ORIGINAL CONTRIBUTION

Effects of Protein, Monounsaturated Fat, and Carbohydrate Intake on Blood Pressure and Serum Lipids

Results of the OmniHeart Randomized Trial

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Context Reduced intake of saturated fat is widely recommended for prevention of cardiovascular disease. The type of macronutrient that should replace saturated fat remains uncertain.

Objective To compare the effects of 3 healthful diets, each with reduced saturated fat intake, on blood pressure and serum lipids.

Design, Setting, and Participants Randomized, 3-period, crossover feeding study (April 2003 to June 2005) conducted in Baltimore, Md, and Boston, Mass. Participants were 164 adults with prehypertension or stage 1 hypertension. Each feeding period lasted 6 weeks and body weight was kept constant.

Interventions A diet rich in carbohydrates; a diet rich in protein, about half from plant sources; and a diet rich in unsaturated fat, predominantly monounsaturated fat.

Main Outcome Measures Systolic blood pressure and low-density lipoprotein cholesterol.

Results Blood pressure, low-density lipoprotein cholesterol, and estimated coronary heart disease risk were lower on each diet compared with baseline. Compared with the carbohydrate diet, the protein diet further decreased mean systolic blood pressure by 1.4 mm Hg ($P = .002$) and by 3.5 mm Hg ($P = .006$) among those with hypertension and decreased low-density lipoprotein cholesterol by 3.3 mg/dL (0.09 mmol/L; $P = .01$), high-density lipoprotein cholesterol by 1.3 mg/dL (0.03 mmol/L; $P = .02$), and triglycerides by 15.7 mg/dL (0.18 mmol/L; $P < .001$). Compared with the carbohydrate diet, the unsaturated fat diet decreased systolic blood pressure by 1.3 mm Hg ($P = .005$) and by 2.9 mm Hg among those with hypertension ($P = .02$), had no significant effect on low-density lipoprotein cholesterol, increased high-density lipoprotein cholesterol by 1.1 mg/dL (0.03 mmol/L; $P = .03$), and lowered triglycerides by 9.6 mg/dL (0.11 mmol/L; $P = .02$). Compared with the carbohydrate diet, estimated 10-year coronary heart disease risk was lower and similar on the protein and unsaturated fat diets.

Conclusion In the setting of a healthful diet, partial substitution of carbohydrate with either protein or monounsaturated fat can further lower blood pressure, improve lipid levels, and reduce estimated cardiovascular risk.

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DESPITE WIDESPREAD CONSENSUS that a reduced intake of saturated fat lowers cardiovascular disease (CVD) risk, the optimal type of macronutrient (protein, unsaturated fat, or carbohydrate) that should replace saturated fat is uncertain. In the absence of convincing evidence that favors one macronutrient, reports from the Institute of Medicine[1] and the Adult Treatment Panel III[2] concluded that a wide range of macronutrients is acceptable.

Two major goals of dietary recommendations are to lower blood pressure and improve serum lipids, 2 of the primary determinants of CVD risk. A persuasive body of evidence has implicated several aspects of diet in the etiology of elevated blood pressure. Early research documented the adverse effects of increased salt, insufficient potassium, elevated weight, and excess alcohol intake, and the beneficial effects of vegetarian dietary patterns.[3,4] Subsequently, in the Dietary Approaches to Stop Hypertension (DASH) trials,[5,6] a carbohydrate-rich diet that emphasizes fruits, vegetables, and low-fat dairy prod-

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ucts and that is reduced in saturated fat, total fat, and cholesterol, substantially lowered blood pressure.

The carbohydrate-rich diet used in the DASH trials, commonly termed the DASH diet, is currently advocated in several scientific reports and guidelines, including the report of the 2005 Dietary Guidelines Scientific Advisory Committee.[7] This diet meets the major nutrient recommendations established by the Institute of Medicine.[8] In addition to lowering blood pressure, the DASH diet lowers low-density lipoprotein (LDL) cholesterol.[9,10] However, this diet also reduces high-density lipoprotein (HDL) cholesterol, which is inversely associated with CVD risk,[2] and has no effect on triglycerides, which is directly associated with CVD risk.[11] Whether partial replacement of carbohydrate with either unsaturated fat or protein can improve blood pressure and lipid risk factors is uncertain.

Some leading authorities have recommended diets rich in monounsaturated fats as a means to reduce CVD risk.[12] Such diets typically lower triglycerides and raise HDL cholesterol, but their effects on blood pressure have received scant attention. An expanding body of evidence suggests that diets rich in protein, particularly protein from plants, lower blood pressure[13-16] and reduce CVD risk.[17,18] In small feeding studies, increased protein intake from mixed sources had favorable effects on lipids.[19-21]

In this setting, we conducted a randomized trial to compare the effects on blood pressure and serum lipids of 3 healthful diets, each reduced in saturated fat: a carbohydrate-rich diet, similar to the DASH diet; a diet rich in protein, approximately half from plant sources; and a diet rich in unsaturated fat, predominantly monounsaturated fat.

Table 1. Nutrient Targets and Average Daily Servings of Foods by Diet at 2100 kcal

	Diet		
	Carbohydrate*	Protein	Unsaturated Fat
Nutrient targets, kcal%†			
Fat	27	27	37
Saturated	6	6	6
Monounsaturated	13	13	21
Polyunsaturated	8	8	10
Carbohydrate‡	58	48	48
Protein	15	25	15
Meat	5.5	9	5.5
Dairy	4	4	4
Plant§	5.5	12	5.5
Food groups, servings/d			
Fruit and juices	6.6	3.8	4.8
Vegetables	4.4	5.4	6.3
Grains	5.3	5	4.3
Low-fat dairy products	1.4	2.3	1.6
High-fat dairy products	0.7	0.2	0.3
Legumes, nuts, seeds, and other vegetable protein	1.3	3	1.2
Beef, pork, and ham	0.9	1.1	1
Poultry	1.6	2.6	1.8
Fish	1.1	1.3	1
Egg product substitutes	0.2	1.1	0.1
Desserts and sweets	4.6	2.5	1.7
Fats and oils	6	3.5	12

*The carbohydrate diet replicated the nutrient profile of the Dietary Approaches to Stop Hypertension (DASH) diet except that the percentage of kilocalories from protein and carbohydrates in the DASH diet were 18% and 55%, respectively.
†By design, the following nutrient targets were similar in each diet: cholesterol lower than 150 mg/d; fiber more than 30 g/d; sodium 2300 mg/d, potassium 4700 mg/d, magnesium 500 mg/d, and calcium 1200 mg/d.
‡The total dietary glycemic index of the 3 diets was moderate and similar (68 in the carbohydrate, 71 in the protein, and 75 in the unsaturated fat diets).
§The average daily intake of soy protein was 0.5 g in the carbohydrate, 7.3 g in the protein, and 0.5 g in the unsaturated fat diets.

METHODS

The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) was an investigator-initiated, National Heart, Lung, and Blood Institute–funded feeding study with a randomized, 3-period crossover design.[22] Two clinical centers (Johns Hopkins Medical Institutions and Brigham and Women's Hospital) and a coordinating unit at Brigham and Women's Hospital conducted the trial. Institutional review boards at each center and an independent data and safety monitoring board approved the protocol and monitored the trial. Each participant provided written informed consent.

Participants

Trial participants were generally healthy adults, aged 30 years and older, with a systolic blood pressure of 120 to 159 mm Hg or a diastolic blood pressure of 80 to 99 mm Hg. This range includes individuals with prehypertension (systolic, 120-139 mm Hg or diastolic, 80-89 mm Hg) and stage 1 hypertension (systolic, 140-159 mm Hg or diastolic, 90-99 mm Hg). Prehypertensive individuals are a group at high risk of developing hypertension and CVD, justifying special attempts to lower blood pressure.[23]

Major exclusion criteria were diabetes, active or prior CVD, LDL cholesterol greater than 220 mg/dL (>5.70 mmol/L), fasting triglycerides greater than 750 mg/dL (>8.48 mmol/L), weight more than 350 lb (>159 kg), taking medications that affect blood pressure or blood lipid levels, unwillingness to stop taking vitamin and mineral supplements, and alcoholic beverage intake of more than 14 drinks per week. Mass mailing of brochures and advertisements were primary recruitment strategies. Because of the disproportionate burden of CVD in African Americans, a recruitment goal was to achieve a cohort that was about 50% African American. Race and ethnicity were self-reported. The first participants began the

protocol in April 2003; the last participants ended the study in June 2005.

Participant Flow

During 3 screening visits, eligibility was ascertained and baseline data were collected. After a 6-day run-in period, in which participants ate 2 days of meals from each study diet, they were randomly assigned to 1 of 6 sequences of the 3 diets. Randomization assignments were generated centrally by a computer program and were stratified by clinic. At each clinical center, an unblinded staff member opened a sealed, opaque envelope with the randomized diet sequence. Each feeding period lasted 6 weeks. A washout period of 2 to 4 weeks separated the feeding periods. During the washout, participants ate their own food.

Study Diets

TABLE 1 displays the nutrient targets for each diet and the average estimated servings per day of foods for the 2100-kcal version of the diets. TABLE 2 displays a sample, 1-day set of meals. The primary distinguishing feature of the 3 diets is their macronutrient composition. By design, each diet was reduced in saturated fat, cholesterol, and sodium, and rich in fruits, vegetables, fiber, potassium, and other minerals at recommended levels.[7]

The carbohydrate diet used in this trial is similar to the DASH diet, except that the carbohydrate intake of the DASH diet was 55% of kcal vs 58% of kcal in the carbohydrate diet and the protein intake of the DASH diet was 18% of kcal vs 15% of kcal in the carbohydrate diet. The protein intake was reduced to 15% of kcal to achieve a 10% of kcal contrast with the protein diet. Approximately two thirds of the increase in protein from the carbohydrate to the protein diets came from plants (legumes, grains, nuts, and seeds). However, sources of protein were varied and also included meat, poultry, egg product substitutes, and dairy products. The protein diet included some soy products, but the amount was low, on average just 7.3 g per day. The unsaturated fat diet emphasized monounsaturated fat. This diet included olive, canola, and safflower oils, as well as a variety of nuts and seeds, to meet its target fatty acid distributions. The type of carbohydrate in each diet was similar, as indicated by the total dietary glycemic index (68 in carbohydrate diet, 71 in the protein diet, and 75 in unsaturated fat diet, relative to the white bread index).[24]

Controlled Feeding

A 7-day menu cycle at 5 caloric levels (1600, 2100, 2600, 3100, and 3600 kcal) was developed for each diet. Menus were designed using commonly available foods. Throughout the feeding periods, participants were provided all of their food, which was prepared in research kitchens. On each weekday, participants ate their main meal on-site. All other meals were consumed off-site. Participants were instructed to drink no more than 3 caffeinated beverages and no more than 2 alcoholic beverages per day. Weight was measured each weekday and was kept stable by adjusting caloric levels, by adding 100-kcal cookies with the nutrient content of the assigned diet, or both. The goal was to keep weight within 2% of their baseline weight. Participants were advised to maintain their same level of exercise and alcohol consumption as before the trial. For each day of controlled feeding, participants completed a diary in which they indicated whether they ate any nonstudy foods and whether they did not eat all study foods.

Measurements

Participants and personnel involved in collection of outcome data were masked

Table 2. Sample Menus From the OmniHeart Study

	Diet		
	Carbohydrate	Protein	Unsaturated Fat
Breakfast	Grapefruit juice Multi-bran cereal Skim milk Banana	Tomato juice Scrambled egg substitute with low-fat shredded cheese Hot cereal: bulgur wheat with soy, olive oil margarine, raisins, and sugar Skim milk	Orange juice Cereal with raisins, skim milk White bread toast with olive oil margarine and jelly
Lunch	Chicken sandwich: whole wheat bread, chicken breast, mayonnaise Salad: lettuce with olive oil, Trail mix: almonds, dried apricots	Vegetarian burger: hamburger roll, vegetarian patty, barbeque sauce, lettuce with tomato slices Broccoli salad Unsalted potato chips Chocolate pudding	Chicken sandwich: white bread, chicken breast, barbeque sauce, olive oil margarine Olive oil potato chips Spinach salad with tomato and olive oil balsamic dressing Broccoli salad with safflower oil Tomato juice
Dinner	Penne bean pasta with spinach, tomatoes, and olive oil,* beef meatballs, parmesan cheese Tossed salad: romaine lettuce, cherry tomatoes, Italian dressing with safflower oil Fresh grapes Peppermint patty	Black bean taco: black beans and wheat protein with vegetables, 3-grain pilaf with olive oil* Tortilla chips Chicken breast Fresh orange Skim milk	Black bean taco: black beans with vegetables, 3-grain pilaf with olive oil* Tortilla chips Carrots, cooked Pecan cookie Skim milk
Snack	Small fresh apple Yogurt	Cottage cheese–fat free Mandarin oranges Almonds	Mandarin oranges Almonds

*While each diet provided olive oil, the quantities provided in the unsaturated fat diet exceeded that provided in the carbohydrate and protein diets.

to diet sequence. Blood pressure was measured at each screening visit and at 1 visit during the run-in period. During each feeding period, blood pressure was measured at one visit each week during the first 4 weeks and at 5 visits during the last 10 days (at least 2 visits during the final 5 days). At each visit, 3 readings were obtained in the seated position by trained and certified observers. Blood pressure was determined by the OMRON HEM-907 device (Omron Healthcare Inc, Bannockburn, Ill) for persons requiring a normal adult or large adult cuff and from the SpaceLabs 90207 device (Space Labs Inc, Redmond, Wash) for persons requiring a thigh cuff. Both devices have been validated.[25,26] Baseline blood pressure was the average of all measurements obtained during the 3 screening visits. End-of-period blood pressure was the average of all readings obtained during the 5 visits over the last 10 days of each period.

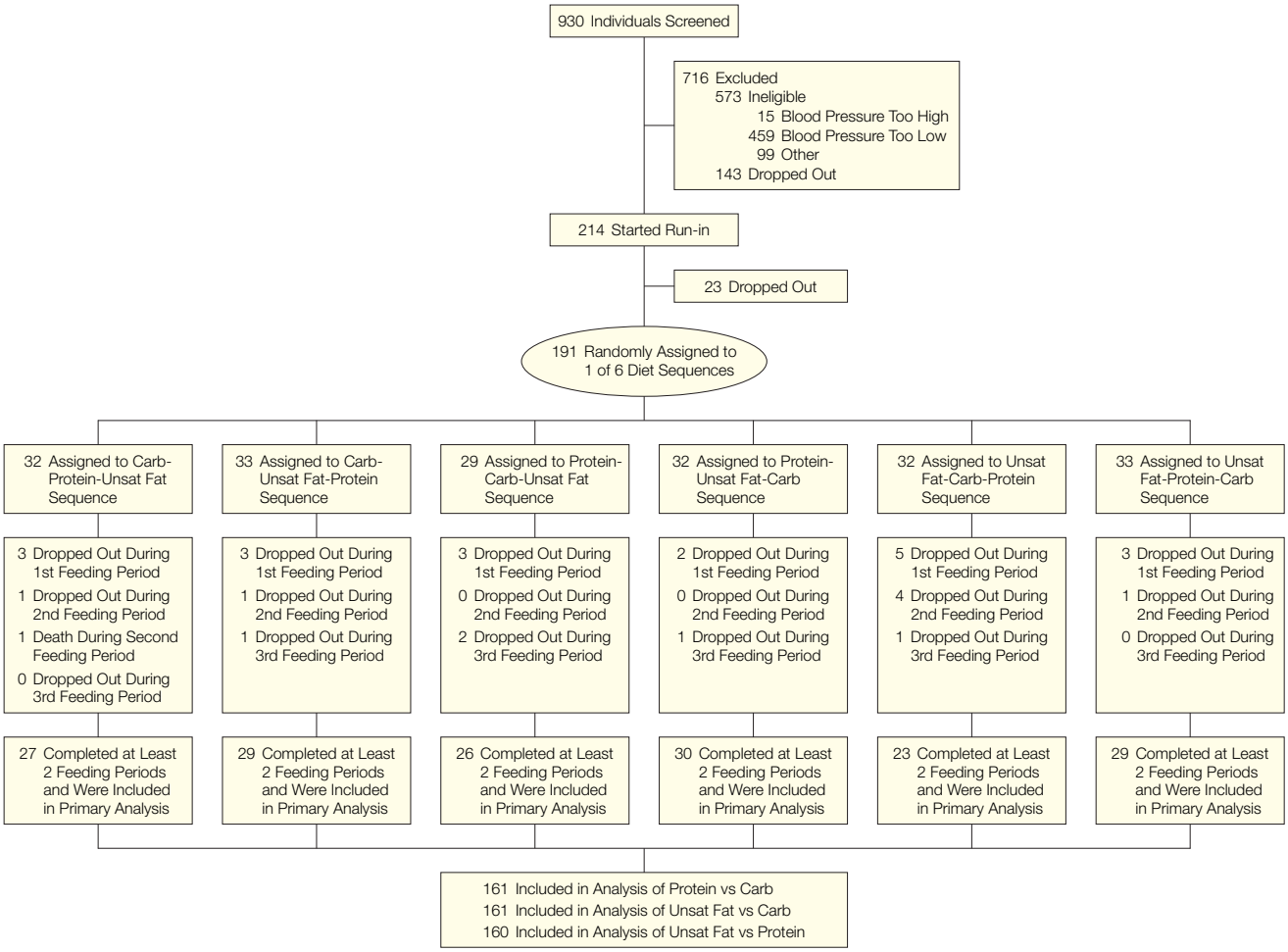
Blood samples after an 8- to 12-hour fast were collected during a screening visit and at weeks 4 and 6 of each feeding period. Measurements obtained at 4 weeks were compared with values at 6 weeks to determine whether a steady state had been reached. Blood samples were collected and then centrifuged. The resulting serum was frozen at –70°C and shipped in batches to the Core Laboratory for Clinical Studies (Washington University School of Medicine, St Louis, Mo). Conventional enzymatic assays were used to measure total triglycerides, total cholesterol, and HDL cholesterol levels. Low-density lipoprotein cholesterol levels were estimated by the Friedewald equation for specimens with a triglyceride concentration below 400 mg/dL (10.36 mmol/L).[27] Non–high-density lipoprotein cholesterol levels were calculated as the difference between total cholesterol and HDL cholesterol levels.

Twenty-four-hour urine collections were obtained at baseline prior to feeding and once during the last 2 weeks of each feeding period. At the end of each feeding period, participants completed a self-administered, 15-item symptom checklist and a physical activity questionnaire.

Analytic Considerations

Of primary interest were the contrasts between the carbohydrate and protein di-

Figure 1. Participant Flow in the OmniHeart Trial



ets and between the carbohydrate and unsaturated fat diets. The contrast between the protein and unsaturated fat diets was of secondary interest. Systolic blood pressure and LDL cholesterol were coprimary outcomes. Diastolic blood pressure, triglycerides, and HDL cholesterol were secondary outcomes, and total cholesterol and non-HDL cholesterol were other prespecified outcomes. For each outcome, both overall and in subgroups, between-diet differences in end-of-period measurements were used to perform paired *t* tests of the hypothesis that the mean between-diet difference was 0. In each analysis, statistical significance was defined by $P<.05$ (2-sided) without adjustment for multiple comparisons. There was no evidence of differential carryover effects between diets.[28] Protocol-specified subgroups included sex, race, and subgroups defined by baseline levels above and below conventional diagnostic thresholds. In addition to between-diet differences, mean (95% confidence interval [CI]) change from baseline to the end of the feeding period are reported. Primary analyses were performed using SAS version 8 (SAS Institute Inc, Cary, NC).

The primary results of this crossover trial derive from an analysis of efficacy on a per protocol basis. Participants qualified for inclusion in the primary analyses if they had measurements of both blood pressure and lipid levels in at least 2 of the 3 diet periods. For these analyses, no imputation of missing data occurred. Sensitivity analyses were performed to understand the impact of missing data and to verify that parametric methods were appropriate. Missing data, that is, between-diet differences in outcomes, were replaced with 0 or with differences from model-based multiple imputation.[29] Nonparametric (Wilcoxon rank-based and permutation-based) tests were also performed. Analysis of covariance was used to assess the effects of weight change on trial outcomes.

To estimate the overall effects of risk factor changes, we calculated the average 10-year risk of coronary heart disease (CHD) at baseline and in each diet by applying individual level data to the Framingham risk equation[30] and the Prospective Cardiovascular Munster (PROCAM) risk equation.[31]

The target sample size of 160 provided 90% power to detect a mean between-diet difference of 1.7 mm Hg in systolic blood pressure and 5.9 mg/dL (0.15 mmol/L) in LDL cholesterol.

RESULTS

Participants

Twenty-six persons dropped out prior to outcome ascertainment in the second period (19 during the first and 7 during the second period, FIGURE 1). These 26 persons were evenly distributed across diets (10 in the carbohydrate, 7 in the protein, and 9 in the unsaturated fat diets). One participant while assigned to the protein diet died after surgery; his death was unrelated to the study. A total of 164 persons completed at least 2 feeding periods (TABLE 3); 159 completed all 3 periods.

Adherence. Participants consumed each diet for an average of 41 days (TABLE 4). According to participant self-reports, adherence was high, ie, all study food was consumed and no nonstudy food was eaten on 95% to 96% of person-days on each diet. From run-in to the end of the first period, weight fell by an average of about 1 kg. However, mean end-of-period weights were similar across the 3 diets, as was mean energy intake, alcohol beverage intake, physical activity and urinary excretion of sodium, potassium and phosphorus. Mean urine urea nitrogen, reflecting protein intake, was highest on the protein diet.

Outcomes. *Changes From Baseline.* Compared with baseline, systolic and diastolic blood pressure and levels of LDL, total, and HDL cholesterol were lower on each diet (TABLE 5). High-density lipoprotein cholesterol levels decreased from baseline on the carbohydrate and protein diets but were unchanged on the unsaturated fat diet. Compared with baseline, triglyceride levels were lower on the protein and unsaturated fat diets but not on the carbohydrate diet.

Between-Diet Contrasts. FIGURE 2 shows the mean (95% CI) between-diet differences.

Table 3. Baseline Characteristics of Participants (n = 164)

Age, mean (SD), y	53.6 (10.9)
Women, No. (%)	73 (45)
Race, No. (%)	
African American	90 (55)
Non-Hispanic white	65 (40)
Other	9 (6)
Weight, mean (SD), kg	87.3 (18.7)
Body mass index, mean (SD)*	30.2 (6.1)
Obesity status, No. (%)	
Not overweight or obese	34 (21)
Overweight	57 (34)
Obese	73 (45)
Alcohol intake	
Drink any alcohol, No. (%)	73 (45)
Servings/wk among drinkers, mean (SD)	4 (4)
Education, No. (%)	
≤High school	33 (20)
Some college	56 (34)
College graduate	75 (46)
Annual household income, $, No. (%)	
<30 000	52 (33)
30 000 to 59 999	60 (38)
≥60 000	45 (29)
Smoking, No. (%)	
Current	18 (11)
Former	46 (28)
Never	100 (61)
Postmenopausal, No. (%)†	53 (73)
Urinary electrolyte excretion, mean (SD), mg/24 h	
Sodium	3378 (1470)
Potassium	2424 (1173)

*Body mass index is calculated as weight in kilograms divided by the square of height in meters.
†Among the 73 women enrolled in the trial.

Blood Pressure. Compared with the carbohydrate diet, both the protein and unsaturated fat diets significantly lowered systolic and diastolic blood pressure in all participants and in those who were hypertensive. In prehypertensive participants, the protein and the unsaturated fat diets each lowered blood pressure similarly, but blood pressure reductions were statistically significant only for the protein diet. Of the 32 persons who were hypertensive at baseline, 12 (38%) remained hypertensive on the carbohydrate, 7 (22%) on the protein, and 6 (19%) on the unsaturated fat diets.

Lipids. The protein diet but not the unsaturated fat diet significantly lowered LDL cholesterol levels compared with the carbohydrate diet. The protein diet significantly reduced HDL cholesterol levels compared with the carbohydrate and the unsaturated fat diets, whereas the unsaturated fat diet significantly increased HDL cholesterol levels compared with the carbohy-

drate diet. Compared with the carbohydrate diet, both the protein and the unsaturated fat diets significantly lowered triglyceride, total cholesterol, and non-HDL cholesterol levels. The protein diet also lowered triglyceride and total cholesterol levels compared with the unsaturated fat diet.

Sensitivity Analyses

Sensitivity analyses (nonparametric tests, imputation of missing values with 0 difference, imputation with differences from multiple imputation models, adjustment for weight) yielded results that were virtually identical to the primary analyses. Under the model-based multiple imputation, the protein diet compared with the carbohydrate diet reduced systolic blood pressure by a mean of 1.5 mm Hg ($P = .001$) vs 1.4 mm Hg ($P = .002$) for primary analysis, and the unsaturated diet compared with the carbohydrate diet reduced systolic blood pressure by a mean of 1.4 mm Hg ($P = .003$) vs 1.3 mm Hg ($P = .005$) for the primary analysis. Results from lipid analyses at week 4 were similar to the corresponding primary analyses at week 6.

Subgroup Analyses

The pattern of results was similar in subgroups defined by sex and race. However, results were not always statistically significant, possibly because of reduced sample size. Compared with the carbohydrate diet, the protein diet decreased systolic blood pressure by a mean of 1.5 mm Hg ($P = .009$) in African Americans, 1.4 mm Hg ($P = .06$) in non–African Americans, 1.1 mm Hg ($P = .10$) in men, and 1.9 mm Hg ($P = .003$) in women while the unsaturated fat diet lowered systolic blood pressure by a mean of 1.2 mm Hg ($P = .05$) in African Ameri-

Table 4. Measures of Adherence and Potential Confounders by Diet

	Diet		
	Carbohydrate	Protein	Unsaturated Fat
Measures of adherence			
No. of feeding days, mean (SD)	41 (1.0)	41 (0.8)	41 (0.9)
Energy intake, mean (SD), kcal/d*	2599 (578)	2558 (538)	2564 (556)
Person-days of perfect adherence, %†	96	95	96
Weight, mean (SD), kg‡	86.3 (18.2)	86.0 (18.2)	86.7 (18.4)
Physical activity, No. (%)§	36 (22)	30 (19)	37 (23)
Alcohol beverage intake, mean (SD), oz/d‖	1.9 (5.5)	2.1 (6.0)	2.1 (5.9)
Urinary excretion, mean (SD), mg/d			
Sodium	2674 (1387)	2605 (1295)	2524 (1293)
Potassium	3296 (1584)	3194 (1489)	3535 (1883)
Urea nitrogen	11 148 (5172)	15 340 (7091)	11 227 (5382)
Phosphorus	845 (422)	916 (450)	813 (428)
Creatinine	1.6 (0.8)	1.5 (0.7)	1.6 (0.8)

*Sum of kilocalories from the provided meals and supplemental cookies.
†Perfect adherence is self-report of all study food eaten and no nonstudy food eaten expressed as a percentage of person-days of feeding.
‡Mean during last week of feeding.
§Percent reporting moderate or vigorous physical activity on 4 or more days per week.
‖Ounces per day of beverages that contain alcohol.

Table 5. Baseline Levels of Risk Factors and Changes From Baseline by Diet

			Mean (95% Confidence Interval) Change From Baseline by Diet		
	No.*	Mean (SD) at Baseline	Carbohydrate	Protein	Unsaturated Fat
Blood pressure, mm Hg†					
Systolic					
All	164	131.2 (9.4)	–8.2 (–9.6 to –6.8)	–9.5 (–10.9 to –8.2)	–9.3 (–10.6 to –8.0)
Stage 1 hypertension	32	146.5 (5.7)	–12.9 (–16.6 to –9.2)	–16.1 (–19.7 to –12.5)	–15.8 (–19.4 to –12.3)
Prehypertension	132	127.5 (5.5)	–7.0 (–8.5 to –5.6)	–8.0 (–9.3 to –6.6)	–7.7 (–8.9 to –6.4)
Diastolic					
All	164	77.0 (8.2)	–4.1 (–5.0 to –3.3)	–5.2 (–6.1 to –4.4)	–4.8 (–5.6 to –4.0)
Stage 1 hypertension	32	84.2 (7.8)	–6.3 (–8.4 to –4.3)	–8.6 (–10.9 to –6.4)	–8.2 (–10.4 to –6.0)
Prehypertension	132	75.3 (7.4)	–3.6 (–4.5 to –2.7)	–4.4 (–5.3 to –3.6)	–3.9 (–4.7 to –3.2)
Cholesterol, mg/dL					
LDL‡					
All	161	129.2 (32.4)	–11.6 (–14.6 to –8.6)	–14.2 (–17.5 to –10.9)	–13.1 (–16.4 to –9.8)
≥130	75	156.7 (21.0)	–19.8 (–24.2 to –15.5)	–23.6 (–28.5 to –18.8)	–21.9 (–26.9 to –16.8)
<130	86	105.2 (18.5)	–4.4 (–7.8 to –0.9)	–6.1 (–9.9 to –2.2)	–5.4 (–9.1 to –1.8)
HDL	164	50.0 (16.1)	–1.4 (–2.5 to –0.3)	–2.6 (–3.6 to –1.6)	–0.3 (–1.3 to 0.7)
Total	164	203.7 (35.7)	–12.4 (–15.7 to –9.1)	–19.9 (–23.5 to –16.4)	–15.4 (–19.1 to –11.8)
Non-HDL	164	153.8 (36.8)	–11.0 (–14.2 to –7.8)	–17.3 (–20.8 to –13.8)	–15.1 (–18.6 to –11.6)
Triglycerides, mg/dL§	164	101.5 (75 to 159)	0.1 (–8.6 to 8.8)	–16.4 (–25.5 to –7.3)	–9.3 (–17.5 to –1.2)

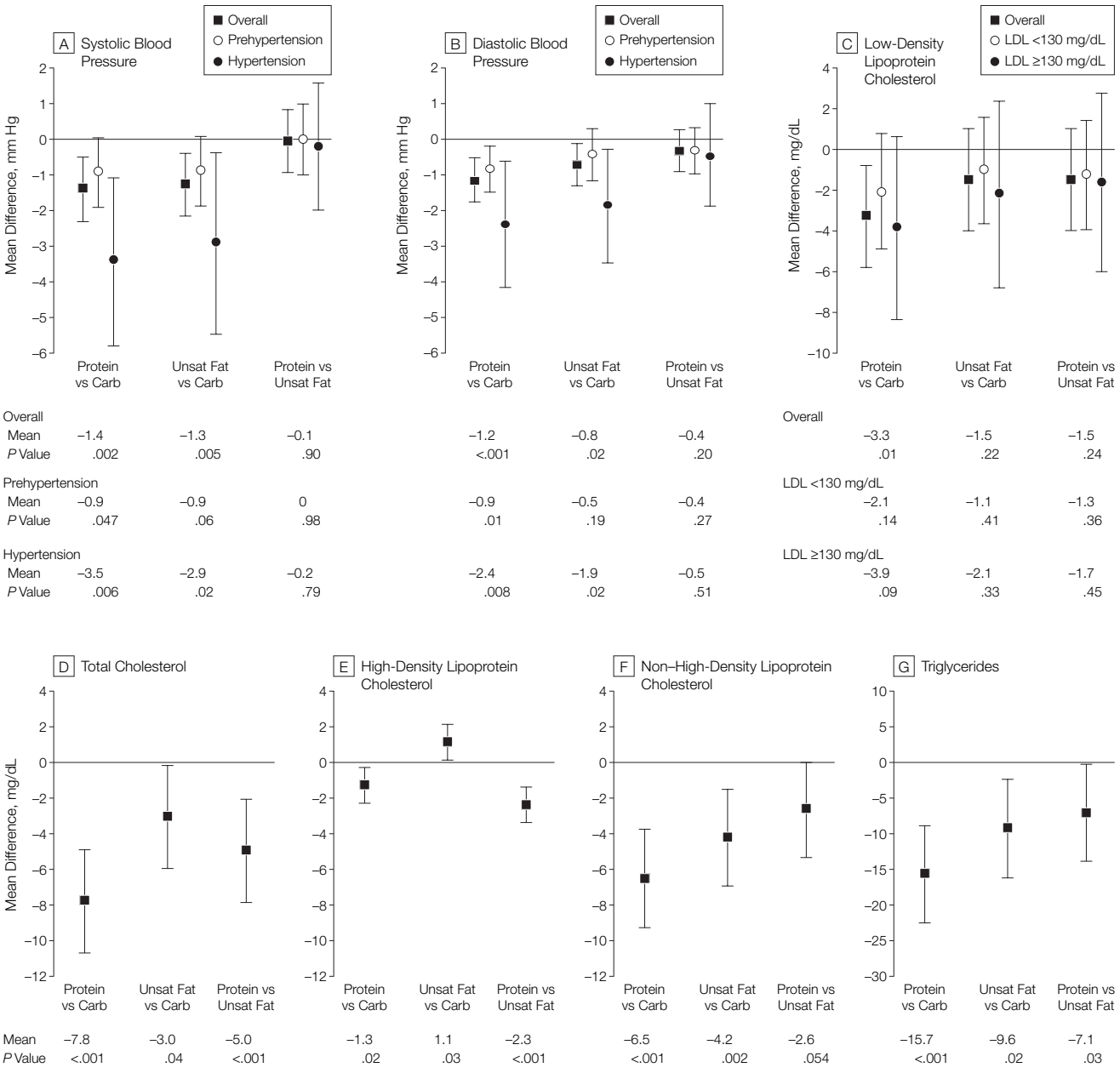
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
SI conversion factors: to convert cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, 0.0113.
*No. for baseline data. No. for changes from baseline is slightly less because 5 participants did not complete all 3 diets.
†Prehypertension is defined by a systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 80 to 89 mm Hg; stage 1 hypertension is defined as a systolic blood pressure of 140 to 159 mm Hg or diastolic blood pressure of 90 to 99 mm Hg.
‡In the 3 persons who had a triglyceride concentration higher than 400 mg/dL, LDL cholesterol could not be estimated, and values were treated as missing.
§Triglyceride values at baseline are reported as median and interquartile range.

cans, by 1.5 mm Hg (P=.05) in non–African Americans, 1.9 mm Hg (P=.001) in men, and 0.6 mm Hg (P=.46) in women. Compared with the carbohydrate diet, the protein diet lowered LDL cholesterol by 3.4 mg/dL (0.09 mmol/L; P=.09) in African Americans, 3.2 mg/dL (0.08 mmol/L; P=.06) in non–African Americans, 3.0 mg/dL (0.08 mmol/L; P=.07) in men, and 3.6 mg/dL (0.09 mmol/L; P=.10) in women. The unsaturated diet compared with the carbohydrate diet had no significant effect on LDL cholesterol in any sex or race subgroup.

Estimated Cardiovascular Risk

Compared with baseline, the 10-year risk of CHD was lower on each study diet by 16.1% to 21.0%, as estimated from the Framingham risk equation (TABLE 6). Compared with the carbohydrate diet, both the protein and the unsaturated fat

Figure 2. Between-Diet Differences in Trial Outcomes at 6 Weeks



	Protein vs Carb	Unsat Fat vs Carb	Protein vs Unsat Fat
A Systolic Blood Pressure			
Overall			
Mean	−1.4	−1.3	−0.1
P Value	.002	.005	.90
Prehypertension			
Mean	−0.9	−0.9	0
P Value	.047	.06	.98
Hypertension			
Mean	−3.5	−2.9	−0.2
P Value	.006	.02	.79
B Diastolic Blood Pressure			
Overall			
Mean	−1.2	−0.8	−0.4
P Value	<.001	.02	.20
Prehypertension			
Mean	−0.9	−0.5	−0.4
P Value	.01	.19	.27
Hypertension			
Mean	−2.4	−1.9	−0.5
P Value	.008	.02	.51
C Low-Density Lipoprotein Cholesterol			
Overall			
Mean	−3.3	−1.5	−1.5
P Value	.01	.22	.24
LDL <130 mg/dL			
Mean	−2.1	−1.1	−1.3
P Value	.14	.41	.36
LDL ≥130 mg/dL			
Mean	−3.9	−2.1	−1.7
P Value	.09	.33	.45
D Total Cholesterol			
Mean	−7.8	−3.0	−5.0
P Value	<.001	.04	<.001
E High-Density Lipoprotein Cholesterol			
Mean	−1.3	1.1	−2.3
P Value	.02	.03	<.001
F Non–High-Density Lipoprotein Cholesterol			
Mean	−6.5	−4.2	−2.6
P Value	<.001	.002	.054
G Triglycerides			
Mean	−15.7	−9.6	−7.1
P Value	<.001	.02	.03

Error bars indicate 95% confidence intervals. To convert high-density lipoprotein, low-density lipoprotein (LDL), non–high-density lipoprotein cholesterol, and total cholesterol to mmol/L, multiply by 0.0259; triglycerides to mmol/L, 0.0113. Because 5 participants did not complete all 3 diets, between-diet differences are not identical to corresponding differences that can be estimated from Table 5.

Table 6. Estimated 10-Year Risk of Coronary Heart Disease at Baseline and by Diet From the Framingham and PROCAM Risk Equations*

		Diet		
	Baseline	Carbohydrate	Protein	Unsaturated Fat
CHD Risk by Framingham Equation, %				
All				
Estimated 10-y CHD risk†	5.1	4.3	4.0	4.1
Change from baseline‡		−16.1	−21.0	−19.6
Change from carbohydrate‡			−5.8	−4.2
Men				
Estimated 10-y CHD†	7.5	6.4	6.1	6.2
Change from baseline‡		−13.8	−18.7	−17.2
Change from carbohydrate‡			−5.6	−3.9
Women				
Estimated 10-y CHD†	2.2	1.7	1.5	1.5
Change from baseline‡		−21.2	−30.0	−31.3
Change from carbohydrate‡			−11.1	−12.9
CHD Risk by PROCAM Equation, %				
Men				
Estimated 10-y CHD risk†	6.4	5.1	4.4	4.5
Change from baseline‡		−20.0	−30.7	−29.4
Change from carbohydrate‡			−13.4	−11.8

Abbreviations: CHD, coronary heart disease; PROCAM, Prospective Cardiovascular Munster.
*The Framingham risk equation was developed in men and women and includes 6 independent variables: age, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, medication treatment for hypertension, and smoking. The PROCAM risk equation was developed in men, ages 35 to 65 years and cannot be used in women. It was applied to data from the 73 male OmniHeart participants in this age range. The 8 independent variables included in this equation are age, low-density lipoprotein cholesterol, smoking, high-density lipoprotein cholesterol, systolic blood pressure, family history of premature myocardial infarction, diabetes mellitus, and triglycerides.
†Estimated percentage of individuals experiencing a CHD event over 10 years.
‡Estimated change in risk from baseline or carbohydrate diet, expressed as percentage.

diets further lowered CHD risk. Risk reductions, as estimated from the PROCAM equation, were greater than corresponding estimates from the Framingham equation, which did not include triglycerides as an independent variable.

Symptoms

From a 15-symptom checklist, there were statistically significant between-diet differences in 3 symptoms. Poor appetite was reported by 17 (10%) of participants on protein, 6 (4%) on the carbohydrate, and 5 (3%) on the unsaturated fat diets; bloating or fullness was reported by 19 (12%) of participants on protein and 9 (6%) on both the carbohydrate and unsaturated fat diets; and dry mouth was reported by 10 (6%) on the protein, 5 (3%) on the carbohydrate, and 11 (7%) on the unsaturated fat diets.

COMMENT

Results from this trial build on findings of our earlier research, which documented the beneficial effects of the DASH diet on blood pressure and LDL cholesterol levels.[5,6,9,10] In OmniHeart, a diet that partially replaced carbohydrates with protein, about half from plant sources, lowered blood pressure, LDL cholesterol levels, and triglyceride levels, as well as HDL cholesterol levels among adults with prehypertension or stage 1 hypertension. A diet that partially replaced carbohydrates with unsaturated fat, predominantly monounsaturated fat, lowered blood pressure and triglyceride levels and increased HDL cholesterol levels cholesterol but had no significant effect on LDL cholesterol levels. Estimated CHD risk was similar on the protein and unsaturated fat diets and lower than that of the carbohydrate diet.

OmniHeart results extend previous observations on the effects of protein and unsaturated fat on blood pressure. Evidence from the International Study of Macronutrients and Blood Pressure (INTERMAP)[16] and other observational studies suggested an inverse association between protein intake, particularly from plant sources, and blood pressure; however, trial results were inconsistent.[13,14] Two recent trials documented that increased protein intake from soy supplements, replacing carbohydrate, lowers blood pressure.[15,32,33] Results from OmniHeart indicate that protein mainly from nonsoy sources also reduces blood pressure in both prehypertensive and hypertensive individuals. A few observational studies and small trials suggested that increased monounsaturated fat should lower blood pressure,[34-36] and OmniHeart results confirm these preliminary findings.

Animal studies and a few small trials in humans have suggested that increased sugar consumption raises blood pressure.[37,38] Both the protein and the unsaturated fat diets lowered blood pressure to a similar extent. Hence, it is possible that a reduced intake of carbohydrate, rather than an increased intake of protein or monounsaturated fat, is the dietary factor that lowers blood pressure. Previous studies have tested the blood pressure effects of sugars rather than starch or foods rich in low-glycemic index carbohydrate. The glycemic index in the 3 diets used in OmniHeart is considered moderate (range, 68-75). Because the glycemic index influences the metabolic effects of dietary carbohydrate,[39] there is a need for additional research that explores the effects of different types of carbohydrate on blood pressure.

Previous lipid research has focused on the effects of different types of protein rather than different levels. In OmniHeart, the protein diet lowered LDL cholesterol, triglyceride, and HDL cholesterol levels compared with the carbohydrate diet. These findings are consistent with a series of small trials[19-21] that documented that replacement of carbohydrate with protein from mixed sources, providing about 25% of kcal from protein, lowered total cholesterol, LDL cholesterol, and triglyceride levels. In OmniHeart, the small reduction in HDL cholesterol levels from the protein diet (2.6% vs carbohydrate; 4.7% vs unsaturated fat) is unexpected, whereas the carbohydrate diet showed its well-established HDL cholesterol–lowering effects compared with fat.[40]

It is well-known that replacement of carbohydrate with dietary fat lowers triglyceride levels.[40] In OmniHeart, the protein diet substantially lowered serum triglycerides compared with the carbohydrate diet. Because the protein diet reduced serum triglycerides to a greater extent than did the unsaturated fat diet, protein may have a direct triglyceride-lowering effect beyond that of replacing carbohydrate, a nutrient that increases triglyceride concentrations. These novel effects of dietary protein on lipid risk factors merit further study.

The fact that each study diet provided recommended levels of saturated fat, cholesterol, fiber, fruits, vegetables, sodium, potassium, and other minerals has implications for the interpretation of trial results. We did not test an unhealthful control diet because previous trials documented the benefits of the DASH diet, which is similar to the carbohydrate diet. However, inferences on the effects of the OmniHeart diets, relative to a typical diet in the United States, can be drawn from changes from baseline when participants were eating their own diets. These observed changes, while often substantial, should be interpreted cautiously because they are subject to regression to the mean. Because there were exclusion criteria for low blood pressure but not for low lipid levels, the phenomenon of regression to the mean likely affected the magnitude of blood pressure change from baseline more so than the magnitude of corresponding lipid changes.

Still, the effects of the carbohydrate diet, net of baseline, and the effects of the DASH diet tested in 2 other feeding studies[5,6,9,10] appeared similar. The magnitude of blood pressure and LDL cholesterol reduction from the DASH diet and the carbohydrate diet were nearly identical (systolic blood pressure, 6 mm Hg vs 8 mm Hg; LDL cholesterol 11 mg/dL [0.28 mmol/L] for both), whereas HDL cholesterol levels decreased more from the DASH diet than the carbohydrate diet (3.8 vs 1.4 mg/dL [0.10 vs 0.04 mmol/L]).[5,9] Factors that might have lowered blood pressure from baseline are reduced sodium intake, increased potassium intake, and other aspects of the DASH diet from which the study diets were formulated. Given these considerations, changes from baseline in OmniHeart are likely to be real and indicate major benefits from all 3 diets.

As a feeding study, OmniHeart has several strengths. The trial achieved high rates of dietary adherence as evidenced by self-report and objective measurements. Follow-up data collection was virtually complete. Second, the trial controlled weight and held constant other potential confounders. Third, results should be widely applicable to the US population. The study population was large and demographically heterogeneous. The blood pressure inclusion criteria were broad; more than 50% of US adults (>100 million in the United States) have blood pressure in this range.[41] By using commonly available food products, typically no more than moderately priced, the trial tested diets that the general population could afford and adopt.

The trial also has limitations. The duration of feeding on each diet was brief, just 6 weeks. Still, the effects of dietary interventions on risk factors tend to persist as long as adherence is maintained.[42,43] Second, the trial did not adjust for multiple comparisons, an actively debated issue.[44] However, our main results are robust even at a significance level corresponding to strict Bonferroni adjustment with 4 comparisons ($P<.0125$), reflecting 2 primary between-diet contrasts and 2 primary outcomes). Third, trial outcomes were CVD risk factors, not clinical events. Nevertheless, in longitudinal observational studies, substitution of carbohydrates with increased protein intake from plants is associated with reduced risk of CVD.[17,18] Likewise, an increased intake of monounsaturated fat has been associated with reduced CVD and total mortality.[45] These results from observational studies corroborate our findings in which CHD risk, as estimated from the Framingham and PROCAM risk equations, was lower on all 3 diets compared with baseline and lower on the protein and the unsaturated fat diets compared with the carbohydrate diet.

Despite the fact that the majority of participants were overweight, the trial was an isocaloric feeding study in which weight was held constant. As an isocaloric feeding study, OmniHeart has the advantage of comparing the effects of different macronutrient profiles without the confounding effects of weight loss. Whether the study diets, as consumed by free-living persons, might also affect weight is uncertain. Worldwide, most lean populations traditionally consume diets that are high in complex carbohydrate and low in fat. However, emerging evidence suggests that hypocaloric diets that are either high in protein[46] or monounsaturated fat[47] might facilitate weight loss. Hence, overweight persons who adopt either the protein or the unsaturated fat diets should consume hypocaloric versions to concomitantly lose weight.

Results from OmniHeart have important implications. First, our results provide strong evidence that, in addition to salt, potassium, weight, alcohol, and the DASH diet, macronutrients also affect blood pressure. Second, the DASH diet, as tested in this trial, can be improved; partial substitution of carbohydrates with protein, about half from plant sources, or with unsaturated fat, predominantly monounsaturated fat, has beneficial effects on blood pressure and serum lipid levels. Third, the magnitude of effects have both public health and clinical importance. The blood pressure reductions and improved lipid profiles should reduce CVD risk in the general population[2,23] and mitigate the need for drug therapy in persons with risk factor levels above treatment thresholds.

In conclusion, in the setting of recommended levels of saturated fat, cholesterol, fiber, fruit, vegetables, and minerals, diets that partially replace carbohydrates with protein or monounsaturated fat can further lower blood pressure, improve lipid risk factors, and reduce CVD risk.

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