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Mediterranean diet and antihypertensive drug use: a randomized controlled trial

Short title: MedDiet and antihypertensive drug use

Margarita RIBÓ-COLL[a,b]; Camille LASSALE[c,d]; Emilio SACANELLA[a,c,e]; Emilio ROS[a,c,f]; Estefanía TOLEDO[c,g]; José V. SORLÍ[c,h]; Nancy BABIO[c,i,j]; José LAPETRA[c,k]; Enrique GÓMEZ-GRACIA[c,l]; Ángel M. ALONSO-GÓMEZ[c,m]; Miquel FIOL[c,n]; Lluis SERRA-MAJEM[c,o,p]; Xavier PINTO[c,q]; Olga CASTAÑER[c,d]; Javier DÍEZ-ESPINO[c,g,r,s]; José I. GONZÁLEZ[c,h]; Nerea BECERRA-TOMÁS[c,h,i,j]; Montserrat COFÁN[a,c,f]; Andrés DÍAZ-LÓPEZ[c,i,j]; Ramón ESTRUCH[a,c,e]; Álvaro HERNÁEZ[a,c,t,*]

a. Cardiovascular Risk, Nutrition, and Aging Research Group; August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
b. PhD program in Food Science and Nutrition, Faculty of Pharmacy and Food Science, Universitat de Barcelona, Barcelona, Spain
c. Consorcio CIBER, M.P. Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain
d. Cardiovascular Risk and Nutrition Research Group, Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain
e. Internal Medicine Service, Hospital Clínic, Barcelona, Spain
f. Lipid Clinic, Endocrinology and Nutrition Service, Hospital Clínic, Barcelona, Spain
g. Department of Preventive Medicine and Public Health, Universidad de Navarra, Pamplona, Spain
h. Department of Preventive Medicine, Universidad de Valencia, Valencia, Spain
i. Unitat de Nutrició Humana, Departament de Bioquimica i Biotecnologia, Universitat Rovira i Virgili, Reus, Spain

j. Institut d'Investigació Pere Virgili (IISPV), Hospital Universitari Sant Joan de Reus, Reus, Spain
k. Department of Family Medicine. Research Unit. Distrito Sanitario Atención Primaria Sevilla, Sevilla, Spain
l. Department of Preventive Medicine and Public Health, Universidad de Málaga, Málaga, Spain
m. Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba University Hospital, University of the Basque Country UPV/EHU, Vitoria-Gasteiz, Spain
n. Health Research Institute of the Balearic Islands (IdISBa). Hospital Son Espases. Palma de Mallorca, Spain
o. Instituto de Investigaciones Biomédicas y Sanitarias. Universidad de Las Palmas de Gran Canaria, Las Palmas, Spain
p. Centro Hospitalario Universitario Insular Materno Infantil, Servicio Canario de Salud, Las Palmas, Spain
q. Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Spain
r. Centro de Salud de Tafalla, Gerencia de Atención Primaria, Servicio Navarro de Salud-Osasunbidea, Tafalla, Spain
s. Instituto de Investigación Sanitaria de Navarra (IDISNA), Pamplona, Spain
t. Blanquerna School of Life Sciences, Universitat Ramon Llull, Barcelona, Spain

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Conflicts of interest

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Author for correspondence

Álvaro Hernáez, PharmD, PhD

August Pi i Sunyer Biomedical Research Institute (IDIBAPS)

IDIBAPS-Mallorca Offices, Carrer Mallorca 183, 08036, Barcelona

Telephone: (+34) 679384179

e-mail: alvaro.hernaez1@gmail.com

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ABSTRACT

Objective: To examine in older individuals at high cardiovascular risk whether following a Mediterranean diet decreased the necessity of antihypertensive drugs and modulated their associated cardiovascular risk.

Methods: In the *PREvención con DIeta MEDiterránea* study, we assessed whether volunteers randomly allocated to an intervention with a Mediterranean diet enriched with extra-virgin olive oil or nuts (relative to a low-fat control diet) disclosed differences in the risk of: initiating antihypertensive medication in nonusers at baseline (*n*=2188); and escalating therapy in participants using one, two, or three drugs at baseline (*n*=2361, *n*=1579, and *n*=554, respectively). We also assessed whether allocation to Mediterranean diet modified the association between antihypertensive drug use and incident cardiovascular events.

Results: Participants allocated to Mediterranean diet interventions were associated with lower risk of initiating antihypertensive therapy (5-year incidence rates: 47.1% in the control diet, 43.0% in MedDiets; hazard ratio=0.84, 95% CI: [0.74; 0.97], in a model adjusted for age, sex, and recruitment site). Volunteers using two drugs at baseline in the Mediterranean diet intervention enriched with extra-virgin olive oil decreased their risk of therapy escalation (5-year incidence rates: 22.9% in the control diet, 20.1% in the MedDiet; hazard ratio=0.77, 95% CI: [0.60; 0.99]). Allocation to Mediterranean diet interventions attenuated the association between antihypertensive therapy at baseline and incidence of major adverse cardiovascular events (*P*-interaction=0.003).

Conclusion: In an older population at high cardiovascular risk, following a Mediterranean diet reduced the risk of initiating or escalating antihypertensive medication and attenuated cardiovascular risk in antihypertensive drug users.

KEYWORDS

Antihypertensive agent, Mediterranean diet, nutritional sciences, preventive medicine, randomized controlled trial

INTRODUCTION

Following a Mediterranean Diet (MedDiet) is associated with a lower risk of cardiovascular disease, as reported by large scale observational studies and intervention trials, including the PREDIMED (*PREvención con DIeta MEDiterránea*) trial [1–3]. A probable mechanism for this benefit could be an improvement of blood pressure, glucose and lipid metabolism, oxidative stress, and low-grade inflammation by the MedDiet [4]. Regarding hypertension features, dietary approaches can contribute to the control of high blood pressure as co-adjuvants to antihypertensive therapy [5]. Following a MedDiet decreased blood pressure levels in the PREDIMED Study [6,7] and this effect was confirmed in meta-analyses of observational studies [8] and randomized controlled trials [9]. However, whether MedDiet effects on blood pressure are relevant, in particular regarding the use of antihypertensive medication, remains to be elucidated. In addition, whether adopting a MedDiet can act synergistically with antihypertensive drug use on cardiovascular risk has not been studied.

Our first objective was to evaluate whether following a MedDiet decreased the risk of initiating antihypertensive drug use in untreated individuals and incorporating additional antihypertensive medication in treated patients. Our second aim was to evaluate whether MedDiet modulates the association between the use of antihypertensive drugs and the risk of suffering a major cardiovascular event.

METHODS

Study population

Participants belong to the PREDIMED study. It was a multicenter, randomized, controlled trial aiming to determine the effects of following MedDiet-style diets on the primary prevention of cardiovascular outcomes in individuals at high cardiovascular risk. Eligible participants were men aged 55-80 and women aged 60-80 free of cardiovascular disease at enrolment but presenting type 2 diabetes or three or more of the following cardiovascular risk factors: 1) smoking; 2) hypertension; 3) high levels of low-density lipoprotein cholesterol; 4) low concentrations of high-density lipoprotein cholesterol; 5) overweight/obesity; and 6) family history of premature coronary heart disease. Enrollment commenced on June 25, 2003, and finished on June 30, 2009. The study protocol complied with the principles in the Declaration of Helsinki, was approved by Institutional Review Boards of all recruiting centers, was registered under the International Standard Randomized Controlled Trial Number ISRCTN35739639 (http://www.isrctn.com/ISRCTN35739639), and is detailed in previous publications [1,3]. All participants provided written informed consent before joining the study.

7,447 volunteers were initially included in the PREDIMED trial. We excluded 27 individuals with no blood pressure values at baseline, and 85 volunteers with missing values in MedDiet adherence or alcohol intake at baseline. In the analyses regarding the risk of initiating antihypertensive medication, we excluded antihypertensive drug users at baseline and volunteers with no information on antihypertensive drug use in the follow-ups. In the analyses in relation to the risk of escalating antihypertensive therapy, we selected only those volunteers who were using one, two, or three antihypertensive medications at the start of the study and presented information of further drug use in the study visits. The study flowchart is available in **Figure 1**. The CONSORT checklist for the present study is available in **Supplemental Table 1**.

Dietary intervention

In the PREDIMED Study, three intervention groups (to which volunteers were randomly allocated on a 1:1:1 ratio) were compared: 1) a MedDiet enriched with extra-virgin olive oil (MedDiet-EVOO); 2) a MedDiet enriched with mixed nuts (MedDiet-Nuts); and 3) a control diet with advice to reduce all dietary fat. The MedDiet interventions promoted: 1) the consumption of plant-based foods (such as vegetables, fruits, mixed nuts, and pulses) and fish; 2) a decrease in the intake of red and processed meats (substituted for poultry), spread fats, sugary drinks, commercial bakery goods, pastries, and sweets and 3) the use of extra-virgin olive oil as main culinary fat and traditional cooking methods such as “sofrito”. Volunteers in the MedDiet-EVOO arm were provided with 1L/week of extra-virgin olive oil and those in the MedDiet-Nuts group were given 30 g/day of mixed nuts (almonds, hazelnuts, and walnuts) plus extra allowances to account for family needs. Participants allocated to the control group were advised: 1) to promote the consumption of vegetables, fruits, pulses, low-fat dairy products, and lean fish; 2) to reduce their intake of red and processed fatty meat, visible fat in meats and soups, fatty fish, seafood canned in oil, spread fats, commercial bakery goods. The detailed protocol for the PREDIMED dietary intervention is available [1,3].

Outcomes

We classified complexity of antihypertensive therapy according to the number of antihypertensive agents of different pharmacological families used. At each study visit, we collected data on the use/non-use of the main classes of antihypertensive drugs (renin-angiotensin-aldosterone system inhibitors, calcium antagonists, thiazide/thiazide-like/loop diuretics, mineralocorticoid receptor antagonists, beta-blockers, and alpha-blockers). We defined the following levels: no use of antihypertensive agents (level 0), and treatment with one (level 1), two (level 2), three (level 3), four or more drugs of different classes (level 4). Finally, using these data, we registered incidence and time-to-event of the following

outcomes: 1) initiation of antihypertensive therapy (moving from level 0 to higher levels); 2) addition of at least one extra antihypertensive drug in participants treated with a single agent (moving from level 1 to higher levels); 3) addition of at least one extra antihypertensive drug in participants treated with two agents (moving from level 2 to higher levels); and 4) addition of at least one extra antihypertensive drug in participants treated with three agents (moving from level 3 to level 4). Regarding doubtful events, we only considered as a valid outcome any onset that persisted in at least three consecutive visits and intercalated no more than one visit without the condition. As sensitivity analyses, we additionally assessed whether there was a different risk in the onset of use of the six drug families studied [10] and explored whether the MedDiet interventions were associated with changes in the risk of onset of resistant hypertension according to antihypertensive drug use (defined as the use of three antihypertensive medications, of which at least one is a diuretic –thiazide, thiazide-like, loop, or potassium-sparing–) [11].

For our secondary aim, we collected information on the development of any major adverse cardiovascular event (composite of non-fatal coronary heart disease, non-fatal stroke, and death from these causes). The Clinical Events Committee of the study determined the incidence (up to December 1st 2010) and time-to-event values of these conditions through follow-up study visits, repeated direct contact with the participants, yearly review of medical records between 2011 and 2017, and linkage with the national death registry as previously reported [1,3].

Clinical and lifestyle variables

Trained personnel collected data on age, sex, educational level, diabetes, hypercholesterolemia, hypertriglyceridemia, systolic and diastolic blood pressure, body mass index, and tobacco use via face-to-face interviews [1,3]. From a 137-item food frequency questionnaire validated in Spanish population [12], we estimated the intake of

alcohol (in g/day) and sodium (in mg/day). Finally, we appraised leisure-time physical activity levels in metabolic equivalents of task·minute per day using the Minnesota Leisure-Time Physical Activity Questionnaire validated for the Spanish population [13,14].

Power analysis

The number of total individuals and cases observed in the study allowed to detect as significant (*P*-value <0.05) with ≥80% power hazard ratios (HR) for the comparisons between control diet and MedDiet-EVOO or MedDiet-Nuts, respectively, of: ≤0.80 and ≤0.80 (antihypertensive initiation); ≤0.78 and ≤0.77 (escalation in one-drug users); ≤0.70 and ≤0.69 (escalation in two-drug users); and ≤0.43 and ≤0.43 (escalation in three-drug users). We performed these calculations and those for sensitivity analyses using the "powerSurvEpi" package in R Software [15] and are available in **Supplemental Table 2**.

Statistical analyses

We defined baseline characteristics of the four sub-groups of volunteers using proportions (categorical variables), means and standard deviations (normally distributed continuous ones), and medians and interquartile ranges (non-normally distributed continuous ones).

We assessed whether there were risk differences in the risk of initiation of antihypertensive drug use among non-treated volunteers and escalation in the pharmacological treatment among drug users between the MedDiet interventions (individually and combined) and the control diet group by multivariable Cox proportional hazards regressions. We defined follow-up time as the number of days between date of enrollment and: 1) the midpoint between the last visit without the condition and the first one in which it was reported [16]; 2) 5 years of maximum follow-up (to study the effects of the dietary modification in the first years of the intervention [17]); and 3) December 1st,

2010, whichever came first. We defined two Cox models. Model 1 was stratified by sex and recruitment site, and adjusted for age (continuous). Model 2 was further stratified by education level (primary/secondary/higher/unavailable), and adjusted for: systolic blood pressure (continuous), diabetes (yes/no), hypercholesterolemia (yes/no), hypertriglyceridemia (yes/no), tobacco use (current/former/never), body mass index (continuous), alcohol intake (continuous), sodium consumption (continuous), leisure-time physical activity (continuous), and two propensity scores to correct for the theoretical deviations in the randomization process (calculated from 30 baseline variables) [1]. We used robust variance estimators to account for intra-cluster correlations and fitted Cox models using the “survival” package in R Software [18]. These analyses were also performed to study differences in the incidence of resistant hypertension in MedDiet intervention groups relative to the low-fat control diet. In addition, we represented Kaplan-Meier cumulative incidence curves for each study group (weighted by inverse probability weighting using a propensity score model of assignment to intervention or control group based on the covariates above listed).

As sensitivity analyses, we additionally assessed whether there was a different risk in the onset of use of the six main antihypertensive drug families considering a competitive risk approach (the risk of initiation of one drug family could be affected by the risk of initiation of the rest of antihypertensive medications) by cause-specific hazard models [10]. The competing events we considered were the initiation of use of the drug family of interest and the initiation of use of any of the other families as a whole. These sub-analyses were performed for the main events whose incidence was different in individuals on MedDiet interventions compared to the low-fat control diet.

Our second objective was to assess whether MedDiet modified the association between antihypertensive drug use at baseline and the incidence of major adverse cardiovascular events. We compared the volunteers randomly allocated to the MedDiet

interventions combined relative to those in the control group. We fitted Cox models where the outcome was the incidence of the first major cardiovascular event, included an interaction product-term “antihypertensive therapy use x group”, and applied a likelihood ratio test between the models with and without the interaction term. We stratified by/adjusted for the covariates in the main objective, minimized indication bias by adjusting for a propensity score that estimated the probability of being a antihypertensive drug user at baseline (calculated according to the covariates of the model) [19], and used robust variance estimators.

We performed all analyses with R Software, version 3.5.2 [20].

Data sharing

The dataset analyzed during the current study is not publicly available due to national data regulations and for ethical reasons, including that we do not have the explicit written consent of the study volunteers to make their deidentified data available at the end of the study. However, collaboration for data analyses can be requested by sending a letter to the PREDIMED Steering Committee (predimed-steering-committe@googlegroups.com). The request will then be passed to all the members of the Committee for deliberation.

RESULTS

Participants

For this study, four sub-groups of PREDIMED participants (66-68 years old on average, 53-62% of women) were generated according to their use of antihypertensive therapy at baseline: non-users (*n*=2,188), and users of one (*n*=2,401), two (*n*=1,702), or

three drugs (*n*=641). Average systolic and diastolic blood pressure were progressively higher in volunteers with an increasing number of antihypertensive drugs at baseline (148-158 and 82-84 mmHg, respectively). By study design, apart from hypertension, there was a high prevalence of cardiovascular risk factors (69-74% hypercholesterolemia, 44-55% diabetes, 39-62% obesity, 24-34% hypertriglyceridemia, 9-18% current smoking habit). The distribution of the participants' allocation to the three intervention groups was well equilibrated (**Table 1**). Median follow-up times were 2.6, 3.1, 3.5, and 4.1 years for antihypertensive drug initiation, escalation in one-drug users, escalation in two-drug users, and escalation in three-drug users, respectively.

MedDiet effects on the use of antihypertensive therapy

As observed in **Table 2**, MedDiet interventions combined were associated with 16% less risk of initiating the use of antihypertensive drugs among non-treated participants (HR=0.84 [0.74; 0.97], according to the model adjusted for age, sex, and recruitment site). MedDiet interventions individually were linked to similar risk decreases ($HR_{MedDiet\text{-}EVOO}$=0.83 [0.72; 0.97]; $HR_{MedDiet\text{-}Nuts}$=0.85 [0.73; <1.00]). In particular, we observed a decrease in the risk of initiating calcium antagonist therapy (27% less risk was suggested when both MedDiet interventions were combined –HR: 0.73 [0.53; 1.00], *P*=0.051–, and a 34% decrement was observed for the MedDiet-EVOO intervention group –HR: 0.66 [0.46; 0.96], *P*=0.029–). Decreases in the risk of initiation of mineralocorticoid receptor antagonists when both MedDiet interventions were combined (HR: 0.50 [0.23; 1.08], *P*=0.078) and in the risk of initiation of use of beta-blockers (HR: 0.69 [0.46; 1.05], *P*=0.085) and alpha-blockers (HR: 0.41 [0.16; 1.07], *P*=0.068) after the MedDiet-EVOO intervention were also suggested (**Supplemental Table 3**).

The risk of escalating antihypertensive therapy in participants using two drugs at baseline also decreased in the MedDiet-EVOO intervention arm (HR=0.77 [0.60; 0.99]).

Particularly, both MedDiets combined were associated with a 26% decrement in the risk of adding a calcium antagonist to the therapy (HR: 0.74 [0.55; 0.99], *P*=0.044). This association was particularly hinted in the MedDiet-EVOO intervention group (HR: 0.71 [0.51; 1.01], *P*=0.054). A 38% decrease in the risk of adding a beta-blocker to the therapy after the MedDiet-EVOO was also suggested (HR: 0.62 [0.38; 1.01], *P*=0.055) (**Supplemental Table 4**).

No significant differences in escalation risk were observed for participants treated with one or three drugs (**Table 2**), and for the risk of resistant hypertension (**Supplemental Table 5**). Kaplan-Meier curves are available in **Supplemental Figure 1**.

Interaction between antihypertensive therapy at baseline and MedDiet on the incidence of cardiovascular events

Antihypertensive drug use at baseline was more strongly linked to a greater risk of suffering a major adverse cardiovascular event in volunteers in the control group than in those allocated to the MedDiet interventions ($HR_{control}$= 1.51 [0.90; 2.51]; $HR_{MedDiet}$= 1.01 [0.73; 1.41]; *P*-value for interaction=0.003) (**Figure 2**). Full description of this analysis are available in **Supplemental Table 6**.

DISCUSSION

Our results suggest that following a MedDiet decreased the necessity of antihypertensive drug use in non-treated individuals. MedDiet decreased the necessity of escalating antihypertensive therapy in patients using two drugs at baseline and attenuated the association of antihypertensive drug use with the risk of incident cardiovascular events.

These findings point out several MedDiet benefits in relation to the use of antihypertensive drugs in an older population at high cardiovascular risk.

There is evidence of a salutary effect of the MedDiet on blood pressure. In the PREDIMED Study, the MedDiet interventions were associated with lower blood pressure levels [6,7] and improved biomarkers of endothelial function such as nitric oxide metabolites (in the MedDiet-EVOO group) and endothelin-1 in plasma (in the MedDiet-Nuts intervention arm) [21]. Our findings further support the antihypertensive effects of MedDiet, as it decreased the antihypertensive drug use in non-treated individuals, delayed pharmacological escalation, and attenuated cardiovascular risk in treated individuals. The effects of MedDiet on blood pressure may be related to its key nutrients beyond the decrease in sodium intake described in the three PREDIMED intervention arms [7]. First, antioxidants (present in extra-virgin olive oil, fruits, vegetables, pulses, and nuts) neutralize oxidative stress and decrease its capacity to induce endothelial dysfunction [22], which in turn may be linked to an increased endothelial production of nitric oxide and vasodilation [23]. Less hyperglycemia [24] and low-grade inflammation [25] due to the MedDiet intervention could also contribute to a improve endothelial function and greater vasodilation. Additionally, as antioxidants scavenge superoxide anions that react with nitric oxide to generate peroxynitrite, they increase nitric oxide half-life and bioavailability [26]. Second, unsaturated fats in MedDiet may promote vasodilatory responses. Oleic acid (the major fatty acid in olive oil, the main source of fat in the MedDiet) is known to improve membrane structures and the activation of G-protein receptors involved in vasodilation [27]. In addition, omega-3 polyunsaturated fatty acids (present in fish, seafood, and some nuts like walnuts) promote the generation of vasodilatory eicosanoids such as 3-series prostaglandins and thromboxanes and 5-series leukotrienes [28]. Finally, short-chain fatty acids (derived from the fermentation of dietary fiber by intestinal probiotic bacteria) and some phenolic compounds have been shown to promote the activation of AMP-activated

protein kinase [29,30], an enzyme complex capable of promoting the activity of inducible nitric oxide synthases and the production of nitric oxide [31]. Short-chain fatty acids are also known to decrease renin production and downregulate blood pressure through their capacity to stimulate Olfr78 receptors in juxtaglomerular cells in the kidney [32].

Our study has some limitations. First, as major limitation, we could only collect information of use/non-use of antihypertensive drugs and, therefore, we were unable to assess dose changes of individual drugs in treated individuals. Second, variables related to the use of antihypertensive drugs were not a predetermined endpoint in the PREDIMED trial and, therefore, these analyses should be considered as exploratory. Third, since our volunteers were older individuals at high cardiovascular risk, we cannot generalize our results to other populations. Fourth, the MedDiet interventions were modest real-life changes of the dietary pattern and we used an active comparator as control group, as the recommended low-fat diet also was a health-promoting dietary pattern. Therefore, these aspects may have hindered our capacity to observe differences in some comparisons. Fifth, some covariates in our analyses (leisure-time physical activity) were based on self-reported data and this may imply some residual confounding. Finally, we could only adjust our analyses for baseline values of body mass index values (and not for time-dependent changes in this parameter). This parameter is available for all participants and accurate as possible since the PREDIMED intervention did not reduce energy intake and did not promote physical activity [1,3] and was not associated with substantial changes in body mass index in a secondary analysis of the study [33].

In conclusion, our findings suggest a reduction in the necessity of initiating antihypertensive drug use in the individuals allocated to a MedDiet intervention. Among treated individuals, the MedDiet-EVOO intervention arm decreased the risk of increasing the number of antihypertensive medications in those treated with two drugs. In both cases, lower risks of initiating calcium antagonist and beta-blocker therapies were suggested.

Finally, following a MedDiet also attenuated the association between antihypertensive drug use and the risk of suffering a cardiovascular event. To the best of our knowledge, this is the first study to report the long-term effects of MedDiet on the use of antihypertensive drugs. Our results support the vascular protection attributed to this dietary pattern and suggest that MedDiet can be recommended to prevent or delay the onset and escalation of antihypertensive medication in older individuals at high cardiovascular risk.

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TABLES

Table 1. Study population according to antihypertensive drug use at baseline

	Non-treated (*n*=2,188)	**One-drug users (*n*=2,401)**	**Two-drug users (*n*=1,702)**	**Three-drug users (*n*=641)**
Age (years), mean ± SD	66.0 ± 6.06	67.2 ± 6.11	67.8 ± 6.27	67.6 ± 6.09
Female sex, *n* (%)	1,155 (52.8)	1,411 (58.8)	1,060 (62.3)	386 (60.2)
Systolic blood pressure (mmHg), mean ± SD	148 ± 19.6	153 ± 19.0	154 ± 20.3	157 ± 20.4
Diastolic blood pressure (mmHg), mean ± SD	81.9 ± 10.3	84.2 ± 10.5	83.8 ± 10.8	83.9 ± 11.2
Diabetes, *n* (%)	1,209 (55.3)	1,054 (43.9)	782 (45.9)	319 (49.8)
Hypercholesterolemia, *n* (%)	1,507 (68.9)	1,757 (73.2)	1,255 (73.7)	469 (73.2)
Hypertriglyceridemia, *n* (%)	530 (24.2)	724 (30.2)	537 (31.6)	217 (33.9)
Smoking habit:				
Never smokers, *n* (%)	1,214 (55.5)	1,514 (63.1)	1,129 (66.3)	409 (63.8)
Actual smokers, *n* (%)	390 (17.8)	314 (13.1)	202 (11.9)	59 (9.20)
Former smokers, *n* (%)	584 (26.7)	573 (23.9)	371 (21.8)	173 (27.0)
Weight status:				
Normal weight, *n* (%)	222 (10.1)	182 (7.58)	88 (5.17)	26 (4.06)
Overweight, *n* (%)	1,124 (51.4)	1,107 (46.1)	703 (41.3)	219 (34.2)
Obese, *n* (%)	842 (38.5)	1,112 (46.3)	911 (53.5)	396 (61.8)
PREDIMED Intervention groups:				

MedDiet-EVOO, *n* (%)	784 (35.8)	809 (33.7)	618 (36.3)	209 (32.6)
MedDiet-Nuts, *n* (%)	742 (33.9)	787 (32.8)	524 (30.8)	215 (33.5)
Control diet, *n* (%)	662 (30.3)	805 (33.5)	560 (32.9)	217 (33.9)
Leisure-time physical activity (METs·min/d), median (1^{st}-3^{rd} quartile)	187 (75.1-336)	179 (70.0-321)	161 (54.0-297)	153 (50.0-294)

MedDiet-Nuts: Mediterranean diet intervention enriched with nuts; *MedDiet-EVOO*: Mediterranean Diet intervention enriched with extra-virgin olive oil; *METs·min/d*: metabolic equivalents of task·minute/day.

Table 2. Changes in incidence of antihypertensive drug initiation and escalation in the PREDIMED intervention groups.

	Initiation of antihypertensive therapy			**Escalation in one-drug users**		
	Cases/Total	**Model 1**	**Model 2**	**Cases/Total**	**Model 1**	**Model 2**
Control diet	312/662 (47.1%)	1 (Ref.)	1 (Ref.)	254/805 (31.6%)	1 (Ref.)	1 (Ref.)
MedDiets combined	656/1,526 (43.0%)	0.84 [0.74; 0.97] (*P*=0.014)	0.92 [0.80; 1.05] (*P*=0.207)	515/1,596 (32.3%)	0.98 [0.84; 1.14] (*P*=0.772)	1.04 [0.89; 1.22] (*P*=0.644)
MedDiet-EVOO	341/784 (43.5%)	0.83 [0.72; 0.97] (*P*=0.023)	0.93 [0.79; 1.08] (*P*=0.333)	276/809 (34.1%)	1.00 [0.84; 1.18] (*P*=0.993)	1.05 [0.88; 1.25] (*P*=0.597)
MedDiet-Nuts	315/742 (42.5%)	0.85 [0.73; <1.00] (*P*=0.048)	0.91 [0.78; 1.06] (*P*=0.213)	239/787 (30.4%)	0.95 [0.80; 1.14] (*P*=0.609)	1.03 [0.85; 1.23] (*P*=0.786)
	Escalation in two-drug users			**Escalation in three-drug users**		
	Cases/Total	**Model 1**	**Model 2**	**Cases/Total**	**Model 1**	**Model 2**
Control diet	128/560 (22.9%)	1 (Ref.)	1 (Ref.)	25/217 (11.5%)	1 (Ref.)	1 (Ref.)

MedDiets combined	230/1,142 (20.1%)	0.80 [0.65; 1.00] (*P*=0.050)	0.81 [0.65; 1.01] (*P*=0.061)	52/424 (12.3%)	0.91 [0.57; 1.45] (*P*=0.685)	0.83 [0.51; 1.34] (*P*=0.442)
MedDiet-EVOO	124/618 (20.1%)	0.76 [0.59; 0.98] (*P*=0.033)	0.77 [0.60; 0.99] (*P*=0.041)	27/209 (12.9%)	0.95 [0.56; 1.63] (*P*=0.863)	0.91 [0.51; 1.63] (*P*=0.75)
MedDiet-Nuts	106/524 (20.2%)	0.86 [0.66; 1.11] (*P*=0.237)	0.86 [0.66; 1.12] (*P*=0.255)	25/215 (11.6%)	0.87 [0.50; 1.49] (*P*=0.605)	0.76 [0.44; 1.32] (*P*=0.329)

We used Cox proportional hazards regression models. Model 1 was stratified by sex and recruitment site, and adjusted for age. Model 2 was further stratified by educational level and adjusted for: systolic blood pressure, diabetes, hypercholesterolemia, hypertriglyceridemia, smoking, leisure-time physical activity, body mass index, alcohol consumption, sodium intake (at baseline), and two propensity scores that used 30 baseline variables to estimate the probability of assignment to each of the intervention groups. Robust standard errors to account for intra-cluster correlations were used.

MedDiet-EVOO: Mediterranean diet enriched with extra-virgin olive oil; *MedDiet-Nuts*: Mediterranean diet enriched with nuts.

FIGURE LEGENDS

Figure 1. Study flowchart

Figure 2. Associations of baseline use of antihypertensive drugs with the risk of suffering a major cardiovascular event stratified by intervention group

Figure 2 – Legend. Cox proportional hazards regression models were stratified by sex, recruitment site, and educational level; and adjusted for: age, systolic blood pressure, diabetes, hypercholesterolemia, hypertriglyceridemia, smoking, leisure-time physical activity, body mass index, alcohol consumption, sodium intake (at baseline), two propensity scores that used 30 baseline variables to estimate the probability of assignment to each of the intervention groups, and another propensity score to minimize indication bias (which estimated the probability of being user of antihypertensive drugs at baseline). We used robust standard errors to account for intra-cluster correlations. *MedDiet*: Mediterranean diet.