PREDIMED PUBLICATIONS WITH NUT COHORT

*Walnuts are a traditional component in the Mediterranean diet and a key ingredient in the landmark Prevencion con DietaMediterranea (PREDIMED) study: a multicenter, randomized, primary prevention trial of cardiovascular disease funded by Instituto de Salud Carlos III (ISCIII), Spanish Health Ministry through Instituto de Salud Carlos III funds the PREDIMED trial through the research networks CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn) and RTIC RD 06/0045. Participants in the study (nearly 7500 people at high cardiovascular risk) were randomized to three intervention arms: a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with one ounce mixed nuts (one-half ounce walnuts) and a control low-fat diet. The study began in 2003 and was completed in 2011 after an average follow-up of 5 years. To share from the primary publication, "**In conclusion, in this primary prevention trial, we observed that an energy-unrestricted Mediterranean diet, supplemented with extra-virgin olive oil or nuts, resulted in a substantial reduction in the risk of major cardiovascular events among high-risk persons. The results support the benefits of the Mediterranean diet for the primary prevention of cardiovascular disease".** The California Walnut Commission provided walnuts for this important study.*

2013

Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, and Martínez-González MA, for the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. February 25, 2013DOI: 10.1056/ *NEJM* oa1200303.

Abstract: Background Observational cohort studies and a secondary prevention trial have shown an inverse association between adherence to the Mediterranean diet and cardiovascular risk. We conducted a randomized trial of this diet pattern for the primary prevention of cardiovascular events. Methods In a multicenter trial, we randomly assigned participants who were at high cardiovascular risk, but with no cardiovascular disease at enrollment, to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advice to reduce dietary fat). Participants received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil, mixed nuts, or small nonfood gifts. The primary end point was the rate of major cardiovascular events (myocardial infarction, stroke, or death from cardiovascular causes). On the basis of the results of an interim analysis, the trial was stopped after a median follow-up of 4.8 years. Results A total of 7447 persons were enrolled (age range, 55 to 80 years); 57% were women. The two Mediterranean-diet groups had good adherence to the intervention, according to self-reported intake and biomarker analyses. A primary end-point event occurred in 288 participants. The multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI], 0.54 to 0.92) and 0.72 (95% CI, 0.54 to 0.96) for the group assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). No diet-related adverse effects were reported. Conclusions Among persons at high cardiovascular risk, a Mediterranean diet supplemented with extra-virgin olive oil or nuts reduced the incidence of major cardiovascular events.

Ibarrola-Jurado N, Bullo M, Guasch-Ferre M, Ros E,Martı´nez- Gonzalez MA, Corella D, Fiol M, Warnberg J, Estruch R, Roman P, Aros F, Vinyoles E, Serra-Majem L, Pinto´ X, Covas MI, Basora J, Salas-Salvado J, on behalf of the PREDIMED Study Investigators. Cross-Sectional Assessment of Nut Consumption and Obesity,

Metabolic Syndrome and Other Cardiometabolic Risk Factors: The PREDIMED Study. *PLoS One.* 2013;8(2):e57367.

Abstract: Introduction: Prospective studies have consistently suggested that nut consumption is inversely related to fatal and nonfatal coronary heart disease. Limited data are available on the epidemiological associations between nut intake and cardiometabolic risk factors. Objective: To evaluate associations between frequency of nut consumption and prevalence of cardiometabolic risk factors [obesity, metabolic syndrome (MetS), type-2 diabetes, hypertension, and dyslipidemia] in a Mediterranean population at high cardiovascular risk. Materials and Methods: Cross-sectional study of 7,210 men and women (mean age, 67 y) recruited into the PREDIMED study. MetS was defined by the harmonized ATPIII and IDF criteria. Diabetes and hypertension were assessed by clinical diagnosis and dyslipidemia (high triglycerides, low HDL-cholesterol, and hypercholesterolemia) by lipid analyses. Nut consumption was assessed using a validated food frequency questionnaire and categorized as ,1, 1–3, and .3 servings/ wk. Control of confounding was done with multivariate logistic regression. Results: Compared to participants consuming ,1 serving/wk of nuts, those consuming .3 servings/wk had lower adjusted odds ratios (OR) for obesity (0.61, 95% confidence interval 0.54 to 0.68; P-trend ,0.001), MetS (0.74, 0.65 to 0.85; Ptrend, 0.001), and diabetes (0.87, 0.78 to 0.99; P-trend = 0.043). Higher nut consumption was also associated with lower risk of the abdominal obesity MetS criterion (OR 0.68, 0.60 to 0.79; P-trend,0.001). No significant associations were observed for the MetS components high blood pressure, dyslipidemia, or elevated fasting glucose. Conclusions: Nut consumption was inversely associated with the prevalence of general obesity, central obesity, MetS, and diabetes in subjects at high cardiovascular risk.

Tresserra-Rimbau A, Medina-Remón A, Pérez-Jiménez J, Martínez-González MA, Covas MI, Corella D, Salas-Salvadó J, Gómez-Gracia E, Lapetra J, Arós F, Fiol M, Ros E, Serra-Majem L, Pintó X, Muñoz MA, Saez GT, Ruiz-Gutiérrez V, Warnberg J, Estruch R, Lamuela-Raventós RM. Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: The PREDIMED study. *Nutr Metab Cardiovasc Dis*. 2013 Jan 16. pii: S0939-4753(12)00245-1. doi: 10.1016/j.numecd.2012.10.008.

Abstract: BACKGROUND AND AIMS: Epidemiological data have shown an inverse association between the consumption of polyphenol-rich foods and the risk of cardiovascular disease or overall mortality. A comprehensive estimation of individual polyphenol intake in nutritional cohorts is needed to gain a better understanding of this association. The aim of this study was to estimate the quantitative intake of polyphenols and the major dietary sources in the PREDIMED (PREvención con DIeta MEDiterránea) cohort using individual food consumption records. METHODS AND RESULTS: The PREDIMED study is a large, parallel-group, multicentre, randomised, controlled 5-year feeding trial aimed at assessing the effects of the Mediterranean diet on the primary prevention of cardiovascular disease. A total of 7200 participants, aged 55-80 years, completed a validated 1-year food frequency questionnaire (FFQ) at baseline. Polyphenol consumption was calculated by matching food consumption data from the FFQ with the recently developed Phenol-Explorer database on polyphenol content in foods. The mean total polyphenol intake was 820 ± 323 mg day(-1) (443 ± 218 mg day(-1) of flavonoids and 304 ± 156 mg day(-1) of phenolic acids). Hydroxycinnamic acids were the phenolic group with the highest consumption and 5-caffeoylquinic acid was the most abundantly ingested individual polyphenol. The consumption of olives and olive oil was a differentiating factor in the phenolic profile of this Spanish population compared with other countries. CONCLUSION: In Mediterranean countries, such as Spain, the main dietary source of polyphenols is coffee and fruits, but the most important differentiating factor with respect to other countries is the consumption of polyphenols from olives and olive oil.

2012

Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D, Covas MI, Schröder H, Arós F, Gómez-Gracia E, Fiol M, Ruiz-Gutiérrez V, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Muñoz MA, Wärnberg J, Ros E, Estruch R; PREDIMED Study Investigators. A 14-item Mediterranean diet assessment tool and obesity indexes among high-risk subjects: the PREDIMED trial. PLoS One. 2012;7(8):e43134.

Abstract: OBJECTIVE: Independently of total caloric intake, a better quality of the diet (for example, conformity to the Mediterranean diet) is associated with lower obesity risk. It is unclear whether a brief dietary assessment tool, instead of full-length comprehensive methods, can also capture this association. In addition to reduced costs, a brief tool has the interesting advantage of allowing immediate feedback to participants in interventional studies. Another relevant question is which individual items of such a brief tool are responsible for this association. We examined these associations using a 14-item tool of adherence to the Mediterranean diet as exposure and body mass index, waist circumference and waist-to-height ratio (WHtR) as outcomes. DESIGN: Cross-sectional assessment of all participants in the "PREvención con DIeta MEDiterránea" (PREDIMED) trial. SUBJECTS: 7,447 participants (55-80 years, 57% women) free of cardiovascular disease, but with either type 2 diabetes or ≥ 3 cardiovascular risk factors. Trained dietitians used both a validated 14-item questionnaire and a full-length validated 137-item food frequency questionnaire to assess dietary habits. Trained nurses measured weight, height and waist circumference. RESULTS: Strong inverse linear associations between the 14-item tool and all adiposity indexes were found. For a two-point increment in the 14-item score, the multivariable-adjusted differences in WHtR were -0.0066 (95% confidence interval, -0.0088 to -0.0049) for women and -0.0059 (-0.0079 to -0.0038) for men. The multivariable-adjusted odds ratio for a WHtR>0.6 in participants scoring ≥ 10 points versus ≤ 7 points was 0.68 (0.57 to 0.80) for women and 0.66 (0.54 to 0.80) for men. High consumption of nuts and low consumption of sweetened/carbonated beverages presented the strongest inverse associations with abdominal obesity. CONCLUSIONS: A brief 14-item tool was able to capture a strong monotonic inverse association between adherence to a good quality dietary pattern (Mediterranean diet) and obesity indexes in a population of adults at high cardiovascular risk.

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*Martínez-González MA, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, Wärnberg J, Aros F, Ruíz-Gutiérrez V, Lamuela-Raventós RM, Lapetra J, Muñoz MA, Martínez JA, Sáez G, Serra-Majem L, Pintó X, Mitjavila MT, Tur JA, Portillo MD, Estruch R; for the PREDIMED Study Investigators. Cohort Profile: design and methods of the PREDIMED study. *Int J Epidemiol.* 2012;41:377–85.

This is a question and answer article regarding the PREDIMED study.

Valls-Pedret C, Lamuela-Raventós RM, Medina-Remón A, Quintana M, Corella D, Pintó X, Martínez-González MA, Estruch R, Ros E. Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *J Alzheimers Dis.* 2012;29 (4):773-82.

Abstract: Brain oxidative processes play a major role in age-related cognitive decline, thus consumption of antioxidant-rich foods might help preserve cognition. Our aim was to assess whether consumption of antioxidant-rich foods in the Mediterranean diet relates to cognitive function in the elderly. In asymptomatic subjects at high cardiovascular risk (n = 447; 52% women; age 55-80 y) enrolled in the PREDIMED study, a primary prevention dietary-intervention trial, we assessed food intake and cardiovascular risk profile, determined apolipoprotein E genotype, and used neuropsychological tests to evaluate cognitive function. We also measured urinary polyphenols as an objective biomarker of intake. Associations between energy-adjusted food consumption, urinary polyphenols, and cognitive scores were assessed by multiple linear regression models adjusted for potential confounders. Consumption of some foods was independently related to better cognitive function. The specific associations [regression coefficients (95% confidence intervals)] were: total

olive oil with immediate verbal memory [0.755 (0.151-1.358)]; virgin olive oil and coffee with delayed verbal memory [0.163 (0.010-0.316) and 0.294 (0.055-0.534), respectively]; walnuts with working memory [1.191 (0.061-2.322)]; and wine with Mini-Mental State Examination scores [0.252 (0.006-0.496)]. Urinary polyphenols were associated with better scores in immediate verbal memory [1.208 (0.236-2.180)]. Increased consumption of antioxidant-rich foods in general and of polyphenols in particular is associated with better cognitive performance in elderly subjects at high cardiovascular risk. The results reinforce the notion that Mediterranean diet components might counteract age-related cognitive decline.

2011

Bulló M, Lamuela-Raventós R, Salas-Salvadó J. Mediterranean diet and oxidation: nuts and olive oil as important sources of fat and antioxidants. *Curr Top Med Chem*. 2011;11(14):1797-810.

Abstract: Oxidative stress has been involved in the aetiology of hypertension, insulin resistance, the metabolic syndrome, cardiovascular disease and other chronic conditions. Several epidemiological studies suggest that a diet rich in natural antioxidants is associated with protective effects against major diseases, especially cardiovascular disease. The Mediterranean diet is rich in fat and foods with important antioxidant properties, such as fruits and vegetables, olive oil, and nuts. In this review we focus on epidemiological evidence and clinical trials that relate the Mediterranean diet with oxidative stress markers. We focus our review on two important Mediterranean vegetable sources of potentially oxidized fat-olive oil and nuts.

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Casas-Agustench P, Bulló M, Ros E, Basora J, Salas-Salvadó J; on behalf of the Nureta-PREDIMED investigators. Cross-sectional association of nut intake with adiposity in a Mediterranean population. *Nut rMetab Cardiovasc Dis*. 2011 Jul; 21(7):518-25.

BACKGROUND AND AIMS: Nut intake has been inversely related to body mass index (BMI) in prospective studies. We examined dietary determinants of adiposity in an elderly Mediterranean population with customarily high nut consumption. METHODS AND RESULTS: A cross-sectional study was conducted in 847 subjects (56% women, mean age 67 years, BMI 29.7 g/m^2) at high cardiovascular risk recruited into the PREDIMED study. Food consumption was evaluated by a validated semi-quantitative questionnaire, energy expenditure in physical activity by the Minnesota Leisure Time Activity questionnaire, and anthropometric variables by standard measurements. Nut intake decreased across quintiles of both BMI and waist circumference (P-trend <0.005; both). Alcohol ingestion was inversely related to BMI (P-trend=0.020) and directly to waist (P-trend=0.011), while meat intake was directly associated with waist circumference (P-trend=0.018). In fully adjusted multivariable models, independent dietary associations of BMI were the intake of nuts inversely (P=0.002) and that of meat and meat products directly (P=0.042). For waist circumference, independent dietary associations were intake of nuts (P=0.002) and vegetables (P=0.040), both inversely, and intake of meat and meat products directly (P=0.009). From the regression coefficients, it was predicted that BMI and waist circumference decreased by 0.78kg/m(2) and 2.1cm, respectively, for each serving of 30g of nuts. Results were similar in men and women. CONCLUSION: Nut consumption was inversely associated with adiposity independently of other lifestyle variables. It remains to be explored whether residual confounding related to a healthier lifestyle of nut eaters might in part explain these results.

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Casas-Agustench P, López-Uriarte P, Ros E, Bulló M, Salas-Salvadó J. Nuts, hypertension and endothelial function. *Nutr Metab Cardiovasc Dis*. 2011; 21Suppl 1:S21-33.

BACKGROUND AND AIMS: High blood pressure (BP) is considered a major risk factor for cardiovascular disease. Among lifestyle factors, diet plays a key role in the prevention and control of high BP. Therefore, it is important to elucidate which dietary components can exert beneficial effects on BP through modulation of endothelial function (EF) or by other mechanisms. In this paper we review the role of nutrients, foods, particularly nuts, and dietary patterns on BP control. DATA SYNTHESIS: Because nuts are low in sodium and contain significant amounts of mono- and polyunsaturated fatty acids, fiber, minerals such as magnesium, potassium and calcium, and antioxidants, they have been suggested as potentially protective foods against hypertension. Limited evidence from prospective studies and clinical trials suggests that nut consumption has a beneficial effect on both BP and EF. However, BP changes were a secondary outcome in nut feeding trials and no study used ambulatory BP monitoring as the standard for BP measurements. CONCLUSIONS: Further clinical trials, ideally using ambulatory BP monitoring, are needed to establish the potential protective effect of nut consumption on hypertension and vascular reactivity.

Casas-Agustench P, López-Uriarte P, Bulló M, Ros E, Cabré-Vila JJ, Salas-Salvadó J. Effects of one serving of mixed nuts on serum lipids, insulin resistance and inflammatory markers in patients with the metabolic syndrome. *Nutr Metab Cardiovasc Dis.* 2011; 21(2):126-35.

BACKGROUND AND AIMS: Knowledge of the effect of nut consumption on metabolic syndrome (MetS) components is limited. We assessed the effects of nut intake on adiposity, serum lipids, insulin resistance, and inflammatory biomarkers in patients with MetS. METHODS AND RESULTS: In a randomized, parallel-group, 12-week feeding trial, 50 patients with MetS were given recommendations for a healthy diet with or without supplementation with 30 g/day of raw nuts (15 g walnuts, 7.5 g almonds and 7.5 g hazelnuts) (Nut and Control diet groups, respectively). Adiposity measures, serum lipids, insulin, Homeostasis Model Assessment (HOMA), interleukin-6 (IL-6) and other inflammatory biomarkers, and 48-h fecal fat were determined basally and at study's completion. Moderate weight loss, decreased adiposity, and lower blood pressure occurred similarly after both diets. The Control, but not the Nut diet, was associated with significant ($P<0.05$) reduction of LDL-cholesterol, with mean changes of -0.36 versus -0.13 mmol/L, respectively (between-group differences, $P=0.154$). The Nut diet reduced fasting insulin by 2.60 μU/mL (95% CI, -4.62 to -0.59) and HOMA-insulin resistance by 0.72 (-1.28 to -0.16) ($P<0.05$ versus Control diet; both). Among inflammatory markers, the Nut diet resulted in changes of median plasma IL-6 of -1.1 ng/L (-2.7 to -0.1; $P=0.035$ versus Control diet), but adjustment for weight loss attenuated the significance of the association. Stool fat decreased with the Control diet and slightly increased with the Nut diet ($P<0.05$ for between-group differences). CONCLUSION: Patients with MetS show decreased lipid responsiveness but improved insulin sensitivity after daily intake of 30 g of mixed nuts.

Murie-Fernandez M, Irimia P, Toledo E, Martínez-Vila E, Buil-Cosiales P, Serrano-Martínez M, Ruiz-Gutiérrez V, Ros E, Estruch R, Martínez-González MA; on behalf of the PREDIMED Investigators. Carotid intima-media thickness changes with Mediterranean diet: A randomized trial (PREDIMED-Navarra). *Atherosclerosis.* 2011; 219(1):158-62.

OBJECTIVE: Observational studies have reported inverse associations between adherence to the Mediterranean diet (MedDiet) and atherosclerotic disease. We tested the effect of two types of MedDiet on progression of subclinical carotid atherosclerosis. METHODS: We randomized 187 high-cardiovascular-risk asymptomatic subjects (51% women, mean age 67 years) to three treatment arms: MedDiet with supplemental virgin olive oil (VOO), n=66; MedDiet with supplemental nuts, n=59; and control diet, n=62. Participants received nutrition behavioral counseling in quarterly group and individual educational sessions. Free supplemental foods were provided to the MedDiet groups. Changes in mean intima-media thickness (IMT) were measured ultrasonographically in the far wall of bilateral common carotid arteries after 1 year. RESULTS: Overall, no significant between-group differences in IMT progression were observed after 1-year. However, a significant

interaction (p=0.03) between baseline IMT and treatment effect was apparent. Among participants with baseline IMT≥0.9mm, 1-year IMT changes versus control showed significant differences of -0.079mm (95% confidence interval, -0.145 to -0.012) for the MedDiet with VOO and -0.072mm (-0.140 to -0.004) for the MedDiet with nuts. No IMT changes occurred in any intervention group among participants with lower baseline IMT values (<0.9mm). CONCLUSIONS: MedDiets enhanced with VOO or nuts were not effective in inducing ultrasonographic regression of carotid atherosclerosis after 1 year intervention. However, they were effective among subjects with elevated baseline IMT, suggesting that subclinical atherosclerosis may respond to dietary intervention within a relatively short time frame only among subjects with a high initial atherosclerotic burden.

Salas-Salvadó J, Martinez-González MÁ, Bulló M, Ros E. The role of diet in the prevention of type 2 diabetes. *Nutr Metab Cardiovasc Dis*. 2011;21Suppl 2:B32-48.

Abstract: Type 2 diabetes mellitus is an important preventable disease and a growing public health problem. Epidemiologic and interventional studies suggest that weight loss is the main driving force to reduce diabetes risk. Landmark clinical trials of lifestyle changes in subjects with prediabetes have shown that diet and exercise leading to weight loss consistently reduce the incidence of diabetes. However, from these studies it cannot be established whether dietary changes alone play a significant role in preventing diabetes. Here we review epidemiologic and clinical trial evidence relating nutrients, foods and dietary patterns to diabetes risk and the possible mechanisms involved. The differential effects of carbohydrate and fat quantity and quality, and those of specific foods and whole diets are discussed. Importantly, most dietary components influencing diabetes risk have similar effects on biomarkers of cardiovascular risk and inflammation. The conclusion is that there is no universal dietary strategy to prevent diabetes or delay its onset. Together with the maintenance of ideal body weight, the promotion of the so-called prudent diet (characterized by a higher intake of food groups that are generally recommended for health promotion, particularly plant-based foods, and a lower intake of red meat, meat products, sweets, high-fat dairy and refined grains) or a Mediterranean dietary pattern rich in olive oil, fruits and vegetables, including whole grains, pulses and nuts, low-fat dairy, and moderate alcohol consumption (mainly red wine) appears as the best strategy to decrease diabetes risk, especially if dietary recommendations take into account individual preferences, thus enabling long-time adherence.

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*Sala-Vila A, Harris WS, Cofán M, Pérez-Heras AM, Pintó X, Lamuela-Raventós RM, Covas MI, Estruch R, Ros E. Determinants of the omega-3 index in a Mediterranean population at increased risk for CHD. *Br J Nutr*. 2011;106(3):425-31.

The omega-3 index, defined as the sum of EPA and DHA in erythrocyte membranes expressed as a percentage of total fatty acids, has been proposed as both a risk marker and risk factor for CHD death. A major determinant of the omega-3 index is EPA+DHA intake, but the impact of other dietary fatty acids has not been investigated. In a cross-sectional study on 198 subjects (102 men and 96 women, mean age 66 years) at high cardiovascular risk living in Spain, the country with low rates of cardiac death despite a high prevalence of cardiovascular risk factors, dietary data were acquired from FFQ and blood cell membrane fatty acid composition was measured by GC. The average consumption of EPA+DHA was 0•9 g/d and the mean omega-3 index was 7•1 %. In multivariate models, EPA+DHA intake was the main predictor of the omega-3 index but explained only 12 % of its variability (P < 0•001). No associations with other dietary fatty acids were observed. Although the single most influential determinant of the omega-3 index measured here was the intake of EPA+DHA, it explained little of the former's variability; hence, the effects of other factors (genetic, dietary and lifestyle) remain to be determined. Nevertheless, the high omega-3 index could at least partially explain the paradox of low rates of fatal CHD in Spain despite a high background prevalence of cardiovascular risk factors.

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Salas-Salvadó J, Bulló M, Babio N, Martínez-González MA, Ibarrola-Jurado N, Basora J, Estruch R, Covas MI, Corella D, ArósF,Ruiz-Gutiérrez V, Ros E, For the PREDIMED Study investigators. Reduction in the incidence of type 2 diabetes with the Mediterranean diet: results of the PREDIMED-Reus nutrition intervention randomized trial. *Diabetes Care.* 2011;34(1):14-9.

OBJECTIVE: To test the effects of two Mediterranean diet (MedDiet) interventions versus a low-fat diet on incidence of diabetes. RESEARCH DESIGN AND METHODS: This was a three-arm randomized trial in 418 nondiabetic subjects aged 55-80 years recruited in one center (PREDIMED-Reus, northeastern Spain) of the Prevención con DietaMediterránea [PREDIMED] study, a large nutrition intervention trial for primary cardiovascular prevention in individuals at high cardiovascular risk. Participants were randomly assigned to education on a low-fat diet (control group) or to one of two MedDiets, supplemented with either free virgin olive oil (1 liter/week) or nuts (30 g/day). Diets were ad libitum, and no advice on physical activity was given. The main outcome was diabetes incidence diagnosed by the 2009 American Diabetes Association criteria. RESULTS: After a median follow-up of 4.0 years, diabetes incidence was 10.1% (95% CI 5.1-15.1), 11.0% (5.9-16.1), and 17.9% (11.4-24.4) in the MedDiet with olive oil group, the MedDiet with nuts group, and the control group, respectively. Multivariable adjusted hazard ratios of diabetes were 0.49 (0.25-0.97) and 0.48 (0.24-0.96) in the MedDiet supplemented with olive oil and nuts groups, respectively, compared with the control group. When the two MedDiet groups were pooled and compared with the control group, diabetes incidence was reduced by 52% (27-86). In all study arms, increased adherence to the MedDiet was inversely associated with diabetes incidence. Diabetes risk reduction occurred in the absence of significant changes in body weight or physical activity. CONCLUSIONS: MedDiets without calorie restriction seem to be effective in the prevention of diabetes in subjects at high cardiovascular risk.

Sánchez-Villegas A, Galbete C, Martinez-González MA, Martinez JA, Razquin C, Salas-Salvadó J, Estruch R, Buil-Cosiales P, Martí A. The effect of the Mediterranean diet on plasma brain-derived neurotrophic factor (BDNF). *Nutr Neurosci.* 2011;14(5):195-201.

OBJECTIVES: There are no human studies assessing the effect of nutritional interventions on plasma brain-derived neurotrophic factor (BDNF) concentrations. The aim of this study was to assess the role of a nutritional intervention based on a Mediterranean diet (MeDiet) on plasma BDNF levels. METHODS: PREvención con Dieta MEDiterránea (PREDIMED) is a randomized clinical trial designed to assess the effect of a Mediterranean diet (MeDiet) on the primary prevention of cardiovascular disease. For this analysis, 243 participants from the Navarra centre were randomly selected. Participants were assigned to one of three dietary interventions: control (low-fat) diet, MeDiet supplemented with virgin olive oil (MeDiet+VOO), or MeDiet supplemented with nuts (MeDiet+Nuts). Plasma BDNF levels were measured after 3 years of intervention. Multivariate-adjusted means of BDNF for each intervention were compared using generalized linear models. Logistic regression models were fit to assess the association between the dietary intervention and the likelihood to have low plasma BDNF values (<13 μg/ml, 10th percentile). Analyses were repeated after stratifying the sample according to baseline prevalence of different diseases. RESULTS: Higher but non-significant plasma BDNF levels were observed for participants assigned to both MeDiets. Participants assigned to MeDiet+Nuts showed a significant lower risk (odds ratios (OR)=0.22; 95% confidence intervals (CI)=0.05-0.90) of low plasma BDNF values (<13 μg/ml) as compared to the control group. Among participants with prevalent depression at baseline, significantly higher BDNF levels were found for those assigned to the MeDiet+Nuts. DISCUSSION: Adherence to a MeDiet was associated to an improvement in plasma BDNF concentrations in individuals with depression.

2010

Llorente-Cortés V, Estruch R, Mena MP, Ros E, González MA, Fitó M, Lamuela-Raventós RM, Badimon L. Effect of Mediterranean diet on the expression of pro-atherogenic genes in a population at high cardiovascular risk.*Atherosclerosis.*2010;208(2):442-50.

Experimental and epidemiological studies have demonstrated the beneficial effects of the traditional Mediterranean diet (TMD) on the incidence and progression of atherosclerosis. Several genes play a major role in determining atherosclerosis susceptibility. We compared the short-term effects of two TMD diets versus a control diet on the expression of pro-atherogenic genes. One TMD diet was supplemented with virgin olive oil (VOO) (TMD+VOO) and the other with nuts (TMD+nuts). Gene expression was analyzed in monocytes from 49 asymptomatic high cardiovascular-risk participants (23 men, 26 women), aged 55-80 years. Monocytes were isolated from blood before and 3 months after dietary intervention. We analyzed the expression of genes involved in inflammation [cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2) and monocyte chemoattractant protein (MCP-1)], genes involved in foam cell formation [low-density lipoprotein receptor-related protein (LRP1), LDL receptor and CD36], and genes involved in thrombosis [tissue factor (TF) and tissue factor pathway inhibitor (TFPI)]. We found that TMD+VOO intervention prevented an increase in COX-2 and LRP1, and reduced MCP-1 expression compared to TMD+nuts or control diet interventions. TMD+nuts specifically increased the expression of CD36 and TFPI compared to TMD+VOO and control diet intervention. Our findings showed that the Mediterranean diet influences expression of key genes involved in vascular inflammation, foam cell formation and thrombosis. Dietary intervention can thus actively modulate the expression of pro-atherothrombotic genes even in a high-risk population.

Perona JS, Covas MI, Fitó M, Cabello-Moruno R, Aros F, Corella D, Ros E, Garcia M, Estruch R, Martinez-Gonzalez MA, Ruiz-Gutierrez V. Reduction in systemic and VLDL triacylglycerol concentration after a 3-month Mediterranean-style diet in high-cardiovascular-risk subjects. *J Nutr Biochem.*2010;21(9):892-8.

The first results of the PREDIMED (PREvencion con DietaMEDiterranea) randomized trial, after 3-month intervention, showed that the Mediterranean Diet (MD), supplemented with either virgin olive oil (VOO) or nuts, reduced systolic blood pressure, serum cholesterol and triacylglycerol (TG) concentrations and increased high-density lipoprotein (HDL)-cholesterol when compared to a control (low-fat diet) group. Serum TG levels are an independent risk factor for coronary heart disease and are strongly determined by very low-density lipoprotein (VLDL) composition, which can be specifically modified by dietary lipid source. Within the context of the PREDIMED study, we assessed the VLDL composition in 50 participants after 3 months of intake of two MD, supplemented with VOO or nuts, compared with a low-fat diet. Total and low-density lipoprotein cholesterol concentrations were reduced in subjects on the MD+nuts, whereas HDL-cholesterol increased after consumption of the MD+VOO. Serum TG concentrations were significantly lowered in both intervention groups (either the MD+nuts or MD+VOO). However, only the MD+VOO reduced the VLDL-cholesterol and VLDL-TG content and the TG/apolipoprotein B ratio in VLDL, which was used to estimate particle size. Although VLDL-TG fatty acids were very slightly modified, VLDL-TG molecular species in VLDL after consumption of the MD+nuts were characterized by a higher presence of linoleic acid (18:2, n-6), whereas after the intake of MD+VOO, they were rich in oleic acid (18:1, n-9). Therefore, we conclude that the reduction in systemic TG concentrations observed after consumption of the MD may be explained by reduction of the lipid core of VLDL and a selective modification of the molecular species composition in the particle.

Razquin C, Martínez JA, Martínez-González MA, Salas-Salvadó J, Estruch R, Marti A. A 3-year Mediterranean-style dietary intervention may modulate the association between adiponectin gene variants and body weight change. *Eur J Nutr.* 2010;49(5):311-9.

PURPOSE: Adiponectin gene variations have been associated with obesity. There are few interventional studies analyzing this association. The aim of this study was to analyze the effects of a nutritional intervention with Mediterranean-style diet and three (-4034A/C, +45T/G, and +276 G/T) adiponectin gene variants on 3-year body weight changes in high cardiovascular risk patients. SUBJECTS AND METHODS: A total of 737 participants, aged 55-80 at high cardiovascular risk were assigned to a low-fat diet or to a Mediterranean-style diet (MD) groups, one with high intake of virgin olive oil (VOO) and the other with high intake of nuts. Anthropometric parameters were taken at baseline and after 3-year follow-up, and the genotyping of the -4034A/C, +45T/G, and +276 G/T polymorphisms was done. RESULTS: GG genotype of the +45T/G polymorphism was associated with 3-year higher body weight gain (B = 1.399; B = 0.043). TT genotype of the +276G/T polymorphism was linked to the highest 3-year body weight gain in men. Both Mediterranean diets appeared to reverse this effect (p for interaction = 0.053).CONCLUSION: Adiponectin gene variation appeared to be associated with 3-year body weight changes in a high cardiovascular risk population. This association may be modulated by a nutritional intervention with a Mediterranean-style diet.

Zazpe I, Estruch R, Toledo E, Sánchez-Taínta A, Corella D, Bulló M, Fiol M, Iglesias P, Gómez-Gracia E, Arós F, Ros E, Schröder H, Serra-Majem L, Pintó X, Lamuela-Raventós R, Ruiz-Gutiérrez V, Martínez-González MA. Predictors of adherence to a Mediterranean-type diet in the PREDIMED trial. *Eur J Nutr.* 2010;49(2):91-9.

BACKGROUND: Determinants of dietary changes obtained with a nutritional intervention promoting the Mediterranean diet have been rarely evaluated. AIM: To identify predictors of higher success of an intervention aimed to increase adherence to a Mediterranean diet (MeDiet) in individuals at high cardiovascular risk participating in a trial for primary prevention of cardiovascular disease: the PREDIMED (PREvención con DIetaMEDiterránea) trial. Candidate predictors included demographic and socioeconomic characteristics, cardiovascular risk factors, and baseline dietary habits. METHODS: A total of 1,048 asymptomatic subjects aged 55-80 years allocated to the active intervention groups (subjects in the control group were excluded). Participants' characteristics were assessed at baseline among subjects. Dietary changes were evaluated after 12 months. Main outcome measures were: attained changes in five dietary goals: increases in (1) fruit consumption, (2) vegetable consumption, (3) monounsaturated fatty acid (MUFA)/saturated fatty acid (SFA) ratio, and decreases in (4) sweets and pastries consumption, (5) and meat consumption. Univariate and multivariate logistic regression analyses were used to examine associations between the candidate predictors and likelihood of attaining optimum dietary change (improved adherence to a MeDiet). RESULTS: Among men, positive changes toward better compliance with the MeDiet were more frequent among non-diabetics, and among those with worse dietary habits at baseline (higher consumption of meat, higher SFA intake, lower consumption of fruit and vegetables). Among women, marital status (married) and worse baseline dietary habits (high in meats, low in fruits and vegetables) were the strongest predictors of success in improving adherence to the MeDiet. CONCLUSIONS: Some participant characteristics (marital status and baseline dietary habits) could contribute to predicting the likelihood of achieving dietary goals in interventions aimed to improve adherence to a MeDiet, and may be useful for promoting individualized long-term dietary changes and improving the effectiveness of dietary counseling.

2009

Bulló M, Amigó-Correig P, Márquez-Sandoval F, Babio N, Martínez-González MA, Estruch R, Basora J, Solà R, Salas-Salvadó J.Mediterranean diet and high dietary acid load associated with mixed nuts: effect on bone metabolism in elderly subjects. *J Am Geriatr Soc.* 2009;57(10):1789-98.

OBJECTIVES: To analyze the effect of differing diet on the acid load content on bone metabolism.DESIGN: Multicentric, randomized, single-blind, parallel-group clinical trial.SETTING: Outpatient clinics.PARTICIPANTS: Two hundred thirty-eight elderly men and women aged 60 to 80 at high risk for cardiovascular disease were randomly assigned to three interventional groups: a recommended low-fat diet (control diet group), a Mediterranean diet supplemented with virgin olive oil, or a Mediterranean diet supplemented with mixed nuts.MEASUREMENTS: Main outcomes were 12-month changes from baseline in bone formation and resorption markers and bone mass measured according to quantitative ultrasound scanning.RESULTS: The baseline data on the anthropometric, bone densitometry, and biochemical variables did not differ between the three groups. Dietary potential renal acid load (PRAL) and daily net endogenous acid production (NEAP) at baseline did not differ between groups. After intervention, subjects allocated to the Mediterranean diet with mixed nuts had a significant increase of PRAL and NEAP. In comparison, subjects in the Mediterranean diet with nuts group had higher parathyroid hormone (PTH) levels (2.63, 95% confidence interval (CI)=-1.01-6.35, P=.02) and a nonsignificantly higher (0.31, 95% CI=-0.13-0.74, P=.14) urine free deoxypyridoxine:creatinine ratio, a marker of bone resorption, than the control group and the Mediterranean diet with virgin olive oil group.CONCLUSION: A Mediterranean dietary pattern associated with a high dietary acid load derived from consumption of mixed nuts does not seem to have a much greater effect on bone metabolism biomarkers, with the exception of PTH levels, than a Mediterranean diet without mixed nuts or a control diet in elderly subjects.

Corella D, González JI, Bulló M, Carrasco P, Portolés O, Díez-Espino J, Covas MI, Ruíz-Gutierrez V, Gómez-Gracia E, Arós F, Fiol M, Herrera MC, Santos JM, Sáez G, Lamuela R, Lahoz C, Vinyoles E, Ros E, Estruch R. Polymorphisms cyclooxygenase-2 -765G>C and interleukin-6 -174G>C are associated with serum inflammation markers in a high cardiovascular risk population and do not modify the response to a Mediterranean diet supplemented with virgin olive oil or nuts. *J Nutr.* 2009;139(1):128-34.

Inflammation is involved in cardiovascular diseases. Some studies have found that the Mediterranean diet (MD) can reduce serum concentrations of inflammation markers. However, none of these studies have analyzed the influence of genetic variability in such a response. Our objective was to study the effect of the -765G>C polymorphism in the cyclooxygenase-2 (COX-2) gene and the -174G>C polymorphism in the interleukin-6 (IL-6) gene on serum concentrations of IL-6, C-reactive protein, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule-1 as well as their influence on the response to a nutritional intervention with MD. An intervention study in a high cardiovascular risk Mediterranean population (314 men and 407 women) was undertaken. Participants were randomly assigned to consume a low-fat control diet or a MD supplemented with virgin olive oil or nuts. Measures were obtained at baseline and after a 3-mo intervention period. At baseline, the COX-2 -765G>C polymorphism was associated with lower serum IL-6 (5.85 +/- 4.82 in GG vs. 4.74 +/- 4.14 ng/L in C-allele carriers; P = 0.002) and ICAM-1 (265.8 +/- 114.8 in GG vs. 243.0 +/- 107.1 microg/L in C-carriers; P = 0.018) concentrations. These differences remained significant after multivariate adjustment. The IL-6 -174G>C polymorphism was associated with higher (CC vs. G-carriers) serum ICAM-1 concentrations in both men and women and with higher serum IL-6 concentrations in men. Following the dietary intervention, no significant gene x diet interactions were found. In conclusion, although COX-2 -765G>C and IL-6 -174G>C polymorphisms were associated with inflammation,consuming a MD (either supplemented with virgin olive oil or nuts) reduced the concentration of inflammation markers regardless of these polymorphisms.

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Escurriol V, Cofán M, Serra M, Bulló M, Basora J, Salas-Salvadó J, Corella D, Zazpe I, Martínez-González MA, Ruiz-Gutiérrez V, Estruch R, Ros E.Serum sterol responses to increasing plant sterol intake from natural foods in the Mediterranean diet. *Eur J Nutr.* 2009;48(6):373-82.

BACKGROUND: Phytosterols in natural foods are thought to inhibit cholesterol absorption. The Mediterranean diet is rich in phytosterol-containing plant foods.AIM OF THE STUDY: To assess whether increasing phytosterol intake from natural foods was associated with a cholesterol-lowering effect in a substudy of a randomized trial of nutritional intervention with Mediterranean diets for primary cardiovascular prevention (PREDIMED study).METHODS: One hundred and six high cardiovascular risk subjects assigned to two Mediterranean diets supplemented with virgin olive oil (VOO) or nuts, which are phytosterol-rich foods, or advice on a low-fat diet. Outcomes were 1-year changes in nutrient intake and serum levels of lipids and non-cholesterol sterols. RESULTS: Average phytosterol intake increased by 76, 158 and 15 mg/day in participants assigned VOO, nuts and low-fat diets, respectively. Compared to participants in the low-fat diet group, changes in outcome variables were observed only in those in the Mediterranean diet with nuts group, with increases in intake of fibre, polyunsaturated fatty acids and phytosterols ($P < 0.020$, all) and significant ($P < 0.05$) reductions of LDL-cholesterol (0.27 mmol/l or 8.3%) and the LDL/HDL-cholesterol ratio (0.29 mmol/l or 11.5%). Variations in saturated fat, cholesterol or fibre intake were unrelated to LDL-cholesterol changes. In the whole group, changes in serum sitosterol-to-cholesterol, which reflect those of dietary phytosterol intake and absorption, correlated inversely to LDL-cholesterol changes ($r = -0.256$; $P = 0.008$). In multivariate analyses, baseline LDL-cholesterol, increases in serum sitosterol ratios and statin use were independently associated with LDL-cholesterol reductions.CONCLUSIONS: Small amounts of phytosterols in natural foods appear to be bioactive in cholesterol lowering.

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Guxens M, Fitó M, Martínez-González MA, Salas-Salvadó J, Estruch R, Vinyoles E, Fiol M, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Lapetra J, Ros E, Vila J, Covas MI. Hypertensive status and lipoprotein oxidation in an elderly population at high cardiovascular risk. *Am J Hypertens.*2009;22(1):68-73.

BACKGROUND: In elderly individuals, hypertension is a main risk factor for cardiovascular disease and oxidative damage is increased. Our aim was to assess the relationship between the degree of in vivo low-density lipoprotein (oxLDL) oxidation and the hypertensive status in an elderly population at high cardiovascular risk. METHODS: Cross-sectional study with baseline data from the PREDIMED (PREvención con DIetaMEDiterránea) trial, an intervention study directed at testing the efficacy of the Mediterranean diet on the primary prevention of cardiovascular disease. Participants were 1,130 subjects at high cardiovascular risk aged 55-80. At baseline, in vivo circulating oxLDL was measured, and stages of hypertension determined according to the USA Joint National Committee guidelines. RESULTS: A positive relationship between in vivo oxLDL and systolic and diastolic blood pressure (DBP) was observed after adjusting for confounding factors ($P < 0.05$). OxLDL concentrations increased in a linear manner from low to high hypertensive stages ($P < 0.05$). CONCLUSIONS: Elderly individuals at high cardiovascular risk showed higher levels of circulating oxLDL when their hypertensive status increased. This fact identifies the hypertensive elderly population as a target for antioxidant preventive measures.

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Mena MP, Sacanella E, Vazquez-Agell M, Morales M, Fitó M, Escoda R, Serrano-Martínez M, Salas-Salvadó J, Benages N, Casas R, Lamuela-Raventós RM, Masanes F, Ros E, Estruch R. Inhibition of circulating immune cell activation: a molecular antiinflammatory effect of the Mediterranean diet. *Am J Clin Nutr.*2009;89(1):248-56.

BACKGROUND: Adherence to the Mediterranean diet (Med-Diet) is associated with a reduced risk of cardiovascular disease (CVD). However, the molecular mechanisms involved are not fully understood. OBJECTIVE: The objective was to compare the effects of 2 Med-Diets with those of a low-fat diet on immune cell activation and soluble inflammatory biomarkers related to atherogenesis in subjects at high risk of CVD. DESIGN: In a controlled study, we randomly assigned 112 older subjects with diabetes or > or =3 CVD risk factors to 3 dietary intervention groups: Med-Diet with supplemental virgin olive oil (VOO), Med-Diet with supplemental nuts, and low-fat diet. Changes from baseline in cellular and serum inflammatory biomarkers were assessed at 3 mo. RESULTS: One hundred six participants (43% women; average age: 68 y) completed the study. At 3 mo, monocyte expression of CD49d, an adhesion molecule crucial for leukocyte homing, and of CD40, a proinflammatory ligand, decreased ($P < 0.05$) after both Med-Diets but not after the low-fat diet. Serum interleukin-6 and soluble intercellular adhesion molecule-1, inflammatory mediators crucial in firm adhesion of leukocytes to endothelial surfaces, decreased ($P < 0.05$) in both Med-Diet groups. Soluble vascular cellular adhesion molecule-1 and C-reactive protein decreased only after the Med-Diet with VOO ($P < 0.05$), whereas interleukin-6, soluble vascular cellular adhesion molecule-1, and soluble intercellular adhesion molecule-1 increased ($P < 0.05$) after the low-fat diet. CONCLUSIONS: Med-Diets supplemented with VOO or nuts down-regulate cellular and circulating inflammatory biomarkers related to atherogenesis in subjects at high risk of CVD. The results support the recommendation of the Med-Diet as a useful tool against CVD.

2008

Salas-Salvadó J, Fernández-Ballart J, Ros E, Martínez-González MA, Fitó M, Estruch R, Corella D, Fiol M, Gómez-Gracia E, Arós F, Flores G, Lapetra J, Lamuela-Raventós R, Ruiz-Gutiérrez V, Bulló M, Basora J, Covas MI; PREDIMED Study Investigators. Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch Intern Med.* 2008;168(22):2449-58.

BACKGROUND: Epidemiological studies suggest that the Mediterranean diet (MedDiet) may reduce the risk of developing the metabolic syndrome (MetS). We compared the 1-year effect of 2 behavioral interventions to implement the MedDietvs advice on a low-fat diet on MetS status. METHODS: A total of 1224 participants were recruited from the PREDIMED (Prevención con DietaMediterránea) Study, a multicenter, 3-arm, randomized clinical trial to determine the efficacy of the MedDiet on the primary prevention of cardiovascular disease. Participants were older subjects at high risk for cardiovascular disease. Interventions were quarterly education about the MedDiet plus provision of either 1 L/wk of virgin olive oil (MedDiet + VOO) or 30 g/d of mixed nuts (MedDiet + nuts), and advice on a low-fat diet (control diet). All diets were ad libitum, and there was no increase in physical activity for any of the interventions. Lifestyle variables and MetS features as defined by the National Cholesterol Education Program Adult Treatment Panel III criteria were assessed. RESULTS: At baseline, 61.4% of participants met criteria for the MetS. One-year prevalence was reduced by 6.7%, 13.7%, and 2.0% in the MedDiet + VOO, MedDiet + nuts, and control diet groups, respectively (MedDiet + nuts vs control groups, $P = .01$; MedDiet + VOO vs control group, $P = .18$). Incident rates of the MetS were not significantly different among groups (22.9%, 17.9%, and 23.4%, respectively). After adjustment for sex, age, baseline obesity status, and weight changes, the odds ratios for reversion of MetS were 1.3 (95% confidence interval, 0.8-2.1) for the MedDiet + VOO group and 1.7 (1.1-2.6) for the MedDiet + nuts group compared with the control diet group. CONCLUSION: A traditional MedDiet enriched with nuts could be a useful tool in the management of the MetS.

Salas-Salvadó J, Garcia-Arellano A, Estruch R, Marquez-Sandoval F, Corella D, Fiol M, Gómez-Gracia E, Viñoles E, Arós F, Herrera C, Lahoz C, Lapetra J, Perona JS, Muñoz-Aguado D, Martínez-González MA, Ros E; PREDIMED Investigators. Components of the Mediterranean-type food pattern and serum inflammatory markers among patients at high risk for cardiovascular disease.*Eur J Clin Nutr.* 2008;62(5):651-9.

OBJECTIVE: To evaluate associations between components of the Mediterranean diet and circulating markers of inflammation in a large cohort of asymptomatic subjects at high risk for cardiovascular disease. SUBJECTS/METHODS: A total of 339 men and 433 women aged between 55 and 80 years at high cardiovascular risk because of presence of diabetes or at least three classical cardiovascular risk factors, food consumption was determined by a semi-quantitative food frequency questionnaire. Serum concentrations of high-sensitivity C-reactive protein (CRP) were measured by immunonephelometry and those of interleukin-6 (IL-6), intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) by enzyme-linked immunosorbent assay.RESULTS: After adjusting for age, gender, body mass index, diabetes, smoking, use of statins, non-steroidal antiinflammatory drugs and aspirin, a higher consumption of fruits and cereals was associated with lower concentrations of IL-6 (P for trend 0.005;both). Subjects with the highest consumption of nuts and virgin olive oil showed the lowest concentrations of VCAM-1, ICAM-1, IL-6 and CRP; albeit only for ICAM-1 was this difference statistically significant in the case of nuts (for trend 0.003) and for VCAM-1 in the case of virgin olive oil (P for trend 0.02). Participants with higher adherence to the Mediterranean-type diet did not show significantly lower concentrations of inflammatory markers (P<0.1 for VCAM-1 and ICAM-1). CONCLUSIONS: The consumption of some typical Mediterranean foods (fruits, cereals, virgin olive oil and nuts) was associated with lower serum concentrations of inflammatory markers especially those related to endothelial function, in subjects with high cardiovascular risk living in a Mediterranean country.

Sánchez-Taínta A, Estruch R, Bulló M, Corella D, Gómez-Gracia E, Fiol M, Algorta J, Covas MI, Lapetra J, Zazpe I, Ruiz-Gutiérrez V, Ros E, Martínez-González MA; PREDIMED group. Adherence to a Mediterranean-type diet and reduced prevalence of clustered cardiovascular risk factors in a cohort of 3,204 high-risk patients. *Eur J Cardiovasc Prev Rehab.* 2008t;15(5):589-93.

BACKGROUND: The Mediterranean food pattern (MeDiet) has been suggested to have beneficial effects on cardiovascular risk factors. Scarcity of assessment of this effect on large samples of patients at high risk is, however, observed. Our objective was to estimate the association between adherence to MeDiet and the prevalence of risk factors in 3,204 asymptomatic high-risk patients. DESIGN: Cross-sectional assessment of baseline characteristics of participants in a primary prevention trial. METHODS: Participants were assessed by their usual primary-care physicians to ascertain the prevalence of diet-related cardiovascular risk factors (diabetes, hypertension, dyslipidemia, or obesity) using standard diagnostic criteria. A dietitian interviewed each participant to obtain a 14-point score measuring the degree of adherence to MeDiet. RESULTS: Adherence to MeDiet was inversely associated with individual risk factors and, above all, with the clustering of them. The multivariate adjusted odds ratio to present simultaneously the four risk factors for those above the median value of the MeDiet score was 0.67 (95% confidence interval: 0.53-0.85). The multivariate odds ratios for successive categories of adherence to MeDiet were 1 (ref.), 1.03, 0.85, 0.70 and 0.54 (P for trend <0.001). CONCLUSION: Following a MeDiet was inversely associated with the clustering of hypertension, diabetes, obesity, and hypercholesterolemia among high-risk patients.

Zazpe, I, Sanchez-Tainta A, Estruch R, Lamuela-Raventos RM, Schröder H, Salas-Salvado J, Corella D, Fiol M, Gomez-Gracia E, Aros F, Ros E, Ruíz-Gutierrez V, Iglesias P, Conde-Herrera M, Martinez-Gonzalez MA. A large randomized individual and group intervention conducted by registered dietitians increased adherence to Mediterranean-type diets: the PREDIMED study. *J Am Diet Assoc.* 2008;108:1134-1143.

OBJECTIVE: To assess the effectiveness of an intervention aimed to increase adherence to a Mediterranean diet. DESIGN: A 12-month assessment of a randomized primary prevention trial. SUBJECTS/SETTINGS: One thousand five hundred fifty-one asymptomatic persons aged 55 to 80 years, with diabetes or > or =3 cardiovascular risk factors. INTERVENTION: Participants were randomly assigned to a control group or two Mediterranean diet groups. Those allocated to the two Mediterranean diet groups received individual

motivational interviews every 3 months to negotiate nutrition goals, and group educational sessions on a quarterly basis. One Mediterranean diet group received free virgin olive oil (1 L/week), the other received free mixed nuts (30 g/day). Participants in the control group received verbal instructions and a leaflet recommending the National Cholesterol Education Program Adult Treatment Panel III dietary guidelines. MAIN OUTCOME MEASURES: Changes in food and nutrient intake after 12 months. STATISTICAL ANALYSES: Paired t tests (for within-group changes) and analysis of variance (for between-group changes) were conducted. RESULTS: Participants allocated to both Mediterranean diets increased their intake of virgin olive oil, nuts, vegetables, legumes, and fruits ($P<0.05$ for all within- and between-group differences). Participants in all three groups decreased their intake of meat and pastries, cakes, and sweets ($P<0.05$ for all). Fiber, monounsaturated fatty acid, and polyunsaturated fatty acid intake increased in the Mediterranean diet groups ($P<0.005$ for all). Favorable, although nonsignificant, changes in intake of other nutrients occurred only in the Mediterranean diet groups. CONCLUSIONS: A 12-month behavioral intervention promoting the Mediterranean diet can favorably modify an individual's overall food pattern. The individual motivational interventions together with the group sessions and the free provision of high-fat and palatable key foods customary to the Mediterranean diet were effective in improving the dietary habits of participants in this trial.

2007

Fitó M, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, Francés F, Cabezas C, López-SabaterMdel C, Marrugat J, García-Arellano A, Arós F, Ruiz-Gutierrez V, Ros E, Salas-Salvadó J, Fiol M, Solá R, Covas MI; for the PREDIMED Study Investigators. Effect of a traditional Mediterranean diet on lipoprotein oxidation: a randomized controlled trial. *Arch Intern Med.* 2007; 11; 167:1195-203.

BACKGROUND: Despite the richness in antioxidants of the Mediterranean diet, to our knowledge, no randomized controlled trials have assessed its effect on in vivo lipoprotein oxidation. METHODS: A total of 372 subjects at high cardiovascular risk (210 women and 162 men; age range, 55-80 years), who were recruited into a large, multicenter, randomized, controlled, parallel-group clinical trial (the Prevención con DietaMediterránea [PREDIMED] Study) directed at testing the efficacy of the traditional Mediterranean diet (TMD) on the primary prevention of coronary heart disease, were assigned to a low-fat diet (n = 121) or one of 2 TMDs (TMD + virgin olive oil or TMD + nuts). The TMD participants received nutritional education and either free virgin olive oil for all the family (1 L/wk) or free nuts (30 g/d). Diets were ad libitum. Changes in oxidative stress markers were evaluated at 3 months.RESULTS: After the 3-month interventions, mean (95% confidence intervals) oxidized low-density lipoprotein (LDL) levels decreased in the TMD + virgin olive oil (-10.6 U/L [-14.2 to -6.1]) and TMD + nuts (-7.3 U/L [-11.2 to -3.3]) groups, without changes in the low-fat diet group (-2.9 U/L [-7.3 to 1.5]). Change in oxidized LDL levels in the TMD + virgin olive oil group reached significance vs that of the low-fat group (P = .02). Malondialdehyde changes in mononuclear cells paralleled those of oxidized LDL. No changes in serum glutathione peroxidase activity were observed. CONCLUSIONS: Individuals at high cardiovascular risk who improved their diet toward a TMD pattern showed significant reductions in cellular lipid levels and LDL oxidation. Results provide further evidence to recommend the TMD as a useful tool against risk factors for CHD

2006

Estruch R, Martínez-González MA, Corella D, Salas-Salvadó J, Ruiz-Gutiérrez V, Covas MI, Fiol M, Gómez-Gracia E, López-Sabater MC, Vinyoles E, Arós F, Conde M, Lahoz C, Lapetra J Sáez G, Ros E for the PREDIMED Study. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. *Ann Intern Med.* 2006;145:1-11.

BACKGROUND: The Mediterranean diet has been shown to have beneficial effects on cardiovascular risk factors.OBJECTIVE: To compare the short-term effects of 2 Mediterranean diets versus those of a low-fat diet on intermediate markers of cardiovascular risk. DESIGN: Substudy of a multicenter, randomized, primary prevention trial of cardiovascular disease (Prevención con DietaMediterránea [PREDIMED] Study). SETTING: Primary care centers affiliated with 10 teaching hospitals. PARTICIPANTS: 772 asymptomatic persons 55 to 80 years of age at high cardiovascular risk who were recruited from October 2003 to March 2004. Interventions:

Participants were assigned to a low-fat diet (n = 257) or to 1 of 2 Mediterranean diets. Those allocated to Mediterranean diets received nutritional education and either free virgin olive oil, 1 liter per week (n = 257), or free nuts, 30 g/d (n = 258). The authors evaluated outcome changes at 3 months. MEASUREMENTS: Body weight, blood pressure, lipid profile, glucose levels, and inflammatory molecules. RESULTS: The completion rate was 99.6%. Compared with the low-fat diet, the 2 Mediterranean diets produced beneficial changes in most outcomes. Compared with the low-fat diet, the mean changes in the Mediterranean diet with olive oil group and the Mediterranean diet with nuts group were -0.39 mmol/L (95% CI, -0.70 to -0.07 mmol/L) and -0.30 mmol/L (CI, -0.58 to -0.01 mmol/L), respectively, for plasma glucose levels; -5.9 mm Hg (CI, -8.7 to -3.1 mm Hg) and -7.1 mm Hg (CI, -10.0 to -4.1 mm Hg), respectively, for systolic blood pressure; and -0.38 (CI, -0.55 to -0.22) and - 0.26 (CI, -0.42 to -0.10), respectively, for the cholesterol-high-density lipoprotein cholesterol ratio. The Mediterranean diet with olive oil reduced C-reactive protein levels by 0.54 mg/L (CI, 1.04 to 0.03 mg/L) compared with the low-fat diet. LIMITATIONS: This short-term study did not focus on clinical outcomes. Nutritional education about low-fat diet was less intense than education about Mediterranean diets. CONCLUSION: Compared with a low-fat diet, Mediterranean diets supplemented with olive oil or nuts have beneficial effects on cardiovascular risk factors.

*General PREDIMED publication

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