Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med 2013;368:1279-90. DOI: 10.1056/NEJMoa1200303

(PDF updated March 1, 2013.)

SUPPLEMENTARY APPENDIX

Table of Contents

PREDIMED INVESTIGATORS

Steering Committee — R. Estruch (principal investigator), D. Corella, M.I. Covas, MA Martínez-González, E. Ros, and J. Salas-Salvadó.

Clinical End Point Committee — F. Arós (chair), M. Aldamiz, A. Alonso, J. Berjón, L. Forga, J. Gállego, M. A. García Layana, A. Larrauri, J. Portu, J. Timiraus, and M. Serrano-Martínez.

Dietary Intervention Committee — E. Ros (chair), M.I. Covas, M.A. Martínez-González, A. Pérez-Heras, J. Salas-Salvadó, and M. Serra,

Independent Data and Safety Monitoring Board — X. Pi-Sunyer (chair), C.A. González, F.B. Hu, J. Sabaté.

Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain: M. Serra, A. Pérez-Heras, C. Viñas, R. Casas, L. de Santamaría, S. Romero, E. Sacanella, G. Chiva. P. Valderas, S. Arranz J.M. Baena, M. García, M. Oller, J. Amat, I. Duaso, Y. García, C. Iglesias, C. Simón, Ll. Quinzavos, Ll. Parra, M. Liroz, J. Benavent, J. Clos, I. Pla, M. Amorós, M.T. Bonet, M.T. Martin, M.S. Sánchez, J. Altirriba, E. Manzano, A. Altés, M. Cofán, C. Valls-Pedret, A. Sala-Vila, M. Doménech, R. Gilabert, and N. Bargalló.

University of Navarra, Primary Care Centres, Pamplona, Spain: A. Sánchez-Tainta, B. Sanjulián, E. Toledo, M. Bes-Rastrollo, A. Martí, C. Razquin, P. Buil-Cosiales, M. Serrano-Martínez, J. Díez-Espino, A. García-Arellano, I. Zazpe, F.J. Basterra-Gortari, E.H. Martínez-Lapiscina, A. Gea, M. Garcia-Lopez, J.M. Nuñez-Córdoba, N. Ortuño, N. Berrade, V. Extremera-Urabayen, C. Arroyo-Azpa, L García-Pérez, J. Villanueva Tellería, F. Cortés Ugalde, T. Sagredo Arce, Mª D. García de la Noceda Montoy, Mª D. Vigata López, Mª T. Arceiz Campo, A. Urtasun Samper, Mª V. Gueto Rubio, and B. Churio Beraza.

University Rovira i Virgili, Reus, Spain: M. Bulló, R. González, C. Molina, F. Márquez, N. Babio, M. Sorli, J. García Roselló, F. Martin, R. Tort, A. Isach, B. Costa, J.J. Cabré, J. Fernández-Ballart, N. Ibarrola, C. Alegret, P. Martínez, S. Millán, J.L.Piñol, T. Basora and J.M. Hernández.

Institute de Recerca Hospital del Mar, Barcelona, Spain: S. Tello, J. Vila, M. Fitó, H. Schröder, R. De la Torre, D. Muñoz-Aguayo, R. Elosúa, J. Marrugat, and M. Ferrer.

University of Valencia, Valencia, Spain: P. Carrasco, R. Osma, M. Guillén, P. Guillem-Saiz, O. Portolés, V. Pascual, C. Riera, J. Valderrama, A. Serrano, E. Lázaro, A. Sanmartín, A. Girbés, V. Santamaría, C. Sánchez, Z. Plá, E. Sánchez, C. Ortega-Azorín, J.I. González, C. Saiz, O.Coltell and E.M. Asensio.

University Hospital of Alava, Vitoria, Spain: I. Salaverría, T. del Hierro, J. Algorta, S. Francisco, A. Alonso, J. San Vicente, E. Sanz, I. Felipe, A. Alonso Gómez, and A. Loma-Osorio.

University of Málaga, Málaga, Spain: R. Benítez Pont, M. Bianchi Alba, J. Fernández-Crehuet Navajas, J. Wärnberg, R. Gómez-Huelgas, J. Martínez-González, V. Velasco García, J. de Diego Salas, A. Baca Osorio, J. Gil Zarzosa, J.J. Sánchez Luque, and E. Vargas López.

Instituto de la Grasa, Consejo Superior de Investigaciones Científicas, Sevilla, Spain: J. Sánchez Perona, E. Montero Romero, M. García García, and E. Jurado Ruiz.

Institute of Health Sciences IUNICS, University of Balearic Islands, and Hospital Son Espases, Palma de Mallorca, Spain: M. García-Valdueza, M. Moñino, A. Proenza, R. Prieto, G. Frontera, M. Ginard, F. Fiol, A. Jover, and J. García.

Department of Family Medicine, Primary Care Division of Sevilla, Sevilla, Spain: M. Leal, E. Martínez, J.M. Santos, M. Ortega-Calvo, P. Román, F. José García, P. Iglesias, Y. Corchado, E. Mayoral, and C. Lama.

School of Pharmacy, University of Barcelona, Barcelona, Spain: M.C. López-Sabater, A.I. Castellote-Bargallo, A. Medina-Remón, and A. Tresserra-Rimbau.

University of Las Palmas de Gran Canaria, Las Palmas, Spain: J. Álvarez-Pérez, E. Díez Benítez, I. Bautista Castaño, I. Maldonado Díaz, A. Sánchez-Villegas, F. Sarmiendo de la Fe, C. Simón García, I. Falcón Sanabria, B. Macías Gutiérrez, and A.J. Santana Santana.

Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain: E. de la Cruz, A. Galera, Y. Soler, F. Trias, I. Sarasa, E. Padres, R. Figueras, X. Solanich, R. Pujol and E. Corbella.

Primary Care Division, Catalan Institute of Health, Barcelona, Spain: C. Cabezas, E. Vinyoles, M.A. Rovira, L. García, G. Flores, J.M. Verdú, P. Baby, A. Ramos, L. Mengual, P. Roura, M.C. Yuste, A. Guarner, A. Rovira, M.I. Santamaría, M. Mata, C. de Juan, and A. Brau.

Other investigators of the PREDIMED network: M.T. Mitjavila (University of Barcelona), M.P. Portillo (University of Basque Country), G. Sáez (University of Valencia), and J. Tur (University of Balearic Islands).

TRIAL ENROLLMENT CRITERIA

Trial participants were community-dwelling high-risk persons, with ages 55 to 80 years for men and 60 to 80 years for women. They should be free of cardiovascular disease and meet at least one of the two inclusion criteria.

Inclusion criteria. Either **a)** or **b)** should be met:

a) Type 2 diabetes. Diagnosis of diabetes was based on at least one of the following criteria:
- Current treatment with insulin or oral hypoglycemic drugs.
- Fasting glucose > 126 mg/dl (fasting is defined as no caloric intake at least for 8 hours).
- Casual glucose > 200 mg/dl with polyuria, polydipsia, or unexplained weight loss.
- Glucose > 200 mg/dl in two measurements after an oral glucose tolerance test

OR

b) Three or more of the following **risk factors**:
- Current smoker (>1 cig/day during the last month)
- Hypertension (systolic blood pressure >=140 mm Hg or diastolic blood pressure >=90 mmHg or under antihypertensive medication)
- LDL-cholesterol >= 160 mg/dl
- HDL-cholesterol <= 40 mg/dl independently of lipid-lowering therapy
- Body mass index >=25 kg/m^2
- Family history of premature CHD (definite myocardial infarction or sudden death before 55 years in father or male 1st-degree relative, or before 65 years in mother or female 1st-degree relative)
- If the HDL-cholesterol level was >=60 mg/dL, one risk factor was subtracted.

Exclusion criteria. Major exclusion criteria were:

- Documented history of previous cardiovascular disease, including CHD (angina, myocardial infarction, coronary revascularization procedures or existence of abnormal Q waves in the electrocardiogram (EKG)), stroke (either ischemic or hemorrhagic, including transient ischemic attacks), or clinical peripheral artery disease with symptoms of intermittent claudication.
- Severe medical condition that may impair the ability of the person to participate in a nutrition intervention study (e.g. digestive disease with fat intolerance, advanced malignancy, or major neurological, psychiatric or endocrine disease)
- Any other medical condition thought to limit survival to less than 1 year.
- Immunodeficiency or HIV-positive status.
- Illegal drug use, chronic alcoholism or problematic use of alcohol or total daily alcohol intake >80 g/d.
- Body mass index > 40 kg/m^2.
- Difficulties or major inconvenience to change dietary habits
- Impossibility to follow a Mediterranean-type diet, for religious reasons or due to the presence of disorders of chewing or swallowing (e.g., difficulties to consume nuts)

- A low predicted likelihood to change dietary habits according to the Prochaska and DiClemente stages of change model (1).
- History of food allergy with hypersensitivity to any of the components of olive oil or nuts.
- Participation in any drug trial or use of any investigational drug within the last year.
- Institutionalized patients for chronic care, those who lacked autonomy, were unable to walk, lacked a stable address, or were unable to attend visits in the Primary Care Health Centres every 3 months.
- Illiteracy.
- Patients with an acute infection or inflammation (e.g., pneumonia) were allowed to participate in the study 3 months after the resolution of their condition.

DIETARY INTERVENTION PROTOCOL

Generalities

The PREDIMED trial is a large controlled, randomized clinical trial in a high-risk population aimed to assess whether Mediterranean diets enriched with extra-virgin olive oil or mixed nuts prevent cardiovascular diseases in comparison with a Control group where participants receive advice to follow a low-fat diet. As secondary outcomes, we will also assess diet effects on all-cause mortality and the incidence of heart failure, diabetes, cancer, cognitive decline, and other neurodegenerative disorders.

The PREDIMED dietary intervention followed a behavioral strategy focused on modifying the way an individual views the dietary pattern, appraises its meaning, and makes informed choices. We applied common cognitive behavioral techniques, including goal setting, self-monitoring, feedback and reinforcement, self-efficacy enhancement, incentives, problem solving, relapse prevention, and motivational interviewing in quarterly individual and group sessions throughout the duration of the trial. Measurable realistic goals easily identifiable by the participant and attainable in specified time frames were set. The provision of extra-virgin olive oil and nuts contributes to a higher compliance with the overall food pattern of the Mediterranean diet in the corresponding groups. Even if the Mediterranean diet itself contains both olive oil and nuts, the supplementation with either virgin olive oil or nuts increases the intake of fat coming from natural vegetable sources. This also increases the palatability of the diet and represents an incentive for participants to maintain an adequate long-term compliance with the intended dietary changes. In addition, this approach ensures that the variety of olive oil consumed in the first group corresponds to a polyphenol-rich extra-virgin olive oil, and a high amount of nuts is consumed in the second group. Critical to this aspect of the study is the fact that we could assure the generous donation of these food items throughout the trial. Due to the difficulty to choose amongst the wide variety of low-fat foods and to budget restraints, participants in the Control diet group received only small non-food gifts, such as kitchenware, tableware, aprons, or shopping bags to promote retention into the trial.

From a public health perspective, a behavioral intervention coupled with an easy (free) access to representative healthy foods is a realistic test of the effectiveness to be attained with official policies and health promotion activities. The PREDIMED trial attempts to obtain relevant information for public health use because the nutritional intervention is undertaken in free-living persons who receive information, motivation, support and empowerment to modify their food habits in a real-life context, i.e., they continue to buy their foods and cook their meals. Such an intervention provides a real life scenario that may be easily applied to public health policies. Given that the palatability of meals is critical to ensure compliance, the PREDIMED protocol included the quarterly delivery of shopping lists, menus, and recipes with these characteristics to participants in the three study groups.

The rationale for comparing 2 Mediterranean diet groups (one with supplemental extra-virgin olive oil and one with supplemental nuts) instead of one to the Control diet group was as follows. Besides being a rich source of monounsaturated fatty acids, extra-virgin olive oil used in one arm of the study is a good source of phenolic antioxidants. One-half the dose of the nuts used in another arm of the study was made up of walnuts, thus containing sizeable amounts of polyunsaturated fatty acids, particularly linoleic acid and alpha-linolenic acid, the plant-derived omega-3 fatty acid, in addition to polyphenols. The other half of nut doses was almonds and hazelnuts, both rich in monounsaturated fatty acids and polyphenols. Thus, one Mediterranean diet was enriched in monounsaturated fatty acids and polyphenols and the other Mediterranean diet was enriched in n-9, n-6 and n-3

polyunsaturated fatty acids as well as polyphenols. Although having the same general food pattern of the Mediterranean diet, the two arms of the study differed in the intake of two foods (extra-virgin olive oil and nuts) and two nutrients (monounsaturated fatty acids and polyunsaturated fatty acids, including alpha-linolenic acid) that are all felt to be important in cardiovascular prevention and might have differential beneficial effects.

The main focus of the PREDIMED Study was to change the dietary pattern instead of focusing on changes in macronutrients. As opposed to recommendations to participants allocated the Control diet, total fat intake for the 2 Mediterranean diet groups was *ad libitum* (a high fat intake was allowed, as long as most fat was derived from fatty fish and vegetable sources, particularly olive oil and nuts). There were no specific energy restrictions for any study arm. Importantly, caution was taken to minimize the possibility that participants with obesity, diabetes, hypertension or dyslipidemia received contradictory dietary advice from other health professionals external to the PREDIMED trial.

Registered dietitians were directly responsible for all aspects of the dietary intervention at each site. All PREDIMED dietitians were trained and certified to deliver the intervention protocol. Before implementation of the protocol, training consisted of: 1. approximately 24 hours of initial theoretical and practical group discussion with experts in nutrition education; and 2) discussion in between 3 to 5 conference calls to review and improve the protocol. During these calls each dietitian discussed his/her practice sessions with the team in order to identify problems and find solutions in the implementation of the protocol. Feedback and discussion also took place among the dietitians and the site coordinators. These calls were continued quarterly throughout the study. In addition, a yearly 1-day conference with attendance of all the dietitians and Dietary Intervention Committee members was scheduled. This meeting dealt, amongst others, with the following critical points: 1. update on personnel and affiliations in all participating sites; 2. assessment of site-specific needs regarding personnel and/or study materials; 3. review of food frequency and physical activity questionnaires collected per site and online updating procedures; 4. evaluation of the appropriateness of dietary instructions per treatment group made by the Dietary Intervention Committee and posted quarterly online in the PREDIMED website; 5. review of the adherence to the intervention, diet-related adverse effects and solutions thereof; 6. appraisal of the quality of supplemental foods last shipped per site; 7. update on protocols of shipping and storage of biological samples; and 8. site-specific problems with follow-up and how to solve them.

Description of the Interventions

First visit with the dietitian. At screening visit 2, after participants had signed the informed consent and were randomized to one of three diet groups, the following procedures were implemented during an individual visit with the dietitian of at least 1-h duration:

a) In a face-to-face interview with the candidate, the dietitian explained in detail the purpose and anticipated development of the study.

b) The dietitian reviewed (and completed with the participant if needed) the food frequency and physical activity questionnaires that were provided at screening visit 1. Alternatively, the participant who had difficulties to fill in the questionnaires at home did it during the visit with continuous help by the dietitian.

c) During the same visit, the study nurse filled in a general medical questionnaire, performed anthropometrical and blood pressure measurements, determined the ankle-arm blood

pressure index, performed an electrocardiogram, and obtained pre-specified biological samples.

Individual motivational interview. After screening visit 2, participants randomized to any of the three study arms had a face-to-face interview with the dietitian that comprised the following points:

a) Administration of the validated 14-item questionnaire of adherence to the Mediterranean diet (**Table S1**), including a point-by-point review and construction of the individual score.

b) Personal individual recommendations for changes to be introduced in the participant's diet in order to achieve a personalized goal depending on group assignment. The dietitian provided a comprehensive number of reasons to adopt a Mediterranean diet or a low-fat diet, highlighting the advantages of following this diet rather than the risks of not adhering to it, and transmitting a positive message with stress on the particular benefits for the high cardiovascular risk status of the participants. The dietitian personalized the message by adapting it to the participant's clinical condition, preferences, and beliefs. The training of the PREDIMED dietitians emphasized the holistic approach to lifestyle change in order to tailor the intervention to nutritional assessment and individual needs. A contracting procedure was used and a negotiated change in diet was the targeted goal, working with the subject to determine what he or she considered an attainable goal. The focus could be shifted from changing portion sizes to frequency of intake or cooking methods.

c) The participant was scheduled for a group session in the next 1 to 2 weeks. The visit ended with an agreement to participate in the group session.

Group sessions. The PREDIMED dietitians run the group sessions, which were scheduled quarterly and attended by up to 20 participants per session. Separate sessions were organized for each of the three study groups (Mediterranean diet with extra-virgin olive oil, Mediterranean diet with nuts, and Control diet). Each group session included:

a) Informative talk with recall of the dietary goals for the particular study arm, with open discussion.

b) Description of the following written material, with printed copies given to each participant:

-Elaborate descriptions of 4 to 5 foods typical of the dietary pattern corresponding to the particular arm of the study and adapted to the season of the year.

-A quantitative 1-week shopping list of food items, according to the season of the year (see: www.predimed.org).

-A weekly plan of meals (with detailed menus) corresponding to the shopping list (see: www.predimed.org).

-The recipes for preparing the meals of the suggested menus.

c) Clarifications of any doubts regarding the instructions provided.

d) Depending on group assignment, 3-month allotments of supplemental foods were provided to participants in the Mediterranean diet groups, together with instructions about their use and conservation. Alternatively, non-food gifts were given to participants in the Control diet group during the corresponding session.

e) The session ended with an agreement to participate in the next visit 3 months later.

Follow-up visits and reiteration of individual and group sessions. The individual motivational interviews and group sessions were repeated every 3 months with the same contents. Each visit included three steps: assessment, intervention, and future directions.

Peculiarities of the intervention by group assignment.

1. Mediterranean diet groups. In these two groups the 14-item questionnaire of adherence to the Mediterranean diet (**Table S1**) was instrumental for the intervention. Based on the last assessment of individual Mediterranean diet scores, the dietitian gave personalized dietary advice to each participant, with recommendations on the desired frequency of intake of specific foods directed to upscale the score. Accomplishments in the previous months, even if minor (i.e., a one point increase in the score), were considered as support to provide further empowerment and self-reward.

The general guidelines to follow the Mediterranean diet that dietitians provided to participants included the following positive recommendations: a) abundant use of olive oil for cooking and dressing dishes; b) consumption of ≥ 2 daily servings of vegetables (at least one of them as fresh vegetables in a salad), discounting side dishes; c) ≥ 2-3 daily servings of fresh fruits (including natural juices); d) ≥ 3 weekly servings of legumes; e) ≥ 3 weekly servings of fish or seafood (at least one serving of fatty fish); f) ≥ 1 weekly serving of nuts or seeds; g) select white meats (poultry without skin or rabbit) instead of red meats or processed meats (burgers, sausages); h) cook regularly (at least twice a week) with tomato, garlic and onion adding or not other aromatic herbs, and dress vegetables, pasta, rice and other dishes with tomato, garlic and onion adding or not aromatic herbs. This sauce is made by slowly simmering the minced ingredients with abundant olive oil. Negative recommendations are also given to eliminate or limit the consumption of cream, butter, margarine, cold meat, pate, duck, carbonated and/or sugared beverages, pastries, industrial bakery products (such as cakes, donuts, or cookies), industrial desserts (puddings, custard), French fries or potato chips, and out-of-home pre-cooked cakes and sweets.

The dietitians insisted that two main meals per day should be eaten (seated at a table, lasting more than 20 minutes). For usual drinkers, the dietitian's advice was to use wine as the main source of alcohol (maximum 300 ml, 1-3 glasses of wine per day). If wine intake was customary, a recommendation to drink a glass of wine per day (bigger for men, 150 ml, than for women, 100 ml) during meals was given. *Ad libitum* consumption was allowed for the following food items: nuts (raw and unsalted), eggs, fish (recommended for daily intake), seafood, low-fat cheese, chocolate (only black chocolate, with more than 50% cocoa), and whole-grain cereals. Limited consumption (≤1 serving per week) was advised for cured ham, red meat (after removing all visible fat), and cured or fatty cheeses.

Depending on group allocation, either a 15-liter (1 liter per week for 15 weeks) supply of extra-virgin olive oil (®Hojiblanca and ®Fundación Patrimonio Comunal Olivarero, both from Spain) or 3-month allowances of nuts consisting of 2 Kg (15 g per day) sachets of walnuts (®California Walnut Commission, Sacramento, CA), 1 Kg (7.5 g per day) sachets of almonds (®Borges SA, Reus, Spain), and 1 Kg (7.5 g per day) sachets of hazelnuts (®La Morella Nuts, Reus, Spain) were delivered to participants in the corresponding Mediterranean diet groups during each quarterly group session. Individualized methods of supplemental food delivery were devised for occasions in which participants needed to have their 3-month session rescheduled. Provisions were made to improve participants' compliance. Thus, the extra-virgin olive oil allowance (1 liter per week) and additional amounts of mixed nuts took into account the needs of the whole family.

In the Mediterranean diet with nuts group we offered participants three types of tree nuts, walnuts, hazelnuts and almonds. As stronger evidence supports that alpha-linolenic acid-rich walnuts might offer special advantages in cardiovascular prevention, we supplied a higher amount of walnuts than of almonds and hazelnuts.

Fatty foods such as olive oil and nuts, even if rich in unsaturated fatty acids, are still perceived as fattening by some nutrition experts. Due to this, it was particularly important to allay the fear of an eventual weight gain that might have both the person who is on a weight-management program and his/her nutritionist. This was done by a comprehensive exposition of recent scientific evidence suggesting that these foods do not promote weight gain and might even help to lose weight. In the case of nuts, consistent evidence indicates that their lack of a fattening effect is mainly due to satiety with subsequent food compensation. For this reason, the dietitian specifically pointed out that nuts could be eaten anytime during the day except after dinner, when food compensation in the next meal could not reasonable take place.

2. *Control diet group*. The focus in the control group was to reduce all types of fat, with particular emphasis in recommending the consumption of lean meats, low-fat dairy products, cereals, potatoes, pasta, rice, fruits and vegetables (**Table S2**).

In the Control group, advice on vegetables, red meat and processed meats, high-fat dairy products, and sweets concurred with the recommendations of the Mediterranean diet, but use of olive oil for cooking and dressing and consumption of nuts, fatty meats, sausages, and fatty fish were discouraged. A 9-item quantitative score of compliance with the low-fat control diet was constructed (**Table S3**) as an instrument for dietitians to assess and modify the participant's dietary pattern. The last assessment of the 9-item score helped dietitians to give personalized advice in order to upgrade it in a similar way than the 14-item Mediterranean diet score was instrumental to enhance the Mediterranean diet in the corresponding intervention groups. Similarly, accomplishments in the previous months were used as support to provide further empowerment and self-reward. Cooking instructions were also given to participants in the control group about the preparation of foods to avoid frying and using instead steaming, broiling, or microwaving.

The initial dietary protocol for the Control group started with the delivery of a leaflet summarizing the recommendations to follow a low-fat diet (**Table S2-S3**) and scheduled one yearly visit. In October 2006, 3 years into the trial, we realized that such a low-grade intervention might potentially represent a weakness of the trial and amended the protocol to include quarterly individual and group sessions with delivery of food descriptions, shopping lists, meal plans and recipes (adapted to the low-fat diet) in such a way that the intensity of the intervention was similar to that of the Mediterranean diet groups, except for the provision of supplemental foods for free. This amendment of the protocol in no way meant a change in the quality and specific goals of the recommendations to the control group; it was only an enhancement in the eagerness of the intervention to make it similar to that delivered to participants in the Mediterranean diet groups.

BIOMARKERS OF COMPLIANCE

Methods

At 1, 3, and 5 years of follow-up we determined objective biomarkers of adherence to the supplemental foods in random samples of participants (urinary hydroxytyrosol, the main phenolic compound in extra-virgin olive oil, by gas chromatography–mass spectrometry, and the plasma proportion of alpha-linolenic acid by gas-chromatography, as a measure of adherence to walnut consumption).

DIAGNOSTIC CRITERIA FOR TRIAL END POINTS

(Version July, 2005 – Modified December, 2006)

1. Primary end point

The primary end point is a composite end point that is defined as the first occurrence of cardiovascular death, myocardial infarction, or stroke. All of these components of the primary end point are also secondary end points as defined below.

2. Secondary end points

A. Myocardial infarction (MI)

Criteria for acute, evolving or recent MI

Either one of the following criteria satisfies the diagnosis of acute MI (2):

- Typical rise or gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:
  - Ischemic symptoms: Include chest, epigastric, arm, wrist or jaw discomfort with exertion or rest, that usually lasts at least for 20 min and may be associated with unexplained nausea and vomiting, persistent shortness of breath, weakness, dizziness, lightheadedness or syncope, or a combination of these.
  - Development of pathologic Q waves in the ECG: Any Q waves in leads V_1 through V_3 or Q wave higher or equal to 30 ms (0.03 s) in leads I, II, aVL, aVF, V_4, V_5 or V_6. The Q wave changes must be present in any two contiguous leads, and be above or equal to 1 mm in depth;
  - ECG changes indicative of ischemia (ST segment elevation or depression):
    - New or presumed new ST segment elevation at the J point in two or more contiguous leads with the cutoff points $\geq$ 0.2 mV in leads V1, V2 or V3 and $\geq$ 0.1 mV in other leads.
    - ST segment depression in at least two contiguous leads.
    - T wave inversion $\geq$ 0.1 mV in at least two contiguous leads.
  - Coronary artery intervention (e.g., coronary angioplasty)
- Findings of acute MI at pathological examination.

Established MI

Myocardial necrosis or clinically established MI (2) is defined from standard 12-lead ECG criteria in the absence of QRS confounders (e.g., bundle branch block, left ventricular hypertrophy or Wolff-Parkinson-White syndrome) when the following QRS changes are present:

- Any Q waves in leads V_1 through V_3 or
- Q wave higher or equal to 30 ms (0.03 s) in leads I, II, aVL, aVF, V_4, V_5 or V_6. The Q wave changes must be present in any two contiguous leads, and be higher or equal to 1 mm in depth.

B. Stroke

Acute neurological deficit lasting more than 24 hours caused by an abrupt impairment of brain function due to blockage of blood flow in a particular artery supplying the brain (thrombosis or arterial embolism) or a cerebral hemorrhage This definition does no include the transient ischemic attack (TIA). To exclude other diagnosis such as hypoglycemia or seizures, a brain imaging technique (computed tomography [CT] or magnetic resonance imaging [MRI]) should demonstrate a cerebral infarction or hemorrhage (3-5).

C. Cardiovascular death

For the purpose of this study, cardiovascular death included the following causes of death: coronary heart disease deaths (i.e., acute myocardial infarction, unstable angina pectoris, and other forms of chronic ischemic heart disease), stroke, arrhythmias, dysrrhythmias, congestive heart failure, pulmonary edema, pulmonary embolisms, and ruptured aortic aneurysm (6,7).

D. All-cause mortality

This end point includes all causes of death, including cardiovascular and non-cardiovascular causes. All deaths should be confirmed by reviewing the National Death Index.

APPROACHES FOR DEALING WITH MISSING DATA

We followed the suggestions given by Groenwold et. al. (8) to handle potentially missing outcome data in randomized trials.

In order to conduct sensitivity analyses on missing outcomes, we considered as missing outcome data the potential occurrence of a primary end-point (major cardiovascular event) among 516 participants for whom we had no documented primary event and who were lost to follow-up for 2 years or longer.

We conducted three sensitivity analyses:

a) In the complete case analysis (adjusted) we excluded these 516 subjects from the computation of hazard ratios and adjusted the Cox model for all the covariates mentioned in Table 3 of the main text (recruiting centre, sex, age, family history of premature coronary

heart disease, smoking, body mass index, waist-to-height ratio, baseline hypertension, dyslipidemia, and diabetes).

b) In the single imputation approach, observed participant data for the above-mentioned covariates were used as predictors of the major end-point among the 516 participants lost to follow-up. The missing data were imputed with predicted values from a multivariable logistic regression model that included these observed participant data as predictors.

c) In multiple imputations we tried to overcome the problem that the single imputed values are not actually observed but predicted values, and imputing the most probable value therefore overestimates the precision and distorts the distribution of the data. Instead of a single (most likely) value, 10 values were sampled from an estimated uniform distribution (also taking into account the previously mentioned predictors) and imputed for the 516 participants lost to follow-up adding a random term. Hence, 10 data sets with imputed outcomes were created. We allowed for several scenarios of cumulative absolute incidence rates of the major end-point ranging from 2.0% to 10.0% among drop outs (516 participants lost to follow-up). Each data set was analyzed using multivariable-adjusted Cox models and, subsequently, the results were pooled by using standard techniques, also taking into account the variation between imputed data sets (9).

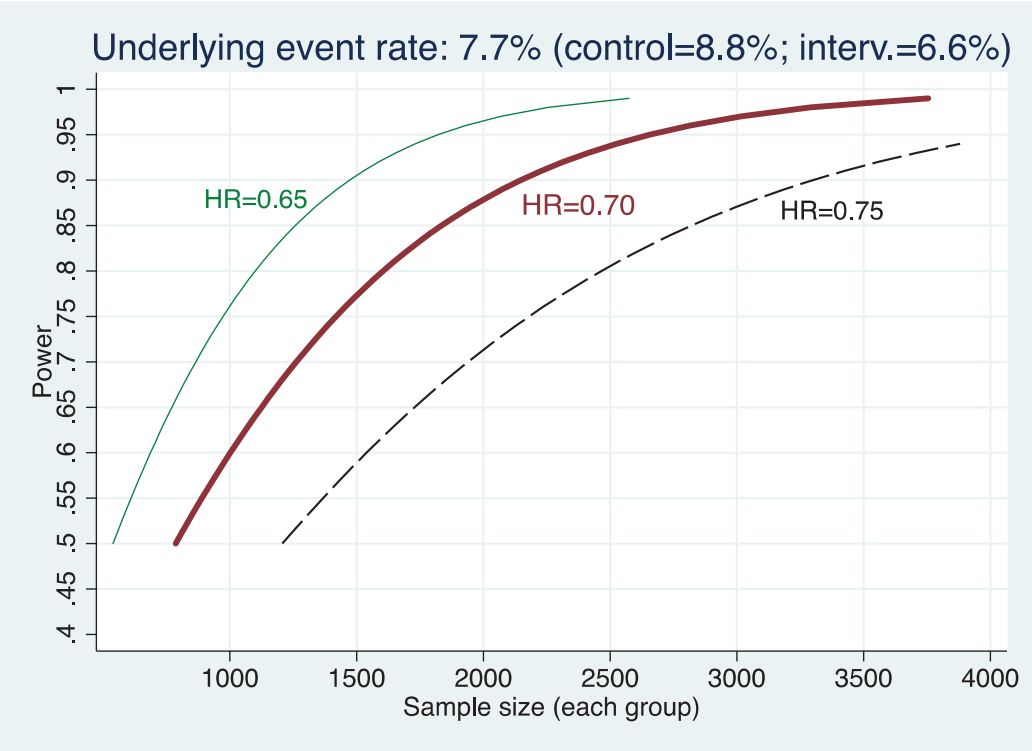
ADVERSE EVENTS

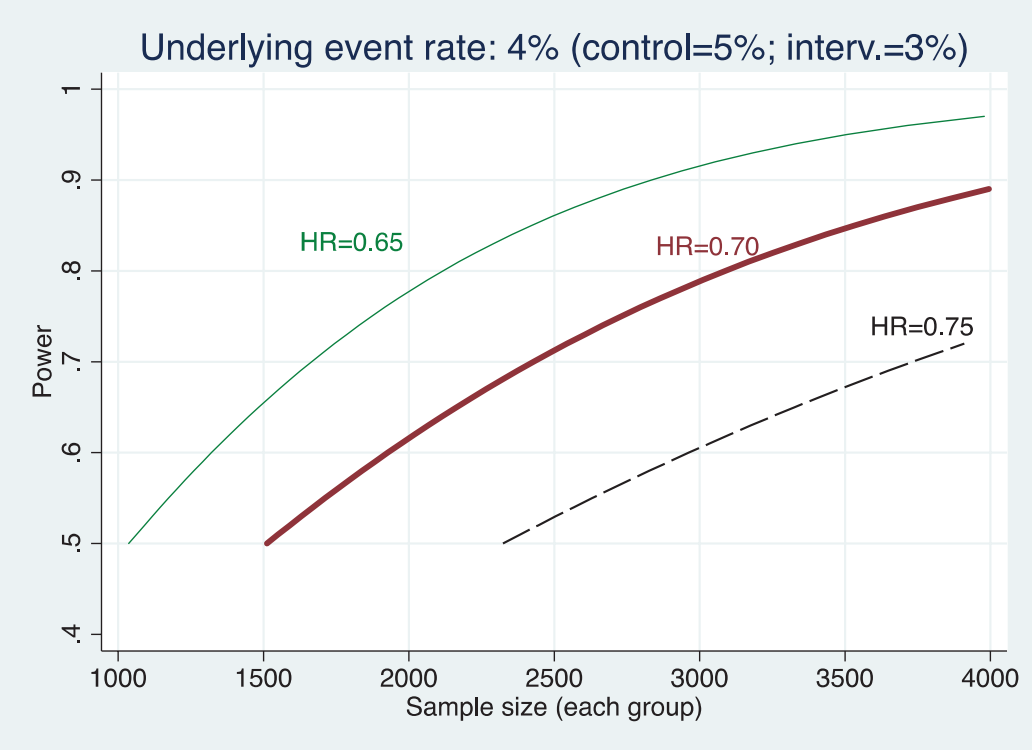
Yearly tolerance and side effect questionnaires inquired about mouth complaints; bloating, fullness, or indigestion; altered bowel habit; and any other diet-related symptom.

A small proportion of participants (<4%) assigned to the MeDiet with nuts had difficulties in chewing the nuts. These problems were solved satisfactorily by the advice to consume the nuts crushed and mixed, for instance, with low-fat yogurt. A still lower proportion of participants reported inconveniences to follow the MeDiet with EVOO or the control diet, which were due mainly to temporary complaints of bloating and fullness.

SAMPLE SIZE AND STATISTICAL POWER CONSIDERATIONS

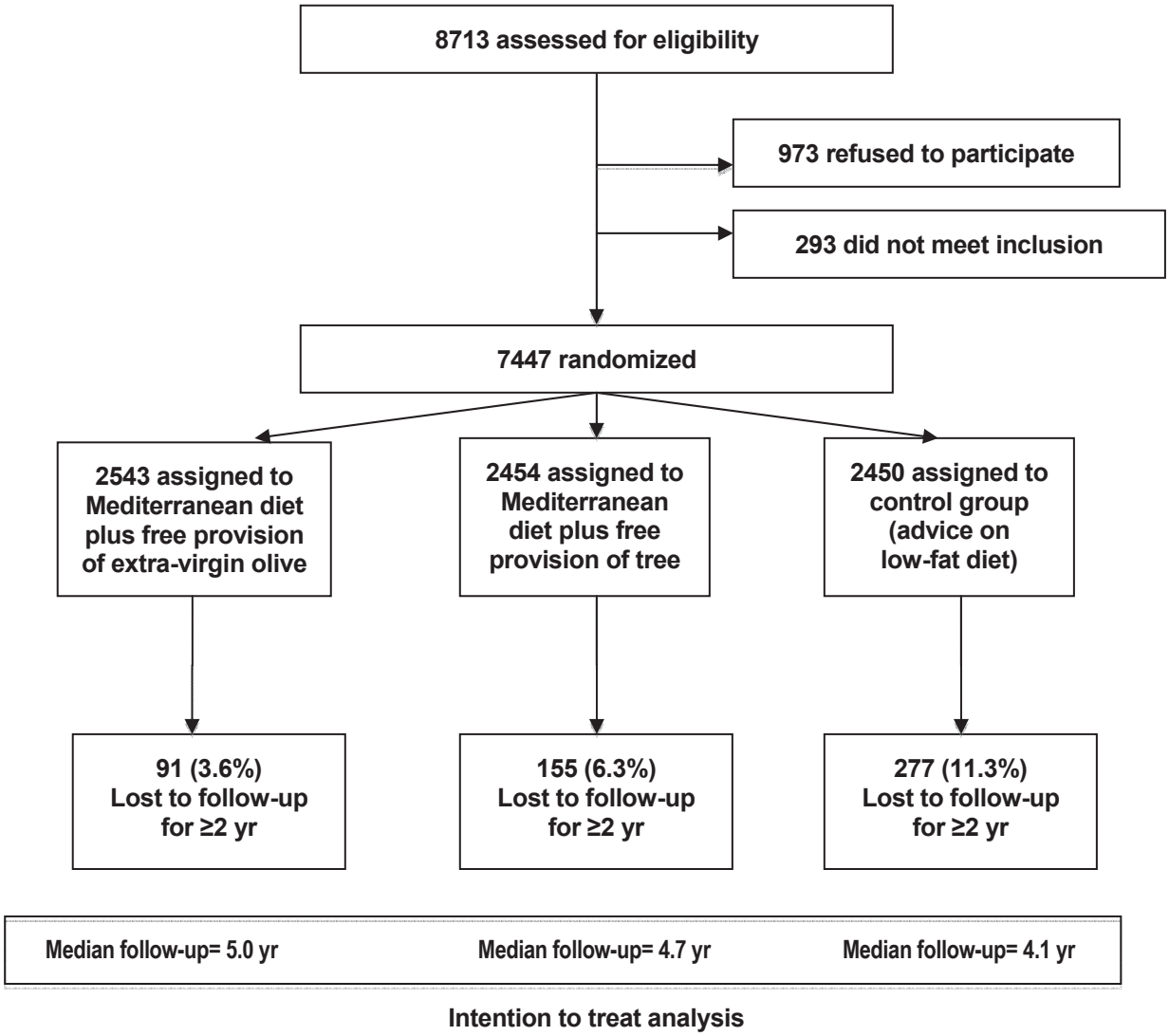
Figure S1. Power Curves under Several Assumptions for Anticipated Effect Estimates (as of April 2008) for the Comparison of a Mediterranean Diet Intervention Group versus the Control Diet Group.





HR= Hazard ratio.

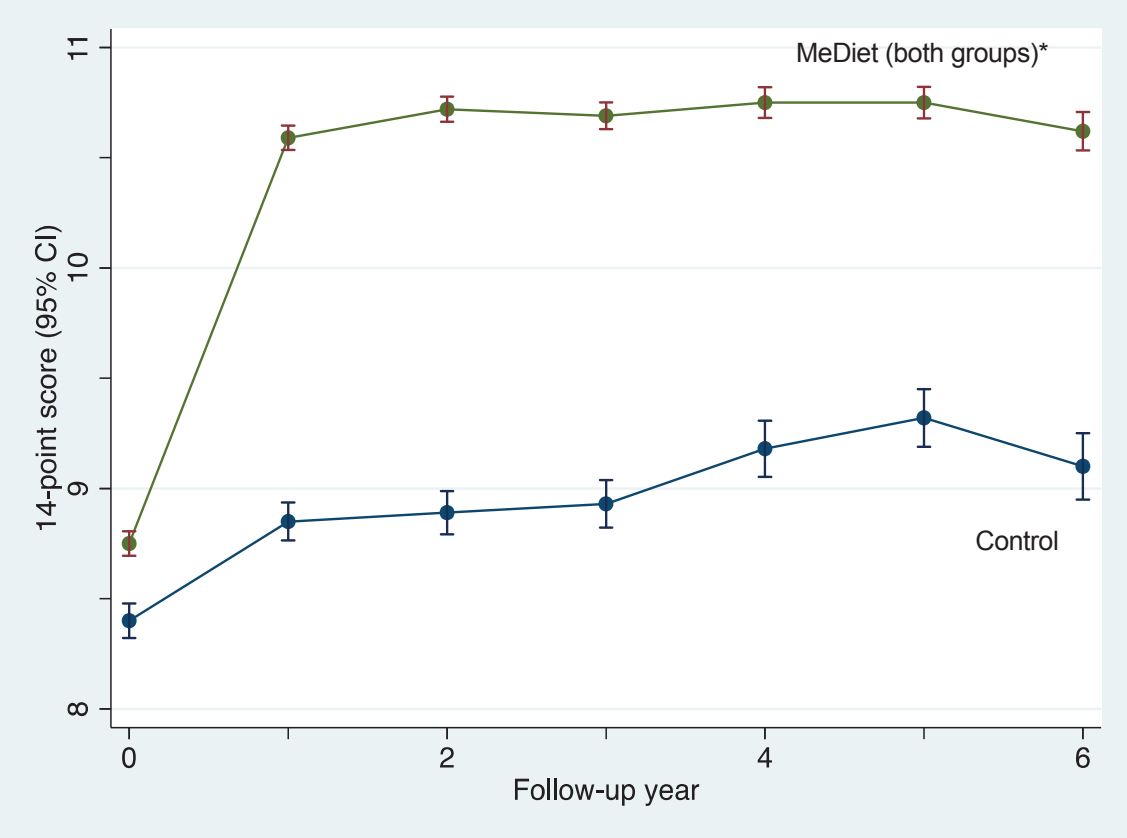
Figure S2. Trial Profile.



COMPLIANCE WITH THE DIETARY INTERVENTION

After the first follow-up year, mean scores of adherence to the Mediterranean diet were significantly higher in the two Mediterranean diet groups than in the control diet group ($p<0.0001$ for all yearly comparisons from year 1 to 6 of follow-up). However, the magnitude of differences in the 14-point score between the Mediterranean diet intervention (both groups merged) and the control diet group was not large, ranging from 1.4 to 1.8 points.

Figure S3. Changes in Mean Adherence to the Mediterranean Diet during Follow-up. Mean adherence to the 14-item score of Mediterranean diet (95% confidence intervals) during follow-up. The two Mediterranean diet intervention groups were merged together.

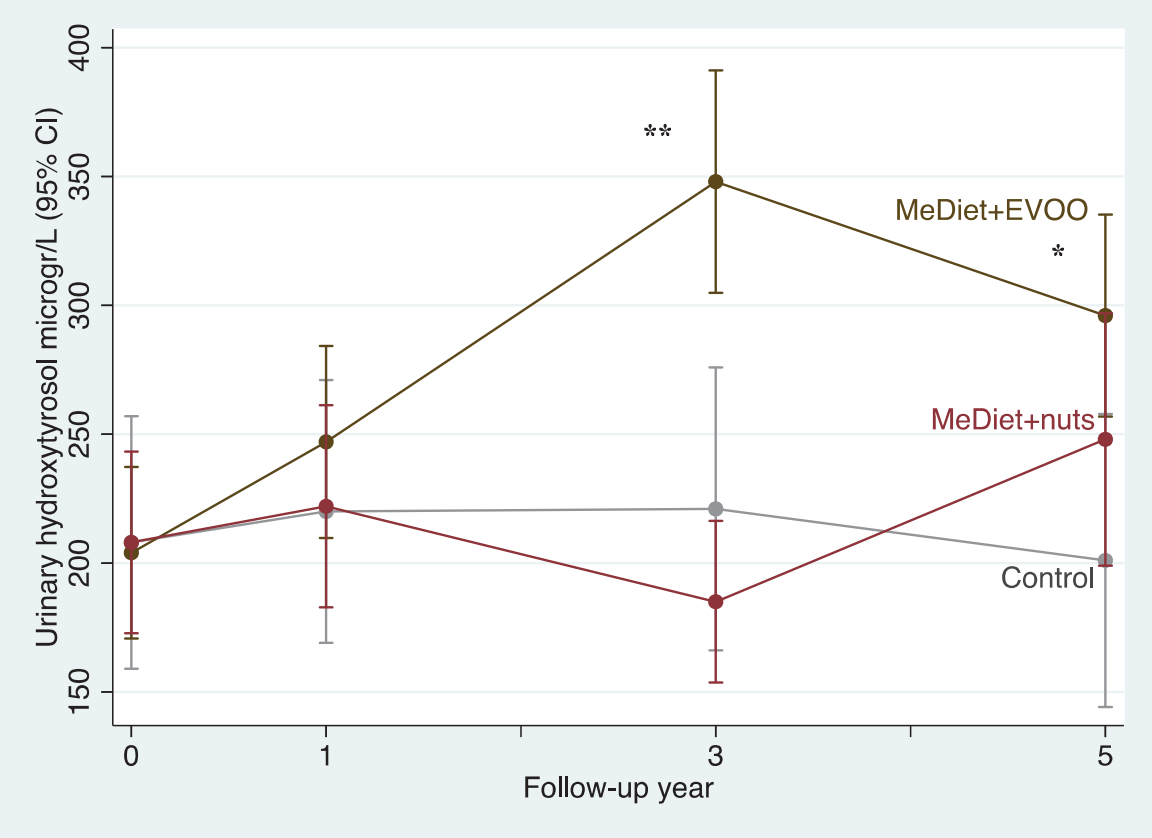


*P<0.001 for all six comparisons in years 1 to 6 by analysis of variance.
MeDiet, Mediterranean diet; CI, confidence interval.

CHANGES IN OBJECTIVE BIOMARKERS

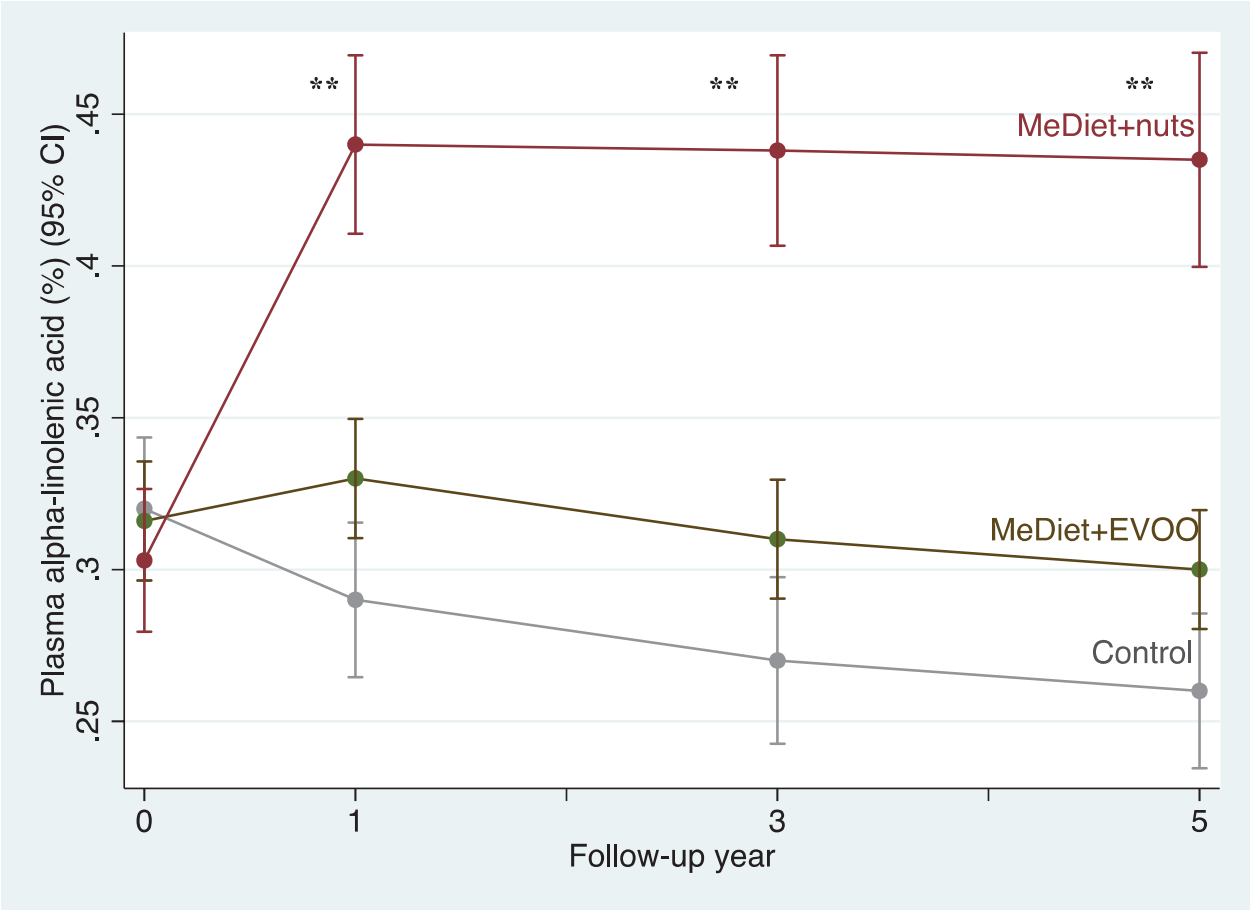
Changes in objective biomarkers of EVOO and walnut consumption, determined in random samples of participants [N=750 (10.1%) and 375 (5.0%), respectively], also indicated good compliance.

Figure S4. Urinary Hydroxytyrosol Concentrations (95% Confidence Intervals) at Baseline and at 1, 3 and 5 Years of Follow-up (N = 750).



*P < 0.05, **P<0.001 from baseline. Paired t-tests.
MeDiet, Mediterranean diet; EVOO, extra-virgin olive oil.

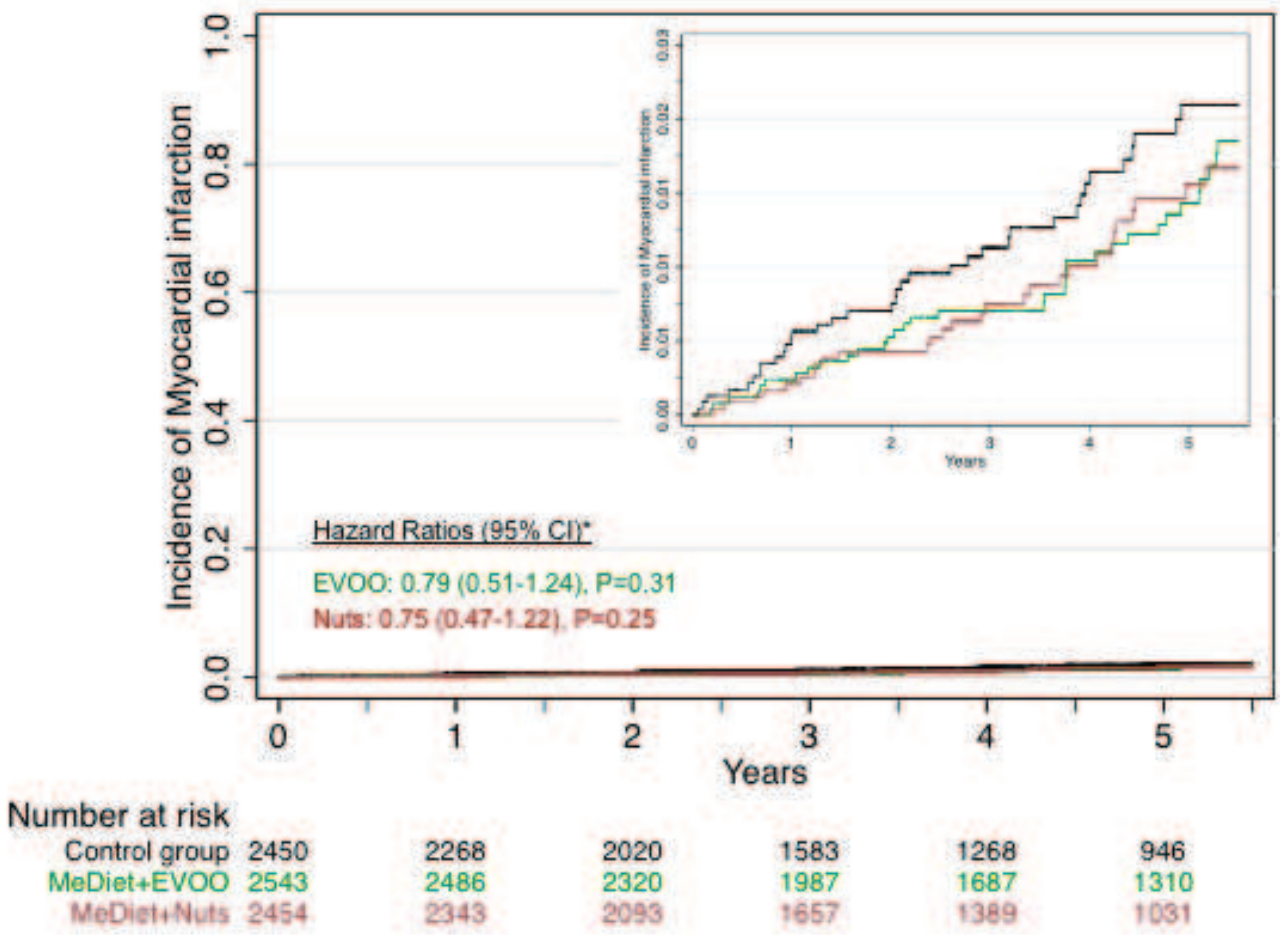
Figure S5. Plasma Alpha-Linolenic Acid (%) in the Three Arms of the Trial (95% Confidence Intervals) at Baseline and at 1, 3 and 5 Years of Follow-up (N = 375).



**P<0.001 from baseline by paired t-test.
MeDiet, Mediterranean diet; EVOO, extra-virgin olive oil.

Figure S6. Kaplan-Meier Estimates of Incidence of each Separate Component of the Primary End-point.

A) Myocardial Infarction



Number at risk

Control group	2450	2268	2020	1583	1268	946
MeDiet+EVOO	2543	2486	2320	1987	1687	1310
MeDiet+Nuts	2454	2343	2093	1657	1389	1031

Figure S6. Kaplan-Meier Estimates of Incidence of each Separate Component of the Primary End-point (cont.).

B) Stroke

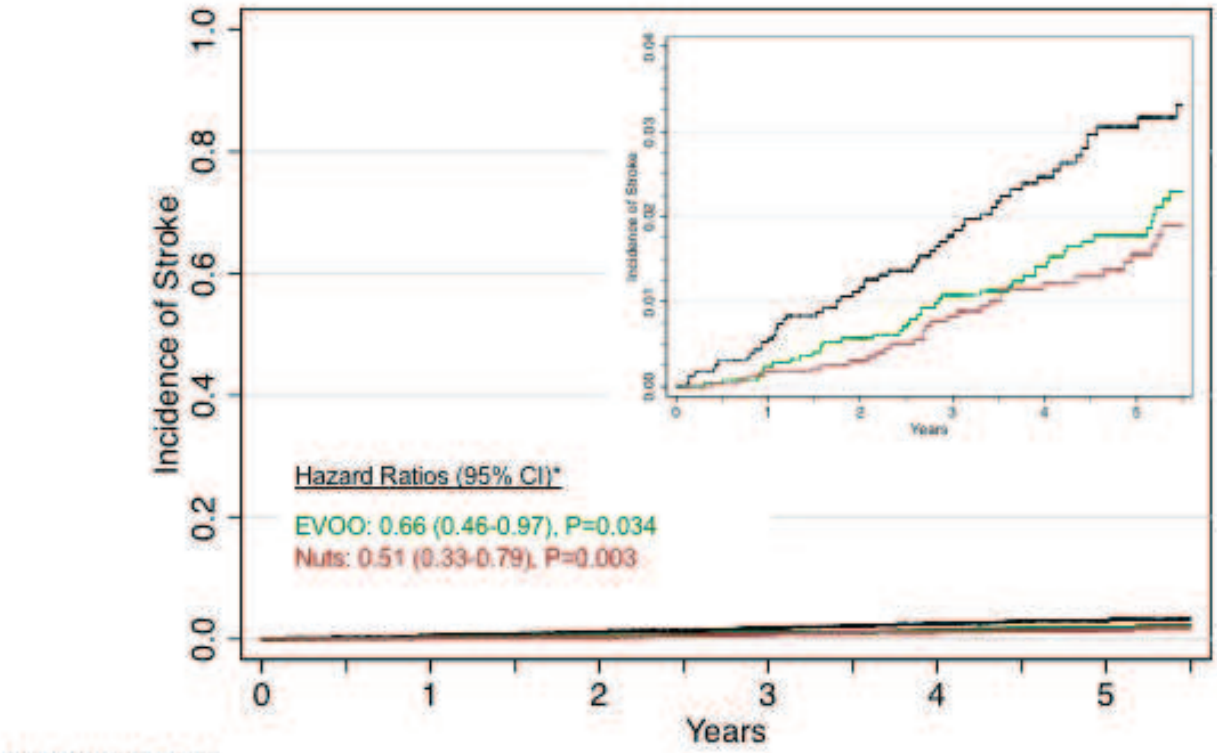


Figure S6. Kaplan-Meier Estimates of Incidence of each Separate Component of the Primary End-point (cont.).

C) Cardiovascular Death

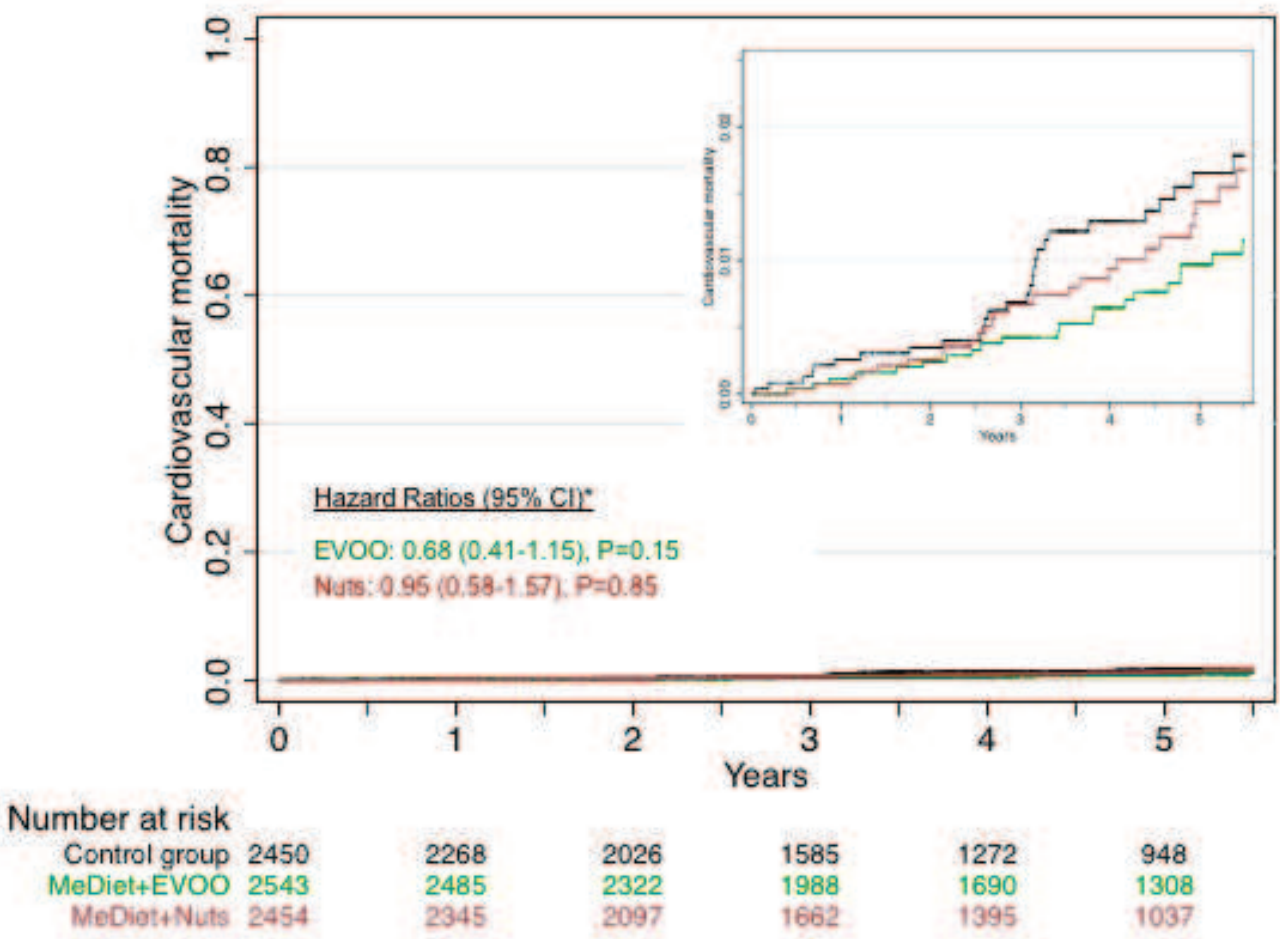


Table S1. Quantitative Score of Compliance with the Mediterranean Diet.

	Foods and frequency of consumption	Criteria for 1 point*
1	Do you use olive oil as main culinary fat?	Yes
2	How much olive oil do you consume in a given day (including oil used for frying, salads, out of house meals, etc.)?	4 or more tablespoons
3	How many vegetable servings do you consume per day? *(1 serving = 200g - consider side dishes as 1/2 serving)*	2 or more *(at least 1 portion raw or as salad)*
4	How many fruit units (including natural fruit juices) do you consume per day?	3 or more
5	How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? *(1 serving = 100-150 g)*	Less than 1
6	How many servings of butter, margarine, or cream do you consume per day? *(1 serving = 12 g)*	Less than 1
7	How many sweet/carbonated beverages do you drink per day?	Less than 1
8	How much wine do you drink per week?	7 or more glasses
9	How many servings of legumes do you consume per week? *(1 serving = 150 g)*	3 or more
10	How many servings of fish or shellfish do you consume per week? (1 serving: 100-150 g fish, or 4-5 units or 200 g shellfish)	3 or more
11	How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	Less than 3
12	How many servings of nuts (including peanuts) do you consume per week? *(1 serving = 30 g)*	3 or more
13	Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburger or sausage?	Yes
14	How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with *sofrito* (sauce made with tomato and onion, leek, or garlic, simmered with olive oil)?	2 or more

* 0 points if these criteria are not met.

Table S2. Leaflet of General Recommendations to Follow a Low-Fat Diet.

Bread, pasta, rice, fruit, vegetables, legumes and salads are part of a healthy diet. Prepare these foods in a healthy way and help you and your family eat less fat.

BUY LOW-FAT FOODS

- Bread
- Cereals and pasta
- Rice
- Potatoes
- Fruit and vegetables
- Beans, lentils, chick-peas
- Low-fat milk, cheese, and other dairy products
- Lean fish and seafood
- Chicken and duck meat with the skin removed
- Meat cuts low in fat instead of high-fat ones such as beacon, beef and lamb

COOK WITH LESS FAT

- Avoid using oil, butter or fat-based sauces
- Dress dishes with the least possible oil
- Employ simple cooking methods, such as boiling, baking or broiling. Avoid stewing, frying, breading and use of “sofrito”
- Use the least possible amount of oil in the frying pan, enough to avoid sticking of food

REMOVE FAT

- Do not smear bread or toast with butter, margarine, oil or other fat spreads
- Remove all visible fat from meat before cooking
- Remove all fat released from meat while cooking
- Cool soups and broths to remove fat layer on top before heating

WHICH FOODS CONTAIN MOST FAT AND SHOULD NOT BE CONSUMED?

- Oils and oil-based dressings
- Butter, margarine, lard
- Fat-enriched dairy products, heavy cream, custard, ice cream
- Fatty meats, sausages, cold cuts, beacon, cracklings
- Liver, kidney and offal in general
- Fried foods
- Commercial sauces, mayonnaise
- Commercially cooked foods
- Tree nuts and peanuts
- Sunflower seeds, French fries and other salty snacks
- Cakes, pies, pastries, cookies, crackers

Table S3. Quantitative Score of Compliance with the Control (Low-Fat) Diet.

	Foods and frequency of consumption	Criteria for 1 point*
1	How much olive oil do you consume in a given day (including oil used for frying, salads, out of house meals, etc.)?	2 or less tablespoons *(1 tablespoon=10 ml)*
2	Do you remove visible fat (or the skin) of chicken, duck, pork, lamb or veal meats before cooking and the fat of soups, broths, and cooked meat dishes before consumption?	Yes
3	How many servings of fat-rich meats, hamburger, commercial ground meat, sausage, cold meat, cured ham, bacon, salami, or offal do you consume per week? (meat serving: 100 g; salami or bacon: 30 g)	1 or less
4	How many servings of butter, margarine, lard, mayonnaise, milk cream, or milk-based ice cream do you consume per week? (spread fat: serving: 12 g; ice cream: 100 g)	1 or less
5	Do you exclusively consume low-fat dairy products?	Yes *(id. If no dairy consumption)*
6	How many times per week do you prepare rice, pasta, potato, or legume dishes by using "sofrito" sauce (based on olive oil), bacon, salami, or fatty meats such as pork or lamb ribs?	2 or less
7	How many times per week do you consume fatty fish or fish or seafood canned in oil?	1 or less
8	How many servings of commercial sweets or industrial bakery products (not homemade), such as cakes, cookies, biscuits, or custard do you consume per week? (cake serving: 80 g; 6 biscuits: 40 g)	1 or less
9	How many times per week do you consume nuts (including peanuts), potato chips, French fries, or commercial snacks?	1 or less

* 0 points if these criteria are not met.

Table S4. Use of Medication (%) during Follow-up according to Randomized Group.

	MeDiet + Extra-Virgin Olive Oil	MeDiet + Nuts	Control Diet	p*
Blood pressure-lowering drugs				
3-year follow-up	77.6	76.6	79.3	0.11
5-year follow-up	80.5	80.4	81.4	0.71
Lipid-lowering agents				
3-year follow-up	55.3	53.3	55.9	0.10
5-year follow-up	58.5	55.8	56.6	0.69
Anti-platelet therapy				
3-year follow-up	24.6	26.0	27.5	0.17
5-year follow-up	29.4	28.8	28.4	0.39
Insulin				
3-year follow-up	9.1	8.2	7.6	0.11
5-year follow-up	9.9	9.9	10.1	0.95
Oral antidiabetic agents				
3-year follow-up	37.5	35.5	37.0	0.085
5-year follow-up	39.7	38.2	41.4	0.55

*Chi square test.

Table S5. Participants with a Positive Answer (%) to each of the 14 Items of the Mediterranean Diet Score by Treatment Arm during Follow-up.

	1-year follow-up			3-year follow-up			5-year follow-up		
	MeDiet+ EVOO	MeDiet+ Nuts	Control	MeDiet+ EVOO	MeDiet+ Nuts	Control	MeDiet+ EVOO	MeDiet+ Nuts	Control
1. Use olive oil as main culinary fat	99.2	96	91.6	99.2	97.2	92.1	99.9	97.5	96.3
2. Olive oil >4 tablespoons	92.8	78	58.4	93	76.3	51.1	93.6	79.5	58.9
3. Vegetables ≥ 2 servings/d	65.8	64.4	49.8	68.8	68.5	58.3	74.1	73.7	64.5
4. Fruits ≥ 3 servings/d	61.7	61.2	50.7	62.7	65.3	54.2	65.2	67.9	60.9
5. Red or processed meats < 1/d	*93.7*	*94.9*	*93.9* [b]	*94.2*	*95.2*	*93.1* [a]	*97.3*	*96.6*	*97.1* [b]
6. Butter. cream. margarine < 1/d	96.2	95.7	91.7	97.4	95.3	93.5	97.8	96.6	94.8
7. Soda drinks < 1/d	93.6	94	91.6	*93.3*	*93.6*	*92.5* [b]	*94.6*	*93.9*	*94.7* [b]
8. Wine glasses ≥ 7/ wk	31.4	33.7	26.4	28.1	31.0	26.1	29.9	32.3	25.1
9. Legumes ≥3 /wk	43.4	44	28.8	45.3	46.2	30.8	41.5	36.9	31.2
10. Fish or seafood ≥ 3/wk	75.5	73.5	63.3	77.6	75.7	62.1	74.7	75.9	66.1
11. Commercial bakery ≤ 2/wk	78.2	75.9	72.1	76.3	74.9	71.6	*75.9*	*73.5*	*71.9* [a]
12. Nuts ≥ 3/wk	44.5	93.6	24.7	42.2	94.4	22.0	42.2	90.7	16.7
13. Poultry more than red meats	82.4	84.7	78.2	84.3	85.1	80.4	*84.0*	*84.0*	*83.2* [b]
14. Use of sofrito sauce ≥ 2 /wk	84.1	81.7	62.5	87.6	82.0	63.5	86.9	84.3	65.1

MeDiet denotes Mediterranean diet; EVOO extra-virgin olive oil.
All comparisons between each of the two MeDiet groups and the control group for each year were statistically significant (Chi squared tests), with the exception of those with superscript letter [a] ($0.05 < p < 0.10$) or superscript letter [b] ($p>0.10$).

Table S6. Mean Baseline Values and Changes in the Consumption of Key Foods in the three Arms of the Study.

Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean diet intervention (versus the control diet) are shown. The change is follow-up minus baseline; hence a positive sign indicates increase over time (the last available follow-up food frequency questionnaire of each participant was used).

	Mean baseline			Within-group mean changes			Between-group changes (differences vs.control)			
	MeDiet + EVOO (n = 2364)	MeDiet + Nuts (n = 2108)	Control diet (n = 1941)	MeDiet + EVOO	MeDiet + Nuts	Control diet	MeDiet + EVOO vs. Control diet		MeDiet + nuts vs. Control diet	
Servings/d		*Mean (SD)*			*Mean (95% CI)*		*Mean (95% CI)*	*P value*	*Mean (95% CI)*	*P value*
Virgin olive oil (10 g)	2.1 ± 2.3	2.2 ± 2.3	2.0 ± 2.3	2.93 (2.82, 3.04)	0.99 (0.88, 1.11)	0.27 (0.16, 0.38)	2.66 (2.47, 2.86)	< 0.001	0.72 (0.53, 0.92)	< 0.001
Refined- mixed olive oil (10 g)	1.8 ± 2.0	1.6 ± 2.0	1.7 ± 2.0	-1.71 (-1.80, -1.62)	-0.57 (-0.67, -0.47)	-0.44 (-0.55, -0.34)	-1.27 (-1.10, -1.43)	< 0.001	-0.13 (-0.30, 0.05)	0.24
Total nuts (25 g)	0.4 ± 0.5	0.5 ± 0.6	0.4 ± 0.5	0.001 (-0.03, 0.03)	0.71 (0.67, 0.75)	-0.13 (-0.16, -0.11)	0.13 (0.09, 0.18)	< 0.001	0.84 (0.78, 0.90)	< 0.001
Vegetables (125 g)	2.8 ± 1.2	2.7 ± 1.2	2.6 ± 1.1	-0.08 (-0.13,-0.01)	-0.01 (-0.06, 0.05)	-0.09 (-0.14, -0.03)	0.014 (-0.08, 0.11)	0.98	0.08 (-0.01, 0.18)	0.12
Wholegrain cereal (60 g)	0.5 ± 1.0	0.5 ± 0.9	0.5 ± 0.9	-0.05 (-0.10, -0.01)	-0.03 (-0.07, 0.02)	-0.04 (-0.09, 0.01)	-0.01 (-0.09, 0.05)	0.98	0.01 (-0.07, 0.09)	0.98
Refined cereal and potatoes (60 g)	3.3 ± 1.9	3.3 ± 1.7	3.2 ± 1.8	-0.29 (-0.37, -0.21)	-0.34 (-0.42, -0.26)	-0.31 (-039, -0.23)	0.02 (-0.12, 0.16)	0.98	-0.03 (-0.17, 0.11)	0.94
Legumes (40 g)	0.5 ± 0.3	0.5 ± 0.4	0.5 ± 0.3	0.06 (0.04, 0.07)	0.06 (0.04, 0.08)	0.002 (-0.01, 0.02)	0.06 (0.03, 0.08)	< 0.001	0.06 (0.003, 0.08)	< 0.001
Fruits (125 g)	3.0 ± 1.7	3.0 ± 1.6	2.8 ± 1.6	0.21 (0.13, 0.28)	0.25 (0.17, 0.33)	0.15 (0.07, 0.23)	0.05 (-0.09, 0.19)	0.75	0.10 (-0.04, 0.24)	0.25
Fish or seafood (125)	0.8 ± 0.4	0.8 ± 0.4	0.8 ± 0.4	0.01 (-0.01, 0.03)	0.02 (0.001, 0.04)	-0.03 (-0.05, -0.01)	0.04 (0.01, 0.07)	0.01	0.05 (0.02, 0.08)	0.001
Meat or meat products (150 g)	0.9 ± 0.4	0.9 ± 0.4	0.8 ± 0.4	-0.11 (-0.12, -0.09)	-0.11 (-0.13, -0.10)	-0.10 (-0.11, -0.08)	-0.01 (-0.04, 0.02)	0.72	-0.01 (-0.01, 0.04)	0.53
Pastries, cakes or sweets (50 g)	0.4 ± 0.5	0.4 ± 0.6	0.4 ± 0.5	-0.07 (-0.10, -0.05)	-0.09 (-0.12, -0.06)	-0.06 (-0.09,-0.03)	-0.01 (-0.06, 0.03)	0.86	-0.03 (-0.08, 0.02)	0.41
Dairy products (200 g)	1.9 ± 1.1	1.9 ±1.1	1.9 ± 1.1	-0.07 (-0.12, -0.02)	-0.05 (-0.09, 0.003)	-0.08 (-0.13, -0.04)	0.02 (-0.07, 0.10)	0.96	0.03 (-0.05, 0.12)	0.61
Alcohol (g/d)	8.6 ± 14.5	9.2 ± 15.0	7.4 ± 12.9	-1.40 (-1.86, -0.95)	-1.40 (-1.92, -0.89)	-0.88 (-1.31, -0.45)	-0.52 (-1.28, 0.24)	0.27	-0.52 (-1.33, 0.29)	0.34

NOTE: Of participants in the MeDiet with extravirgin olive oil, MeDiet with mixed nuts, and control groups, 42, 57 and 25 participants, respectively, were excluded from calculations of food intake because energy was outside the prespecified ranges. Dietary assessment was conducted using a food frequency questionnaire (136 items) previously validated for the Spanish population.

MeDiet denotes Mediterranean diet; EVOO extra-virgin olive oil;

Table S7. Intake of Energy, Nutrients and Supplemental Foods at Baseline and the end of the Trial by Study Group.

	MeDiet + Extra-Virgin Olive Oil (n = 2364)		MeDiet + Nuts (n = 2108)		Control Diet (n = 1941)	
	Baseline	End of trial	Baseline	End of trial	Baseline	End of trial
	Mean (SD)		*Mean (SD)*		*Mean (SD)*	
Energy (kcal)	2,257 ± 550	2,172 ±475	2,276 ± 527	2,229 ±477	2,186 ± 535	1960 ± 497
Total protein (% E)	16.7 ± 2.8	16.2 ±2.4	16.6 ± 2.7	16.4 ±2.5	16.6 ± 2.8	17.1 ± 3.0
Total carbohydrate (% E)	41.7 ± 7.2	40.4 ±5.9	41.4 ± 7.0	39.7 ±6.3	42.2 ± 7.1	43.7 ± 7.0
Fiber (g/d)	25.7 ± 9.1	25.4 ±7.5	25.7 ± 8.6	27.0 ±8.0	24.7 ± 8.4	23.7 ± 7.7
Total fat (% E)	39.2 ± 6.9	41.2 ±5.4	39.4 ± 6.5	41.5 ±6.1	39.0 ± 7.0	37.0 ± 7.0
Saturated fatty acids (% E)	10.0 ± 2.2	9.4 ±2	10.0 ± 2.1	9.3 ±2.0	10.0 ± 2.3	9.1 ± 2.1
Monounsaturated fatty acids (% E)	19.6 ± 4.6	22.1 ±3.7	19.6 ± 4.3	20.9 ±4.1	19.3 ± 4.7	18.8 ± 4.6
Polyunsaturated fatty acids (% E)	6.1 ± 2.1	6.1 ±1.4	6.4 ± 2.0	7.7 ±1.8	6.2 ± 2.1	5.5 ± 1.7
Linoleic acid, (g/d)	12.9 ± 6.0	12.2 ±4.6	13.6 ± 6.1	16.0 ±5.5	12.6 ± 6.0	10.0 ± 4.8
α- linolenic acid, (g/d)	1.4 ± 0.7	1.3 ±0.7	1.5 ± 0.7	1.9 ±0.7	1.3 ± 0.6	1.1 ± 0.5
Marine n-3 fatty acids (g/d)	0.8 ± 0.5	0.9 ±0.5	0.8 ± 0.5	0.8 ±0.5	0.8 ± 0.5	0.7 ± 0.4
Olive oil (% E)	16.3 ±7.1	22.0 ±6.0	15.9 ± 6.7	17.6 ±6.4	15.8 ± 7.4	16.4 ± 6.8
Nuts (% E)	2.5 ±3.4	2.6 ±3.1	3.3 ± 3.7	8.2 ±4.5	2.4 ± 3.2	1.6 ± 2.5
Cholesterol (mg/d)	363 ± 131	339 ±101	367 ± 117	338 ±99	356 ± 122	32 ± 106

NOTE: In the Mediterranean diet with extra-virgin olive oil, Mediterranean diet with nuts, and control diet groups, 42, 57 and 25 participants, respectively, were excluded from calculations of food intake because their total energy intake was outside the prespecified ranges.

MeDiet denotes Mediterranean diet; E, energy intake.

Table S8. Mean Baseline Values and Changes in Energy, Nutrient and Supplemental Food Intake by Study Arm.

Within group (95 % CI) changes and between-group changes for the 2 groups receiving the Mediterranean diet intervention (versus the control diet) are shown. The change is follow-up minus baseline; hence a positive sign indicates increase over time (the last available follow-up food frequency questionnaire of each participant was used).

	Within-group mean changes						Between-group changes (differences vs. control)					
	MeDiet + Extra-virgin Olive Oil (n = 2364)		MeDiet + Nuts (n = 2108)		Control Diet (n = 1941)		MeDiet + Extra-Virgin Olive Oil vs. Control Diet			MeDiet + Nuts vs. Control Diet		
	Mean	*(95% CI)*	*Mean*	*(95% CI)*			*Mean*	*(95% CI)*	P value*	*Mean*	*(95% CI)*	P value*
Energy (kcal)	-85	(-109, -60)	-47	(-73, -20)	-227	(-253, -200)	141	(97, 185)	<0.001	180	(134, 225)	<0.001
Total protein (% E)	-0.44	(-0.57, -0.32)	-0.12	(-0.24, 0.01)	0.51	(0.37, 0.66)	-0.98	(-1.19, -0.73)	<0.001	-0.62	(-0.96, -0.40)	<0.001
Total carbohydrate (% E)	-1.29	(-1.61, -0.98)	-1.65	(-1.98, -1.32)	1.50	(1.16, 1.85)	-2.79	(-3.37, -2.23)	<0.001	-3.15	(-3.74, -2.58)	<0.001
Fiber (g/d)	-0.29	(-0.71, 0.12)	1.36	(0.93, 1.79)	-0.93	(-1.35, -0.51)	0.64	(-0.08, 1.36)	0.10	2.29	(1.56, 3.03)	<0.001
Total fat (% E)	2.03	(1.72, 2.35)	2.10	(1.74, 2.40)	-1.96	(-2.32, -1.59)	3.99	(3.41, 4.57)	<0.001	4.03	(3.44, 4.62)	<0.001
Saturated fatty acids (% E)	-0.56	(-0.65, -0.46)	-0.67	(-0.77, -0.57)	-0.79	(-0.90, -0.70)	0.24	(0.06, 0.41)	0.004	0.12	(-0.06, 0.30)	0.30
Monounsaturated fatty acids (% E)	2.52	(2.30, 2.74)	1.32	(1.11, 1.55)	-0.53	(-0.78, -0.28)	3.05	(2.65, 3.46)	<0.001	1.89	(1.45, 2.26)	<0.001
Polyunsaturated fatty acids (% E)	-0.03	(-0.13, 0.06)	1.31	(1.20, 1.41)	-0.65	(-0.75, -0.55)	0.62	(0.45, 0.79)	<0.001	1.96	(1.77, 2.14)	<0.001
Linoleic acid, (g/d)	-0.65	(-0.92, -0.37)	2.45	(2.13, 2.79)	-2.59	(-2.88, -2.30)	1.94	(1.45, 2.43)	<0.001	5.05	(4.51, 5.58)	<0.001
α- linolenic acid, (g/d)	-0.05	(-0.09, -0.02)	0.43	(0.40, 0.48)	-0.25	(-0.29, -0.22)	0.20	(0.14, 0.26)	<0.001	0.69	(0.63, 0.76)	<0.001
Marine n-3 fatty acids (g/d)	0.04	(0.01, 0.06)	0.04	(0.02, 0.07)	-0.07	(-0.10, -0.05)	0.11	(0.07, 0.16)	<0.001	0.12	(0.08, 0.16)	<0.001
Olive oil (% E)	5.63	(5.27, 6.00)	1.74	(1.39, 2.10)	0.67	(0.27, 1.06)	4.97	(4.31, 5.62)	<0.001	1.08	(0.43, 1.72)	<0.001
Nuts (% E)	0.11	(-0.06, 0.28)	4.95	(4.70, 5.20)	-0.71	(-0.87, -0.55)	0.82	(0.53, 1.10)	<0.001	5.65	(5.30, 6.01)	<0.001
Cholesterol (mg/d)	-24.89	(-30.5, -19.2)	-28.4	(-33.9, -22.9)	-32.3	(-38.1, -26.6)	7.48	(-2.34, 17.30)	0.19	3.97	(-5.69, 13.62)	0.70

* Analysis of variance followed by the Dunnett post hoc test. NOTE: In the MeDiet with extravirgin olive oil, MeDiet with nuts, and low-fat diet groups, 42, 57 and 25 participants, respectively, were excluded from calculations of energy and nutrient intake because their total energy intake was out of the predefined range.

MeDiet denotes Mediterranean diet; E, energy intake.

Table S9. Sensitivity Analyses.

	Multivariable-adjusted* Hazard Ratios (95% confidence intervals) for the primary end point (mayor cardiovascular event[¶]) (p value)**	
	(MeDiet+ EVOO vs. control)	(MeDiet+ Nuts vs. control)
Including angina plus revascularization **(306 events included)**	**0.74 (0.57-0.97)** **0.028**	**0.77 (0.58-1.01)** **0.062**
Excluding centres with low incidence[≠] **(222 events included)**	**0.70 (0.52-0.95)** **0.023**	**0.70 (0.50-0.97)** **0.034**
Excluding centres with high incidence[¢] **(221 events included)**	**0.67 (0.49-0.91)** **0.012**	**0.76 (0.55-1.06)** **0.103**
Excluding the centre with highest # of events **(226 events included)**	**0.73 (0.54-0.99)** **0.042**	**0.71 (0.51-0.99)** **0.043**
Excluding 2 centres with lower retention[§] **(231 events included)**	**0.69 (0.51-0.93)** **0.016**	**0.63 (0.46-0.88)** **0.006**
Modelling centre as a random factor	**0.70 (0.53-0.93)** **0.013**	**0.72 (0.54-0.96)** **0.026**
Only events observed in the 2 first years **(94 events included)**	**0.57 (0.36-0.91)** **0.018**	**0.46 (0.27-0.78)** **0.004**
Only events occurring between 2-4 years **(105 events included)**	**0.62 (0.38-0.98)** **0.039**	**0.80 (0.51-1.27)** **0.350**
Only events occurring after 4 years **(89 events included)**	**1.11 (0.66-1.88)** **0.688**	**1.08 (0.62-1.90)** **0.776**
Excluding early cases (< 1 yr) **(239 events included)**	**0.78 (0.57-1.05)** **0.100**	**0.82 (0.60-1.13)** **0.231**
Excluding late cases (>4 yr) **(199 events included)**	**0.58 (0.42-0.81)** **0.001**	**0.62 (0.44-0.88)** **0.007**
Potentially missing events (see last footnote)		
Complete case analysis (adjusted, 516 drop outs excluded) **(288 events included)**	**0.69 (0.53-0.91)** **0.008**	**0.70 (0.53-0.94)** **0.018**
Single imputation **(294 events included)**	**0.70 (0.53-0.91)** **0.008**	**0.72 (0.54-0.96)** **0.023**
Multiple imputation **(underlying rates 2 to 10% in drop outs)**	**0.67 (0.50-0.89)** **0.006**	**0.70 (0.52-0.94)** **0.016**

MeDiet denotes Mediterranean diet; EVOO extra-virgin olive oil.

* All models are adjusted for sex, age (as continuous), body mass index (continuous), waist-to-height ratio (continuous), diabetes, smoking, hypertension, dyslipidemia, and family history of early CHD. All models were stratified by center.

**Likelihood ratio test.

(¶) Stroke, myocardial infarction or cardiovascular death.

(≠) Three centres (#2, 6 & 7, accounting for 2129 participants) where a significantly lower age-, sex-, and risk factors adjusted-incidence of major events was observed.

(¢) Two centres, accounting for 1741 participants (not significant differences in adjusted rates vs. centre with the highest number of events).

(§) Excluding two centres (#2 & #1) located in Southern Spain, accounting for 1261 participants, with some administrative and logistic problems to access and retrieve the medical information from participants lost to follow-up.

Table S10. Subgroup Analyses.
Hazard Ratios (95% confidence intervals) of major cardiovascular event within subgroups.

		Multivariable-adjusted* Hazard Ratios (95% CI)			
Subgroups	(n, events)	**MeDiet + EVOO**	**MeDiet + Nuts**	**Control**	**P for interaction**
Sex					
Men	**(3165, 171)**	**0.73 (0.51-1.04)**	**0.65 (0.45-0.95)**	**1 (ref.)**	
Women	**(4282, 117)**	**0.64 (0.42-0.98)**	**0.86 (0.55-1.36)**	**1 (ref.)**	**0.37**
Age					
<70 yr	**(4776, 133)**	**0.74 (0.49-1.12)**	**0.73 (0.48-1.11)**	**1 (ref.)**	**0.94**
≥70 yr	**(2671, 155)**	**0.68 (0.47-0.99)**	**0.74 (0.50-1.11)**	**1 (ref.)**	
Diabetes					
No	**(3833, 98)**	**0.69 (0.43-1.12)**	**0.66 (0.40-1.07)**	**1 (ref.)**	**0.88**
Yes	**(3614, 190)**	**0.69 (0.50-0.97)**	**0.74 (0.51-1.06)**	**1 (ref.)**	
Hypertension					
No	**(1285, 51)**	**1.29 (0.63-2.64)**	**1.20 (0.56-2.57)**	**1 (ref.)**	**0.15**
Yes	**(6162, 237)**	**0.64 (0.48-0.87)**	**0.66 (0.48-0.91)**	**1 (ref.)**	
Dyslipidemia					
No	**(2064, 113)**	**1.04 (0.67-1.61)**	**0.84 (0.52-1.37)**	**1 (ref.)**	**0.07**
Yes	**(5383, 175)**	**0.54 (0.38-0.78)**	**0.66 (0.46-0.94)**	**1 (ref.)**	
Smoking					
Never	**(4564, 134)**	**0.58 (0.38-0.86)**	**0.79 (0.52-1.20)**	**1 (ref.)**	**0.30**
Ever	**(2883, 154)**	**0.80 (0.55-1.16)**	**0.68 (0.46-1.02)**	**1 (ref.)**	
Family history of early CHD					
No	**(5779, 231)**	**0.69 (0.51-0.94)**	**0.75 (0.55-1.04)**	**1 (ref.)**	**0.67**
Yes	**(1668, 263)**	**0.81 (0.44-1.48)**	**0.66 (0.33-1.32)**	**1 (ref.)**	
Body mass index					
<25 kg/m^2	**(557, 25)**	**0.70 (0.27-1.82)**	**0.68 (0.26-1.83)**	**1 (ref.)**	**0.94**
≥25 kg/m^2	**(6890, 263)**	**0.70 (0.53-0.93)**	**0.71 (0.52-0.96)**	**1 (ref.)**	
Waist circumference					
<median†	**(3738, 135)**	**0.75 (0.50-1.12)**	**0.77 (0.50-1.17)**	**1 (ref.)**	**0.93**
≥median	**(3709, 153)**	**0.66 (0.45-0.95)**	**0.68 (0.46-1.02)**	**1 (ref.)**	
Waist-to-height ratio					
<median	**(3731, 128)**	**0.73 (0.48-1.10)**	**0.76 (0.50-1.16)**	**1 (ref.)**	
≥median	**(3716, 160)**	**0.67 (0.47-0.96)**	**0.69 (0.47-1.02)**	**1 (ref.)**	**0.97**
MeDiet adherence‡					
Low (<9)	**(3434, 154)**	**0.80 (0.55-1.16)**	**0.81 (0.55-1.21)**	**1 (ref.)**	
High (>=9)	**(4013, 134)**	**0.63 (0.42-0.95)**	**0.66 (0.43-1.01)**	**1 (ref.)**	**0.73**

MeDiet denotes Mediterranean diet; EVOO extra-virgin olive oil; CHD, coronary heart disease.

* Adjusted for sex, age (as continuous variable), diabetes, smoking (3 categories), hypertension, and family history of early CHD. All models were stratified by center.

† Waist circumference medians: 103 cm for men and 98 for women

‡ Baseline adherence to the Mediterranean diet: 0 (minimum) to 14 (maximum) score.

REFERENCES

1. Nigg CR, Burbank PM, Padula C, Dufresne R, Rossi JS, Velicer WF, Laforge RG, Prochaska JO. Stages of change across ten health risk behaviors for older adults. Gerontologist. 1999;39:473-82.
2. Myocardial infarction redefined. A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. The Joint European Society of Cardiology/American College of Cardiology Committee. J Am Coll Cardiol 2000;36:959-969.
3. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008. Cerebrovasc Dis 2008;25:457–507.
4. Morgenstern LB, Hemphil JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. A Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke 2010;41;2108-2129.
5. Kidwell CS, Chalela JA, Saver JL, et al. Comparison of MRI and CT for detection of acute cerebral hemorrhage. JAMA 2004;292:1823-30.
6. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and prevention of sudden cardiac death. J Am Coll Cardiol 2006;48:247-346.
7. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis. A population-based study. Arthritis Rheum 2005;52:722-732.
8. Groenwold RH, Donders AR, Roes KC, Harrell FE Jr, Moons KG. Dealing with missing outcome data in randomized trials and observational studies. Am J Epidemiol 2012;175:210-7.
9. Raghunathan TE. What do we do with missing data? Some options for analysis of incomplete data. Annu Rev Public Health 2004;25:99-117.