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Lead Article

Effects of macronutrient intake in obesity: a meta-analysis of low-carbohydrate and low-fat diets on markers of the metabolic syndrome

Anouk E.M. Willems ⓘ, Martina Sura–de Jong, André P. van Beek, Esther Nederhof, and Gertjan van Dijk

The metabolic syndrome (MetS) comprises cardiometabolic risk factors frequently found in individuals with obesity. Guidelines to prevent or reverse MetS suggest limiting fat intake, however, lowering carbohydrate intake has gained attention too. The aim for this review was to determine to what extent either weight loss, reduction in caloric intake, or changes in macronutrient intake contribute to improvement in markers of MetS in persons with obesity without cardiometabolic disease. A meta-analysis was performed across a spectrum of studies applying low-carbohydrate (LC) and low-fat (LF) diets. PubMed searches yielded 17 articles describing 12 separate intervention studies assessing changes in MetS markers of persons with obesity assigned to LC (<40% energy from carbohydrates) or LF (<30% energy from fat) diets. Both diets could lead to weight loss and improve markers of MetS. Meta-regression revealed that weight loss most efficaciously reduced fasting glucose levels independent of macronutrient intake at the end of the study. Actual carbohydrate intake and actual fat intake at the end of the study, but not the percent changes in intake of these macronutrients, improved diastolic blood pressure and circulating triglyceride levels, without an effect of weight loss. The homeostatic model assessment of insulin resistance improved with both diets, whereas high-density lipoprotein cholesterol only improved in the LC diet, both irrespective of aforementioned factors. Remarkably, changes in caloric intake did not play a primary role in altering MetS markers. Taken together, these data suggest that, beyond the general effects of the LC and LF diet categories to improve MetS markers, there are also specific roles for weight loss, LC and HF intake, but not reduced caloric intake, that improve markers of MetS irrespective of diet categorization. On the basis of the results from this meta-analysis, guidelines to prevent MetS may need to be re-evaluated.

INTRODUCTION

The metabolic syndrome (MetS) is a cluster of cardio-metabolic risk factors found in individuals with obesity and that frequently escalate in cardiometabolic diseases like diabetes and cardiovascular disease.[1–5] MetS is defined by the International Diabetes Federation[4] as "a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure." There are additional metabolic and endocrine criteria that may aggravate the condition of MetS; insulin resistance is one of the most important causative factors.[4]

To prevent progression toward cardiovascular disease and/or diabetes, individuals with MetS are recommended to lose weight and limit caloric intake.[4] However, dietary guidelines are confusing because reductions of saturated fat intake[6,7] and carbohydrate intake[8] have been suggested. Several thorough reviews have been published on the short- and long-term health consequences of low-carbohydrate (LC) and low-fat (LF) diets. In reviews in which studies included patients with diabetes, results were positive for both diets.[9–14] However, differential dietary benefits on weight loss and markers of MetS in persons with obesity without a cardiometabolic diagnosis (eg, type 2 diabetes, myocardial infarction, stroke) are less consistent and, therefore, it is difficult to determine whether an LC diet can prevent or reverse cardiometabolic derangements in MetS as well as an LF diet can.[15] For that reason, Mansoor et al[16] performed a meta-analysis on the long-term effects of LC and LF diets in individuals with obesity without cardiometabolic disease and concluded that they experienced greater weight loss and lower plasma triglyceride (or triacylgyceride [TAG]) levels on an LC diet than on an LF diet, with variable effects on plasma levels of high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol. Although their meta-analysis was very insightful, Mansoor et al[16] stated that dietary intake diverted from the prescribed diet and there was a wide range of macronutrient intakes. These findings raise the question of whether these results can be attributed to type of diet or if actual dietary macronutrient composition is a better explanation for changes in body weight and markers of MetS. Another question is how much of the changes in markers of MetS were due to weight loss or change in caloric intake.

To answer these questions, the variations in the Mansoor et al[16] study characteristics were used, and a meta-analysis on the existing LC and LF studies that provided the actual macronutrient compositions as well as caloric intake was performed, and their efficacy to induce weight loss and changes in markers of MetS in persons with obesity without cardiometabolic disease

was assessed. Then meta-regression analyses were performed to assess whether the actual macronutrient composition, caloric intake, and/or weight loss could explain changes in markers of MetS.

METHODS

Search strategy

A search of PubMed was conducted in December 2018 and updated in April 2020. The search was limited to articles published in English about studies performed in humans, without restriction of publication date, using the following search terms: "low carbohydrate diet" insulin cardiovascular human; Atkins insulin cardiovascular human; "low carbohydrate" diet insulin cardiovascular human; "low fat diet" insulin cardiovascular human; and "low fat" diet insulin cardiovascular human. Relevant articles emerging from the search were studied and reference lists were screened for articles that met the inclusion criteria.

Inclusion and exclusion criteria

Studies had to meet the following criteria to be included: (1) the design of the study was a randomized intervention; (2) study designs according to national or international guidelines and practices were used; (3) study participants were adults, defined as at least 18 years old; (4) average body mass index (BMI) of the included participants was greater than $30 \, kg/m^2$; (5) study participants had neither diabetes nor cardiovascular disease; (6) the study investigated both an LC and an LF dietary intervention; (7) minimum duration of the dietary intervention was 6 months, including follow-up; (8) study reported body weight loss and at least 2 markers of MetS at 6 and/or 12 months; (9) studies reported data on caloric intake and carbohydrate and fat intake at 6 and/or 12 months; and (10) studies were excluded when pharmaceutical intervention or specific testing of supplements was noted. An LC diet was defined as prescribed intake of carbohydrates less than 40% (200 g carbohydrates per 2000 kcal) of the total energy intake to include a range of LC diets, and an LF diet was defined as prescribed fat intake less than 30% of total energy intake (67 g fat per 2000 kcal). The criteria for the diagnosis of MetS, according to the International Diabetes Federation, are central obesity (assessed by waist circumference > 94 cm for European men and >80 cm European women; circumference may vary with different ethnicities) and at least 2 of the following 4 factors:(1) elevated TAG level (> 150 mg/dL or > 1.7 mmol/L); (2) reduced HDL cholesterol level (men: < 40 mg/dL or <1.03 mmol/L; women: <50 mg/dL

or <1.29 mmol/L); (3) increased blood pressure (systolic blood pressure [SBP] >130 mmHg or diastolic blood pressure [DBP] >85 mmHg), and (4) increased fasting plasma glucose level (>100 mg/dL or >5.6 mmol/L).[4] Energy-restricted and ad libitum diets were included. Several popular weight loss diets also could be included in this review if they met the aforementioned criteria for macronutrient composition. For example, in the Atkins diet, carbohydrate intake is reduced to <20 g/d for the first 8 weeks, after which carbohydrate intake is gradually increased until a balance between carbohydrate intake and weight maintenance is found.[17] A Weight Watchers diet is a low-calorie, LF diet; and the Ornish diet is an LF diet (fat intake $<10\%$).[18,19]

Studies were initially screened on the basis of title and abstract content. Relevant studies were assessed in full text and included if they fulfilled the inclusion criteria. For the articles that passed full-text screening, data were extracted for one LC diet and one LF diet per study. One investigator performed the searches and the screening and extracted the data. Another investigator checked whether the selected articles fulfilled criteria and if the data were extracted correctly.

Data extraction

From the included articles, information about study design was extracted, including participant characteristics, sex, age, BMI, number of participants per intervention, duration and location of the intervention, and dietary intake assessment. For each dietary intervention, changes from baseline were extracted for body weight, SBP and DBP, and plasma levels of TAGs, HDL cholesterol, and fasting glucose for all time points exceeding 6 months. Homeostatic model assessment of insulin resistance (HOMA-IR) values were calculated for all studies that reported fasting glucose and fasting insulin values using the HOMA calculator, version 2. All values were converted to SI units, except HOMA-IR, which is an arbitrary unit. Where results are presented graphically, data were extracted as precisely as possible. When available, only data from participants who completed the study were extracted; otherwise, data from the intention-to-treat principle were extracted.

Food intake data were extracted as energy percentage (en%) for carbohydrate, protein, fat, and saturated fat (SFA) intakes, as kilocalories for caloric intake, and as grams per day for fiber intake. Data were extracted at baseline and at 6 and 12 months, as actual intake and as change from baseline intake. This allowed us to analyze the change of, as well as the final macronutrient intake of, a given participant. No requests for additional data were made of authors of studies included in this review.

Quality assessment

Methodological quality was evaluated using the Cochrane Risk of bias assessment.[20] The following bias categories were assessed: (1) selection bias (random sequence generation); (2) allocation concealment; (3) performance bias (blinding of the outcome assessments); (4) attrition bias (incomplete outcome data); and (5) reporting bias (selective outcome reporting). The blinding of participants and personnel was not assessed, because blinding is not possible in these dietary interventions. Publication bias was evaluated using funnel plots and the Egger regression test for body weight loss in both diets after 6 and 12 months.[21]

Statistical analysis

Mean difference from baseline was computed for every marker for each diet. Meta-analysis was performed for all markers. Summary weighted mean difference from baseline and 95%CIs were calculated using the random effects model, unless variance between studies was less than zero, in which case the fixed-effects model was used. Meta-regression analyses were conducted with body weight loss and change in caloric intake as moderators. The effect of these moderators was investigated on all markers of MetS, separately for each diet, after both 6 and 12 months. Meta-regression analyses, irrespective of diet type, also were conducted on the relation between body weight change and changes in caloric intake, changes in en% of macronutrient and SFA intakes, and changes (grams per day) of fiber intake; and between body weight change and actual caloric intake, actual en% of macronutrient and SFA intakes, and actual fiber intake (grams per day) after 6 and 12 months. Significance for these meta-regression analyses was detected using the false-discovery rate for multiple comparisons as described by Benjamini and Hochberg.[22] The false-discovery rate was set at 5%. The meta-analysis and meta-regression analysis were conducted using the Meta-Essentials tool developed by Suurmond et al.[23]

Linear stepwise meta-regression modeling (stepwise criteria: probability of F: entry <0.05, removal >0.10) was used to explore which independent variables best predicted changes in markers of MetS (all corrected for weight of the study). For analysis of actual intakes, the independent variables were body weight change, change of caloric intake, diet type (categorical variable, LC [defined as 0] vs LF [defined as 1]), and one of the following combinations, measured as en%: actual carbohydrate intake and actual fat intake; actual carbohydrate intake and actual protein intake; and actual fat intake and actual protein intake. For analysis of changes
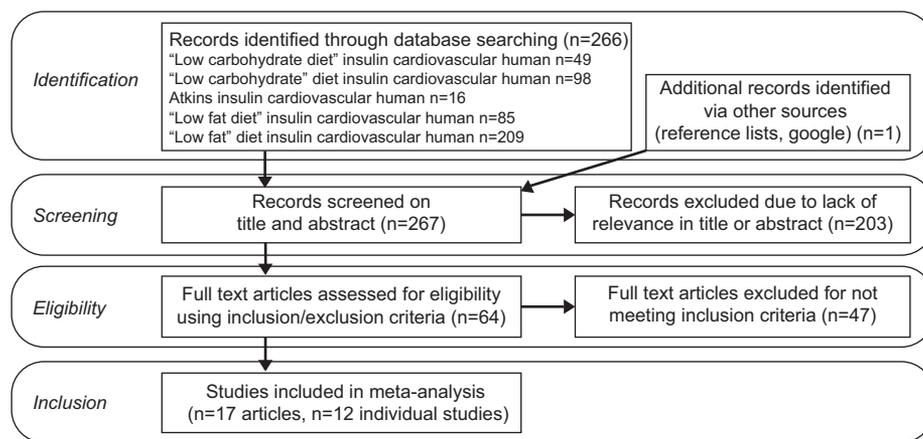
Figure 1 **Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram of study selection process.**

in intake from baseline, the independent variables were body weight change, change of caloric intake, and one of the following combinations, measured as en%: change from baseline in carbohydrate intake and change from baseline in fat intake; change from baseline in carbohydrate intake and change from baseline in protein intake; and change from baseline in fat intake and change from baseline in protein intake.

When carbohydrate was significantly related to one of the outcomes, a post hoc regression analysis was performed with fiber intake (grams per day) and the ratio of fiber intake (grams per day) to total carbohydrate intake (grams per day) as independent variables to determine whether one of these outcomes was related to the change in metabolic marker. When fat was significantly related to one of the outcomes, a post hoc regression analysis was performed with SFA intake (en%) and the ratio of SFA intake (en%) to total fat intake (en%) as independent variables to determine whether one of these outcomes was related to the change in metabolic marker. These post hoc analyses were performed for the absolute intakes and the changes in intakes. A false-discovery rate of 5% was used for detection of statistical significance. Linear regression modeling was performed in SPSS, version 25.

RESULTS

Studies

On the basis of the aforementioned criteria, 17 articles were included for the analyses, out of a search result of 267 articles (Figure 1). These articles included five follow-up studies that reported on already included cohorts, leaving a total of 12 separate studies. These studies used LC and Atkins diets and compared them with LF, Ornish, and Weight Watchers diets. The duration of the studies varied between 6 and 24 months.

Because only one study had data at 18 months and one had data at 24 months, these time points were not taken into consideration for the meta-analysis; only the 6- and 12-month time points were used. Seven studies used food records from multiple days, four studies used 24-hour dietary recalls, and one study used a food frequency questionnaire. Seven of these studies applied an energy-reduced regimen rather than an ad libitum regimen. A summary of the experimental details of the studies is provided in Table 1[18,19,24–38] and a summary of the diets used is listed in Table 2.[18,19,24–38] Table 3[18,19,24–38] lists the changes in cardiometabolic and endocrine markers of participants compared with their baseline levels. In particular, reported macronutrient intake varied markedly between studies (Table 2). Despite the LC diet being prescribed as < 40 en% from carbohydrates, actual carbohydrate intakes ranged from 8 to 45 at 6 months and from 9 to 43 en% at 12 months. Similarly, despite the LF diet being described as < 30 en% fat intake, actual fat intakes ranged from 24 to 36 en% at 6 months and from 24 to 31 en% at 12 months.

Risk of bias of included studies

All studies had a low risk of bias. One bias was unclear, but it is not expected that this bias influenced the outcome of the interventions (Table 4).

Risk of publication bias

No evidence for publication bias was found for body weight change for either diet at 6 or 12 months (Figure S1 in the Supporting Information online).

Table 1 **Study and participant characteristics of each study**

Reference	Participants	Age, mean (SD) (years), by diet type	BMI, mean (SD) (kg/m²), by diet type	Duration[a] (mo)	Location	Food intake assessment	Type of data extracted
Bazzano et al (2014)[31] Hu et al (2015)[32]	OB	LC: 45.8 (9.9) LF: 47.8 (10.4)	LC: 35.2 (3.8) LF: 35.6 (4.5)	12	United States	2-d, 24-h dietary recalls, (1 weekday and 1 weekend day)	Imputed missing data with Markov Chain Monte Carlo
Brehm et al (2003)[33]	OB	LC: 44.2 (6.9) LF: 43.1 (8.6)	LC: 33.2 (1.8) LF: 34.0 (1.8)	6	United States	Weekly food records	Completers
Dansinger et al (2005)[34]	OB, >1MF	LC: 47 (12) LF: 49 (12)	LC: 35 (3.5) LF: 35 (3.9)	12	United States	3-d food records	Completers
Ebbeling et al (2007)[35]	OB	LC: 28.2 (3.8) LF: 26.9 (4.2)	>30	18	United States	3-d, 24-h dietary recalls (2 weekdays and 1 weekend day)	Intention to treat
Frisch et al (2009)[36]	OB	LC: 47 (10.3) LF: 47 (10.8)	LC: 33.5 (3.9) LF: 33.8 (4.8)	12	Germany	3-Day food records	Intention to treat
Gardner et al (2007)[19]	OB	LC: 42 (5) LF: 42 (6)	LC: 32 (4) LF: 32 (3)	12	United States	3-d, 24-h dietary recalls (2 weekdays and 1 weekend day)	Completers
Haufe et al (2011)[37]	OB	LC: 43.2 (8.6) LF: 45.1 (9)	LC: 33.4 (3.9) LF: 33.0 (3.4)	6	Germany	7-d food records	Completers
McAuley et al (2005)[38] McAuley et al (2006)[24]	OB	LC: 45 (7.4) LF: 45 (7.5)	LC: 36.0 (3.9) LF: 36.6 (5.6)	12	New Zealand	3-d food records	Intention to treat
Sacks et al (2009)[25]	OB	LC: 51 (9) LF: 51 (9)	LC: 33 (4) LF: 33 (4)	24	United States	5-d food record at baseline and 24-h recall on 3 nonconsecutive days at 6 mo	Intention to treat
Tay et al (2008)[26] Brinkworth et al (2009)[27] Wycherly et al (2010)[28]	OB, >1MF	LC: 50.3 (8.4) LF: 51.0 (7.5)	LC: 33.9 (4.3) LF: 33.5 (4.1)	12	Australia	3-d food record (2 weekdays and 1 weekend day)	Intention to treat
Thomson et al (2010)[29]	OB, C	All: 56.2 (9.4)	All: 31.8 (4.3)	6	United States	Arizona Food Frequency Questionnaire	Intention to treat
Truby et al (2006)[30] Morgan et al (2009)[18]	OB	LC: 40.9 (9.7) LF: 39.9 (10.9)	LC: 31.9 (2.2) LF: 31.2 (2.7)	6	England	7-d food record	Intention to treat

[a]Duration of the total study including follow-up.
Abbreviations: >1MF, participants with >1 metabolic syndrome risk factor; BMI, body mass index; C, cancer survivor; LC, low cholesterol; LF, low fat; OB, participants with obesity.

Table 2 **Dietary characteristics of each study at baseline and after 6 and 12 months**

Reference	Diet	Energy intake	No.	Time (mo)	Energy intake (kcal)	Carbohydrate intake (en%)	Fat intake (en%)	Protein intake (en%)	Saturated fatty acids (en%)	Fiber intake (g)
Bazzano et al (2014)[31]	LC	ad lib	70	BL	1998 (740)	48.1 (8.8)	32.5 (7.2)	17.3 (5.0)	10.5 (3.4)	18.5 (8.7)
Hu et al (2015)[32]			54	6	1324 (537)	27.5 (12.1)	43.4 (11.8)	26.3 (5.6)	13.4 (4.5)	15.1 (7.5)
			54	12	1448 (610)	34 (13.9)	40.7 (10.6)	23.6 (7.4)	13.4 (4.8)	15.1 (8.7)
	LF	ad lib	69	BL	2034 (702)	46 (7.8)	34.7 (6.6)	17.6 (5.2)	11.6 (2.9)	16.7 (6.6)
			50	6	1481 (483)	52.4 (8.9)	27.9 (7.3)	18.3 (5.0)	8.4 (2.9)	16.4 (8.1)
			49	12	1527 (522)	54 (9.6)	29.8 (8.8)	18.6 (5.8)	9.0 (3.2)	15.6 (7.7)
Brehm et al (2003)[33]	LC	ad lib	22	BL	1608 (577)	47	37	16	12.4	12.03
			22	6	1302	30	46	23	17.4	8.4
	LF	ER	20	BL	1707 (465)	47	38	15	12.3	12.48
			20	6	1247	53	29	18	11.1	12.35
Dansinger et al (2005)[34]	LC	ad lib	39	BL	1898	51.6	36.2	18.5	12.3	16.0
			15	6	1846	42.1	38.3	18.2	12.4	13.0
			17	12	1886	41.3	37.6	18.7	13.0	15.0
	LF	ad lib	39	BL	1947	49.7	34.1	18.3	11.8	14.0
			15	6	1711	56.8	28.0	17.7	9.7	14.5
			17	12	1819	49.1	31.0	17.2	10.1	15.0
Ebbeling et al (2007)[35 a]	LC	ad lib	36	BL	2050	48	34	18	11.4	16.6
			32	6	1630	39	39	22	11.3	21.4
			29	12	1680	41	38	21	12.6	18.6
	LF	ad lib	37	BL	2050	46	35	19	12.5	15.2
			34	6	1580	55	24	21	8.0	17.9
			26	12	1550	54.5	24	21.5	7.8	10.9
Frisch et al (2009)[36]	LC	ER	100	BL	2140 (696)	44.8 (8.6)	35.2 (8.1)	16.8 (3.6)		
			100	6	1742 (624)	40.9 (10.1)	36.5 (9.5)	19.3 (4.7)		
			100	12	1866 (710)	43.5 (9.9)	34.2(8.7)	18.9 (4.4)		
	LF	ER	100	BL	2192 (668)	47.1 (7.9)	33.7 (6.9)	16.0 (3.9)		
			100	6	1783 (597)	49.5 (7.6)	29.7 (6.5)	17.7 (4.0)		
			100	12	1854 (624)	50.1 (8.2)	30.2 (7.0)	16.7 (3.1)		
Gardner et al (2007)[19]	LC	ad lib	77	BL	1888 (512)	45.6 (10.5)	36.2 (7.8)	16.6 (4.1)	12.6 (5.3)	17.4 (6.6)
			71	6	1538 (401)	29.5 (14.5)	47 (11.9)	22.4 (6.3)	16.4 (6.5)	14.0 (6.3)
			68	12	1599 (494)	34.5 (14.4)	44.3 (12.5)	20.6 (5.3)	15.3 (7.5)	15.2 (6.6)
	LF	ad lib	76	BL	1850 (541)	47.9 (8.6)	35.1 (7)	16.3 (3.1)	12.1 (5.0)	16.6 (6.6)
			67	6	1553 (530)	53.4 (13.4)	28.3 (10.7)	18.1 (4.8)	9.4 (5.9)	19.3 (11.1)
			56	12	1505 (437)	52.4 (12.3)	29.8 (10.5)	18.3 (4.0)	10.1 (7.5)	19.3 (9.4)
Haufe et al (2011)[37 a]	LC	ER	80	BL	2180	45.1	34.3	20.6[b]	14.0	
			52	6	1580	29.8	43.4	26.7[b]	11.1	
	LF	ER	83	BL	2190	44.9	38.2	16.9[b]	14.4	
			50	6	1750	51.5	27.7	20.8[b]	5.9	
McAuley et al (2005)[38]	LC	ad lib	31	BL	2006 (448)	44 (6)	34 (6)	18 (4)	14 (3)	10 (3)
McAuley et al (2006)[24]			31	6	1623 (434)	26 (11)	47 (8)	24 (6)	19 (4)	9 (3)
			22	12	1781 (473)	33 (11)	41 (8)	21 (6)	16 (4)	18 (6)
	LF	ad lib	32	BL	1812 (406)	45 (7)	31 (6)	18 (3)	12 (3)	11 (3)
			32	6	1460 (294)	45 (7)	28 (7)	21 (3)	10 (4)	13 (3)
			21	12	1474 (301)	45 (9)	29 (9)	22 (4)	11 (3)	18 (6)
Sacks et al (2009)[25]	LC	ER	201	BL	1979 (599)	44 (7)	38 (6)	18 (3)	12 (2)	
				6	1624 (484)	43 (6.7)	34.3 (7.8)	22.6 (4.4)	9.0 (2.6)	
	LF	ER	204	BL	2015 (505)	44 (8)	38 (6)	18 (4)	12 (3)	
				6	1636 (484)	57.5 (11.1)	26.2 (8)	17.6 (3.4)	7.5 (3.2)	
Tay et al (2008)[26]	LC	ER	33	6	1603 (1046)	7.6 (2.9)	55.9 (3.4)	33.3 (0.5)	20.4 (0.5)	
Brinkworth et al (2009)[27]			33	12	1643 (213)	8.9 (4.6)	54.9 (4.6)	32.3 (0.4)	20.4 (0.5)	
Wycherly et al (2010)[28]	LF	ER	36	6	1529 (1044)	44.9 (3.6)	26.8 (4.2)	22.9 (0.3)	6.1 (0.2)	
			36	12	1624 (300)	46.4 (3.6)	26.4 (4.2)	21.8 (0.4)	6.2 (0.2)	
Thomson et al (2010)[29]	LC	ER	19	BL	2043 (1036)	55.1 (11.3)	25.3 (15.5)	16.8 (6.4)		
			13	6	1523 (705)	45.4 (21.8)	33.6 (14.3)	22.2 (10.7)		
	LF	ER	21	BL	1826 (462)	57.6 (33.5)	32.2 (22.1)	18.6 (11.2)		
			19	6	1517 (678)	60.5 (25.0)	24.9 (17.4)	17.8 (9.1)		
Truby et al (2006)[30]	LC	ad lib	44	BL	2281 (641)	40	38	16		
Morgan et al (2009)[18]			8	6	1630 (364)	18	51	26		
	LF	ER	53	BL	2318 (743)	43	37	16		
			16	6	1650 (499)	40	36	20		

Data are reported as mean (SD) unless otherwise indicated.
[a] Estimation of values.
[b] When protein intake was not specified it was calculated by deducting carbohydrate and fat intake from 100%. Alcohol intake was not specified in this study.
Abbreviations: ad lib, ad libitum energy intake; BL, baseline; en%, percentage of energy; ER, restricted energy intake; LC, low-carbohydrate diet; LF, low-fat diet.

Table 3 **Study outcomes after 6 and 12 months**

Reference	Diet	Time (mo)	No.	Body weight (kg)	SBP (mmHg)	DBP (mmHg)	TAG (mmol/L)	HDL (mmol/L)	Glucose (mmol/L)	HOMA-IR
Bazzano et al (2014)[31]	LC	6	75	−5.6 (4.0)	−2.9 (7.1)	−1.7 (4.9)	−0.22 (0.40)	0.10 (0.22)	0.03 (0.71)	−0.39 (0.18)
Hu et al (2015)[32]		12	75	−5.3 (6.6)	−0.2 (10.6)	−0.5 (7.5)	−0.23 (0.49)	0.24 (0.31)	0.02 (0.57)	−0.25 (0.22)
	LF	6	73	−2.3 (3.5)	−2.2 (7.0)	−0.5 (5.2)	−0.01 (0.39)	0.0 (0.22)	−0.10 (0.44)	−0.39 (0.18)
		12	73	−1.8 (6.5)	−1.3 (10.0)	0.2 (7.4)	−0.07 (0.48)	0.06 (0.31)	−0.10 (0.52)	−0.45 (0.22)
Brehm et al (2003)[33]	LC	6	22	−8.5 (1.0)	−2.0 (4.3)	−5 (3.5)	−0.39 (2.29)	0.18 (0.10)	−0.50 (0.19)	−0.36 (0.12)
	LF	6	20	−3.9 (1.0)	−2.0 (3.5)	−1 (2.6)	0.02 (1.76)	0.11 (0.09)	0.20 (0.16)	−0.65 (0.15)
Dansinger et al (2005)[34]	LC	6	22	−5.8 (5.3)	−6.7 (12.0)	−7.3 (7.4)	−0.21 (0.60)	0.18 (0.19)	−0.78 (1.89)	−0.61 (0.83)
		12	21	−3.9 (6.0)	0.3 (17.0)	−2.6 (10.3)	−0.02 (1.32)	0.17 (0.23)	0.14 (2.33)	−0.30 (0.52)
	LF	6	21	−6.7 (8.0)	−1.2 (12.0)	−0.5 (8.6)	−0.35 (1.12)	−0.08 (0.25)	−0.53 (1.89)	−0.17 (1.35)
		12	20	−6.6 (9.3)	0.9 (11.0)	0.4 (6.6)	0.12 (0.60)	−0.03 (0.24)	−0.46 (2.39)	−0.81 (0.47)
Ebbeling et al (2007)[35]	LC	6	32	−4.5 (6.1)a	−5.1 (2.3)	−2.4 (1.7)	−21.2%	0.04 (0.04)	0.09 (0.07)	−0.36 (0.15)
		12	29	−2.9 (5.5)a						
	LF	6	34	−3.7 (5.9)a	−4.8 (2.3)	−2.0 (1.7)	−4.0%	−0.11 (0.03)	−0.02 (0.07)	−0.11 (0.03)
		12	26	−2.5 (5.2)a						
Frisch et al (2009)[36]	LC	6	100	−7.2 (5.4)	−6 (16.0)	−3 (8.0)	−0.18 (0.40)	−0.02 (0.20)	−0.26 (0.76)	
		12	100	−5.8 (6.1)	−5 (14.0)	−3 (9.0)	−0.10 (0.47)	−0.02 (0.21)	−0.25 (0.75)	
	LF	6	100	−6.2 (4.8)	−4 (15.0)	−3 (9.0)	−0.03 (0.55)	−0.09 (0.19)	−0.28 (0.59)	
		12	100	−4.3 (5.1)	−1 (15.0)	−2 (8.0)	−0.04 (0.50)	−0.03 (0.17)	−0.14 (0.46)	
Gardner et al (2007)[19]	LC	6	77	−5.8 (2.7)	−6.4 (9.5)	−3.3 (6.9)	−0.40 (0.72)	0.13 (0.25)	0.01 (0.42)	−0.36 (0.15)
		12	77	−4.7 (7.2)	−7.6 (11.0)	−4.4 (8.4)	−0.33 (0.67)	0.13 (0.24)	−0.10 (0.74)	−0.24 (0.14)
	LF	6	76	−2.4 (2.2)	−1.7 (7.0)	−1.0 (5.6)	−0.09 (0.61)	0.0 (0.24)	−0.03 (0.41)	−0.02 (0.13)
		12	76	−2.6 (5.3)	−1.9 (7.7)	−0.7 (6.0)	−0.17 (0.52)	0.0 (0.16)	−0.04 (0.44)	−0.03 (0.11)
Haufe et al (2011)[37]	LC	6	52	−7.5 (4.3)			−0.19 (0.43)	−0.09 (0.72)	−0.34 (0.52)	−0.61 (0.18)
	LF	6	50	−6.5 (4.9)			−0.14 (0.57)	−0.10 (0.49)	−0.29 (0.67)	−0.43 (0.11)
McAuley et al (2005)[38]	LC	6	28	−7.1 (14.8)	−4 (19.3)	−2 (12.4)	−0.71 (0.83)	0.9 (0.42)	−0.30 (0.83)	−0.54 (0.31)
McAuley et al (2006)[24]		12	24	−5.4 (15.4)	−4 (20.5)	−4 (14.1)	−0.47 (1.24)	0.12 (0.48)	−0.20 (0.92)	−0.41 (0.31)
	LF	6	30	−4.7 (20.6)	−2 (15.3)	1 (13.9)	−0.22 (0.89)	−0.04 (0.35)	−0.30 (0.71)	−0.48 (0.18)
		12	24	−4.4 (22.3)	−6 (17.0)	−3 (14.9)	−0.31 (0.97)	−0.02 (0.48)	−0.10 (0.78)	−0.58 (0.33)
Sacks et al (2009)[25]	LC	6	201	−5.8 (11.3)	−1.7 (19.2)	−1.8 (13.5)	−0.22 (1.38)	0.10 (0.53)	−0.07 (1.95)	
		12	201	−5.3 (14.2)						
	LF	6	201	−5.7 (11.4)	−1.2 (17.7)	−1.4 (24.8)	−0.16 (1.24)	−0.01 (0.51)	−0.17 (0.90)	
		12	201	−5.2 (14.3)						
Tay et al (2008)[26]	LC	6	45	−11.9 (6.3)	−12.3 (14.1)	−4.58 (9.78)	−0.64 (0.62)	0.25 (0.28)	−0.18 (0.40)	−0.40 (0.02)
Brinkworth et al (2009)[27]		12	26	−14.5 (1.7)	−13.8 (14.4)	−6.3 (9.2)	−0.58 (0.63)	0.30 (0.40)	−0.30 (0.06)	−0.08 (0.02)
Wycherly et al (2010)[28]	LF	6	43	−10.1 (5.7)	−10.8 (13.2)	−5.50 (8.6)	−0.35 (0.49)	0.08 (0.17)	−0.21 (0.40)	−0.08 (0.01)
		12	23	−11.5 (1.2)	−14.6 (12.0)	−7.9 (9.6)	−0.22 (0.66)	0.07 (0.36)	−0.30 (0.60)	−0.08 (0.02)
Thomson et al (2010)[29]	LC	6	21	−5.9 (4.1)	−0.8 (14.1)	1.6 (11.0)	−0.35 (0.41)	0.06 (0.21)	−0.06 (0.48)	−0.34 (0.27)
	LF	6	19	−6.3 (5.6)	−8.6 (16.3)	0.9 (6.9)	0.08 (0.76)	0.01 (0.21)	−0.07 (0.45)	−0.58 (0.33)
Truby et al (2006)[30]	LC	6	57	−6.0 (6.4)	−7.2 (11.6)	−4.9 (8.1)	−0.64 (0.77)	−0.08 (0.39)	−0.19 (0.50)	−0.36 (0.31)
Morgan et al (2009)[18]	LF	6	58	−6.5 (5.4)	−4.1 (11.7)	−4.4 (8.6)	−0.35 (0.90)	−0.18 (0.28)	−0.46 (0.60)	−0.20 (0.33)

Outcomes are depicted as mean (SD) change from baseline. When no absolute values were available, percentage change is shown, if available. Not all standard deviations could be calculated.

a Estimation of value.

Abbreviations: DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LC, low-carbohydrate diet; LF, low-fat diet; ND, no data available; SBP, systolic blood pressure; TAG, plasma triglyceride.

Table 4 **Risk of bias assessed using the Cochrane Risk of Bias tool**

Reference	Selection bias			Attrition bias	Reporting bias	Overall
	Randomization	Allocation	Blinding outcome assessment	Incomplete outcome data	Selective reporting	
Bazzano et al (2014)[31]	Low	Low	Low	Low	Low	Low
Hu et al (2015)[32]						
Brehm et al (2003)[33]	Low	Low	Low	Low	Low	Low
Dansinger et al (2005)[34]	Low	Low	Low	Low	Low	Low
Ebbeling et al (2007)[35]	Low	Low	Low	Low	Low	Low
Frisch et al (2009)[36]	Low	Low	Low	Low	Low	Low
Gardner et al (2007)[19]	Low	Low	Low	Low	Low	Low
Haufe et al (2011)[37] #	Low	Unclear	Low	Low	Low	Low
McAuley et al (2005)[38]	Low	Low	Low	Low	Low	Low
McAuley et al (2006)[24]						
Sacks et al (2009)[25]	Low	Low	Low	Low	Low	Low
Tay et al (2008)[26]	Low	Low	Low	Low	Low	Low
Brinkworth et al (2009)[27]						
Wycherly et al (2010)[28]						
Thomson et al (2010)[29]	Low	Low	Low	Low	Low	Low
Truby et al (2006)[30]	Low	Low	Low	Low	Low	Low
Morgan et al (2009)[18]						

Body weight, caloric and macronutrient intake, and markers of MetS per diet type

Data from 732 participants were available for LC diets after 6 months and from 553 participants after 12 months. For LF diets, data from 725 and 543 participants were available after 6 and 12 months, respectively. In all studies the mean BMI was >30, showing that, on average, the participants had obesity. Eleven studies reported baseline dietary intake, all 12 studies reported dietary intake after 6 months, and 7 of these 12 studies also reported dietary intake after 12 months. Baseline caloric and macronutrient intakes were equal in both diet types ([Figure 2]).

Both the LC and LF diet types significantly reduced caloric intake at 6 months (LC: $P < 0.001$; LF: $P < 0.001$) and 12 months (LC: $P < 0.01$; LF: $P < 0.001$). In addition, comparable significant reductions in body weight were found in either diet at 6 (LC: $P < 0.001$; LF: $P < 0.001$) and 12 months (LC: $P < 0.001$; LF: $P < 0.001$; [Table S1] in the Supporting Information online). LC diets, at 6 and 12 months, significantly increased en% fat intake ($P < 0.01$ and $P = 0.01$, respectively) and en% protein intake ($P < 0.001$ and $P < 0.01$, respectively), significantly reduced en% carbohydrate intake ($P < 0.001$ and $P < 0.01$, respectively), and significantly increased en% SFA intake ($P = 0.03$), but only after 12 months. There was no change in fiber intake at either 6 or 12 months.

LF diet types, at 6 and 12 months, significantly reduced en% fat intake ($P < 0.001$ and $P < 0.001$, respectively) and significantly increased en% carbohydrate intake after 6 months ($P = 0.04$); en% protein intake

was increased ($P < 0.01$ and $P = 0.02$, respectively), and en% SFA intake was significantly decreased ($P < 0.001$ and $P < 0.001$, respectively). Fiber intake was not changed after 6 or 12 months ([Figure 2]). Results of the meta-analysis of dietary effects on the various markers of MetS are listed in [Table S1] in the Supporting Information online.

Meta-regression per diet type revealed that changes in caloric intake were not correlated with any changes in markers of MetS in either diet type at 6 and 12 months. In the LC diet type, body weight loss was positively correlated with reductions in glucose levels ($P = 0.03$) at 6 months and with reductions in SBP ($P = 0.03$) and TAG ($P = 0.04$) at 12 months. In the LF diet type, body weight loss was positively correlated with reductions in SBP ($P = 0.01$), DBP ($P < 0.01$), TAG ($P < 0.01$), and glucose levels ($P = 0.04$) at 6 months, and with reductions in SBP ($P < 0.01$), DBP ($P < 0.01$), and glucose levels ($P = 0.02$) at 12 months ([Table S2] in the Supporting Information online).

Focus on actual macronutrient and caloric intake vs body weight loss irrespective of diet type

Instead of treating the LC and LF diets separately, the variation in caloric and macronutrient intakes could be viewed as a continuum. In a linear regression analysis across all studies irrespective of diet type, no correlation of change in body weight was found with change in caloric intake or actual caloric intake at 6 ([Figure 3A]) or 12 months. Actual carbohydrate intake had negative correlations with change in body weight (6 months: $B = 0.093$, $R^2 = 0.321$; 12 months: $B = 0.156$,
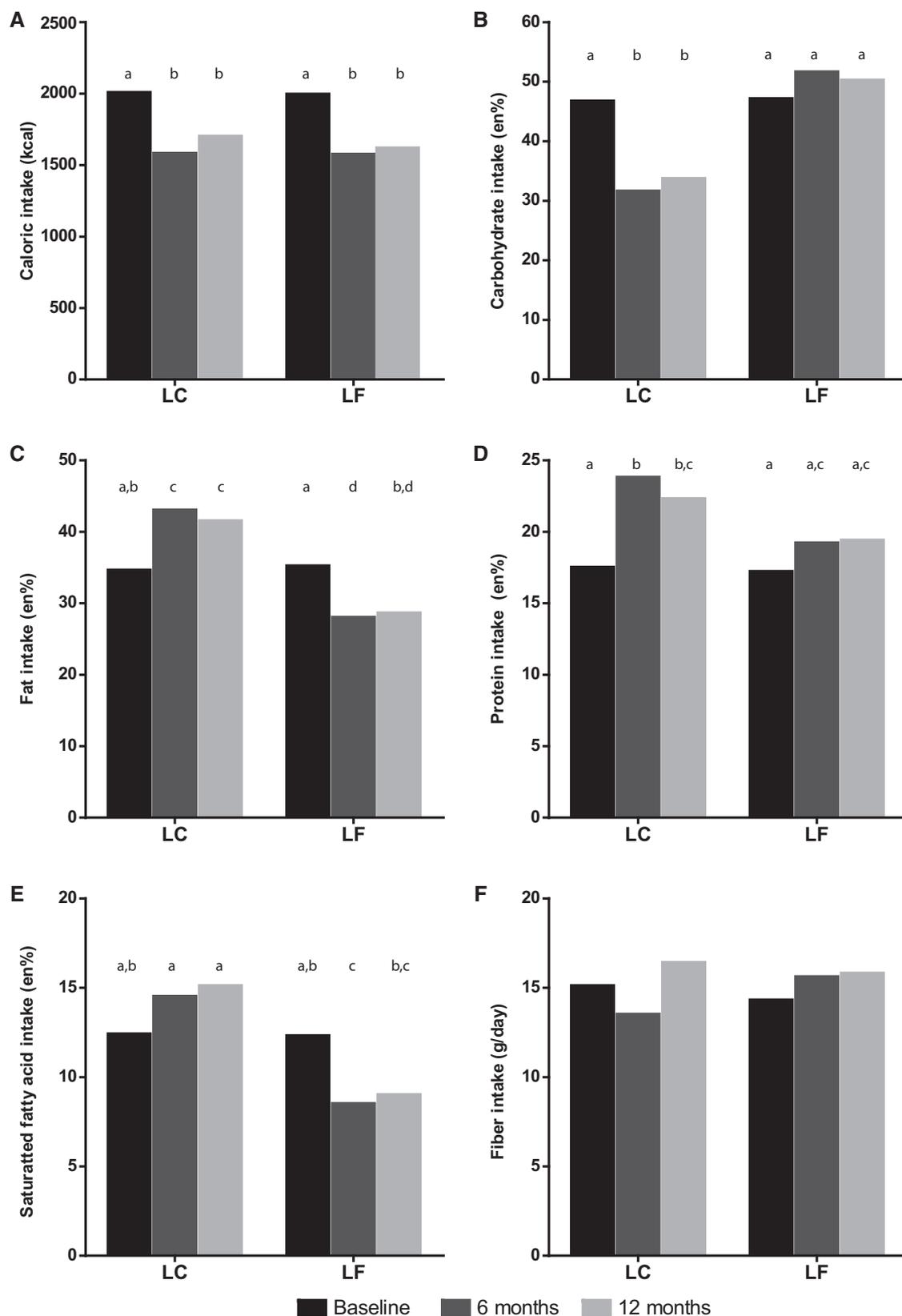
Figure 2 **Intake in the LC and LF groups at different time points.** (A) Caloric intake (kcal); (B) carbohydrate intake (en%); (C) fat intake (en%); (D) protein intake (en%); (E) saturated fatty acid intake (en%); and (F) fiber intake (grams per day). Different letters (a, b, c, and d) show significant differences among diets and time points. *Abbreviations*: en%, energy percentage; LC, low-carbohydrate diet; LF, low-fat diet.
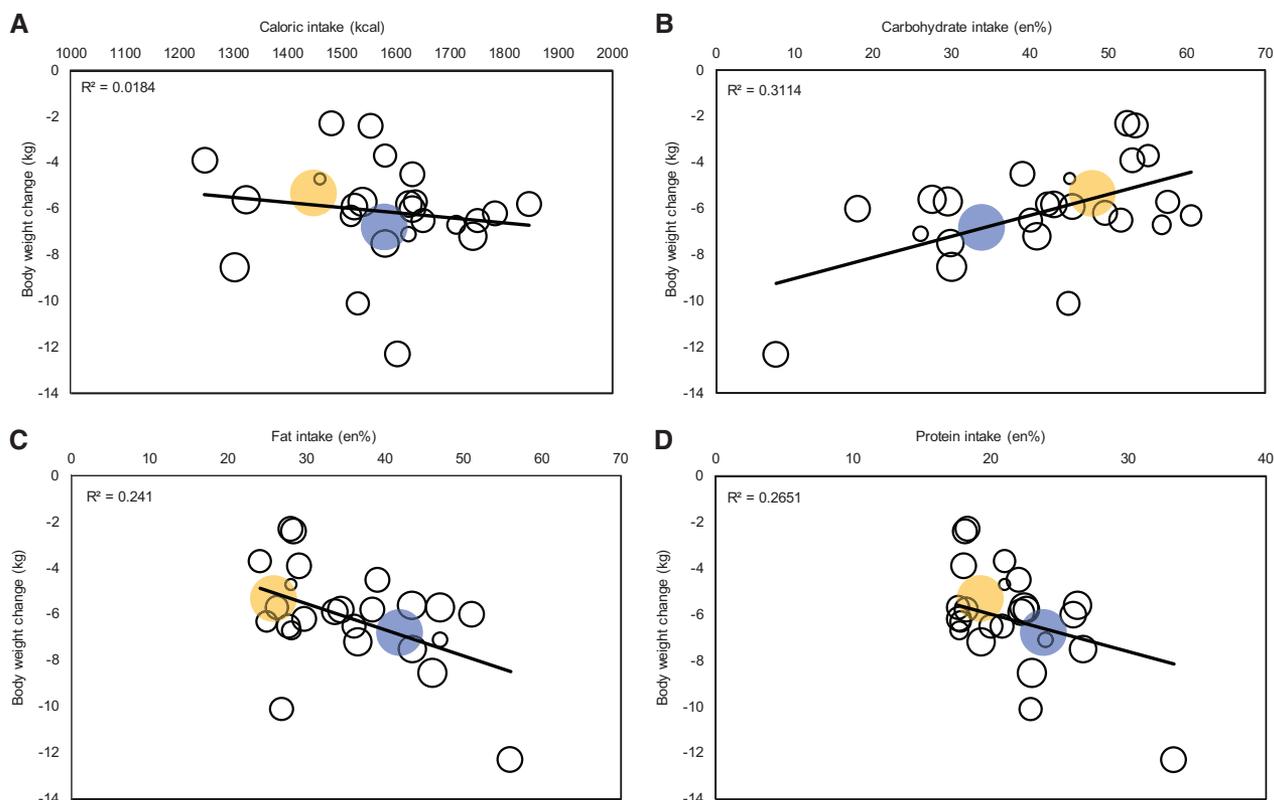
Figure 3 **Bubble plot of body weight change moderator analysis**. The size of the bubbles represents the precision of the effect size; larger bubbles indicate greater precision. Blue bubbles represent the meta-analysis outcome for body weight vs actual intake in the LC group. Yellow bubbles represent the meta-analysis outcome for body weight vs actual intake in the LF group. The regression line fitted to the raw data shows the slope of the relation between the body weight change and (A) caloric intake (kcal) after 6 months; (B) actual carbohydrate intake after 6 months (en**%**); (C) actual fat intake after 6 months (en**%**); and (D) actual protein intake after 6 months (en**%**). *Abbreviations:* en**%**, energy percentage; LC, low-carbohydrate diet; LF, low-fat diet.

$R^2 = 0.485$), with a 1 kg lowering of body weight related to a 10.8 en% decrease in carbohydrate intake ($P < 0.01$; Figure 3B) at 6 months and a 6.4 en% decrease at 12 months ($P < 0.01$). Actual fat intake had positive correlations with change in body weight (6 months: $B = -0.118$, $R^2 = 0.237$; 12 months: $B = -0.162$, $R^2 = 0.238$), with a 1 kg lowering of body weight related with an 8.5 en% increase in fat intake ($P < 0.01$; Figure 3C) at 6 months and a 6.2 en% increase at 12 months ($P < 0.01$). Actual protein intake also had positive correlations with change in body weight (6 months: $B = -0.345$, $R^2 = 0.368$; 12 months: $B = -0.441$, $R^2 = 0.390$), with a 2.9 en% increase in protein intake ($P < 0.01$; Figure 3D) at 6 months and a 2.3 en% increase at 12 months ($P < 0.001$) related with a 1 kg lowering of body weight. Similar to actual fat intake, actual SFA intake was also positively correlated with change in body weight (6 months: $B = -0.262$, $R^2 = 0.187$, $P = 0.02$; 12 months: $B = -0.33914$, $R^2 = 0.197$, $P < 0.01$). Actual fiber intake was not correlated with change in body weight. Neither percent changes in macronutrient and SFA intake from baseline nor the

absolute change in fiber intake were correlated with body weight loss at 6 and 12 months.

Meta-regression of markers of MetS across all studies irrespective of diet type

Meta-regression of markers of MetS was performed with available data from the 6 month time point, because the 12-month time point did not contain enough data. Actual fat intake ($B = -0.135$; $R^2 = 0.341$) and actual carbohydrate intake ($B = 0.093$; $R^2 = 0.316$), respectively, had negative and positive correlations with change in DBP, with every 1 mmHg lowering in DBP related to a 7.4% increase in fat intake ($P < 0.01$) and with 10.8% reduction in carbohydrate intake ($P < 0.01$; Table 5). Additional analysis showed no relation between the ratio of SFA or fiber intake and DBP. Actual fat intake ($B = -0.018$; $R^2 = 0.590$) and actual carbohydrate intake ($B = 0.012$; $R^2 = 0.582$), respectively, had negative and positive correlations with change in TAG, albeit small, with every 1 mmol/L lowering in TAG levels related with 55.6% increase in actual fat intake

Table 5 **Stepwise linear meta-regression modeling with actual macronutrient intakes at 6 months**

Model	Individual variable	B	SE	r^2	df	F	P
DBP							
1[a,c]	Constant	2.389	1.426	0.341	18	10.833	0.004
	Actual fat intake	−0.135	0.041				
2[b]	Constant	−6.322	1.367	0.316	18	9.768	0.006
	Actual carbohydrate intake	0.093	0.030				
Triglyceride							
1[a,c]	Constant	0.427	0.118	0.590	18	28.342	0.000
	Actual fat intake	−0.018	0.003				
2[b]	Constant	−0.736	0.109	0.582	18	27.411	0.000
	Actual carbohydrate intake	0.012	0.002				
3[e]	Constant	0.093	0.094	0.441	16	12.853	0.003
	Actual SFA intake	−0.030	0.008				
4[f]	Constant	−0.922	0.247	0.481	10	9.355	0.016
	Actual fiber intake	0.049	0.016				
HDL cholesterol							
1[a,b,c]	Constant	0.076	0.023	0.317	20	10.751	0.004
	LF diet (with LC as referent)	−0.118	0.036				
2[a,b,c]	Constant	0.191	0.049	0.472	19	10.386	0.001
	LF diet (with LC as referent)	−0.116	0.032				
	Δ Caloric intake	0.000	0.000				
3[a,c,d]	Constant	−0.068	0.086	0.397	19	7.914	0.003
	Δ Caloric intake	0.000	0.000				
	Actual fat intake	0.007	0.002				
4[b,d]	Constant	−0.197	0.133	0.362	19	6.956	0.005
	Actual protein intake	−0.020	0.007				
	Δ Caloric intake	0.000	0.000				
5[e]	Constant	−0.146	0.052	0.512	18	18.804	0.001
	Actual SFA intake	0.018	0.004				
Glucose level							
1[a,b,c]	Constant	0.168	0.099	0.360	20	12.796	0.002
	Δ Body weight	0.065	0.018				

Stepwise regression analysis reveals at each model the strongest correlate (independent variable) to the dependent variable of interest (eg, DBP).

[a]Entered independent variables: diet type (LF diet with LC diet as referent), Δ body weight, Δ caloric intake, actual carbohydrate intake, and actual fat intake.

[b]Entered independent variables: diet type (LF diet with LC diet as referent), Δ body weight, Δ caloric intake, actual carbohydrate intake, and actual protein intake.

[c]Entered independent variables: diet type (LF diet with LC diet as referent), Δ body weight, Δ caloric intake, actual fat intake, and actual protein intake.

[d]Diet type was excluded as an individual variable.

[e]Entered independent variables: actual ratio of SFA to total fat, and actual SFA intake.

[f]Entered independent variables: actual ratio of fiber to carbohydrate intake, and actual fiber intake.

Abbreviations: Δ, change in; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LC, low-cholesterol diet; LF, low-fat diet; SFA, saturated fat

($P < 0.001$) and with 83.3% reduction in actual carbohydrate intake ($P < 0.001$). SFA ($P < 0.01$) and fiber ($P = 0.02$) intakes were related to TAG, in line with fat and carbohydrate intake. Studies reporting fiber intake ($n = 5$) no longer showed a significant decrease in TAG levels in the LF diet, whereas there was a decrease in TAG levels in the meta-analysis of all studies. In the studies reporting SFA intake ($n = 8$), there was a similar decrease in TAG levels compared with the meta-analysis results from all studies (data not shown).

For HDL cholesterol, actual intake of macronutrients appeared not to be of importance. Instead, type of diet was the most important factor, with the LF diet category associated with significantly lower HDL cholesterol levels compared with the LC diet category (a difference of 0.116–0.118 mmol/L; $0.004 < P < 0.001$,

depending on the model used). Exclusion of diet type resulted in models in which change in caloric intake in conjunction with actual fat intake or actual carbohydrate only marginally explained difference in HDL cholesterol (Table 5). Additional analysis also showed a correlation of SFA with HDL cholesterol, albeit small. There was no difference in meta-analysis outcome between the studies that reported SFA and all studies combined (data not shown).

Finally, change in body weight had a positive correlation with blood glucose levels ($B = 0.065$; $R^2 = 0.360$), meaning that every 1 mmol/L lowering of blood glucose was related to a 15.4 kg reduction in body weight. Analyses with changes in macronutrient intakes instead of actual intake yielded similar results, as mentioned (Table S3 in the Supporting Information online).
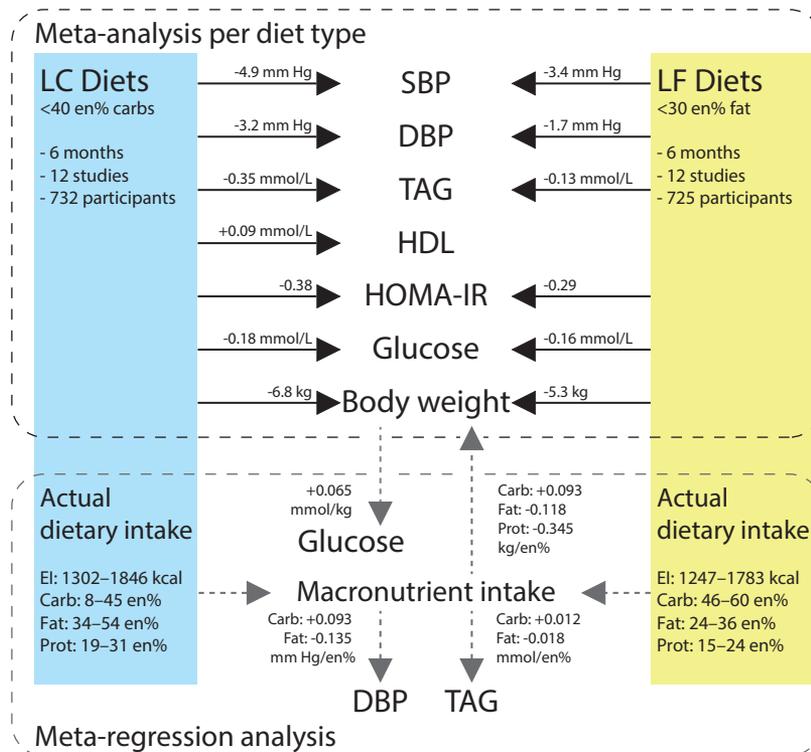
Figure 4 **Graphical summary of the meta-analysis and meta-regression at 6 months**. In the blocks on the side, the requirements for each diet are seen in the upper half; actual intakes at 6 months are shown in the lower half. In the upper half of the figure is shown that both diets have significant effects on the markers of MetS. The numbers represent the outcomes of the meta-analysis per diet. In the lower half of the figure, the effect of actual macronutrient intake on markers of MetS and the effect of body weight on glucose levels are shown. The numbers represent the change in marker, per en**%** intake of macronutrient or, in the case of glucose, per kilogram of body weight. For instance, a diet consisting of 50 en**%** carbohydrates, 30 en**%** fat, and 20 en**%** protein results in a body weight change after 6 months of (0.093 × 50 − 0.118 × 30 − 0.345 × 20) − 5.8 kg. *Abbreviations*: carb, carbohydrate intake; DBP, diastolic blood pressure; EI, energy intake; en**%**, percentage of energy; glucose, fasting glucose levels; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LC, low-carbohydrate diet; LF, low-fat diet; prot, protein intake; SBP, systolic blood pressure; TAG, plasma triglyceride levels.

DISCUSSION

The aim of this meta-analysis was to unravel the potential roles of changes in caloric and macronutrient intake across the spectrum of studies using LC and LF diets to explain alterations in weight loss and changes in markers of MetS in participants with obesity without cardiometabolic disease. The most important outcome of this analysis was that final, but not changes in, macronutrient intake explained reductions in markers of MetS much better than did LC vs LF dietary characterization per se, and these improvements did not necessarily depend on weight loss. Furthermore, the effect of carbohydrate intake on markers of MetS generally mirrored those observed for effects of fat and protein intake, irrespective of diet type. However, an increase in protein intake appeared to be most relevant for reducing body weight, whereas increased fat intake and reduced carbohydrate intake appeared to be most relevant for improving markers of MetS. Interestingly, caloric intake was not related to changes in body weight or markers of MetS.

An issue that became clear from this analysis is that the different MetS indices were not uniformly altered by the various changes in dietary components and/or weight loss (Figure 4). For instance, glucose was only lowered by body weight loss. DBP was affected by body weight loss and by macronutrient composition. Reduction in SBP, however, was only correlated with body weight loss when both diets types were analyzed separately. TAG levels also appeared to be influenced differentially by the two diet types (ie, body weight loss in the LF diet category appeared to improve TAG levels, whereas in the LC diet category, both body weight loss and macronutrient composition were correlated with improvement of TAG levels). Mechanistically, such an effect may be explained by reduced hepatic TAG production in response to body weight loss, which is then accentuated by decreased carbohydrate substrate delivery.[39–41]

Another example refers to the influences on HDL, which was selectively increased by the LC diet category, but there also was a relation between HDL cholesterol increase and lower carbohydrate and higher fat intake irrespective of diet type. Increases in HDL cholesterol levels may be explained by reduced TAG production and by the actions of cholesterol ester transferase.[1,39,40,42] Downregulation of hepatic scavenger receptor B1 may play a role because this receptor binds HDL cholesterol and facilitates cholesterol transport to the liver, which may be modulated by dietary fats.[39,40] In their study, Foster et al,[43] indeed, found an increase in HDL cholesterol after TAG levels returned to baseline. In turn, increased HDL cholesterol levels may defend against cardiac events and insulin resistance.[44,45] HOMA-IR (a proxy for insulin resistance[46]), however, was improved by LC and by LF diet types, apparently without any additional role for body weight and/or macronutrient composition, in the present meta-analysis.

Thus, these results can be summarized (Figure 4) as indicating that (1) both LF and LC diets are capable of inducing weight loss and improving MetS markers, (2) the resulting weight loss contributes to a reduction in glucose, and (3) lower carbohydrate intake and higher fat and protein intake reduce markers of MetS independent of weight loss. It can then be concluded that combined weight loss and changed macronutrient composition are most efficacious in reducing markers of MetS. Important for consideration of these results is that the actual macronutrient compositions were generally better at explaining improvements and variations in markers of MetS, than the changes in dietary macronutrient composition from baseline to end point.

The mechanisms by which the two main diet types reduce body weight and markers of MetS remain a matter of debate. Changes in body weight and changes in MetS indices were not explained by caloric intake. It is uncertain whether body weight loss is due to an increase in energy expenditure; only six studies measured physical activity, of which one showed an increase of activity over time that was similar in both diet groups. Alterations in macronutrient intake can also influence satiety. The increased fat intake of an LC diet can lead to stimulation of secretion of postprandial peptide YY, which is also known to reduce appetite and/or increase satiety.[29,47] Increased protein intake is associated with greater weight loss,[48] possibly due to the increased satiety effect of protein, among others, as a consequence of increased amino acid sensing by specific receptors in the gastrointestinal tract.[49,50] In this meta-analysis, there was an increase in protein intake in both diets, albeit smaller in the LF diets compared with the LC diets, but this apparently did not contribute to alterations in caloric intake that could explain alterations in markers of MetS.

A correlation between weight loss and reduction of markers of MetS is in line with a plethora of weight loss studies indicating improvement of MetS indices by body-fat reduction, a factor contributing mostly to weight loss. Favorable alterations of adipokines (eg, leptin, adiponectin, resistin) have been mentioned as directly affecting autonomic, metabolic, and inflammatory pathways known to underlie reduced MetS indices.[51] Furthermore, a reduction in visceral fat content often leads to reduced ectopic fat accumulation in organs like heart, pancreas, and skeletal muscle, which improves cardiometabolic functioning, as well.[52,53]

One of the findings of this meta-analysis is that a higher intake of SFA was related to body weight loss and beneficial changes in markers of MetS, whereas the ratio of SFA to total fat intake was not. This is counterintuitive because most studies recommended limiting SFA intake to <10 en%, as has been done since the publication of the Seven Nations Study, in which a higher SFA intake was related to a higher risk for cardiovascular disease.[54] However, since then, several studies have shown that lower SFA intake is not related to a lower risk of cardiovascular disease.[55,56] This is in accordance with the proposed mechanism that the presence of hypermetabolism (eg, in people with obesity) promoting fat oxidation (ie, fasting or increasing fat intake at the expense of carbohydrate intake) may improve cardiovascular function.[57] No relation among fiber intake, body weight, and markers of MetS was found.

Limitations

Although this meta-analysis revealed several interesting insights, there are also several limitations. One of the factors that was not investigated in this meta-analysis but that could be of influence on changes in MetS markers is waist circumference, indicative of the amount of visceral fat. Because visceral fat is important for the development of MetS, as shown by the first criterion of having central obesity,[4] it is recommended that future studies also look at changes in central obesity. Unfortunately, in this meta-analysis, only half of the studies specified change in waist circumference and even fewer specified change in fat percentage, making it difficult to draw conclusions.

Another concern in this meta-analysis is that different methods of food intake assessment were used. Because all but one study used intake from several days to assess average food intake, either by 24-hour recall or food records, it is unlikely that one study will influence the food intake data substantially, or that one method

influenced the data substantially. In addition, the one study that used the food frequency questionnaire reported very similar intakes as the other studies, making it unlikely that this study had a large influence on the data analysis. All in all, due to the similar methodology used, it is believed that the method of food intake assessment did not substantially influence the data.

Not all studies reported SFA intake, and few reported unsaturated or polyunsaturated fatty acid intake or n-3 vs n-6 ratios. These could be additional mechanisms that affect several metabolic pathways, including cholesterol metabolism,[58] intracellular lipid fat trafficking,[59] and cardiovascular functioning.[60] Types and sources of carbohydrates (simple or complex carbohydrates, carbohydrates from fruits and vegetables vs grains) also may differentially influence markers of MetS.[61] Only half of the studies reported fiber intake and no relation to weight loss or markers of MetS was found, which could also be due to the little variation in intake, because there was no change in intake.

Another limitation is that few data have been published on trials lasting longer than 12 months. One indication of a habitual, and thus chronic, dietary effect was shown in a Korean study in which individuals with a high fat intake or an LC intake had lower occurrence of markers of MetS.[58,62,63] Unfortunately, there are relatively few longitudinal data (beyond the time frames that were studied) supporting these claims. This may be due to loss of adherence to diets.[18] Last, only one search engine was used to find articles. However, in this analysis, many of the same articles were found as in previously published reviews with a similar subject.[14,16] Also, no additional request for data was made to the authors of included studies.

Conclusions and recommendations

Study results suggest reducing carbohydrate intake and increasing fat and protein intake (at least in the range found in the studies analyzed in this review) are beneficial for improving markers of MetS in obese persons without cardiovascular disease and type 2 diabetes. On the basis of the results of this meta-analysis, guidelines to prevent MetS may need to be reevaluated. It is clear that more long-term studies are needed with high levels of dietary adherence focused on the effects of macronutrient intake on weight loss and improvement of markers of MetS. Dietary adherence may depend on diet type, which could influence study outcomes considerably with respect to improvements of markers of MetS. To increase dietary adherence or prevent uneven drop-out, carbohydrate or fat preference of participants can be taken into account and evenly distributed among groups.

It may also be of interest to assess mood effects during dietary interventions, because changes in mood may interfere with dietary adherence in the setting of these studies.[27] Also, the age of the participants may be of interest because the geometric framework hypothesis suggests that at different ages, different nutrients are required.[64] Besides fat quality, the future studies may focus on the role of dietary fiber, which has been generally underappreciated in the comparison between LF and LC diets. The rapidly expanding microbiome field will undoubtedly shed light on the roles of consumption of fiber type[65] and fat quality[66] but also protein intake[67] in cardiometabolic health of the host in relation to the efficacy of LF and LC diet types.

SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website.

Figure S1 **Funnel plots with 95%CIs for publication bias of body weight change, separately for each diet at 6 and 12 months**. The plots are weighted mean differences from individual studies (horizontal axis) against the standard error of the weighted mean difference (vertical axis). The solid vertical line represents the summary estimate of the weighted mean difference from baseline, derived using random-effects meta-analysis. (A) Body weight change in the LC group at 6 months; (B) body weight change in the LF group at 6 months; (C) body weight change in the LC group at 12 months; (D) body weight change in the LF group at 12 months. LC, low-carbohydrate diet; LF, low-fat diet.

Table S1 **Meta-analysis outcomes in LC and LF diets after 6 and 12 months**

Table S2 **Meta-regression analysis with change in body weight or change in caloric intake as moderator, per diet**

Table S3 **Stepwise linear meta-regression modeling with change in macronutrient intakes**

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