Association Between Vitamin K and the Metabolic Syndrome: A 10-Year Follow-Up Study in Adults

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Context: The Metabolic Syndrome (MetS) is a cluster of metabolic abnormalities and is associated with increased risk of diabetes and cardiovascular diseases. Phylloquinone, menaquinones, and vitamin K status are associated with several components of MetS, but the association with MetS has hardly been studied to date.

Objective: This study aimed to examine whether the intake and/or status of vitamin K is associated with MetS and its components.

Design: This study comprised two cohorts, one of 402 women and one of 400 men (age 40–80 y). At followup 625 participants were still alive and willing to participate. Data were analyzed both cross sectionally and longitudinally with Poisson and linear regression adjusted for multiple confounders. Baseline phylloquinone/menaquinone intakes were measured with a validated food frequency questionnaire and vitamin K status with serum desphospho-uncarborxylated matrix-Gla protein level.

Results: At baseline 270 (34.5%) participants had MetS and 171 (35.7%) at followup. Cross sectionally, high menaquinones intakes were associated ($P_{trend} = .08$) with a lower prevalence of MetS with a prevalence ratio (PR) of 0.74 (95% confidence interval [CI], 0.54–1.03) for the highest vs the lowest tertile. At followup, the highest tertiles of menaquinones intake (PR = 0.62; 95% CI, 0.40–0.95) and vitamin K status (PR = 0.57; 95% CI, 0.38–0.87) were associated ($P_{trend} = .01$) with a lower occurrence of MetS. These associations were mainly driven by relations with lower triacylglycerol concentrations for menaquinones and lower waist circumference for vitamin K status. Phylloquinone intake was not associated with MetS prevalence.

Conclusions: This study shows that a high intake of menaquinones and high vitamin K status are associated with a lower occurrence of MetS. **(*J Clin Endocrinol Metab* 100: 2472–2479, 2015)**

The prevalence of the Metabolic Syndrome (MetS) is still increasing in the United States (1) and almost one fourth of the European population is diagnosed with MetS (2). MetS is a cluster of metabolic abnormalities and is diagnosed when three or more of the following risk factors are present: abdominal obesity, moderate hypertension, low high-density lipoprotein (HDL) cholesterol, high glucose level, and high triacylglycerol concentrations (3). MetS is associated with increased risk of developing diabetes (4, 5), cardiovascular diseases, and higher all-cause mortality (1, 6).

Vitamin K is a fat-soluble vitamin and present in the diet in two forms: phylloquinone and menaquinones. Phylloquinone is found in green leafy vegetables and menaquinones in animal products such as meat, eggs, and cheese (7). A healthy lifestyle and diet may prevent MetS

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Abbreviations: BMI, body mass index; CI, confidence interval; dp-ucMGP, desphospho-uncarboxylated matrix Gla protein; FFQ, food frequency questionnaire; Gla, gammacarboxyglutamate; HDL, high-density lipoprotein; MetS, the metabolic syndrome; PR, prevalence ratio; PROFIEL, Preservation of Function in Elderly.

(6) and vitamin K intake has been associated with several components of MetS. High intakes of both phylloquinone and menaquinones have been associated with improved insulin sensitivity (7, 9, 10) and with a more favorable lipoprotein profile (8, 11). In addition, recent studies have shown associations of high vitamin K intakes with lower body mass index (BMI) and a more favorable body composition (11, 12).

The best-known function of vitamin K is as a cofactor for gammaglutamate carboxylase in a posttranslational conversion of protein-bound glutamate residues into gammacarboxyglutamate (Gla). Functional vitamin K insufficiency thus results in the appearance of uncarboxylated species of these Gla proteins, which are generally inactive. Low vitamin K intake results in poor vitamin K status, as detected from high levels of circulating uncarboxylated Gla proteins (13).

Pan and Jackson (14) investigated the relation between phylloquinone intake and MetS. The findings of this study suggest that higher intakes of phylloquinone may favorably influence the prevalence of MetS. However, the relation of vitamin K status and menaquinones intake with the occurrence of MetS has not been investigated to date. Moreover, the former study had a cross-sectional design and the prospective association of vitamin K (intake and status) with MetS has not been investigated yet. The aim of this study was therefore to examine whether the intake of phylloquinone and menaquinones and vitamin K status are associated with MetS and its individual components both cross sectionally and longitudinally.

Subjects and Methods

Subjects

This study examined data of two cohort studies, one comprised 402 women age 49–70 years old, methods of recruitment are described elsewhere (15). In short, women were recruited from the PROSPECT study (16). They were selected when they had experienced a natural menopause, had an intact uterus and at least one intact ovary, and they should not have used sex steroids after the reported date of last menstruation. The second cohort consisted of 400 independently living men age 40–80 years old (17). Men were selected if they lived independently and were physically and mentally able to visit the study center. In total 802 participants were included at baseline. Participants taking oral anticoagulants and participants with missing values in vitamin K intake or status were excluded for analyses. This resulted in a total of 681 (85%) participants for the analyses with vitamin K intake and 758 (95%) participants for the analyses with vitamin K status.

Data used for the longitudinal analyses are from the Preservation of Function in Elderly (PROFIEL) study. This study contacted the participants of the two above-mentioned cohorts. Of the 802 original participants, 700 were still alive and not living abroad and in total 625 people (51% men, 49% women) agreed to participate, methods of recruitment are described elsewhere (18, 19). Participants with missing values in vitamin K intake, status, or taking oral anticoagulants at baseline were excluded; therefore, 418 (67%) participants were available for follow-up analyses with vitamin K intake and 459 (73%) participants for analyses with vitamin K status. All participants gave written informed consent before enrolment onto the study. The study protocol was approved by the Institutional Review Board of the University Medical Center Utrecht.

Determinants

Vitamin K status was measured at baseline by assessing desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) in plasma. The measurement of dp-ucMGP was performed with a dual antibody ('sandwich') ELISA as described elsewhere (20). Several studies have shown that a high level of dp-ucMGP indicates a low vitamin K status (20, 21).

Dietary intake was measured at baseline with a validated food frequency questionnaire (FFQ). The FFQ contained questions regarding the amount and mean consumption of 77 main food categories during the past year and estimates the mean daily consumption of 178 food products (22, 23). The Dutch food composition table was used to calculate nutrient and energy intake from the FFQ (24). Phylloquinone and menaquinone concentrations are derived from a study by Schurgers and Vermeer (25). Published data from others were used to amplify the vitamin K database (26–29).

The FFQ was validated against 12 24-hour recalls in 121 men and women (22, 23). A relatively low validity of phylloquinone intake ($r = 0.30$) was observed. In addition, a reasonable-to-good relative validity was observed for menaquinone intakes ($r = 0.58$). All dietary variables were energy adjusted for analyses using the nutrient residual method (30).

MetS and its components

Both at baseline and followup, the components of MetS were measured. MetS was present when three or more of the criteria set by the Joint Interim Statement were met (3). These criteria are abdominal obesity (waist circumference: men $\geq$ 102 cm, women $\geq$ 88 cm), moderate hypertension (systolic $\geq$ 130 mm Hg and/or diastolic $\geq$ 85 mm Hg and/or antihypertensive medication), low HDL cholesterol (men $<$ 1.0mM, women $<$ 1.3mM and/or cholesterol-lowering medication), increased glucose level (fasting $\geq$ 5.6mM and/or diabetes medication) and increased triacylglycerol level ($\geq$1.7mM).

Height, weight (Seca floor scale), as well as waist and hip circumference were measured with the participant in standing position wearing indoor clothing and no shoes. Furthermore, blood pressure was measured in the left arm twice with a 5-minute interval. Venous blood was collected (30 mL) after an overnight fast for at least 8 hours; all blood samples were centrifuged immediately to prepare plasma, which was stored at -70°C until required for analysis. HDL cholesterol, triacylglycerol levels, and glucose levels were determined using routine methods.

Other measurements

Information regarding participants' health was obtained by medical history. This included a self-reported physician diagnosis of stroke, coronary heart disease, or diabetes mellitus. In addition, participants were asked about current use of medication and information was obtained on age, smoking history (cur-

rent, former, never), alcohol use, education (low, middle, high, university), BMI (kg/m^2), and physical activity [measured with the Voorrips questionnaire (31)].

Statistical analyses

Baseline characteristics are presented by tertiles of phylloquinone, menaquinones and vitamin K status. Confounding was examined by adding the possible confounding factor to the crude model. When the regression coefficient of vitamin K changed by 10% or more, the variable was included as a confounder. Sex was assessed as effect modifier by including an interaction term to the final model. Whenever this interaction term was significant ($P < .05$), analyses were stratified for sex, this was only the case for waist circumference. In addition, when an outcome variable was skewed, a natural logarithmic transformation (ln) was applied. This was applied for triacylglycerol and glucose (cross sectional) and for triacylglycerol, HDL, and glucose (longitudinal). Results for these analyses are presented as geometric means (95% confidence interval [CI]). To account for missing values in the confounding variables, the mean of the variable was used for every missing value, given that only two variables had a few missing values (6 [0.9%] for physical activity and 10 [1.5%] for alcohol).

The cross-sectional relation between vitamin K intake (total, phylloquinone, menaquinones) and vitamin K status and the prevalence of MetS was investigated with a Poisson regression. The P_{trend} was calculated over the tertiles by entering the median in each tertile as a linear covariate in the model. Two models were used to adjust for several confounding factors. The first model adjusted for age, sex, education, BMI, physical activity, and smoking. The fully adjusted model additionally adjusted for alcohol and the dietary factors (energy adjusted) saturated fat, protein, and fiber. Given that waist circumference is included in the definition of the MetS a third model without adjustment for BMI was added.

The cross-sectional relation between vitamin K intake (total, phylloquinone, menaquinones) and vitamin K status and the individual components of MetS was analyzed with linear regression analysis. For these analyses the first two models, equal to the cross-sectional models, were used to adjust for confounders, the third model was used only in the analyses with waist circumference.

All eligible participants were included in the follow-up analyses. To check and correct for selective loss to followup, baseline characteristics of participants and dropouts were compared. Inverse-probability weighting in a sensitivity analysis was used to correct for such selection in the linear regression analyses of the components. If the results did not differ, we assumed this would also be the case for the analyses with MetS.

At followup the same analyses and models were used as cross sectionally, but in all models the variable "time to followup" (years) was added to correct for differences in time to followup (range, 8–14 y). In addition, the longitudinal analyses were adjusted for MetS at baseline. The longitudinal analyses with the individual components were also adjusted for the baseline values of the components. Furthermore, we conducted a sensitivity analysis were we excluded participants with MetS at baseline. The statistical analyses were performed with SPSS statistics version 20.0 (SPSS Inc., Chicago, IL). Results were considered statistically significant at two-sided $P \leq .05$.

Results

At baseline, participants had a mean age of 63.3 ± 9.0 years and a mean phylloquinone and menaquinones intake of 210.3 ± 127.0 and 31.1 ± 12.5 μg/day, respectively. Their mean dp-ucMGP concentration was 299.6 ± 344.8 pM. MetS was present in 270 (34.5%) of the participants. Participants in the highest phylloquinone tertile were more often women, were older, had higher glucose levels, and higher fiber intakes compared with participants in the lowest tertile (Table 1). Participants in the highest menaquinones tertile were more often men, were younger, and had higher protein intakes compared with those in the lowest tertile. Participants in the highest tertile of vitamin K status (Supplemental Table 1) were younger, had a lower BMI, waist circumference, glucose level, systolic and diastolic blood pressure, and higher protein intakes compared with those in the lowest tertile.

A substantial loss to followup of 251 (31.3%) of the participants occurred, due to death (98; 39.0%) or other reasons, (161; 64.1%). However, baseline characteristics in dropouts and participants were comparable and the inverse-probability weighting in a sensitivity analysis for the linear regression analyses of the components yielded only minor differences in the results (data not shown). Furthermore, the longitudinal sensitivity analysis, excluding participants with MetS at baseline, showed comparable results.

The MetS

In cross-sectional analyses, phylloquinone intake was not associated with MetS with a fully adjusted prevalence ratio (PR) of 1.11 (95% CI, 0.80–1.54) for the highest vs the lowest tertile ($P_{trend} = .61$) (Table 2). Total vitamin K intake gave similar associations (data not shown). A higher menaquinones intake was associated with a lower prevalence of MetS. Participants in the highest tertile of menaquinones had a crude PR of 0.74 (95% CI, 0.54–1.00) compared with those in the lowest tertile ($P_{trend} = .05$). After full adjustment the PR became borderline significant (PR = 0.74; 95% CI, 0.54–1.03; $P_{trend} = .08$) and significant again when BMI was excluded as confounder (PR = 0.72; 95% CI, 0.52–0.99; $P_{trend} = .05$). In addition, participants in the highest tertile of vitamin K status had a crude PR of 0.67 (95% CI, 0.50–0.90) compared with participants in the lowest tertile ($P_{trend} < .01$). After full adjustment this reduced to a nonsignificant association (PR = 0.93; 95% CI, 0.68–1.27; $P_{trend} = .46$). However, when BMI was excluded from the model a PR of 0.76 (95% CI, 0.55–1.03) for the highest tertile compared with the lowest was observed ($P_{trend} = .06$).

In the longitudinal analyses, high menaquinone intakes were associated with a lower occurrence of MetS, with a

Table 1. Baseline Characteristics Divided by Tertiles of Phylloquinone and Menaquinones Intake

	Phylloquinone Intake			Menaquinones Intake		
Characteristic	**Tertile 1**	**Tertile 2**	**Tertile 3**	**Tertile 1**	**Tertile 2**	**Tertile 3**
Amount, μg/d	23–153	154–230	230–1681	6–25	25–34	35–86
N	228	228	227	224	227	232
Phylloquinone,[a] μg/d	109.5 ± 28.7	191.4 ± 21.4	330.4 ± 151.2	220.7 ± 169.9	215.9 ± 101.8	194.7 ± 99.1
Menaquinones,[a] μg/d	32.3 ± 13.3	31.0 ± 12.2	30.3 ± 12.0	18.8 ± 3.9	29.4 ± 2.8	45.0 ± 9.9
Dp-ucMGP, pM	287.1 ± 340.1	272.4 ± 200.3	293.8 ± 389.6	281.8 ± 199.6	306.0 ± 319.0	266.2 ± 402.0
Sex, women	86 (37.7%)	100 (43.9%)	109 (48.0%)	121 (54.0%)	96 (42.3%)	78 (33.6%)
Age, y	60.7 ± 10.4	63.6 ± 8.4	63.8 ± 8.8	63.0 ± 9.0	63.7 ± 8.5	61.4 ± 10.2
BMI, kg/m^2	26.1 ± 4.0	26.1 ± 3.5	26.3 ± 3.9	26.2 ± 3.7	26.3 ± 3.9	26.0 ± 3.7
Waist circumference, cm	92.4 ± 12.6	91.3 ± 12.9	91.7 ± 12.7	90.4 ± 12.8	92.3 ± 13.0	92.5 ± 12.2
HDL-cholesterol, mM	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4
Serum triacylglycerol, mM	1.6 ± 1.2	1.5 ± 0.8	1.5 ± 1.3	1.7 ± 1.4	1.5 ± 0.9	1.4 ± 0.9
Systolic blood pressure, mm Hg	143.3 ± 20.2	146.4 ± 21.1	146.2 ± 22.8	145.0 ± 21.3	146.3 ± 21.5	144.6 ± 21.4
Diastolic blood pressure, mm Hg	78.8 ± 12.5	79.5 ± 11.4	78.5 ± 11.9	77.5 ± 13.1	79.1 ± 10.9	80.2 ± 11.6
Serum Glucose, mM	5.6 ± 1.1	5.7 ± 1.3	5.8 ± 1.8	5.6 ± 1.3	5.7 ± 1.2	5.8 ± 1.7
Physical activity score[b]	16.5 ± 8.2	16.4 ± 7.2	16.1 ± 7.5	15.4 ± 7.2	17.0 ± 8.0	16.6 ± 7.6
Current smokers	50 (21.9%)	34 (14.9%)	46 (20.3%)	44 (19.6%)	39 (17.2%)	47 (20.3%)
High Education	84 (37.0%)	71 (31.1%)	55 (24.2%)	63 (28.1%)	69 (30.5%)	78 (33.6%)
MetS	77 (33.9%)	85 (37.3%)	83 (36.7%)	96 (44.9%)	76 (33.6%)	73 (31.6%)
Total energy, kcal/d	2052 ± 588	2030 ± 557	1950 ± 514	1950 ± 534	2009 ± 526	2073 ± 595
Saturated Fat,[a] g/d	30.9 ± 11.0	30.9 ± 10.4	29.3 ± 9.2	27.3 ± 8.4	29.8 ± 9.1	33.9 ± 11.8
Protein,[a] g/d	75.4 ± 21.3	77.1 ± 19.1	75.6 ± 16.9	70.2 ± 17.2	75.1 ± 16.6	82.5 ± 21.3
Fiber,[a] g/d	22.5 ± 6.1	24.6 ± 5.7	25.5 ± 6.1	24.5 ± 6.3	23.8 ± 5.5	24.3 ± 6.4
Alcohol, units/wk	11.9 ± 13.8	7.6 ± 9.2	8.8 ± 10.8	8.5 ± 11.1	10.0 ± 11.6	9.7 ± 11.9

Data are presented as mean ± SD or N (%).

[a] Adjusted for energy intake.

[b] Examined with Voorrips questionnaire. Sum of scores, no maximum score.

fully adjusted PR of 0.62 (95% CI, 0.40–0.95; P_{trend} = .01) for the highest tertile compared with the lowest (Table 3). This remained unchanged when BMI was excluded as a confounder (PR = 0.62; 95% CI, 0.40–0.95; P_{trend} = 0.01). A higher vitamin K status was also associated with a reduced occurrence of MetS with a fully adjusted PR of 0.57 (95% CI, 0.38–0.87; P_{trend} = .01). This changed slightly when BMI was excluded as a confounder (PR = 0.58; 95% CI, 0.38–0.87; P_{trend} = .01). No significant association was found between phylloquinone (fully adjusted PR = 0.87; 95% CI, 0.57–1.34; P_{trend} = .68 for the highest vs the lowest tertile) or total vitamin K intake (fully adjusted PR = 1.06; 95% CI, 0.78–1.45; P_{trend} = .72 for the highest vs the lowest tertile) and MetS.

Components

High menaquinone intakes were associated with lower triacylglycerol concentrations both cross sectionally and longitudinally (cross sectional: fully adjusted B = 0.91; 95% CI, 0.83–0.99, P_{trend} = .05; longitudinal: fully adjusted: B = 0.90; 95% CI, 0.81–1.00; P_{trend} = .06).

Cross sectionally, only a borderline significant association was found between menaquinones and waist circumference in men (B = −1.96; 95% CI, −4.23–0.31; P_{trend} = .10) for the highest tertile compared with the lowest. Furthermore, a high vitamin K status was associated with a lower waist circumference in women, with a fully adjusted B of −6.69 (95% CI, −9.35–−4.04) for the highest tertile compared with the lowest ($P_{trend} < .001$). In men, a borderline significant association between high vitamin K status and lower waist circumference was found (B = −2.04; 95% CI, −4.25–0.18) when the highest tertile was compared with the lowest (P_{trend} = .10). Longitudinally, a borderline significant association was found between vitamin K status and waist circumference in men (B = −1.39; 95% CI, −3.05–0.27; P_{trend} = .08) (Supplemental Tables 2–4).

Discussion

This study showed that high intakes of menaquinones and high vitamin K status were associated with a reduced occurrence of MetS, both cross sectionally and longitudinally. These associations were mainly driven by triacylglycerol and waist circumference. Phylloquinone and total vitamin K intake were not significantly associated with MetS.

Table 2. Results for the Association Between Energy-Adjusted Intake of Phylloquinone/Menaquinones and Vitamin K Status and the MetS (Cross-Sectional)

	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Phylloquinone				
No. cases	77	85	83	
Mean intake, μg/d	109.5	191.4	330.4	
Crude	1.0	1.10 (0.81–1.50)	1.08 (0.79–1.48)	.64
Model 1	1.0	1.17 (0.85–1.60)	1.06 (0.78–1.46)	.76
Model 2	1.0	1.23 (0.88–1.68)	1.11 (0.80–1.54)	.61
Model 3	1.0	1.12 (0.82–1.54)	1.08 (0.78–1.50)	.66
Menaquinones				
No. cases	96	76	73	
Mean intake, μg/day	18.8	29.4	45.0	
Crude	1.0	0.79 (0.58–1.06)	0.74 (0.54–1.00)	.05
Model 1	1.0	0.73 (0.54–0.99)	0.74 (0.55–1.01)	.06
Model 2	1.0	0.72 (0.52–0.98)	0.74 (0.54–1.03)	.08
Model 3	1.0	0.75 (0.54–1.02)	0.72 (0.52–0.99)	.05
Vitamin K status				
No. cases	104	86	75	
Dp-ucMGP, pmol/L	525.0	229.3	106.4	
Crude	1.0	0.76 (0.57–1.02)	0.67 (0.50–0.90)	<.01
Model 1	1.0	0.83 (0.62–1.11)	0.92 (0.67–1.25)	.41
Model 2	1.0	0.84 (0.63–1.12)	0.93 (0.68–1.27)	.46
Model 3	1.0	0.79 (0.59–1.06)	0.76 (0.55–1.03)	.06

Data are PR (95% CI) from Poisson regression.

Model 1: Adjusted for age, sex, education, BMI, physical activity, and smoking.

Model 2: Model 1 + alcohol, saturated fat, total protein, and fiber.

Model 3: Model 2 without BMI.

A previous cross-sectional study examined the relationship between phylloquinone intake and MetS and found that high phylloquinone intakes were related to a lower prevalence of MetS (odds ratio = 0.72; 95% CI, 0.25–2.09) (14). Conversely, we could not detect a cross-sectional association between phylloquinone intake and MetS. However, longitudinally we do find similar associations between high phylloquinone intake and the occurrence of MetS, albeit not significant. The differences between our results and the previous study by Pan and Jackson (14) could be due to their larger study population (5800 participants) or their more detailed dietary assessment method (24-hour recall obtained through an in-person interview). Furthermore, the participants in our study were from a different age category (40–80 y) than those in the study of Pan and Jackson (age 20–45 y). The severity of MetS in both age groups could be different, given that the older age group we used might suffer from more comorbidities and might use drugs that could influence the results. However, we adjusted the analyses for age and excluded participants using anticoagulants. Moreover, the results of Pan and Jackson show a much lower prevalence of MetS (23.0%) than our study (34.5%) and there could be a difference in lifestyles between the two age groups.

In contrast with phylloquinone, high menaquinone intakes were associated with a reduced occurrence of MetS both cross sectionally and longitudinally. The different associations for phylloquinone and menaquinones might be explained by their transport and distribution over the body. They are mainly transported in plasma by lipoproteins, from which phylloquinone is effectively cleared by the liver for activation of clotting factors, whereas menaquinones are redistributed via low-density lipoproteins (32). We indeed observed that the associations for menaquinones were mainly driven by triacylglycerol. In addition, the long half-life time of long chain menaquinones makes them available longer for extra hepatic tissues (33). Finally, the absorption of phylloquinone from vegetables is 5–10% only, whereas menaquinones are absorbed almost completely (25).

A comparable association as found for menaquinones was observed for vitamin K status, confirming a potential relation between vitamin K and MetS. To measure vitamin K status, plasma dp-ucMGP was used, which seems to be a reliable marker for overall vitamin K status (20, 34). However, in our study the results for dp-ucMGP were particularly in line with those for menaquinones, which could be explained by the absorption of phylloquinone and menaquinones (25), making menaquinones more available for carboxylation of MGP.

Pan and Jackson (14) also studied the components of MetS and found that high phylloquinone intakes are associated with a lower risk of having low HDL cholesterol,

Table 3. Results for the Association Between Energy-Adjusted Intake of Phylloquinone/Menaquinones and Vitamin K Status and the MetS (Longitudinal)

	Tertile 1	Tertile 2	Tertile 3	P_{trend}
Phylloquinone				
No. cases	52	57	42	
Mean intake, μg/d	112.1	191.7	314.7	
Crude	1.0	1.20 (0.82–1.75)	0.93 (0.62–1.39)	.68
Model 1	1.0	1.11 (0.75–1.63)	0.87 (0.57–1.33)	.49
Model 2	1.0	1.11 (0.75–1.65)	0.87 (0.57–1.34)	.68
Model 3	1.0	1.12 (0.75–1.65)	0.88 (0.57–1.35)	.69
Menaquinones				
No. cases	52	60	39	
Mean intake, μg/d	19.1	29.5	44.6	
Crude	1.0	1.03 (0.71–1.50)	0.65 (0.43–0.99)	.04
Model 1	1.0	1.05 (0.72–1.52)	0.66 (0.44–1.01)	.05
Model 2	1.0	0.99 (0.68–1.44)	0.62 (0.40–0.95)	.01
Model 3	1.0	0.98 (0.67–1.43)	0.62 (0.40–0.95)	.01
Vitamin K status				
No. cases	58	58	50	
Dp-ucMGP, pmol/L	484.1	228.1	108.2	
Crude	1.0	0.78 (0.54–1.12)	0.61 (0.42–0.89)	.01
Model 1	1.0	0.74 (0.51–1.07)	0.60 (0.41–0.89)	.01
Model 2	1.0	0.65 (0.44–0.98)	0.57 (0.38–0.87)	.01
Model 3	1.0	0.66 (0.44–0.98)	0.58 (0.38–0.87)	.01

Data are PR (95% CI) from Poisson regression.

Model 1: Adjusted for age, sex, education, BMI, physical activity, smoking, MetS baseline.

Model 2: Model 1 + alcohol, saturated fat, total protein, fiber, and time to followup.

Model 3: Model 2 without BMI.

hypertriglyceridemia, and hyperglycemia. In our study, the relation of menaquinones with MetS was mainly driven by an association with lower triacylglycerol concentrations. A similar effect was found in rats by Sogabe et al (12), who demonstrated that the phylloquinone and menaquinones groups had a significantly lower level of serum triacylglycerol than the control group. Beulens et al (7) also found higher menaquinone intakes associated with an improved lipid profile.

The relation of vitamin K status with MetS was explained by associations with lower waist circumference. A study by Knapen et al (35) found an association between poor vitamin K status and high body weight, BMI, and fat mass, which was confirmed in studies by Shea et al (36) and Sogabe et al (12). Higher body fat could suggest a higher waist circumference; therefore, these findings partly complement the findings of our study with waist circumference. In addition, it has been hypothesized that adipose tissue sequesters fat-soluble nutrients, which lowers their bioavailability. The possibility exists that retention of vitamin K in adipose tissue decreases the vitamin K status (36). Furthermore, the fact that the associations of menaquinones and vitamin K status with MetS are mainly driven by triacylglycerol and waist circumference is a suggestion that inflammation may be a major contributor for the deregulatory state found in individuals with MetS.

Strengths of this study are the inclusion of both cross-sectional and longitudinal analyses and the elaborate investigation of phylloquinone and menaquinone intakes in combination with dp-ucMGP. Dp-ucMGP was used instead of plasma phylloquinone and menaquinones because plasma phylloquinone only reflects recent intakes and plasma menaquinones are often below detection limit in the general population (33, 37).

The main limitation of this study is the use of an FFQ to measure the vitamin K intake. The relative validity for phylloquinone intake measured with this FFQ was low, but for menaquinones intake it was reasonable, therefore, results for phylloquinone intake should be interpreted with caution. Furthermore, the intake of vitamin K, measured with the FFQ, was estimated with food composition tables. Although the most important sources of vitamin K were included in the database we used, variation within food products such as cheese is not always taken into account. However, there are no other options to estimate intake in observational studies. We, therefore, complemented the intake measurements with measurements of dp-ucMGP to achieve the most reliable results. However, measurement of dp-ucMGP also has limitations because levels are higher in patient populations compared with healthy populations and levels seem to be higher in older people compared with younger people (20, 38), which might have influenced our results.

Furthermore, we did not account for menaquinones produced by microbiota in the intestine. However, because the absorption of intestinally produced menaquinones is low [eg, 0.2% for MK-9 (39, 40)] it will probably not influence our results to a large extent. Furthermore, changes induced in the microbiota by MetS, could affect the synthesis and availability of vitamin K. We accounted for this in the longitudinal analyses, because vitamin K intake and status were measured before the onset of MetS and excluding baseline MetS gave comparable results. The cross-sectional analyses were in line with the longitudinal analyses; therefore it probably did not influence our results.

Moreover, phylloquinone is mostly found in green leafy vegetables, the consumption of which is associated with a healthier lifestyle. Conversely, menaquinones are mostly found in meat, eggs, and cheese, which are related to an unhealthier lifestyle. Although adjustment was performed for these confounding factors, residual confounding may be present. Another limitation is that phylloquinone, menaquinones, and vitamin K status were measured only at baseline. Both vitamin K intake and vitamin K status could have changed over time. A final limitation is the substantial loss to followup of 251 (31.3%) participants. Because baseline characteristics of participants were comparable with those of dropouts (data not shown), we assumed that no selective loss to followup exists. Moreover, we used inverse-probability weighting in a sensitivity analysis to adjust for such selection bias for the linear regression analyses of the components. This did not substantially affect our results, indicating that also the analyses with MetS would not differ after correction for such selection bias.

In conclusion, high intakes of menaquinones and high vitamin K status were associated with a reduced occurrence of MetS both in cross-sectional and longitudinal analyses. The associations of menaquinones and vitamin K status are mainly driven by associations with triacylglycerol and waist circumference.

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