RESEARCH LETTER

Association of Mediterranean Diet With Peripheral Artery Disease: The PREDIMED Randomized Trial

The role of nutrition in preventing peripheral artery disease (PAD) remains elusive.[1]

Mediterranean diets reduce the risk of myocardial infarction and stroke.[2,3] They also may reduce the risk of PAD, but this hypothesis has never been tested in a randomized trial. We assessed the association of Mediterranean diets with the occurrence of symptomatic PAD in an exploratory, nonprespecified analysis of a randomized trial.

Methods | The Prevención con Dieta Mediterránea (PREDIMED) was a multicenter, randomized, primary prevention feeding trial with blinded assessment of end points conducted in Spain between October 2003 and December 2010.[3,4]

Eligible participants were men aged 55 to 80 years and women aged 60 to 80 years without clinical PAD or baseline cardiovascular disease but with type 2 diabetes mellitus or at least 3 cardiovascular risk factors.

Participants were randomized in a 1:1:1 ratio to 1 of 3 groups: a Mediterranean diet supplemented with extra-virgin olive oil; a Mediterranean diet supplemented with nuts; or counseling on a low-fat diet (control group). All participants received a comprehensive dietary educational program on a quarterly basis. The intensity of the program delivered to the control group was increased in October 2006.

The protocol was approved by institutional review boards and written informed consent was obtained from all participants.

New symptomatic PAD events were confirmed by a central end-point adjudication committee that was blinded to the allocated group. A confirmed diagnosis of PAD in symptomatic patients required at least 1 of the following criteria: an ankle-brachial index of less than 0.9 at rest, a clinical diagnosis of arterial occlusive disease based on imaging tests (duplex ultrasonography, magnetic resonance angiography, computed tomographic angiography, or catheter-based radiocontrast angiography), or an endovascular or open surgical procedure (revascularization or amputation).

We used Stata version 12.1 (StataCorp) for statistical analyses. Kaplan-Meier curves and Cox proportional hazards models adjusted for baseline factors were used to compare the risk of PAD for each diet group vs the control group on an intention-to-treat basis.

The number needed to treat (NNT) was estimated for each diet group vs control group. As a sensitivity analysis, we used multiple imputation algorithms for participants without any events or study contact for at least 2 years.

Results | Of 8713 eligible candidates, 7477 were initially included and randomized in the PREDIMED trial.[3] Among them, 12 participants were excluded for intermittent claudication symptoms at baseline.

Table. Incident Peripheral Artery Disease by Intervention Group

	Mediterranean Diet		
	Extra-Virgin Olive Oil	Nuts	Control
No. of patients	2539	2452	2444
No. of cases	18	26	45
Person-years of follow-up	11 796	10 329	9676
Crude rate/1000 person-years (95% CI)	1.5 (1.0-2.4)	2.5 (1.7-3.7)	4.7 (3.5-6.2)
Hazard ratios of PAD by intervention group (95% CI)[a]			
Model			
Crude	0.32 (0.19-0.56)	0.51 (0.32-0.83)	1 [Reference]
Age and sex adjusted	0.31 (0.18-0.54)	0.48 (0.29-0.78)	1 [Reference]
Multivariable adjusted[b]	0.34 (0.20-0.58)	0.50 (0.30-0.81)	1 [Reference]
Multivariable adjusted[c]	0.36 (0.20-0.62)	0.52 (0.32-0.86)	1 [Reference]
Multivariable adjusted[d]	0.36 (0.21-0.65)	0.54 (0.32-0.92)	1 [Reference]

Abbreviation: PAD, peripheral artery disease.

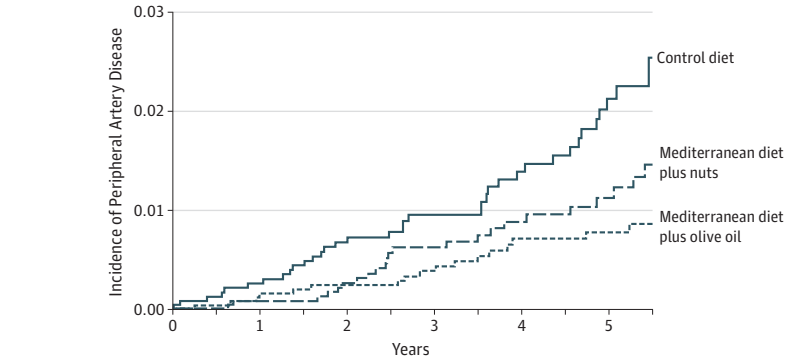
[a] Stratified by center.

[b] Adjusted for age, sex, smoking (current or former), diabetes, hypertension, and hyperlipidemia.

[c] Additionally adjusted for height, waist circumference, body mass index, baseline adherence to the Mediterranean diet (14-point score), leisure-time physical activity (metabolic equivalent tasks in minutes/day), educational level (illiterate or elementary education vs secondary education or university), hormone therapy, antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors, β-blockers, diuretics, insulin, other hypoglycemic agents, total vitamin D intake, dietary vitamin B_{12} intake, dietary folic acid intake, and family history of premature cardiovascular disease.

[d] Complete case analysis excluding 514 participants for whom there was no documented event or who were lost to follow-up for 2 years or longer.

Figure. Kaplan-Meier Estimates of the Incidence of PAD in the Total Study



No. at risk						
Control diet	2444	2258	2006	1569	1254	928
Mediterranean diet						
Nuts	2452	2342	2092	1649	1382	1023
Olive oil	2539	2478	2311	1977	1675	1298

The mean (SD) age of included participants was 67 (6.2) years, and 58% were women. We observed 89 confirmed new cases of clinical PAD after a median follow-up of 4.8 years.

Both Mediterranean diet interventions were associated with a lower risk of PAD compared with the control group (**Table**). In the model adjusted for classic atherosclerotic risk factors, the hazard ratio (HR) was 0.34 (95% CI, 0.20-0.58) for participants in the Mediterranean diet plus extra-virgin olive oil group and 0.50 (95% CI, 0.30-0.81) for the Mediterranean diet plus nuts group vs control group.

The multiple imputation procedure rendered similar estimates. No statistically significant difference between the 2 active intervention groups was apparent (adjusted HR, 0.71; 95% CI, 0.38-1.33).

The Kaplan-Meier curves diverged early in the trial (**Figure**). The NNT to prevent 1 case of PAD per year was 336 (95% CI, 269-566) for the Mediterranean diet plus extra-virgin olive oil group and 448 (95% CI, 316-1536) for the Mediterranean diet plus nuts group.

Discussion | To our knowledge, this is the first randomized primary prevention trial to suggest an association between a dietary intervention and PAD. These results are consistent with previous observational studies and relevant from a public health perspective.[5,6]

Because PAD was not a prespecified end point in the trial protocol, this is only an exploratory analysis. Other potential limitations include that the observed number of events was small and the study was restricted to clinically symptomatic cases. Replication by another randomized controlled trial with PAD as a prespecified end point is needed before causal conclusions can be drawn.

The randomized design, blinded assessment and adjudication of events, and adjustment for a large number of potential confounders minimize the threat of biases in this study.

We cannot ascertain whether the observed association is due to a reduced incidence of asymptomatic PAD (true primary prevention) or to a reduced conversion from this early stage of PAD to symptomatic and clinically meaningful PAD.

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Author Contributions: Dr Martínez-González had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Estruch, Corella, Salas-Salvadó.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Ruiz-Canela, Martínez-González.
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Trial Registration: isrctn.org Identifier: ISRCTN35739639

1. Brostow DP, Hirsch AT, Collins TC, Kurzer MS. The role of nutrition and body composition in peripheral arterial disease. *Nat Rev Cardiol*. 2012;9(11):634-643.

2. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med*. 2009;169(7):659-669.

3. Estruch R, Ros E, Salas-Salvadó J, et al; PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368(14):1279-1290.

4. Martínez-González MÁ, Corella D, Salas-Salvadó J, et al; PREDIMED Study Investigators. Cohort profile: design and methods of the PREDIMED study. *Int J Epidemiol*. 2012;41(2):377-385.

5. Lane JS, Magno CP, Lane KT, Chan T, Hoyt DB, Greenfield S. Nutrition impacts the prevalence of peripheral arterial disease in the United States. *J Vasc Surg*. 2008;48(4):897-904.

6. Naqvi AZ, Davis RB, Mukamal KJ. Dietary fatty acids and peripheral artery disease in adults. *Atherosclerosis*. 2012;222(2):545-550.

COMMENT & RESPONSE

Hormone Therapy Use and Outcomes in the Women's Health Initiative Trials

To the Editor The study by Dr Manson and colleagues[1] provided considerable information about the 2 Women's Health Initiative (WHI) hormone trials, especially regarding outcomes stratified by the age of the participants at the time of trial entry.

During the intervention phase of the WHI Estrogen-Alone Trial, participants aged 50 to 79 years randomized to conjugated equine estrogens (CEE) had significantly worse outcomes for stroke, deep venous thrombosis, urinary incontinence, and gallbladder disease.[1] Information on all of these outcomes (stratified by age of the participants by decade at trial entry) for the intervention phase has been published,[1-4] except for data on gallbladder disease.

Gallbladder outcomes have been reported for WHI participants using a semiannual safety questionnaire and, if present, confirmed by an examination of medical and hospital records.[5] There was "a suggestion" ($P = .06$) for gallbladder disease outcomes to vary by age in the WHI Estrogen-Alone Trial intervention phase[5] but no decade-specific information has been published.

Could the authors provide gallbladder disease outcome information stratified by decade of age for the intervention phase of the WHI Estrogen-Alone Trial? These data could assist physicians in assessing the risk to benefit ratio of CEE monotherapy in younger women without a uterus.

In addition, could the authors clarify the data for the gallbladder end point used in their study, which shows 461 gallbladder events in the CEE group and 312 events in the placebo group in the intervention phase?

The one prior WHI publication with gallbladder disease data showed many fewer outcomes, with 228 gallbladder events for the CEE group and 143 for the placebo group.[5] Also, in the prior publication,[5] the annualized incidence percentage for gallbladder events is reported as 0.78% for the CEE group, whereas in the study by Manson et al,[1] the annualized incidence percentage for the CEE group is reported as 1.64%.

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA*. 2013;310(13):1353-1368.

2. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA*. 2007;297(13):1465-1477.

3. Curb JD, Prentice RL, Bray PF, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. *Arch Intern Med*. 2006;166(7):772-780.

4. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. *JAMA*. 2005;293(8):935-948.

5. Cirillo DJ, Wallace RB, Rodabough RJ, et al. Effect of estrogen therapy on gallbladder disease. *JAMA*. 2005;293(3):330-339.

In Reply Dr Roehm requests more information about the gallbladder disease outcome in the WHI trials. The goal of our article was to provide a comprehensive, integrated overview of findings from the 2 hormone therapy trials, including results from extended postintervention follow-up.

Due to the large number of outcomes presented (including primary and secondary adjudicated end points and quality-of-life outcomes), we only had space to present age-stratified analyses for the primary and secondary outcomes. We presented the hazard ratio (HR) for gallbladder disease in the overall cohort for each trial and noted that no significant differences by age group were observed.

As requested by Roehm, we present the detailed findings for gallbladder disease by age group for both hormone therapy trials (**Table**). Tests for interaction by age group were not statistically significant ($P = .66$ for both trials).

Our results for gallbladder disease in the overall cohort are nearly identical to those previously presented by Cirillo et al.[1] Cirillo et al reported an HR of 1.59 (95% CI, 1.28-1.97) for gallbladder procedure/disease (confirmed by hospitalization records) in the WHI trial of CEE plus medroxyprogesterone acetate (MPA) compared with an HR of 1.57 (95% CI, 1.36-1.80) in our analyses based on self-reported diagnosis