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Comparison of Weight-Loss Diets with Different Compositions of Fat, Protein, and Carbohydrates

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ABSTRACT

BACKGROUND

The possible advantage for weight loss of a diet that emphasizes protein, fat, or carbohydrates has not been established, and there are few studies that extend beyond 1 year.

METHODS

We randomly assigned 811 overweight adults to one of four diets; the targeted percentages of energy derived from fat, protein, and carbohydrates in the four diets were 20, 15, and 65%; 20, 25, and 55%; 40, 15, and 45%; and 40, 25, and 35%. The diets consisted of similar foods and met guidelines for cardiovascular health. The participants were offered group and individual instructional sessions for 2 years. The primary outcome was the change in body weight after 2 years in two-by-two factorial comparisons of low fat versus high fat and average protein versus high protein and in the comparison of highest and lowest carbohydrate content.

RESULTS

At 6 months, participants assigned to each diet had lost an average of 6 kg, which represented 7% of their initial weight; they began to regain weight after 12 months. By 2 years, weight loss remained similar in those who were assigned to a diet with 15% protein and those assigned to a diet with 25% protein (3.0 and 3.6 kg, respectively); in those assigned to a diet with 20% fat and those assigned to a diet with 40% fat (3.3 kg for both groups); and in those assigned to a diet with 65% carbohydrates and those assigned to a diet with 35% carbohydrates (2.9 and 3.4 kg, respectively) ($P>0.20$ for all comparisons). Among the 80% of participants who completed the trial, the average weight loss was 4 kg; 14 to 15% of the participants had a reduction of at least 10% of their initial body weight. Satiety, hunger, satisfaction with the diet, and attendance at group sessions were similar for all diets; attendance was strongly associated with weight loss (0.2 kg per session attended). The diets improved lipid-related risk factors and fasting insulin levels.

CONCLUSIONS

Reduced-calorie diets result in clinically meaningful weight loss regardless of which macronutrients they emphasize. (ClinicalTrials.gov number, NCT00072995.)

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THERE IS INTENSE DEBATE ABOUT WHAT types of diet are most effective for treating overweight — those that emphasize protein, those that emphasize carbohydrates, or those that emphasize fat.¹⁻³ Several trials showed that low-carbohydrate, high-protein diets resulted in more weight loss over the course of 3 to 6 months than conventional high-carbohydrate, low-fat diets,⁴⁻¹² but other studies did not show this effect.¹³⁻¹⁷ A smaller group of studies that extended the follow-up to 1 year did not show that low-carbohydrate, high-protein diets were superior to high-carbohydrate, low-fat diets.^{6,10,16,18-21} In contrast, other researchers found that a very-high-carbohydrate, very-low-fat vegetarian diet was superior to a conventional high-carbohydrate, low-fat diet.²²⁻²⁴ Among the few studies that extended beyond 1 year, one showed that a very-low-fat vegetarian diet was superior to a conventional low-fat diet,²⁴ one showed that a low-fat diet was superior to a moderate-fat diet,²⁵ two showed that a moderate-fat, Mediterranean-style diet was superior to a low-fat diet,^{12,26} one showed that a low-carbohydrate diet was superior to a low-fat diet,¹² and another showed no difference between high-protein and low-protein diets.¹⁰ Small samples, underrepresentation of men, limited generalizability, a lack of blinded ascertainment of the outcome, a lack of data on adherence to assigned diets, and a large loss to follow-up limit the interpretation of many weight-loss trials.²⁷ The novelty of the diet, media attention, and the enthusiasm of the researchers could affect the adherence of participants to any type of diet. The crucial question is whether overweight people have a better response in the long term to diets that emphasize a specific macronutrient composition. Thus, we recognized the need for a large trial that would be designed to overcome the limitations of previous trials and that would compare the effects of three principal dietary macronutrients. We studied weight change over the course of 2 years, since weight loss typically is greatest 6 to 12 months after initiation of the diet, with steady regain of weight subsequently.²⁸

METHODS

STUDY DESIGN AND SITES

We designed a randomized clinical trial to compare the effects on body weight of energy-reduced diets that differed in their targets for intake of macronutrients — low or high in fat, average or

high in protein, or low or high in carbohydrates — and otherwise followed recommendations for cardiovascular health.²⁹ The trial was conducted from October 2004 through December 2007. An expanded description of the methods is available in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was conducted at two sites: the Harvard School of Public Health and Brigham and Women's Hospital, Boston; and the Pennington Biomedical Research Center of the Louisiana State University System, Baton Rouge. The data coordinating center was at Brigham and Women's Hospital. The project staff of the National Heart, Lung, and Blood Institute also participated in the development of the protocol, monitoring of progress, interpretation of results, and critical review of the manuscript.

PARTICIPANTS

Our goal was to recruit 800 overweight and obese subjects (400 at each site), of whom about 40% would be men. Participants had to be 30 to 70 years of age and have a body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 to 40. Major criteria for exclusion were the presence of diabetes or unstable cardiovascular disease, the use of medications that affect body weight, and insufficient motivation as assessed by interview and questionnaire. The study was approved by the human subjects committee at each institution and by a data and safety monitoring board appointed by the National Heart, Lung, and Blood Institute. All participants gave written informed consent. They were informed that the study would be comparing diets with different fat, protein, and carbohydrate contents and that they would be assigned a diet at random. Mass mailings were the primary means of recruitment; names were identified with the use of lists of registered voters or drivers. Random assignments to one of four diet groups were generated by the data manager at the coordinating center on request of a study dietitian, after eligibility of a participant was confirmed.

WEIGHT-LOSS INTERVENTION

The nutrient goals for the four diet groups were: 20% fat, 15% protein, and 65% carbohydrates (low-fat, average-protein); 20% fat, 25% protein, and 55% carbohydrates (low-fat, high-protein); 40% fat, 15% protein, and 45% carbohydrates (high-fat, average-protein); and 40% fat, 25% protein, and 35% carbohydrates (high-fat, high-protein). Thus, two diets were low-fat and two were high-fat, and two

were average-protein and two were high-protein, constituting a two-by-two factorial design. The four diets also allowed for a dose–response test of carbohydrate intake that ranged from 35 to 65% of energy. Other goals for all groups were that the diets should include 8% or less of saturated fat, at least 20 g of dietary fiber per day, and 150 mg or less of cholesterol per 1000 kcal. Carbohydrate-rich foods with a low glycemic index were recommended in each diet. Each participant's caloric prescription represented a deficit of 750 kcal per day from baseline, as calculated from the person's resting energy expenditure and activity level.

Blinding was maintained by the use of similar foods for each diet. Staff and participants were taught that each diet adhered to principles of a healthful diet²⁹ and that each had been recommended for long-term weight loss, thereby establishing equipoise.^{1,2,26} Investigators and staff who measured outcomes were unaware of the diet assignment of the participants.

Group sessions were held once a week, 3 of every 4 weeks during the first 6 months and 2 of every 4 weeks from 6 months to 2 years; individual sessions were held every 8 weeks for the entire 2 years. Daily meal plans in 2-week blocks were provided (see the Supplementary Appendix). Participants were instructed to record their food and beverage intake in a daily food diary and in a Web-based self-monitoring tool that provided information on how closely their daily food intake met the goals for macronutrients and energy. Behavioral counseling was integrated into the group and individual sessions to promote adherence to the assigned diets. Contact among the groups was avoided.

The goal for physical activity was 90 minutes of moderate exercise per week. Participation in exercise was monitored by questionnaire³⁰ and by the online self-monitoring tool.

MEASUREMENTS

Body weight and waist circumference were measured in the morning before breakfast on 2 days at baseline, 6 months, and 2 years, and on a single day at 12 and 18 months. Dietary intake was assessed in a random sample of 50% of the participants, by a review of the 5-day diet record at baseline and by 24-hour recall during a telephone interview on 3 nonconsecutive days at 6 months and at 2 years.³¹ Questionnaires that asked for information on satiety, food craving, eating behavior, and satisfaction with the diet^{32,33} were admin-

istered at baseline (except for diet satisfaction) and at 6 months and 2 years. Fasting blood samples, 24-hour urine samples, and measurement of resting metabolic rate were obtained on 1 day, and blood-pressure measurement on 2 days, at baseline, 6 months, and 2 years. Levels of serum lipids, glucose, insulin, and glycated hemoglobin were measured at the clinical laboratory at the Pennington Biomedical Research Center. Blood pressure was measured with the use of an automated device (HEM-907XL, Omron). The participants were evaluated for the presence of the metabolic syndrome, which was defined by the presence of at least three of the following five criteria: waist circumference of more than 102 cm in men or more than 88 cm in women, a triglyceride level of 150 mg per deciliter (1.69 mmol per liter) or more, a high-density lipoprotein (HDL) cholesterol level of less than 40 mg per deciliter (1.03 mmol per liter) in men or less than 50 mg per deciliter (1.29 mmol per liter) in women, a blood pressure of 130/85 mm Hg or more, and a fasting glucose level of 110 mg per deciliter (6.1 mmol per liter) or more.

STATISTICAL ANALYSIS

The primary outcome of the study was the change in body weight over a period of 2 years, and the secondary outcome was the change in waist circumference. Data were pooled from the diets for the two factorial comparisons: low fat versus high fat and average protein versus high protein. The analysis also included a comparison of two of the four diets, the diet with the lowest carbohydrate content and the diet with the highest carbohydrate content, and included a test for trend across the four levels of carbohydrates. The effects of protein, fat, and carbohydrate levels were evaluated independently with the use of two-sample t-tests at a two-sided significance level of 0.05. Exploratory post hoc analyses were performed with threshold amounts of weight loss as outcomes, with Bonferroni's adjustment for multiple comparisons. Associations between adherence to the fat and protein goals and weight loss were also explored in post hoc analyses (see Methods in the Supplementary Appendix).

We performed an intention-to-treat analysis in which long-term weight loss for persons who withdrew from the study early (after at least 6 months of participation) was imputed on the basis of a rate of 0.3 kg per month of regained weight³⁴ and a rate of 0.3 cm per month of regained waist circumference after withdrawal (see Methods in the Sup-

plementary Appendix). Risk factors for cardiovascular disease and diabetes were also analyzed according to the intention-to-treat principle, with zero change from baseline imputed for missing data. The study was powered to detect a 1.67-kg weight loss as an effect of the level of protein or fat in the diet over the 2-year period, assuming a withdrawal rate of 40%.

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic	Low-Fat, Average-Protein Group (N=204)	Low-Fat, High-Protein Group (N=202)	High-Fat, Average-Protein Group (N=204)	High-Fat, High-Protein Group (N=201)	All Participants (N=811)	Participants Who Completed the Study (N=645)
Age — yr	51±9	50±10	52±9	51±9	51±9	52±9
Sex — no. (%)						
Female	126 (62)	135 (67)	125 (61)	129 (64)	515 (64)	397 (62)
Male	78 (38)	67 (33)	79 (39)	72 (36)	296 (36)	248 (38)
Race or ethnic group — no. (%)†						
White	159 (78)	158 (78)	165 (81)	161 (80)	643 (79)	525 (81)
Black	33 (16)	33 (16)	28 (14)	33 (16)	127 (16)	88 (14)
Asian	1 (<1)	1 (<1)	1 (<1)	2 (1)	5 (1)	3 (<1)
Hispanic	8 (4)	7 (3)	9 (4)	5 (2)	29 (4)	23 (4)
Other	3 (1)	3 (1)	1 (<1)	0	7 (1)	6 (1)
Height — m	1.69±0.09	1.67±0.08	1.68±0.09	1.68±0.09	1.68±0.09	1.68±0.09
Weight — kg	94±16	92±13	92±17	94±16	93±16	93±16
Body-mass index‡						
Mean	33±4	33±4	32±4	33±4	33±4	33±4
25.0–29.9 — no. (%)	51 (25)	54 (27)	60 (29)	58 (29)	223 (27)	183 (28)
≥30.0 — no. (%)	153 (75)	148 (73)	144 (71)	143 (71)	588 (73)	462 (72)
Waist circumference — cm	104±13	102±12	103±14	104±13	103±13	104±13
Hypertension — no. (%)	70 (34)	70 (35)	67 (33)	80 (40)	287 (35)	233 (36)
Use of medication — no. (%)						
Antihypertensive agents	54 (26)	58 (29)	55 (27)	61 (30)	228 (28)	192 (30)
Lipid-lowering agents	32 (16)	48 (24)	40 (20)	31 (15)	151 (19)	128 (20)
Smoking status — no. (%)						
Current smoker	8 (4)	5 (2)	8 (4)	10 (5)	31 (4)	24 (4)
Former smoker	84 (41)	59 (29)	80 (39)	75 (37)	298 (37)	241 (37)
Never smoked	112 (55)	138 (68)	116 (57)	116 (58)	482 (59)	380 (59)
Educational level — no. (%)						
High school or less	23 (11)	15 (7)	19 (9)	19 (9)	76 (9)	65 (10)
Some college	47 (23)	47 (23)	45 (22)	41 (20)	180 (22)	132 (20)
College graduate or beyond	134 (66)	140 (69)	140 (69)	141 (70)	555 (68)	448 (69)
Marital status — no. (%)						
Married	132 (65)	146 (72)	144 (71)	143 (71)	565 (70)	448 (69)
Divorced or separated	36 (18)	24 (12)	33 (16)	29 (14)	122 (15)	94 (15)
Widowed	8 (4)	4 (2)	4 (2)	2 (1)	18 (2)	16 (2)
Never married	28 (14)	28 (14)	23 (11)	27 (13)	106 (13)	87 (13)

Table 1. (Continued.)

Characteristic	Low-Fat, Average-Protein Group (N=204)	Low-Fat, High-Protein Group (N=202)	High-Fat, Average-Protein Group (N=204)	High-Fat, High-Protein Group (N=201)	All Participants (N=811)	Participants Who Completed the Study (N=645)
Household income — no. (%)						
<\$50,000	56 (27)	45 (22)	48 (24)	46 (23)	195 (24)	153 (24)
\$50,000 to <\$100,000	79 (39)	82 (41)	78 (38)	84 (42)	323 (40)	260 (40)
\$100,000 to \$150,000	46 (23)	43 (21)	43 (21)	32 (16)	164 (20)	123 (19)
>\$150,000	21 (10)	30 (15)	33 (16)	36 (18)	120 (15)	100 (16)
Information not provided	2 (1)	2 (1)	2 (1)	3 (1)	9 (1)	9 (1)
Risk factors						
Blood pressure — mm Hg						
Systolic	118±13	120±13	120±13	120±15	119±13	119±14
Diastolic	75±9	75±9	76±9	76±10	75±9	75±9
Glucose — mg/dl	93±12	92±17	92±12	92±13	92±14	92±12
Insulin — μ U/ml	12±7	12±8	12±7.5	12±8	12±8	12±7
HOMA	2.8±1.9	2.8±2.2	2.9±1.9	2.8±1.9	2.8±2	2.8±1.9
Cholesterol — mg/dl						
Total	199±38	203±36	203±37	204±35	202±37	202±37
LDL	124±33	126±32	128±32	126±31	126±32	125±32
HDL	49±15	49±13	48±12	51±16	49±14	49±15
Triglycerides — mg/dl	135±82	144±79	147±93	141±85	142±85	144±87
Dietary intake per day [§]						
No. of participants who provided information	103	106	105	102	416	330
Energy — kcal	2015±505	1862±566	2012±597	1979±599	1966±570	1978±563
Carbohydrate — %	44±8	46±8	45±8	44±7	45±8	45±8
Fat — %	38±6	36±6	37±5	38±6	37±6	37±6
Saturated fat — %	12±3	12±3	12±3	12±2	12±3	12±3
Protein — %	18±4	18±4	18±3	18±3	18±3	18±3
Dietary fiber — g	18±7	17±7	18±6	17±6	17±7	18±7
Cholesterol — mg	303±121	278±120	306±135	305±134	298±128	298±128
Alcohol — g	6±8	4±7	6±9	6±9	5±8	5±8
Respiratory quotient	0.84±0.04	0.84±0.04	0.85±0.05	0.84±0.04	0.84±0.04	0.84±0.04

* Plus-minus values are means \pm SD. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, HOMA homeostasis model assessment of insulin sensitivity, and LDL low-density lipoprotein.

† Race or ethnic group was reported by the participants.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

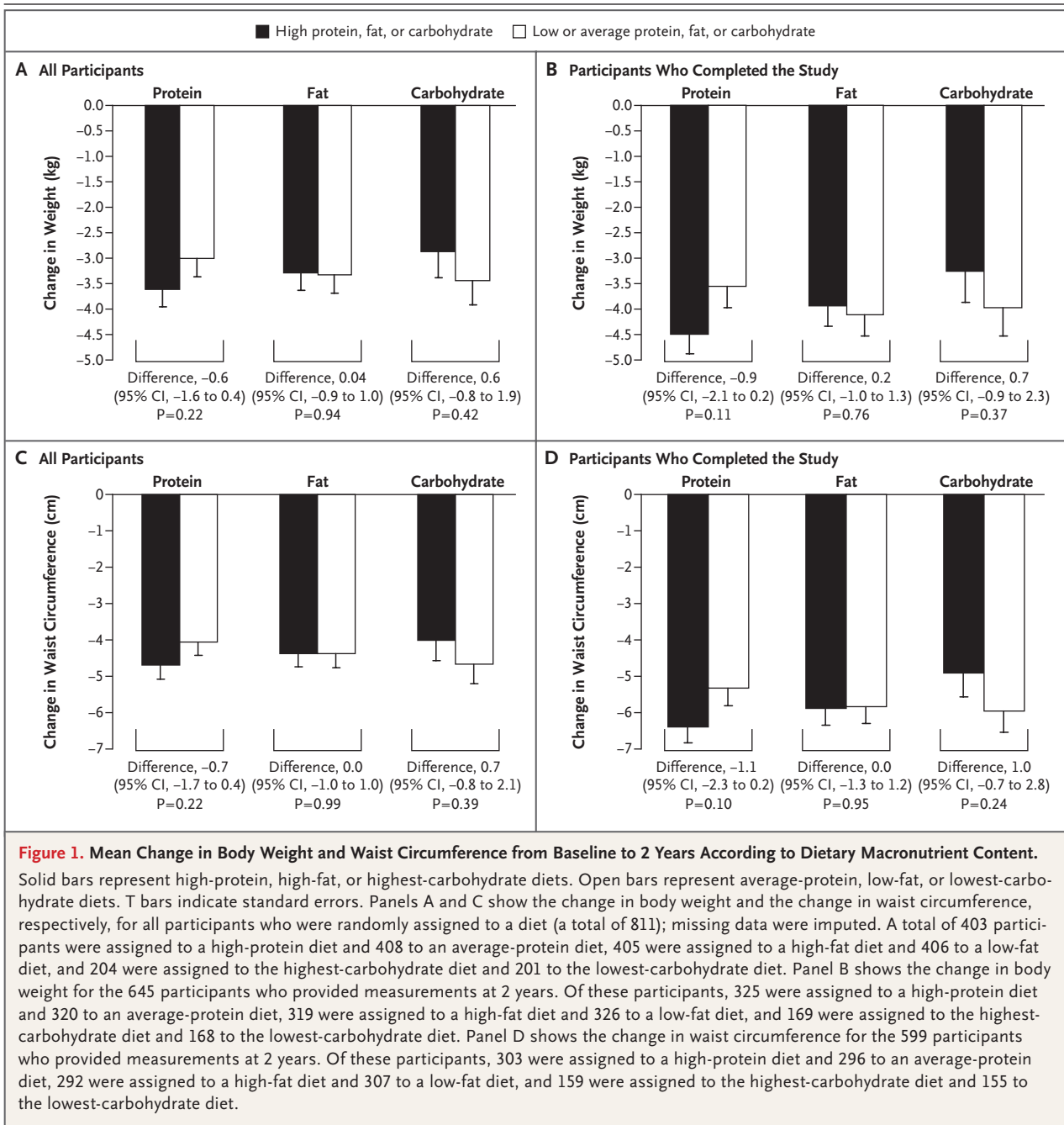
§ Data are from a 50% random sample.

RESULTS

PARTICIPANTS

Of 1638 participants who were screened, 811 (50%) were randomly assigned to a diet, and 645 (80%

of those assigned) completed the study (i.e., provided a body-weight measurement at 2 years) (Fig. 1 in the Supplementary Appendix). Baseline characteristics were similar among participants assigned to the four diets and between those who were as-



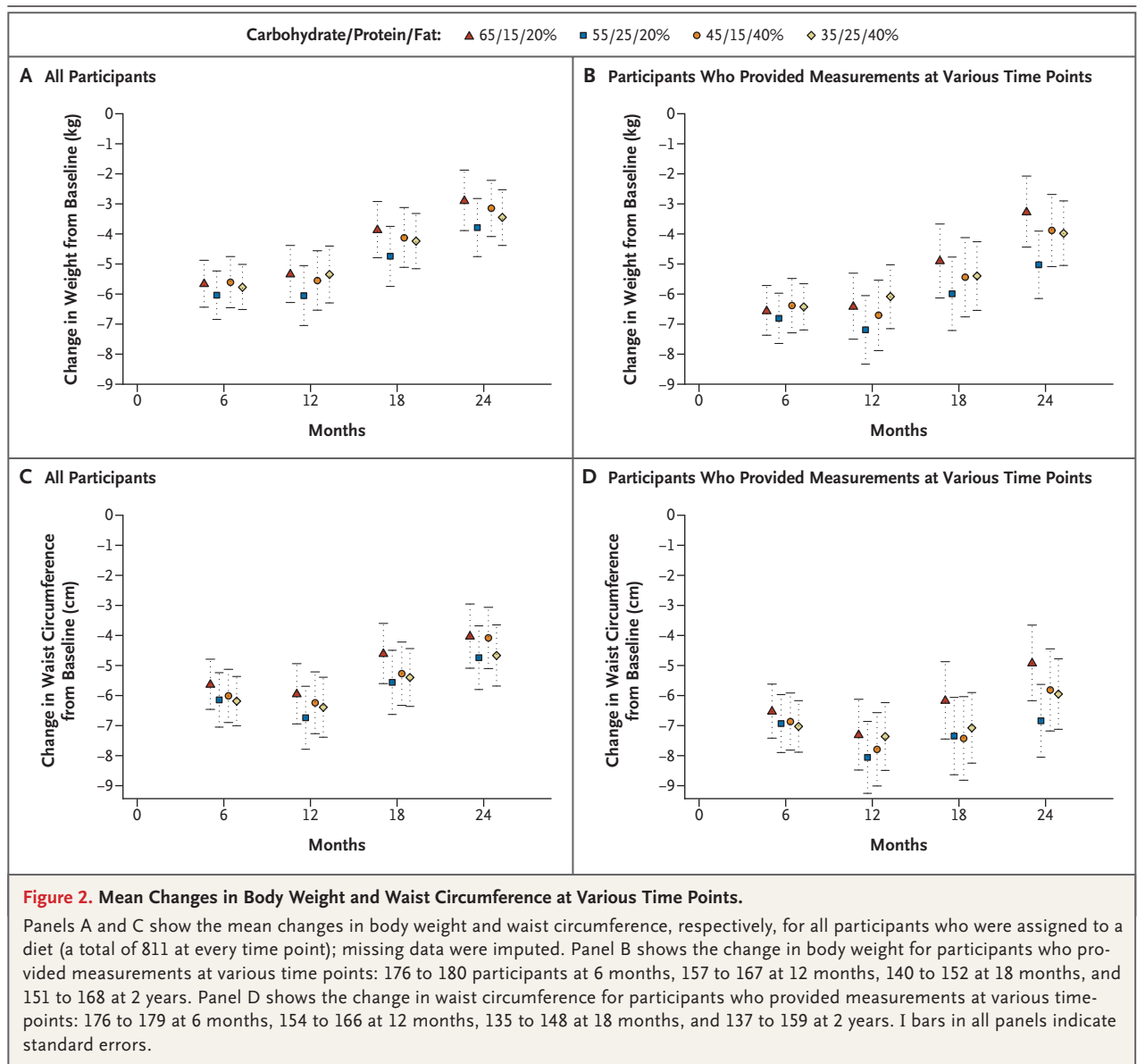
signed to a diet and those who completed the study (Table 1).

WEIGHT LOSS

The amount of weight loss after 2 years was similar in participants assigned to a diet with 25% protein and those assigned to a diet with 15% protein (3.6 and 3.0 kg, respectively; P=0.22) and among those who completed each of those diets (4.5 and 3.6 kg, respectively; P=0.11) (Fig. 1). Weight

loss was the same in those assigned to a diet with 40% fat and those assigned to a diet with 20% fat (3.3 kg, P=0.94) and was similar among those who completed each of those diets (3.9 and 4.1 kg, respectively; P=0.76). There was no effect on weight loss of carbohydrate level through the target range of 35 to 65% (Fig. 1 and 2). The change in waist circumference did not differ significantly among the diet groups (Fig. 1 and 2).

Most of the weight loss occurred in the first



6 months. Changes from baseline differed among the diet groups by less than 0.5 kg of body weight and 0.5 cm of waist circumference (Fig. 2). After 12 months, all groups, on average, slowly regained body weight. A total of 185 of the participants (23%) continued to lose weight from 6 months to 2 years; the mean (\pm SD) additional weight loss was 3.6 ± 3.5 kg, for a mean total loss from baseline of 9.3 ± 8.2 kg, with no significant differences among the diet groups. At 2 years, 31 to 37% of the participants had lost at least 5% of their initial body weight, 14 to 15% of the participants in each diet group had lost at least 10% of their initial weight,

and 2 to 4% had lost 20 kg or more ($P>0.20$ for the comparisons between diets).

RISK FACTORS FOR CARDIOVASCULAR DISEASE AND DIABETES

All the diets reduced risk factors for cardiovascular disease and diabetes at 6 months and 2 years (Table 2). At 2 years, the two low-fat diets and the highest-carbohydrate diet decreased low-density lipoprotein cholesterol levels more than did the high-fat diets or the lowest-carbohydrate diet (low-fat vs. high-fat, 5% vs. 1% [$P=0.001$]; highest-carbohydrate vs. lowest-carbohydrate, 6% vs. 1%

Table 2. Risk Factors, Nutrient Intake, and Biomarkers of Adherence, According to Diet, at 6 Months and 2 Years.*

Variable	Low Fat, Average Protein				Low Fat, High Protein			
	6-Mo Value	Change from Baseline	2-Yr Value	Change from Baseline	6-Mo Value	Change from Baseline	2-Yr Value	Change from Baseline
Risk factors†								
Cholesterol (mg/dl)								
Total	188±36	-5.9	192±37	-3.7	193±39	-4.9	197±40	-2.9
LDL	116±29	-6.6	117±31	-5.9	120±33	-4.8	121±33	-3.9
HDL	49±13	-0.4	51±15	5.6	51±13	2.7	53±15	6.5
Triglycerides (mg/dl)								
	116±73	-14.2	120±83	-11.5	114±63	-20.4	120±67	-16.6
Blood pressure (mm Hg)								
Systolic	116±12	-1.2	117±12	-0.8	117±12	-2.6	118±13	-1.7
Diastolic	74±9	-1.4	74±9	-0.8	73±9	-3.1	74±9	-1.3
Glucose (mg/dl)								
	90±11	-3.0	94±12	1.1	90±16	-2.6	93±17	1.0
Insulin (μU/ml)								
	10±7	-16.2	12±10	-2.4	10±6	-19.9	11±8	-11.5
HOMA								
	2.3±1.6	-18.7	2.8±2.3	-1.4	2.2±1.6	-22.7	2.5±2.2	-10.4
Nutrient intake per day								
Energy (kcal)	1636±484	-477	1531±480	-554	1572±568	-353	1560±461	-402
Carbohydrate (%)	57.5±11.1	12.8	53.2±11	9.3	53.4±8.5	7.4	51.3±9.2	6.8
Protein (%)	17.6±3.4	0.2	19.6±3.9	2.1	21.8±3.8	3.9	20.8±4	2.5
Fat (%)	26.2±8	-11.8	26.5±8	-12.0	25.9±6.8	-10.1	28.4±8.1	-8.4
Saturated fat (%)	7.5±3.2	-4.9	8±3.1	-4.3	7.9±2.7	-3.9	8.9±3.8	-3.1
Biomarkers of adherence								
Urinary nitrogen (g)‡	11.1±4.1	-11.5	11.8±4.6	-9.1	11.9±4.3	-2.5	11.8±3.9	-2.8
Respiratory quotient§	0.84±0.04	0.58	0.83±0.04	-0.48	0.84±0.04	0.16	0.84±0.04	-0.84

* Plus-minus values are means ±SD. Change from baseline is percent change in the case of risk factors and biomarkers of adherence and actual change in the case of nutrient intake per day. Nutrient intake was determined by three 24-hour recalls. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. HDL denotes high-density lipoprotein, HOMA homeostasis model assessment of insulin sensitivity, and LDL low-density lipoprotein.

† Data were included for 201 participants per group; missing values were imputed.

‡ Data were included for 200 to 204 participants per group at baseline, 139 to 153 at 6 months, and 88 to 109 at 2 years.

§ Data were included for 201 to 204 participants per group at baseline, 157 to 164 at 6 months, and 113 to 132 at 2 years.

[$P=0.01$]). The lowest-carbohydrate diet increased HDL cholesterol levels more than the highest-carbohydrate diet (9% vs. 6%, $P=0.02$). All the diets decreased triglyceride levels similarly, by 12 to 17%. All the diets except the one with the highest carbohydrate content decreased fasting serum insulin levels by 6 to 12%; the decrease was larger with the high-protein diet than with the average-protein diet (10% vs. 4%, $P=0.07$). Blood pressure decreased from baseline by 1 to 2 mm Hg, with no significant differences among the groups ($P>0.59$ for all comparisons). These changes in risk factors in the intention-to-treat population were about 30 to 40% smaller than the changes seen among

participants who provided data at 2 years, reflecting the effect of the imputation of missing values (Table 1 in the Supplementary Appendix). The metabolic syndrome³⁵ was present in 32% of the participants at baseline, and the percentage was lower at 2 years, ranging from 19 to 22% in the four diet groups ($P=0.81$ for the four-way comparison).

ADHERENCE, DIET ACCEPTABILITY, SATIETY, AND SATISFACTION

Mean reported intakes at 6 months and 2 years did not reach the target levels for macronutrients (Table 2). The reported intakes represented differ-

6-Mo Value	High Fat, Average Protein			High Fat, High Protein			
	Change from Baseline	2-Yr Value	Change from Baseline	6-Mo Value	Change from Baseline	2-Yr Value	Change from Baseline
195±39	-3.7	202±39	-0.3	199±35	-2.3	202±38	-0.8
123±33	-3.2	127±33	-0.2	124±31	-1.1	124±31	-1.3
49±13	2.9	51±13	6.3	53±15	4.0	55±17	8.8
120±88	-18.1	129±89	-12.4	114±71	-19.5	118±71	-16.7
118±12	-1.5	118±12	-1.3	119±12	-1.7	120±14	-0.7
74±9	-2.3	75±9	-1.5	74±9	-1.8	76±9	-0.3
90±12	-1.9	93±13	1.6	91±12	-1.2	94±15	2.8
10±7	-18.2	12±8	-6.4	10±9	-14.4	11±7	-9.2
2.4±1.8	-18.6	2.8±2.1	-3.5	2.4±2.9	-13.4	2.6±1.9	-6.3
1607±499	-456	1521±530	-434	1624±484	-385	1413±427	-389
49.1±8.6	5.0	48.6±10	2.4	43±6.7	-0.2	42.9±8.3	-0.4
18.4±4.5	0.5	19.6±5.2	2.1	22.6±4.4	4.3	21.2±5.2	3.4
33.9±6.7	-3.8	33.3±8.2	-3.5	34.3±7.8	-3.7	35.1±7	-3.4
9±2.5	-3.0	9.8±3.3	-2.1	9±2.6	-3.7	10.5±2.7	-1.7
10.3±4.4	-17.3	11.2±3.8	-8.8	12.6±4.7	0.7	12.5±5.3	-1.9
0.84±0.04	-1.58	0.83±0.04	-3.16	0.84±0.04	-0.52	0.83±0.04	-1.92

ences from target levels of fat, protein, and carbohydrate intake of 8.0, 4.2, and 14.4 percentage points, respectively, at 6 months and 6.7, 1.4, and 10.2 percentage points, respectively, at 2 years. Reported energy intakes and physical activity were similar among the diet groups. The participants who completed the study had a mean weight loss of 6.5 kg at 6 months, which corresponds to a reduction in daily energy intake of approximately 225 kcal.

There was a larger increase from baseline in the HDL cholesterol level, a biomarker for dietary carbohydrate, in the lowest-carbohydrate group than in the highest-carbohydrate group (a difference in the change of 2 mg per deciliter at 2 years) (Table 1 in the Supplementary Appendix); this difference corresponds to a predicted difference in carbohydrate intake of 6%.³⁶ There was a larger decrease in urinary nitrogen excretion from baseline in the average-protein group than in the high-

protein group (a difference in the change of 1.6 g at 6 months and 0.8 g at 2 years) (Table 3); these differences correspond to a difference in dietary protein of 10 g per day and 5 g per day, respectively. The respiratory quotient was 0.84 at baseline in both the high-fat and low-fat groups, and the between-group difference in the change at 2 years (the value in the high-fat group minus the value in the low-fat group) was -0.02 ($P=0.002$) (Table 3). Thus, changes in biomarkers confirmed that differences among the groups in macronutrient intake were consistent with those recorded in the dietary reports and that participants modified their intake of macronutrients in the direction of the goals, although the targets were not fully achieved.

Craving, fullness, and hunger and diet-satisfaction scores were similar at 6 months and at 2 years among the diets (Table 2 in the Supplementary Appendix).

Table 3. Factorial-Design Estimates of Effect of Diet Type on Mean Changes from Baseline in Risk Factors, Nutrient Intake, and Biomarkers of Adherence.*

Variable	Change with High Fat minus Change with Low Fat			Change with High Protein minus Change with Average Protein			Change with Highest Carbohydrate minus Change with Lowest Carbohydrate					
	At 6 Mo	P Value	At 2 Yr	P Value	At 6 Mo	P Value	At 2 Yr	P Value	At 6 Mo	P Value	At 2 Yr	P Value
Risk factors†												
Cholesterol (mg/dl)												
Total	4.7±1.8	0.01	5.6±1.9	0.003	2.3±1.8	0.20	0.2±1.9	0.92	-7.0±2.6	0.007	-5.8±2.6	0.02
LDL	4.4±1.6	0.005	5.1±1.6	0.001	2.4±1.6	0.13	0.5±1.6	0.74	-6.8±2.3	0.003	-5.7±2.2	0.01
HDL	1.1±0.5	0.01	0.7±0.5	0.12	1.1±0.5	0.02	0.9±0.5	0.05	-2.2±0.6	0.001	-1.7±0.7	0.01
Triglycerides (mg/dl)	-2.8±4.3	0.52	-1.2±4.0	0.76	-5.4±4.3	0.21	-6.7±4.0	0.10	8.1±5.0	0.10	7.9±6.0	0.19
Blood pressure (mm Hg)												
Systolic	0.4±0.7	0.59	0.3±0.7	0.64	-1.0±0.7	0.14	-0.2±0.7	0.77	0.6±0.9	0.51	-0.1±0.9	0.89
Diastolic	0.1±0.5	0.77	0.1±0.5	0.85	-0.5±0.5	0.32	0.2±0.5	0.59	0.3±0.7	0.62	-0.3±0.7	0.61
Glucose (mg/dl)	1.2±0.6	0.04	1.1±0.5	0.05	0.5±0.6	0.38	0.5±0.6	0.34	-1.7±0.9	0.04	-1.6±0.8	0.06
Insulin (μU/ml)	0.2±0.4	0.68	-0.1±0.4	0.77	0.0±0.4	0.91	-0.7±0.4	0.07	-0.2±0.7	0.74	0.8±0.6	0.19
HOMA	0.13±0.13	0.31	0.03±0.10	0.78	0.03±0.13	0.84	-0.16±0.10	0.12	-0.15±0.21	0.46	0.13±0.16	0.42
Nutrient intake per day												
Energy (kcal)	11.4±53.9	0.83	-75.6±70.9	0.29	-23.2±53.9	0.67	-35.5±71.0	0.62	11.1±71.8	0.88	118.1±96.6	0.23
Carbohydrate (%)	-9.5±1.0	<0.001	-6.4±1.5	<0.001	-5.2±1.1	<0.001	-3.6±1.5	0.02	14.4±1.4	<0.001	10.2±2.1	<0.001
Protein (%)	0.9±0.5	0.06	0.2±0.7	0.77	4.2±0.4	<0.001	1.4±0.7	0.05	-5.0±0.6	<0.001	-1.6±1.0	0.10
Fat (%)	8.0±0.8	<0.001	6.7±1.2	<0.001	0.2±0.9	0.82	1.8±1.3	0.15	-8.1±1.2	<0.001	-8.6±1.6	<0.001
Saturated fat (%)	1.3±0.3	<0.001	1.7±0.5	<0.001	0.2±0.3	0.43	0.8±0.5	0.12	-1.5±0.4	0.001	-2.5±0.6	<0.001
Biomarkers of adherence												
Urinary nitrogen (g)‡	-0.11±0.39	0.77	0.08±0.42	0.84	1.64±0.38	<0.001	0.81±0.42	0.06	-1.50±0.55	0.006	-0.89±0.65	0.18
Respiratory quotient§	-0.01±0.00	0.005	-0.02±0.00	0.002	0.00±0.00	0.52	0.00±0.00	0.51	0.01±0.01	0.13	0.01±0.01	0.07

* Plus-minus values are means ±SE. Nutrient intake was determined by three 24-hour recalls. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for glucose to millimoles per liter, multiply by 0.05551. HDL denotes high-density lipoprotein, HOMA homeostasis model assessment of insulin sensitivity, and LDL low-density lipoprotein.

† Data were included for 201 participants per group; missing values were imputed.

‡ Data were included for 200 to 204 participants per group at baseline, 139 to 153 at 6 months, and 88 to 109 at 2 years.

§ Data were included for 201 to 204 participants per group at baseline, 157 to 164 at 6 months, and 113 to 132 at 2 years.

WEIGHT CHANGE ACCORDING TO ATTENDANCE AT GROUP SESSIONS AND DIETARY ADHERENCE

Attendance at group sessions strongly predicted weight loss at 2 years (0.2 kg for every session attended) and was similar among the diet groups ($P=0.22$ for a test of difference in slopes) (Fig. 3). Adherence to the goal for protein intake was associated with more weight loss only in the high-protein groups, and adherence to the goal for fat intake was associated with more weight loss only in the low-fat groups ($P<0.001$) (Fig. 4). The ranges of protein and fat intakes overlapped substantially in the diet groups. Thus, a low-fat intake of 25% was associated with increased weight loss in the low-fat groups but not in the high-fat groups, and a high-protein intake of 24 to 25% was associated with increased weight loss in the high-protein groups but not in the average-protein groups. Attendance at group sessions was associated with adherence to the fat and protein goals only in the high-protein and low-fat groups (Fig. 4).

ADVERSE EFFECTS

Serious adverse events were reported by 57 participants (7%); there were no significant differences in the rates among diets. The ratio of urinary microalbumin to creatinine was more than 30 in five participants in the average-protein group and in five participants in the high-protein group at 6 months and in seven participants, all in the average-protein groups, at 2 years.

DISCUSSION

In this population-based trial, participants were assigned to and taught about diets that emphasized different contents of carbohydrates, fat, and protein and were given reinforcement for 2 years through group and individual sessions. The principal finding is that the diets were equally successful in promoting clinically meaningful weight loss and the maintenance of weight loss over the course of 2 years. Satiety, hunger, satisfaction with the diet, and attendance at group sessions were similar for all diets. The diets improved lipid risk factors and fasting insulin levels in the directions that would be expected on the basis of macronutrient content. The study had a large sample, a high rate of retention, and the sensitivity to detect small changes in weight. The population was diverse with respect to age, income, and geography and included a large percentage of men. The participants were

eager to lose weight and to attempt whatever type of diet they were assigned, and they did well in screening interviews and questionnaires that evaluated their motivation. Thus, the findings should be directly applicable to both clinicians' recommendations for weight loss in individual patients and the development of population-wide recommendations by public health officials.

Despite the intensive behavioral counseling in our study, participants had difficulty achieving the goals for macronutrient intake of their assigned group. The mean differences among the groups in fat, carbohydrate, or protein intake at 6 months were nevertheless often greater than those in several previous trials comparing diets for weight loss.^{11,12,19,21,26} Substantially diminished adherence after the first few months is typical in weight-loss trials^{5,6,8,10-12,19,21,24,26} and occurred between 6 months and 2 years in our trial. Only two trials have reported dietary intake beyond 1 year,^{12,26} and one of them provided foods to the participants.¹² In addition, trials of low-carbohydrate diets have reported a very low incidence of urinary ketosis after 6 months,^{6,8,12} suggesting that in most overweight people, it is futile to sustain a low intake of carbohydrates. Overall, these findings with respect to adherence to macronutrient goals suggest that participants in weight-loss programs revert to their customary macronutrient intakes over time but may nonetheless be able to maintain weight loss.

We explored the association of achieved nutrient intakes with weight loss. We caution that these post hoc analyses do not have the strong validity of the main analysis of this controlled trial, which compared randomized groups. Protein and fat intakes overlapped among the groups. A high-protein intake was associated with weight loss only in the high-protein groups, and a low-fat intake was associated with weight loss only in the low-fat groups. The protein and fat contents of the participants' usual diet were closer to the goals for the average-protein and high-fat diets than to those for the high-protein and low-fat diets. Thus, the participants assigned to an average-protein or high-fat diet did not have to change their customary level of dietary protein and fat very much and could focus more on reducing dietary intake. In contrast, the participants in the high-protein or low-fat groups had more challenging dietary goals. It is therefore not surprising that attendance at group sessions was strongly related to adherence

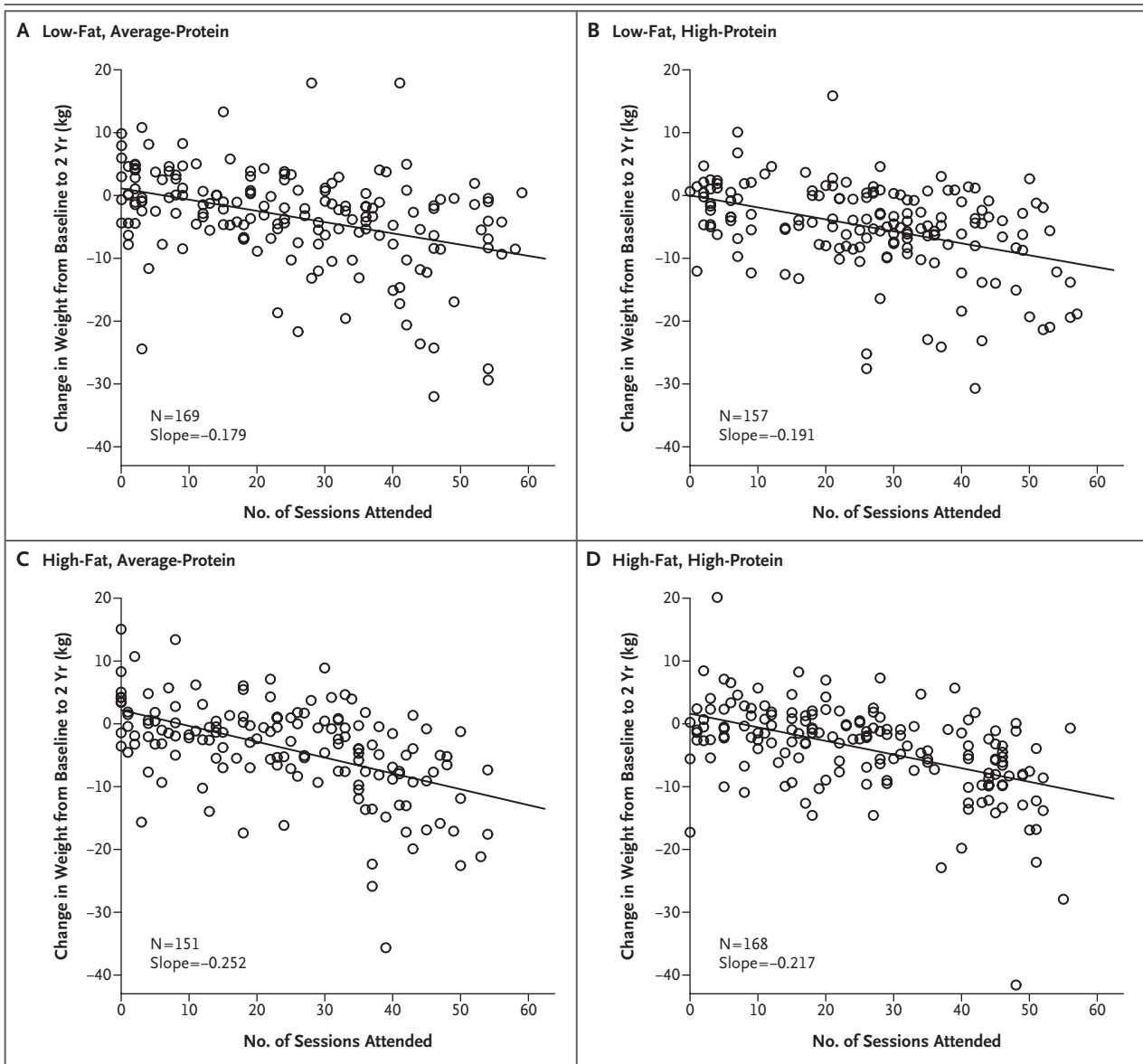


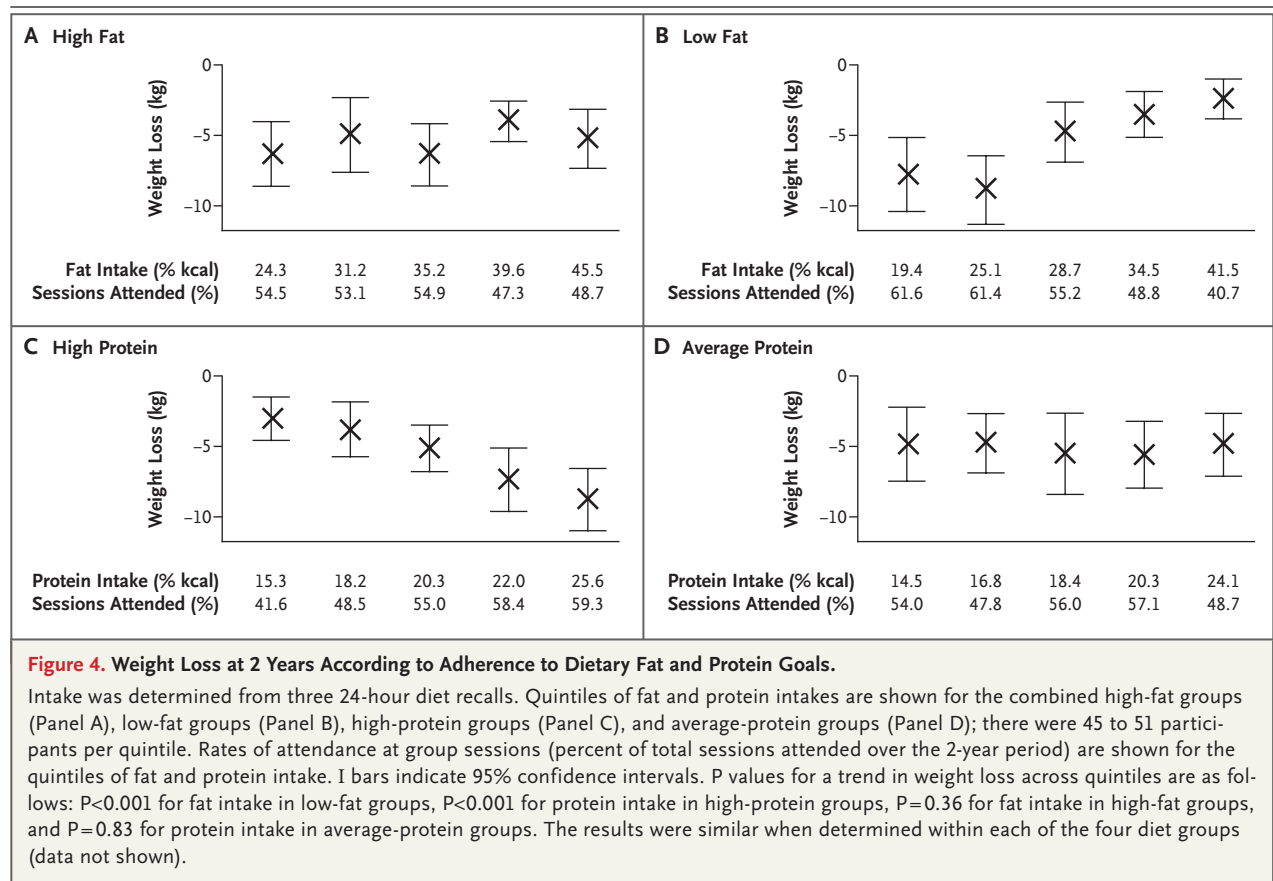
Figure 3. Change in Body Weight from Baseline to 2 Years According to Attendance at Counseling Sessions for Weight Loss, among the 645 Participants Who Completed the Study.

Panel A shows data for the low-fat, average-protein group; Panel B, for the low-fat, high-protein group; Panel C, for the high-fat, average-protein group; and Panel D, for the high-fat, high-protein group. There were no significant differences among the regression coefficients ($P>0.2$ for all comparisons; $R^2=0.2$ for total cohort).

to high-protein or low-fat goals but not to the goals in the average-protein or high-fat groups. However, attendance had a strong association with weight loss, and the association was similar across diet groups. We view attendance at counseling sessions as a proxy for commitment to achieving weight loss and for engagement in the program. Study participants who attended two thirds of the sessions over the course of 2 years lost about 9 kg

of weight. Regain after 6 to 12 months was about 20% of the regain reported in earlier trials.²⁸ Several recent trials have also shown that continued contact with participants after weight loss is associated with less regain.^{12,24,37,38} These findings together point to behavioral factors rather than macronutrient metabolism as the main influences on weight loss.

Conformity to cultural norms, scientific nov-



elty, and media attention are nonbiologic reasons for the success of specific diets. We used a generic approach to developing each diet and the instructions for following it, in order to minimize such influences. No diet was considered to be a control diet, and the dietary counseling and the attention that we provided were the same for all diet groups throughout the study period. We did not confirm previous findings that low-carbohydrate or high-protein diets caused increased weight loss at 6 months³⁻¹² and that the advantage of these diets usually eroded by 12 months, with weight loss that was nearly or fully equivalent to that with low-fat diets^{6,11,18} or other diets.¹² Other studies showed increased weight loss at 1 to 2 years with diets that were high in unsaturated fat^{12,21,26} or with low-fat, high-carbohydrate vegetarian diets.^{22,24} These divergent results suggest that any type of diet, when taught for the purpose of weight loss with enthusiasm and persistence, can be effective. When nonnutritional influences are minimized, as they were in our study, the specific macronutrient content is of minor importance, as was suggested many years ago.³⁹

In conclusion, diets that are successful in causing weight loss can emphasize a range of fat, protein, and carbohydrate compositions that have beneficial effects on risk factors for cardiovascular disease and diabetes.^{29,40} Such diets can also be tailored to individual patients on the basis of their personal and cultural preferences and may therefore have the best chance for long-term success.

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