1% in the intervention groups and 37.7% and 44.3% in the control groups.

Study 4

The objective of this study was to examine the effectiveness of this MCD and commercially available diet products on body weight in overweight women with diabetes. This two-arm, parallel-group RCT was conducted between March 2007 and April 2008 and included multiple centres (Northridge, CA; Bradenton, FL; Miami, FL; Las Vegas, NV; Rochester, NY; Virginia Beach, VA, USA). The study compared the MCD with diet products with the American Diabetes Association exchange diet with a 2092 kJ (500 kcal) energy restriction plus grocery store gift cards of equal value. Included were women, aged 18–55 years of age, with waist circumference ≥87 cm, and a previous diagnosis of type 2 diabetes mellitus. The interventions were 24 weeks in duration. Outcomes (including body weight, BMI and waist circumference) were measured at multiple time points, including at baseline, as well as 12 and 24 weeks. Drop-outs in this study from lost to follow-up and discontinued intervention were 38.3% in the intervention group and 21.7% in the control group.

Statistical analysis

Studies 2–4 were analysed for the same three variables (body weight, BMI and waist circumference) at two time points relative to baseline (12 and 24 weeks). For Study 1, summary results included only body weight at 12-weeks. For Studies 2–4, outlier values of >3 standard deviations were verified by the sponsor, and erroneous values were corrected. The top 5% of Mahalanobis distance scores stratified by study and visit also were verified by the sponsor and corrected when necessary. Study 3 included four dietary interventions: the MCD with and without diet products and an energy-restricted diet with and without diet products. Because preliminary analyses showed no significant interaction of product and diet, the two MCD groups and the two energy-restricted diet groups were combined for subsequent analyses.

The primary outcomes examined were changes in body weight, BMI and waist circumference from baseline to week 12 and baseline to week 24. The analysis was conducted on an intent-to-treat basis. Weight change was calculated as the difference between weights at each of the two follow-up time points (12 weeks only for Study 1) minus weight at baseline. Similar calculations were performed for BMI and waist circumference (Studies 2–4).

Multiple imputation as described and advocated by Elobeid *et al.* (2008) was conducted for the missing outcome values in Studies 2–4 and involved three distinct phases: (i) the missing data were filled in m times to generate m complete data sets; (ii) the m complete data sets were analysed using standard statistical analyses; and (iii) the results from the m complete data sets were combined to produce inferential results. Age, randomised treatment group, measurements over time and gender (for Study 2) were used in the imputation process. Imputation first was conducted by imputing enough data to impose a monotone missing pattern on the original dataset using a Markov chain Monte Carlo method that assumed multivariate normality. In this investigation, $m = 5$, which was an adequate number of data sets to accurately impute the missing outcome values (Schafer, 1997). Second, the complete dataset was used to compute the effect estimates using a generalised linear model with the dependent variable as the change in the measurement, and the independent predictors as the age of the subject at baseline in years, the randomised treatment group, and the value of body weight, BMI or waist circumference at baseline. Univariate and multivariate inference based on Wald tests were derived from the m imputed datasets.

A fixed-effects meta-analysis of the four individual studies was performed by calculating an average weighted effect size and assessing the statistical heterogeneity around this average estimate. The test of inter-study heterogeneity was estimated by Cochran's Q-statistic and P-value (Huedo-Medina *et al.*, 2006). The I^2 index was used to assess the proportion of inconsistency in the individual studies that could be explained by chance (Huedo-Medina *et al.*, 2006). A significant finding of inter-study heterogeneity was found in most cases. Therefore, a random-effects meta-analysis was performed for each endpoint with an estimate of inter-study variance as implemented by the two-step method of DerSimonian & Kacker (2007).

Results

Study 1

At 12 weeks post randomisation, 45 subjects (75.0%) had follow-up weight data. Change in body weight was significantly greater in participants randomised to the MCD than those randomised to the NCEP diet at 12-week follow-up [mean difference of −2.77 kg for MCD – NCEP diet; 95% confidence interval (CI): −3.95, −1.65 kg] (Table 2).

Study 2

Seventy subjects (81.4%) had follow-up weight data at 12 weeks post randomisation, with 59 subjects (68.6%) having follow-up weight data at 24 weeks. Body weight change was significantly greater in participants randomised to the MCD than those randomised to the energy-restricted diet at both 12-week follow-up (mean difference of −2.63 kg for MCD – energy-restricted diet; 95% CI: −3.34, −1.92 kg) and 24-week follow-up (−2.16 kg; 95% CI: −3.15, −1.18 kg). Change in BMI was greater with the MCD at both time points: −0.77 kg m^{-2}; 95% CI: −0.99, −0.54 kg m^{-2} and −0.61 kg m^{-2}; 95% CI: −0.93, −0.29 kg m^{-2} at 12 and 24 weeks, respectively. There was no statistically significant difference in change in waist circumference between the groups at either time point.

Study 3

At 12 weeks post randomisation, 173 subjects (72.1%) had follow-up weight data. At 24 weeks, the number of subjects with follow-up weight data had decreased to 143 (59.6%). Change in body weight was significantly greater in participants randomised to the MCD than those randomised to the energy-restricted diet at 12-week follow-up (−0.83 kg; 95% CI: −1.32, −0.34 kg) but not at the 24-week follow-up. Similarly, change in BMI was greater with the MCD only at 12 weeks: −0.33 kg m^{-2}; 95% CI: −0.51, −0.15 kg m^{-2}. There was no difference in change in waist circumference between the groups at either time point.

Study 4

Ninety-seven subjects (80.8%) had follow-up weight data 12 weeks post randomisation and, at 24 weeks, 83 subjects (69.2%) had follow-up weight data. Change in body weight was significantly greater in participants

Table 2 Changes in body weight, body mass index (BMI) and waist circumference from baseline to 12-week and 24-week follow-up in studies included in the meta-analysis of randomised controlled trials of a specific modified-carbohydrate diet (MCD) compared with various control diets on weight loss

Measure	Between-group difference* Study 1: comparison of the MCD with a reduced-fat, isocaloric diet	Study 2: comparison of the MCD with a reduced-fat, portion-controlled (energy-restricted) diet		Study 3: comparison of the MCD (with and without diet products) with an energy-restricted diet (with and without diet products)		Study 4: comparison of the MCD with diet products with an energy restricted diet with grocery store gift cards	
	12 weeks Mean (95% CI)	12 weeks Mean (95% CI)	24 weeks Mean (95% CI)	12 weeks Mean (95% CI)	24 weeks Mean (95% CI)	12 weeks Mean (95% CI)	24 weeks Mean (95% CI)
Weight (kg)	−2.77† (−3.95, −1.65)	−2.63† (−3.34, −1.92)	−2.16† (−3.15, −1.18)	−0.83† (−1.32, −0.34)	−0.40 (−1.32, 0.52)	−1.69† (−2.36, −1.02)	−1.34† (−2.31, −0.36)
BMI (kg m^{-2})	NR	−0.77† (−0.99, −0.54)	−0.61† (−0.93, −0.29)	−0.33† (−0.51, −0.15)	−0.17 (−0.51, 0.17)	−0.66† (−0.94, −0.38)	−0.59† (−1.02, − 0.16)
Waist circumference (cm)	NR	−0.79 (−1.64, 0.04)	−1.00 (−2.05, 0.05)	−0.65 (−1.43, 0.13)	0.44 (−0.56, 1.43)	−1.89† (−2.86, −0.91)	−2.24† (−3.52, −0.96)

CI, confidence interval; NR, not reported.
*Difference between mean changes in both groups (MCD – control diet).
†$P < 0.05$.

randomised to the MCD than those randomised to the energy-restricted diet at both 12-week follow-up (−1.69 kg; 95% CI: −2.36, −1.02 kg) and 24-week follow-up (−1.34 kg; 95% CI: −2.31, −0.36 kg). Change in BMI was significantly greater with the MCD at 12 weeks (−0.66 kg m^{-2}; 95% CI: −0.94, −0.38 kg m^{-2}) and at 24 weeks (−0.59 kg m^{-2}; 95% CI: −1.02, −0.16 kg m^{-2}). There were significantly greater reductions in waist circumference with the MCD at 12 weeks (−1.89 cm; 95% CI: −2.86, −0.91 cm) and at 24 weeks (−2.24 cm; 95% CI: −3.52, −0.96 cm).

Meta-analysis

Results of the fixed-effects meta-analysis showed that body weight (mean difference of −1.66 kg; 95% CI: −1.98, −1.34 kg), BMI (−0.53 kg m^{-2}; 95% CI: −0.66, −0.41 kg m^{-2}) and waist circumference (−1.02 cm; 95% CI: −1.49, −0.54 cm) were reduced to a significantly greater degree in participants randomised to the MCD compared to those randomised to the control diets (Table 3, Figs 2–4). Although the mean differences between the groups were greatest at 12 weeks, the changes for all three anthropometric measures remained significantly greater in the MCD at 24 weeks.

Because Cochran's *Q*-statistic and I^2 index indicated significant heterogeneity of the results across the studies (Table 3), random-effects meta-analysis also was performed. The results of the random-effects meta-analysis were very similar to those of the fixed-effects meta-analysis. There were significantly greater reductions in body weight, BMI and waist circumference in subjects randomised to the MCD compared to those randomised to the control diets at both 12 and 24 weeks post randomisation (Table 4), with the exception that the difference in change in waist circumference at 24 weeks was not statistically significant.

Discussion

This meta-analysis of RCTs of weight loss comparing a specific MCD to control diets showed significantly greater reductions in body weight (1.66 kg), BMI (0.53 kg m^{-2}) and waist circumference (1.02 cm) in subjects randomised to the MCD compared to control diets at 12-week follow-up. Reductions in body weight and BMI also were significantly greater with the MCD at 24-week follow-up, although the differences between the diets were diminished in magnitude compared to the 12-week results. Although the reductions in anthropometric measures seen with the MCD compared to the control diets at both time points were relatively small, as with any weight-loss

Table 3 Fixed-effects meta-analysis results of changes in body weight, body mass index (BMI) and waist circumference from baseline to 12-week and 24-week follow-up in studies included in the meta-analysis of randomised controlled trials of a specific modified-carbohydrate diet (MCD) compared with various control diets on weight loss

	Between-group difference* 12 weeks		Between-group difference* 24 weeks	
Measure	Mean (95% CI)	Cochran's Q (P) I^2 value	Mean (95% CI)	Cochran's Q (P) I^2 value
Weight (kg)	−1.66 (−1.98, −1.34)†	24.3 (<0.0001) 0.92	−1.20 (−1.73, −0.68)†	77.5 (0.02) 0.73
BMI (kg m^{-2})	−0.53 (−0.66, −0.41)†	10.7 (0.005) 0.81	−0.43 (−0.62, −0.23)†	4.6 (0.09) 0.57
Waist circumference (cm)	−1.02 (−1.49, −0.54)†	4.5 (0.10) 0.56	−0.69 (−1.29, −0.09)†	12.6 (0.002) 0.84

CI, confidence interval.
*Difference between mean changes in both groups (MCD – control diet).
†$P < 0.05$.

Table 4 Random-effects meta-analysis results of changes in body weight, body mass index (BMI) and waist circumference from baseline to 12-week and 24-week follow-up in studies included in the meta-analysis of randomised controlled trials of a specific modified-carbohydrate diet (MCD) compared with various control diets on weight loss

	Between-group difference*	
Measure	12 weeks Mean (95% CI)	24 weeks Mean (95% CI)
Weight (kg)	−1.93 (−2.82, −1.03)†	−1.28 (−2.28, −0.27)†
BMI (kg m^{-2})	−0.54 (−0.77, −0.31)†	−0.44 (−0.73, −0.15)†
Waist circumference (cm)	−1.07 (−1.82, −0.32)†	−0.91 (−2.42, 0.60)

CI, confidence interval.
*Difference between mean changes in both groups (MCD – control diet).
†$P < 0.05$.

intervention, apparently small differences can be meaningful when considered at the population level.

The results of the present study are consistent with previous RCTs, which demonstrated that carbohydrate-restricted diets are effective in promoting weight loss. For example, the Atkins diet resulted in weight loss at 12 months that was comparable with three other popular diets, including a low-fat, high-carbohydrate diet (Dansinger *et al.*, 2005), and with a low-fat, high-carbohydrate diet (Foster *et al.*, 2003). Other short-term studies (of 6–12 months duration) showed that subjects randomised to carbohydrate-restricted diets lost either more weight (Brehm *et al.*, 2003; Samaha *et al.*, 2003) or similar amounts of weight (Brinkworth *et al.*, 2009) than subjects randomised to low-fat, high-carbohydrate diets. Longer-term studies (of 24 months duration) also have demonstrated that carbohydrate-restricted diets produced greater weight loss (Shai *et al.*, 2008) or similar weight loss (Foster *et al.*, 2010) compared to low-fat diets.

The results of this study illustrate the power of meta-analysis. Meta-analysis offers a way to critically evaluate and statistically combine results of comparable studies or trials by increasing the numbers of observations. This results in an increase in statistical power and improves the estimates of the effect size of an intervention or an association (Fagard *et al.*, 1996). When the results of the individual studies included in the meta-analysis were reviewed, the effects of the MCD compared to control diets on change in body weight, BMI and waist circumference were somewhat mixed, with no definitive conclusions possible. For example, the differences in changes in body weight for the individual diets ranged from −0.83 kg (Study 3) to −2.77 kg (Study 1) at 12 weeks and −0.40 kg (Study 3) to −2.16 kg (Study 2) at 24 weeks post randomisation. When meta-analysis was employed, the picture became much clearer, with the overall statistically significant differences of −1.93 kg at 12 weeks and −1.28 kg at 24 weeks follow-up.

It should be noted that the control diets utilised in the four studies were not identical. Nevertheless, the 'portion-controlled' diet in Study 2, 'calorie-restricted' diet in Study 3 and American Diabetes Association exchange diet (diabetes meal plan) in Study 4 had much in common, including portion control and fat reduction, resulting in energy restriction. In addition, all three diets included two phases, with more severe energy restriction in Phase I (all 12 weeks in duration), followed by more moderate restriction in Phase II (for the remainder of the intervention periods). The control diet in study 1 (i.e. the NCEP diet) primarily is a reduced-fat diet, although it also incorporated energy restriction.

The greater reductions in body weight, BMI and waist circumference in subjects randomised to the MCD compared to those randomised to control diets diminished between 12 and 24 weeks post randomisation. Diminishing effects of dietary interventions over time have been well documented in the weight-loss literature, and MCD interventions are no exception. For example, in an RCT

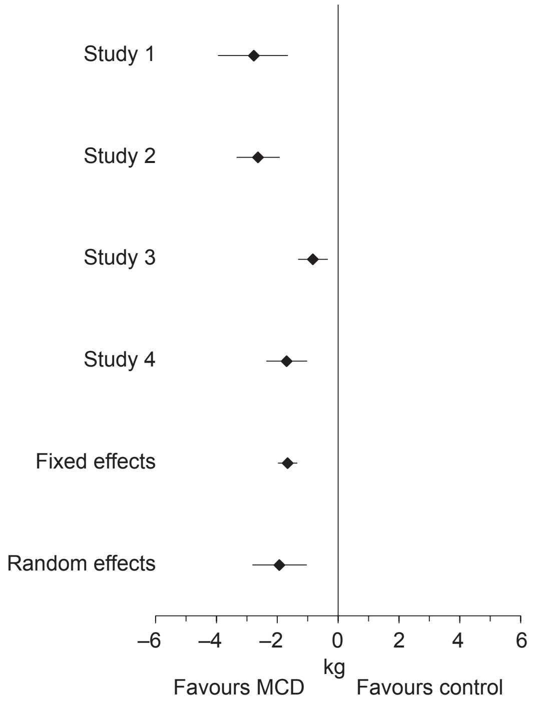

Figure 2 Difference in change in body weight [modified-carbohydrate diet (MCD) – control diet] in individual studies and meta-analyses (fixed effects and random effects) of randomised controlled trials of a specific MCD compared with various control diets on weight loss at 12 weeks. Study 1: comparison of the MCD with a reduced-fat, isocaloric diet. Study 2: comparison of the MCD with a reduced-fat, portion-controlled (energy-restricted) diet. Study 3: comparison of the MCD (with and without diet products) with an energy-restricted diet (with and without diet products). Study 4: comparison of the MCD with diet products with an energy restricted diet with grocery store gift cards.

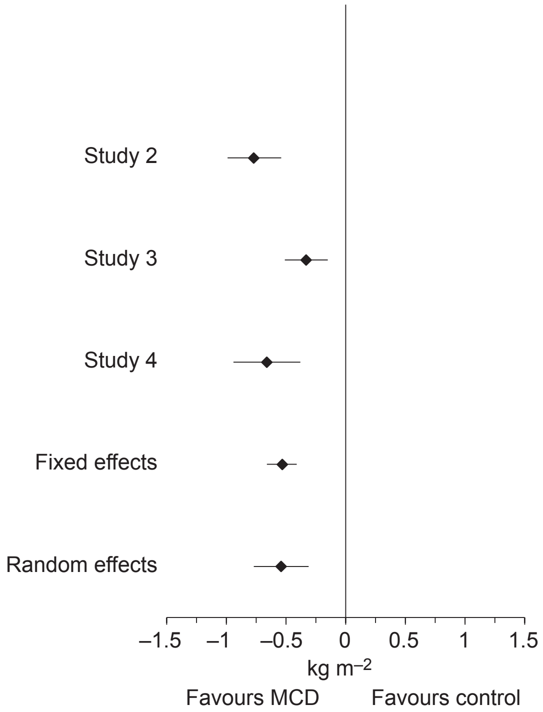

Figure 3 Difference in change in body mass index [modified-carbohydrate diet (MCD) – control diet] in individual studies and meta-analyses (fixed effects and random effects) of randomised controlled trials of a specific MCD compared with various control diets on weight loss at 12 weeks. Study 2: comparison of the MCD with a reduced-fat, portion-controlled (energy-restricted) diet. Study 3: comparison of the MCD (with and without diet products) with an energy-restricted diet (with and without diet products). Study 4: comparison of the MCD with diet products with an energy restricted diet with grocery store gift cards.

comparing a low-carbohydrate diet with a low-calorie diet in obese men and women, there was significantly greater loss of weight in the low-carbohydrate group at 6 months follow-up, although the difference at 12 months was no longer significant (Foster *et al.*, 2003).

Regarding the degree of weight loss which reasonably can be expected from this MCD, the study by Maki *et al.* (2007) demonstrated an absolute weight loss at 12 weeks of approximately 5% of baseline body weight in the MCD group. This compares favourably with the weight loss recommendation of 5–10% of original weight promulgated by multiple agencies, including the National Institute for Health and Clinical Excellence in the UK (NICE, 2006).

Concern has been expressed over possible adverse metabolic effects of carbohydrate-restricted diets, especially in individuals with cardiovascular disease, type 2 diabetes mellitus, dyslipidaemia, or hypertension. Specifically, it has been cautioned that carbohydrate-restricted diets may cause an accumulation of ketones, possibly resulting in abnormal metabolism of insulin and impaired hepatic and renal function; increased animal protein consumption, which may result in hyperuricosuria, hypercalciuria and a reduction in urinary pH, increasing the risk of stone formation; excessive consumption of animal proteins and fats that may contribute to hyperlipidaemia; and higher overall dietary protein loads that may impair renal function (Bravata *et al.*, 2003; Friedman, 2004). Nevertheless, multiple studies have failed to demonstrate deleterious effects of carbohydrate-restricted diets on multiple metabolic and physiological parameters, at least in the short term (Bravata *et al.*, 2003; Brehm *et al.*, 2003; Foster *et al.*, 2003; Dyson, 2008; Sacks *et al.*, 2009). However, because of the limited number of studies lasting beyond 12 months, the long-term safety of carbohydrate-restricted diets remains undetermined (Noble & Kushner, 2006; Kushner & Doerfler, 2008).

Study 4 included only subjects with diabetes. Because carbohydrate is the major secretagogue of insulin, some

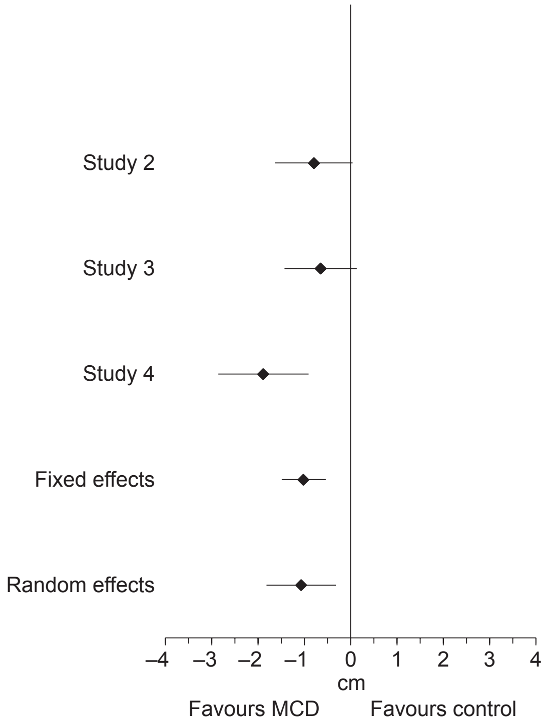

Figure 4 Difference in change in waist circumference [modified-carbohydrate diet (MCD) – control diet] in individual studies and meta-analyses (fixed effects and random effects) of randomised controlled trials of a specific MCD compared with various control diets on weight loss at 12 weeks. Study 2: comparison of the MCD with a reduced-fat, portion-controlled (energy-restricted) diet. Study 3: comparison of the MCD (with and without diet products) with an energy-restricted diet (with and without diet products). Study 4: comparison of the MCD with diet products with an energy restricted diet with grocery store gift cards.

form of carbohydrate restriction has been promoted by some experts (American Diabetes Association, 2011) as a potentially important avenue for dietary control of diabetes; indeed, individuals with diabetes may be the ideal target group. Carbohydrate-restricted diets have been shown to be comparable or better than traditional low-fat, high-carbohydrate diets for weight reduction and improvement in the dyslipidaemia of diabetes, as well as for the control of blood pressure, post-prandial glycaemia and insulin secretion. The ability of carbohydrate-restricted diets to reduce triglycerides and to increase high-density lipoprotein cholesterol is of particular importance (Arora & McFarlane, 2005). Overall, there is a growing body of evidence that carbohydrate-restricted diets are more effective, at least in the short term, for reducing weight and improving insulin sensitivity without significant adverse cardiovascular effects (Worth & Soran, 2007). Some form of carbohydrate-restricted diet, in combination with exercise, may be a viable option for patients with diabetes. Such diets may be desirable in that, in addition to their potential to promote weight loss and improve glucose tolerance, they give the patient more options. Patients also may find it easier to comply with these types of diets than standard dietary therapy (Kennedy *et al.*, 2005).

The present study has limitations that are worthy of note. The raw data from Study 1 were not available. In addition, not all measurements were available for each participant at each time point in Studies 2–4. Participant drop-outs and missing data are ubiquitous in RCTs of weight-loss interventions and are a threat to the validity and generalisability of the results (Elobeid *et al.*, 2008). Although there are several approaches to handling missing data during analysis, multiple imputation was utilised. Although other approaches are available (including last observation carried forward and mixed models), multiple imputation has been demonstrated to be at least as good as, and in some cases superior to, other methods for addressing missing data in weight-loss RCTs (Elobeid *et al.*, 2008). There is always the possibility of publication bias when the studies that are included in a meta-analysis are systematically unrepresentative of the population of completed studies, potentially leading to erroneous conclusions (Allison *et al.*, 1996). As noted, extensive literature searches were conducted to identify other pertinent RCTs, identifying only one additional study [the study by Aude *et al.* (2004) included in this meta-analysis]. Only one of the four studies included reported on race/ethnicity of participants. Therefore, this could not be controlled for in the analysis. Finally, the effects of the MCD relative to standard reduced-energy diets beyond 24 weeks could not be reported because only one of the studies (Study 2) included follow-up extending beyond this time point. Clearly, there is a need for studies addressing the long-term (≥12 months) effects of this MCD on body weight and related measures.

In summary, the results of individual RCTs of this MCD compared to control diets on measures of weight loss were somewhat inconsistent. When meta-analytic methodology was applied, there was a modest benefit of this MCD over the control diets: 1.66 kg greater reduction in body weight, 0.53 kg m^{-2} greater reduction in BMI and 1.02 cm greater reduction in waist circumference at 12 weeks, which diminished slightly at 24 weeks, although remaining statistically significant.

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Conflict of interest, source of funding and authorship

JMS, RD and RM report that they have no conflicts of interest.

DBA reports receiving grants, honoraria, consulting fees, and donations from multiple for-profit and not-for-profit entities with interests in obesity, including Kraft and other food companies.

JMS and DBA contributed to the conception and design of the paper, the analysis and interpretation of the data, and the drafting of the paper; critically reviewed the content of the paper; and approved the final version submitted for publication. RD contributed to the analysis and interpretation of the data and drafting of the paper; critically reviewed the content of the paper; and approved the final version submitted for publication. RM contributed to the analysis and interpretation of the data; critically reviewed the content of the paper; and approved the final version submitted for publication.

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