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Dietary Intake of Vitamin K Is Inversely Associated with Mortality Risk[1–3]

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Abstract

Vitamin K has been related to cardiovascular disease and cancer risk. However, data on total mortality are scarce. The aim of the present study was to assess the association between the dietary intake of different types of vitamin K and mortality in a Mediterranean population at high cardiovascular disease risk. A prospective cohort analysis was conducted in 7216 participants from the PREDIMED (Prevención con Dieta Mediterránea) study (median follow-up of 4.8 y). Energy and nutrient intakes were evaluated using a validated 137-item food frequency questionnaire. Dietary vitamin K intake was calculated annually using the USDA food composition database and other published sources. Deaths were ascertained by an end-point adjudication committee unaware of the dietary habits of participants after they had reviewed medical records and linked up to the National Death Index. Cox proportional hazard models were fitted to assess the RR of mortality. Energy-adjusted baseline dietary phylloquinone intake was inversely associated with a significantly reduced risk of cancer and all-cause mortality after controlling for potential confounders (HR: 0.54; 95% CI: 0.30, 0.96; and HR: 0.64; 95% CI: 0.45, 0.90, respectively). In longitudinal assessments, individuals who increased their intake of phylloquinone or menaquinone during follow-up had a lower risk of cancer (HR: 0.64; 95% CI: 0.43, 0.95; and HR: 0.41; 95% CI: 0.26, 0.64, respectively) and all-cause mortality (HR: 0.57; 95% CI: 0.44, 0.73; and HR: 0.55; 95% CI: 0.42, 0.73, respectively) than individuals who decreased or did not change their intake. Also, individuals who increased their intake of dietary phylloquinone had a lower risk of cardiovascular mortality risk (HR: 0.52; 95% CI: 0.31, 0.86). However, no association between changes in menaquinone intake and cardiovascular mortality was observed (HR: 0.76; 95% CI: 0.44, 1.29). An increase in dietary intake of vitamin K is associated with a reduced risk of cardiovascular, cancer, or all-cause mortality in a Mediterranean population at high cardiovascular disease risk. This trial was registered at http://www.controlled-trials.com as ISRCTN35739639. J. Nutr. 144: 743–750, 2014.

Introduction

Vitamin K includes a group of fat-soluble vitamins that occur in 2 natural active forms: *1*) phylloquinone (vitamin K-1), mainly found in green leafy vegetables and vegetable oils; and *2*) menaquinone [vitamin K-2 or menaquinone (MK)[21]-*n*], produced by intestinal bacteria and found in fermented foods. Vitamin K acts as a

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[3] Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

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cosubstrate for the enzyme γ-glutamyl carboxylase in the carboxylation of specific glutamic residues into γ-carboxyglutamyl acid residues in some proteins (1). Matrix γ-carboxyglutamyl acid protein, present in the vascular wall, is a powerful inhibitor of vascular calcification (2). It has been proposed that vitamin K deficiency can increase the amount of nonfunctional matrix γ-carboxyglutamyl acid protein, thus leading to increased calcium deposition and cardiovascular disease (1). This is supported by the results of a population-based survey conducted in elderly individuals in whom lower concentrations of vitamin K were associated with aortic calcification (3).

However, limited evidence shows that vitamins K-1 and K-2 should be expected to have different effects on the modulation of aortic calcification or the risk of cardiovascular disease, mainly attributed to their differences in plasma transport and delivery to target tissues (4), and the results of prospective studies that separately analyze both forms of vitamin K are far from conclusive. In the Nurses' Health Study, a higher dietary phylloquinone intake was inversely associated with the risk of coronary heart disease (CHD) (5), although these results could not be replicated by the same authors in men (6). Unfortunately, data on menaquinone were not available in either study.

In the Rotterdam Study, the relative risk of CHD and all-cause mortality was lower in the upper than the lower tertile of dietary menaquinone intake (7). Data from the Prospect-EPIC (European Prospective Investigation into Cancer and Nutrition) study showed an inverse relation between dietary menaquinone intake and the risk of CHD but no association between phylloquinone intake and CHD risk in postmenopausal women. After analyzing menaquinone subtypes, MK-7, MK-8, and MK-9 were the subclasses that had the strongest associations with a decreased risk of CHD incidence (8).

Apart from its well-known physiologic function that activates coagulation, vitamin K exerts inhibitory effects on cell growth in several cancer cell lines (9–11). Although most studies focused on menadione (vitamin K-3)—a synthetic analogue that acts as a provitamin—phylloquinone, and especially menaquinone, seem to have an antiproliferative capacity (9). These results are supported by a randomized clinical trial conducted on individuals with viral cirrhosis, in which the risk of hepatocellular carcinoma at 6 y of follow-up was significantly lower in individuals who were administered high doses of MK-4 for 2 y than in the control group (12). However, few epidemiologic studies evaluated the association between dietary vitamin K and risk of cancer (13,14). Although no effect has been reported for phylloquinone intake, an inverse association has been noted between menaquinone intake and prostate cancer, total cancer incidence, and mortality (14).

To our knowledge, this is the first study to evaluate the specific association of both active forms of vitamin K (vitamins K-1 and K-2), and their changes during the follow-up, with cancer mortality, cardiovascular mortality, or all-cause mortality in a prospective longitudinal study of Mediterranean individuals at high cardiovascular disease risk and using repeated measurements of dietary intake.

Participants and Methods

Study population. A prospective cohort analysis was conducted in 7216 participants in the framework of the PREDIMED (Prevención con Dieta Mediterránea) cohort. The PREDIMED study is a large, parallel-group, multicenter, controlled, randomized clinical trial aiming to assess the effect of Mediterranean diets on the primary prevention of cardiovascular disease in elderly individuals at high cardiovascular disease risk. Full details of the PREDIMED study protocol have been published previously, and the trial was registered at http://www.controlled-trials.com as ISRCTN35739639 (15,16). Participants were community-dwelling men and women, aged 55–80 and 60–80 y, respectively, with no cardiovascular disease at enrollment and who had either type 2 diabetes mellitus (T2DM) or ≥3 of the following cardiovascular disease risk factors: *1*) smoking; *2*) hypertension; *3*) dyslipidemia; *4*) HDL cholesterol concentration ≤40 mg/dL; *5*) overweight or obesity (BMI ≥ 25 kg/m^2); or *6*) family history of premature cardiovascular disease. The exclusion criteria were as follows: *1*) severe chronic illness; *2*) drug or alcohol addiction; *3*) history of allergy or intolerance to olive oil or nuts; *4*) a low predicted likelihood of changing dietary habits according to Prochaska and DiClemente's stages-of-change model; and *5*) illiteracy and other medical or social conditions that make compliance with the intervention difficult. The protocol was approved by the institutional review boards at all study locations, and participants provided written informed consent.

Dietary assessment. At baseline and annually thereafter, participants were assessed by trained dieticians who administered a validated 137-item FFQ (17). Energy and nutrient intake and food groups were calculated from Spanish food composition tables (18,19). Dietary phylloquinone intake was calculated using the USDA nutrient database (20). Menaquinone intake was calculated using previously published composition data sources (21–23). Reproducibility and relative validity of a self-administered FFQ used in the study was validated for dietary phylloquinone and menaquinone intake. The FFQ was administered twice to explore reproducibility at 1 y, and 4 3-d dietary records were used as reference to explore validity. Reproducibility for dietary phylloquinone and menaquinone intake estimated by the Pearson correlation coefficient (r) was 0.755 and 0.655, respectively, and the intraclass correlation coefficient was 0.860 and 0.798, respectively ($P < 0.001$) (M. Juanola-Falgarona, J. Salas-Salvadó, J. Fernández-Ballart, M. Bulló, unpublished data).

Mortality and medical records. Cardiovascular mortality, cancer mortality, and all-cause mortality were the primary outcomes of our analysis. Four different approaches were used to identify outcomes: *1*) repeated contact with participants; *2*) contact with family physicians; *3*) annual review of medical records; and *4*) consultation of the National Death Index. The end-point adjudication committee, whose members were unaware of the dietary information from participants, evaluated all medical records related to end points. Additional information about health status and medication use was collected directly from the participants in the yearly programmed visits and their medical records.

Anthropometric and biochemical measurements. Baseline weight and height were measured by trained personnel with calibrated scales and a wall-mounted stadiometer, respectively. Waist circumference was measured with an anthropometric tape midway between the lower rib and the superior border of the iliac crest. Blood pressure was measured in triplicate with a validated semiautomatic oscillometer (Omron HEM-705CP). Leisure-time physical activity was evaluated using the validated Spanish version of the Minnesota leisure-time physical activity questionnaire (24).

Statistical analysis. Descriptive data of participants' baseline characteristics were presented as means ± SDs, and categorical variables were presented as percentages. Participants who were outside the predefined values for total energy intake (>4000 or <800 kcal/d in men and >3500 or <500 kcal/d in women) were excluded from the analysis. All nutrients were adjusted for total energy intake using the residuals method (25). Energy-adjusted phylloquinone and menaquinone intake was divided into quartiles on the basis of the total cohort. Survival time was calculated as the number of days between entering the study and death or end of follow-up, whichever occurred first. Time-to-event data were analyzed using the Kaplan-Meier method. Cox proportional hazards regression models were fitted to estimate HRs and the corresponding

[21] Abbreviations used: CHD, coronary heart disease; MK, menaquinone; PREDIMED, Prevención con Dieta Mediterránea; T2DM, type 2 diabetes mellitus.

95% CIs for cardiovascular mortality, cancer mortality, and all-cause mortality. Dietary intake of phylloquinone and menaquinone was entered into the models categorized into energy-adjusted vitamin K quartiles, with the lowest quartile as the reference category. Tests for linear trend were performed by modeling the median values of phylloquinone and menaquinone quartiles as continuous variables. Additionally, 3 multivariate models were used: *1*) model 1 was adjusted for sex, age, BMI, recruiting center, intervention group, smoking (never, current, past), leisure time activity (metabolic equivalent of task per day), and education (primary education, secondary education, higher education); *2*) model 2 was additionally adjusted for history of diabetes, hypertension, and hypercholesterolemia, use of oral antidiabetic medication, use of antihypertensive medication, and use of statins; and *3*) model 3 was additionally adjusted for energy-adjusted dietary variables in quintiles (vegetables, fruits, legumes, cereals, dairy products, meat, fish, olive oil, nuts), alcohol, and alcohol squared in grams per day to account for departures from linearity. Dietary phylloquinone intake and dietary menaquinone intake were not adjusted for vegetables and dairy products, respectively, because both dietary variables are the major source of vitamin K types. We had yearly updated information on dietary phylloquinone and menaquinone intake, so to take advantage of this updated information, we repeated the analysis using generalized estimating equations to assess the association between repeated measurements of vitamin K consumption and mortality. For each 1-y period, we used as exposure the mean phylloquinone or menaquinone intake of all repeated measurements from baseline to the beginning of that yearly period.

Cox regression models were also fitted to estimate HRs for cardiovascular mortality, cancer mortality, or all-cause mortality for participants who increased their dietary phylloquinone intake compared with participants who reduced or did not change their intake during the entire follow-up. Additional Cox regression models were used to assess the risk of total mortality, cardiovascular mortality, and cancer mortality according to the increasing or not increasing total dietary phylloquinone intake and the intervention group. Linear trends were also tested.

Interaction tests for sex, T2DM, and intervention group (sex × vitamin K intake, T2DM × vitamin K intake, intervention group × vitamin K intake) were not statistically significant. All statistical tests were 2-tailed, and the significance level was $P < 0.05$. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS) and STATA 12.0 (StataCorp).

Results

Of the 7447 participants randomly assigned to the PREDIMED trial, 153 were excluded from the present analysis because their total energy intake was outside the predefined limits, and an additional 78 participants were also excluded because their dietary data at baseline were incomplete. Selected baseline participant characteristics across quartiles of energy-adjusted dietary phylloquinone and menaquinone for the 7216 participants available for analyses are shown in **Table 1**.

Participants with higher intakes of dietary phylloquinone had a lower BMI and waist circumference, were more physically active, and were less likely to be current smokers. Those participants allocated to the higher quartiles of dietary menaquinone intake had higher BMI and waist circumference but they were more physically active and fewer were smokers. A small but significant correlation was found between total phylloquinone and menaquinone intake ($r = 0.05$, $P < 0.001$). Participants in the upper quartile of energy-adjusted dietary phylloquinone intake consumed nearly twice as many vegetables (especially leafy green vegetables and fruits) as those in the lower quartile. Increased menaquinone intake was associated with higher consumption of dairy products and meat (**Supplemental Table 1**). In a median follow-up of 4.8 y (IQR: 2.8–5.8), 81 fatal cardiovascular events and 130 deaths from cancer occurred. A total of 323 participants died from any cause. The survival curves of cardiovascular mortality, cancer mortality, or all-cause mortality by quartiles of energy-adjusted dietary phylloquinone and menaquinone intake are shown in **Figure 1**. The number of participants at risk by energy-adjusted vitamin K intake quartiles at different time points is also shown in Figure 1.

Multivariate-adjusted HRs for cardiovascular mortality, cancer mortality, or all-cause mortality according to quartiles of energy-adjusted phylloquinone and menaquinone intake are shown in **Table 2**. Participants in the upper quartiles of phylloquinone or menaquinone intake had a nonsignificantly lower risk of cardiovascular mortality than those in the lowest quartiles in all the fitted models ($P > 0.1$). Dietary phylloquinone intake was inversely associated with cancer mortality risk (HR for the highest and all-cause mortality compared with the lowest quartile: 0.54; 95% CI: 0.30, 0.96; P-trend = 0.033). The relation between dietary phylloquinone intake and cancer or total mortality risk has an apparently inverse linear shape in all the fitted models (P-trend < 0.05). When we used generalized estimating equations to assess the association between yearly updated measurements of total vitamin K consumption and all-cause mortality risk, we also found a significant inverse association. The fully adjusted RR was 0.68 (95% CI: 0.50, 0.93) with a significant linear trend test. When we repeated the analysis using generalized estimating equations to assess the association between yearly updated measurements of dietary phylloquinone or menaquinone intake and mortality, the fully adjusted RR for the highest compared with the lowest quintile were 0.55 (95% CI: 0.27, 1.14) and 1.27 (95% CI: 0.73, 2.23) for cardiovascular mortality, 0.80 (95% CI: 0.46, 1.40) and 0.75 (95% CI: 0.42, 1.32) for cancer mortality, and 0.81 (95% CI: 0.57, 1.15) and 1.12 (95% CI: 0.82, 1.54) for all-cause mortality. Linear trend tests were not significant ($P > 0.1$).

The HRs for cardiovascular mortality, cancer mortality, and all-cause mortality for individuals who increased their dietary vitamin K intake along the follow-up compared with those who reduced or did not change it are shown for **Table 3**. During the follow-up, 3141 and 2572 participants increased their consumption of phylloquinone and menaquinone, respectively. On the contrary, 4057 and 4626, respectively, reduced or did not change it. A decreased risk in cardiovascular mortality (HR: 0.52; 95% CI: 0.31, 0.86; P-trend = 0.012), cancer mortality (HR: 0.64; 95% CI: 0.43, 0.95; P-trend = 0.026), and all-cause mortality (HR: 0.57; 95% CI: 0.44, 0.73; P-trend < 0.001) was observed in those participants who increased their intake of dietary phylloquinone during the follow-up, even after adjusting for other dietary confounders. Similarly, participants who increased their intake of dietary menaquinone were likely to have a lower risk of mortality by cancer and all-cause mortality ($P < 0.001$). The multivariate adjusted HRs for total mortality, cardiovascular mortality, or cancer mortality by changes in both dietary phylloquinone and menaquinone intakes and intervention group are shown in **Supplemental Figure 1** and **Supplemental Table 2**. In the 3 arms of the trial, individuals who increased dietary intake of both forms of vitamin K during the follow-up tended to have a lower risk of mortality than those in the reference category.

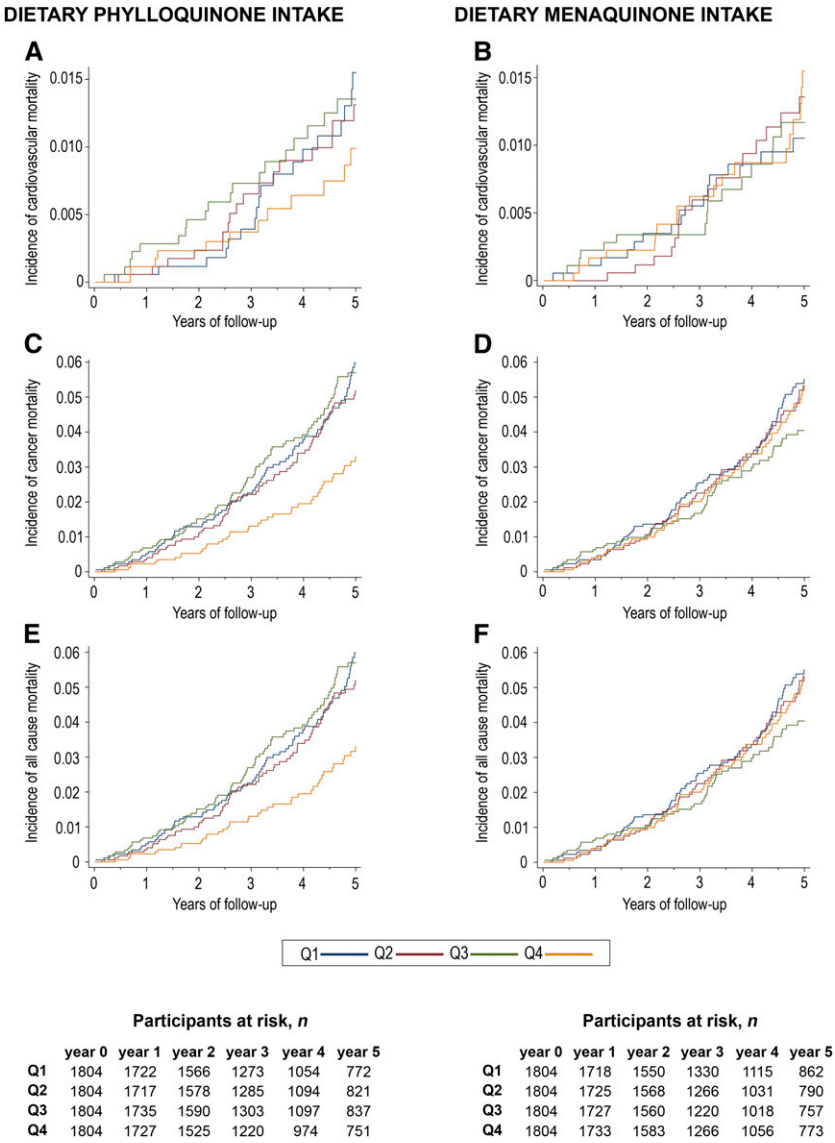
Discussion

To the best of our knowledge, the results of the present study show, for the first time, an inverse association between an increased intake of both dietary phylloquinone and menaquinone, and cancer mortality or all-cause mortality. Moreover,

TABLE 1 Baseline characteristics of 7216 Mediterranean adults at high cardiovascular disease risk by quartiles of energy-adjusted phylloquinone and menaquinone intakes[1]

	Energy-adjusted quartiles of phylloquinone intake[2] (μg/d)					Energy-adjusted quartiles of menaquinone intake[3] (μg/d)				
Variable	Q1	Q2	Q3	Q4	P^4	Q1	Q2	Q3	Q4	P^4
Women, *n (%)*	966 (53.6)	1012 (56.1)	1051 (58.3)	1114 (61.8)	<0.001	940 (52.1)	1083 (60.0)	1097 (60.8)	1025 (56.8)	<0.001
Age, *y*	67 ± 7	67 ± 6	67 ± 6	67 ± 6	0.083	67 ± 6	67 ± 6	67 ± 6	67 ± 6	0.001
BMI, *kg/m^2*	30.2 ± 3.9	30.0 ± 3.7	29.8 ± 3.8	29.9 ± 4.0	0.009	29.5 ± 3.7	30.1 ± 3.8	30.2 ± 3.9	30.1 ± 4.0	<0.001
Waist circumference, *cm*	101.6 ± 10.5	100.3 ± 10.3	99.9 ± 10.6	100.1 ± 10.8	<0.001	99.2 ± 10.1	100.6 ± 10.7	100.7 ± 10.6	101.4 ± 11.0	<0.001
Smoking status, *n (%)*					0.005					0.001
Never	1056 (59)	1110 (61)	1123 (62)	1150 (64)		1048 (58)	1158 (64)	1139 (63)	1094 (61)	
Current	279 (15)	268 (15)	249 (14)	208 (11)		297 (16)	220 (12)	244 (14)	243 (13)	
Former	469 (26)	426 (24)	432 (24)	446 (25)		459 (25)	426 (24)	421 (23)	467 (26)	
Education, *n (%)*					0.07					0.010
Primary education	1376 (77)	1333 (75)	1390 (79)	1372 (77)		1364 (76)	1410 (79)	1375 (79)	1322 (75)	
Secondary education	276 (15)	313 (18)	245 (14)	262 (15)		282 (16)	262 (15)	249 (14)	303 (17)	
Higher education	129 (7)	124 (7)	124 (7)	139 (8)		144 (8)	103 (6)	127 (7)	142 (8)	
Type 2 diabetes, *n (%)*	835 (46)	846 (47)	863 (48)	965 (53)	<0.001	752 (42)	881 (49)	912 (51)	964 (53)	<0.001
Hypertension, *n (%)*	150 (84)	149 (83)	150 (83)	146 (81)	0.21	1501 (83)	1509 (84)	1497 (83)	1463 (81)	0.19
Hypercholesterolemia, *n (%)*	132 (73)	128 (71)	128 (71)	132 (74)	0.18	1349 (75)	1293 (72)	1334 (74)	1236 (69)	<0.001
Intervention group, *n (%)*					<0.001					0.64
Mediterranean diet with EVOO	598 (33)	628 (35)	610 (34)	637 (35)		623 (35)	614 (34)	598 (33)	639 (35)	
Mediterranean diet with nuts	540 (30)	569 (32)	647 (36)	602 (33)		581 (32)	582 (32)	596 (33)	601 (33)	
Control diet	665 (37)	606 (34)	547 (30)	564 (31)		600 (33)	608 (34)	610 (34)	564 (31)	
Leisure-time physical activity, *MET-min/d*	209 ± 230	230 ± 233	238 ± 230	248 ± 260	<0.001	246 ± 261	221 ± 224	226 ± 232	231 ± 237	0.011

[1] Data are means ± SDs or *n* (%) unless otherwise indicated. *n* = 1804 participants in each quartile. EVOO, extra virgin olive oil; MET, metabolic equivalent of task; Q, quartile.
[2] The mean energy-adjusted phylloquinone intakes for Q1, Q2, Q3, and Q4 were as follows: 170.5 μg/d, 276.1 μg/d, 349.7 μg/d, and 626.4 μg/d, respectively.
[3] The mean energy-adjusted menaquinone intakes for Q1, Q2, Q3, and Q4 were as follows: 18.4 μg/d, 29.9 μg/d, 39.0 μg/d, and 57.5 μg/d, respectively.
[4] *P* values are based on the difference between quartiles of energy-adjusted dietary vitamin K intake (ANOVA for the continuous variables and χ^2 test for categorical variables).



Participants at risk, *n*

	year 0	year 1	year 2	year 3	year 4	year 5
Q1	1804	1722	1566	1273	1054	772
Q2	1804	1717	1578	1285	1094	821
Q3	1804	1735	1590	1303	1097	837
Q4	1804	1727	1525	1220	974	751

Participants at risk, *n*

	year 0	year 1	year 2	year 3	year 4	year 5
Q1	1804	1718	1550	1330	1115	862
Q2	1804	1725	1568	1266	1031	790
Q3	1804	1727	1560	1220	1018	757
Q4	1804	1733	1583	1266	1056	773

FIGURE 1 Nelson-Aalen estimates of incidence of cardiovascular (*A, B*), cancer (*C, D*), and total (*E, F*) mortality by quartiles of energy-adjusted vitamin K intake. Q, quartile.

increasing dietary phylloquinone intake, but not menaquinone intake, was related to a lower risk of cardiovascular mortality.

Interest in vitamin K has been aroused recently by evidence to suggest that it has a physiologic role that goes beyond mere coagulation processes. Vitamin K has acquired importance in the physiopathology of vascular calcification and atherosclerotic diseases but also in the modulation of bone metabolism and cancer initiation and progression (26,27). Therefore, higher phylloquinone dietary intake has been associated with a lower risk of developing age-related chronic diseases, such as abdominal aortic calcification (3), insulin resistance (28), and osteoporosis (29). These beneficial effects could be explained by several mechanisms involving vitamin K–dependent proteins. However, there is evidence emerging from in vitro and in vivo studies to indicate that the biochemical function of vitamin K could be extended to other mechanisms [i.e., modulating inflammatory molecules (28,30,31) or controlling carcinogenesis (10,32)].

Few epidemiologic studies evaluated the role of the dietary intake of vitamin K in cardiovascular disease and all-cause mortality, and the results are far from consistent or conclusive. Although most (7,8) but not all (5) published studies observed no consistent association between phylloquinone intake and fatal or nonfatal CHD, the available evidence seems to suggest that menaquinone intake has a protective effect against the incidence of fatal and nonfatal CHD or all-cause mortality (7,8). In our study, we found no significant association between phylloquinone or menaquinone dietary intake and cardiovascular mortality, although we did find a significant inverse association between dietary phylloquinone intake and all-cause mortality.

There may be several reasons for the apparent differences between our results and those reported previously by other cohorts. First, the PREDIMED study population was composed of elderly individuals at high cardiovascular disease risk, whereas the other studies were of healthy participants. Although in our study Cox regression models were adjusted for several cardiovascular disease risk factors, these factors still had a residual effect on cardiovascular mortality, masking a potential protective effect of vitamin K. Thus, in a sensibility analysis, dietary vitamin K intake in those participants having ≤ 3 cardiovascular disease risk factors was significantly lower than those at higher risk (mean ± SE: 352.91 ± 2.73 vs. 363.54 ± 4.75, respectively; $P = 0.048$). Second, the definition of the outcome is not the same in all studies. In the Rotterdam Study and the Nurses' Health Study, the outcome was CHD incidence, but in our study, we included within cardiovascular mortality not only fatal CHD but also fatal stroke and other deaths from atherosclerotic cardiovascular disease. Only 1 study evaluated

TABLE 2 Adjusted HRs of cardiovascular, cancer, and all-cause mortality according to quartile categories of vitamin K intake of 7216 Mediterranean adults at high cardiovascular disease risk[1]

	Energy-adjusted quartiles of vitamin K intake, HR (95% CI)				
	Q1 (n = 1804)	Q2 (n = 1804)	Q3 (n = 1804)	Q4 (n = 1804)	P-trend
Cardiovascular mortality					
Phylloquinone[2] (μg/d)	170.5	276.1	349.7	626.4	
Person-years	7672	7858	7955	7594	
Cases, n	25	21	21	14	
Crude model	1 (Reference)	0.81 (0.45, 1.44)	0.79 (0.44, 1.41)	0.55 (0.29, 1.06)	0.08
Model 1[3]	1 (Reference)	0.78 (0.43, 1.41)	0.82 (0.46, 1.49)	0.54 (0.28, 1.07)	0.09
Model 2[4]	1 (Reference)	0.76 (0.42, 1.37)	0.77 (0.43, 1.40)	0.50 (0.25, 1.00)	0.06
Model 3[5]	1 (Reference)	0.89 (0.49, 1.64)	1.04 (0.56, 1.92)	0.63 (0.31, 1.28)	0.20
Menaquinone[2] (μg/d)	18.4	29.9	39.0	57.5	
Person-years	7940	7721	7626	7792	
Cases, n	18	18	19	26	
Crude model	1 (Reference)	1.04 (0.54, 2.01)	1.11 (0.58, 2.12)	1.48 (0.81, 2.70)	0.17
Model 1	1 (Reference)	1.08 (0.56, 2.08)	1.02 (0.52, 1.98)	1.57 (0.86, 2.87)	0.13
Model 2	1 (Reference)	1.04 (0.54, 2.01)	0.93 (0.47, 1.82)	1.44 (0.79, 2.65)	0.23
Model 3	1 (Reference)	1.04 (0.52, 2.06)	0.89 (0.44, 1.83)	1.18 (0.60, 2.34)	0.63
Cancer mortality					
Phylloquinone (μg/d)	170.5	276.1	349.7	626.4	
Person-years	7672	7858	7955	7594	
Cases, n	38	36	39	17	
Crude model	1 (Reference)	0.91 (0.58, 1.44)	0.95 (0.61, 1.49)	0.48 (0.27, 0.84)	0.009
Model 1	1 (Reference)	0.86 (0.54, 1.37)	0.95 (0.60, 1.50)	0.49 (0.28, 0.87)	0.014
Model 2	1 (Reference)	0.87 (0.54, 1.38)	0.94 (0.59, 1.48)	0.49 (0.28, 0.87)	0.014
Model 3	1 (Reference)	0.90 (0.56, 1.45)	1.01 (0.63, 1.62)	0.54 (0.30, 0.96)	0.033
Menaquinone (μg/d)	18.4	29.9	39.0	57.5	
Person-years	7940	7721	7626	7792	
Cases, n	34	34	34	38	
Crude model	1 (Reference)	1.04 (0.65, 1.68)	1.07 (0.66, 1.72)	0.85 (0.52, 1.41)	0.55
Model 1	1 (Reference)	1.03 (0.53, 1.98)	0.99 (0.51, 1.93)	1.52 (0.83, 2.78)	0.08
Model 2	1 (Reference)	1.12 (0.69, 1.82)	1.14 (0.70, 1.86)	0.90 (0.54, 1.50)	0.66
Model 3	1 (Reference)	0.88 (0.55, 1.43)	1.00 (0.60, 1.67)	0.62 (0.32, 1.21)	0.45
All-cause mortality					
Phylloquinone (μg/d)	170.5	276.1	349.7	626.4	
Person-years	7672	7858	7955	7594	
Cases, n	93	84	92	54	
Crude model	1 (Reference)	0.87 (0.65, 1.17)	0.92 (0.69, 1.23)	0.59 (0.42, 0.82)	0.002
Model 1	1 (Reference)	0.85 (0.63, 1.14)	0.96 (0.71, 1.28)	0.61 (0.44, 0.86)	0.006
Model 2	1 (Reference)	0.83 (0.62, 1.13)	0.92 (0.69, 1.24)	0.59 (0.42, 0.83)	0.003
Model 3	1 (Reference)	0.90 (0.67, 1.22)	1.03 (0.76, 1.40)	0.64 (0.45, 0.90)	0.011
Menaquinone (μg/d)	18.4	29.9	39.0	57.5	
Person-years	7940	7721	7626	7792	
Cases, n	79	85	72	87	
Crude model	1 (Reference)	1.12 (0.83, 1.53)	0.97 (0.70, 1.33)	1.13 (0.84, 1.54)	0.58
Model 1	1 (Reference)	1.21 (0.89, 1.65)	1.00 (0.72, 1.39)	1.24 (0.92, 1.69)	0.28
Model 2	1 (Reference)	1.17 (0.86, 1.60)	0.96 (0.69, 1.33)	1.16 (0.85, 1.58)	0.55
Model 3	1 (Reference)	1.14 (0.83, 1.58)	0.89 (0.62, 1.26)	1.02 (0.72, 1.43)	0.81

[1] Cox regression models were used to assess the risk of mortality according to the quartile of energy-adjusted dietary vitamin K intake. MET, metabolic equivalent of task; Q, quartile.

[2] Phylloquinone and menaquinone intakes are expressed as means.

[3] Model 1 was adjusted for sex, age, BMI, recruiting center, intervention group, smoking (never, current, past), leisure time activity (MET/d), and education (primary education, secondary education, higher education).

[4] Model 2 was additionally adjusted for history of diabetes, hypertension, and hypercholesterolemia, use of oral antidiabetic medication, use of antihypertensive medication, and use of statin medication.

[5] Model 3 was additionally adjusted for dietary variables in energy-adjusted quintiles (vegetables, fruits, legumes, cereals, dairy products, meat, fish, olive oil, nuts) and alcohol and alcohol squared in grams per day. Dietary phylloquinone intake and dietary menaquinone intake were not adjusted for vegetables and dairy products, respectively, because both dietary variables are the major source of vitamin K types.

TABLE 3 Adjusted HRs of cardiovascular, cancer, and total mortality among Mediterranean adults at high cardiovascular disease risk (n = 3141) who increased their dietary phylloquinone or menaquinone intake during the follow-up compared with those (n = 2572) who reduced or did not change intake[1]

	HR (95% CI)	P
Cardiovascular mortality		
Phylloquinone		
Crude model	0.56 (0.35, 0.90)	0.017
Model 1[2]	0.50 (0.30, 0.82)	0.006
Model 2[3]	0.50 (0.30, 0.83)	0.007
Model 3[4]	0.52 (0.31, 0.86)	0.012
Menaquinone		
Crude model	0.69 (0.43, 1.12)	0.14
Model 1	0.73 (0.43, 1.25)	0.25
Model 2	0.74 (0.44, 1.26)	0.27
Model 3	0.76 (0.44, 1.29)	0.31
Cancer mortality		
Phylloquinone		
Crude model	0.81 (0.57, 1.15)	0.23
Model 1	0.62 (0.42, 0.91)	0.014
Model 2	0.65 (0.44, 0.95)	0.027
Model 3	0.64 (0.43, 0.95)	0.026
Menaquinone		
Crude model	0.48 (0.31, 0.72)	<0.001
Model 1	0.40 (0.26, 0.63)	<0.001
Model 2	0.41 (0.26, 0.64)	<0.001
Model 3	0.41 (0.26, 0.64)	<0.001
Total mortality		
Phylloquinone		
Crude model	0.63 (0.50, 0.80)	<0.001
Model 1	0.54 (0.42, 0.69)	<0.001
Model 2	0.55 (0.43, 0.71)	<0.001
Model 3	0.57 (0.44, 0.73)	<0.001
Menaquinone		
Crude model	0.56 (0.44, 0.73)	<0.001
Model 1	0.55 (0.42, 0.72)	<0.001
Model 2	0.55 (0.42, 0.72)	<0.001
Model 3	0.55 (0.42, 0.73)	<0.001

[1] Cox regression models were used to assess the risk of cardiovascular, cancer, and all-cause mortality.
[2] Model 1 was adjusted for sex, age, changes in BMI, recruiting center, intervention group, smoking (never, current, past), changes in leisure time activity (metabolic equivalent of task/d), and education (primary education, secondary education, higher education).
[3] Model 2 was additionally adjusted for history of diabetes, hypertension, and hypercholesterolemia, use of oral antidiabetic medication, use of antihypertensive medication, and use of statins.
[4] Model 3 was additionally adjusted for dietary variables in energy-adjusted quintiles (vegetables, fruits, legumes, cereals, dairy products, meat, fish, olive oil, nuts), alcohol and alcohol squared in grams per day, and changes in energy intake. Dietary phylloquinone intake and dietary menaquinone intake were not adjusted for vegetables and dairy products, respectively, because both dietary variables are the major sources of vitamin K types.

the association between vitamin K intake and cancer mortality. That study showed that cancer mortality was significantly lower among individuals with higher intakes of menaquinone but not phylloquinone. However, the reduction in cancer risk associated with menaquinone intake was only significant in men, and no results for cancer mortality separated by sex were reported previously (14). Our study showed inverse associations between increased dietary intake of both phylloquinone and menaquinone and total cancer mortality, and this association remained when it was assessed in men and women separately, which is additional evidence suggesting a possible protective role of vitamin K intake. These discrepancies with the previous study could be partly due to differences in study population and in food-database and dietary assessment instruments used, thus explaining the substantially higher dietary intake of vitamin K observed in the PREDIMED study compared with the cohort studied by Nimptsch et al. (14). It is important to note that results of both cross-sectional and longitudinal analysis in our study are in the same direction, although no statistical differences were observed in the first case. This could be explained by the fact that multiple assessments of the FFQ may reduce misclassification from a single FFQ, but we also have to consider that longitudinal analysis preserves the temporal sequence and it is better protected against several biases, especially if a dietary intervention has been conducted.

Because this was a nutritional epidemiologic study that did not use biomarkers, 1 of the main limitations of our study was the relative validity of estimating dietary intake of vitamin K by data from FFQs. We cannot discount that vitamin K intake has been overestimated because of the use of FFQs and the USDA food-database composition. However, analyzing the data of a previous validation study conducted in this population (17), the Pearson correlation coefficient between the 3-d dietary records and the FFQ was reasonable for phylloquinone (r = 0.78) and menaquinone (r = 0.66). These correlations compared favorably with results of the validation studies described previously (33,34). Moreover, although there is no 1:1 correlation between vitamin K intake and vitamin K absorption, a significant association between dietary phylloquinone intake and plasma phylloquinone was reported previously (35). Dietary intake of menaquinone has also been reflected in the menaquinone serum concentrations of a healthy Japanese cohort of regular consumers of nattō, a fermented soybean product, the richest menaquinone food product (36). The individuals in our study reported a higher dietary intake of phylloquinone than those enrolled in previous epidemiologic studies, probably because the PREDIMED study participants are from a Mediterranean country in which the consumption of fruit and vegetables is quite high. In other populations with a lower consumption of phylloquinone or poorer nutrition, it is unknown whether or not an increase in dietary vitamin K would be much more beneficial in terms of mortality. Another limitation of our analysis is that it has been conducted in individuals consuming a healthy Mediterranean diet, which could partly account for a reduction in mortality risk. The individuals classified in the highest quartiles of dietary vitamin K generally had a healthier diet, and they were also more physically active and less likely to be smokers. To minimize the potential residual confounding effects of a healthy lifestyle on mortality, we adjusted the Cox regression models for several dietary and lifestyle confounding variables. Even so, the possibility of residual or incompletely controlled confounding cannot be excluded. Thus, because the design of our study does not reveal whether or not phylloquinone is a marker of leafy green vegetable intake or an independent causality factor, the results of the present study should be interpreted cautiously. Finally, an important strength of our study is the prospective and longitudinal analysis with repeated measurements of dietary vitamin K intake because this reduces misclassification and enables longitudinal changes in exposure to be assessed.

Overall, our results suggest that the dietary intake of both active forms of vitamin K has a potential protective role in cardiovascular mortality, cancer mortality, and all-cause mortality in a cohort of Mediterranean individuals at high cardiovascular disease risk with a relatively high consumption of this vitamin.

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