PRELIMINARY COMMUNICATION

Effects of Dietary Composition on Energy Expenditure During Weight-Loss Maintenance

Cara B. Ebbeling, PhD
Janis F. Swain, MS, RD
Henry A. Feldman, PhD
William W. Wong, PhD
David L. Hachey, PhD
Erica Garcia-Lago, BA
David S. Ludwig, MD, PhD

Context Reduced energy expenditure following weight loss is thought to contribute to weight gain. However, the effect of dietary composition on energy expenditure during weight-loss maintenance has not been studied.

Objective To examine the effects of 3 diets differing widely in macronutrient composition and glycemic load on energy expenditure following weight loss.

Design, Setting, and Participants A controlled 3-way crossover design involving 21 overweight and obese young adults conducted at Children's Hospital Boston and Brigham and Women's Hospital, Boston, Massachusetts, between June 16, 2006, and June 21, 2010, with recruitment by newspaper advertisements and postings.

Intervention After achieving 10% to 15% weight loss while consuming a run-in diet, participants consumed an isocaloric low-fat diet (60% of energy from carbohydrate, 20% from fat, 20% from protein; high glycemic load), low–glycemic index diet (40% from carbohydrate, 40% from fat, and 20% from protein; moderate glycemic load), and very low-carbohydrate diet (10% from carbohydrate, 60% from fat, and 30% from protein; low glycemic load) in random order, each for 4 weeks.

Main Outcome Measures Primary outcome was resting energy expenditure (REE), with secondary outcomes of total energy expenditure (TEE), hormone levels, and metabolic syndrome components.

Results Compared with the pre–weight-loss baseline, the decrease in REE was greatest with the low-fat diet (mean [95% CI], –205 [–265 to –144] kcal/d), intermediate with the low–glycemic index diet (–166 [–227 to –106] kcal/d), and least with the very low-carbohydrate diet (–138 [–198 to –77] kcal/d; overall $P=.03$; P for trend by glycemic load $=.009$). The decrease in TEE showed a similar pattern (mean [95% CI], –423 [–606 to –239] kcal/d; –297 [–479 to –115] kcal/d; and –97 [–281 to 86] kcal/d, respectively; overall $P=.003$; P for trend by glycemic load $<.001$). Hormone levels and metabolic syndrome components also varied during weight maintenance by diet (leptin, $P<.001$; 24-hour urinary cortisol, $P=.005$; indexes of peripheral [$P=.02$] and hepatic [$P=.03$] insulin sensitivity; high-density lipoprotein [HDL] cholesterol, $P<.001$; non-HDL cholesterol, $P<.001$; triglycerides, $P<.001$; plasminogen activator inhibitor 1, P for trend $=.04$; and C-reactive protein, P for trend $=.05$), but no consistent favorable pattern emerged.

Conclusion Among overweight and obese young adults compared with pre–weight-loss energy expenditure, isocaloric feeding following 10% to 15% weight loss resulted in decreases in REE and TEE that were greatest with the low-fat diet, intermediate with the low–glycemic index diet, and least with the very low-carbohydrate diet.

Trial Registration clinicaltrials.gov Identifier: NCT00315354

JAMA. 2012;307(24):2627-2634 www.jama.com

Author Affiliations: New Balance Foundation Obesity Prevention Center (Drs Ebbeling and Ludwig and Ms Garcia-Lago) and Clinical Research Center (Dr Feldman), Children's Hospital Boston, Boston, Massachusetts; Brigham and Women's Hospital, Boston, Massachusetts (Ms Swain); Baylor College of Medicine, US Department of Agriculture/Agricultural Research Services Children's Nutrition Research Center, Houston, Texas (Dr Wong); and Vanderbilt University, Nashville, Tennessee (Dr Hachey).
Corresponding Author: David S. Ludwig, MD, PhD, New Balance Foundation Obesity Prevention Center, Children's Hospital Boston, 300 Longwood Ave, Boston, MA 02115 (david.ludwig@childrens.harvard.edu).

MANY PEOPLE CAN LOSE weight for a few months, but most have difficulty maintaining clinically significant weight loss over the long term. According to data from the National Health and Nutrition Examination Survey (1999-2006), only 1 in 6 overweight and obese adults report ever having maintained weight loss of at least 10% for 1 year.[1] Among dietary weight-loss trials, in which reporting bias can be eliminated, the long-term success rates may be even lower.[2] One explanation for the poor long-term outcome of weight-loss diets relates to behavior, in that the motivation to adhere to restrictive regimens typically diminishes with time. An alternative explanation is that weight loss elicits biological adaptations—specifically a decline in energy expenditure (adaptive thermogenesis) and an increase in hunger—that promote weight regain.[3,4]

Obesity treatment should emphasize behavioral methods to foster and maintain decreased energy intake. Several recent clinical trials indicate a direct relationship between dietary ad-

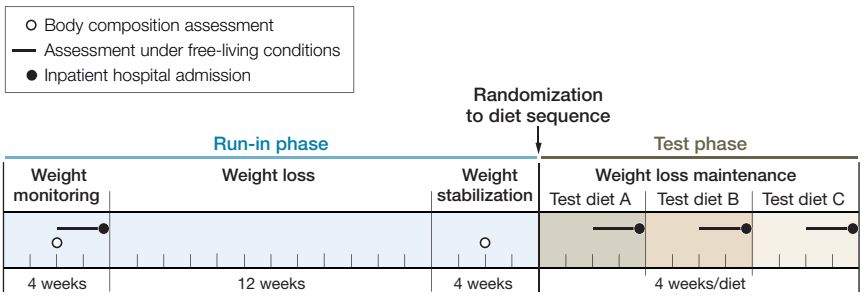
See also pp 2617 and 2641.

herence and weight loss, regardless of dietary treatment group assignment.[5-7] However, because metabolic pathways vary in energetic efficiency, dietary composition could affect energy expenditure directly by virtue of macronutrient differences or indirectly through hormonal responses to diet that regulate metabolic pathways.[8,9]

Diets that aim to attenuate the increase in blood glucose levels after eating—specifically, low–glycemic index (emphasizing carbohydrate source)[10] and very low-carbohydrate (focusing on carbohydrate restriction)[11] diets—have been hypothesized to confer such a "metabolic advantage." Acutely, reducing dietary glycemic load diet may elicit hormonal changes that improve the availability of metabolic fuels in the late postprandial period, and thereby decrease hunger and voluntary food intake.[9,12] Chronically, a low–glycemic load diet may attenuate the decline in resting energy expenditure (REE) that occurs during weight loss.[13,14]

We conducted a controlled feeding study to evaluate the effects of 3 weight-loss maintenance diets, which encompass prevailing ranges of macronutrient composition and glycemic load (a low-fat diet, a low–glycemic index diet, and a very low-carbohydrate diet) on energy expenditure, hormones, and components of the metabolic syndrome.

Figure 1. Study Design of the Run-in and Test Phases



Body composition was assessed during the weight monitoring period of the run-in phase and following weight loss. Assessments during inpatient hospital admissions and under free-living conditions occurred during the weight monitoring period and at the end of each test diet period. Immediately before the 3-day inpatient hospital admission, the assessments under free-living conditions were conducted over 14 (total energy expenditure) or 7 (physical activity) days. There were 6 possible diet sequences to which each participant could be randomly assigned (as described in the eMethods; http://www.jama.com).

Table 1. Composition of the Run-in and Test Diets During Weight-Loss Maintenance (per 2000 kcal)

Nutrient	Run-in Diet[b]	Test Diets During Weight-Loss Maintenance[a]		
		Low Fat	Low Glycemic Index	Very Low Carbohydrate
Targeted macronutrient distribution, % energy				
Carbohydrate	45	60	40	10
Fat	30	20	40	60
Protein	25	20	20	30
Dietary intake, mean (SD)				
Carbohydrate, g/d	229.5 (9.1)	310.4 (1.7)	205.1 (3.3)	50.1 (1.2)
Glycemic index	52.6 (5.9)	67.7 (2.5)	32.9 (3.2)	28.4 (9.0)
Glycemic load, g/d	68.9 (13.1)	185.1 (8.6)	51.1 (6.3)	3.9 (2.2)
Fat, g/d	68.6 (2.7)	46.5 (0.3)	90.2 (4.3)	133.4 (2.7)
Saturated	15.0 (2.0)	12.8 (0.5)	22.4 (3.7)	47.8 (8.4)
Monounsaturated	27.1 (4.4)	15.3 (2.2)	40.0 (5.8)	47.7 (7.1)
Polyunsaturated	16.6 (3.8)	15.7 (2.4)	22.3 (6.3)	22.0 (7.4)
Protein, g/d	126.9 (5.6)	104.8 (0.6)	105.5 (2.0)	151.5 (1.1)
Fiber, g/d	27.1 (3.4)	30.3 (2.8)	32.8 (1.8)	11.2 (2.0)
Cholesterol, mg/d	216.4 (47.5)	140.3 (12.2)	280.1 (173.1)	978.1 (329.7)
Sodium, mg/d	2363 (604)	2546 (379)	2647 (329)	2646 (718)

[a] The energy content of diets throughout the test phase remained constant, at the level required for weight stabilization at the end of the run-in phase.
[b] The diet for the weight loss and weight stabilization periods of the run-in phase provided 60% and 100% of estimated energy requirements, respectively.

METHODS

The study comprised run-in and test phases (FIGURE 1). During the run-in phase, we obtained baseline data for study outcomes, restricted energy intake of participants to achieve a 12.5% decrease in body weight, and established energy requirements for stabilizing weight at the reduced level. We assessed body composition by dual-energy x-ray absorptiometry before and after weight loss. During the test phase, we used a 3-way crossover design to evaluate test diets (low-fat, low–glycemic index, and very low-carbohydrate) in random order under conditions of weight maintenance. We measured study outcomes during an inpatient hospital admission and under free-living conditions at baseline and the end of each test diet period. Data were collected at Children's Hospital Boston and Brigham and Women's Hospital, Boston, Massachusetts, between June 16, 2006, and June 21, 2010. Stable isotope analysis for assessing total energy expenditure (TEE) was conducted at Baylor College of Medicine, Houston, Texas. The institutional review boards at all participating institutions approved the study protocol, and participants provided written informed consent. Methodological detail can be found in the eMethods (http://www.jama.com).

Participants

Participants included men and women aged 18 to 40 years with a body mass index (calculated as weight in kilograms divided by height in meters

squared) of 27 or higher. To compensate participants for their effort, we provided $500 at the end of the run-in phase, following at least 10% weight loss, and an additional $2000 upon completion of the final inpatient hospital admission.

Dietary Interventions

Our goal was to design test diets that (1) would encompass a broad range of macronutrient composition and glycemic load, (2) have been commonly recommended for obesity treatment, and (3) could be physiologically sustainable for long periods. To avoid bias, we formulated menus with healthful components inherent to typical prescriptions for respective diets. In view of the mechanistic nature of this study, relying on a feeding protocol, we did not design the diets for long-term practicality.

TABLE 1 shows the composition of the run-in and test diets. The run-in diet was consistent with the Acceptable Macronutrient Distribution Range specified by the Institute of Medicine,[15] with protein intake at the upper end of the range to enhance satiety during weight loss.[16] The low-fat diet, which had a high glycemic load, was designed to reflect conventional recommendations to reduce dietary fat, emphasize whole grain products, and include a variety of vegetables and fruits.[17] The low–glycemic index diet aimed to achieve a moderate glycemic load by replacing some grain products and starchy vegetables with sources of healthful fat and low–glycemic index vegetables, legumes, and fruits. The low-fat and low–glycemic index diets had similar protein and fiber contents. The very low-carbohydrate diet was modeled on the Atkins Diet and had a low glycemic load due to more severe restriction of carbohydrate. We provided 3 g of fiber with each meal (Metamucil, Procter & Gamble) during the very low-carbohydrate diet as recommended.[11] To ensure micronutrient adequacy and minimize the influence of micronutrient differences among test diets, we gave each participant a daily multivitamin and mineral supplement.

Study Outcomes

Assessments conducted during inpatient hospital admissions included the primary outcome of REE by indirect calorimetry and secondary outcomes of hormones (leptin, thyroid stimulating hormone, triiodothyronine, and free urinary cortisol), insulin sensitivity (indexes derived from an oral glucose tolerance test[18]), other metabolic syndrome components (high-density lipoprotein [HDL] cholesterol, total cholesterol, triglycerides, plasminogen activator inhibitor 1 activity, high sensitivity C-reactive protein [CRP], and blood pressure), and participant ratings of hunger and well-being. (To convert triiodothyronine to nmol/L, multiply by 0.0154; HDL and non-HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; plasminogen activator inhibitor 1 to pmol/L, multiply by 19.231; and CRP to nmol/L, multiply by 9.524.) Assessments conducted under free-living conditions included TEE by doubly-labeled water and physical activity by accelerometry.

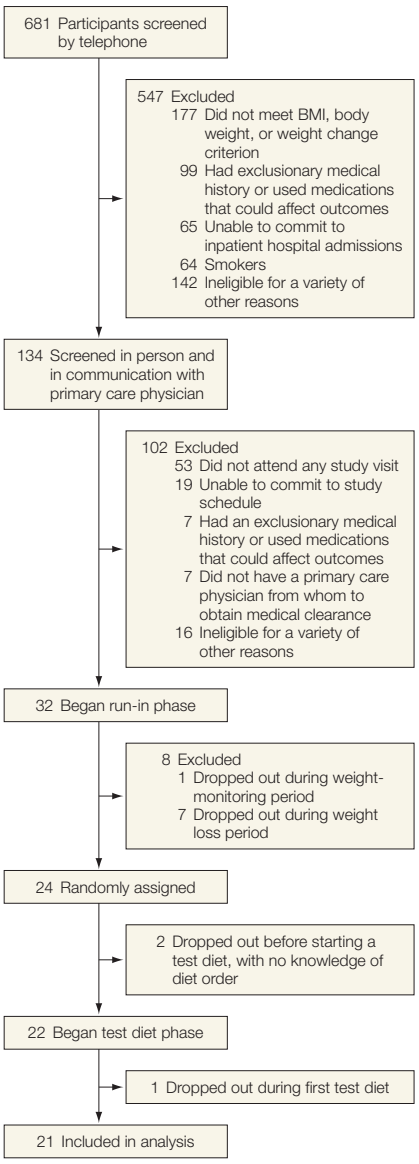
Statistical Analyses

The crossover trial was designed to provide more than 80% power to detect a difference of 80 kcal/d in REE between diets, as observed in our prior study.[14] The order of diets in the test phase was randomly assigned for each participant. We followed the intention-to-treat principle, ascribing the assigned diet to each measure regardless of adherence.

Analytical procedures were based on methods for crossover trials described by Senn.[19] For each outcome, we fitted a repeated-measures mixed-effects model with measurement period as independent variable (baseline, low-fat diet, low–glycemic index diet, very low-carbohydrate diet), adjusting for sex, age, weight after run-in phase, sequence of diets, mean weight during measurement period, order of measurement period (baseline always first; test-phase diets second, third, or fourth), within-participant covariance among measurement periods, and where applicable correlation among 3 daily measures within the measurement period. Variables with skewed distribution were log-transformed for analysis. One variable with extreme skew (CRP) was rank transformed for analysis.[20]

We tested the overall null hypothesis of equal mean in the 3 test-phase

Figure 2. Flow Diagram of Participants



BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared.

Table 2. Baseline Characteristics of the Study Participants[a]

Characteristics	Study Participants (N = 21)
Continuous variables, mean (SD)	
Age, y	30.3 (5.7)
Height, cm	174.3 (11.3)
Weight, kg	105.0 (20.1)
BMI	34.4 (4.9)
Waist circumference, cm	103.5 (12.9)
Categorical variables, No. (%)	
Sex	
Male	13 (62)
Female	8 (38)
Race	
White	4 (19)
Black	8 (38)
Asian	4 (19)
Other[b]	5 (24)
Hispanic ethnicity	4 (19)

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.
[a] Age was calculated from date of birth and date of baseline hospital admission. Waist was measured at the midpoint between the lower rib and iliac crest. Participants were asked to self-report race and ethnicity.
[b] Other race included no response (n = 2), Caribbean (n = 1), Latino (n = 1), and Persian (n = 1).

periods (H_0: low fat = low glycemic index = very low carbohydrate) using a 2-sided criterion of $P < .05$. Whenever this hypothesis was rejected, we performed pairwise comparisons with a Bonferroni-adjusted criterion of $P < .017$ (= .05/3). We also constructed a test for linear trend across diets, proceeding from highest to lowest glycemic load.

We applied an outlier-deletion algorithm with optimal properties, equivalent to robust regression.[21] As missing values were uncommon (typically 1 per outcome), we did not perform any imputation, relying on the unbiasedness of mixed-effects regression when data are missing at random.[22] We used SAS version 9.2 (SAS Institute Inc) for all computations. Data are shown as mean (95% CI) unless otherwise noted.

RESULTS

We enrolled 32 participants, including 17 men and 15 women. Of these, 11 participants did not complete the study (FIGURE 2). Baseline characteristics for the 21 participants who completed the study are shown in TABLE 2. Noncompleters did not differ from completers with respect to any of these characteristics. During the run-in phase, participants lost a mean (SD) of 14.3 (0.9) kg, corresponding to 13.6% of baseline body weight. Percentage body fat by dual-energy x-ray absorptiometry decreased from a mean of 33.6% (95% CI, 30.0%-37.2%) at baseline to 29.1% (95% CI, 25.1%-33.1%) after weight loss. Mean (SD) energy intake during the test diet phase was 2626 (686) kcal/d. Body weight did not differ significantly among the 3 diets (mean [95% CI], 91.5 [87.4-95.6] kg for low fat; 91.1 [87.0-95.2] kg for low glycemic index; and 91.2 [87.1-95.3] kg for very low carbohydrate; $P = .80$).

Energy Expenditure

Energy expenditure during weight-loss maintenance differed significantly among the 3 diets (TABLE 3 and FIGURE 3). The decrease in REE from pre–weight-loss levels, measured by indirect calorimetry in the fasting state, was greatest for the low-fat diet (mean relative to baseline [95% CI], –205 [–265 to –144] kcal/d), intermediate with the low–glycemic index diet (–166 [–227 to –106] kcal/d), and least for the very low-carbohydrate diet (–138 [–198 to –77] kcal/d; overall $P = .03$; P for trend by glycemic load = .009). The decrease in TEE, assessed using the doubly-labeled water method, also differed significantly by diet (mean [95% CI], –423 [–606 to –239] kcal/d for low fat; –297 [–479 to –115] kcal/d for low glycemic index; and –97 [–281 to 86] kcal/d for very low carbohydrate; overall $P = .003$; P for trend by glycemic load $< .001$). This result was not materially changed when substituting measured respiratory quotient (RQ) for calculated food quotient (FQ). Neither total physical activity nor time spent in moderate- to vigorous-intensity physical activity differed among the diets.

Hormones and Components of the Metabolic Syndrome

Serum leptin was highest with the low-fat diet (mean [95% CI], 14.9 [12.1-18.4] ng/mL), intermediate with the low–glycemic index diet (12.7 [10.3-15.6] ng/mL), and lowest with the very low-carbohydrate diet (11.2 [9.1-13.8] ng/mL; overall $P < .001$) (Table 3). For the 3 diets, cortisol excretion measured with a 24-hour urine collection (mean [95% CI], 50 [41-60] µg/d for low fat; 60 [49-73] µg/d for low glycemic index; and 71 [58-86] µg/d for very low carbohydrate; overall $P = .005$) and serum thyroid-stimulating hormone (mean [95% CI], 1.27 [1.01-1.60] µIU/mL for low fat; 1.22 [0.97-1.54] µIU/mL for low glycemic index; and 1.11 [0.88-1.40] µIU/mL for very low carbohydrate; overall $P = .04$) also differed in a linear fashion by glycemic load. Serum triiodothyronine was lower with the very low-carbohydrate diet compared with the other 2 diets (mean [95% CI], 121 [108-135] ng/dL for low-fat diet and 123 [110-137 ng/dL for low–glycemic index diet vs 108 [96-120] ng/dL for very low-carbohydrate diet; overall $P = .006$).

Regarding components of the metabolic syndrome, indexes of peripheral ($P = .02$) and hepatic ($P = .03$) insulin sensitivity were lowest with the low-fat diet. Comparing the low-fat, low–glycemic index, and very low-carbohydrate diets, serum HDL cholesterol (mean [95% CI], 40 [35-45] mg/dL; 45 [41-50] mg/dL; and 48 [44-53] mg/dL, respectively; overall $P < .001$), triglycerides (107 [87-131] mg/dL; 87 [71-106] mg/dL; and 66 [54-81] mg/dL, respectively; overall $P < .001$), and plasminogen activator inhibitor 1 (mean [95% CI], 1.39 [0.94-2.05] ng/mL; 1.15 [0.78-1.71] ng/mL; and 1.01 [0.68-1.49] ng/mL, respectively; P for trend by glycemic load = .04) were most favorable with the very low-carbohydrate diet and least favorable with the low-fat diet. However, CRP tended to be higher with the very low-carbohydrate diet (median [95% CI], 0.78 [0.38-1.92] mg/L for low-fat diet; 0.76 [0.50-2.20] mg/L for low–glycemic index diet; and 0.87 [0.57-2.69] mg/L for very low-carbohydrate diet; P for trend by glycemic load = .05).

Blood pressure did not differ among the 3 diets.

Hunger and Well-being

Using a 10-cm visual analog scale, ratings of subjective hunger (mean [95% CI], 5.7 [4.6-6.8] cm; 5.4 [4.4-6.5] cm; and 5.8 [4.8-6.9] cm, respectively; $P=.62$) and well-being (6.1 [5.2-7.0] cm; 6.9 [6.0-7.8] cm; and 6.3 [5.3-7.2] cm, respectively; $P=.21$) obtained before breakfast did not differ significantly among the low-fat, low–glycemic index, and very low-carbohydrate diets.

COMMENT

The results of our study challenge the notion that a calorie is a calorie from a

Table 3. Study Outcomes

Variable	Mean (95% CI)				*P* Value[a]	
		Test Diets During Weight-Loss Maintenance				
	Pre–Weight-Loss Baseline	Low Fat	Low Glycemic Index	Very Low Carbohydrate	Overall	Trend
Energy Metabolism						
REE, kcal/d	1781 (1737 to 1824)	1576 (1528 to 1624)	1614 (1566 to 1662)	1643 (1595 to 1691)	.03[b,c]	.009
REE, kcal/kg FFM/d	27.4 (26.6 to 28.5)	24.4 (23.6 to 25.2)	25.0 (24.2 to 25.8)	25.5 (24.7 to 26.4)	.04[b,c]	.01
Resting RQ	0.901 (0.884 to 0.918)	0.905 (0.894 to 0.924)	0.861 (0.845 to 0.875)	0.826 (0.817 to 0.848)	<.001	<.001
TEE, kcal/d						
Using calculated FQ	3234 (3081 to 3388)	2812 (2599 to 3024)	2937 (2730 to 3145)	3137 (2926 to 3348)	.003[b]	<.001
Using measured RQ	3235 (3082 to 3389)	2767 (2564 to 2970)	2926 (2729 to 3124)	3013 (2811 to 3216)	.02[b,c]	.007
TEE, kcal/kg FFM/d						
Using calculated FQ	49.8 (46.6 to 52.9)	43.7 (40.3 to 47.1)	45.8 (42.4 to 49.1)	47.6 (44.2 to 51.0)	.008[b,c]	.003
Using measured RQ	49.7 (46.5 to 52.8)	42.9 (39.4 to 46.4)	45.2 (41.8 to 48.7)	46.6 (43.0 to 50.1)	.02[b,c]	.005
Physical activity						
Total counts, thousands	299 (259 to 339)	301 (258 to 344)	314 (271 to 358)	287 (245 to 330)	.20	.33
MVPA, min/d[d]	13.5 (10.2 to 18.0)	15.8 (10.9 to 22.8)	14.7 (10.3 to 20.9)	11.7 (8.2 to 16.6)	.18	.08
Hormone Levels						
Leptin, ng/mL[d]	29.2 (24.3 to 35.1)	14.9 (12.1 to 18.4)	12.7 (10.3 to 15.6)	11.2 (9.1 to 13.8)	<.001[c]	<.001
Urinary cortisol, μg/d[d]	58 (47 to 73)	50 (41 to 60)	60 (49 to 73)	71 (58 to 86)	.005[b,c]	.001
Thyroid function						
TSH, μIU/mL[d]	1.15 (0.97 to 1.37)	1.27 (1.01 to 1.60)	1.22 (0.97 to 1.54)	1.11 (0.88 to 1.40)	.04[b,c]	.01
Triiodothyronine, ng/dL[d]	137 (127 to 149)	121 (108 to 135)	123 (110 to 137)	108 (96 to 120)	.006[b]	.007
Components of the Metabolic Syndrome						
Insulin sensitivity indexes[e]						
Peripheral	0.24 (–0.11 to 0.59)	0.53 (0.24 to 0.83)	0.87 (0.56 to 1.18)	0.93 (0.63 to 1.22)	.02[b,c]	.008
Hepatic[d]	0.56 (0.41 to 0.78)	0.93 (0.71 to 1.23)	1.04 (0.78 to 1.37)	1.24 (0.94 to 1.63)	.03[b,c]	.01
Cholesterol, mg/dL						
HDL	46 (41 to 50)	40 (35 to 45)	45 (41 to 50)	48 (44 to 53)	<.001	<.001
Non-HDL	131 (121 to 142)	109 (95 to 122)	111 (98 to 124)	127 (114 to 140)	<.001[b]	<.001
Triglycerides, mg/dL[d]	116 (93 to 144)	107 (87 to 131)	87 (71 to 106)	66 (54 to 81)	<.001	<.001
Blood pressure, mm Hg						
Systolic	116 (114 to 119)	110 (107 to 113)	109 (107 to 112)	111 (109 to 114)	.34	.32
Diastolic	67 (64 to 70)	61 (59 to 64)	62 (59 to 65)	63 (61 to 66)	.35	.16
PAI-1, ng/mL[d]	3.90 (2.54 to 5.98)	1.39 (0.94 to 2.05)	1.15 (0.78 to 1.71)	1.01 (0.68 to 1.49)	.11	.04
CRP, mg/L[f]	1.75 (0.44 to 4.61)	0.78 (0.38 to 1.92)	0.76 (0.50 to 2.20)	0.87 (0.57 to 2.69)	.13	.05

Abbreviations: CRP, C-reactive protein; FFM, fat-free mass; FQ, food quotient; HDL, high-density lipoprotein; MVPA, moderate- to vigorous-intensity physical activity; PAI-1, plasminogen activator inhibitor 1; RQ, respiratory quotient; REE, resting energy expenditure; TEE, total energy expenditure; TSH, thyroid-stimulating hormone.

SI conversions: To convert triiodothyronine to nmol/L, multiply by 0.0154; HDL and non-HDL cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; PAI-1 to pmol/L, multiply by 19.231; and CRP to nmol/L, multiply by 9.524.

[a] From repeated-measures analysis of variance modeling variation among the 4 measurement periods, adjusted for sex, age, order of diets, baseline weight, and mean weight during each period as well as covariance among periods within participant and covariance among 3 measurement days within period. Overall *P* value tests the hypothesis that mean outcome was equal in the 3 test diet periods. *P* for trend tests the hypothesis of linear change in mean outcome from low-fat diet to low–glycemic index diet to very low-carbohydrate diet, assuming equal spacing.

[b] Indicates that means for the low-fat diet vs low–glycemic index diet for a particular outcome were not significantly different as judged by Bonferroni-adjusted comparison ($P>.017$) following significant overall test of the null hypothesis: low fat=low glycemic index=very low carbohydrate ($P<.05$).

[c] Indicates that means for the low–glycemic index diet vs very low-carbohydrate diet for a particular outcome were not significantly different as judged by Bonferroni-adjusted comparison ($P>.017$) following significant overall test of the null hypothesis: low fat=low glycemic index=very low carbohydrate ($P<.05$).

[d] Log transformed for analysis (adjusted mean and 95% CI retransformed to natural units).

[e] Parameters calculated from oral glucose tolerance test according to Abdul-Ghani et al.[18] Peripheral insulin sensitivity is defined as rate of decline of glucose between 60 and 120 minutes divided by time-weighted mean insulin between baseline and 120 minutes: $\{-[Glu_{120}-Glu_{60}]\div[(5\times Ins_{Fast}+10\times Ins_{10}+10\times Ins_{20}+20\times Ins_{30}+30\times Ins_{60}+30\times Ins_{90}+15\times Ins_{120})/120]\}$. Hepatic insulin sensitivity is defined as the reciprocal product of area under the glucose curve and area under the insulin curve between baseline and 30 minutes: $\{[(5\times Glu_{Fast}+10\times Glu_{10}+10\times Glu_{20}+5\times Glu_{30})/60]^{-1}\times[(5\times Ins_{Fast}+10\times Ins_{10}+10\times Ins_{20}+5\times Ins_{30})/60]^{-1}\}$. In these formulas, glucose is expressed in mg/dL and insulin in μIU/mL. In the table, hepatic insulin sensitivity is scaled up by 10^3 for readability.

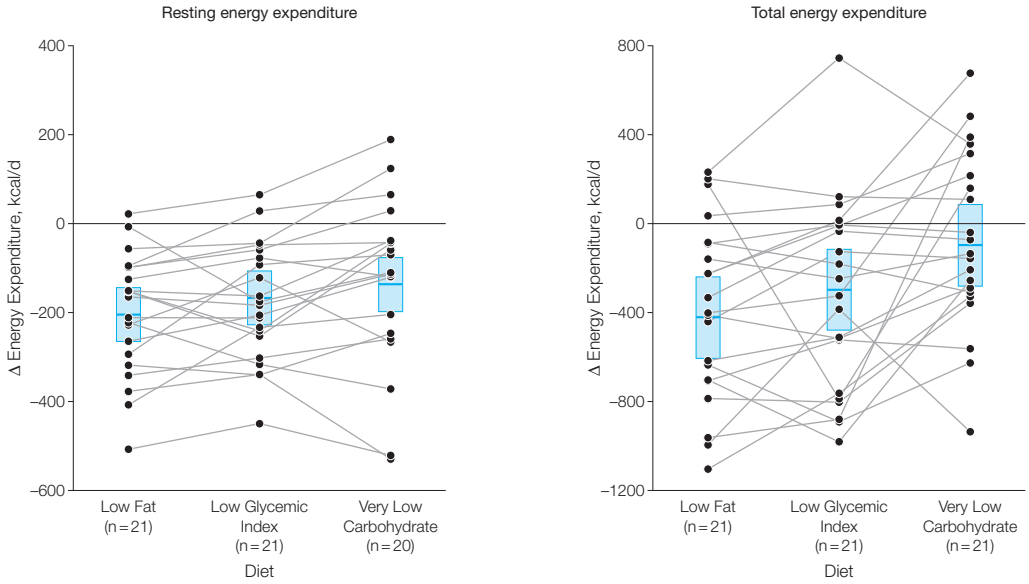
[f] Rank transformed for analysis (entries are median and 95% CI in natural units).

metabolic perspective. During isocaloric feeding following weight loss, REE was 67 kcal/d higher with the very low-carbohydrate diet compared with the low-fat diet. TEE differed by approximately 300 kcal/d between these 2 diets, an effect corresponding with the amount of energy typically expended in 1 hour of moderate-intensity physical activity.

The physiological basis for the differences in REE and TEE remains subject to speculation. Triiodothyronine was lowest with the very low-carbohydrate diet, consistent with previously reported effects of carbohydrate restriction[23]; thus, changes in thyroid hormone concentration cannot account for the higher energy expenditure on this diet. The thermic effect of food (the increase in energy expenditure arising from digestive and metabolic processes) dissipates in the late postprandial period and would not affect REE measured in the fasting state. Because the thermic effect of food tends to be greater for carbohydrate than fat,[24,25] it would also not explain the lower TEE on the low-fat diet. Although protein has a high thermic effect of food,[16] the content of this macronutrient was the same for the low-fat and low–glycemic index diets and contributed only 10% more to total energy intake with the very low-carbohydrate diet compared with the other 2 diets. Furthermore, physical activity as assessed by accelerometry did not change throughout the study. Alternative explanations for the observed differences in REE and TEE may involve intrinsic effects of dietary composition on the availability of metabolic fuels[13,14] or metabolic efficiency, changes in hormones (other than thyroid) or autonomic tone affecting catabolic or anabolic pathways, and (for TEE) skeletal muscle efficiency as regulated by leptin.[26-29] Regarding the last possibility, the ratio of energy expenditure to leptin concentration has been proposed as a measure of leptin sensitivity,[30] and this ratio varied as expected in our study among the 3 diets (very low carbohydrate>low glycemic index>low fat).

Although the very low-carbohydrate diet produced the greatest improvements in most metabolic syndrome components examined herein, we identified 2 potentially deleterious effects of this diet. Twenty-four hour urinary cortisol excretion, a hormonal measure of stress, was highest with the very low-carbohydrate diet. Consistent with this finding, Stimson et al[31] reported increased whole-body regeneration of cortisol by 11β-HSD1 and reduced inactivation of cortisol by 5α- and 5β-reductases over 4 weeks on a very low- vs moderate-carbohydrate diet. Higher cortisol levels may promote adiposity, insulin resistance, and cardiovascular disease, as observed in epidemiological studies.[32-34] In a 6-year prospective, population-based study of older adults in Italy,[35] individuals in the highest vs lowest tertile of 24-hour cortisol excretion, with or without preexisting cardiovascular disease, had a 5-fold increased risk of cardiovascular mortality. C-reactive protein also tended to be higher with the very low-carbohydrate diet in our study, consis-

Figure 3. Changes in Resting and Total Energy Expenditure During 3 Test Diets for Weight-Loss Maintenance



Each summary box (shown in cyan) with error bars indicates mean (95% CI) change from a common baseline period preceding weight loss obtained from analysis of crossover experiment and adjusted for sex, age, order of diets, baseline weight, and mean weight during the 4-week diet period. Connected lines indicate individual outcomes for each participant. Both resting and total energy expenditure showed a significant linear trend in mean change from low-fat to low–glycemic index to very low-carbohydrate diets ($P<.01$).

tent with the findings of Rankin and Turpyn.[36] Other studies also have found reductions in measures of chronic inflammation, including CRP with a low–glycemic index diet.[37-39]

A main strength of our study was use of a controlled feeding protocol to establish weight stability following weight loss. Other strengths included a crossover design to allow for within-individual comparisons, examination of 3 physiologically sustainable diets spanning a wide range of prevailing macronutrient compositions, control for dietary protein between the low-fat and low–glycemic index diets, state-of-the-art methods to assess TEE under free-living conditions, collection of other study outcomes under direct observation during inpatient hospital admissions to a metabolic ward, and use of observed RQ by indirect calorimetry to verify macronutrient differences among the diets.

Main study limitations are the relatively short duration of the test diets and the difficulty extrapolating findings from a feeding study to a more natural setting, in which individuals consume self-selected diets. In particular, the very low-carbohydrate diet involved more severe carbohydrate restriction than would be feasible for many individuals over the long term. Therefore, the study may overestimate the magnitude of effects that could be obtained by carbohydrate restriction in the context of a behavioral intervention. In addition, participants in the study were selected for ability to comply with the rigors of a 7-month feeding protocol and may not represent overweight and obese individuals in the general population. Although we could not assess participant adherence during the outpatient phases of the study, good maintenance of weight loss throughout the test phase provides some reassurance on this point.

A methodological issue in crossover feeding studies involves the possibility of carry-over effects between test diets. However, random assignment of participants to a diet sequence and statistical control for order effects would diminish this possibility. In addition, we used compartmental modeling for analysis of TEE to correct for residual tracer and possible variations in dilution spaces and water kinetics among study periods. Another limitation relating to TEE measurement involves reliance on several assumptions, including the FQ of the test diets. However, sensitivity analysis demonstrated that our results would withstand plausible inaccuracies in estimates of FQ and qualitatively similar results were obtained when substituting measured RQ for calculated FQ. In addition, we did not assess physiological differences among participants (for example, involving insulin secretion[40,41]) that might influence individual responses to the test diets.

In conclusion, our study demonstrates that commonly consumed diets can affect metabolism and components of the metabolic syndrome in markedly different ways during weight-loss maintenance, independent of energy content. The low-fat diet produced changes in energy expenditure and serum leptin[42-44] that would predict weight regain. In addition, this conventionally recommended diet had unfavorable effects on most of the metabolic syndrome components studied herein. In contrast, the very low-carbohydrate diet had the most beneficial effects on energy expenditure and several metabolic syndrome components, but this restrictive regimen may increase cortisol excretion and CRP. The low–glycemic index diet appears to have qualitatively similar, although smaller, metabolic benefits to the very low-carbohydrate diet, possibly without the deleterious effects on physiological stress and chronic inflammation. These findings suggest that a strategy to reduce glycemic load rather than dietary fat may be advantageous for weight-loss maintenance and cardiovascular disease prevention. Ultimately, successful weight-loss maintenance will require behavioral and environmental interventions to facilitate long-term dietary adherence. But such interventions will be most effective if they promote a dietary pattern that ameliorates the adverse biological changes accompanying weight loss.

Author Contributions: Dr Ludwig had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Ebbeling, Swain, Feldman, Wong, Ludwig.
Acquisition of data: Ebbeling, Swain, Wong, Garcia-Lago.
Analysis and interpretation of data: Ebbeling, Feldman, Wong, Hachey, Ludwig.
Drafting of the manuscript: Ebbeling, Swain, Feldman, Wong, Ludwig.
Critical revision of the manuscript for important intellectual content: Ebbeling, Feldman, Wong, Hachey, Garcia-Lago, Ludwig.
Statistical analysis: Feldman.
Obtained funding: Ebbeling, Feldman, Ludwig.
Administrative, technical, or material support: Ebbeling, Swain, Wong, Garcia-Lago, Ludwig.
Study supervision: Ebbeling, Swain, Ludwig.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ebbeling reported receiving grants from the National Institutes of Health and foundations for obesity-related research. Dr Ludwig reported receiving grants from the National Institutes of Health and foundations for obesity-related research, mentoring, and patient care; and royalties from a book about childhood obesity. No other authors reported any conflicts of interest.
Funding/Support: This study was supported by grants R01DK072428 and K24DK082730 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland; grant M01RR02172 from the National Center for Research Resources, National Institutes of Health, to the Children's Hospital Boston General Clinical Research Center; grant M0102635 from the National Center for Research Resources, National Institutes of Health, to the Brigham and Women's Hospital General Clinical Research Center; grant UL1RR02575801 from the National Center for Research Resources, National Institutes of Health, to the Harvard Catalyst Clinical and Translational Science Center; and a grant from the New Balance Foundation.
Role of the Sponsors: The funding organizations had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript.
Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases, National Center for Research Resources, the National Institutes of Health, or the US Department of Agriculture.
Online-Only Material: The eMethods are available at http://www.jama.com.
Additional Contributions: Michael Leidig, RD, and Carolyn Walsh, MD (Children's Hospital Boston, Boston, Massachusetts), organized daily study operations; Karen Yee, MS, RD, Rachel Froelich, MS, RD, and Lisa Bielak, MS, RD (Brigham and Women's Hospital, Boston, Massachusetts), developed and delivered the dietary interventions; Robert Markowitz, MD (Children's Hospital Boston, Boston, Massachusetts), provided help with hospital admissions and blood sample collections; and Sarah Kalil, MSN, Hope Forbes, MA, and Elizabeth Scarola, MA (Children's Hospital Boston, Boston, Massachusetts), provided assistance with data collection and management. Drs Walsh and Markowitz, Mr Leidig, and Mss Yee, Froelich, Bielak, Kalil, Forbes, and Scarola received compensation for their work in the form of salary support.

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