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Effect of a Low-Fat Vegan Diet on Body Weight, Insulin Sensitivity, Postprandial Metabolism, and Intramyocellular and Hepatocellular Levels in Overweight Adults

A Randomized Clinical Trial

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Key Points

Question

What are the effects of a low-fat vegan diet on body weight, insulin resistance, postprandial metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults?

Findings

In this 16-week randomized clinical trial, a low-fat plant-based dietary intervention reduced bo weight by reducing energy intake and increasing postprandial metabolism, which was associate reductions in hepatocellular and intramyocellular fat and increased insulin sensitivity.

Meaning

A low-fat plant-based diet is an effective tool for reducing body weight and increasing insulin sensitivity and postprandial metabolism.

Abstract

Importance

Excess body weight and insulin resistance lead to type 2 diabetes and other major health proble There is an urgent need for dietary interventions to address these conditions.

Objective

To measure the effects of a low-fat vegan diet on body weight, insulin resistance, postprandial metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults.

Design, Setting, and Participants

This 16-week randomized clinical trial was conducted between January 2017 and February 201 Washington, DC. Of 3115 people who responded to flyers in medical offices and newspaper ar advertisements, 244 met the participation criteria (age 25 to 75 years; body mass index of 28 to after having been screened by telephone.

Interventions

Participants were randomized in a 1:1 ratio. The intervention group (n = 122) was asked to foll low-fat vegan diet and the control group (n = 122) to make no diet changes for 16 weeks.

Main Outcomes and Measures

At weeks 0 and 16, body weight was assessed using a calibrated scale. Body composition and fat were measured by dual x-ray absorptiometry. Insulin resistance was assessed with the home model assessment index and the predicted insulin sensitivity index (PREDIM). Thermic effect was measured by indirect calorimetry over 3 hours after a standard liquid breakfast (720 kcal). subset of participants (n = 44), hepatocellular and intramyocellular lipids were quantified by pr magnetic resonance spectroscopy. Repeated measure analysis of variance was used for statistic analysis.

Results

Among the 244 participants in the study, 211 (87%) were female, 117 (48%) were White, and (SD) age was 54.4 (11.6) years. Over the 16 weeks, body weight decreased in the intervention 5.9 kg (95% CI, 5.0-6.7 kg; $P < .001$). Thermic effect of food increased in the intervention grou 14.1% (95% CI, 6.5-20.4; $P < .001$). The homeostasis model assessment index decreased (−1.3 CI, −2.2 to −0.3; $P < .001$) and PREDIM increased (0.9; 95% CI, 0.5-1.2; $P < .001$) in the inter group. Hepatocellular lipid levels decreased in the intervention group by 34.4%, from a mean (

3.2% (2.9%) to 2.4% (2.2%) ($P = .002$), and intramyocellular lipid levels decreased by 10.4%, mean (SD) of 1.6 (1.1) to 1.5 (1.0) ($P = .03$). None of these variables changed significantly in t control group over the 16 weeks. The change in PREDIM correlated negatively with the chang weight ($r = -0.43$; $P < .001$). Changes in hepatocellular and intramyocellular lipid levels correl changes in insulin resistance (both $r = 0.51$; $P = .01$).

Conclusions and Relevance

A low-fat plant-based dietary intervention reduces body weight by reducing energy intake and increasing postprandial metabolism. The changes are associated with reductions in hepatocellu intramyocellular fat and increased insulin sensitivity.

Trial Registration

ClinicalTrials.gov Identifier: NCT02939638

Introduction

Overweight and associated diseases, particularly type 2 diabetes and metabolic syndrome, rem worldwide challenges. There is an urgent need for dietary interventions to address these proble for a better understanding of how different dietary interventions work.

Obesity is uncommon in individuals whose diets are based on plant-derived foods.[1,2] In clinica such diets caused weight loss, for which 2 explanations have been offered.[3] First, a high-fiber, diet has a low energy density, which reduces energy intake. Second, a low-fat, vegan diet incre thermic effect of food, which accounts for approximately 10% of total energy expenditure.[4] Hc in the latter randomized clinical trial, the control group was following an active diet based on N Cholesterol Education Program guidelines.[5] Because there was no untreated control group, the a low-fat vegan diet on thermogenesis remains unclear.

Studies have reported that people following a vegan diet have lower concentrations of intramy lipids compared with those following omnivorous diets, suggesting that by reducing intramyoc hepatocellular lipid levels, a plant-based diet may lead to increased mitochondrial activity and postprandial metabolism.[6,7] This is particularly important because the accumulation of lipids ir and liver cells may also be associated with insulin resistance and type 2 diabetes.[8,9,10] The aim study was to measure the effects of a low-fat vegan diet on body weight, insulin resistance, pos metabolism, and intramyocellular and hepatocellular lipid levels in overweight adults.

Methods

Study Design and Eligibility

This randomized clinical trial using a single-center, open parallel design was conducted betwe January 2017 and February 2019 in Washington, DC, in 4 replications (the trial protocol is giv Supplement 1). Adults aged 25 to 75 years with a body mass index (BMI) (calculated as weigh

kilograms divided by height in meters squared) of 28 to 40 were enrolled. Exclusion criteria w diabetes, smoking, alcohol or drug use, pregnancy or lactation, and current use of a vegan diet. additional exclusion criteria for the subset of participants undergoing the proton magnetic reso spectroscopy were the presence of any metal implant, claustrophobia, BMI higher than 38, and circumference of more than 102 cm. The study protocol was approved by the Chesapeake Insti Review Board. All participants gave written informed consent. This study followed the Consol Standards of Reporting Trials (CONSORT) reporting guideline.[11]

Randomization and Study Groups

With use of a computer-generated system, participants were randomly assigned (in a 1:1 ratio) intervention group, which was asked to follow a low-fat vegan diet, or a control group, which asked to make no diet changes. The randomization protocol could not be accessed by the partic the staff allocating the participants into groups beforehand. Because assignment was done simultaneously, allocation concealment was unnecessary. The participants were not blinded to group assignment.

The intervention diet (approximately 75% of energy from carbohydrates, 15% protein, and 10% consisted of vegetables, grains, legumes, and fruits without animal products or added fats. Vita was supplemented (500 μg/d). The intervention group attended weekly classes for detailed inst and cooking demonstrations and received printed materials and small food samples. No meals provided.

For both groups, alcoholic beverages were limited to 1 per day for women and 2 per day for m participants were asked to maintain their customary exercise habits and medications unless mo their personal physicians.

Outcomes

All measurements were performed at baseline and 16 weeks. The outcome assessors (K.F.P., C A.T.) were blinded to group assignment. The primary outcomes were body weight, insulin resi postprandial metabolism, and the concentrations of intramyocellular and hepatocellular lipids.

At baseline and at 16 weeks, dietary intake data over 3 consecutive days were collected and an by staff members certified in the Nutrition Data System for Research, version 2016, developed Nutrition Coordinating Center, University of Minnesota, Minneapolis.[12] In addition, study diet made unannounced telephone calls to assess participants' dietary adherence. All study particip asked not to alter their exercise habits and to continue their preexisting medication regimens fo duration of the study. Physical activity was assessed by the International Physical Activity Questionnaire.[13]

Laboratory assessments were made after an overnight fast. Height (baseline only) and weight v measured using a stadiometer and a calibrated digital scale, respectively. Body composition an visceral fat volume were assessed using dual energy x-ray absorptiometry (iDXA; GE Healthc

which has been validated against computed tomography[14] and magnetic resonance imaging.[15] measurement of total body fat and visceral fat had a coefficient of variation (CV) of 1.0% and respectively.[16,17]

Insulin secretion was assessed after a standardized liquid breakfast (Boost Plus, Nestle) (720 k of energy from fat, 16% protein, and 50% carbohydrate). Plasma glucose, immunoreactive insu C-peptide concentrations were measured at 0, 30, 60, 120, and 180 minutes. Plasma glucose concentration was analyzed using the Hexokinase UV end point method (the intra-assay CV w and the inter-assay CV was 1.9%), and immunoreactive insulin and C-peptide concentrations v determined using insulin and C-peptide electro-chemiluminescence immunoassay (the intra-as were 5.1% and 3.8%, respectively, and the inter-assay CVs were 5.7% and 3.9%, respectively) Glycated hemoglobin level was measured by turbidimetric inhibition immunoassay (the intra-a was 3.7%, and the inter-assay CV was 3.5%), and lipid concentrations were measured by enzy colorimetric methods (intra-assay CV: total cholesterol, 2.1%; high-density lipoprotein cholest 2.4%; low-density lipoprotein cholesterol, 2.0%; and triglycerides 2.2%; inter-assay CV: total cholesterol, 2.7%; high-density lipoprotein cholesterol, 3.8%; low-density lipoprotein cholest 3.0%; and triglycerides 3.2%). All test kits were made by Roche.

Insulin resistance was calculated using the homeostasis model assessment index.[18] The predict insulin sensitivity index (PREDIM) provided a validated measure of dynamic insulin sensitivit Resting energy expenditure and postprandial metabolism were measured by indirect calorimetr (Cosmed Quark CPET) using a ventilated hood system (accuracy of measurement with a CV< repeatability of measurement with a CV of 1.2%).[20,21] Each measurement was performed for 1 minutes after an overnight fast and 30, 60, 120, and 180 minutes after the standard breakfast.

In a subset of 44 participants (23 in the intervention group and 21 in the control group), proton magnetic resonance spectroscopy was performed at the Magnetic Resonance Research Center, School of Medicine. Hepatocellular and intramyocellular lipids were quantified by proton mag resonance spectroscopy at 4T (Bruker).[22] This method has been shown to provide a precise quantification of fat fractions, with a mean bias of −1.1% to 0.5%.[23] Hepatocellular lipid conte measured by ^{1}H respiratory-gated stimulated echo acquisition mode spectroscopy in a 15 × 15 mm^3 voxel. Acquisition was synchronized to the respiratory cycle and triggered at the end of expiration. A water-suppressed lipid spectrum and a lipid-suppressed water spectrum were acq 3 locations of the liver to account for liver inhomogeneity, and the total lipid content was avera calculated. In addition, hepatocellular lipid content was corrected for transverse relaxation usin transverse relaxation times of 22 ms for water and 44 ms for lipid.[24] Intramyocellular lipid con measured in the soleus muscle using an 8.5-cm diameter circular ^{13}C surface coil with twin, or circular 13-cm ^{1}H quadrature coils. Scout images of the lower leg were obtained to ensure corr positioning of the participant and to define an adequate volume for localized shimming using t FastMap procedure.[25]

Power Analysis

Sample size was based on the change in body weight, insulin resistance, and postprandial meta previously observed with a plant-based diet,[4] with an α level of 0.05. The assumed change for l weight was a mean (SD) of 5.8 (3.2) kg in the intervention arm and 1 (3.2) kg in the control arı insulin sensitivity, the assumed change was 1.1 (2.1) in the intervention arm and 0.1 (2.1) in th arm; and for the thermic effect of food, the assumed change was 4.7 (12) (area under the curve intervention arm and 0.3 (9.4) in the control arm. For the primary efficacy comparison, a total participants (11 per arm) were required for 90% power to detect a significant treatment effect c weight between the 2 study arms. For insulin sensitivity, a total of 142 participants (71 in each were required for 90% power. Assuming that the treatment effect for postprandial metabolism the same magnitude at each of the 5 evaluation points used in metabolic assessment and that th was approximately 10.85 points for all observations, with 5 observations per participant correla magnitude of 0.7 with each other, and assuming an attrition of 10%, the required sample size w per group (162 total) for 80% power and 108 per group (216 total) for 90% power.

For the substudy assessing the role of intramyocellular and hepatocellular lipids in insulin sens study[26] from 2012 provided a basis for a power analysis. In that study, 7 lean individuals with resistance followed a hypocaloric (1200 kcal/d) diet for 9 weeks. The mean (SD) intramyocellu level decreased from 1.1% (0.2%) to 0.8% (0.1%). Assuming a mean (SD) change in the intramyocellular lipid level of 0.3% (0.2%) in the intervention arm and a mean change of 0 wit similar SD in the control arm, to have 90% power to detect a difference of this magnitude betw 2 arms would each require 11 individuals (22 total). Because this was an exploratory substudy variability in response to the diet was largely unknown, 20 participants were recruited per arm of 40 participants).

Statistical Analysis

For baseline characteristics, between-group *t* tests were performed for continuous variables anc Fisher exact test for categorical variables. A repeated measure analysis of variance (ANOVA) was used with between-person and within-person factors and interactions, including group, per time. The interaction between group and time was calculated for each variable. For thermic eff food, minutes were included in the ANOVA model. Data from only individuals with measuren both time points were included in the ANOVA model. Within each group, paired comparison *t* were calculated to test whether the changes from baseline to 16 weeks were statistically signifi

To eliminate skewed data distribution and heteroscedasticity, data were transformed to a gauss distribution before further processing by a power transformation using the statistical software Statgraphics Centurion, version XV (Statpoint Inc). The transformed data underwent multivari regression using the method of orthogonal projections to latent structure.[27] This method is effe addressing severe multicollinearity within the matrix of independent variables. In our model, c thermic effect of food and in hepatocellular lipid levels were chosen as the dependent variables metabolic variables (body weight, fat mass, visceral fat, and insulin resistance) represented the independent variables. The variability was separated into 2 independent components. The pred component contained the variability in the metabolic variables, which was shared with changes

dependent variables, and the orthogonal component contained the variability shared within the metabolic variables. A detailed description of the orthogonal projections to latent structure mo available elsewhere.[28] The statistical software SIMCA-P, version 11.5 (Umetrics AB) identifie number of relevant components using the prediction error sum of squares and also allowed the of multivariable nonhomogeneities and testing for multivariable normal distribution and homoscedasticity (constant variance). The statisticians (M.H, R.H.) were blinded to the interve and group assignment. Results are presented as means with 95% CIs. Two-tailed tests were us determine significance at the 5% level.

Results

Participant Characteristics

Of 3115 people screened by telephone, 244 met the participation criteria, signed the consent fo were randomly assigned to the intervention (n = 122) or control (n = 122) groups in a 1:1 ratio Figure 1). The mean (SD) age of the intervention group was 53 (10) years compared with 57 (1 in the control group (P = .01) (eTable 1 in Supplement 2). There were no other significant diffe between the groups. Five intervention group and 16 control group participants dropped out, mo reasons unrelated to the study, leaving 222 (91.0%) individuals who completed the study. eTab Supplement 2 shows the baseline characteristics of those who completed the study and those w dropped out. There were no significant differences between these groups. The main outcomes reported in Table 1. The treatment effects were largely unaffected by the adjustment for age an race/ethnicity (eTable 4 in Supplement 2). eTable 3 in Supplement 2 shows the characteristics subgroup that underwent magnetic resonance spectroscopy. This group had a lower BMI comp with the rest of the study population. The model adjusted for baseline BMI for magnetic reson spectroscopy is presented in eFigure 2 in Supplement 2.

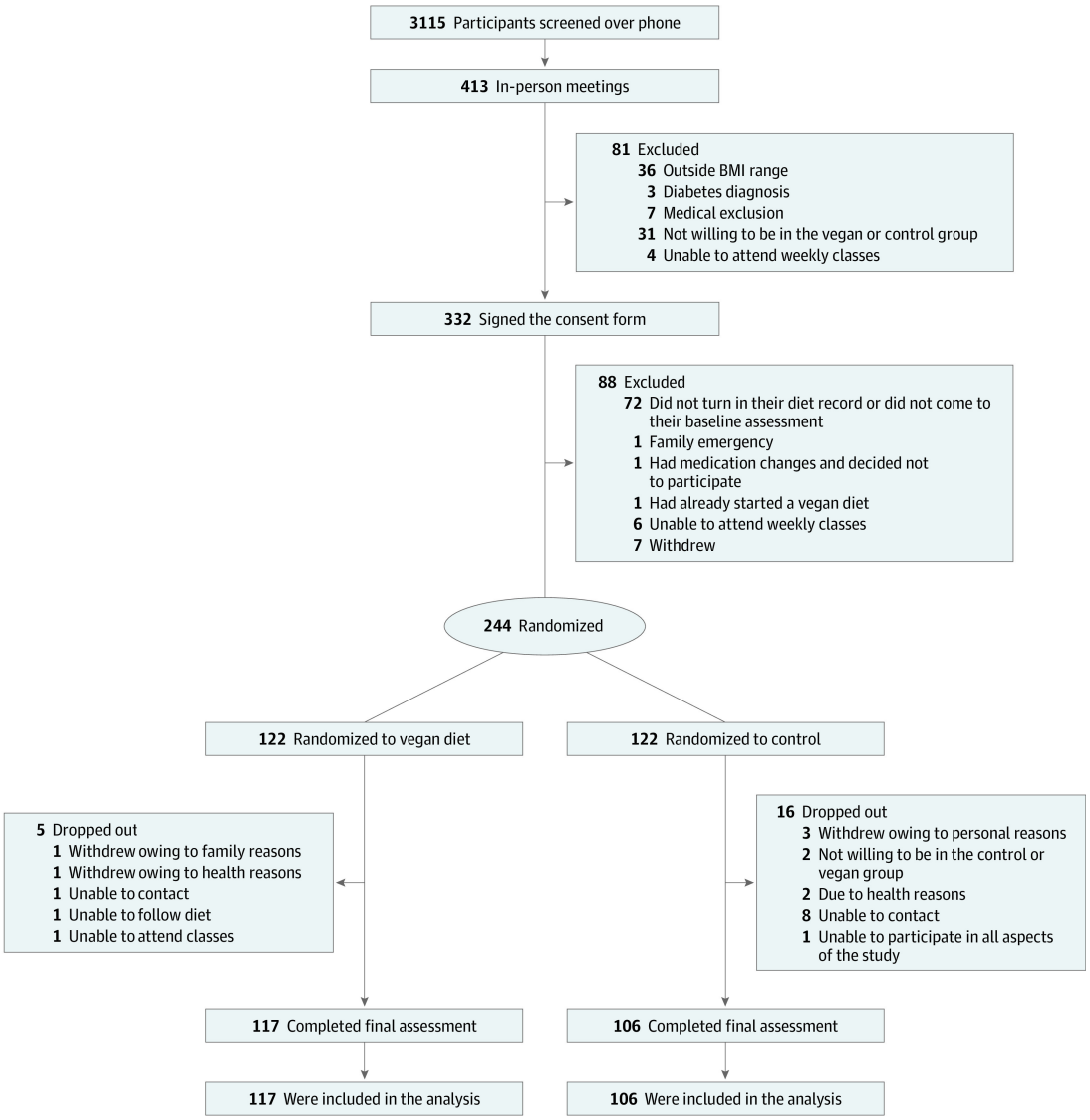

Figure 1.

CONSORT Diagram of Participant Flow Through Trial

Table 1.

Changes in Outcomes During the Study in the Low-Fat Vegan Dietary Intervention G vs the Control Group

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Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters square DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprot HOMA, homeostasis model assessment; LDL, low-density lipoprotein; METs, metabolic equivalents; PREI predicted insulin sensitivity index; VAT, visceral adipose tissue.

SI conversion factors: To convert plasma insulin level to μIU/mL, divide by 6.945; plasma glucose level to r divide by 0.0555; and lipid levels to mg/dL, divide by 0.0259.

[a]*P* values are for the interaction between group and time assessed by repeated measures analysis of variance.
[b]$P < .05$ for within-group changes from baseline assessed by paired comparison *t* tests.
[c]$P < .001$ for within-group changes from baseline assessed by paired comparison *t* tests.

Dietary Intake and Physical Activity

Self-reported energy intake decreased in both groups but more so in the intervention group (tre effect, −354.9 kcal/d; 95% CI, −519.0 to −190.8 kcal/d; $P < .001$) (Table 2). In the intervention mean intakes of carbohydrate and fiber increased, whereas mean fat, protein, and cholesterol ir decreased. These values did not change significantly in the control group. Physical activity dec slightly in both groups (−709.8 metabolic equivalents [95% CI, −1346 to −73.9 metabolic equi in the control group and −604.8 metabolic equivalents [95% CI, −1388 to −178.6 metabolic equivalents] in the intervention group; between-group $P = .84$).

Table 2.

Relationship Between Changes in Thermic Effect of Food and the First Predictive Component as Evaluated by the OPLS Model

Variable	OPLS predictive component				Multiple regression	
	Component loading[a]	*t* Statistic	R^b	*P* value for *R*	Regression coefficient	*t* Stat
Matrix X						
Baseline BMI	0.191	2.46	0.209	<.05	−0.015	−0.3
Baseline fat mass	0.256	2.89	0.283	<.05	−0.014	−0.2
Baseline TEF	−0.850	−11.96	−0.938	.005	−0.505	−5.6
Change in PREDIM	0.324	2.41	0.359	<.05	0.105	1.37
Change in fat mass	−0.271	−2.59	−0.301	<.05	−0.122	−1.5
Matrix Y						
Change in TEF	1.000	5.27	0.540	.003	NA	NA

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Abbreviations: BMI, body mass index; NA, not applicable; OPLS, orthogonal projections to latent structure; PREDIM, predicted insulin sensitivity index; TEF, thermic effect of food.

[a]The explained variability was 29.2% (24.3% after cross-validation).
[b]Component loadings expressed as a correlation coefficients with predictive component.

Body Weight, Body Composition, and Blood Lipid Levels

Mean body weight decreased by 6.4 kg in the intervention group compared with 0.5 kg in the c group (treatment effect, −5.9 kg; 95% CI, −6.7 to −5.0; interaction between group and time, *P* · This difference was largely attributable to a reduction in body fat, as noted by significant decre fat mass and visceral fat volume in the intervention group participants. Total and low-density lipoprotein cholesterol levels decreased by 0.5 mmol/L and 0.4 mmol/L (to convert to milligra deciliter, divide by 0.0259), respectively, in the intervention group, with no significant changes control group (0.1 mmol/L and 0.07 mmol/L, respectively) ($P < .001$ for both).

Insulin Sensitivity

Fasting plasma insulin concentration decreased by 21.6 pmol/L (to convert to micro-IU per mil divide by 6.945) in the intervention group, with no significant change in the control group (23. pmol/L; 95% CI, −5.0 to 54.3; between-group $P = .006$). The homeostasis model assessment in measure of insulin resistance) decreased significantly (−1.3; 95% CI, −2.2 to −0.3; $P < .001$), a PREDIM (a measure of insulin sensitivity) increased significantly in the intervention group (0. CI, 0.5-1.2; $P < .001$); neither changed significantly in the control group (Table 2). Within the intervention group, the change in PREDIM correlated negatively with the change in body weig −0.43; $P < .001$).

Postprandial Metabolism

Postprandial energy expenditure (the thermic effect of food) increased by 18.7% (95% CI, 4.4% in the intervention group from baseline to 16 weeks and did not change significantly in the con group (14.1%; 95% CI, 6.5%-20.4%) (interaction between group and time, $P < .001$) (Figure 2. F values were as follows: group, $F = 1.7$ ($P = .19$); week, $F = 15.4$ ($P < .001$); time, $F = 122.4$ ($< .001$); group × week, $F = 11.9$ ($P < .001$); group × time, $F = 1.1$ ($P = .35$); week × time, $F = 1.$ $= .25$). The results were similar in models adjusted for age and race/ethnicity (eFigure 1 in Sup 2). Within the intervention group, the change in thermic effect of food did not correlate signific with changes in body weight ($r = −0.15$; $P = .09$), PREDIM ($r = 0.06$; $P = .54$), energy intake (r $P = .90$), or fiber consumption ($r = 0.07$; $P = .48$). In both groups combined, changes in thermic food correlated negatively with changes in fat mass ($r = −0.30$; $P < .05$) and positively with cha PREDIM ($r = 0.36$; $P < .05$). That is, as fat mass decreased and insulin sensitivity improved, postprandial metabolism increased (Table 2).

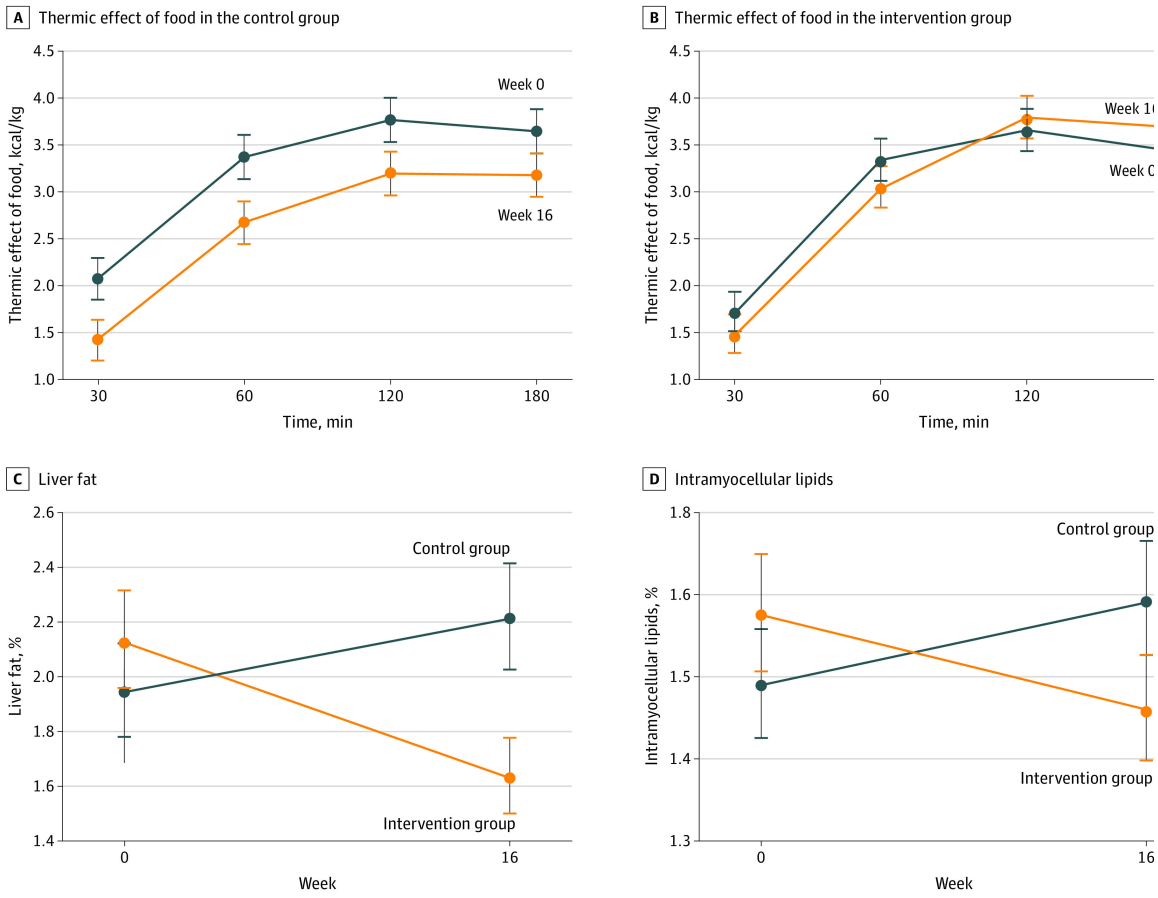

Figure 2.

Changes in the Thermic Effect of Food, Liver Fat, and Intramyocellular Lipid Levels in the Intervention and Control Groups

Whiskers represent 95% CIs.

A linear regression model for changes in reported energy intake and body weight showed that 100 kcal/d change in energy intake was associated with a 0.15 kg change in body weight (eFig Supplement 2). The mean (SD) reported energy reduction of 355 (617) kcal in the intervention compared with the control group would therefore be associated with a mean (SD) weight loss (4.4) kg. For changes in postprandial energy expenditure and body weight, every change in pos energy expenditure of 10 000 U in area under the curve was associated with a change in body 0.48 kg (eFigure 3 in Supplement 2). The mean (SD) decrease in postprandial energy expendit 8588 (34 020) U of area under the curve was associated with an mean (SD) weight loss of 0.41

Hepatocellular and Intramyocellular Lipid Levels

In the 44 participants for whom hepatocellular and intramyocellular lipid levels were quantifie baseline hepatocellular lipid content was generally in the normal range.[29,30] Nonetheless, hepat lipid content decreased in the intervention group by 34.4% (from a mean [SD] of 3.2% [2.9%] [2.2%]; $P = .03$) and remained unchanged in the control group (from a mean [SD] of 3.3% [4.3 3.6% [4.7%]) (group, $F = 3.1$ [$P = .09$]; week, $F = 1.27$ [$P = .27$]; group × week, $F = 10.8$ [$P = .$ Figure 2B). Results were similar in models adjusted for age and race/ethnicity (eFigure 1 in Su 2) and for baseline BMI (eFigure 2 in Supplement 2).

Within the intervention group, the decrease in hepatocellular lipid levels was significantly asso with change in body weight ($r = 0.42$; $P = .04$) but not with changes in reported energy intake ($P = .27$) or fiber consumption ($r = 0.07$; $P = .76$). In both groups combined, changes in hepatoc lipid levels correlated negatively with changes in PREDIM ($r = −0.47$; $P < .05$). That is, as hepatocellular lipid level decreased, insulin sensitivity increased. Changes in hepatocellular lip correlated positively with changes in body weight ($r = 0.91$; $P < .01$), BMI ($r = 0.90$; $P < .01$), f ($r = 0.91$; $P < .01$), and visceral fat ($r = 0.80$; $P < .01$) (Table 3).

Table 3.

Relationship Between Changes in Liver Fat and the First Predictive Component as Evaluated by OPLS Model

Variable	OPLS predictive component				Multiple regression		
	Component loading[a]	*t* Statistic	*R*[b]	*P* value for *R*	Regression coefficient	*t* Statistic	*P* va for
Matrix X							
Control group	0.339	9.88	0.795	.004	0.069	3.69	.007
Intervention group	−0.339	−9.88	−0.795	.004	−0.069	−3.69	.007
Baseline PREDIM	0.214	8.89	0.498	.003	0.038	4.99	.005
Baseline HOMA	−0.218	−2.71	−0.509	<.05	−0.060	−2.07	<.05
Baseline weight	−0.228	−2.18	−0.535	<.05	−0.065	−2.19	<.05
Baseline fat mass	−0.221	−2.18	−0.518	<.05	−0.058	−2.42	<.05
Change in PREDIM	−0.199	−2.35	−0.468	<.05	−0.021	−2.54	<.05
Change in weight	0.388	14.13	0.910	.005	0.079	5.47	.005
Change in BMI	0.384	13.92	0.901	.005	0.077	5.64	.003
Change in fat mass	0.389	21.06	0.911	.002	0.078	5.87	.006
Change in visceral fat	0.341	8.23	0.798	.007	0.060	2.63	<.05
Matrix Y							
Change in liver fat	1.000	4.66	0.495	.009	NA	NA	NA

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Abbreviations: BMI, body mass index; HOMA, homeostasis model assessment; OPLS, orthogonal projectio latent structure; NA, not applicable; PREDIM, predicted insulin sensitivity index.

[a]Explained variability was 24.5% (20.8% after cross-validation).
[b]Component loadings expressed as a correlation coefficients with predictive component.

Changes in intramyocellular lipid levels were not statistically significant in within-group comp but owing to the opposite trends, the treatment effect was significantly decreased in the interve group by 10.4%, from a mean (SD) of 1.6 (1.1) to 1.5 (1.0) ($P = .03$) (group, $F = 4.7$ [$P = .04$]; = 0.02 [$P = .88$]; group × week, $F = 5.1$ [$P = .03$]) (Figure 1C). Within the intervention group (r changes in both hepatocellular and intramyocellular lipid levels correlated with changes in insu resistance, as measured by the homeostasis model assessment index (both $r = 0.51$; $P = .01$). In groups combined, changes in intramyocellular lipid levels correlated positively with changes ir mass ($r = 0.51$; $P < .05$) and homeostasis model assessment index score ($r = 0.52$; $P < .05$). Tha fat mass decreased, intramyocellular lipid levels and insulin resistance decreased.

Discussion

In this trial, the dietary intervention reduced body weight, apparently owing to its tendency to r energy intake and increase postprandial energy expenditure. The intervention also improved gl control and reduced insulin concentrations, owing in part to reduced lipid accumulation in liver muscle cells and thus reduced insulin resistance in these organs.

The intervention diet's effect on weight and insulin action are clinically important. Hepatocellu intramyocellular lipids play central roles in hepatic and muscle insulin resistance, respectively, type 2 diabetes. A 16-week diet of 1200 kcal per day resulted in a moderate weight loss of approximately 8 kg, which was sufficient to normalize liver lipid content and fasting plasma gl concentrations as well as reverse hepatic insulin resistance in patients with obesity and type 2 diabetess.[31] A potential mechanism explaining the improvement in insulin sensitivity is the red intracellular diacylglycerol levels, which reduce insulin signaling in liver and muscle, leading t specific insulin resistance.[22,32,33]

The effects of the dietary intervention on hepatocellular and intramyocellular lipid levels and ir sensitivity—the presumed basis for the improved glycemic control—has not previously been q in clinical trials. Energy restriction has been shown to reduce intramyocellular and hepatocellu levels and improve glycemic control in healthy young individuals without diabetes.[26,34,35] In yo lean individuals with insulin resistance, a hypocaloric diet (approximately 1200 kcal) led to a r weight loss of 4.1 kg and a 30% reduction of intramyocellular lipids during a 9-week intervent contrast, the intervention diet in the present study did not restrict energy intake but nonetheless 34% and 10% reductions in hepatocellular and intramyocellular lipid levels, respectively. The reductions in hepatocellular and intramyocellular lipid levels correlated with the reduction in fa consistent with prior studies.[26,36,37]

The present finding that the increase in thermic effect of food was associated with decreased fa and increased insulin sensitivity confirm the findings of previous research.[38,39] The increased i sensitivity may have contributed to the increased postprandial metabolism. In addition, increas postprandial metabolism may have promoted further reduction in fat mass and an increase in ir sensitivity.

Despite the ad libitum diet, the participants in the intervention group reduced their energy intak consistent with many previous trials using vegan diets. This not only contributes to weight loss may have contributed to the decrease in hepatocellular triglyceride content.[31]

Postprandial metabolism is influenced by meal composition.[40,41,42,43] In the present study, how test meal was identical for all study phases. These results suggest that the increased postprandi thermogenesis was attributable to improved insulin sensitivity.

Strengths and Limitations

This study has several strengths. The randomized parallel design in which all participants withi cohort began the study simultaneously controlled for seasonal diet fluctuations. The study dura provided sufficient time for adaptation to the diet. Physiologic stimulation by a standard mixed permitted quantification of insulin sensitivity and insulin secretion during a physiologic perturb Measurement of visceral, hepatocellular, and intramyocellular lipid levels, in addition to the de assessment of the thermic effect of food, are also strengths. The low attrition suggests that the intervention was acceptable.

The study also has limitations. Self-reports of dietary intake have well-known limitations.[44] Hc is reassuring that the reported diet changes were paralleled by changes in weight and plasma lip levels. Health-conscious participants may not be representative of the general population but m representative of a clinical population seeking help for weight problems or type 2 diabetes. We followed the participants for 16 weeks and were not able to estimate the effects of the diet over period. In addition, the study design did not allow separation of the specific effects of the low-f diet from the weight loss it causes.

Conclusions

This randomized clinical trial found that a low-fat plant-based dietary intervention reduces bod by reducing energy intake and increasing postprandial metabolism, apparently owing to increas insulin sensitivity resulting from reduced hepatocellular and intramyocellular fat. This interven be an effective treatment for overweight adults.

Notes

Supplement 1.

Trial Protocol

Click here for additional data file.(414K, pdf)

Supplement 2.

eTable 1. Baseline characteristics of the study population

eTable 2. Baseline characteristics of the study population, comparing study completers and drop-outs

eTable 3. Baseline characteristics of the study population, comparing the subsample under magnetic resonance spectroscopy (MRS) with the rest of the study population

eTable 4. Treatment effects for the main outcomes, adjusted for age and race

eFigure 1. Changes in the thermic effect of food, liver fat, and intramyocellular lipids after adjustment for race and age

eFigure 2. Changes in liver fat and intramyocellular lipids after adjustment for baseline BM

eFigure 3. Linear regression model for changes in energy and body weight and postprandia energy expenditure and body weight

Click here for additional data file.(319K, pdf)

Supplement 3.

Data Sharing Statement

Click here for additional data file.(21K, pdf)

References

1. Qian F, Liu G, Hu FB, Bhupathiraju SN, Sun Q. Association between plant-based dietary pa and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA Intern Med*. 2019. doi:10.1001/jamainternmed.2019.2195 [PMC free article] [PubMed] [CrossRef] [Google Scho

2. Tonstad S, Butler T, Yan R, Fraser GE. Type of vegetarian diet, body weight, and prevalenc 2 diabetes. *Diabetes Care*. 2009;32(5):791-796. doi:10.2337/dc08-1886 [PMC free article] [Pu [CrossRef] [Google Scholar]

3. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in weight in clinical trials of vegetarian diets. *J Acad Nutr Diet*. 2015;115(6):954-969. doi:10.1016/j.jand.2014.11.016 [PubMed] [CrossRef] [Google Scholar]

4. Barnard ND, Scialli AR, Turner-McGrievy G, Lanou AJ, Glass J. The effects of a low-fat, p based dietary intervention on body weight, metabolism, and insulin sensitivity. *Am J Med*. 200 (9):991-997. doi:10.1016/j.amjmed.2005.03.039 [PubMed] [CrossRef] [Google Scholar]

5. National Cholesterol Education Program Summary of the second report of the National Cho Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blo Cholesterol in Adults (Adult Treatment Panel II). *JAMA*. 1993;269(23):3015-3023. doi:10.1001/jama.1993.03500230097036 [PubMed] [CrossRef] [Google Scholar]

6. Goff LM, Bell JD, So P-W, Dornhorst A, Frost GS. Veganism and its relationship with insu resistance and intramyocellular lipid. *Eur J Clin Nutr*. 2005;59(2):291-298. doi:10.1038/sj.ejcn.1602076 [PubMed] [CrossRef] [Google Scholar]

7. Gojda J, Patková J, Jaček M, et al. . Higher insulin sensitivity in vegans is not associated wit mitochondrial density. *Eur J Clin Nutr*. 2013;67(12):1310-1315. doi:10.1038/ejcn.2013.202 [P [CrossRef] [Google Scholar]

8. Itani SI, Ruderman NB, Schmieder F, Boden G. Lipid-induced insulin resistance in human m associated with changes in diacylglycerol, protein kinase C, and IkappaB-alpha. *Diabetes*. 200 (7):2005-2011. doi:10.2337/diabetes.51.7.2005 [PubMed] [CrossRef] [Google Scholar]

9. Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with i resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr*. 2000;71(4):885-892. doi:10.1093/ajcn/71.4.885 [PubMed] [CrossRef] [Google Scholar]

10. Yatsuya H, Nihashi T, Li Y, et al. . Independent association of liver fat accumulation with resistance. *Obes Res Clin Pract*. 2014;8(4):e350-e355. doi:10.1016/j.orcp.2013.08.002 [PubM [CrossRef] [Google Scholar]

11. Schulz KF, Altman DG, Moher D; CONSORT Group . CONSORT 2010 statement: update guidelines for reporting parallel group randomised trials. *BMC Med*. 2010;8(1):18. doi:10.118 7015-8-18 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

12. Schakel SF, Sievert YA, Buzzard IM. Sources of data for developing and maintaining a nu database. *J Am Diet Assoc*. 1988;88(10):1268-1271. [PubMed] [Google Scholar]

13. Hagströmer M, Oja P, Sjöström M. The International Physical Activity Questionnaire (IPA study of concurrent and construct validity. *Public Health Nutr*. 2006;9(6):755-762. doi:10.1079/PHN2005898 [PubMed] [CrossRef] [Google Scholar]

14. Kaul S, Rothney MP, Peters DM, et al. . Dual-energy X-ray absorptiometry for quantificati visceral fat. *Obesity (Silver Spring)*. 2012;20(6):1313-1318. doi:10.1038/oby.2011.393 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

15. Neeland IJ, Grundy SM, Li X, Adams-Huet B, Vega GL. Comparison of visceral fat mass measurement by dual-X-ray absorptiometry and magnetic resonance imaging in a multiethnic c the Dallas Heart Study. *Nutr Diabetes*. 2016;6(7):e221. doi:10.1038/nutd.2016.28 [PMC free a [PubMed] [CrossRef] [Google Scholar]

16. Mellis MG, Oldroyd B, Hind K. In vivo precision of the GE Lunar iDXA for the measuren visceral adipose tissue in adults: the influence of body mass index. *Eur J Clin Nutr*. 2014;68(1 1367. doi:10.1038/ejcn.2014.213 [PubMed] [CrossRef] [Google Scholar]

17. Carver TE, Christou NV, Andersen RE. In vivo precision of the GE iDXA for the assessme total body composition and fat distribution in severely obese patients. *Obesity (Silver Spring)*. (7):1367-1369. doi:10.1002/oby.20323 [PubMed] [CrossRef] [Google Scholar]

18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasi assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412-419. doi:10.1007/BF00280883 [PubMed [CrossRef] [Google Scholar]

19. Tura A, Chemello G, Szendroedi J, et al. . Prediction of clamp-derived insulin sensitivity fi oral glucose insulin sensitivity index. *Diabetologia*. 2018;61(5):1135-1141. doi:10.1007/s0012 4568-4 [PubMed] [CrossRef] [Google Scholar]

20. Kaviani S, Schoeller DA, Ravussin E, et al. . Determining the accuracy and reliability of in calorimeters utilizing the methanol combustion technique. *Nutr Clin Pract*. 2018;33(2):206-21 doi:10.1002/ncp.10070 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

21. Blond E, Maitrepierre C, Normand S, et al. A new indirect calorimeter is accurate and relia measuring basal energy expenditure, thermic effect of food and substrate oxidation in obese an subjects. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism 2011;6(1):e7–(doi:10.1016/j.eclnm.2010.12.001 [CrossRef]

22. Petersen KF, Dufour S, Feng J, et al. . Increased prevalence of insulin resistance and nonal fatty liver disease in Asian-Indian men. *Proc Natl Acad Sci U S A*. 2006;103(48):18273-18277 doi:10.1073/pnas.0608537103 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

23. Lee SS, Lee Y, Kim N, et al. . Hepatic fat quantification using chemical shift MR imaging spectroscopy in the presence of hepatic iron deposition: validation in phantoms and in patients chronic liver disease. *J Magn Reson Imaging*. 2011;33(6):1390-1398. doi:10.1002/jmri.22583 [PubMed] [CrossRef] [Google Scholar]

24. Rabøl R, Petersen KF, Dufour S, Flannery C, Shulman GI. Reversal of muscle insulin resis with exercise reduces postprandial hepatic de novo lipogenesis in insulin resistant individuals. *Natl Acad Sci U S A*. 2011;108(33):13705-13709. doi:10.1073/pnas.1110105108 [PMC free ar [PubMed] [CrossRef] [Google Scholar]

25. Gruetter R. Automatic, localized in vivo adjustment of all first- and second-order shim coil
Reson Med. 1993;29(6):804-811. doi:10.1002/mrm.1910290613 [PubMed] [CrossRef]
[Google Scholar]

26. Petersen KF, Dufour S, Morino K, Yoo PS, Cline GW, Shulman GI. Reversal of muscle in
resistance by weight reduction in young, lean, insulin-resistant offspring of parents with type 2
Proc Natl Acad Sci U S A. 2012;109(21):8236-8240. doi:10.1073/pnas.1205675109 [PMC free
[PubMed] [CrossRef] [Google Scholar]

27. Trygg J, Holmes E, Lundstedt T. Chemometrics in metabonomics. *J Proteome Res*. 2007;6
479. doi:10.1021/pr060594q [PubMed] [CrossRef] [Google Scholar]

28. Sosvorova L, Hill M, Mohapl M, Vitku J, Hampl R. Steroid hormones in prediction of nor
pressure hydrocephalus. *J Steroid Biochem Mol Biol*. 2015;152:124-132.
doi:10.1016/j.jsbmb.2015.05.004 [PubMed] [CrossRef] [Google Scholar]

29. Romeo S, Kozlitina J, Xing C, et al. . Genetic variation in PNPLA3 confers susceptibility t
nonalcoholic fatty liver disease. *Nat Genet*. 2008;40(12):1461-1465. doi:10.1038/ng.257
[PMC free article] [PubMed] [CrossRef] [Google Scholar]

30. Szczepaniak LS, Nurenberg P, Leonard D, et al. . Magnetic resonance spectroscopy to mea
hepatic triglyceride content: prevalence of hepatic steatosis in the general population. *Am J Ph*
Endocrinol Metab. 2005;288(2):E462-E468. doi:10.1152/ajpendo.00064.2004 [PubMed] [Cros
[Google Scholar]

31. Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalc
hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction i
patients with type 2 diabetes. *Diabetes*. 2005;54(3):603-608. doi:10.2337/diabetes.54.3.603
[PMC free article] [PubMed] [CrossRef] [Google Scholar]

32. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. *Physiol Re*
2018;98(4):2133-2223. doi:10.1152/physrev.00063.2017 [PMC free article] [PubMed] [CrossR
[Google Scholar]

33. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing
Cell. 2012;148(5):852-871. doi:10.1016/j.cell.2012.02.017 [PMC free article] [PubMed] [Cros
[Google Scholar]

34. Lara-Castro C, Newcomer BR, Rowell J, et al. . Effects of short-term very low-calorie diet
intramyocellular lipid and insulin sensitivity in nondiabetic and type 2 diabetic subjects. *Metab*
2008;57(1):1-8. doi:10.1016/j.metabol.2007.05.008 [PMC free article] [PubMed] [CrossRef]
[Google Scholar]

35. Jazet IM, Schaart G, Gastaldelli A, et al. . Loss of 50% of excess weight using a very low e diet improves insulin-stimulated glucose disposal and skeletal muscle insulin signalling in obes insulin-treated type 2 diabetic patients. *Diabetologia*. 2008;51(2):309-319. doi:10.1007/s00125 0862-2 [PubMed] [CrossRef] [Google Scholar]

36. Sinha R, Dufour S, Petersen KF, et al. . Assessment of skeletal muscle triglyceride content nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insuli sensitivity, total body fat, and central adiposity. *Diabetes*. 2002;51(4):1022-1027. doi:10.2337/diabetes.51.4.1022 [PubMed] [CrossRef] [Google Scholar]

37. Moro C, Galgani JE, Luu L, et al. . Influence of gender, obesity, and muscle lipase activity intramyocellular lipids in sedentary individuals. *J Clin Endocrinol Metab*. 2009;94(9):3440-34 doi:10.1210/jc.2009-0053 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

38. Camastra S, Bonora E, Del Prato S, Rett K, Weck M, Ferrannini E; EGIR (European Grou Study of Insulin Resistance) . Effect of obesity and insulin resistance on resting and glucose-in thermogenesis in man. *Int J Obes Relat Metab Disord*. 1999;23(12):1307-1313. doi:10.1038/sj.ijo.0801072 [PubMed] [CrossRef] [Google Scholar]

39. Ravussin E, Acheson KJ, Vernet O, Danforth E, Jéquier E. Evidence that insulin resistance responsible for the decreased thermic effect of glucose in human obesity. *J Clin Invest*. 1985;7 (3):1268-1273. doi:10.1172/JCI112083 [PMC free article] [PubMed] [CrossRef] [Google Schc

40. Bowden VL, McMurray RG. Effects of training status on the metabolic responses to high carbohydrate and high fat meals. *Int J Sport Nutr Exerc Metab*. 2000;10(1):16-27. doi:10.1123/ijsnem.10.1.16 [PubMed] [CrossRef] [Google Scholar]

41. Nagai N, Sakane N, Moritani T. Metabolic responses to high-fat or low-fat meals and asso with sympathetic nervous system activity in healthy young men. *J Nutr Sci Vitaminol (Tokyo)*. (5):355-360. doi:10.3177/jnsv.51.355 [PubMed] [CrossRef] [Google Scholar]

42. Thyfault JP, Richmond SR, Carper MJ, Potteiger JA, Hulver MW. Postprandial metabolisn resistance-trained versus sedentary males. *Med Sci Sports Exerc*. 2004;36(4):709-716. doi:10.1249/01.MSS.0000121946.98885.F5 [PubMed] [CrossRef] [Google Scholar]

43. Barr SB, Wright JC. Postprandial energy expenditure in whole-food and processed-food m implications for daily energy expenditure. *Food Nutr Res*. 2010;54:54. doi:10.3402/fnr.v54i0.5 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

44. Yuan C, Spiegelman D, Rimm EB, et al. . Relative validity of nutrient intakes assessed by questionnaire, 24-hour recalls, and diet records compared with urinary recovery and plasma concentration biomarkers: findings for women. *Am J Epidemiol*. 2017. doi:10.1093/aje/kww10 [PMC free article] [PubMed] [CrossRef] [Google Scholar]