Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Sacks FM, Bray GA, Carey VJ, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N Engl J Med 2009;360:859-73.

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Sacks FM, et al. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrate

METHODS FOR ONLINE PUBLICATION

The design is a randomized clinical trial on the effects of four diets differing in fat, protein, and carbohydrate composition on weight-loss during 2 years. The trial was conducted at two sites; in Boston at Harvard School of Public Health and Brigham & Women's Hospital; and in Baton Rouge at Pennington Biomedical Research Center, Louisiana State University System. The coordinating center was at the Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School. The primary outcome was change in total body weight after 24 months. Three primary comparisons were specified to determine the effect of level of dietary fat, protein, and carbohydrate.

The study was designed initially by the authors at Harvard and Pennington. The authors requested and received approval from the National Heart, Lung and Blood Institute (NHLBI) to submit a formal application for a grant to the National Institutes of Health (NIH). The application was reviewed by a regular NIH peer-review group and was recommended for funding as a cooperative agreement award by the NHLBI advisory committee. After the award, the protocol received additional development in consultation with the NHBLI authors and statisticians. It was evaluated and approved by the DSMB appointed by the NHLBI. The data were gathered by staff at the two centers and analyzed by the coordinating center at Brigham & Women's Hospital. Dr. Sacks, Principal Investigator of the grant and study chairperson; Dr. Bray, the study co-chairperson and director of the center at Pennington; and Dr. Carey, director of the coordinating center vouch for the data and results. The original grant application stated the authors' intention to publish the results. Dr. Sacks drafted the manuscript and it underwent critical analysis and revision by the authors and critique by the DSMB. There was no confidentiality agreement restricting the publication of any study data.

Participants

The goal was to recruit 800 overweight or obese participants, 400 at each site, 60% women, age 30-70 y, body mass index $\geq$25 kg/M^2 and $\leq$40 kg/M^2. People with type 2 diabetes controlled with diet, or with hypertension or hyperlipidemia treated with diet or drugs, were eligible to participate. Exclusions were diabetes treated with oral medications or insulin, serious gastrointestinal disease, alcohol or drug abuse, treatment for an eating disorder, unstable or recent onset of cardiovascular disease, or other serious illness; weight-loss medications and other drugs that affect body weight such as some anti-psychotic or anti-depressant drugs, or corticosteroids; hypothyroidism defined by abnormal thyroid stimulating hormone (TSH); urinary microalbumin >100 ug/g creatinine; or unstable dose of medication for hyperlipidemia, hypertension, or psychiatric disorder. The goal for the study population was generalizability of the results to the population needing weight loss.

Recruitment, screening, baseline measurements, and randomization

Mass mailings were the primary means of recruitment. The primary sources of mailing lists were commercial vendors and local governments (for lists of registered voters or drivers). Secondary methods included advertisements on buses and subways, worksite advertisements, newspaper advertisements, distribution of recruitment flyers, and mailings to local healthcare centers and businesses.

People who responded to recruitment were interviewed by phone to describe the study and to ascertain eligibility. Those interested and potentially eligible attended two screening visits at the clinical sites. During the first screening visit, informed consent was obtained. There were measurements of height, weight, blood pressure, urinary microalbumin, and TSH. Dietary patterns were reviewed to identify eating disorders or other unusual or prescriptive diets that could interfere with acceptability or adherence to any of the 4 diet types. Eligible participants were given a 5-day food diary to complete at home, and a pedometer to measure activity for 7 days. Participants attended a second screening visit 7-28 days later. At this visit, blood pressure was measured again, and the study dietitians reviewed the food diary. At

either screening visit, the participants were interviewed by a study dietitian or behavioral psychologist to evaluate their suitability and enthusiasm for the study. After the second visit, participants were discussed at a staff meeting to determine if they should be enrolled.

Baseline nutrient intake was determined from the 5-day diet records. Other baseline measurements were obtained after the screening visits. Body weight, height and waist circumference were measured on 2 separate days, and averaged. A 24 hour urine sample was collected for microalbumin, creatinine, sodium, potassium, and urea nitrogen. Questionnaires were obtained on satiety, food craving, eating behavior, quality of life (SF-36), and physical activity.[1] A food frequency questionnaire (Block) was also completed. Fasting blood was obtained for TSH, glucose, insulin, hemoglobin A1C, and plasma lipids and lipoproteins. Respiratory quotient (RQ) and resting energy expenditure (Deltatrac) were obtained by DeltaTrac II metabolic cart.

Randomization assignments to one of 4 diet groups were generated by the data manager at the coordinating center, upon request of a study dietitian, after confirming, by computer program, that all screening activities had occurred, that the participant met all eligibility criteria, and that all required baseline data had been collected. Diet group assignments were stratified by site with varying block sizes to ensure a balance at each site.

Weight loss intervention

Nutrient goals for the 4 diet groups were: (1) Low-fat, average protein: 20% fat, 15% protein, 65% carbohydrate; (2) Low-fat, high protein: 20% fat, 25% protein, 55% carbohydrate; (3) High-fat, average protein: 40% fat, 15% protein, 45% carbohydrate; (4) High-fat, high-protein: 40% fat, 25% protein, 35% carbohydrate. The goals for classes of fatty acids were: saturated fat, 8% for each group; mono-unsaturated fat, 6% for low-fat and 22% for high-fat groups; polyunsaturated fat, 6% for low-fat and 10% for high-fat groups. The goal for dietary fiber was 20g per day minimum, and for dietary cholesterol was 150 mg per 1000 kcal, for all groups. Carbohydrate-rich foods were used having a lower glycemic index. Participants were instructed to take a multivitamin with calcium 200-250 mg/d. Estimated energy needs were calculated from resting energy expenditure. Each participant's diet prescription represented a 750 kcal/day deficit. Prescribed energy deficit was calculated using the REE x activity coefficient minus 750 kcal/d. No initial diets had less than 1200 kcal/d

Menus that were used in each diet are shown at the end of this document. The diets used similar foods in different proportions.

Blinding was established by naming each diet with colors, and using the same foods for each diet. Blinding and equipoise were strictly maintained by emphasizing to intervention staff and participants that each diet adheres to healthy principles[2], and each is advocated by certain experts to be superior for long-term weight-loss. Except for the interventionists (dietitians and behavioral psychologists), investigators and staff were kept blind to diet assignment of the participants. The trial adhered to established procedures to maintain separation between staff that take outcome measurements and staff that deliver the intervention. Staff members who obtained outcome measurements were not informed of the diet group assignment. Intervention staff, dietitians and behavioral psychologists who delivered the intervention did not take outcome measurements. All investigators, staff, and participants were kept masked to outcome measurements and trial results.

The participants were told to avoid discussing their diet with anyone not in their group. When they came to a counseling session, they were greeted by a staff member, weighed, and taken directly to the classroom. They had little if any opportunity to mingle with participants in other groups. Each dietitian taught at least 2 of the 4 diets since we did not want to allow the possibility that expertise of a specific dietitian would influence the results. All diet allocations were done by random assignment for each participant. Participants were not paid except for expenses for attending the visits for measurements.

Physical activity goals were established for sedentary participants, gradually increasing from 30 minutes of moderate intensity exercise per week to 90 minutes per week during the first six months, the same for each diet group. This goal remained constant over the remainder of the trial. Participants who were accustomed to or desired to achieve a higher exercise goal were encouraged to do so. Minutes of exercise were monitored using self-monitoring forms.

Implementation. After a participant was randomized, the data manager contacted the assigned dietitian to schedule the first individual visit consisting of an orientation and counseling session on the assigned diet. After 40-60 participants were enrolled, the program of group sessions began. The study was conducted in 6 cohorts, the first beginning in November, 2004, and the last in November, 2005; and follow-up concluded December 31, 2007.

Dietary teaching. The participants were encouraged to attend all group sessions which were held 3 out of 4 weeks during the first 6 months, and 2 out of 4 weeks during 6 to 24 months; and individual sessions held every 8 weeks for the entire 24 months. Structured meal plans were provided based on the American Dietetic Association (ADA) exchange system. Daily meal plans in 2-week blocks were given to the participants. The participants were taught to follow the meal plans exactly so that they could achieve the nutrient goals. The exchange system offered to the participants the most flexibility in diet planning once the concept was learned. Food shopping lists and easy-to-prepare recipes were provided. Participants were instructed to write their food and beverage intake in a food diary every day. In addition, participants were counseled to use a computer web-based self-monitoring tool that provided feedback on how closely the daily food intake met the nutrient and energy goals. Physical activity was also monitored by the computer program. Behavioral counseling was integrated into the group and individual sessions to promote adherence to the assigned diets.

Measurements

Body weight and waist circumference. Body weight, the primary outcome variable, was measured by calibrated hospital scales, in the morning before breakfast and after urinating, clothed in a hospital gown, on two nonconsecutive days at baseline, and at 6 and 24 months; and on a single day at 12 and 18 months. The mean number of days between measurements was 5 for baseline, 10 for 6 months, and 9 for 24 months. Waist circumference was also measured at these visits using a non-stretchable tape measure, 4 cm above the iliac crest.

Psychological factors:

(i) Dietary Program Satisfaction. A questionnaire[3] assessed the extent that the 4 diets affected diet satisfaction at 6, 12 and 24 months. The questionnaire produces six scores for the following factors: wellness, distaste, costs, inconvenience, deprivation, inconvenience for family. A total score is not computed.

(ii) Satiety. Hunger, level of fullness after meals, thoughts about food, and food cravings were each measured using 100 mm visual analogue scales (VAS).[4,5] Higher scores indicate greater hunger, fullness, etc. The scores are not summed. The VAS was administered at baseline, 6, 12 and 24 months.

(iii) Food Craving. The Food Craving Inventory-II (FCI-II) is a 33-item self-administered measure designed to assess the subjective experience of food craving across 33 different foods.[6] The measure consists of 5 empirically derived factors: (1) high fats, (2) sweets, (3) carbohydrates and starches, (4) fast food fats, and (5) fruits and vegetables. The FCI-II was administered at baseline, 6, 12 and 24 months. The FCI is scaled in a frequency format assessing the frequency an individual experiences a craving for a particular food. All items are scored in the following manner: Never = 1, Rarely = 2, Sometimes = 3, Often = 4, Always =5. The subscales of the FCI-II are used as outcome, predictor, and potential mediator variables in this study.

(iv) Dietary restraint, disinhibition, and hunger. The Three Factor Eating Questionnaire (TFEQ) measures dietary restraint, disinhibition (susceptibility to overeating), and perceived hunger.[7] Dietary restraint refers to the intent and ability to restrict caloric intake and disinhibition refers to the tendency to

episodically overeat. Perceived hunger refers to the subjective sense of hunger. The TFEQ was administered at baseline, 6, 12 and 24 months.

(v) Quality of Life. The RAND 36-item Health Survey (SF-36) is a well-validated measure of health-related quality of life.[8] The SF-36 measures eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, vitality (energy/fatigue), emotional well being, bodily pain, social functioning, and general health perceptions. The SF-36 was administered at baseline, 6, 12, and 24 months.

Cardiovascular disease and diabetes risk factors.

Blood samples were collected in the fasting state on one day at baseline, 6 months and 24 months. Serum was aliquotted, frozen at –80^{o}C, stored at each clinical site and run in batches as participants completed the trial. Analyses of serum lipids, glucose, insulin and hemoglobin A1C were performed at the Clinical Laboratory at Pennington. Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were measured on the Synchron CX7 (Beckman Coulter, Brea CA). LDL cholesterol was calculated from the total cholesterol, HDL cholesterol and triglyceride[9], except when triglycerides concentration exceeded 400 mg/dl in which case LDL cholesterol was measured directly on all samples of the participant. Glucose and insulin were measured using an immunoassay with chemiluminescent detection on the Immulite analyzer (Diagnostic Products Corporation, Los Angeles CA). Hemoglobin A1C was measured on a Synchron CX5 (Beckman Coulter, Brea CA). In addition, the HOMA index of insulin resistance was calculated from the fasting glucose and insulin.[10]

Blood pressure was measured on two days during screening and at 6, 12, and 24 months, by automated device (Omron HeathCare, IntelliSense Professional Digital Blood Pressure Monitor, HEM907XL), by methods established in other large NIH trials.[11] The calibration was evaluated at regular intervals using a mercury manometer.

Resting energy expenditure was measured in the morning after a 12-hour overnight fast at baseline, 6 and 24 months. Participants were instructed not to consume any caffeine or alcohol during the evening and morning preceding each test, as well as not to perform any strenuous activities. Measurements of oxygen consumption and CO2 production began after a 30 minute rest, and proceeded for 30 minutes. Energy expenditure was then calculated. The within-individual coefficient of variation was 3.2%. Respiratory quotient was computed as the quantity of carbon dioxide produced divided by the amount of oxygen consumed. Non-protein respiratory quotient is a biomarker of carbohydrate intake and was computed from the RQ and urinary nitrogen measured in 24-hour sample collected contemporaneously.

Urinary measurements. A 24 hour urine sample was collected at baseline, 6 months and 2 years for sodium and potassium (to interpret changes in blood pressure), creatinine, and urea (as a biomarker of protein intake), measured at the Core Laboratory at Pennington.

Dietary intake assessment. Dietary intake was assessed by 24-hour recalls at 6 months and 2 years. Three telephone interviews were performed within a 3-week period, 2 weekdays and a weekend day selected at random during each assessment period in a 50% random sample. The 3 days were averaged. Moore's Extended Nutrient Database was used to analyze the diet recalls.[12]

Physical activity assessment. The Baecke physical activity questionnaire is a valid and reliable 16-item self-report inventory that is used to determine an individual's level of habitual physical activity[1,13] This questionnaire was administered at baseline, 12 and 24 months. Self-reported physical activity was also tracked through the computer tracking system during each week of the study.

Statistical Analysis

Data were analyzed by the coordinating center at the Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, under the direction of Dr. Carey. The primary outcome of the study

was the change in body weight (kg) over 2 years, and the secondary outcome was waist circumference. Data were pooled from 2 of the diets for the 2 factorial comparisons, low vs high fat and average vs high-protein. The analysis also compared 2 of the 4 diets, low- (35%kcal) and high-carbohydrate (65%kcal) for the carbohydrate analyses, and included a trend analysis across the 4 levels of carbohydrate. Effects of protein, fat, and carbohydrate level were evaluated independently at significance level 0.05 using two-sample t tests. All p-values are 2-sided. Exploratory post-hoc analyses were conducted on threshold amounts of weight loss, and Bonferroni corrected for multiple comparisons.

An intent-to-treat paradigm was adopted in which long-term weight loss for individuals who dropped out early (after at least 6 months participation in the behavioral experiment) were imputed using a weight regain rate of 0.3 kg/month after dropout.[14] Regain was extrapolated from time of dropout up to 6 or 24 months according to this rate, but regain was truncated at no change from baseline whenever the extrapolation would lead to a positive weight gain. When an individual's weight at dropout represented a gain in weight relative to baseline, no additional gain was imputed, but the unfavorable gain was simply carried forward to 6 or 24 months as needed. No evidence of differential early or later dropout across diet assignments was found (chi-squared 9 df, p=0.3). Zero weight change was assumed for participants who did not return after enrollment (very early dropout, N=55 in this study). Missing data for changes in waist circumference were imputed similarly using a regain rate of 0.3 cm/month after dropout, which corresponds to an assertion of 1 kg change in weight = 1cm change in waist circumference. Sensitivity analyses included imputation of zero change for all missing data, and unimputed analysis restricted to those who presented 24 months worth of observation; inferences on diet type and weight loss were preserved. Secondary outcomes of risk factors for cardiovascular disease and diabetes were analyzed by intention-to-treat imputing zero change from baseline for missing data. There were no statistically significant interactions between the effects of fat and protein on weight change thereby justifying a main-effects factorial approach. The study was powered to detect an effect between level of protein or of fat of 1.67 kg after 2 years, assuming a dropout rate of 40%.

Analyses of subgroups defined by differential adherence as measured by reported macronutrient composition were initiated post-hoc and a statistically significant interaction was identified between reported level of adherence to macronutrient targets and magnitude of 24-month weight loss. Subgroups were formed within major experimental factors (average or high protein; low or moderate fat) using quintiles of the discrepancy between target and reported macronutrient consumption, and quintiles of reported intake of fat and protein. We report nominal 95% confidence intervals for mean weight loss within quintiles and Cochran-Armitage tests of trend in mean weight lost across quintiles.

References

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MENUS
a. 1400 Calories

	High fat, Avg protein	High fat, High protein	Low fat, Avg Protein	Low fat, high Protein
Breakfast	Amounts	Amounts	Amounts	Amounts
Egg, whole, poached	1 large	1 large	1 large	1 large
Bagel, whole wheat	½ medium (2 ¾" to 3 ¼" dia) or about 1 oz.	½ medium (2 ¾" to 3 ¼" dia) or about 1 oz.	1 medium (2 ¾" to 3 ¼" dia, about 2 oz)	½ medium (2 ¾" to 3 ¼" dia) or about 1 oz.
Apple juice	4 fl oz.	____	10 fl oz	6 fl oz
Milk, skim or nonfat, 0.5% or less fat	1 cup	1 cup	1 cup	1 cup
Cheese, cream, low fat	½ tablespoon	½ tablespoon	____	____
Lunch				
Spaghetti, cooked, whole wheat, fat not added in cooking	½ cup, cooked	½ cup, cooked	1 cup, cooked	½ cup, cooked
Turkey, light meat, cooked, skin not eaten	----	2 oz, boneless, cooked, skinless	____	2 oz, boneless, cooked, skinless
Squash, summer, cooked, from fresh, fat not added in cooking	½ cup, slices	½ cup, slices	⅓ cup, slices	½ cup, slices
Peppers, red, cooked, fat not added in cooking	½ cup	½ cup	½ cup	½ cup
Mushrooms, cooked, from fresh, fat not added in cooking	½ cup	½ cup	½ cup	½ cup
Olive oil	1 ½ tablespoons	2 teaspoons	1 ¼ tablespoons	2 teaspoons
Banana, raw	1 small (6" to 6 ⅞" long)	½ small (6" to 6 ⅞" long)	¾ of a large (8" to 8 ⅞" long)	1 large (8" to 8-⅞" long)
Dinner				
Beef, roast, roasted, lean only eaten	2 oz, boneless, cooked, lean only	4 oz, boneless, cooked, lean only	1 ½ oz, boneless, cooked, lean only	4 oz, boneless, cooked, lean only
White potato, from fresh, mashed, not made with milk or fat	1 small (1 ¾" to 2 ¼" dia)	½ small (1 ¾" to 2 ¼" dia)	1 small (1 ¾" to 2 ¼" dia)	1 small (1 ¾" to 2 ¼" dia)
Mixed vegetables (corn, lima beans, peas, green beans, and carrots), cooked, from frozen, fat not added in cooking	¼ cup	¼ cup	⅓ cup	¼ cup
Cabbage, red, raw		¼ cup, shredded	¼ cup, shredded	¼ cup, shredded
Cabbage, green, raw	¼ cup, shredded	¼ cup, shredded	¼ cup, shredded	¼ cup, shredded
Vinegar	¼ cup, shredded	1 fl oz	2 tablespoons	1 fl oz
Raisins	1 fl oz	1 miniature box (.5 oz)	1½ miniature boxes	1½ miniature boxes
Apple, raw	1 miniature box (½ oz) 1 small (2 ½ " dia (approx 4 per lb)	____	1 small (2 ½ " dia (approx 4 per lb)	1 small (2 ½ " dia (approx 4 per lb)
Olive oil	4 teaspoons	1 tablespoon	____	____
Walnuts	½ oz (7 halves)	1 oz (14 halves)	____	____
		1 cup	½ cup	1 cup

Snack Milk, cow's, fluid, skim or nonfat, 0.5% or less butterfat Crackers, graham	½ cup 1 large rectangular piece	1 large rectangular piece	1½ large rectangular pieces	1½ large rectangular pieces

b. 2000 Calories

Foods	High fat, Avg protein	High fat, High protein	Low fat, Avg protein	Low fat, High protein
Breakfast	Amounts	Amounts	Amounts	Amounts
Egg, whole, poached or boiled	1 large	1 large	1 large	1 large
Bagel, whole wheat	1 medium (2-3/4" to 3-1/4" dia) or about 2 oz	1 medium (2-3/4" to 3-1/4" dia) or about 2 oz	2 medium (2-3/4" to 3-1/4" dia) or about 4 oz	1 medium (2-3/4" to 3-1/4" dia) or about 2 oz
Apple juice	6 fl oz	----	12 fl oz	8 fl oz
Milk, skim or nonfat, 0.5% or less fat	1 cup	1 cup	6 fl oz	1 cup
Cheese, cream, low fat	1 tablespoon	1 teaspoon	----	----
Margarine, tub	----	----	1 teaspoon	----
Lunch				
Spaghetti, cooked, whole wheat, fat not added in cooking	¾ cup, cooked	¾ cup, cooked	1 ¼ cups, cooked	1 cup, cooked
Turkey, light meat, cooked, skin not eaten	----	3 oz, boneless, cooked, skinless	----	4 oz, boneless, cooked, skinless
Squash, summer, cooked, from fresh, fat not added in cooking	¾ cup, slices	½ cup, slices	¾ cup, slices	1 cup, slices
Peppers, red, cooked, fat not added in cooking	½ cup	½ cup	½ cup	½ cup
Mushrooms, cooked, from fresh, fat not added in cooking	½ cup	½ cup	½ cup	½ cup
Olive oil	2 tablespoons	1 tablespoon	4 teaspoons	1 tablespoon
Banana, raw	1 small (6" to 6-⅞" long)	1 small (6" to 6-⅞" long)	1 large (8" to 8-⅞" long)	1 large (8" to 8-⅞" long)
Dinner				
Beef, roast, roasted, lean only eaten	3 ½ oz, boneless, cooked, lean only	6 oz, boneless, cooked, lean only	3 oz, boneless, cooked, lean only	5 oz, boneless, cooked, lean only
White potato, from fresh, mashed, not made with milk or fat	¾ cup	1 small (1-¾" to 2-¼" dia)	¾ cup	1 ½ small (1-¾" to 2-¼" dia)
Mixed vegetables (corn, lima beans, peas, green beans, and carrots), cooked, from frozen, fat not added in cooking	½ cup	⅓ cup	⅔ cup	½ cup
Cabbage, red, raw	¼ cup, shredded	½ cup, shredded	⅓ cup, shredded	½ cup, shredded
Cabbage, green, raw	¼ cup, shredded	½ cup, shredded	⅓ cup, shredded	½ cup, shredded
Vinegar	1 fl oz	1 fl oz	2 tablespoons	1 fl oz
Raisins	1 miniature box (.5 oz)	1 miniature box (.5 oz)	2 miniature boxes (.5 oz ea)	1½ miniature boxes (.5 oz ea)
Apple, raw	1 medium (2-¾" dia) (approx 3 per lb)	----	1 large (3-¼" dia) (approx 2 per lb.)	1 medium (2-¾" dia) (approx 3 per lb)
Olive oil	5 teaspoons	1 tablespoon	----	----
Walnuts	1 oz (14 halves	2 oz (28 halves)	----	----

Snack Milk, skim or nonfat Crackers, graham	½ cup 1 large rectangular piece	1 cup 1 large rectangular piece	½ cup 2 large rectangular pieces	1 cup 3 large rectangular pieces

Table 1, Supplementary Appendix. Risk Factors. Participants providing data, no imputation of missing values

Variable	6-mo value (sd); percentage change from baseline				2-yr value (sd); percentage change from baseline				2-yr difference in mean changes from baseline (SE), p-value		
	Low fat, avg protein	Low fat, high protein	High fat, avg protein	High fat, high protein	Low fat, avg protein	Low fat, high protein	High fat, avg protein	High fat, high protein	High Fat - Low Fat	High prot - Avg prot	High Carb - Low Carb
Total Chol	186 (36); -7.1	192 (39); -5.7	193 (39); -4.5	198 (35); -2.7	191 (38); -5.1	196 (41); -4.1	198 (40); -0.4	201 (38); -1.1	7.7 (2.6), p=0.003	0.7 (2.6), p=0.79	-8.0 (3.4), p=0.02
LDL Chol	116 (29); -7.9	119 (33); -5.7	121 (33); -3.9	123 (30); -1.3	116 (32); -8.0	119 (33); -5.4	123 (33); -0.4	122 (30); -1.7	7.1 (2.3), p=0.002	1.1 (2.3), p=0.62	-7.8 (2.9), p=0.008
HDL Chol	48 (13); -0.4	51 (13); 3.1	50 (13); 3.6	53 (16); 4.7	53 (15); 7.7	54 (15); 9.1	52 (14); 10.0	57 (17); 11.5	1.2 (0.6), p=0.06	1.0 (0.6), p=0.13	-2.1 (0.9), p=0.02
TG	113 (66); -17.1	111 (58); -23.9	120 (92); -22.1	113 (70); -22.7	118 (81); -15.7	114 (64); -23.2	125 (96); -19.7	115 (71); -21.9	-2.7 (5.6), p=0.62	-7.2 (5.6), p=0.19	9.6 (8.0), p=0.23
SBP	116 (12); -1.4	116 (12); -3.0	117 (13); -1.7	118 (11); -1.9	116 (12); -1.1	117 (13); -2.3	118 (13); -1.9	118 (12); -0.9	0.3 (0.9), p=0.72	-0.2 (0.9), p=0.84	-0.2 (1.2), p=0.90
DBP	73 (9); -1.7	73 (8); -3.6	74 (9); -2.7	74 (8); -2.1	74 (9); -1.0	73 (9); -1.7	74 (9); -2.2	75 (9); -0.4	0.1 (0.6), p=0.91	0.4 (0.6), p=0.54	-0.4 (0.9), p=0.61
Glucose	89 (11); -3.6	89 (8); -3.1	90 (13); -2.3	91 (13); -1.4	95 (12); 1.5	94 (11); 1.4	95 (14); 2.6	96 (15); 3.7	1.6 (0.8), p=0.04	0.6 (0.8), p=0.47	-2.0 (1.1), p=0.07
Insulin	10 (7); -20.1	9 (6); -24.4	10 (7); -22.9	10 (9); -17.2	12 (11); -3.4	10 (6); -16.3	11 (7); -10.3	11 (7); -12.3	-0.2 (0.6), p=0.71	-0.9 (0.6), p=0.11	1.1 (0.9), p=0.21
HOMA	2.3 (1.7); -23.2	2.1 (1.4); -27.9	2.4 (1.8); -23.3	2.4 (3.1); -16.1	2.9 (2.5); -2.0	2.4 (1.8); -14.7	2.8 (2.1); -5.8	2.6 (2.0); -8.3	0.03 (0.15), p=0.82	-0.21 (0.15), p=0.15	0.17 (0.22), p=0.44

N per group: baseline 201, 6 month 167-178, 2 year 124-156

Abbreviations and units: see Table 2 for data related to 6 month and 2 year values, Table 3 for data related to 2 year difference in mean changes from baseline.

Table 2, Supplementary Appendix. Satiety, diet satisfaction, physical activity

	6 month values, mean (sd)				24 Month values, mean (sd)				Comparison among the diets at 6 Months, p-values			Comparison among the diets at 24 Months, p-values		
	Low fat, avg protein	Low fat, high protein	High fat, avg protein	High fat, high protein	Low fat, avg protein	Low fat, high protein	High fat, avg protein	High fat, high protein	high fat, low fat	high prot, avg prot	high carb, low carb trend	high fat, low fat	high prot, avg prot	high carb, low carb trend
Craving	56.2 (26.2)	51.3 (26.5)	55.3 (27.1)	51.3 (26.8)	53.3 (25.4)	53.7 (25.4)	56.6 (25.6)	53.3 (25.9)	0.84	0.03	0.26	0.57	0.54	0.82
Fullness	63.5 (20.4)	62.7 (20)	63.3 (20.3)	64.1 (18.9)	62 (21.3)	61.4 (19.6)	63.1 (18.9)	62.8 (19.3)	0.71	0.98	0.75	0.49	0.79	0.62
Hunger	37.1 (21.9)	37.1 (20.9)	34.9 (22.1)	36.5 (20.7)	42.2 (21.2)	38 (20.1)	39 (20.3)	41.4 (19.2)	0.39	0.63	0.59	0.89	0.59	0.91
How much desired to eat last week	60.1 (18.8)	60.1 (17.4)	59.4 (17.3)	61.7 (17.6)	61 (16.5)	61 (16.3)	61.5 (18.2)	61.2 (17.7)	0.74	0.40	0.51	0.79	0.94	0.84
Wellness	5.2 (1.1)	5.2 (1.2)	4.9 (1.3)	5 (1.2)	4.8 (1.4)	4.9 (1.5)	4.7 (1.4)	4.6 (1.8)	0.03	0.94	0.05	0.06	0.76	0.07
Distaste	0.1 (0.4)	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.4)	0.1 (0.3)	0.1 (0.4)	0.51	0.78	0.64	0.63	0.63	0.83
Cost	3 (1.2)	3.1 (1.1)	3 (1.2)	3.2 (1.1)	2.8 (1.3)	2.7 (1.5)	2.8 (1.3)	2.8 (1.4)	0.81	0.09	0.33	0.72	0.68	0.90
Personal Inconvenience	2.2 (0.8)	2.3 (0.8)	2.2 (0.9)	2.2 (0.9)	2.1 (0.9)	2.1 (0.8)	2.1 (0.9)	2.1 (0.9)	0.32	0.39	0.61	0.99	0.64	0.84
Family Inconvenience	1.2 (0.9)	1.1 (1)	1.2 (0.9)	1.2 (1)	1.2 (1.1)	1.2 (1)	0.9 (0.9)	1.2 (1)	0.60	0.66	0.78	0.23	0.23	0.60
Deprivation	2.1 (1.3)	2 (1.4)	2.2 (1.3)	2.2 (1.2)	2.1 (1.4)	2 (1.2)	2 (1.3)	2.3 (1.3)	0.24	0.75	0.36	0.41	0.38	0.26
Baecke activity score	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	0.60	0.70	0.52	0.16	0.58	0.33

Craving, fullness, hunger, how much desired to eat, N per group, 6 month 162-166, 2 year 113-128

Wellness, distaste, cost, inconvenience, deprivation, activity: N per group 6 month 160-173, 2 year 127-150

Supplementary Appendix Figure 1, Participant Flow