Obesity Treatment/Physiology

Impact of low-carbohydrate diet on body composition: meta-analysis of randomized controlled studies

Y. Hashimoto, T. Fukuda, C. Oyabu, M. Tanaka, M. Asano, M. Yamazaki and M. Fukui

Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan

Received 22 December 2015; revised 27 January 2016; accepted 12 February 2016

Address for correspondence: M Fukui, Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
E-mail: sayarinapm@hotmail.com

Summary

The effect of low-carbohydrate diet (LCD) on body composition, especially fat mass, in obese individuals remains to be elucidated.

We performed a meta-analysis to provide quantitative summary estimates of the mean change of body weight (kg) and fat mass (kg) in LCD comparing to those in control diet. Literature searches were performed using EMBASE, MEDLINE and Cochrane Library until Dec 2014.

Fourteen randomized controlled studies were included in this meta-analysis. Eight studies including very LCD (50 g carbohydrate or 10% calorie from carbohydrate) and seven studies including mild LCD (about 40% calorie from carbohydrate). Meta-analysis carried out on data of 1416 obese individuals, showed that LCD was associated with decrease in body weight (−0.70 kg [95% CI −1.07/−0.33]) or fat mass (−0.77 kg [−1.55/−0.32]). Subgroup meta-analysis of studies in over 12 months suggested that LCD was not associated with decrease in body weight (−0.44 kg [−0.94/0.07]), but LCD was associated with decrease in fat mass (−0.57 kg [−1.05/−0.09]). In addition, very LCD was associated with decrease in fat mass (−0.97 kg [−1.50/−0.44]), but mild LCD was not associated with decrease in fat mass (−0.43 kg [−1.15/0.33]).

LCD, especially very LCD, might be effective for decrease in fat mass in obese individuals. © 2016 World Obesity

Keywords: Body fat, body weight, carbohydrate(s), nutrition.

obesity reviews (2016) **17**, 499–509

Introduction

Overweight and obesity are growing global health problems. According to the World Health Organization, in 2014, more than 1.9 billion adults worldwide were overweight and of these over 600 million were obese (1). Obesity is associated with several life threaten diseases, such as hypertension (2,3), type 2 diabetes (4,5), chronic kidney diseases (6,7) and cardiovascular disease (8,9).

The debate about which type of diet is the most effective for the treatment of overweight and obesity has become more intense in recent years. It has reported that a high-carbohydrate diet has appeared to be associated with obesity, type 2 diabetes and metabolic syndrome (10–12). Low-carbohydrate diet (LCD) has recently become very popular for weight loss (13–15). In fact, several meta-analyses showed that LCD is effective for weight loss (16–20).

On the other hand, recent studies revealed that not only body weight but also body composition, including body fat mass, is important for cardiovascular risk and mortality (21,22). In addition, recent studies revealed a subset of individuals with non-obese whom the volume of skeletal muscle, and its strength was decreased, so-called sarcopenia (23). Sarcopenia is a risk of several life-threatening diseases

(24–26). Thus, not only body weight but also body composition is an important target of diet. However, the effect of LCD on body composition, especially fat mass, in obese individuals remains to be elucidated. In this meta-analysis, therefore, we aimed to investigate the effect of LCD on fat mass in obese individuals.

Methods

Data sources and searches

We used the MEDLINE, EMBASE and Cochrane Database of Systematic Reviews. We selected the manuscripts reported from their inception until Dec 2014, in human published English language. Using the following search term: 'low carbohydrate diet' and 'clinical trial' or 'observational study' or 'cohort study'. The reference lists of the pertinent articles were also inspected.

Study selection

We used the following inclusion and exclusion criteria. Inclusion criteria: (i) the original articles; (ii) the abstract of articles should include the term or abbreviations of 'low carbohydrate diet'; (iii) the individuals with overweight or obesity; and (iv) the articles should include the data of body weight and fat mass. Exclusion criteria: (i) duplicated article in three web sites; (ii) no original raw data of both body weight and fat mass; (iii) no data of standard deviation (SD) for assessed data; and (iv) no data for the control group. Two investigators independently reviewed all potentially relevant publications and made decisions on inclusion. Where these decisions conflicted, additional investigators (co-authors) were involved to discuss discrepancies until mutual agreement was reached.

Data extraction

We extracted all following data from all assessed articles; the author's name, study title, country, year and source of publication, study design, study length, sample size, dropout number, body weight, fat mass, age, dietary composition and method of measurement of body composition. Change of body weight (kg) or fat mass (kg) was the outcome of interest in this meta-analysis.

In some studies, we found just average and SD of body weight or fat mass at baseline and at endpoint. In these cases, we estimated mean change of body weight (or fat mass) as follows; body weight (or fat mass) at endpoint – body weight (or fat mass) at baseline. In the same way, SD of change of body weight (or fat mass) as follows; SD of change of body weight (or fat mass) = the square root of ((SD of body weight (or fat mass) at endpoint) × 2 + (body weight (or fat mass) at baseline) × 2).

Validity and quality assessment

Two reviewers independently checked and selected all references. We assessed quality of evidence for each study by using the Grading of Evidence, Assessment, Development and Evaluation (GRADE) approach (27). We validated and performed Quality Assessment of all articles, which was satisfied with all inclusion and exclusion criteria, according to AMSTAR (27).

Quantitative data synthesis and analysis

We performed quantitative data synthesis based on PRISMA Statement (28). We performed a meta-analysis to provide quantitative summary estimates of the mean change of body weight and fat mass because of LCD comparing to control diet. Summary averages were calculated using random-effects model according to Peto and Mantel-Haenszel following a test of heterogeneity (29). The presence of heterogeneity was assessed with the Q test and the extent of heterogeneity was quantified with the I^2 index. The I^2 statistic were calculated to assess statistical heterogeneity across studies: 0% suggests no heterogeneity, 0–25% very low heterogeneity, 25–50% low heterogeneity, 50–75% moderate heterogeneity and a value of 75% high heterogeneity (30,31). Statistical significance was defined as P values less than 0.05. Studies with significant differences or those with generally expected results tend to be submitted and accepted, leading to publication bias in meta-analysis. Funnel plots were produced for intervention effects to compare each study. Asymmetry may indicate that there might be unpublished studies with insignificant results or unexpected results. All analyses were conducted using R version 3.0.1 (R project for Statistical Computing).

Additional analysis

In addition to the primary analysis of all pooled data combined, stratified analyses were performed. Because previous studies reported that the effect of LCD disappeared after 12 months follow-up (16,32). Therefore, we investigated the impact of LCD in over 12 months or in less than 12 months on change of body weight or fat mass, compared to control diet.

We also investigated the impact of very LCD (18); approximately 50 g carbohydrate or 10% of calorie from carbohydrate or that of moderate LCD (33); about 40% of calorie from carbohydrate, on change of body weight or fat mass, compared to control diet.

In addition, we also investigated the impact of LCD on change of body weight or fat mass, compared to control diet in measurement, including bio impedance (BIA) and dual-energy X-ray absorptiometry (DXA) method, separately.

Results

The flow of studies in our meta-analysis is depicted in Fig. 1. From 199 potentially relevant references. Among them, 95 references did not report original data. A total of 104 full-text references were reviewed for eligibility. Of those, 14 randomized controlled trials met all of the eligibility criteria and were included in the meta-analysis (34–47). These studies included data from 1805 participants (906 on LCD and 899 on control diet).

The characteristics of these 14 randomized controlled trials are presented in Table 1. Trial participants were usually not blinded to their assignment because of the nature of the intervention; most interventions provided dietary instruction and/or preparation to the participants. Study duration ranged from 2 to 24 months. All trials were conducted among overweight or obese individuals. The baseline characteristics of LCD groups, including body weight and fat mass, were almost the same as those of control diet groups. The goal dietary nutritional composition varied across the studies, with carbohydrate consumption ranging from 20 g/day to 45% of energy intake in LCD group (Table 2). Eight studies including very LCD (34,36,38,39,41,42,44,47) and seven studies including mild LCD (35–37,40,43,45,46).

All data

We found asymmetry in funnel plots for change of body weight or change of fat mass (Fig. S1). To compare the effect of LCD on body weight or body fat, the participants who dropped out were excluded from the analyses. Therefore, the meta-analysis encompassed a total of 1416 participants, with 697 in LCD group and 719 in control diet group. Mean change of body weight or fat mass in LCD was −14.50 to −2.50 kg or −11.30 to −0.75 kg and that in control diet was −11.5 to −0.61 kg or −9.40 to 0.54 kg. The change of body weight or fat mass in LCD group was higher than that in control diet group (−0.70 kg [95% CI −1.07/−0.33] in change of body weight, −0.82 kg [95% CI −1.22/−0.42] in change of fat mass) (Figs 2 and 3).

Data of over 12 months or less than 12 months

Six studies (35,37,41,42,46,47) investigated the effect of LCD on the change of body weight or body fat in over 12 months. The meta-analyses encompassed a total of 770 participants, with 374 in LCD group and 396 in control diet group. Mean change of body weight or fat mass in LCD was −14.50 to −2.50 kg or −11.30 to −3.00 kg and that in control diet was −11.5 to −1.70 kg or −9.40 to 0.54 kg. There was no statically difference between the change of body weight in LCD in over 12 months group and that in control group (−0.44 kg [95% CI −0.94/0.07]) (Fig. S2). On the other hand, the change of fat mass in LCD group was higher than that in control diet group (−0.57 kg [95% CI −1.05/ −0.09]) (Fig. 4).

Eight studies (34,36,38–40,43–45) investigated the effect of LCD on the change of body weight or body fat in less than 12 months. The meta-analysis encompassed a total of 666 participants, with 323 in LCD group and 343 in control diet group. Mean change of body weight or fat mass

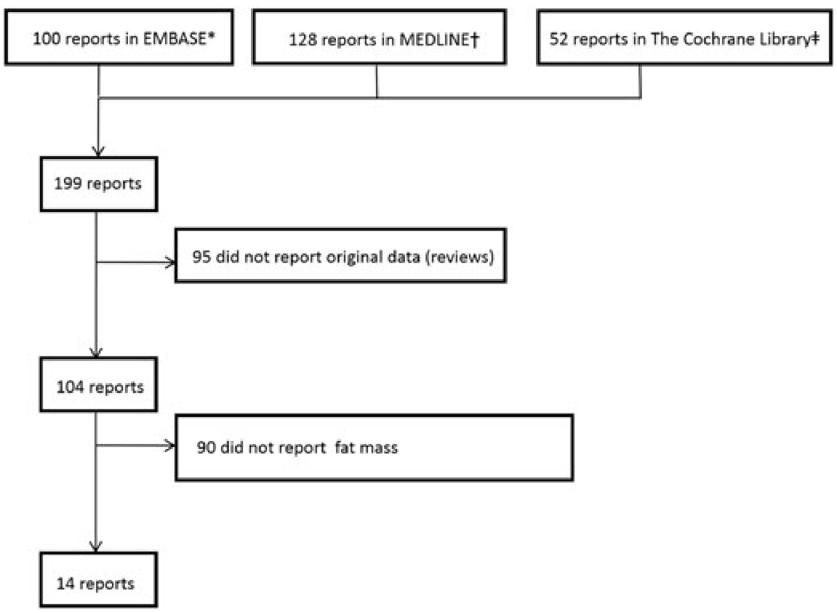

Figure 1 Flow diagram of study selection. Reports were selected from their inception until Dec 2014 by 'low carbohydrate diet' and 'clinical trial' or 'observational study' or 'cohort study' words.

Table 1 Characteristics of 9 randomized controlled clinical trials

First author, year (Ref)	Country	Follow-up (month)	LCD N of complete study	LCD N of drop out	Control diet N of complete study	Control diet N of drop out	Inclusion criteria	Body weight of LCD, kg (SD)	Body weight of control diet, kg (SD)	Fat mass of LCD, kg (SD)	Fat mass of control diet, kg (SD)	Measurement of fat mass
Brehm (34)	United States	6	22	4	20	7	BMI of 30 to 35 kg/m^2	91.2 (8.4)	92.3 (6)	41.3 (3.7)	41.3 (2.7)	DXA
Brinkworth (35)	Australia	12	21	8	22	7	BMI of 27 to 43 kg/m^2, fasting serum insulin over 12 mU/L	94 (3.4)	94 (3.2)	41.8 (8.1)	40.6 (1.9)	DXA
McAuley (36)	New Zealand	6	27	3	30	2	BMI of over 27 kg/m^2, women	93.2 (14.5)	98 (15.1)	42.1 (8)	46.1 (9.9)	BIA
			27	4				96 (10.8)		44.2 (6.9)		
Ebbeling (37)	United States	18	28	8	23	14	BMI of over 30 kg/m^2	103.5 (17.3)	103.3 (15.1)	42.5 (5.6)	41.4 (6.0)	DXA
Wal (38)	United States	3	42	3	44	3	BMI of over 25 kg/m^2	90.5 (17.9)	97.1 (23.2)	40.7 (7.2)	43.9 (8.6)	Air displacement plethysmography
			40	6				105.2 (27.5)		49 (8.0)		
Keogh (39)	Australia	2	52	5	47	3	BMI of 27 to 44 kg/m^2 and abdominal obesity and at least one additional MetS risk factor	94 (15.3)	97 (14.4)	39.5 (10.8)	39.6 (8.1)	DXA
Lasker (40)	United States	4	25	0	25	0	BMI of over 26 kg/m^2 and body weight under 140 kg	96.6 (3.9)	94.3 (2.1)	35.2 (1.8)	36.3 (1.8)	DXA
Brinkworth (41)	Australia	12	33	22	36	16	Abdominal obesity and at least one additional MetS risk factor	93.9 (15.5)	94.5 (12.7)	40 (1.7)	39.2 (.5)	DXA
Foster (42)	United States	24	89	64	105	49	BMI of 30 to 40 kg/m^2 and body weight under 136 kg	103.3 (15.5)	103.5 (14.4)	40 (7.6)	40.4 (7.8)	DXA
Ballesteros-Pomar (43)	Spain	4	10	0	11	0	BMI of 28 to 35 kg/m^2	93 (14.3)	85.4 (8.4)	29 (7.6)	32 (4.1)	BIA
			8	0	7	0		88 (12)	85.6 (8.8)	30 (8.9)	27.3 (5.0)	
Summer (44)	United States	4	42	0	39	0	BMI of 30 to 35 kg/m^2	91.2 (1.8)	92.3 (1.3)	37.3 (1)	37.8 (0.6)	DXA
Rodríguez-Hernández (45)	Mexico	6	28	3	26	2	BMI of over 30 kg/m^2	96.3 (15.7)	92.5 (17)	45.5 (4.2)	42.2 (4.8)	BIA
Krebs (46)	New Zealand	24	144	63	150	61	BMI of over 30 kg/m^2 and type 2 diabetes	103.4 (19.7)	101.9 (20.1)	43.9 (13.9)	45.2 (14.3)	BIA
Bazzano (47)	United States	12	59	16	60	13	BMI of 30 to 45 kg/m^2	96.3 (12.7)	97.9 (13.5)	40 (10)	40 (10)	BIA

BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual-energy x-ray absorptiometry; LCD, low carbohydrate diet; MetS, metabolic syndrome; N, number.

Table 2 Dietary and nutrition intake of study participants

First author, year (Ref)	Age of LCD, year (SD)	Age of control diet, year (SD)	Definition of LCD	Definition of control diet	Nutrition intake at endpoint: LCD	Nutrition intake at endpoint: Control diet
Brehm (34)	43.1 (8.6)	44.2 (6.7)	Atkins diet	55% from C, 15% from P and 30% from F	30% from C, 23% from P and 46% from F	53% from C, 18% from P and 29% from F
Brinkworth (35)	52.0 (2.6)	51.5 (1.6)	40% from C (<140 g/d), 30% from P (<110 g/d) and 30% from F (<50 g/d)	55% from C (200 g/d), 15% from P (<60 g/d) and 30% from F (<50 g/d)	46% from C, 22% from P and 31% from F	46% from C, 21% from P and 32% from F
McAuley (36)	No date	No date	40% from C, 30% from P and 30% from F	High-carbohydrate, high-fiber diet	35% from C, 26% from P and 28% from F	45% from C, 21% from P and 28% from F
	No date		Atkins diet		26% from C, 24% from P and 35% from F	
Ebbeling (37)	28.2 (3.8)	26.9 (4.2)	40% from C, 25% from P and 35% from F	55% from C, 25% from P and 20% from F	No date	No date
Wal (38)	50.5 (9.6)	49.6 (8.8)	Atkins diet	Normal daily routines	No date	No date
	49.6 (9.9)		Special K Low Carb ® of breakfast and lunch and 2512 kJ dinner with low C	Normal daily routines	No date	No date
Keogh (39)	50.5 (8.1)	49.4 (8.2)	4% from C, 35% from P and 61% from F	46% from C, 24% from P and 30% from F	No date	No date
Lasker (40)	No date	No date	Under 40% from C and under 30% from P	Under 55% from C and under 15% from P	39% from C, 31% from P and 32% from F	61% from C, 19% from P and 25% from F
Brinkworth (41)	51.5 (7.7)	51.4 (6.5)	Atkins diet	46% from C, 24% from P and 30% from F	9% from C, 32% from P and 55% from F	46% from C, 22% from P and 26% from F
Foster (42)	46.2 (9.2)	44.9 (10.2)	Atkins diet	55% from C, 15% from P and 30% from F	No date	No date
Ballesteros-Pomar (43)	36.4 (12.6)	44.0 (14.4)	40% from C, 30% from P and 30% from F	55% from C, 15% from P and 30% from F	41% from C, 24% from P and 35% from F	57% from C, 16% from P and 25% from F
	47.3 (11.8)	40.6 (14.5)			43% from C, 23% from P and 33% from F	51% from C, 20% from P and 29% from F
Summer (44)	44.5 (81.4)	41.9 (1.8)	Atkins diet	Normal daily routines	27% from C, 24% from P and 49% from F	50% from C, 19% from P and 31% from F
Rodríguez-Hernández (45)	46.3 (9.1)	45.0 (9.1)	45% from C, 27% from P and 28% from F	54% from C, 25% from P and 21% from F	No date	No date
Krebs (46)	57.7 (9.9)	58.0 (9.2)	40% from C, 30% from P and 30% from F	55% from C, 15% from P and 30% from F	46% from C, 21% from P and 33% from F	48% from C, 20% from P and 30% from F
Bazzano (47)	45.8 (9.9)	47.8 (10.4)	<40 g/day from C	55% from C, <30% from F	34% from C, 24% from P and 41% from F	54% from C, 19% from P and 30% from F

C, carbohydrate; F, fat; LCD, low carbohydrate diet; P, protein.

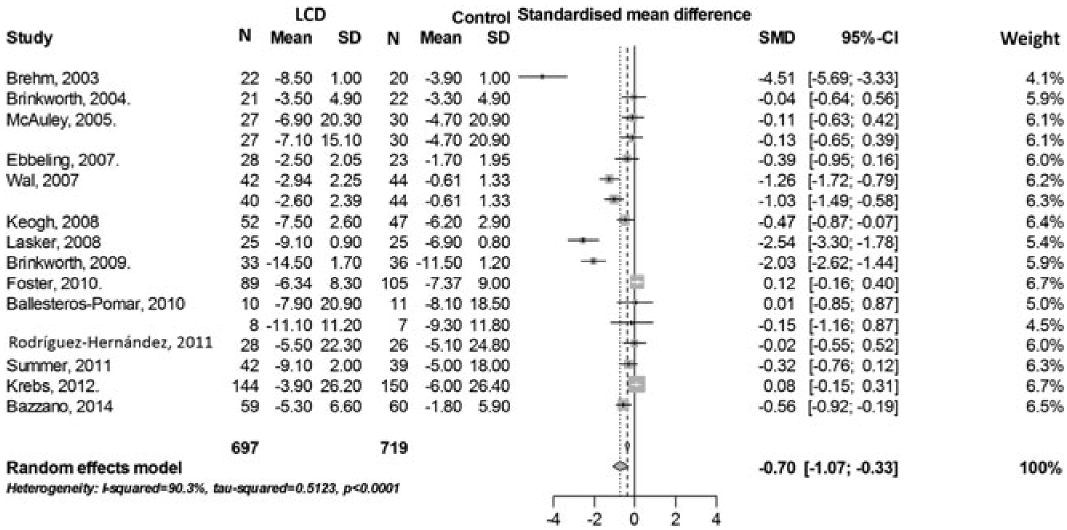

Figure 2 Forest plot for change of body weight associated to low carbohydrate diet. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

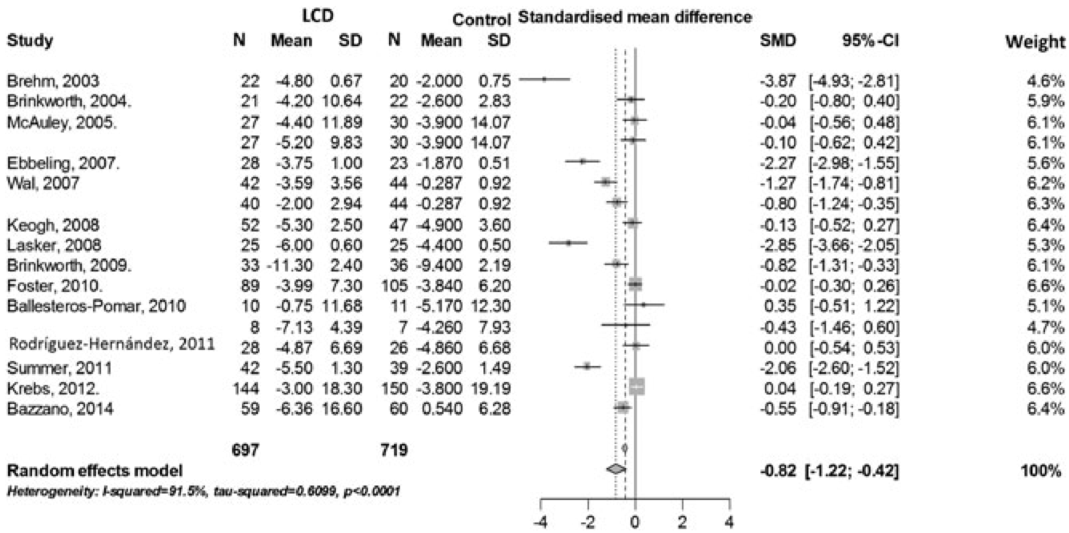

Figure 3 Forest plot for change of body fat associated to low carbohydrate diet. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

in LCD was −11.1 to −2.60 kg or −7.13 to −0.75 kg and that in control diet was −9.30 to −0.61 kg or −5.17 to −0.287 kg. The change of body weight or fat mass in LCD was higher than that in control group (−0.89 kg [95% CI −1.43/0.35] in change of body weight or −0.98 kg [95% CI −1.60/−0.36] in change of fat mass) (Fig. S3 and Fig. 5).

Data of very low carbohydrate diet

Eight studies (34,36,38,39,41,42,44,47) investigated the effect of very LCD on the change of body weight or fat mass. There were 831 participants (406 on very LCD and 425 on control diets). The change of body weight or fat mass in very LCD group was higher than that in control diet group (−1.00 kg [95% CI −1.54/−0.45] in change of body weight or −0.97 kg [95% CI −1.50/−0.44] in change of fat mass) (Fig. S4 and Fig. 6).

Data of moderate low carbohydrate diet

Seven studies (35–37,40,43,45,46) investigated the effect of mild LCD on the change of body weight or fat mass. There were 585 participants (291 on mild LCD and 294 on control diets). The change of body weight or fat mass in mild LCD group was not difference from that in control group (−0.37 kg [95% CI −0.85/0.12] in change of body weight or −0.65 kg [95% CI −1.32/0.02] in change of fat mass) (Fig. S5 and Fig. 7).

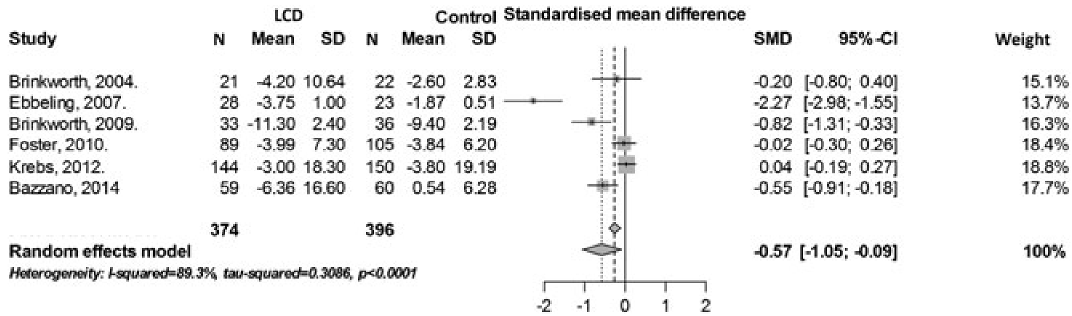

Figure 4 Forest plot for change of body fat associated to low carbohydrate diet among the studies over 12 months. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

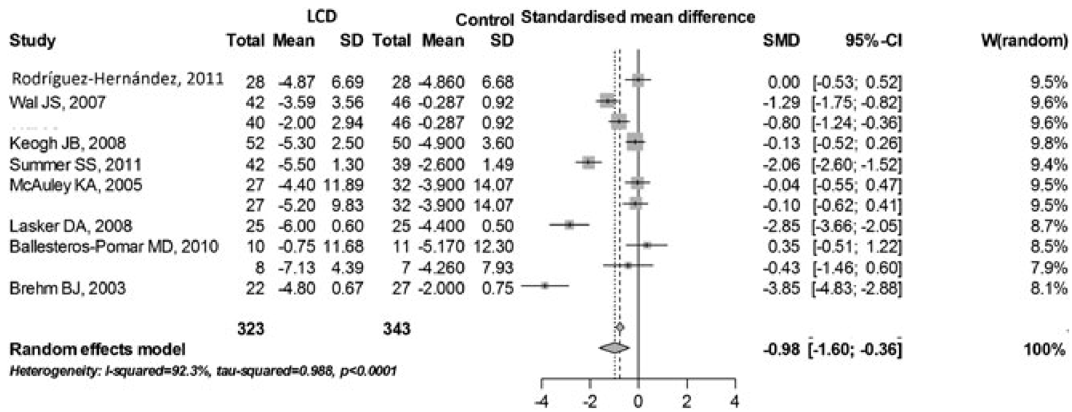

Figure 5 Forest plot for change of body fat associated to low carbohydrate diet among the studies less than 12 months. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

Date of difference methods of body composition

Five studies (36,43,45–47) investigated the effect of LCD on the change of body fat by BIA method. The meta-analysis encompassed a total of 786 participants, with 392 in LCD group and 394 in control diet group. Mean change of body weight or fat mass in LCD was −11.1 to −3.9 kg or −7.13 to −0.75 kg and that in control diet was −9.3 to −1.8 kg or −5.17 to 0.54 kg. There was no significant difference between the change of body weight or fat mass in LCD and that in control group (−0.13 kg [95% CI −0.36/0.10] in change of body weight or −0.12 kg [95% CI −0.35/0.11] in change of fat mass) (Figs S6 and S7). On the other hand, eight studies (34,35,37,39–42,44) investigated the effect of LCD on the change of body fat by DEXA method. The meta-analysis encompassed a total of 629 participants, with 312 in LCD group and 317 in control diet group in DXA method. Mean change of body weight or fat mass in LCD was −14.5 to −2.5 kg or −11.3 to −3.75 kg and that in control diet was −11.5 to −1.70 kg or −9.40 to −1.87 kg. The change of body weight or fat mass in LCD group was higher than that in control diet group (−1.17 kg [95% CI −1.91/−0.42] in change of body weight or −1.46 kg [95% CI −2.28/−0.64] in change of fat mass) (Figs S8 and S9).

Discussion

In this present meta-analyses of randomized controlled trials comparing LCD with control diet, we found that both LCD and control diet were effective for reducing body weight and body fat mass. Previous studies revealed that LCD is effective for weight loss (16–20) and cardiovascular disease risk factors (19,20). We identified the possibility that LCD was more effective for reducing body weight and body fat mass compared with control diet in this meta-analysis. Stratified analyses of over 12 months showed that LCD was more effective for change of fat mass than control diet, although there was no statically difference between the change of body weight in LCD in over 12 months group and that in control group. In addition, very LCD was effective for reducing body weight and fat mass compared with control diet. On the other hand, mild LCD was not effective

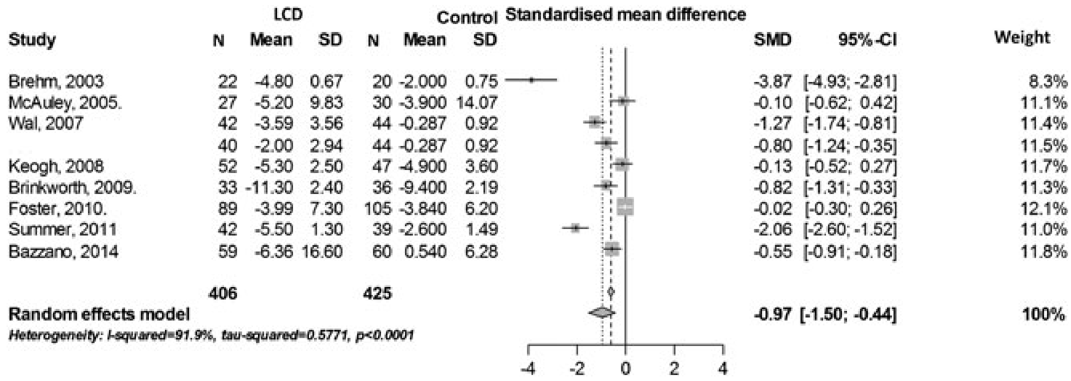

Figure 6 Forest plot for change of body fat associated to very low carbohydrate diet. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

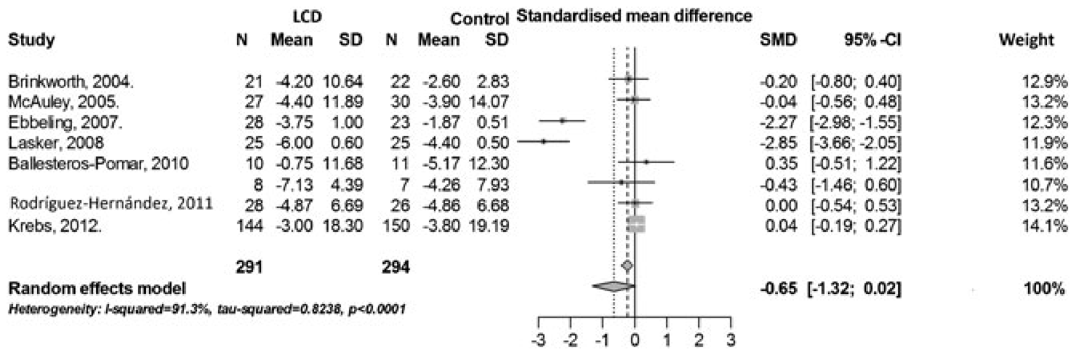

Figure 7 Forest plot for change of body fat associated to moderate low carbohydrate diet. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

for reducing body weight and body fat mass compared with control diet. However, because of asymmetry in funnel plots, we could not deny the publication bias. Therefore, a further study should be needed.

One of the possible reasons why LCD was effective for change of fat mass might be dietary composition of protein. The low-carbohydrate diet is accompanied by high protein (48–50). Dietary protein is absorbed as amino acids. Amino acids help muscle growth (51,52) and fat mass loss (52). It has been reported that protein intake is positively associated with lean mass (53,54). In fact, not mild LCD but very LCD was effective for reducing body weight and fat mass in this meta-analysis. In addition, the proportions of protein intake of LCD tended to be higher than those of control diet.

This meta-analysis showed that the change of body weight or fat mass in LCD in less than 12 months was higher than that in control group in less than 12 months. However, it has been reported that it is desirable to investigate in at least 12 months to evaluate the effect of diet, because there is an initial drop in body weight which is followed by a re-gain in over 12 months studies (16,32). In addition, there are considerable changes in body composition which affect the underlying assumptions, especially in the short term studies (55). The studies of very LCD over 12 months were few to combined data and performed meta-analysis. Thus, we could not conclude that very LCD was effective for decreasing fat mass in long term.

We should show the limitations of this meta-analysis. First, the study participants were relatively small and study duration was short. In addition, none of large-scale clinical trial for fat mass was published. Moreover, according to the funnel plots, there is a possibility of existence of publication bias. Thus, there still remains insufficient evidence to provide clear effect of LCD on body composition. Second, dropout rates of long-term follow-up studies were high (34,35,37,41,42,46,47). In addition, poor adherence of study participants is also the limitation. Most of participants in these studies were not able to achieve and maintain target diet compositions. In fact, the diet compositions tended to be restored to baseline proportions in these study participants, indicating that it is difficult to change the habitual dietary patterns to another dietary pattern. Therefore, none of the studies is well-controlled in a strict sense. In addition, it was difficult to distinguish the effects of the other diet compositions, including protein and fat, on body weight or fat mass. Therefore, there is a possibility that both of these factors might be related to the magnitude on change of body weight or fat mass in this study. In fact, protein and fat sources are associated with cardiovascular risk, cancer and mortality (56,57). However, the proportion of carbohydrate in LCD group was consistently lower than that in control group. Thus, we, at least, showed the effect of lower carbohydrate intake on body weight or fat mass, compared to higher carbohydrate diet intake on body weight or fat mass. Third, although body composition methods, including BIA and DXA, are widely used in clinical settings, the precision of these methods is in the order of 1 to 2 kg. In addition, there are considerable changes in body composition which affect the underlying assumptions, especially in the short term studies (55). Therefore, long-term follow-up studies, at least over one-year follow-up, are required to better understand the difference between the effect of LCD on body composition and that of control diet (58). Furthermore, the changes in body composition accompanied by weight loss are associated with Forbes' Rule, which indicated that fat mass is occupied three-fourth of weight loss (59). Therefore, the initial body weight or fat mass have to be matched. However, there was no significant difference between body weight or fat mass of LCD and that of control diet at baseline examinations in this meta-analysis. Thus, the effect of Forbes' Rule in this meta-analysis was small. Fourth, we could not match age and sex in the different diet groups because of the absence of individual participant data. Fifth, although we performed stratified analyses of over 12 months studies and less than 12 months studies, we could not differentiate if the participants were weight-stable after weight loss or weight-regaining in a strict sense. Finally, we did not evaluate physical activity or other life habits. Therefore, the contribution of any changes in physical activity or other life habits on the body weight or fat mass could not be determined.

Recent studies revealed that not only body weight but also body composition, including body fat, is important for cardiovascular risk and mortality. This is the first meta-analysis of the effect of LCD on body fat mass, compared to that of control diet. However, data quality of the studies is relatively poor or even limited in this meta-analysis, because of poor adherence of diets, the precision of methods of body composition and short duration follow-up. Therefore, not randomized control trial but long-term observational might be suitable for the observation of effect of diet treatment on body composition.

In conclusion, this meta-analysis revealed that the decrease of body weight or body fat mass in LCD, especially very LCD, was higher than that in control diet. However, additional studies are needed to evaluate the effects of LCD on fat mass in obese individuals because of insufficient number of participants, insufficient follow-up periods and the possibility of publication bias.

Conflict of interest statement

Mai Asano, Masahiro Yamazaki and Michiaki Fukui have received grants, honoraria and research supports from AstraZeneca plc., Astellas Pharma Inc., Nippon Boehringer Ingelheim Co., Ltd., Daiichi Sankyo Co., Ltd., Eli Lilly Japan K.K., Kyowa Hakko Kirin Company Ltd., Kissei Pharmaceutical Co., Ltd., MSD K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Sanofi K.K., Ono Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. The sponsors were not involved in the study design; in the collection, analysis, interpretation of data; in the writing of this manuscript; or in the decision to submit the article for publication. The authors, their immediate families and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article. The authors declare that although they are affiliated with a department that is supported financially by pharmaceutical company, the authors received no current funding for this study and this does not alter their adherence to all the journal policies on sharing data and materials. The other authors have nothing to disclose.

Contributors

YH contributed to the data research, extraction and analyses and wrote the manuscript. TF, CO, MT, MA, MY and MF contributed substantially to the study conception and design, data analysis and interpretation, and drafting and critical revision of the manuscript for important intellectual content. MF is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the writing of the manuscript and approved the final version in this article.

Supporting information

Additional supporting information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12405

Figure S1. Funnel plot of 14 randomized controlled trials for change of body weight or change of fat mass

Figure S2. Forest plot for change of body weight associated to low carbohydrate diet among the studies over 12 months. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

Figure S3. Forest plot for change of body weight associated

to low carbohydrate diet among the studies less than 12 months. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.
Figure S4. Forest plot for change of body weight associated to very low carbohydrate diet. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.
Figure S5. Forest plot for change of body weight associated to mild low carbohydrate diet. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.
Figure S6. Forest plot for change of body weight according to bio impedance method. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.
Figure S7. Forest plot for change of body fat according to bio impedance method. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.
Figure S8. Forest plot for change of body weight according to dual-energy X-ray absorptiometry. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.
Figure S9. Forest plot for change of body fat according to dual-energy X-ray absorptiometry. LCD; low-carbohydrate diet, SD; standard deviation, SMD; standardized mean difference, CI; confidence interval. The line corresponds to each study's SD. The size of the boxes corresponds to each study's weight.

Reference

1. WHO | Obesity and overweight. World Health Organization; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/ (Accessed 20 Dec. 2015)
2. Gelber RP, Gaziano JM, Manson JE, Buring JE, Sesso HD. A prospective study of body mass index and the risk of developing hypertension in men. *Am J Hypertens* 2007; **20**: 370–377.
3. Shihab HM, Meoni LA, Chu AY *et al.* Body mass index and risk of incident hypertension over the life course: the Johns Hopkins Precursors Study. *Circulation* 2012; **126**: 2983–2989.
4. Hu FB, Manson JE, Stampfer MJ *et al.* Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001; **345**: 790–797.
5. Fukuda T, Hamaguchi M, Kojima T *et al.* The impact of non-alcoholic fatty liver disease on incident type 2 diabetes mellitus in non-overweight individuals. *Liver Int* 2016; **36**: 275–283.
6. Hashimoto Y, Tanaka M, Okada H *et al.* Metabolically healthy obesity and risk of incident CKD. *Clin J Am Soc Nephrol* 2015; **10**: 578–583.
7. Kramer H, Luke A, Bidani A, Cao G, Cooper R, McGee D. Obesity and prevalent and incident CKD: the Hypertension Detection and Follow-Up Program. *Am J Kidney Dis* 2005; **46**: 587–594.
8. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983; **67**: 968–977.
9. Kim KS, Owen WL, Williams D, Adams-Campbell LL. A comparison between BMI and Conicity index on predicting coronary heart disease: the Framingham Heart Study. *Ann Epidemiol* 2000; **10**: 424–431.
10. Liu S, Manson JE, Stampfer MJ *et al.* A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000; **90**: 1409–1415.
11. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PWF, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. *Diabetes Care* 2004; **27**: 538–546.
12. Nanri A, Mizoue T, Kurotani K *et al.* Low-carbohydrate diet and type 2 diabetes risk in Japanese men and women: the Japan Public Health Center-Based Prospective Study. *PLoS One* 2015; **10**: e0118377.
13. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab* 2003; **88**: 1617–1623.
14. Samaha FF, Iqbal N, Seshadri P *et al.* A low-carbohydrate as compared with a low-fat diet in severe obesity. *N Engl J Med* 2003; **348**: 2074–2081.
15. Yancy WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. *Ann Intern Med* 2004; **140**: 769–777.
16. Nordmann AJ, Nordmann A, Briel M *et al.* 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* 2006; **166**: 285–293.
17. Castañeda-González LM, Bacardí Gascón M, Jiménez CA. Effects of low carbohydrate diets on weight and glycemic control among type 2 diabetes individuals: a systemic review of RCT greater than 12 weeks. *Nutr Hosp* 2011; **26**: 1270–1276.
18. Bueno NB, de Melo ISV, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr* 2013; **110**: 1178–1187.
19. Hu T, Mills KT, Yao L *et al.* Effects of low-carbohydrate diets versus low-fat diets on metabolic risk factors: a meta-analysis of randomized controlled clinical trials. *Am J Epidemiol* 2012; **176**(Suppl 7): S44–S54.
20. Naude CE, Schoonees A, Senekal M, Young T, Garner P, Volmink J. Low carbohydrate versus isoenergetic balanced diets for reducing weight and cardiovascular risk: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e100652.
21. Bouchi R, Takeuchi T, Akihisa M *et al.* High visceral fat with low subcutaneous fat accumulation as a determinant of atherosclerosis in patients with type 2 diabetes. *Cardiovasc Diabetol* 2015; **14**: 136.
22. Sahakyan KR, Somers VK, Rodriguez-Escudero JP *et al.* Normal-weight central obesity: implications for total and cardiovascular mortality. *Ann Intern Med* 2015; **163**: 827–835.

23. Kohara K. Sarcopenic obesity in aging population: current status and future directions for research. *Endocrine* 2014; **45**: 15–25.
24. Chin SO, Rhee SY, Chon S *et al.* Sarcopenia is independently associated with cardiovascular disease in older Korean adults: the Korea National Health and Nutrition Examination Survey (KNHANES) from 2009. *PLoS One* 2013; **8**: e60119.
25. Batsis JA, Mackenzie TA, Barre LK, Lopez-Jimenez F, Bartels SJ. Sarcopenia, sarcopenic obesity and mortality in older adults: results from the National Health and Nutrition Examination Survey III. *Eur J Clin Nutr* 2014; **68**: 1001–1007.
26. Atkins JL, Whincup PH, Morris RW, Lennon LT, Papacosta O, Wannamethee SG. Sarcopenic obesity and risk of cardiovascular disease and mortality: a population-based cohort study of older men. *J Am Geriatr Soc* 2014; **62**: 253–260.
27. Oxman AD, Fretheim A, Schünemann HJ. Improving the use of research evidence in guideline development: 8. Synthesis and presentation of evidence. *Health Res Policy Syst* 2006; **4**: 20.
28. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097.
29. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* 2007; **28**: 105–114.
30. Higgins JPT, Thompson SG. Cochrane handbook for systematic reviews of interventions (version 5.1.0). p. Available: http://www.cochrane.org/training/cochr (Accessed 20 Dec. 2015)
31. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–1558.
32. Johnston BC, Kanters S, Bandayrel K *et al.* Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. *JAMA* 2014; **312**: 923–933.
33. Ebbeling CB, Swain JF, Feldman HA *et al.* Effects of dietary composition on energy expenditure during weight-loss maintenance. *JAMA* 2012; **307**: 2627–2634.
34. Brehm BJ. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. *J Clin Endocrinol Metab* 2003; **88**: 1617–1623.
35. Brinkworth GD, Noakes M, Keogh JB, Luscombe ND, Wittert GA, Clifton PM. Long-term effects of a high-protein, low-carbohydrate diet on weight control and cardiovascular risk markers in obese hyperinsulinemic subjects. *Int J Obes Relat Metab Disord* 2004; **28**: 661–670.
36. McAuley KA, Hopkins CM, Smith KJ *et al.* Comparison of high-fat and high-protein diets with a high-carbohydrate diet in insulin-resistant obese women. *Diabetologia* 2004; **48**: 8–16.
37. Ebbeling CB, Leidig MM, Feldman HA, Lovesky MM, Ludwig DS. Effects of a low-glycemic load vs low-fat diet in obese young adults: a randomized trial. *JAMA* 2007; **297**: 2092–2102.
38. Wal JS, McBurney MI, Moellering N, Marth J, Dhurandhar NV. Moderate-carbohydrate low-fat versus low-carbohydrate high-fat meal replacements for weight loss. *Int J Food Sci Nutr* 2007; **58**: 321–329.
39. Keogh JB, Brinkworth GD, Noakes M, Belobrajdic DP, Buckley JD, Clifton PM. Effects of weight loss from a very-low-carbohydrate diet on endothelial function and markers of cardiovascular disease risk in subjects with abdominal obesity. *Am J Clin Nutr* 2008; **87**: 567–576.
40. Lasker DA, Evans EM, Layman DK. Moderate carbohydrate, moderate protein weight loss diet reduces cardiovascular disease risk compared to high carbohydrate, low protein diet in obese adults: a randomized clinical trial. *Nutr Metab (Lond)* 2008; **5**: 30.
41. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. 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* 2009; **90**: 23–32.
42. Foster GD, Wyatt HR, Hill JO *et al.* Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med* 2010; **153**: 147–157.
43. Ballesteros-Pomar MD, Calleja-Fernández AR, Vidal-Casariego A, Urioste-Fondo AM, Cano-Rodríguez I. Effectiveness of energy-restricted diets with different protein:carbohydrate ratios: the relationship to insulin sensitivity. *Public Health Nutr* 2010; **13**: 2119–2126.
44. Summer SS, Brehm BJ, Benoit SC, D'Alessio DA. Adiponectin changes in relation to the macronutrient composition of a weight-loss diet. *Obesity (Silver Spring)* 2011; **19**: 2198–2204.
45. Rodríguez-Hernández H, Cervantes-Huerta M, Rodríguez-Moran M, Guerrero-Romero F. Decrease of aminotransferase levels in obese women is related to body weight reduction, irrespective of type of diet. *Ann Hepatol* 2011; **10**: 486–492.
46. Krebs JD, Elley CR, Parry-Strong A *et al.* The Diabetes Excess Weight Loss (DEWL) Trial: a randomised controlled trial of high-protein versus high-carbohydrate diets over 2 years in type 2 diabetes. *Diabetologia* 2012; **55**: 905–914.
47. Bazzano LA, Hu T, Reynolds K *et al.* Effects of low-carbohydrate and low-fat diets. *Ann Intern Med* 2014; **161**: 309–318.
48. Trichopoulou A, Psaltopoulou T, Orfanos P, Hsieh CC, Trichopoulos D. Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *Eur J Clin Nutr* 2007; **61**: 575–581.
49. Lagiou P, Sandin S, Weiderpass E *et al.* Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *J Intern Med* 2007; **261**: 366–374.
50. Nakamura Y, Okuda N, Okamura T *et al.* Low-carbohydrate diets and cardiovascular and total mortality in Japanese: a 29-year follow-up of NIPPON DATA80. *Br J Nutr* 2014; **112**: 916–924.
51. Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. *Am J Physiol* 1997; **273**: E122–E129.
52. Coker RH, Miller S, Schutzler S, Deutz N, Wolfe RR. Whey protein and essential amino acids promote the reduction of adipose tissue and increased muscle protein synthesis during caloric restriction-induced weight loss in elderly, obese individuals. *Nutr J* 2012; **11**: 105.
53. Bopp MJ, Houston DK, Lenchik L, Easter L, Kritchevsky SB, Nicklas BJ. Lean mass loss is associated with low protein intake during dietary-induced weight loss in postmenopausal women. *J Am Diet Assoc* 2008; **108**: 1216–1220.
54. Houston DK, Nicklas BJ, Ding J *et al.* Dietary protein intake is associated with lean mass change in older, community-dwelling adults: the Health, Aging, and Body Composition (Health ABC) Study. *Am J Clin Nutr* 2008; **87**: 150–155.
55. Minderico CS, Silva AM, Keller K *et al.* Usefulness of different techniques for measuring body composition changes during weight loss in overweight and obese women. *Br J Nutr* 2008; **99**: 432–441.
56. Meinhold CL, Dodd KW, Jiao L *et al.* Available carbohydrates, glycemic load, and pancreatic cancer: is there a link? *Am J Epidemiol* 2010; **171**: 1174–1182.
57. Fung TT, van Dam RM, Hankinson SE *et al.* Low-carbohydrate diets and all-cause and cause-specific mortality: two cohort studies. *Ann Intern Med* 2010; **153**: 289–298.
58. Pietiläinen KH, Kaye S, Karmi A *et al.* Agreement of bioelectrical impedance with dual-energy X-ray absorptiometry and MRI to estimate changes in body fat, skeletal muscle and visceral fat during a 12-month weight loss intervention. *Br J Nutr* 2013; **109**: 1910–1916.
59. Heymsfield SB, Gonzalez MC, Shen W *et al.* Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. *Obes Rev* 2014; **15**: 310–321.

