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Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile

CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet)

Editorial, see p 1114

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BACKGROUND: Only a few randomized dietary intervention studies that investigated the effects of lacto-ovo vegetarian diet (VD) in clinically healthy omnivorous subjects are available.

METHODS: We randomly assigned to overweight omnivores with a low-to-moderate cardiovascular risk profile a low-calorie VD compared with a low-calorie Mediterranean diet (MD), each lasting 3 months, with a crossover design. The primary outcome was the difference in body weight, body mass index, and fat mass changes between the 2 groups. Secondary outcomes were differences in circulating cardiovascular disease risk parameters changes between the 2 groups.

RESULTS: One hundred eighteen subjects (mean age: 51.1 years, females: 78%) were enrolled. The total participation rate at the end of the study was 84.7%. No differences between the 2 diets in body weight were observed, as reported by similar and significant reductions obtained by both VD (−1.88 kg) and MD (−1.77 kg). Similar results were observed for body mass index and fat mass. In contrast, significant differences between the 2 interventions were obtained for low-density lipoprotein cholesterol, triglycerides, and vitamin B_{12} levels. The difference between the VD and MD groups, in terms of end-of-diet values, was recorded at 9.10 mg/dL for low-density lipoprotein cholesterol (P=0.01), 12.70 mg/dL for triglycerides (P<0.01), and 32.32 pg/mL for vitamin B_{12} (P<0.01). Finally, no significant difference was found between VD and MD interventions in oxidative stress markers and inflammatory cytokines, except for interleukin-17, which improved only in the MD group. Forty-six participants during the VD period and 35 during the MD period reached the target values for ≥1 cardiovascular risk factor.

CONCLUSIONS: Both VD and MD were effective in reducing body weight, body mass index, and fat mass, with no significant differences between them. However, VD was more effective in reducing low-density lipoprotein cholesterol levels, whereas MD led to a greater reduction in triglyceride levels.

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Clinical Perspective

What Is New?

- To date, this randomized controlled trial is the first study assessing the effects of a lacto-ovo vegetarian diet (VD) compared with a Mediterranean diet (MD) in the same cohort of omnivorous subjects living in a low-risk country for cardiovascular disease.
- After 3 months of dietary intervention, both VD and MD were effective in reducing body weight, body mass index, and fat mass, with no significant differences between them.
- The VD significantly reduced low-density lipoprotein cholesterol, vitamin B_{12}, and uric acid levels, whereas only the MD showed the potential to improve triglycerides and interleukin-17 levels.

What Are the Clinical Implications?

- Our findings suggest that in the context of behavioral counseling that promotes a reduced caloric intake, VD and MD determine similar reduction in body weight and fat mass.
- The present results suggest that following a VD leads to a significant reduction in low-density lipoprotein cholesterol, whereas the MD could be more effective in reducing triglyceride levels.
- This work could improve the awareness of the general population that both VD and MD may help in reducing cardiovascular disease risk factors.

The lacto-ovo vegetarian diet (VD), the most common type of vegetarian diet, entails the exclusion of meat and fish in their fresh, preserved, and processed form; however, it allows for the consumption of eggs and dairy products.[1] In recent years, the general population has shown considerable interest in the VD, as demonstrated by the progressive and constant increase in the number of individuals who began to adopt a VD when the cohorts of vegetarians were limited to only selected populations.[1] This increase has been predominantly attributed to the findings of different case-control[2,3] and prospective cohort studies[4–6] in the last decade that focus on the health aspects of this diet. In a recent meta-analysis carried out by our group on >130 000 vegetarians, adherence to a VD was found to be associated with many health benefits, ranging from lower levels of cardiovascular risk parameters to a reduced risk of ischemic heart disease.[7] Nevertheless, the medical literature in this field puts forth some unresolved questions that require further investigation. Most of the findings that pointed to the beneficial effects of a VD were from observational studies or studies conducted in countries at a high risk for cardiovascular disease (eg, the United States) or on vegetarians. This approach allowed for the possibility of bias related to the fact that such populations are possibly more health-conscious and thus not completely representative of the general population.[8] Moreover, few and limited randomized dietary intervention studies have investigated the effects of a VD in clinically healthy omnivorous participants.[9–12] Our aim was to compare, in a population of omnivorous individuals living in a low-risk (for cardiovascular disease) European country, the effects of a 3-month period on a low-calorie VD compared with a low-calorie Mediterranean diet (MD) on several markers of cardiovascular disease risk. The MD is widely reported as one of the healthiest models for preventing cardiovascular disease.[13]

METHODS

Study Design

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data are available from the corresponding author on reasonable request. The study protocol was previously described[14] and is briefly reported here. Clinically healthy participants (18–75 years of age) with a low-to-moderate cardiovascular risk profile (<5% at 10 years according to the European Society of Cardiology)[15] were recruited through advertisements in local media, newspapers, social media, official web pages, and websites from the Clinical Nutrition Unit of Careggi University Hospital, Florence, Italy, from March 2014 to June 2015. Eligibility criteria included being overweight (body mass index [BMI] ≥25 kg/m^2) and the simultaneous presence of ≥1 of the following criteria defined by the guidelines for cardiovascular disease prevention of the European Society of Cardiology:[15] total cholesterol levels >190 mg/dL, low-density lipoprotein (LDL) cholesterol levels >115 mg/dL, triglyceride levels >150 mg/dL, and glucose levels >110 but <126 mg/dL.[15] Participants were excluded if they were taking medications for any reason, had a serious illness or an unstable condition, were pregnant or nursing, were participating or had participated in a weight loss treatment program in the last 6 months, or were following or had followed a food profile that, to a certain extent, excluded meat, poultry, or fish in the last 6 months.

The study was a randomized, open, crossover dietary trial with 2 intervention periods, each lasting 3 months.[14] After a 2-week run-in period, which was used to assess participants' motivation, commitment, and availability, participants were randomly assigned to a VD (n=60) or an MD (n=58) group. During the run-in period, participants were asked to complete a 3-day (2 weekdays and 1 weekend day) dietary record. After the first phase of intervention, participants crossed over to the other dietary treatment. During the study, 5 clinical evaluations were performed: at the baseline before the start of treatment, 1.5 months after the start of the first dietary intervention, 3 months after the start of the first dietary intervention and at the time of crossing over, 4.5 months from the start of the study and 1.5 months from the time of crossing over, and finally, 6 months after the start of the study and 3 months from the time of crossing over. Participants were instructed not to alter their lifestyle and exercise habits during the study, and no weight loss goal was given. Before enrollment,

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written informed consent was obtained from each participant. The study was approved by the Ethics Committee (SPE 15.054) of the Tuscany Region, Careggi University Hospital, was registered at https://www.clinicaltrials.gov (Unique identifier: NCT02641834), and adhered to the principles of the Declaration of Helsinki and the Data Protection Act.

Intervention

Interventions were delivered through face-to-face, individual counseling sessions at the Clinical Nutrition Unit of Careggi University Hospital. Participants were provided with a detailed, 1-week menu plan as well as tips and information on the food groups that could be included and those that could not. Both of the diets were low-calorie in nature and acted as dietary interventions to reduce body weight or the risk parameters for cardiovascular disease. The VD plan included recipes for preparing meals. Both diets were hypocaloric with respect to the energy requirements of the participants, but completely isocaloric between them, and consisted of ≈50% to 55% of energy from carbohydrate, 25% to 30% from total fat (≤7% of energy from saturated fat, <200 mg/d of cholesterol), and 15% to 20% from protein. The VD was characterized by abstinence from the consumption of meat and meat products, poultry, fish, and seafood, and the flesh of any other animal. It included eggs and dairy products, as well as all the other food groups. The MD was characterized by the consumption of all the food groups, including meat and meat products, poultry, and fish. The dietary profiles, in terms of servings per week, calculated on the basis of the portion sizes recommended by the Italian Recommended Dietary Allowances,[16] are shown in Table I in the online-only Data Supplement. There were no substantial differences in the frequency of servings per week for cereals, fruits and vegetables, potatoes, sweets, and olive oil. As expected, in the case of VD, a higher frequency of consumption, per week, of legumes (5 versus 2.5 servings), nuts (2 versus 1), eggs (2 versus 1), and dairy products (21.5 versus 18.5) was reported compared to MD.

Data Collection

Data-collection and follow-up measurements were performed at the Clinical Nutrition Unit of Careggi University Hospital. All the participants were examined between 6:30 AM and 9:30 AM after an overnight fast. Participants were asked not to undertake strenuous physical activity on the day before the examination. The baseline assessment for both groups included a questionnaire on demographic information, risk factors, and comorbidities. All participants were asked to report the frequency (times per week), duration (months), and intensity of recreational and physical activities performed during the preceding year.

A physical activity grade was derived for each participant based on frequency, type, and duration of the physical activity and described in terms such as absent or light (ie, inactive or either occasional walking or recreational activity only) and moderate (ie, frequent recreational activity, regular walking for 30 minutes 3–5 times per week, or sporting exercise at least once a week). The grade was not a measure of the total time spent in physical activity; it was a relative qualitative measure of how much physical activity was undertaken.

In addition, before the start of the intervention, each participant completed a 3-day (2 weekdays and 1 weekend day) dietary record analyzed using a nutrition-specific database. Body weight and body composition were measured at each clinical evaluation. Weight and height were measured using a stadiometer. BMI was calculated as the weight (kg)/height (m^2). Participants were classified as overweight if their BMI was ≥25 kg/m^2 but <30 kg/m^2 and obese if their BMI was ≥30 kg/m^2. Body composition was determined by a bioelectrical impedance analysis device (TANITA, model TBF-410).

Compliance

Compliance to the VD was evaluated through unannounced telephone calls, during which a 24-hour diet recall interview was conducted, and through a modified version of the National Health and Nutrition Examination Survey food questionnaire, with the aim of confirming the total absence of any animal flesh in the diet.[17] Adherence to the VD was defined as the absence of the consumption of any animal flesh, reported through both a 24-hour diet recall and a food frequency questionnaire. Compliance to the MD was evaluated at baseline and during follow-up visits using the MD adherence score recently released and validated by our group.[18] Participants in the MD group were considered adherent if they reported ≥10 points in a scale ranging from 0 to 18.

Outcomes

The primary outcomes were differences in changes in total body weight, BMI, and fat mass from the baseline, whereas the secondary outcomes were differences in changes in all the circulating cardiovascular risk parameters from baseline (lipid profile, glycemic profile, oxidative stress profile, and inflammatory profile).

Laboratory Measurements

Venous blood samples were collected at baseline and the end of each intervention phase in evacuated plastic tubes (Vacutainer, Becton Dickinson). Samples were centrifuged at 3000 rpm for 15 minutes (4°C) and stored in aliquots at 80°C until further analyses. Total cholesterol and its subtypes, triglycerides, glucose, insulin, serum electrolytes, standard liver panel enzymes, and mineral and vitamin profiles were measured according to conventional laboratory standard methods. To assess the plasma oxidative stress profile, lipid peroxidation markers were estimated using the Thiobarbituric Acid Reactive Substances assay kit (Oxitek-ZeptoMetrix Corp, Buffalo, NY). Plasma total antioxidant capacity, which represents the overall antioxidant defense system, was measured using the oxygen radical absorbance capacity.[19] The production of reactive oxygen species by leukocytes (lymphocytes, monocytes, and granulocytes) was measured as previously reported.[20] Pro- and anti-inflammatory cytokines were determined by a Bio-Plex cytokine assay (Bio-Rad Laboratories Inc) according to the manufacturer's instructions.

Statistical Analysis

The sample size was determined based on studies previously conducted to verify the effectiveness of vegetarian-like diets

on participants with type 2 diabetes mellitus.[14] We estimated that the randomization of a population size of 110 to 125 participants would be required (a sample size of ≥50 in each group of the study) to obtain 80% power to detect an effect size between 1.25 and 2.1 at an α level of 0.05. This calculation was based on conservative estimates of a 10% to 25% dropout rate.

The results were expressed as mean±SD, median and range, or geometric mean with 95% confidence intervals (CIs) as appropriate. Categorical variables were presented in terms of frequencies and percentages. All data were treated as paired samples from a crossover study. The 2 interventions were analyzed combining the results obtained in the 2 phases of both groups. The results were analyzed within each group using a 2-tailed Student's *t* test. Absolute change (mean baseline value subtracted from mean value after intervention) was estimated by an independent sample *t* test. The Spearman (r) test was used to estimate the correlation between the changes in the vitamin B_{12} and interleukin-6 levels.

To compare the effect of the 2 different diets, a general linear model, adjusted for the order of treatment and weight change (for biochemical, oxidative, and inflammatory parameters), was conducted. Because these tests assume normal data distribution, nondistributed data were transformed into logs, and further analyses were performed with the processed data. However, to facilitate interpretation, the log data were again converted to the original scale (antilog) and presented as geometric means with 95% CIs.

The possibility of a dietary carryover effect, which is considered if the impact of the first treatment is still present when the participant enters the second treatment period, was analyzed. We evaluated the sequence effect to confirm whether the impacts of the VD and MD were different when the order of administration changed. This effect was estimated by comparing the geometric mean change difference between the treatments in the VD and MD groups after adjustment for the order of treatment.

Subgroup analyses were performed to analyze possible differences in the changes according to some characteristics of the study population, such as age (≤50 years, >50 years), sex (females, males), categories of BMI (25–29.9 kg/m^2, ≥30 kg/m^2), obesity status (class I, 30–34.9 kg/m^2; class II, 35–39.9 kg/m^2; class III, ≥40 kg/m^2), years of education (≤13 years, >13 years), physical activity (absent or light/moderate), civil status (married, not married), total cholesterol level (≤190 mg/dL, >190 mg/dL), LDL cholesterol level (≤115 mg/dL, >115 mg/dL), triglycerides level (≤150 mg/dL, >150 mg/dL), and glucose level (<110 mg/dL, 110–126 mg/dL). *P* values <0.05 were considered statistically significant. Outcomes were analyzed through on-treatment procedures. The statistical package PASW 20.0 for Macintosh (SPSS Inc) was used.

RESULTS

Participants' Characteristics

Figure 1 shows the enrollment of participants in the study. A total of 107 participants completed ≥1 phase of intervention and were included in the analysis. One hundred participants (50 participants for each intervention) completed the entire study, with a participation rate of 84.7% at the conclusion. The baseline demographic and clinical characteristics of the population studied, according to the first dietary randomization, are shown in Table 1. No significant differences in the characteristics between the 2 groups, at randomization, were observed.

Dietary Intake

Through the analyses of the dietary profile at the end of the first intervention phase, we found that the total energy, total fat, saturated fat, and cholesterol intakes of the participants significantly decreased compared with baseline (Table II in the online-only Data Supplement). However, no significant differences in the proportions of decrease were observed between the groups, apart from cholesterol intake, which, as expected, decreased more in the VD group (−105.6 versus −49.7 mg/d; *P*=0.001). The protein intake increased in the MD group (+1.4%) and decreased in the VD group (−1.5%), leading to a significant difference between the groups (*P*=0.001).

Body Weight and Body Composition

Figure 2 shows the changes in the anthropometric parameters at the end of the study after combining data from both intervention periods. No significant difference between the 2 diets was found because both the VD and MD produced equally effective results, with the difference between the VD and MD groups, in terms of end-of-diet values, being recorded at 0.11 kg for weight (*P*=0.95), 0.03 kg/m^2 for BMI (*P*=0.84), and 0.23 kg for fat mass (*P*=0.50). With regard to the change within each group, a significant body weight reduction of −1.88 kg (95% CI, −2.42 to −1.35) and −1.77 kg (95% CI, −2.29 to −1.25) with a significant BMI reduction of −0.64 kg/m^2 (95% CI, −0.84 to −0.43) and −0.67 kg/m^2 (95% CI, −0.86 to −0.47), and a significant fat mass reduction of −1.23 kg (95% CI, −1.67 to −0.80) and −1.46 kg (95% CI, −1.93 to −1.01) were reported in the VD and MD groups, respectively. Subgroup analyses showed no significant differences in the changes of all the anthropometric parameters.

Biochemical Profile

The changes in the biochemical parameters, including hematologic variables, vitamins, iron status, minerals, liver function, uric acid, and lipid and glycemic profiles, are shown in Table 2. The diets displayed significant differences in terms of end-of-diet values, LDL cholesterol (9.10 mg/dL; *P*=0.01), triglycerides (12.70 mg/dL; *P*<0.01), vitamin B_{12} (32.32 pg/mL; *P*<0.01), and uric acid levels (0.22 mg/dL; *P*<0.01). Although the VD re-

sulted in a significant decrease (−5.44%) in LDL cholesterol levels, no significant change was observed after the MD period. The MD resulted in a significant decrease (−5.91%) in triglyceride levels compared with the VD, which showed an increasing trend despite it not being significant. For vitamin B_{12}, a significant decrease after the VD (−5.06%) and a nonsignificant increasing trend after the MD were reported. Finally, in the case of the VD, a significant reduction in uric acid levels (−2.89%) was noted; nonsignificant changes were reported during the MD.

Subgroup analyses showed that changes in the lipid profile during the VD were more evident in men, in participants >50 years of age, in nonsmokers, in participants with sedentary lifestyles, and in participants with a BMI >30 kg/m^2, with the most significant results in participants with class I obesity (Table III in the online-only Data Supplement). The change in the vitamin B_{12} levels after the VD phase was more apparent among overweight participants (especially among participants with class I obesity), men, and participants <50 years of age (Table III in the online-only Data Supplement).

Oxidative Stress and Inflammatory Profiles

Changes in the oxidative stress profile are reported in Table 3. No difference between the diets was observed. Although both diets led to a similar and significant reduction in the Thiobarbituric Acid Reactive Substances levels, only the VD resulted in a significant reduction in the leukocyte-derived reactive oxygen species level (−8.42%). Total antioxidant capacity and M- and G-derived reactive oxygen species showed decreasing but nonsignificant trends.

With regard to the inflammatory profile, a significant difference between the diets was observed in the case of interleukin-17 levels (3.39 pg/mL; P<0.01). Indeed, interleukin-17 displayed opposite tendencies during the 2 phases of intervention, as evidenced by an increasing trend (by 37.57%) in the VD phase and a significant decreasing trend (by 36.3%) in the MD phase (Table 4). Overall, the VD resulted in a reduction in the levels of 8 out of 13 cytokines, and in the case of 6, statistical significance was reached. The MD resulted in a reduction in the levels of 11 out of 13 pro- and anti-inflammatory cytokines, and in the case of 7, statistical significance was reached.

Carryover effects were not detected for all the parameters investigated.

Compliance

During the study, 18 (15.3%) participants reported a less-than-optimal compliance to the prescribed diets and were excluded at different time points from the study (Figure 1). The comparison of baseline characteristics between participants who completed the study and those who were excluded for not being adherent showed significant differences in age, BMI, and physical activity. Participants who did not finish the study were significantly younger (41 versus

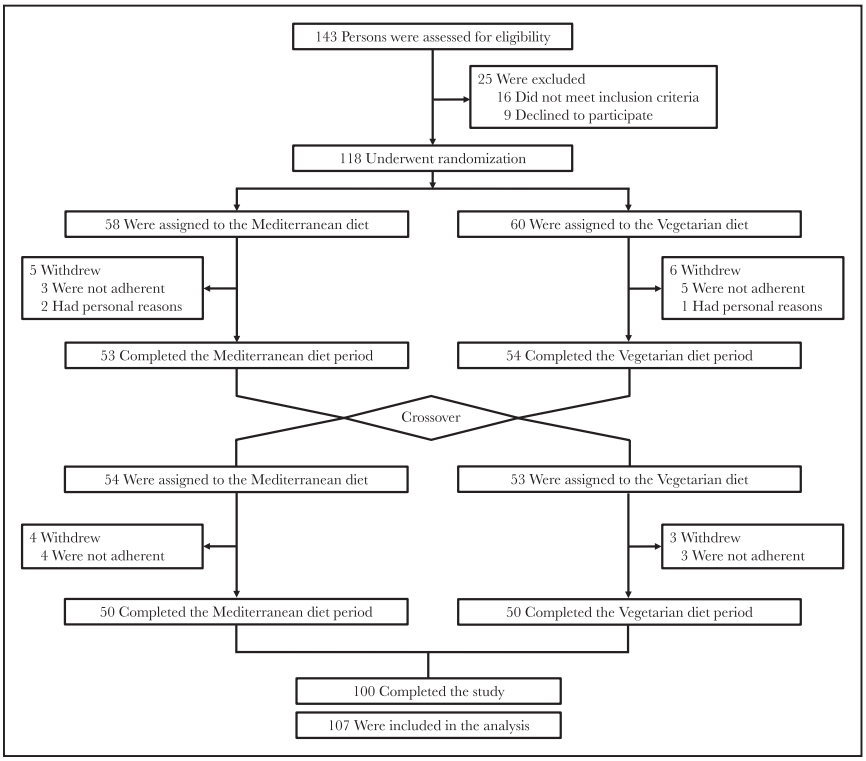

Figure 1. Flow chart of study participants.

Table 1. Baseline Characteristics of the Study Population According to the First Randomization

Characteristic	All (n=118)	Vegetarian Diet (n=60)	Mediterranean Diet (n=58)	*P* Value
Age, y, median (range)	50 (21–75)	49.5 (24–70)	52 (21–75)	0.57
Female sex, n (%)	92 (78)	49 (81.7)	43 (74.1)	0.37
Weight, kg (mean±SD)	83.9±16.8	82.9±16.0	84.9±17.7	0.63
BMI, kg/m^2 (mean±SD)	30.6±4.9	30.1±4.7	31.1±5.1	0.29
Obese (≥30 kg/m^2), n (%)	57 (48.3)	27 (45)	30 (51.7)	0.58
Fat mass, % (mean±SD)	37.9±8.2	38.0±8.4	37.9±8.0	0.66
Dietary profile				
Total energy, kcal/d (mean±SD)	2071.3±548.4	2101.9±527.4	2039.5±572.2	0.39
Carbohydrate, % of energy (mean±SD)	47.2±8.7	47.3±8.6	47±8.9	0.96
Protein, % of energy (mean±SD)	17.1±4.3	16.9±4.7	17.2±3.9	0.51
Total fat, % of energy (mean±SD)	37±6.2	36.8±6.2	37.3±7.1	0.75
Saturated fat, % of energy (mean±SD)	8.1±2.9	7.8±2.2	8.4±3.4	0.57
Total cholesterol, mg/d (mean±SD)	202.7±109.2	198.8±94.5	206.8±124.9	0.96
Risk factors				
Current smokers, n (%)	17 (14.4)	6 (10)	11 (19)	0.20
Absent or light physical activity, n (%)	107 (90.7)	54 (90)	53 (91.4)	0.78
Total cholesterol >190 mg/dL, n (%)	90 (76.3)	47 (78.3)	43 (74.1)	0.59
LDL cholesterol >115 mg/dL, n (%)	87 (73.7)	45 (75)	42 (72.4)	0.75
Triglycerides >150 mg/dL, n (%)	34 (28.8)	16 (26.7)	18 (31)	0.60
Glucose 110–126 mg/dL, n (%)	17 (14.4)	6 (10)	11 (19)	0.17
Blood biomarkers				
Total cholesterol, mg/dL (mean±SD)	212.3±38.3	210.5±34.1	214.2±42.4	0.59
LDL cholesterol, mg/dL (mean±SD)	131.7±32.7	130.8±30.2	132.7±35.5	0.76
Triglycerides, mg/dL (mean±SD)	125.0±62.8	124.4±64.9	125.6±61.1	0.78

To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551. BMI indicates body mass index; and LDL, low-density lipoprotein.

52 years of age), had a higher BMI (33.1 versus 30.1 kg/m^2), and had significantly more sedentary lifestyles than the participants who completed the study (Table IV in the online-only Data Supplement). By conducting all the analyses after the inclusion of the nonadherent participants, through an intention-to-treat analysis, the results of both the anthropometric and circulating biomarkers did not substantially change (data not shown).

Cardiovascular Risk Profile

Both diets resulted in a significant improvement of the participants' cardiovascular risk profile. Forty-six participants during the VD (44.2% of the participants who completed the VD phase) and 35 during the MD (34% of the participants in whom the MD was initiated) modified their risk category by reaching the target values recommended by the European Society of Cardiology[15] for ≥1 cardiovascular risk factor (total cholesterol level ≤190 md/dL, LDL cholesterol level ≤115 mg/dL, triglyceride level ≤150 mg/dL, glucose level ≤110 mg/dL, BMI <25 kg/m^2). Of these participants, during the VD, 16 reached the target values for total cholesterol, 17 for LDL cholesterol, 6 for triglyceride levels, and 14 for BMI. As for the MD, only 7 subjects reached the target values for total cholesterol, 6 for LDL cholesterol, 8 for triglyceride levels, and 10 for BMI.

DISCUSSION

This randomized dietary intervention trial is the first to compare the effectiveness of a low-calorie VD and a similar MD in improving the cardiovascular risk profile of a clinically healthy omnivorous population living in a low-risk country for cardiovascular disease. The most significant result was that, at the end of the 3-month intervention period on a low-calorie VD and MD, similar reductions in total body weight, BMI, and total fat mass were observed, with no differences between the

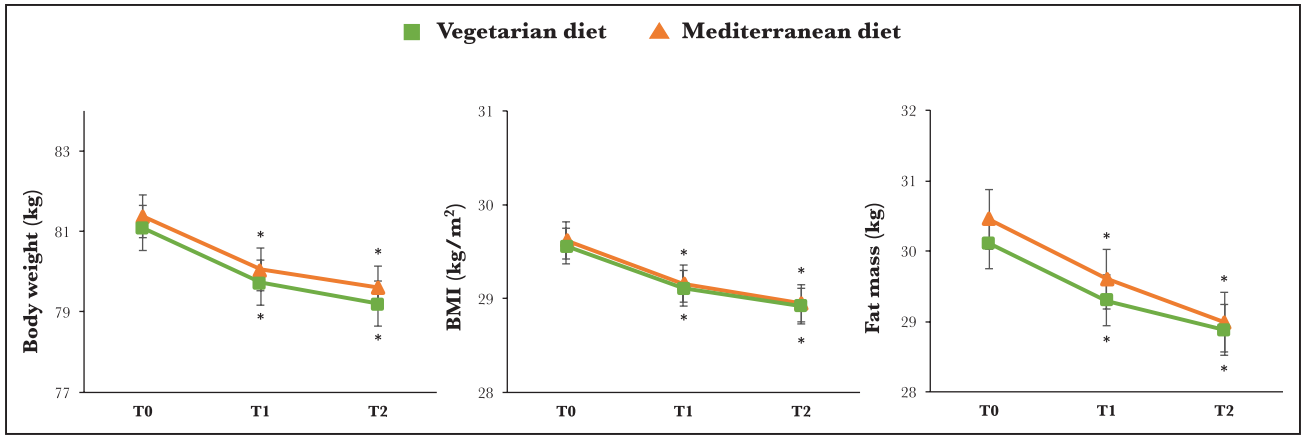

Figure 2. Body weight, BMI, and fat mass changes according to diet group.
Vertical bars indicate SDs. BMI indicates body mass index; T0, baseline; T1, 1.5 months after the onset of dietary intervention; and T2, 3 months after the onset of dietary intervention. **P* value for within-group difference.

diets. In addition, although the VD was more effective in reducing LDL cholesterol levels, the MD was more effective in reducing triglyceride levels. Regarding the oxidative stress and inflammatory profiles, both diets contributed to a significant improvement in most parameters; however, a significant difference was seen

Table 2. Changes in Biochemical Parameters

	Vegetarian Diet: Before (n=104)	Vegetarian Diet: After (n=104)	Mediterranean Diet: Before (n=103)	Mediterranean Diet: After (n=103)	*P* (Δ_{VD} Versus Δ_{MD})†
WBC, × 10^3/mm^3	6.06 (5.80–6.34)	6.22 (5.96–6.48)	6.34 (6.07–6.61)	6.25 (5.98–6.53)	0.42
RBC, × 10^6/mm^3	4.70 (4.63–4.77)	4.67 (4.60–4.74)	4.70 (4.62–4.77)	4.72 (4.64–4.80)	0.04
Hemoglobin, g/dL	13.65 (13.42–13.90)	13.57 (13.31–13.83)	13.68 (13.46–13.90)	13.71 (13.49–13.92)	0.19
Hematocrit, %	41.14 (40.49–41.76)	40.94 (40.25–41.60)	41.06 (40.41–41.72)	41.26 (40.61–41.97)	0.04
Folate, ng/mL	6.67 (6.04–7.36)	7.08 (6.44–7.78)	6.81 (6.17–7.51)	7.26 (6.60–7.99)	0.86
Vitamin B_{12}, pg/mL	380.70 (357.17–404.24)	361.41 (340.36–383.37)*	376.91 (356.02–399.02)	389.94 (367.60–413.64)	<0.01
Ferritin, ng/mL	50.30 (41.14–61.56))	51.01 (41.70–62.43)	56.71 (46.25–69.55)	53.84 (43.90–66.09)	0.48
Iron, µg/dL	79.44 (74.22–84.94)	78.10 (72.53–84.18)	79.68 (73.48–86.40)	78.57 (73.63–83.76)	0.62
Sodium, mEq/L	139.07 (138.80–139.35)	139.49 (139.21–139.91)*	139.21 (138.80–139.49)	139.31 (138.93–139.49)	0.07
Potassium, mEq/L	4.25 (4.20–4.30)	4.26 (4.21–4.31)	4.25 (4.20–4.30)	4.28 (4.22–4.33)	0.96
Calcium, mg/dL	8.83 (8.73–8.93)	8.84 (8.76–8.91)	8.86 (8.84–8.94)	8.84 (8.75–8.93)	0.65
Magnesium, mg/dL	2.02 (1.99–2.05)	2.05 (2.02–2.08)	2.01 (1.98–2.04)	2.05 (2.02–2.09)*	0.48
AST, U/L	17.46 (16.35–18.65)	17.17 (15.91–18.52)	17.18 (15.94–18.50)	17.73 (16.76–18.77)	0.51
ALT, U/L	27.47 (25.64–29.43)	27.83 (26.00–29.78)	27.52 (25.51–29.73)	27.55 (25.87–29.37)	0.45
γ-GT, U/L	23.13 (20.76–25.76)	24.61 (22.13–27.39)	24.39 (21.89–27.19)	24.51 (21.96–27.36)	0.65
Uric acid, mg/dL	4.15 (3.96–4.35)	4.03 (3.85–4.22)*	4.10 (3.92–4.31)	4.20 (4.00–4.41)	<0.01
TC, mg/dL	207.89 (200.74–215.29)	202.55 (195.98–209.56)*	205.41 (197.95–212.94)	205.30 (198.34–212.72)	0.15
HDL-C, mg/dL	53.36 (51.26–55.48)	52.56 (50.30–54.93)	53.09 (50.65–55.70)	53.41 (51.21–55.70)	0.62
LDL-C, mg/dL	128.25 (114.89–134.83)	121.27 (114.89–127.87)*	123.72 (116.86–130.84)	125.84 (119.22–132.69)	0.01
Triglycerides, mg/dL	108.74 (99.29–119.10)	114.66 (104.27–126.09)	114.66 (104.38–125.96)	107.88 (98.59–118.16)*	0.01
Insulin, µU/mL	9.38 (8.59–10.25)	8.89 (8.10–9.76)	9.75 (8.98–10.58)	9.29 (8.51–10.16)	0.42
Glucose, mg/dL	89.93 (87.71–92.11)	90.47 (88.15–92.94)	90.56 (88.23–92.94)	90.83 (88.68–93.13)	0.60
HOMA-IR Index	2.08 (1.89–2.29)	1.99 (1.79–2.21)	2.18 (1.99–2.39)	2.09 (1.78–2.30)	0.37

Data are reported as geometric mean and 95% confidence interval. ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; GT, glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; LDL-C, low-density lipoprotein cholesterol; MD, Mediterranean diet; RBC, red blood cell; VD, vegetarian diet; and WBC, white blood cell.

**P*<0.05 for change within each group, calculated using a general linear model adjusted for order of treatment and weight change.

†Independent *t* test.

Table 3. Changes in Oxidative Stress Parameters

	Vegetarian Diet: Before (n=104)	Vegetarian Diet: After (n=104)	Mediterranean Diet: Before (n=103)	Mediterranean Diet: After (n=103)	P (Δ_{VD} Versus Δ_{MD})†
TBARS, pg/mL	1.73 (1.48–2.01)	1.34 (1.13–1.59) *	1.68 (1.44–1.95)	1.36 (1.15–1.60)*	0.88
TAC, μmol/mL	14.40 (13.76–15.04)	14.06 (13.36–14.79)	14.35 (13.71–15.03)	14.24 (13.61–14.89)	0.60
L-derived ROS, RFU	707.69 (659.84–759.00)	648.07 (598.24–702.05)*	684.03 (635.24–736.57)	666.47 (622.66–714.08)	0.67
M-derived ROS, RFU	1247.6 (1169.1–1332.8)	1187.9 (1104.4–1279.2)	1230.3 (1149.4–1315.5)	1171.5 (1099.9–1248.9)	0.62
G-derived ROS, RFU	1844.6 (1718.1–1980.3)	1737.2 (1611.6–1870.6)	1775.8 (1654.1–1904.6)	1674.1 (1571.8–1782.9)	0.64

Data are reported as geometric mean and 95% confidence interval. G indicates granulocyte; L, leukocyte; M, monocyte; MD, Mediterranean diet; RFU, relative fluorescence unit; ROS, reactive oxygen species; TAC, total antioxidant capacity; TBARS, Thiobarbituric Acid Reactive Substances; and VD, vegetarian diet.

*P<0.05 for change within each group, calculated using general linear model adjusted for order of treatment and weight change.

†Independent t test.

in the interleukin-17 level, which improved only in the MD group.

In line with previously conducted studies, the present study also shows the beneficial effect of VD and MD on body weight, BMI, and fat mass. A recent meta-analysis by Barnard et al[21] identified 6 trials that analyzed a vegetarian-like period and reported a significant reduction in total body weight, with an average mean reduction of 3.4 kg. In the same year, the results of an additional meta-analysis, including 12 randomized controlled trials that involved participants who followed a VD, reported similar findings, with a mean reduction of 2.2 kg with respect to the nonvegetarian group.[22] In our study, despite a similar significant trend, we found a slightly lower reduction in the body weight among the participants following the VD (−1.74 kg). This difference in terms of body weight change can be explained by the fact that the results of previously conducted intervention studies investigated not only VDs but also vegan diets and other forms of vegetarianism, different study populations were analyzed, the durations of intervention were different, and there was a lack of a comparable diet for most studies. In the present study, the comparison diet was the MD, widely reported to be one of the healthiest dietary models in the reduction of the risk burden of chronic degenerative diseases.[13] In recent decades, several intervention studies have demonstrated the beneficial effects of a low-calorie MD on body weight and several anthropometric measurements.[13] The present study confirms this finding and extends the evidence of the beneficial effects of the MD on body weight, in comparison with those of a similar low-calorie VD. The possible mechanisms explaining the effects of both VD and MD in reducing body weight and fat mass may be related to the higher consumption of certain beneficial food groups such as complex carbohydrates, legumes, fruits, and vegetables. All of these food groups are rich in fiber, and several studies have reported an inverse association between fiber consumption and weight loss via effects on satiety, as well as fat reduction and glucose absorption.[23] In the present study, the intervention diets did not differ in the percentage of calories obtained from macronutrients and the main categories of food (except for animal products and legumes) and were isocaloric. However, we cannot exclude the possibility of a greater reduction in kilocalories in the VD compared to the MD.

With regard to the lipid profile, these results demonstrate the beneficial effects of both diets; in the case of the VD, a significant reduction in the LDL cholesterol level was noted, whereas in the case of the MD, the triglyceride levels were significantly reduced. A recent meta-analysis that included 11 randomized trials, conducted on participants who followed vegetarian diets versus those who followed control diets, reported a significant lowering of total cholesterol, LDL cholesterol, and high-density lipoprotein cholesterol levels but not triglyceride levels.[24] Nevertheless, literature on the beneficial effects of VDs on triglyceride levels is inconsistent and contrasting.[7] Some studies reported the beneficial effects of VDs on triglyceride levels, whereas others did not observe any significant effect. In the present study, we confirmed the beneficial effects of the VD in the reduction of LDL cholesterol by extending the results to clinically healthy participants living in a country at low risk for cardiovascular disease. However, no effects of the VD on triglyceride and high-density lipoprotein levels were observed. The null effect of the VD on triglyceride levels may be explained by the paradoxical effects of an increased level of circulating triglyceride levels because of the high content of carbohydrate and total fat that occurs when meat and meat products are eliminated from the diet, as reported by other studies.[25] In our study, the 2 diets were not essentially different in terms of the weekly portions consumed by these food groups, so the null effect on triglyceride does not seem to follow this hypothesis. However, we observed a beneficial effect of the MD on triglyceride levels as reported by intervention studies.[13]

Table 4. Changes in Inflammatory Parameters

	Vegetarian Diet: Before (n=104)	Vegetarian Diet: After (n=104)	Mediterranean Diet: Before (n=103)	Mediterranean Diet: After (n=103)	P (Δ_{VD} Versus Δ_{MD})†
Interleukin-1ra, pg/mL	11.62 (9.82–13.76)	10.33 (8.76–12.18)	13.45 (11.43–15.82)	10.70 (9.23–12.39)*	0.37
Interleukin-4, pg/mL	0.07 (0.05–0.09)	0.12 (0.09–0.16)*	0.07 (0.05–0.09)	0.12 (0.09–0.16)*	0.99
Interleukin-6, pg/mL	0.74 (0.60–0.92)	0.81 (0.66–1.00)	0.84 (0.68–1.04)	0.75 (0.63–0.90)	0.06
Interleukin-8, pg/mL	3.39 (2.72–4.22)	2.86 (2.27–3.61)	3.35 (2.69–4.18)	3.01 (2.42–3.75)	0.71
Interleukin-10, pg/mL	1.71 (1.32–2.21)	1.83 (1.41–2.39)	1.81 (1.37–2.37)	1.50 (1.14–1.95)	0.07
Interleukin-12, pg/mL	15.46 (13.40–17.85)	15.43 (13.40–17.74)	16.48 (14.11–19.26)	14.35 (12.45–16.59)*	0.13
Interleukin-17, pg/mL	3.70 (2.82–4.86)	5.09 (4.14–6.26)*	5.51 (4.54–6.69)	3.51 (2.68–4.61)*	0.01
MCP-1, pg/mL	21.24 (18.90–23.88)	19.13 (17.03–21.50)*	22.76 (20.05–25.87)	17.98 (16.17–19.97)*	0.20
MIP-1β, pg/mL	48.91 (43.90–54.43)	45.11 (41.26–49.25)	52.40 (47.66–57.57)	45.47 (41.06–50.40)*	0.49
VEGF, pg/mL	39.88 (33.72–47.18)	35.30 (29.99–41.55)*	42.86 (35.80–51.32)	36.16 (30.51–42.91)*	0.63
TNF-α, pg/mL	3.05 (2.23–4.17)	3.50 (2.92–4.18)	3.20 (2.53–4.04)	2.86 (2.12–3.87)	0.25
IP-10, pg/mL	479.62 (435.72–527.95)	434.41 (393.07–v480.10)*	475.33 (427.95–527.95)	447.20 (407.48–490.78)	0.40
IFN-γ, pg/mL	3.58 (2.87–4.46)	2.66 (2.06–3.43)*	2.53 (1.93–3.30)	3.22 (2.58–4.00)	0.11

Data are reported as geometric mean and 95% confidence interval. IFN indicates interferon; IP, interferon-γ–induced protein; MCP, monocyte chemoattractant protein; MD, Mediterranean diet; MIP, macrophage inflammatory protein; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; and VD, vegetarian diet.

*P<0.05 for change within each group, calculated using general linear model adjusted for order of treatment and weight change.

†Independent t test.

The VD and MD can reduce lipid parameters through different mechanisms. The VD is low in cholesterol, total fat, and saturated fatty acid,[26] leading to lower intake and thus lower rates of absorption and conversion into cholesterol in the bloodstream.[27] In our dietary study, the VD administered to our study participants entailed a significantly lower daily intake of cholesterol. The MD, in contrast, can reduce triglyceride levels through its beneficial components, including olive oil, dietary fiber, and many phytonutrients.[28]

As expected, in the intervention period with the VD, a significant reduction in vitamin B_{12} levels was observed. This reduction, despite being clinically irrelevant and within the normal range, confirms that the VD may lead to lower levels of this vitamin, as previously reported by other studies.[29] This issue warrants further investigation because, over an extended period, a decrease in vitamin B_{12} associated with VD can lead to a deficiency that may be clinically relevant. Indeed, the official position of scientific societies and agencies is unequivocal: participants following VDs and vegan diets should be screened for vitamin B_{12} deficiency and eventually encouraged to use fortified foodstuffs or supplements to ensure adequate vitamin B_{12} intake.[30]

As for the oxidative profile, no difference between the VD and MD was observed. To the best of our knowledge, this study is the first to evaluate these parameters after a period of intervention with the VD, whereas several results have already been obtained for the MD.[31] Previously conducted studies on food categories such as wheat, fruit, and vegetables have signaled the beneficial role of nutrients in reducing the circulating levels of reactive oxygen species,[32] but no data on the short-term effect of VDs have yet been published.

With regard to the inflammatory parameters, this dietary intervention study is the first to include a VD and evaluate a large pattern of pro- and anti-inflammatory cytokines. A significant difference between the VD and MD was observed only for interleukin-17, which significantly increased during the VD and significantly decreased during the MD period. Several studies in the past reported a strict association between vitamin B_{12} and inflammation, possibly through the modulation of the metabolic cycle of homocysteine.[33] In addition, a relationship between higher levels of interleukin-6 and lower levels of vitamin B_{12} has been previously reported[34] and is supported by our results because we observed an inverse and significant correlation between changes in the interleukin-6 and vitamin B_{12} levels (r=0.22; P=0.026). Thus, it can be postulated that the VD leads to a decrease in vitamin B_{12} levels and an increase in homocysteine levels, with a consequent worsening of the inflammatory profile.

The strengths of the study include the crossover design, the comparability between the 2 diets in terms of total energy and macronutrients, the high rate of adherence, and the various parameters analyzed in the same group of participants at different time points. However, some limitations are present, such as the lack of data on blood pressure levels, the limited duration of the study, and the limited number of participants who completed the whole study. We are aware that 3 months of intervention is a limited period and permits

only the suggestion of the possible interpretation of the results. Studies with a larger population and a longer duration are needed to confirm these results. However, despite the limitations, the present study included the largest cohort of omnivorous participants who underwent a period on a VD.

In conclusion, in the context of the behavioral counseling that promoted a reduced caloric intake, the results of this dietary randomized intervention study, the first comparing a VD and MD in the same group of clinically healthy omnivorous participants, showed no difference in weight change between the VD and MD groups, but the VD reduced LDL cholesterol levels compared with the MD, which reduced triglyceride levels compared with the VD.

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Low-Calorie Vegetarian Versus Mediterranean Diets for Reducing Body Weight and Improving Cardiovascular Risk Profile: CARDIVEG Study (Cardiovascular Prevention With Vegetarian Diet)

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SUPPLEMENTAL MATERIAL

Supplementary Table 1. Frequency of consumption of food groups in the two diets

Food group	Vegetarian diet	Mediterranean diet
Cereals	20.5 servings/week	21.5 servings/week
Pasta	4 servings/week	4 servings/week
Rice	1 serving/week	1 serving/week
Polenta	1 serving/week	-
Pizza	1 serving/week	1 serving/week
Wholegrain bread	6.5 servings/week	8.5 servings/week
Breakfast cereals	2 servings/week	2 servings/week
Rusks	3 servings/week	3 servings/week
Biscuits	1 serving/week	1 serving/week
Croissant	1 serving/week	1 serving/week
Vegetables *(without potatoes)*	15 servings/week	14.5 servings/week
Fruit	18 servings/week	18 servings/week
Nuts	2 servings/week	1 serving/week
Potatoes *(including white and yellow potatoes)*	1.5 serving/week	1.5 serving/week
Legumes	5 servings/week	2.5 servings/week
Eggs	2 servings/week	1 serving/week
Dairy products	21.5 servings/week	18.5 servings/week
Low fat milk	11 servings/week	11 servings/week
Low fat yoghurt	6 servings/week	5 servings/week
Cheese	4.5 servings/week	2.5 servings/week
Poultry	-	2 servings/week
Red meat	-	1.5 serving/week
Processed meat	-	1 serving/week
Fish	-	2.5 servings/week
Sweets	3.5 servings/week	3.5 servings/week
Olive oil	14 servings/week	14 servings/week

Servings/week are calculated according to the portion sizes recommended by the Italian Recommended Dietary Allowances (pasta: 80 g; rice: 80 g; polenta: 80 g; pizza: 200 g; wholegrain bread: 50 g; breakfast cereals: 30 g; rusks: 30 g; biscuits: 50 g; croissant: 50 g; vegetables: 200 g; fruit: 150 g; nuts: 30 g; potatoes: 200 g; legumes: 150 g; eggs: 50 g; low fat milk: 125 ml; low fat yoghurt: 125 g; cheese: 75 g; poultry: 100 g; red meat: 100 g; processed meat: 50 g; fish: 150 g; sweets: 20 g; olive oil: 10 ml)

Supplementary Table 2. Variations in dietary intake according to the first randomization

	All (n=118)	**Vegetarian diet (n=60)**	**Mediterranean diet (n=58)**	**p value †**
Total energy, kcal/day				
Change (after-before)	-542.3 ± 513.4 *	-586.3 ± 486.9 *	-496.7 ± 539.8 *	0.18
Carbohydrate, % of energy				
Change (after-before)	6.1 ± 8.7	6.8 ± 8.6	5.3 ± 8.9	0.37
Protein, % of energy				
Change (after-before)	0.1 ± 4.6	-1.5 ± 4.7	1.4 ± 3.9	0.001
Total fat, % of energy				
Change (after-before)	-7.3 ± 6.7 *	-6.3 ± 6.1 *	-8.2 ± 7.1 *	0.15
Saturated fat, % of energy				
Change (after-before)	-0.7 ± 6.8 *	-0.31 ± 2.2 *	-1.0 ± 3.3 *	0.41
Total cholesterol, mg/day				
Change (after-before)	-20.6 ± 69.7 *	-105.6 ± 91.5 *	-49.7 ± 121.8 *	0.001

Data are reported as mean ± standard deviation
* denotes $p<0.05$ for change (after the first intervention period vs before the first intervention period)
† denotes difference between change in the vegetarian diet group and change in the Mediterranean diet group

Supplementary Table 3. Subgroup analyses for the changes in the lipid profile and vitamin B12 levels

	Vegetarian Diet $\Delta_{post-pre}$	**p value ***	**Mediterranean Diet** $\Delta_{post-pre}$	**p value ***
TC, mg/dL				
Women	-4.95 (-10.84; 0.94)	0.10	-1.49 (-6.38; 3.40)	0.55
Men	-7.25 (-13.67; 0.83)	0.03	4.08 (-4.63; 12.79)	0.34
Age ≤ 50 years	-1.44 (7.41; 4.53)	0.63	-4.02 (-8.86; 0.82)	0.10
Age > 50 years	-9.22 (-16.22; -2.22)	0.01	3.26 (-3.44; 9.95)	0.33
Overweight	-3.41 (-10.92; 4.10)	0.37	2.04 (-4.10; 8.17)	0.51
Obese	-7.90 (-13.63; -2.16)	<0.01	-2.63 (-8.65; 3.40)	0.39
Class I obesity status	-12.18 (5.82; 18.54)	<0.01	0.77 (-6.63; 8.17)	0.83
Class II obesity status	0.91 (-15.81; 17.63)	0.90	-7.80 (-20.04; 4.44)	0.18
Absent or light physical activity	-6.88 (-11.82; -1.94)	<0.01	-0.11 (-4.25; 4.03)	0.96
Moderate physical activity	5.60 (-17.14; 28.34)	0.58	1.20 (-27.04; 29.44)	0.92
HDL-C, mg/dL				
Women	-0.33 (-2.09; 1.44)	0.72	-0.78 (-2.52; 0.95)	0.37
Men	-0.96 (-3.36; 1.45)	0.42	2.20 (0.55; 3.85)	0.01
Age ≤ 50 years	0.42 (-1.71; 2.55)	0.69	-0.90 (-3.09; 1.30)	0.42
Age > 50 years	-1.30 (-3.38; 0.78)	0.22	0.67 (-1.21; 2.56)	0.48
Overweight	-0.57 (-2.90; 1.76)	0.63	-0.13 (-2.21; 1.96)	0.90
Obese	-0.35 (-2.14; 1.43)	0.69	0.02 (-1.93; 1.97)	0.98
Class I obesity status	-0.65 (-2.87; 1.57)	0.56	0.60 (-1.78; 2.98)	0.61
Class II obesity status	-0.27 (-4.70; 4.15)	0.89	-1.30 (-6.31; 3.71)	0.56
Absent or light physical activity	-0.52 (-2.04; 1.01)	0.50	0.28 (-1.19; 1.75)	0.70
Moderate physical activity	0.70 (-6.68; 8.08)	0.83	-3.10 (-9.92; 3.72)	0.32
LDL-C, mg/dL				
Women	-5.35 (-10.78; 0.08)	0.05	0.76 (-3.88; 5.40)	0.75
Men	-10.83 (-18.28; -3.37)	<0.01	4.51 (-3.29; 12.32)	0.24
Age ≤ 50 years	-3.32 (-8.43; 1.79)	0.20	0.04 (-4.24; 4.32)	0.99
Age > 50 years	-9.66 (-16.54; -2.77)	<0.01	3.10 (-3.25; 9.43)	0.33
Overweight	-5.32 (-12.45; 1.81)	0.14	4.31 (-1.73; 10.35)	0.16
Obese	-8.12 (-13.37; -2.87)	<0.01	-1.36 (-6.46; 3.74)	0.59
Class I obesity status	-11.02 (-16.79; -5.26)	<0.01	0.05 (-6.04; 6.14)	0.99

Class II obesity status	-0.38 (-15.75; 14.98)	0.96	-3.20 (-17.69; 11.29)	0.62
Absent or light physical activity	-7.56 (-12.07; -3.04)	<0.01	0.95 (-2.77; 4.67)	0.61
Moderate physical activity	0.02 (-24.65; 24.69)	0.99	9.50 (-18.71; 37.71)	0.45
Triglycerides, mg/dL				
Women	3.11 (-4.87; 11.09)	0.44	-7.32 (-13.69; -0.96)	0.03
Men	22.67 (2.37; 42.96)	0.03	-13.16 (-29.49; 3.17)	0.11
Age ≤ 50 years	6.52 (-8.27; 21.31)	0.38	-15.81 (-25.06; -6.57)	<0.01
Age > 50 years	8.65 (-1.19; 19.21)	0.11	-2.56 (-10.47; 5.34)	0.52
Overweight	12.38 (2.61; 22.14)	0.01	-10.75 (-17.93; -3.56)	<0.01
Obese	2.08 (-13.58; 17.74)	0.79	-6.44 (-16.44; 3.56)	0.20
Class I obesity status	-3.74 (-19.86; 12.38)	0.64	0.60 (-10.93; 12.13)	0.92
Class II obesity status	8.00 (-20.14; 36.14)	0.53	-16.50 (-29.20; -3.80)	0.02
Absent or light physical activity	5.52 (-3.84; 14.87)	0.24	-6.72 (-13.11; -0.33)	0.04
Moderate physical activity	24.40 (-6.32; 55.12)	0.10	-26.00 (-49.19; -2.81)	0.03
Vitamin B12, pg/dl				
Women	-14.51 (-32.10; 3.08)	0.11	8.74 (-11.18; 28.67)	0.39
Men	-40.63 (-72.11; -9.14)	0.01	26.32 (-1.14; 53.78)	0.06
Age ≤ 50 years	-39.40 (-57.58; -21.22)	<0.01	18.58 (-9.64; 46.81)	0.19
Age > 50 years	-3.07 (-25.54; 19.39)	0.79	8.15 (-9.27; 25.57)	0.35
Overweight	-30.93 (-50.44; -11.42)	<0.01	14.76 (-8.97; 38.50)	0.22
Obese	-8.42 (-32.59; 15.75)	0.49	11.00 (-11.80; 33.80)	0.34
Class I obesity status	-5.88 (-35.77; 24.01)	0.69	2.43 (-20.00; 24.86)	0.83
Class II obesity status	-13.55 (-81.89; 54.80)	0.66	52.10 (-24.15; 128.35)	0.15
Absent or light physical activity	-20.76 (-36.83; -4.70)	0.01	10.59 (-6.05; 27.23)	0.21
Moderate physical activity	-21.30 (83.77; 41.17)	0.45	48.80 (-16.36; 113.96)	0.12

Data are reported as geometric mean and 95% confidence interval (CI)
* $p<0.05$ for change within each group, calculated using a general linear model adjusted for order of treatment and weight change

Supplementary Table 4. Baseline characteristics of the study population according to the completion of the study

Characteristic	All (n=118)	Completers (n=100)	Non-completers (n=18)	p value
Age, yr (median and range)	50 (21-75)	52 (21-75)	41 (28-57)	0.004
Female sex, n (%)	92 (78)	76 (76)	16 (88.9)	0.35
Weight, kg (mean ± SD)	83.9 ± 16.8	82.7 ± 16.1	90.6 ± 19.2	0.12
BMI, kg/m^2 (mean ± SD)	30.6 ± 4.9	30.1 ± 4.6	33.1 ± 6.0	0.027
Obese (≥ 30 kg/m^2), n (%)	57 (48.3)	46 (46)	11 (61.1)	0.31
Fat mass, % (mean ± SD)	37.9 ± 8.2	37.3 ± 8.4	41.5 ± 5.5	0.07
Dietary profile				
Total energy, kcal/day (mean ± SD)	2071.3 ± 548.4	2071.4 ± 567.8	2070.3 ± 438.8	0.58
Carbohydrate, % of energy (mean ± SD)	47.2 ± 8.7	47.7 ± 8.8	44.3 ± 7.7	0.07
Protein, % of energy (mean ± SD)	17.1 ± 4.3	16.9 ± 4.3	17.8 ± 4.4	0.37
Total fat, % of energy (mean ± SD)	37 ± 6.2	36.7 ± 6.5	39.1 ± 7.0	0.18
Saturated fat, % of energy (mean ± SD)	8.1 ± 2.9	8.2 ± 2.9	7.9 ± 2.9	0.78
Total cholesterol, mg/day (mean ± SD)	202.7 ± 109.2	199.9 ± 110.9	218.4 ± 101.3	0.45
Risk factors				
Current smokers, n (%)	17 (14.4)	14 (14)	3 (16.7)	0.50
Absent or light physical activity, n (%)	107 (90.7)	89 (89)	15 (100)	0.45
Total cholesterol >190 mg/dl, n (%)	90 (76.3)	76 (76)	14 (77.8)	0.10
LDL-cholesterol >115 mg/dl, n (%)	87 (73.7)	75 (75)	11 (66.7)	0.56
Triglycerides >150 mg/dl, n (%)	34 (28.8)	28 (28)	6 (33.3)	0.78
Glucose 110-126 mg/dl, n (%)	17 (14.4)	13 (13)	1 (5.6)	0.69
Blood biomarkers				
Total cholesterol, mg/dl (mean ± SD)	212.3 ± 38.3	214.1 ± 37.5	202.6 ± 42.2	0.43
LDL-cholesterol, mg/dl (mean ± SD)	131.7 ± 32.7	133.2 ± 33.3	123.5 ± 29	0.37
Triglycerides, mg/dl (mean ± SD)	125.0 ± 62.8	123.8 ± 60.7	131.6 ± 75.4	0.92

To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551.
BMI denotes Body Mass Index and LDL Low-Density Lipoprotein.

Dr Carolyn Lam: Welcome to Circulation on the Run, your weekly podcast summary and backstage pass to the journal and its editors. I'm Dr. Carolyn Lam, Associate Editor from the National Heart Centre and Duke National University of Singapore.

Have you ever wondered, which is better for heart health, low calorie vegetarian or a Mediterranean diet? Well, this week's feature paper provides some answers with a very intriguing discussion coming right up after these summaries.

The first original paper this week suggests that human fat pools are not the same and in fact are highly diverse in their response to lifestyle interventions during weight reduction first author Dr. Gepner, co-corresponding authors Dr. Shai from Israel and Dr. Stampfer from Boston aim to assess whether distinct lifestyle strategies could differentially affect specific body adipose depos. They performed at 18-month randomized control trial among 278 sedentary adults with abdominal obesity or dyslipidemia in an isolated work place with a monitored, provided lunch.

Participants were randomized to an isocaloric low fat or a Mediterranean low carbohydrate diet with or without added moderate physical activity. The overall primary outcome was body fat redistribution and the main specific endpoint was visceral adipose tissue. The authors further followed the dynamics of different fat depos by magnetic resonance imaging. They found that Mediterranean diet was superior to the low fat diet in mobilizing specific ectopic fat depos such as visceral, hepatic, cardiac and pancreatic fats. Exercise had an additional independent contribution to visceral fat loss. Long term persistent moderate weight loss inadequately reflected the significant beneficial effects of diet and exercise on the fat depos. Independent of weight loss, visceral and hepatic fat reduction was mainly associated with improved lipids profile whereas deep subcutaneous fat loss was associated with improved insulin resistance and superficial fat loss was neutral.

In other words, two distinct patterns were identified, a differentially responsive depo that was sensitive to the type of intervention, and those recites mostly directly related cardiometabolic health and a uniformly responsive depo, which corresponded only to weight loss per se irrespective of the intervention. Overall, these results suggest that more specific strategies for weight loss may be considered to treat distinct organ specific fat depos in the management of cardiometabolic risk.

Current guidelines recommend nonvitamin K antagonist oral anticoagulants or NOACs in patients with nonvalvular atrial fibrillation as these drugs have several benefits over the vitamin K antagonists but do these benefits remain when NOACs have to be combined with aspirin therapy? Well co-first authors Dr. Bennaghmouch and de Veer, corresponding author Dr. ten Berg and colleagues from the Netherlands provided a meta analysis comparing NOACs and Vitamin K

antagonists in more than 21700 patients with atrial fibrillation who are treated with concomitant aspirin therapy. NOACs were found to be more effective in terms of stroke or systemic embolism reduction as well as vascular death reduction and as safe as vitamin K antagonist with respect to major bleeding. NOACs were in fact safer with respect to the reduction of intracranial hemorrhage. Thus, these authors found that NOACs were an effective and safe alternative as compared to vitamin K antagonists in atrial fibrillation patients treated with concomitant aspirin therapy.

The next study shows that an integrative approach using genomics and proteomics has the potential to identifying new biological pathways for biomarker discovery and pharmacologic targeting in early cardiovascular disease. Co-first authors Dr. Benson and Yang, co-corresponding authors Dr. Wang and Gerszten from Beth Israel Deaconess Medical Center in Boston had recently identified 156 proteins in the human plasma that were each associated with a net Framingham cardiovascular disease risk score using an aptamer-based proteomic platform in the Framingham Heart Study Offspring participants.

Now, in the current student these authors hypothesized that performing a genome-wide association study and exome array analyses on the levels of each these 156 proteins may identify genetic determinants of risk associated circulating factors and provide insights into early cardiovascular pathophysiology. Indeed, they discovered dozens of novel genetic variants that were each strongly associated with circulating levels of the Framingham Risk Score associated proteins. They highlighted numerous examples of how these novel gene locus protein associations provided new insights into cardiovascular disease risk pathophysiology including a novel pathway by which the gene phosphatase 1G modulated circulating levels of apolipoprotein E, a key regulator of cholesterol handling.

The final study suggests that bariatric surgery represents an effective strategy for reducing antihypertensive drugs in patients with obesity and hypertension. First and corresponding author Dr. Schiavon from Heart Hospital in Sao Paulo, studied 100 patients with obesity and hypertension who were randomized to gastric bypass or medical therapy alone. The patients randomized the gastric bypass were six times more likely to reduce by 30% or more the total number of antihypertensive medications while maintaining controlled blood pressure levels. In addition, 51% of the patients undergoing gastric bypass showed remission of hypertension. Now, the authors are quick to alert that given the morbidity of surgery these results do not imply that all patients with obesity and hypertension should be submitted for bariatric surgery. Rather, these results suggest that gastric bypass surgery represents one extra option to consider in achieving blood pressure control in these patients.

That wraps it up for our summaries now for our feature discussion.

So, which is better for heart health the vegetarian or the Mediterranean diet? Oh, what an awesome topic and to be able to discuss it from Asia to the United States to Italy, I'm so please to have the first and corresponding author of our feature paper this week Dr. Francesco Sofi from University of Florence in Italy and our dear associate editor Dr. Wendy Post from Johns Hopkins. Francesco, could you please start by telling us what inspired you to do this trial?

Dr Francesco Sofi: The aim of the study was to compare two of the most beneficial diets we know from the literature in relation to the occurrence of many chronic degenerative diseases so the Mediterranean diet we have a lot of studies showing that Mediterranean diet is beneficial for many different diseases as well as we have some studies for the beneficial effect of a lacto-ovo vegetarian diet but no studies are available comparing these two diets' dietary profiles. Our hypothesis was to compare in the same population different times the two diets, which were the similar calories, the same isocaloric but just different in terms of composition especially for meat and fish.

Dr Carolyn Lam: Tell us the bottom line. I'm holding my breath because I think I've said it before, I'm vegetarian. Half my household is Mediterranean diet so what did you find?

Dr Francesco Sofi: We found that in the same group of patients, which were a low risk population because a low risk population here in Italy they were already following a Mediterranean diet but if you control their calories and their composition in terms of the Mediterranean, which included all the different food groups and the lacto-ovo vegetarian diet so all the different groups except for meat and meat-based and fish we noticed that after three months, the lacto-ovo vegetarian diet already determined a reduction of total cholesterol and LDL cholesterol and Mediterranean diet already determined reduction of triglycerides and both were effective for reduction of body weight and fat mass.

We noticed with great interest that after three months, all the study population were quite good in [inaudible 00:09:45] with this diet. I mean they didn't have any kind of problems. This is the one of the most important thing and most of the population or many of the patients after the end of the study they started or continued to follow a vegetarian diet. It means that they accepted very well. There was no problem at all. Also, in feasibility and acceptability of this diet and in relation to this also they have a beneficial effect in some parameters such as also oxidative stress parameters and the inflammatory parameters.

Dr Carolyn Lam: Right, so if I could summarize maybe crudely so the vegetarian diet, very effective for LDL, the Mediterranean very effective for triglycerides. I know that's a simplification but Wendy, I'd like to know do you think this is the dawn of maybe a more, "Oh, here we go again individualized diet planning"?

Dr Wendy Post: I think that this study is really important because there really have been few randomized trials about the vegetarian diet and we've learned a lot of the potential beneficial effects of a Mediterranean diet. I think what was really

interesting about this study is seeing that they were both equally effective as a low calorie Mediterranean diet or vegetarian diet at reducing body weight, which is most often the biggest challenge for our patients who are either at risk for cardiovascular disease like these patients potentially were or who have cardiovascular disease.

I think the vegetarian diet is potentially an excellent option for some of our patients but it really is an individual choice and I have trouble getting some patients to just give up the red meat let alone any kind of animal meat. I think it really is potentially an individual choice and those who are interested in becoming vegetarian for either health reasons or other reasons these are additional data to suggest potential beneficial effects more to the Mediterranean diet.

Dr Francesco Sofi: I think one of the most important things to know from this study is that we have now two options. We need to individualize the diets to patients but if a person wants to follow a vegetarian diet for different reasons including also healthy reasons, we can say that it's beneficial. He or she can follow this diet without no problems so without having any health problems as well as if a person wants to follow also a Mediterranean diet, which included meat and fish with a regular and moderate consumption during the week.

Dr Wendy Post: Right but this is just a three month trial with intermediate outcomes so I'm not sure we can necessarily make definitive statements that this is potentially not leading to any adverse effects or some of the other statements that you made. I think we could just make the statements better relative to the outcomes that were seen here related to weight loss and traditional cardiovascular risk factors. Whereas, we have had long term clinical trials of the Mediterranean diet suggesting reduction in risk for events so I think this is definitely supportive of the vegetarian diet but I think we can't say that more studies aren't needed to potentially look at longer term outcomes and more definitive events as opposed to intermediate outcomes that this is a great first start and is really helpful in trying to understand some of the potential differences between the vegetarian diet and the Mediterranean diet.

Dr Francesco Sofi: Of course, I completely agree on that. We need more studies and larger studies and longer duration to establish some things but it was just a pilot study but the good thing is the first comparing two beneficial diets. In the literatures now, most of the studies were investigated either already a vegetarian person or vegetarian diet versus a westernized diet so probably there were some biases.

Dr Carolyn Lam: Indeed, I want to just echo in these words. Congratulations, Francesco. Beautifully done, very elegant, controlled in terms of caloric intact and I like that message that it's not saying that one is bad and the other is good. It's saying, "They're different but they both resulted in weight loss". I love that comment about getting a bigger study. I want to do it right here in Asia because the diets

are just so different here and I'm just wondering how about in the US? Wendy, your perspective? How adoptable are these results?

Dr Wendy Post: Well, again I think it's a personal choice and if somebody is willing to become vegetarian then that's potentially wonderful especially if they have high LDL cholesterol and are trying to lose weight but we have to be careful about with the vegetarian diet is the carbohydrate intake, which might affect triglycerides. It might be an individualized approach based on the patient's individual risk factor profile and they're preferences but this is really impressive data suggesting that the vegetarian diet is very similar to the Mediterranean diet in many aspects especially as it relates to weight loss, which is really important.

Dr Carolyn Lam: You've hit the nail on the head. Let's remember that this is a low calorie vegetarian diet. I think that's the issue. Sometimes when I say vegetarian diet to some communities here in Asia that is actually a lot of calories and a lot of starch, which is not what we're talking about here.

Dr Wendy Post: Right, a low calorie diet so that's the key. That's the hard part isn't it?

Dr Carolyn Lam: Yeah, sadly.

Francesco?

Dr Francesco Sofi: We should say that most diets are similar background I mean in the backbone is similar so a dietary profile full of fruit and vegetables, complex carbohydrates, fiber, so the different things are meat and fish but with you can see in a regular consumption also Mediterranean diet of course, especially Mediterranean diet is beneficial for cardiovascular profile.

Dr. Wendy Post: Yeah, if we could get our patients in the United States to follow either the vegetarian or the Mediterranean diet that would be fabulous because they are obviously eating too much in the way of sugar sweetened beverages and deserts and fast food so just trying to follow either of these diets would be especially beneficial if it was a low fat vegetarian or Mediterranean diet. I think we need to get all our patients to be eating more fruits and vegetables, which is a key component of both of these diets and what they share in common, which often can lead to beneficial effects with weight loss due to the increased fiber and satiety and the healthful benefits of high fruit and vegetable diet.

Dr Carolyn Lam: Thank you so much.

Audience, thanks also for joining us. You've been listening to Circulation on the Run. Don't forget to tune in again next week.