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## A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Cross-over Trial

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### ABSTRACT

**Objective:** Evidence suggests that both Mediterranean and vegan diets improve body weight and cardiometabolic risk factors, but their relative efficacy has not been compared in a randomized trial.

**Methods:** In a randomized crossover trial, 62 overweight adults were randomly assigned to a Mediterranean or vegan diet for a 16-week period. Body weight, plasma lipids, blood pressure, and body composition (dual X-ray absorptiometry) were measured. Secondary measures included insulin resistance (Homeostasis Model Assessment, HOMA-IR), oral glucose insulin sensitivity (OGIS), and predicted insulin sensitivity (PREDIM) indices. Thereafter, participants were asked to return to their baseline diets for 4 weeks, after which they began the opposite diet for 16 weeks. The same parameters were measured before and after this 2<sup>nd</sup> 16-week period.

**Results:** Overall net weight changes were 0.0 (Mediterranean) and -6.0 kg (vegan), (treatment effect -6.0 kg [95% CI -7.5 to -4.5];  $p < 0.001$ ). HOMA-IR decreased and OGIS increased on the vegan diet with no significant change on the Mediterranean diet (treatment effect -0.7 [95% CI, -1.8 to +0.4];  $p = 0.21$ ; and +35.8 mL/min/m<sup>2</sup> [95% CI, +13.2 to +58.3];  $p = 0.003$ , respectively). PREDIM did not change significantly in either group. Among participants with no medication changes, total and LDL-cholesterol decreased 18.7 mg/dL (0.5 mmol/L) and 15.3 mg/dL (0.4 mmol/L), respectively, on the vegan diet, compared with no significant change on the Mediterranean diet (treatment effect -15.6 [-24.6 to -6.6];  $p = 0.001$  and -14.8 [-23.5 to -6.2];  $p = 0.001$ , respectively); systolic and diastolic blood pressure decreased 9.3 and 7.3 mmHg on the Mediterranean diet, compared with 3.4 and 4.1 mmHg on the vegan diet (treatment effect +5.9 [95% CI +1.0 to +10.9];  $p = 0.02$ ; and +1.8 [95% CI -4.6 to +8.1];  $p = 0.58$ , respectively).

**Conclusions:** A low-fat vegan diet improved body weight, lipid concentrations, and insulin sensitivity, both from baseline and compared with a Mediterranean diet. Blood pressure decreased on both diets, more on the Mediterranean diet.

**Clinical trial registration:** ClinicalTrials.gov number, NCT03698955

<https://clinicaltrials.gov/ct2/show/NCT03698955?term=NCT03698955&draw=2&rank=1>

**Abbreviations:** BMI: body mass index; HbA1c: glycated hemoglobin; HOMA-IR: Homeostasis Model Assessment Insulin Resistance; OGIS: oral glucose insulin sensitivity; PREDIM: Predicted insulin sensitivity index

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Cardiometabolic; diet; Mediterranean; nutrition; vegan; weight

## Introduction

Excess body weight and cardiovascular disease are major worldwide health problems. Approximately 70% of US adults are overweight (1), and nearly half have cardiovascular disease (including coronary heart disease, heart failure, stroke or hypertension) (2).

Mediterranean and vegan diets have long been studied for their effects on body weight and cardiometabolic risk.

While a “Mediterranean diet” can refer to a variety of culinary traditions, the term has been codified for research purposes to refer to a diet that includes abundant plant-based foods, favors olive oil as the primary source of fat, and includes low to moderate amounts of meat, dairy products, eggs, and wine (3). In the Prevención con Dieta Mediterránea (PREDIMED) study, including 7,447 individuals at high cardiovascular risk, the risk of a major

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cardiovascular event was reduced by approximately 30% in the groups following a Mediterranean diet supplemented with either extra-virgin olive oil or nuts, compared with an untreated control group (4).

The effect of such a diet on body weight is less clear. A 2016 systematic review (5) reported that clinical trials using Mediterranean diets showed significant weight loss. However, all 5 reviewed studies included either added exercise or calorie restriction, confounding the effects of the dietary change. A later randomized trial reported significant weight loss with a Mediterranean diet, but the study also included a substantial energy restriction and physical exercise (6). In the Lyon Diet Heart Study (7), a Mediterranean diet supplemented with an alpha-linolenic-acid-rich margarine reduced cardiac deaths and nonfatal myocardial infarctions in individuals who had survived a myocardial infarction but led to a small weight gain (1.4 kg) during the 2-year study, rather than weight loss (8). In the PREDIMED study, although 90% of participants had excess body weight at baseline (9), weight loss over the first 3 study months was only 0.19 kg in the olive oil-supplemented group and 0.26 kg in the nut-supplemented group (4).

In epidemiologic studies, individuals following vegan diets tend to have lower body weights (10) and fewer cardiovascular disease risk factors (11), compared with individuals following other dietary patterns. In a meta-analysis of 15 clinical trials, prescription of vegetarian diets was associated with a mean weight loss among study completers of 4.6 kg (12). In a separate meta-analysis of 12 clinical trials including 1151 participants, weight change among participants following a vegan diet was  $-2.52$  kg (95% CI  $-3.02$  to  $-1.98$ ) (13). In randomized studies, a low-fat plant-based diet improves body weight (12), plasma lipids (14), blood pressure (15), and glycemic control (16).

Mediterranean and vegan diets are variations on a theme: one favors plant-based foods; the other consists of plant products exclusively. The European Prospective Investigation into Cancer and Nutrition–Physical Activity, Nutrition, Alcohol Consumption, Cessation of Smoking, Eating out of Home, and Obesity (EPIC-PANACEA) reported that the only aspect of a Mediterranean diet that was associated with protection from weight gain was the avoidance of meat products (17). In the PREDIMED study, a sub-analysis revealed that, the more participants followed a plant-based dietary pattern, the lower their risk of cardiovascular events (18).

None of these studies has examined the relative effects of a Mediterranean and low-fat vegan diet for improving body weight or altering cardiovascular risk factors. Such a study would require random assignment of individuals to these diets followed by a detailed examination of their effects, but no such study has been done. There is particular value to a cross-over study design in which two diets are tested, not in similar individuals, but in precisely the same individuals. Such studies require careful analysis, however, because the physical effects of the diet presented first will necessarily influence the experience of the second diet in such a way that even an extended wash-out period cannot overcome.

To take advantage of the statistical power of a crossover design, it is therefore essential to adjust for differences in body weight and other parameters that have occurred over the course of the study.

The present study directly compared a Mediterranean and a vegan diet for their effects on weight and cardiometabolic parameters, using a cross-over design. Based on the findings of prior studies, it tested the hypothesis that, compared with a Mediterranean diet, a low-fat vegan diet results in greater changes in body weight, total and LDL-cholesterol concentrations, and insulin sensitivity.

## Materials and methods

### Study design and eligibility

The intervention was conducted between February and October 2019 in Washington, DC. Adults with a body mass index between 28 and 40 kg/m<sup>2</sup>, were enrolled. Exclusion criteria were type 1 diabetes, smoking, alcohol or drug abuse, pregnancy or lactation, and current use of a vegan or Mediterranean diet.

### Randomization and study groups

Participants were randomly assigned in a 1:1 ratio to two groups. Group 1 was to begin a Mediterranean diet, and Group 2 was to begin a low-fat vegan diet, both for 16 weeks.

The Mediterranean diet followed the PREDIMED protocol (4). Participants were asked to consume  $\geq 2$  daily servings of vegetables,  $\geq 2$ –3 daily servings of fresh fruits,  $\geq 3$  weekly servings of legumes,  $\geq 3$  weekly servings of fish or shellfish, and  $\geq 3$  weekly servings of nuts or seeds, and to select white meats (with visible fat removed) instead of red meats. Participants were asked to limit or eliminate cream, butter, margarine, processed meats, sweetened beverages, pastries, and processed snacks. Nuts, eggs, fish and shellfish, low-fat cheese, chocolate ( $\geq 50\%$  cocoa) and whole-grain cereals could be consumed ad libitum. Cured ham, red meat, and fatty cheeses were limited to  $\leq 1$  serving per week. Participants were asked to use extra virgin olive oil instead of other fats or oils in food preparation, using 50 g per day as part of (not in addition to) their regular food intake.

The low-fat vegan diet ( $\sim 75\%$  of energy from carbohydrates, 15% protein, and 10% fat) consisted of vegetables, grains, legumes, and fruits. Participants were instructed to avoid animal products and added fats. No meals were provided. Vitamin B<sub>12</sub> was supplemented (500 µg/day) during the vegan phase of the study.

For both diets, no limitations were placed on energy intake. Alcoholic beverages were limited to one per day for women and two per day for men. All study participants were asked not to alter their exercise habits and to continue their preexisting medication regimens for the study duration, except as modified by their personal physicians.

Participants were asked to attend weekly classes of identical intensity but with content appropriate for their respective

diets. Classes covered food preparation, maintaining the assigned diet while traveling or dining at restaurants, and various health topics, were led by registered dietitians, physicians, or other study personnel with particular expertise in the respective diets.

A 3-day dietary record was completed by each participant at baseline and week 16. Dietary intake data were collected and analyzed by a Registered Dietitian or a staff member certified in Nutrition Data System for Research version 2018 (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN) (19). Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ) (20).

## Outcomes

All measurements were performed at baseline and week 16 after a 10 h overnight fast.

### Body weight and composition

Height (baseline only) and weight were measured using a stadiometer and a calibrated scale accurate to 0.1 kg, respectively. Body composition was measured by dual energy x-ray absorptiometry (Lunar iDXA, GE Healthcare; Madison, WI) with Encore® 2005 v.9.15.010 software, equipped with the CoreScan module (GE Healthcare, Madison, WI) to measure visceral adipose tissue volume.

### Blood lipids

Plasma lipid concentrations were measured by enzymatic colorimetric methods (Roche, Basel, Switzerland).

### Insulin sensitivity and glucose tolerance

Insulin secretion and glucose tolerance were assessed after stimulation with a liquid breakfast (Boost Plus, Nestle, Vevey, Switzerland; 720 kcal, 34% of energy from fat, 16% protein, 50% carbohydrate). Plasma concentrations of glucose, immunoreactive insulin, and C-peptide were measured at 0, 30, 60, 120, and 180 min. Serum glucose was analyzed using the Hexokinase UV endpoint method (Roche, Basel, Switzerland). Plasma immunoreactive insulin and C-peptide concentrations were determined using insulin and C-peptide electro-chemiluminescence immunoassay (ECLIA) kits (Roche, Basel, Switzerland). HbA1c was measured by turbidimetric inhibition immunoassay (Roche, Basel, Switzerland). Insulin resistance was calculated using HOMA-IR (The homeostasis model assessment) index (21). Oral glucose insulin sensitivity index was calculated as a measure of dynamic postprandial insulin sensitivity (22). PREDIM index, previously validated against clamp-derived measures of insulin sensitivity (23), was calculated as a measure of dynamic postprandial insulin sensitivity.

After the 16-week point, participants were asked to return to their customary eating habits for four weeks, then to begin the opposite diet (those initially randomized to the Mediterranean diet were asked to begin the vegan diet and

vice versa) for 16 weeks with the same weekly classes and outcome assessments before and after this period.

## Ethics

The study protocol was approved by the Advarra Institutional Review Board in Columbia, MD, USA, on September 20, 2018 (protocol identification number Pro00029777). The trial was prospectively registered with ClinicalTrials.gov (ID: NCT03698955). All participants gave written informed consent.

## Power analysis

Based on previous studies and with an alpha-level 0.05, the expected changes in body weight were  $-0.3$  (95% CI  $-0.61$  to  $0.09$ ) kg on the Mediterranean diet and  $-6.5$  (95% CI  $-8.9$  to  $-4.1$ ) kg on the low-fat vegan diet in 16 weeks. For 90% power to detect a significant treatment effect, we needed 24 participants to complete both interventions in a cross-over fashion. Assuming an attrition of 20%, the required sample size was 30 total for 90% power.

## Statistical analysis

While a cross-over design provides technical advantages, it requires specific statistical operations. The primary analysis included all participants with available data for the four evaluation timepoints for each outcome analyzed. A cross-over ANOVA model was used with between-subject and within-subject factors and interactions. Factors diet (Mediterranean and vegan), subject, time (week), period (1 and 2) were included in the model for participants with complete data.

Evidence of a carryover effect between the two treatment periods was evaluated for each outcome by assessing the significance of an interaction between period and initial treatment assignment in a linear mixed model of the outcome with treatment and period as fixed effects and participant as a random effect, fit for participants with complete data. For all variables for which this interaction was not statistically significant, the magnitude and significance of treatment effect were then evaluated using a one-sample t-test (two-sided with alpha level of 0.05) evaluating differences between change in outcome when on the vegan diet versus change in outcome when on the Mediterranean diet for all participants with complete data. For any outcomes with evidence of a carryover effect, estimated treatment effect for the first period of the trial alone was deemed the more appropriate.

Within each group, paired comparison t-tests were calculated to test whether the changes from baseline to 16 weeks in each treatment period were statistically significant. The statistician was blinded to the hypothesized effects of interventions and group assignment. Results are presented as means with two-sided 95% confidence intervals (CI).

**Table 1.** Baseline characteristics of the study population.

Characteristic	Group 1 (n = 32)	Group 2 (n = 30)	p-value
<b>Age (years)</b>	56.6 (±10.9)	58.3 (±8.4)	0.50
<b>Sex (number, %)</b>			
Female	26 (81.3)	22 (73.3)	0.46
Male	6 (18.8)	8 (26.7)	
<b>Race, (number, %)</b>			
White	15 (46.9)	16 (53.3)	0.90
Black	16 (50.0)	14 (46.7)	
Asian, Pacific Islander	0 (0.0)	0 (0.0)	
American Indian, Eskimo, Aleut	1 (3.1)	0 (0.0)	
Not disclosed	0 (0.0)	0 (0.0)	
<b>Ethnicity, (number, %)</b>			
Non-Hispanic	23 (71.9)	23 (76.7)	0.14
Hispanic	3 (9.4)	0 (0.0)	
Not disclosed	6 (18.8)	7 (23.3)	
<b>Marital status</b>			
Not married	15 (46.9)	15 (50.0)	0.71
Married	17 (53.1)	14 (46.7)	
Not disclosed	0 (0.0)	1 (3.3)	
<b>Education</b>			
High school	0 (0.0)	0 (0.0)	0.28
Associates	7 (21.9)	5 (16.7)	
College	13 (40.6)	9 (30.0)	
Graduate degree	12 (37.5)	16 (53.3)	
<b>Occupation</b>			
Service occupation	7 (21.9)	4 (13.3)	0.29
Technical, sales, administrative	8 (25.0)	9 (30.0)	
Professional or managerial	2 (6.3)	7 (23.3)	
Retired	7 (21.9)	6 (20.0)	
Other	8 (25.0)	4 (13.3)	
<b>Medications</b>			
Lipid-lowering therapy (%)	12 (37.5)	11 (36.7)	0.95
Antihypertensive therapy (%)	16 (50.0)	14 (46.7)	0.79
Thyroid medications (%)	3 (9.4)	1 (3.3)	0.61
<b>Physical Activity (METs)</b>	2290 (±2838)	2666 (±4313)	0.70
<b>Energy intake (kcal)</b>	1826 (±551)	1912 (±549)	0.54
<b>Anthropometrics</b>			
Body weight (kg)	97.6 (±12.0)	98.4 (±13.2)	0.80
BMI (kg/m <sup>2</sup> )	34.3 (±2.7)	33.7 (±3.4)	0.42
Fat mass (kg)	43.9 (±7.1)	41.5 (±6.7)	0.17
Lean mass (kg)	51.5 (±8.1)	54.1 (±9.5)	0.25
VAT <sup>2</sup> volume (cm <sup>3</sup> )	2017 (±956)	2127 (±1147)	0.68
<b>Lipids</b>			
Total cholesterol (mg/dL)	203.3 (±47.6)	202.2 (±47.6)	0.93
LDL-cholesterol (mg/dL)	119.9 (±41.0)	116.6 (±40.4)	0.76
HDL-cholesterol (mg/dL)	58.8 (±15.0)	56.4 (±13.7)	0.53
<b>HbA1c</b>	5.8 (±1.0)	5.8 (±0.5)	0.93

<sup>1</sup>Race and ethnicity were determined via self-report.<sup>2</sup>VAT: visceral adipose tissue.

Data are means ± SD, or number (%). P-values refer to t-tests for continuous variables and  $\chi^2$  or Fisher's exact test for categorical variables. The P-value calculated for ethnicity distribution is for the comparison between Hispanic vs. non-Hispanic categories and all other comparisons also exclude undisclosed datapoints. Group 1 started with the Mediterranean diet and Group 2 started with the vegan diet.

## Results

### Participant characteristics

Of 506 people screened by telephone, 62 met participation criteria and were randomly assigned to Group 1 (Mediterranean first, n = 31) or Group 2 (vegan first, n = 31) diet (Supplemental Figure 1). After randomization, it was discovered that a mother and daughter had been assigned to opposite diets. To avoid contamination of the study, the mother was reassigned to be in the same group as her daughter (final n = 32 Group 1, 30 Group 2). Demographic characteristics are listed in Table 1. There were no significant differences between the groups.

Four participants dropped out during a vegan phase and six dropped out during a Mediterranean phase, mostly for reasons unrelated to the study, leaving 52 (84%) study completers.

### Dietary intake

Dietary intake, physical activity, and cardiometabolic outcomes are presented in Table 2. Changes in the first and second study periods separately, as well as tests for a carry-over effect (indicating non-consistent treatment effects observed in the two periods) are presented in Table 3.

From the analysis of the full crossover study shown in Table 2, self-reported energy intake decreased on the vegan diet by 500 kcal/day ( $p < 0.001$ ) but did not change significantly on the Mediterranean diet. The percentage of energy consumed from fat decreased on the vegan diet ( $p < 0.001$ ) but increased on the Mediterranean diet ( $p < 0.001$ ), mainly due to increased monounsaturated fat intake ( $p < 0.001$ ). Energy from carbohydrates increased on the vegan diet ( $p < 0.001$ ) and decreased on the Mediterranean diet ( $p$



**Table 2.** Changes in outcomes during the study comparing a Mediterranean and low-fat vegan diet, using a standard crossover-trial model, comparing outcome changes on each diet among participants with data from all study periods.

Variable	Mediterranean baseline	Mediterranean final	$\Delta$ Mediterranean	Vegan baseline	Vegan final	$\Delta$ Vegan	Treatment effect	p-value (t test)
<b>Dietary intake</b>								
Energy (kcal)	1776 (1625 to 1928)	1855 (1699 to 2011)	+79 (−120 to +277)	1815 (1649 to 1982)	1315 (1191 to 1440)	−500 (−639 to −362)***	−579 (−801 to −357)	$p < .001$
% Calories from Fat	35 (33 to 38)	43 (40 to 45)	+7 (+4 to +10)***	38 (36 to 40)	17 (15 to 19)	−21 (−24 to −18)***	−28 (−32 to −24)	$p < .001$
% Calories from Carbohydrate	46 (43 to 50)	40 (37 to 42)	−7 (−10 to −4)***	42 (40 to 45)	68 (66 to 71)	+26 (+23 to +29)***	+33 (+29 to +37)	$p < .001$
% Calories from Protein	16 (15 to 18)	15 (14 to 16)	−1 (−3 to 0)	18 (17 to 19)	12 (12 to 13)	−6 (−7 to −4)***	−5 (−6 to −3)	$p < .001$
Alcohol (g)	5 (2 to 8)	5 (3 to 7)	0 (−3 to +3)	5 (3 to 8)	3 (2 to 5)	−2 (−4 to 0)*	−2 (−5 to +2)	$p = 0.31$
Cholesterol (mg)	217 (188 to 296)	217 (179 to 256)	−25 (−93 to +43)	292 (251 to 334)	19 (1 to 37)	−273 (−317 to −230)***	−248 (−331 to −166)	$p < .001$
% Calories from SFA	10 (9 to 11)	9 (8 to 9)	−1 (−2 to 0)*	11 (10 to 12)	4 (3 to 4)	−8 (−9 to −6)***	−6 (−8 to −5)	$p < .001$
% Calories from MUFA	14 (13 to 16)	22 (20 to 24)	+8 (+6 to +10)***	15 (14 to 16)	6 (5 to 6)	−9 (−11 to −8)***	−17 (−20 to −14)	$p < .001$
% Calories from PUFA	9 (8 to 9)	9 (9 to 10)	+1 (−0 to +2)	9 (8 to 10)	6 (6 to 7)	−3 (−4 to −2)***	−4 (−5 to −2)	$p < .001$
Total Fiber (g)	25 (22 to 28)	29 (26 to 32)	+5 (+2 to +7)***	22 (19 to 26)	33 (29 to 37)	+10 (−8 to +13)***	+6 (+2 to +9)	$p < .001$
Soluble Fiber (g)	7 (6 to 8)	7 (7 to 8)	0 (−0 to +1)	6 (5 to 7)	8 (7 to 10)	+2 (+1 to +3)***	+2 (+1 to +3)	$p = 0.002$
Insoluble Fiber (g)	18 (16 to 20)	22 (20 to 24)	+4 (+2 to +6)***	16 (14 to 18)	24 (21 to 27)	+8 (+6 to +10)***	+4 (+1 to +7)	$p = 0.007$
<b>Physical activity</b>								
Physical Activity (MET)	2384 (1693 to 3074)	2740 (2073 to 3406)	+356 (−127 to +839)	2585 (1466 to 3705)	2952 (1822 to 4081)	+366 (−711 to +1444)	+10 (−1251 to +1271)	$p = 0.99$
<b>Anthropometric variables and body composition</b>								
Body weight (kg)	94.5 (90.9 to 98.1)	94.5 (90.7 to 98.3)	+0.0 (−0.9 to +0.9)	97.3 (93.6 to 101.0)	91.3 (87.4 to 95.3)	−6.0 (−7.2 to −4.9)***	−6.0 (−7.5 to −4.5)	$p < .001$
BMI (kg/m <sup>2</sup> )	32.8 (31.9 to 33.8)	32.7 (31.7 to 33.7)	−0.1 (−0.5 to +0.2)	33.8 (32.9 to 34.7)	31.7 (30.6 to 32.8)	−2.1 (−2.5 to −1.7)***	−2.0 (−2.5 to −1.4)	$p < .001$
Total fat mass (kg)	40.6 (38.4 to 42.7)	40.4 (38.1 to 42.6)	−0.2 (−0.9 to +0.6)	42.3 (40.2 to 44.4)	38.6 (36.3 to 40.9)	−3.6 (−4.6 to −2.7)***	−3.4 (−4.7 to −2.2)	$p < .001$
Total lean mass (kg)	52.2 (49.8 to 54.7)	52.1 (49.6 to 54.6)	−0.2 (−0.6 to +0.3)	52.7 (50.1 to 55.3)	50.2 (47.8 to 52.7)	−2.5 (−3.3 to −1.7)***	−2.3 (−3.3 to −1.4)	$p < .001$
VAT volume <sup>1</sup> (cm <sup>3</sup> )	1901.9 (1595.3 to 2208.5)	1915.2 (1600.5 to 2229.8)	+13.3 (−91.4 to +118.0)	2032.8 (1703.3 to 2362.3)	1731.5 (1427.7 to 2035.3)	−301.3 (−401.3 to −191.3)***	−314.5 (−446.7 to −182.4)	$p < .001$
<b>Parameters of glucose control and insulin resistance</b>								
Fasting plasma glucose (mg/dL)	103.3 (96.1 to 110.6)	102.7 (94.9 to 110.5)	−0.7 (−4.4 to +3.1)	105.9 (97.2 to 114.6)	98.7 (93.9 to 103.5)	−7.2 (−12.7 to −1.7)*	−6.6 (−13.6 to +0.5)	$p = 0.07$
Fasting plasma glucose (mmol/L)	5.7 (5.3 to 6.1)	5.7 (5.3 to 6.1)	−0.04 (−0.2 to +0.2)	5.9 (5.4 to 6.4)	5.5 (5.2 to 5.8)	−0.4 (−0.7 to −0.09)*	−0.4 (−0.8 to +0.03)	$p = 0.07$
HbA1c (%) <sup>2</sup>	5.8 (5.6 to 6.0)	5.8 (5.7 to 6.0)	+0.05 (−0.05 to +0.16)	5.8 (5.6 to 6.1)	5.8 (5.6 to 5.9)	−0.07 (−0.17 to +0.03)	−0.13 (−0.22 to −0.03)	$p = 0.01$
HOMA <sup>3</sup> (dimensionless)	2.5 (1.8 to 3.3)	2.5 (1.9 to 3.1)	−0.07 (−0.69 to +0.55)	2.9 (2.0 to 3.8)	2.2 (1.7 to 2.7)	−0.75 (−1.51 to +0.01)	−0.68 (−1.76 to +0.39)	$p = 0.21$
PREDIM <sup>4</sup> (mg/min/kg)	4.5 (4.0 to 5.1)	4.5 (3.9 to 5.0)	−0.06 (−0.51 to +0.38)	4.1 (3.6 to 4.7)	4.6 (4.1 to 5.2)	+0.5 (−0.03 to +1.0)	+0.6 (−0.2 to +1.4)	$p = 0.16$
OGIS <sup>5</sup> (ml/min/m <sup>2</sup> )	375.8 (351.2 to 400.4)	370.0 (344.3 to 395.7)	−5.8 (−22.3 to +10.7)	363.9 (337.0 to 390.9)	395.9 (368.8 to 418.9)	+29.9 (+11.9 to +47.9)**	+35.8 (+13.2 to +58.3)	$p = 0.003$
<b>Blood lipids</b>								
Total cholesterol (mg/dL)	191.1 (178.8 to 203.5)	187.8 (178.7 to 197.0)	−3.3 (−12.4 to +5.9)	194.6 (183.1 to 206.1)	180.1 (170.2 to 190.1)	−14.5 (−23.0 to −5.9)**	−11.2 (−22.0 to −0.3)	$p = 0.04$
Total cholesterol (mmol/L)	5.0 (4.6 to 5.3)	4.9 (4.6 to 5.1)	−0.1 (−0.3 to +0.2)	5.0 (4.7 to 5.3)	4.7 (4.4 to 4.9)	−0.4 (−0.6 to −0.2)**	−0.3 (−0.6 to −0.0)	$p = 0.04$
Total cholesterol (mg/dL)	190.5 (177.0–204.0)	187.4 (178.0–196.8)	−3.1 (−12.2 to +6.0)	195.4 (182.6–208.2)	176.7 (166.4–187.0)	−18.7 (−25.9 to −11.5)***	−15.6 (−24.6 to −6.6)	$p = 0.001$
– No Medication Changes	4.9 (4.6–5.3)	4.9 (4.6–5.1)	−0.1 (−0.3 to +0.2)	5.1 (4.7–5.4)	4.6 (4.3–4.8)	−0.5 (−0.7 to −0.3)***	−0.4 (−0.6 to −0.2)	$p = 0.001$
Triglycerides changes (mg/dL)	121.9 (104.5 to 139.3)	109.5 (95.7 to 123.4)	−12.4 (−22.9 to −1.8)*	127.1 (108.0 to 146.2)	135.3 (119.0 to 151.6)	+8.2 (−7.2 to +23.6)	+20.6 (−4.4 to +36.7)	$p = 0.01$
Triglycerides (mmol/L)	1.4 (1.2 to 1.6)	1.2 (1.1 to 1.4)	−0.1 (−0.3 to −0.0)*	1.4 (1.2 to 1.7)	1.5 (1.3 to 1.7)	+0.1 (−0.1 to +0.3)	+0.2 (+0.0 to +0.4)	$p = 0.01$
Triglycerides (mg/dL)	117.5 (99.5–135.5)	107.8 (93.0–122.5)	−9.8 (−21.7 to +2.2)	120.6 (100.3–140.9)	128.9 (111.8–146.0)	+8.3 (−10.2 to +26.8)	+18.1 (−0.8 to +36.9)	$p = 0.06$
– No Medication Changes	1.3 (1.1–1.5)	1.2 (1.1–1.4)	−0.1 (−0.2 to +0.0)	1.4 (1.1–1.6)	1.5 (1.3–1.7)	+0.1 (−0.1 to +0.3)	+0.2 (−0.0 to +0.4)	$p = 0.06$
HDL-cholesterol (mg/dL)	57.1 (53.2 to 61.0)	56.5 (53.0 to 60.0)	−0.6 (−2.8 to +1.6)	56.4 (52.7 to 60.2)	51.4 (47.8 to 55.1)	−5.0 (−7.4 to −2.6)***	−4.4 (−7.7 to −1.1)	$p = 0.009$
HDL-cholesterol (mmol/L)	1.5 (1.4 to 1.6)	1.5 (1.4 to 1.6)	−0.0 (−0.1 to +0.0)	1.5 (1.4 to 1.6)	1.3 (1.2 to 1.4)	−0.1 (−0.2 to −0.1)***	−0.1 (−0.2 to −0.0)	$p = 0.009$
HDL-cholesterol (mg/dL)	58.2 (53.4–62.9)	57.5 (53.4–61.6)	−0.6 (−3.3 to +2.0)	57.9 (53.5–62.2)	52.8 (48.5–57.1)	−5.1 (−7.9 to −2.3)***	−4.5 (−8.3 to −0.7)	$p = 0.02$
– No Medication Changes	1.5 (1.4–1.6)	1.5 (1.4–1.6)	−0.0 (−0.1 to +0.1)	1.5 (1.4–1.6)	1.4 (1.3–1.5)	−0.1 (−0.2 to −0.1)***	−0.1 (−0.2 to −0.0)	$p = 0.02$
LDL-cholesterol (mg/dL)	109.6 (98.8 to 120.5)	109.4 (101.2 to 117.7)	−0.2 (−8.1 to +7.8)	112.7 (102.8 to 122.5)	101.5 (92.1 to 111.0)	−11.1 (−19.2 to −3.1)**	−11.0 (−21.3 to −0.6)	$p = 0.04$
LDL-cholesterol (mmol/L)	2.8 (2.6 to 3.1)	2.8 (2.6 to 3.0)	−0.0 (−0.2 to +0.2)	2.9 (2.7 to 3.2)	2.6 (2.4 to 2.9)	−0.3 (−0.5 to −0.1)**	−0.3 (−0.6 to −0.0)	$p = 0.04$

(continued)

Table 2. Continued.

Variable	Mediterranean baseline	Mediterranean final	$\Delta$ Mediterranean	Vegan baseline	Vegan final	$\Delta$ Vegan	Treatment effect	p-value (t test)
LDL-cholesterol (mg/dL)	108.9 (96.8–120.9)	108.4 (99.5–117.2)	−0.5 (−8.1 to +7.1)	113.4 (102.1–124.7)	98.1 (88.3–107.8)	−15.3 (−21.6 to −9.0)***	−14.8 (−23.5 to −6.2)	$p = 0.001$
– No Medication Changes								
LDL-cholesterol (mmol/L)	2.8 (2.5–3.1)	2.8 (2.6–3.0)	−0.0 (−0.2 to +0.2)	2.9 (2.6–3.2)	2.5 (2.3–2.8)	−0.4 (−0.6 to −0.2)***	−0.4 (−0.6 to −0.2)	$p = 0.001$
– No Medication Changes								
VLDL-cholesterol (mg/dL)	24.4 (20.9 to 27.9)	21.9 (19.1 to 24.7)	−2.5 (−4.6 to −0.4)*	25.5 (21.7 to 29.2)	27.1 (23.9 to 30.4)	+1.7 (−1.4 to +4.8)	+4.2 (+1.0 to +7.5)	$p = 0.01$
VLDL-cholesterol (mmol/L)	0.6 (0.5 to 0.7)	0.6 (0.5 to 0.6)	−0.1 (−0.1 to −0.0)*	0.7 (0.6 to 0.8)	0.7 (0.6 to 0.8)	+0.0 (−0.0 to +0.1)	+0.1 (+0.0 to +0.2)	$p = 0.01$
VLDL-cholesterol (mg/dL)	23.5 (19.9–27.1)	21.5 (18.6–24.5)	−2.0 (−4.4 to +0.4)	24.2 (20.1–28.2)	25.9 (22.4–29.3)	+1.7 (−2.0 to +5.4)	+3.7 (−0.1 to +7.5)	$p = 0.06$
– No Medication Changes								
VLDL-cholesterol (mmol/L)	0.6 (0.5–0.7)	0.6 (0.5–0.6)	−0.1 (−0.1 to +0.0)	0.6 (0.5–0.7)	0.7 (0.6–0.8)	+0.0 (−0.1 to +0.1)	+0.1 (−0.0 to +0.2)	$p = 0.06$
– No Medication Changes								
<b>Blood pressure</b>								
Systolic Blood pressure (mmHg)	131.6 (127.0 to 136.2)	122.2 (117.8 to 126.6)	−9.4 (−13.8 to −5.0)***	131.9 (127.4 to 136.5)	127.6 (123.3 to 132.0)	−4.3 (−8.6 to −0.0)*	+5.1 (+0.6 to +9.6)	$p = 0.03$ #
Systolic Blood pressure (mmHg) – No Medication Changes	129.6 (124.9–134.3)	120.3 (115.9–124.7)	−9.3 (−13.4 to −5.3)***	130.0 (125.3–134.7)	126.7 (121.9–131.4)	−3.4 (−8.0 to +1.2)	+6.0 (+1.0 to +10.9)	$p = 0.02$
Diastolic Blood pressure (mmHg)	79.9 (77.7 to 82.2)	72.7 (70.7 to 74.7)	−7.3 (−9.4 to −5.1)***	80.3 (78.1 to 82.4)	76.2 (74.0 to 78.3)	−4.1 (−6.4 to −1.8)***	+3.2 (+0.4 to +5.9)	$p = 0.03$
Diastolic Blood pressure (mmHg) – No Medication Changes	79.9 (77.3–82.6)	72.7 (70.4–74.9)	−7.3 (−9.6 to −4.9)***	80.3 (77.8–82.8)	76.3 (73.8–78.7)	−4.1 (−6.7 to −1.5)**	+3.2 (+0.0 to +6.4)	$p = 0.048$

<sup>1</sup>VAT, visceral adipose tissue.<sup>2</sup>HbA1c, glycated hemoglobin.<sup>3</sup>HOMA-IR, Homeostasis Model Assessment Insulin Resistance.<sup>4</sup>PREDIM, Predicted insulin sensitivity index.<sup>5</sup>OGIS, oral glucose insulin sensitivity.

Data shown are means and estimated treatment effects with 95% confidence intervals. The treatment effect is the mean (average) difference between participant outcomes on the vegan versus the Mediterranean diet, and the P-value in the rightmost column is from a one-sample t-test assessing whether this mean within-participant difference is different from zero. \* $p < 0.05$ , \*\* $p < 0.01$  and \*\*\* $p < 0.001$  for paired comparison t-tests assessing whether within-group changes from baseline are different from zero.

# For physical activity and systolic blood pressure in all study participants, including those with changes in antihypertensive medications, the carryover effect was statistically significant. Therefore, the values from the first study phase may be considered as more valid (see Table 3).

**Table 3.** Changes in outcomes and estimated treatment effects for the first and the second period of the study, comparing a Mediterranean and a low-fat vegan diet.

Variable	ΔMediterranean (1 <sup>st</sup> period)	ΔVegan (1 <sup>st</sup> period)	Treatment Effect: 1 <sup>st</sup> period only	p-value for 1 <sup>st</sup> period treatment effect	ΔMediterranean (2 <sup>nd</sup> period)	ΔVegan (2 <sup>nd</sup> period)	Treatment Effect: 2 <sup>nd</sup> period only	p-value for second period treatment effect	p-value: test for carryover effect
<b>Dietary intake</b>									
Energy (kcal)	-53 (-392 to +285)	-654 (-829 to -479)***	-601 (-975 to -226)	p = 0.003	+201 (-32 to +434)	-333 (-543 to -123)**	-534 (-842 to -227)	p = 0.001	p = 0.80
% Calories from Fat	+6 (+1 to +10)*	-22 (-25 to -18)***	-28 (-33 to -22)	p < 0.001	+9 (+5 to +13)***	-20 (-24 to -15)***	-25 (-32 to -18)	p < 0.001	p = 0.82
% Calories from Carbohydrate	-6 (-10 to -1)*	+26 (+23 to +30)***	+32 (+26 to +37)	p < 0.001	-8 (-12 to -4)***	+26 (+21 to +31)***	+34 (+28 to +41)	p < 0.001	p = 0.55
% Calories from Protein	-1 (-4 to +1)	-5 (-6 to -3)***	-3 (-6 to -1)	p = 0.008	-1 (-3 to +1)	-7 (-9 to -4)***	-6 (-8 to -3)	p < 0.001	p = 0.26
Alcohol (g)	0 (-4 to +3)	-2 (-5 to +1)	-2 (-6 to 3)	p = 0.45	0 (-5 to +5)	-2 (-4 to +1)	-2 (-7 to +4)	p = 0.53	p = 0.99
Cholesterol (mg)	-91 (-215 to +32)	-297 (-360 to -235)***	-206 (-342 to -69)	p = 0.004	+37 (-27 to +101)	-247 (-311 to -183)***	-284 (-372 to -196)	p < 0.001	p = 0.33
% Calories from SFA	-2 (-4 to -0)*	-8 (-10 to -7)***	-6 (-8 to -4)	p < 0.001	0 (-1 to +1)	-6 (-9 to -4)***	-7 (-9 to -4)	p < 0.001	p = 0.86
% Calories from MUFA	+7 (+4 to +11)***	-9 (-12 to -7)***	-17 (-21 to -13)	p < 0.001	+8 (+5 to +11)***	-9 (-11 to -7)***	-17 (-20 to -14)	p < 0.001	p = 0.97
% Calories from PUFA	+1 (-1 to +2)	-3 (-4 to -2)***	-4 (-5 to -2)	p < 0.001	+1 (-0 to +2)	-3 (-5 to -1)**	-4 (-6 to -1)*	p = 0.003	p = 0.96
Total Fiber (g)	+6 (+1 to +10)*	+9 (+5 to +13)***	+3 (-3 to 9)	p = 0.26	+4 (0 to +7)*	+12 (+8 to +15)***	+8 (+4 to +13)	p < 0.001	p = 0.26
Soluble Fiber (g)	0 (-1 to +1)	+2 (0 to +3)*	+1 (-0 to +3)	p = 0.11	0 (-1 to +2)	+3 (+2 to +4)***	+2 (+1 to +4)	p = 0.008	p = 0.48
Insoluble Fiber (g)	+5 (+2 to +9)**	+7 (+4 to +11)***	+2 (-3 to +7)	p = 0.40	+3 (0 to +6)*	+9 (+6 to +12)***	+6 (+2 to +10)	p = 0.003	p = 0.25
<b>Physical activity</b>									
Physical Activity (MET)	+847 (+147 to +1548)*	-534 (-2332 to +1265)	-1381 (-3288 to +526)	p = 0.15	-97 (-760 to +565)	+1341 (+211 to +2472)*	+1439 (+155 to +2723)	p = 0.03	p = 0.008
<b>Anthropometric variables and body composition</b>									
Weight (kg)	-1.5 (-2.9 to 0.0)	-7.9 (-9.3 to -6.5)***	-6.4 (-8.4 to -4.5)	< 0.001	+1.4 (+0.4 to +2.3)**	-4.0 (-5.6 to -2.4)***	-5.3 (-7.1 to -3.5)	p < 0.001	p = 0.45
BMI (kg/m <sup>2</sup> )	-0.8 (-1.4 to -0.2)*	-2.7 (-3.2 to -2.2)***	-2.0 (-2.7 to -1.2)	p < 0.001	+0.5 (+0.1 to +0.8)**	-1.4 (-2.0 to -0.9)***	-1.9 (-2.6 to -1.3)	p < 0.001	p = 0.93
Total fat mass (kg)	-1.1 (-2.3 to +0.1)	-4.9 (-6.3 to -3.4)***	-3.8 (-5.6 to -1.9)	p < 0.001	+0.7 (+0.2 to +1.5)	-2.4 (-3.6 to -1.2)***	-3.0 (-4.4 to -1.6)	p < 0.001	p = 0.56
Total lean mass (kg)	-0.7 (-1.3 to -0.1)*	-3.6 (-4.9 to -2.2)***	-2.9 (-4.3 to -1.4)	p < 0.001	+0.3 (+0.2 to +0.9)	-1.4 (-2.1 to -0.6)***	-1.7 (-2.6 to -0.8)	p < 0.001	p = 0.16
VAT <sup>1</sup> volume (cm <sup>3</sup> )	+5.9 (-187.8 to +199.7)	-423.3 (-583.9 to -262.8)***	-429.3 (-673.7 to -184.9)	p < 0.001	+20.3 (-83.1 to +123.7)	-174.4 (-280.2 to -68.5)**	-194.7 (-338.9 to -50.4)	p = 0.009	p = 0.13
<b>Parameters of glucose control and insulin resistance</b>									
Variable	ΔMediterranean (1 <sup>st</sup> period)	ΔVegan (1 <sup>st</sup> period)	Treatment Effect: 1 <sup>st</sup> period only	p-value for 1 <sup>st</sup> period treatment effect	ΔMediterranean (2 <sup>nd</sup> period)	ΔVegan (2 <sup>nd</sup> period)	Treatment Effect: 2 <sup>nd</sup> period only	p-value for second period treatment effect	p-value: test for carryover effect
Fasting plasma glucose (mg/dL)	-5.3 (-10.6 to -0.1)*	-8.0 (-14.9 to -1.2)*	-2.7 (-11.3 to +5.9)	p = 0.53	+3.5 (-1.6 to +8.6)	-6.3 (-15.6 to +3.1)	-9.8 (-20.2 to +0.7)	p = 0.07	p = 0.26
Fasting plasma glucose (mmol/L)	-0.3 (-0.6 to -0.0)*	-0.5 (-0.8 to -0.1)*	-0.1 (-0.6 to +0.3)	p = 0.53	+0.2 (-0.1 to +0.5)	-0.4 (-0.9 to +0.2)	-0.5 (-1.1 to +0.0)	p = 0.07	p = 0.26
HbA1c (%) <sup>2</sup>	-0.1 (-0.2 to +0.1)	-0.1 (-0.2 to +0.0)*	-0.0 (-0.2 to +0.2)	p = 0.75	+0.2 (0.0 to +0.3)**	-0.1 (-0.3 to +0.2)	-0.2 (-0.4 to +0.0)	p = 0.07	p = 0.33
HOMA <sup>3</sup> (dimensionless)	-0.6 (-1.7 to +0.5)	-1.5 (-2.7 to -0.3)*	-0.9 (-2.5 to +0.7)	p = 0.27	0.4 (-0.4 to +1.1)	+0.1 (-0.7 to +0.9)	-0.3 (-1.4 to +0.8)	p = 0.56	p = 0.53
PREDIM <sup>4</sup> (mg/min/kg)	+0.4 (-0.3 to +1.1)	+1.0 (+0.4 to +1.5)**	+0.6 (-0.3 to +1.4)	p = 0.20	-0.5 (-1.1 to +0.1)	0.0 (-1.0 to +0.9)	+0.5 (-0.6 to +1.6)	p = 0.36	p = 0.90
OGIS <sup>5</sup> (ml/min/m2)	+7.9 (-22.0 to +37.8)	+28.8 (+5.9 to +51.7)*	+20.9 (-14.9 to +56.7)	p = 0.24	-17.6 (-35.4 to +0.2)	+31.3 (+0.1 to +62.4)*	+48.8 (+13.9 to +83.8)	p = 0.008	p = 0.29

(continued)



Table 3. Continued.

Variable	ΔMediterranean (1 <sup>st</sup> period Mediterranean)	ΔVegan (1 <sup>st</sup> period vegan)	Treatment Effect: 1 <sup>st</sup> period only	p-value for 1 <sup>st</sup> period treatment effect	ΔMediterranean (2 <sup>nd</sup> period Mediterranean)	ΔVegan (2 <sup>nd</sup> period vegan)	Treatment Effect: 2 <sup>nd</sup> period only	p-value for second period treatment effect	p-value: test for carryover effect
<b>Blood lipids</b>									
Total cholesterol (mg/dL)	-10.7 (-27.7 to +6.3)	-15.2 (-26.0 to -4.3)**	-4.5 (-23.6 to +14.7)	p = 0.64	+3.3 (-5.8 to +12.3)	-13.7 (-28.0 to +0.7)	-16.9 (-33.0 to -0.8)	p = 0.04	p = 0.38
Total cholesterol (mmol/L)	-0.3 (-0.7 to +0.2)	-0.4 (-0.7 to -0.1)**	-0.1 (-0.6 to +0.4)	p = 0.64	+0.1 (-0.1 to +0.3)	-0.4 (-0.7 to 0.0)	-0.4 (-0.9 to -0.0)	p = 0.04	p = 0.38
Total cholesterol (mg/dL) - No Medication Changes	-10.0 (-27.8 to +7.8)	-17.0 (-25.5 to -8.5)**	-7.0 (-26.3 to +12.3)	p = 0.46	+2.5 (-6.4 to +11.4)	-20.8 (-34.1 to -7.6)**	-23.3 (-38.3 to -8.4)	p = 0.003	p = 0.24
Total cholesterol (mmol/L) - No Medication Changes	-0.3 (-0.7 to +0.2)	-0.4 (-0.7 to -0.2)**	-0.2 (-0.7 to +0.3)	p = 0.46	+0.1 (-0.2 to +0.3)	-0.5 (-0.9 to -0.2)**	-0.6 (-1.0 to -0.2)	p = 0.003	p = 0.24
Triglycerides (mg/dL)	-19.4 (-35.7 to -3.1)*	+5.5 (-17.3 to +28.2)	+24.9 (-3.0 to +52.8)	p = 0.08	-6.1 (-20.5 to +8.2)	+11.3 (-10.9 to +33.5)	+17.4 (-7.7 to +42.6)	p = 0.17	p = 0.72
Triglycerides (mmol/L)	-0.2 (-0.4 to -0.0)*	+0.1 (-0.2 to +0.3)	+0.3 (-0.0 to +0.6)	p = 0.08	-0.1 (-0.2 to +0.1)	+0.1 (-0.1 to +0.4)	+0.2 (-0.1 to +0.5)	p = 0.17	p = 0.72
Triglycerides (mg/dL) - No Medication Changes	-13.6 (-33.2 to +5.9)	+5.2 (-21.6 to +32.0)	+18.8 (-14.7 to +52.3)	p = 0.26	-6.6 (-22.8 to +9.6)	+12.1 (-15.6 to +39.8)	+18.7 (-11.0 to +48.4)	p = 0.21	p = 1.0
Triglycerides (mmol/L) - No Medication Changes	-0.2 (-0.4 to +0.1)	+0.1 (-0.2 to +0.4)	+0.2 (-0.2 to +0.6)	p = 0.26	-0.1 (-0.3 to +0.1)	+0.1 (-0.2 to +0.4)	+0.2 (-0.1 to +0.5)	p = 0.21	p = 1.0
HDL-cholesterol (mg/dL)	-0.9 (-4.2 to +2.4)	-4.4 (-6.8 to -2.1)**	-3.6 (-7.4 to +0.3)	p = 0.07	-0.3 (-3.5 to +2.8)	-5.7 (-10.3 to -1.0)*	-5.3 (-10.6 to +0.0)	p = 0.051	p = 0.59
HDL-cholesterol (mmol/L)	0.0 (-0.1 to +0.1)	-0.1 (-0.2 to -0.1)**	-0.1 (-0.2 to +0.0)	p = 0.07	0.0 (-0.1 to +0.1)	-0.2 (-0.3 to -0.0)*	-0.1 (-0.3 to +0.0)	p = 0.051	p = 0.59
HDL-cholesterol (mg/dL) - No Medication Changes	-0.8 (-5.1 to +3.4)	-4.2 (-6.7 to -1.7)**	-3.4 (-7.9 to +1.2)	p = 0.14	-0.5 (-4.1 to +3.2)	-6.2 (-12.0 to -0.3)*	-5.7 (-12.1 to +0.7)	p = 0.08	p = 0.56
HDL-cholesterol (mmol/L) - No Medication Changes	0.0 (-0.1 to +0.1)	-0.1 (-0.2 to -0.0)**	-0.1 (-0.2 to +0.0)	p = 0.14	0.0 (-0.1 to +0.1)	-0.2 (-0.3 to -0.0)*	-0.1 (-0.3 to +0.0)	p = 0.08	p = 0.56
LDL-cholesterol (mg/dL)	-5.9 (-21.1 to +9.4)	-11.8 (-23.3 to -0.4)*	-6.0 (-24.3 to +12.3)	p = 0.51	+4.8 (-2.5 to +12.2)	-10.3 (-22.6 to +1.9)	-15.2 (-29.1 to -1.2)	p = 0.03	p = 0.45
LDL-cholesterol (mmol/L)	-0.2 (-0.5 to +0.2)	-0.3 (-0.6 to -0.0)*	-0.1 (-0.6 to +0.3)	p = 0.51	+0.1 (-0.1 to +0.3)	-0.3 (-0.6 to +0.0)	-0.4 (-0.8 to -0.0)	p = 0.03	p = 0.45
LDL-cholesterol (mg/dL) - No Medication Changes	-6.3 (-21.2 to +8.7)	-13.8 (-22.7 to -5.0)**	-7.5 (-23.6 to +8.5)	p = 0.35	+4.2 (-2.9 to +11.4)	-17.2 (-27.1 to -7.3)**	-21.4 (-32.9 to -9.9)	p < 0.001	p = 0.21
LDL-cholesterol (mmol/L) - No Medication Changes	-0.2 (-0.6 to +0.2)	-0.4 (-0.6 to -0.1)**	-0.2 (-0.6 to +0.2)	p = 0.35	+0.1 (-0.1 to +0.3)	-0.4 (-0.7 to -0.2)**	-0.6 (-0.9 to -0.3)	p < 0.001	p = 0.21
VLDL-cholesterol (mg/dL)	-4.0 (-7.2 to -0.8)*	+1.1 (-3.4 to +5.7)	+5.1 (-0.5 to +10.6)	p = 0.07	-1.2 (-4.1 to +1.7)	+2.3 (-2.1 to +6.8)	+3.6 (-1.5 to +8.7)	p = 0.16	p = 0.72
VLDL-cholesterol (mmol/L)	-0.1 (-0.2 to -0.0)*	0.0 (-0.1 to +0.1)	+0.1 (-0.0 to +0.3)	p = 0.07	0.0 (-0.1 to 0.0)	+0.1 (-0.1 to +0.2)	+0.1 (-0.0 to +0.2)	p = 0.16	p = 0.72
VLDL-cholesterol (mg/dL) - No Medication Changes	-2.9 (-6.8 to +1.0)	+1.0 (-4.3 to +6.4)	+3.9 (-2.8 to +10.6)	p = 0.24	-1.3 (-4.5 to +2.0)	+2.5 (-3.1 to +8.1)	+3.8 (-2.2 to +9.8)	p = 0.21	p = 0.97
VLDL-cholesterol (mmol/L) - No Medication Changes	-0.1 (-0.2 to +0.0)	0.0 (-0.1 to +0.2)	+0.1 (-0.1 to +0.3)	p = 0.24	0.0 (-0.1 to +0.1)	+0.1 (-0.1 to +0.2)	+0.1 (-0.1 to +0.3)	p = 0.21	p = 0.97
<b>Blood pressure</b>									
Systolic Blood pressure (mmHg)	-7.2 (-13.0 to -1.3)*	-10.8 (-17.2 to -4.4)**	-3.6 (-12.1 to +4.8)	p = 0.39	-11.7 (-18.6 to -4.7)**	+2.2 (-2.8 to +7.1)	+13.8 (+5.5 to +22.2)	p = 0.002	p = 0.02
Systolic Blood pressure (mmHg) - No Medication Changes	-9.0 (-14.2 to -3.7)**	-9.0 (-15.8 to -2.1)*	0.0 (-8.4 to +8.4)	p = 1.0	-9.7 (-16.2 to -3.1)**	+2.3 (-3.5 to +8.0)	+11.9 (+3.4 to +20.4)	p = 0.007	p = 0.09

Diastolic Blood pressure (mmHg)	-7.2 (-9.9 to -4.6)***	-5.3 (-9.2 to -1.3)*	+2.0 (-2.7 to +6.6)	<i>p</i> = 0.40	-7.3 (-10.9 to -3.7)***	-2.9 (-5.3 to -0.5)*	+4.3 (+0.1 to +8.6)	<i>p</i> = 0.04	<i>p</i> = 0.49
Diastolic Blood pressure (mmHg)	-7.2 (-10.2 to -4.2)***	-5.0 (-9.7 to -0.4)*	+2.1 (-3.3 to +7.5)	<i>p</i> = 0.43	-7.4 (-11.2 to -3.5)***	-3.1 (-5.8 to -0.4)*	+4.3 (-0.3 to +8.9)	<i>p</i> = 0.06	<i>p</i> = 0.57
- No Medication Changes									

<sup>1</sup>VAT, visceral adipose tissue.

<sup>2</sup>HbA1c, glycated hemoglobin.

<sup>3</sup>HOMA-IR, Homeostasis Model Assessment Insulin Resistance.

<sup>4</sup>PREDIM, Predicted insulin sensitivity index.

<sup>5</sup>OGIS, oral glucose insulin sensitivity.

Data are means and estimated treatment effects with 95% confidence intervals. *p* values for treatment effect are from a two-sample *t*-test comparing mean changes between participants in each treatment arm within each period. The *P*-value for a carryover effect is for significance of an interaction between initial treatment assignment and period, in a mixed model of treatment effect as described in Methods. \**p* < 0.05, \*\**p* < 0.01 and \*\*\**p* < 0.001 for within-group changes from baseline assessed by paired comparison *t* tests.

For physical activity and systolic blood pressure in all study participants, including those with changes in antihypertensive medications, the carryover effect was statistically significant. Therefore, the values from the first study phase may be considered as more valid.

< 0.001). Fiber intake increased on both diets, but more so on the vegan diet (*p* < 0.001). The treatment effect was highly statistically significant for all dietary intake factors examined, except alcohol intake.

On the vegan diet, final 3-day dietary records showed that 42/52 participants (81%) reported avoiding all animal products, 49/52 participants (94%) consistently consumed less than 50 mg cholesterol a day, and 46/52 (86%) consumed less than 25% energy from fat and less than 5% energy from saturated fat. On the Mediterranean diet, 38/52 (73%) consumed 2 or more servings of vegetables per day and 49/52 participants (94%) consumed olive oil as the main culinary fat.

### Medication changes during the study

Despite the request that medications remain constant, 7 participants reduced or discontinued lipid-lowering medications during vegan diet phases, 2 did so during Mediterranean diet phases, and 1 increased them in a Mediterranean diet phase. Similarly, 7 participants reduced or discontinued anti-hypertensive medications during vegan phases; 6 did so during Mediterranean phases. One participant increased these medications during a vegan phase; 1 did so during a Mediterranean phase.

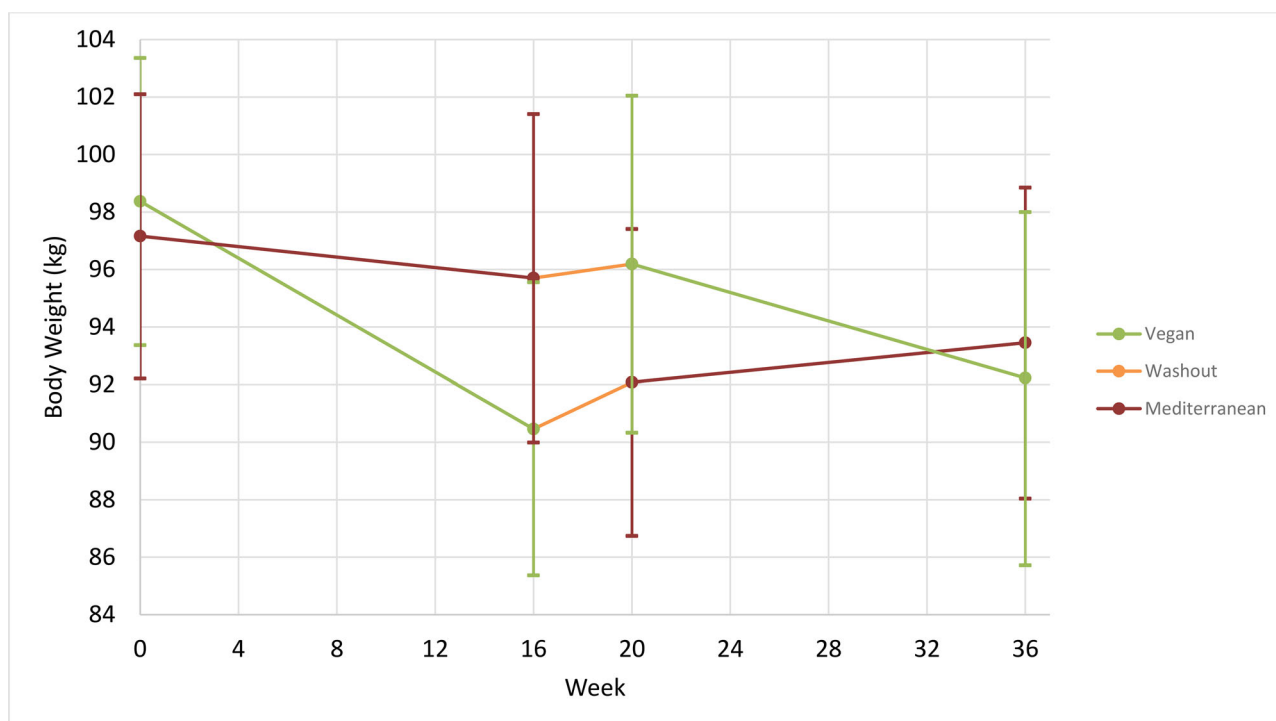
### Body weight and body composition

During the initial 16-week period, mean weight change was -1.5 (-2.9 to +0.02) kg on the Mediterranean diet and -7.9 (-9.3 to -6.5) kg on the vegan diet. In the second study period, mean weight change was +1.4 (+0.4 to +2.3) kg on the Mediterranean diet and -4.0 (-5.6 to -2.4) kg on the vegan diet (see Figure 1 and Table 3). There was no evidence of a difference in treatment effect for weight change between the two periods (*p* = 0.45 for carryover effect). Overall, mean body weight decreased 6.0 kg on the vegan diet, compared with no mean change on the Mediterranean diet (treatment effect -6.0 kg [95% CI -7.5 to -4.5]; *p* < 0.001). Most of the vegan-phase weight change was attributable to a reduction in fat mass and visceral fat volume (treatment effect -3.4 kg [95% CI -4.7 to -2.2]; *p* < 0.001; and -314.5 cm<sup>3</sup> [95% CI -446.7 to -182.4]; *p* < 0.001, respectively). Of the 52 study completers, 26 lost weight during the Mediterranean phase, compared with 48 participants during the vegan phase (see Supplemental Figure 2).

On the Mediterranean diet, weight changes were associated with changes in fiber intake (*r* = -0.30; *p* = 0.02), particularly insoluble fiber (*r* = -0.31; *p* = 0.02). On the vegan diet, weight loss was associated with reduction in energy intake (*r* = +0.37; *p* = 0.007) and decrease in total fat consumption (*r* = +0.47; *p* < 0.001), particularly saturated fat (*r* = +0.40; *p* = 0.003).

### Insulin sensitivity

HOMA-IR index (a measure of fasting insulin resistance) decreased and OGIS (a measure of postprandial insulin



**Figure 1.** Changes in body weight on the Mediterranean (dark red) and vegan (green line) diets in all study completers ( $n = 52$ ). Data are expressed as mean  $\pm$  95% confidence intervals.

sensitivity) increased on the vegan diet; neither changed significantly on the Mediterranean diet (treatment effect  $-0.7$  [95% CI,  $-1.8$  to  $+0.4$ ];  $p = 0.21$ ; and  $+35.8$  mL/min/m<sup>2</sup> [95% CI,  $+13.2$  to  $+58.3$ ];  $p = 0.003$ , respectively). PREDIM did not change significantly on either treatment (Table 2).

### Lipids and blood pressure

Among participants with no changes in lipid-lowering medications ( $n = 43$ ), total and LDL-cholesterol decreased 3.1 mg/dL (0.08 mmol/L) and 0.5 mg/dL (0.01 mmol/L), respectively, during the Mediterranean phase, compared with 18.7 mg/dL (0.5 mmol/L) and 15.3 mg/dL (0.4 mmol/L), respectively, during the vegan phase.

Among participants with no changes to anti-hypertensive medications ( $n = 41$ ), systolic and diastolic blood pressure decreased 9.3 and 7.3 mmHg, respectively, on the Mediterranean diet and 3.4 and 4.1 mmHg, respectively, on the vegan diet (treatment effect, systolic,  $+6.0$  [95% CI  $+1.0$  to  $+10.9$ ];  $p = 0.02$ ; diastolic,  $+3.2$  [95% CI 0.0 to  $+6.4$ ];  $p = 0.048$ ).

### The effect of period 1 vs. 2

Improvements in most cardiometabolic outcomes were more pronounced on both diets during the first study period (representing the change from baseline) than the second study period (reflecting the change from the previous diet and washout period) (Table 3). The interaction test for a carryover effect, which would reflect inconsistency of estimated treatment effects between the first and second study period, was not statistically significant for most outcomes, indicating

statistical validity of the treatment effects in Table 2 estimated using the entire crossover study data. The two outcomes with potential carryover effect were physical activity and systolic blood pressure (the latter only when evaluated among all participants, including those with antihypertensive medication changes).

### Discussion

In the first 16 weeks of the study, a low-fat vegan diet led to greater reductions in body weight (by 6.4 kg), fat mass (by 3.8 kg), visceral fat (by 429 cm<sup>3</sup>) compared with a Mediterranean diet, with no difference in blood lipids and blood pressure between the treatments. Evaluating the data from the whole 36-week cross-over trial, a low-fat vegan diet led to greater reductions in body weight (by 6.0 kg), fat mass (by 3.4 kg), visceral fat (by 315 cm<sup>3</sup>) and plasma lipid concentrations compared with a Mediterranean diet, while both systolic and diastolic blood pressure decreased more on the Mediterranean diet (by 6.0 and 3.2 mmHg, respectively). We observed no carryover effect for most variables, except for physical activity and systolic blood pressure (when evaluated among all participants including those with antihypertensive medication changes). For these two outcomes, the estimated first-period-only treatment effects in Table 3 may be viewed as potentially more valid.

With regard to body weight, it is important to note that despite the fact that neither diet was energy-restricted, participants reduced energy intake on the low-fat vegan diet compared with the Mediterranean diet. The present study confirms the findings of the Lyon and PREDIMED studies, suggesting that a Mediterranean diet, as delivered in these

trials, is not effective for weight loss. This may have been attributable, in part, to the fact that these trials did not actually mirror a traditional Mediterranean diet. Keys' studies of Mediterranean diets used as a point of reference the southern Italian village of Nicotera, where only 23% of typical energy consumption was derived from fat (5, 24). The Lyon and PREDIMED studies used artificial diets, emphasizing margarine and fish (Lyon Study, with a reported fat intake of 30.4% of energy in the experimental group) (8) or fish, oil, and/or nuts (PREDIMED, with a reported fat intake of 41% and 42% of energy in the olive oil and nut groups, respectively); it may be that the presence of energy-dense fish and other animal products, along with oil or nuts, counteracted weight-loss efforts. The present study's Mediterranean intervention followed the PREDIMED guidelines, with similar results for body weight.

The low-fat vegan diet led to significant weight loss, confirming the findings of prior studies (12). Clinical trials suggest that plant-based diets reduce body weight by two concurrent mechanisms. First, a reduction in dietary fat and increase in fiber lead to a reduction in dietary energy density, which reduces energy intake (25). This reduction in energy intake occurs despite the fact that the diet was *ad libitum*, as was the Mediterranean diet. Second, a low-fat vegan diet increases postprandial energy expenditure. The thermic effect of food—i.e., the increased energy expenditure that comes from processing and storing food—accounts for approximately 10% of total energy expenditure. In a study of postmenopausal women, the thermic effect of food, as measured by indirect calorimetry using a standard test meal, was 16% higher after 14 weeks on a low-fat, vegan diet (26). Similar results were achieved in overweight men and women after 16 weeks of a low-fat, vegan diet, where the thermic effect of food increased by 14% compared with the control group (27). In turn, this increased energy expenditure may reflect changes in mitochondrial action. In a 2005 study, a high-fat (50% of energy) diet, followed for 3 days, led to a downregulation of the genes required for mitochondrial oxidative phosphorylation in skeletal muscle (28). Similarly, a 2015 study showed that a high-fat diet may facilitate the passage of bacterial endotoxins through the gut wall (29). In turn, endotoxins appeared to impair postprandial cellular glucose oxidation. Magnetic resonance spectroscopy studies show that a low-fat vegan diet reduces hepatocellular and intramyocellular lipid concentrations and increases insulin sensitivity, thereby increasing energy expenditure in the postprandial period (27). Together, these findings suggest high-fat diets may disrupt postprandial energy expenditure, while low-fat, plant-based diets may have the opposite effect.

A transition from a typical Western diet to a Mediterranean-style diet typically improves plasma lipid concentrations by virtue of reduced intake of saturated fat and cholesterol. In the Medi-RIVAGE study, a Mediterranean-style diet led to a greater reduction in LDL-cholesterol concentrations, compared with a control group following a diet intended to limit fat to 30% of energy (in practice, fat intake was 34% of energy) (30). Likewise, participants in the PREDIMED study following Mediterranean

diets also improved their LDL-cholesterol more than the control group (4). Small reductions in total cholesterol ( $-0.16$  mmol/L) and LDL-cholesterol ( $-0.07$  mmol/L) in response to a Mediterranean diet were demonstrated in a meta-analysis of randomized clinical trials (31).

In the present study, the LDL-cholesterol reduction in response to the low-fat vegan diet was significantly greater than that observed with the Mediterranean diet, reflecting the fact that, while the Mediterranean diet reduced the percentage of energy from saturated fat, the vegan diet reduced it significantly more, along with an effective elimination of cholesterol intake. In a 2015 meta-analysis of 11 clinical trials, vegetarian diets reduced total and LDL-cholesterol by 14 mg/dL (0.36 mmol/L) and 13 mg/dL (0.34 mmol/L), respectively (14). Similarly, in a 2017 meta-analysis of 19 clinical trials, vegetarian diets reduced total and LDL-cholesterol by 12.5 mg/dL (0.32 mmol/L) and 12.2 mg/dL (0.32 mmol/L), respectively (32).

The systolic-blood-pressure-lowering effect was greater with the Mediterranean diet, which may be attributable to its high content of monounsaturated fat and vitamin E, and virgin olive oil's ability to increase antioxidant capacity (33–35). A randomized trial in 164 adults with prehypertension demonstrated that partial substitution of carbohydrate with monounsaturated fat modestly reduced blood pressure (34). In the PREDIMED study, participants allocated to either of the two Mediterranean diet groups, with extra virgin olive oil or with nuts, had significantly lower diastolic blood pressure than the participants in the control group (36). Four tablespoons of olive oil provide 52% of the recommended dietary allowance of vitamin E. Vitamin E has been shown to increase oxidative resistance and the consumption of foods rich in vitamin E has been associated with lower risk of coronary heart disease (35). A 3-year randomized clinical study showed that a Mediterranean diet rich in olive oil was associated with high levels of plasma antioxidant capacity (33).

Plant-based diets also reduce blood pressure, presumably due to reductions in blood viscosity and body weight, and their high potassium content (37). In a meta-analysis of 7 clinical trials using vegetarian and vegan diets, systolic blood pressure was reduced by 4.8 mm Hg and diastolic blood pressure by 2.2 mm Hg (15).

In research studies, the acceptability of plant-based diets is similar to that of other therapeutic diets over both the short and long term, as indicated by rates of retention, diet adherence, and diet acceptance questionnaires (38–41). Likewise, self-reports and objective measures indicate generally good adherence to the Mediterranean diet (4).

This study has several strengths, including a methodologically efficient cross-over design and weekly participant follow-up to facilitate dietary adherence. Despite the length of the trial, retention was reasonably strong (84%). Because the participants were not confined to a metabolic ward, the results can readily translate to nonclinical settings.

The study also has limitations. Although self-reported overall adherence to both diets was high, it is impossible to eliminate uncertainty regarding participants' adherence. The

improvements in most cardiometabolic outcomes were more pronounced on both diets during the first study period (representing the change from baseline) than the second study period, largely because baseline mean body weight was higher than that after the washout period. Nonetheless, weight loss was observed on the vegan diet in both phases of the study with no carryover effect. Self-reported energy intake was lower on both diets in the first period compared to the second one, however, as noted above, estimates of treatment effect were in general largely consistent between the two study periods. While the study duration was sufficient to allow the participants to experience metabolic changes, a longer duration would have provided more evidence about the long-term cardiometabolic effects of both diets. Metabolic adaptation to changes in macronutrient intake, particularly to lower carbohydrate intake, has been previously shown to be affected by the study duration. In a meta-analysis of 29 trials testing the effects of diets varying in carbohydrate content, total energy expenditure appeared to require approximately 2.5 weeks to respond to the dietary intervention and other metabolic measures may take longer, suggesting value of studies with longer durations (42).

In conclusion, this 36-week randomized cross-over trial showed that a low-fat plant-based diet reduced body weight, fat mass, and visceral fat, increased insulin sensitivity, and improved blood lipids, compared with a Mediterranean diet. Systolic and diastolic blood pressure decreased more on the Mediterranean diet.

## Statement of authorship

HK and NDB designed the research study and drafted the manuscript. JA, ER, GN, and KL wrote sections of the manuscript. HK, JA, ER, LB, MN, AG, TH, GN, and KL conducted the research study. AT and RH analyzed the data and performed statistical analyses. HK and NDB reviewed and approved the submitted version. All authors had full access to data and revised and approved the manuscript for publication.

## Disclosure statement

All authors except for AT and RH work for the Physicians Committee for Responsible Medicine in Washington, DC, a nonprofit organization providing educational, research, and medical services related to nutrition. Dr. Barnard is an Adjunct Professor of Medicine at the George Washington University School of Medicine. He serves without compensation as President of the Physicians Committee for Responsible Medicine and the Barnard Medical Center in Washington, DC. He writes books and articles and gives lectures related to nutrition and health and has received royalties and honoraria from these sources.

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