Nutrition, Metabolism & Cardiovascular Diseases (2009) **19**, 504—510

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

A high menaquinone intake reduces the incidence of coronary heart disease

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Received 27 June 2008; received in revised form 14 October 2008; accepted 21 October 2008

KEYWORDS
Coronary heart disease;
Diet;
Food frequency questionnaire;
Vitamin K

Abstract *Background and Aim:* Vitamin K dependent proteins have been demonstrated to inhibit vascular calcification. Data on the effect of vitamin K intake on coronary heart disease (CHD) risk, however, are scarce.
To examine the relationship between dietary vitamins K_1 and K_2 intake, and its subtypes, and the incidence of CHD.
Methods and Results: We used data from the Prospect—EPIC cohort consisting of 16,057 women, enrolled between 1993 and 1997 and aged 49—70 years, who were free of cardiovascular diseases at baseline. Intake of vitamin K and other nutrients was estimated with a food frequency questionnaire. Multivariate Cox proportional hazards models were used to analyse the data.
After a mean ± SD follow-up of 8.1 ± 1.6 years, we identified 480 incident cases of CHD. Mean vitamin K_1 intake was 211.7 ± 100.3 μg/d and vitamin K_2 intake was 29.1 ± 12.8 μg/d. After adjustment for traditional risk factors and dietary factors, we observed an inverse association between vitamin K_2 and risk of CHD with a Hazard Ratio (HR) of 0.91 [95% CI 0.85—1.00] per 10 μg/d vitamin K_2 intake. This association was mainly due to vitamin K_2 subtypes MK-7, MK-8 and MK-9. Vitamin K_1 intake was not significantly related to CHD.
Conclusions: A high intake of menoquinones, especially MK-7, MK-8 and MK-9, could protect against CHD. However, more research is necessary to define optimal intake levels of vitamin K intake for the prevention of CHD.

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doi:10.1016/j.numecd.2008.10.004

Introduction

Vitamin K is a fat-soluble vitamin that occurs in two biologically active forms; phylloquinone (vitamin K_1) and menaquinone (MK-4 through MK-10, vitamin K_2). Vitamin K is the co-substrate for the enzyme gamma-glutamyl carboxylase. This enzyme catalyzes the carboxylation of specific glutamic residues into gamma-carboxyglutamyl acid residues (Gla) in a limited number of proteins [1]. Gla-proteins have an increased affinity for calcium [2]. One of the Gla-proteins, Matrix-Gla Protein (MGP), is a powerful inhibitor of vascular calcification [3]. Vascular vitamin K deficiency might increase the amount of undercarboxylated, non-functional forms of MGP and thereby lead to increased calcium deposition, and, eventually, cardiovascular disease (CVD) [1,4]. Indeed, MGP-knock out mice were shown to develop severe vascular calcification [5]. MGP has also been found in close association with areas of calcification [4]. Moreover, the drug warfarin, which inhibits Gla residue formation, was shown to increase vascular calcification in in vitro and in vivo data from humans and rats [3,6].

In healthy subjects it has been shown that a substantial fraction of MGP occurs in undercarboxylated form with no biological activity [7], suggesting that most apparently healthy adults may be subclinically vitamin K deficient. Thus, although the intake of vitamin K in Western countries is sufficient for haemostasis, it might be suboptimal to maintain maximal gamma-carboxylation of the extrahepatic vitamin K dependent proteins and thus to prevent vascular calcification [5]. These data are supported in a population-based survey, in which an inverse association between dietary intake of vitamin K and the presence of aortic calcification in elderly subjects was found [8]. Vitamins K_1 and K_2 might have different effects in prevention of vascular calcification; a high dose (30 mg/day) of vitamin K_2 (subtype MK-4), but not vitamin K_1, prevented medial calcification in rats [9]. Thus far, only a few prospective studies have been performed on dietary vitamin K intake and risk of CVD. The Rotterdam study reported a strong inverse association between vitamin K_2 intake and coronary heart disease (CHD) [10]. For vitamin K_1 the association was less obvious, which was comparable for two studies in US populations [11,12]. Data on vitamin K_2 were not available in these studies. The aim of the present study was to examine the relationship between dietary vitamins K_1 and K_2 intake and the incidence of CHD. In addition, we have analysed which subtypes of dietary vitamin K_2 intake are related to the incidence of CHD. For this purpose we used data of a cohort of 16,057 women who were followed for 8.1 years.

Methods

Population

PROSPECT is one of the two Dutch contributions to the European Prospective Investigation Into Cancer and Nutrition (EPIC) [13]. Between 1993 and 1997, 17,357 women aged 49–70 years, living in Utrecht and surroundings were enrolled in the PROSPECT–EPIC study. Participants were recruited through the regional breast cancer screening program. Women were excluded if they had a dietary intake below 500 kcal or higher than 6000 kcal per day ($n = 92$), did not fill in a general questionnaire ($n = 117$), did not consent to linkage with vital status registries or could not be traced in these registries ($n = 362$), reported a history of CHD (ICD-9; 410–414, 427.5) or CVA (ICD-9; 430–438) prior to the baseline measurements ($n = 654$), or reported use of vitamin K antagonists. The final study population consisted of 16,057 women.

Baseline measurements

At baseline a general questionnaire containing questions on demographic characteristics, presence of chronic diseases, and risk factors for chronic diseases, such as hypertension, smoking habits and drinking of alcohol were administered. Systolic and diastolic blood pressure were measured twice at the right arm with an automated and calibrated oscillomat (Bosch & Son, Jungingen, Germany) with the subject in supine position, and the mean was calculated. Height and weight were measured and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Smokers were categorized as current (<10, 11–20, >20), past or never smokers. Hypertension was defined present based on several aspects: a physician-diagnosed self-report, measured hypertension (>140 systolic or >90 diastolic) or by the use of hypertensive medication. Hypercholesterolemia and diabetes mellitus were defined present when women reported that these disorders had been diagnosed by a physician [13].

Dietary intake data

Energy and nutrient intake were estimated from a validated food frequency questionnaire (FFQ) [14]. The FFQ contained questions on the usual frequency of consumption of 77 main food items, preparation methods, and additions during the year preceding enrolment. Colour photographs were used to estimate portion size for 28-food items. Overall, the questionnaire allows the estimation of the average daily consumption of 178 foods, by asking for subitems for several food items, like fruit and vegetables, in additional questions. Nutrient intake was calculated using the 1996 version of the Dutch national food composition table, except for total folate, for which the 2001 version was used [15,16]. This table does not contain information on vitamin K contents of foods and therefore the concentrations of vitamins K_1 and vitamin K_2 (MK-4 through MK-9) in a large series of Dutch foods were assessed at the Biochemistry Laboratory, Maastricht University [17]. For some foods, published data by others were used to update the dietary database for vitamin K [18–22]. In total, vitamin K contents of 260 foods were found and added to the NEVO (1996) food database. We used data from our previous validation study to estimate reliability of the FFQ to estimate vitamin K intake against 12–24-h recalls in 58 women, as described in more detail previously [14,23]. We observed a low relative validity of phylloquinone with Spearman correlations of 0.24. Relative validity for intake of menaquinone and MK-4 to MK-9 was reasonable with

Spearman correlation coefficients ranging from 0.51 for MK-7 to 0.72 for MK-5. In our study population of 16,057 women, vegetables contributed 82% of vitamin K_1 intake, while cheese contributed 54%, milk products 22% and meat 15% of vitamin K_2 intake.

Morbidity and mortality

Data on morbidity were obtained from the Dutch Centre for Health Care Information, which holds a standardized computerized register of hospital discharge diagnoses. Admission files have been filed continuously from all general and university hospitals in The Netherlands from 1990. Data on sex, date of birth, dates of admission and discharge were recorded whenever a patient was discharged from hospital. One mandatory principal diagnosis, and up to nine optional additional diagnoses were reported. The principal diagnosis was used for the morbidity endpoint. All diagnoses were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9). The database was linked to the cohort on the basis of birth date, gender, postal code, and general practitioner with a validated probabilistic method [24]. Information on vital status was obtained through linkage with the municipal administration registries. Causes of death were obtained from the Dutch Central Bureau of Statistics, coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10). Whenever multiple events occurred, the first diagnosis was taken as endpoint. For our analyses, coronary events (ICD-9; 410–414, 427.5 or ICD-10; I20, I23–I25) were the endpoints of interest. For all women who had a CHD event, follow up ended at the date of diagnosis or, when hospital admission had not occurred, at the date of death. Moving out of The Netherlands ($n = 56$) and death due to causes other than cardiovascular disease ($n = 513$) were considered censoring events. All others ($n = 14{,}879$) were censored on January 1st 2004.

Data analysis

Characteristics of the study population are described by means $\pm$ SD for normally distributed continuous variables and numbers and frequencies for categorical variables. Correlation between vitamins K_1, K_2 and its subtypes and other variables were calculated using Pearson correlation analysis. The person-time for each woman was calculated from the month of return of the baseline questionnaire to the month of diagnosis of CHD, the month of death from other causes, or the end of the study period (January 1, 2004). Cox proportional hazards regression models were used to estimate the HR for CHD event with 95% confidence intervals (CIs). Vitamins K_1, K_2 (per 10 μg increase) and its subtypes (per 1 μg increase) were evaluated as continuous variables. Univariate analysis (model 1) was performed to identify the crude relation between vitamin K and CHD.

Additionally, three multivariate models were used: model 2, including age at baseline, model 3, including classical cardiovascular risk factors and model 4, including dietary factors. Since calcium intake was strongly correlated with vitamin K_2 intake ($r > 0{,}5$), an additional model (5) was used that included calcium intake in the analyses for vitamin K_2 and its subtypes. Classical risk factors for CHD that were included as confounders were age, BMI, smoking, diabetes, hypertension, hypercholesterolemia, and alcohol intake. Dietary confounding factors for vitamin K_1 intake were dietary fibre, protein from plant origin and folic acid. The dietary confounding factors for vitamin K_2 included saturated fat, poly-unsaturated fatty acids and energy (kJ). All nutrients were adjusted for total energy intake by using the residual method [25]. Results were considered statistically significant at 2-sided $P \leq 0.05$. Statistical analyses were performed by using the program SPSS, version 11.5.

Results

The study had a mean follow-up of 8.1 ± 1.6 years (y) and comprised 130,062 person-years. The mean age of the study group was 57.0 ± 6.0 y. Mean vitamin K_1 intake was 211.7 ± 100.3 μg/d and vitamin K_2 intake was 29.1 ± 12.8 μg/d. The subtypes MK-4, MK-8 and MK-9 were the major contributors to vitamin K_2 intake (Table 1). Vitamins K_1 and K_2 intake were not correlated ($r = -0.02$, $P = 0.01$).

Prevalence of hypertension, hypercholesterolemia and diabetes was more common among women with a high vitamin K_1 intake compared to those with a low vitamin K_1 intake. Intake of vitamins from fruits and vegetables, such as vitamin C and folic acid, were higher in the women with high vitamin K_1 intake (data available on request). Women with a high vitamin K_2 intake were more likely to be diabetic, but less likely to have hypercholesterolemia compared to those with a low vitamin K_2 intake. Intake of protein, saturated fat, cholesterol and calcium became higher with increasing quartiles of vitamin K_2 intake (Table 2).

In total, 480 women experienced a CHD event during follow-up, of which 32 were fatal. Vitamin K_1 intake was not associated with risk of CHD, a pattern that did not change after multivariate adjustment (Table 3).

For vitamin K_2, we found an inverse association with CHD (model 1, Table 4), with a HR of 0.89 [95% CI 0.82–0.96]. Additional adjustment for all other confounders did not change these results. When finally adding calcium to the model (model 5, Table 4), the estimate was still in the same direction, but the CI's became wider (0.92 [95% CI 0.83–1.01]).

Table 1 Intake of energy adjusted vitamins K_1, K_2 and vitamin K_2 subtypes in 16,057 postmenopausal Dutch women.

Vitamin K	Mean $\pm$ SD (μg/d)	Range (μg/d)
Vitamin K_1	211.7 ± 100.3	9.1–991.1
Vitamin K_2	29.1 ± 12.8	0.9–128.0
MK-4	7.1 ± 2.1	0.5–28.2
MK-5	0.3 ± 0.2	0–2.1
MK-6	0.3 ± 0.2	0–1.5
MK-7	0.4 ± 0.3	0–2.2
MK-8	6.0 ± 3.4	0–32.8
MK-9	14.7 ± 8.1	0–81.9

Table 2 Baseline characteristics of all 16,057 postmenopausal women according to quartiles of energy adjusted vitamin K_2 intake.

	Energy adjusted vitamin K_2 intake (μg/d)			
	<20 (*N* = 4014)	20–27 (*N* = 4014)	27–36 (*N* = 4018)	>36 (*N* = 4011)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Follow-up time, months	96.6 ± 19.8	96.7 ± 19.3	97.4 ± 18.7	97.1 ± 19.2
Age, years	57.1 ± 6.1	57.3 ± 6.1	56.9 ± 5.9	56.8 ± 5.9
BMI, kg/m^2	25.9 ± 4.0	26.0 ± 4.0	26.1 ± 4.0	25.9 ± 4.2
Systolic blood pressure, mm Hg	133.8 ± 20.6	133.6 ± 19.9	133.0 ± 19.7	132.1 ± 19.9
Diastolic blood pressure, mm Hg	79.5 ± 10.5	79.6 ± 10.4	79.3 ± 10.5	79.0 ± 10.4
Smoking status	N (%)	N (%)	N (%)	N (%)
Never	1694 (42.2)	1809 (45.1)	1776 (44.2)	1748 (43.6)
Past	1302 (32.4)	1367 (34.1)	1412 (35.1)	1449 (36.1)
Current, <10	406 (10.1)	403 (10.0)	412 (10.3)	408 (10.2)
Current, 11–20	440 (11.0)	307 (7.6)	296 (7.4)	282 (7.0)
Current, >20	172 (4.3)	128 (3.2)	122 (3.0)	124 (3.1)
Hypertension	1163 (29.0)	1155 (28.8)	1125 (28.0)	1108 (27.6)
Diabetes	88 (2.2)	94 (2.3)	111 (2.8)	131 (3.3)
Hypercholesterolemia	263 (6.6)	210 (5.2)	162 (4.0)	129 (3.2)
Daily dietary intake[a]	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Energy, kJ/d	7549 ± 1888.6	7633 ± 1821.7	7612 ± 1757.6	7408 ± 1821.6
Protein, g/d	64.9 ± 10.0	68.8 ± 8.8	71.7 ± 8.8	75.4 ± 9.7
Total fat, g/d	66.8 ± 11.0	68.3 ± 10.1	69.1 ± 9.6	71.2 ± 10.4
Mono-unsaturated fat, g/d	25.1 ± 5.0	25.4 ± 4.5	25.6 ± 4.3	26.0 ± 4.5
Poly-unsaturated fat, g/d	13.7 ± 3.9	13.3 ± 3.5	12.9 ± 3.3	12.3 ± 3.2
Saturated fat, g/d	27.1 ± 5.2	28.7 ± 4.5	29.7 ± 4.6	32.1 ± 5.3
Cholesterol, mg/d	181.9 ± 49.3	196.1 ± 50.9	205.1 ± 53.4	215.4 ± 56.1
Alcohol, g/d	9.5 ± 15.0	8.8 ± 12.6	8.7 ± 12.1	9.4 ± 12.2
Calcium, mg/d	867.4 ± 276.5	1014.3 ± 256.6	1113.7 ± 252.5	1306.0 ± 291.3
Folic acid, μg/d	185.2 ± 41.4	187.6 ± 38.0	189.0 ± 37.9	187.6 ± 38.4

[a] All nutrients were adjusted for energy.

The protective effect of vitamin K_2 appeared to be due mainly to its subtypes MK-7 through MK-9 (Table 5), although correction for confounders slightly attenuated all associations.

Menaquinones mostly occur in animal products like meat, milk products and cheese [17]. We therefore also investigated the association between these products and CHD. All results remained similar after adjusting findings of K_1 for other dietary variables included in the models for K_2 and the other way around.

Table 3 Hazard ratio's for CHD risk by energy adjusted vitamin K_1 intake per 10 μg increase.

	HR (95% CI)	*P*-value
Model 1[a]	1.01 (1.00–1.01)	0.02
Model 2[b]	1.00 (1.00–1.02)	0.14
Model 3[c]	1.00 (0.99–1.01)	0.51
Model 4[d]	1.00 (1.00–1.02)	0.35

[a] Model 1 = Univariate (crude) model.
[b] Model 2 = Adjusted for age at baseline (continuous).
[c] Model 3 = Additionally adjusted for classical risk factors for CHD: BMI (<23, 23–27, >27), smoking (never, past, current <10, 11–20, >20), hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), and energy adjusted alcohol intake (<1, 1–5, 5–15, 15–30, >30 g/d).
[d] Model 4 = Further adjusted for energy-adjusted dietary factors: dietary fibre, protein from plant origin and folic acid.

Table 4 Hazard ratio's for CHD risk by energy adjusted vitamin K_2 intake per 10 μg increase.

	HR (95% CI)	*P*-value
Model 1[a]	0.89 (0.82–0.96)	0.003
Model 2[b]	0.90 (0.84–0.98)	0.009
Model 3[c]	0.93 (0.86–1.00)	0.05
Model 4[d]	0.91 (0.85–1.00)	0.04
Model 5[e]	0.92 (0.83–1.01)	0.08

[a] Model 1 = Univariate (crude) model.
[b] Model 2 = Adjusted for age at baseline (continuous).
[c] Model 3 = Additionally adjusted for classical risk factors for CHD: BMI (<23, 23–27, >27), smoking (never, past, current <10, 11–20,>20), hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), and energy adjusted alcohol intake (<1, 1–5, 5–15, 15–30, >30 g/d).
[d] Model 4 = Further adjusted for energy-adjusted dietary factors: saturated fat, poly-unsaturated fatty acids and energy (kJ).
[e] Model 5 = Model 4 *with* calcium.

Table 5 Hazard ratio's for CHD risk by subtypes of energy adjusted vitamin K_2 intake per 1 μg increase.

	HR (95% CI)	*P*-value
MK-4[a]		
Model 1[a]	1.04 (0.99–1.10)	0.11
Model 2[b]	1.05 (1.00–1.11)	0.08
MK-5[a]		
Model 1[a]	0.82 (0.46–1.45)	0.49
Model 2[b]	1.03 (0.43–2.51)	0.94
MK-6[a]		
Model 1[a]	0.70 (0.40–1.24)	0.22
Model 2[b]	0.75 (0.37–1.51)	0.42
MK-7[a]		
Model 1[a]	0.68 (0.46–1.00)	0.05
Model 2[b]	0.67 (0.42–1.08)	0.10
MK-8[a]		
Model 1[a]	0.97 (0.94–1.00)	0.03
Model 2[b]	0.96 (0.93–1.00)	0.05
MK-9		
Model 1[a]	0.99 (0.97–1.00)	0.02
Model 2[b]	0.98 (0.97–1.00)	0.03

[a] Model 1 = Adjusted for age at baseline, classical risk factors for CHD: BMI (<23, 23–27, >27), smoking (never, past, current <10, 11–20, >20), hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), energy adjusted alcohol intake (<1, 1–5, 5–15, 15–30, >30 g/d), energy-adjusted dietary factors: saturated fat, poly-unsaturated fatty acids, energy (kJ).
[b] Model 2 = Model 1 *with* calcium.

Discussion

This study shows that a higher dietary intake of vitamin K_2 was significantly associated with a lower incidence of CHD. The association was mainly driven by vitamin K_2 subtypes MK-7, MK-8 and MK-9. No association between vitamin K_1 intake and CHD was observed after correction for confounders.

The main strengths of our study are its size, the small percentage of loss to follow-up, and the long follow-up, the latter enabling us to study clinically manifest CHD endpoints, which are more informative than intermediate endpoints. The main limitation of this study is the relative validity of our FFQ to estimate intake of vitamin K. For vitamin K_1 intake the relative validity was low, suggesting that our results regarding vitamin K_1 should be interpreted with caution. For vitamin K_2 intake, however the relative validity was reasonable, with correlation coefficients very similar compared to other nutrients estimated using FFQ's [23].

Our study population was limited to postmenopausal women. Although this limits generalisibility of our results to men, this population may be of particular relevance for this research question. During the menopausal phase, an acceleration of bone loss is seen with a rate of 3–10%. Recent studies have shown that reduced bone mineral density may be a risk factor for CVD [26].

In our analyses we did not take lipid lowering drugs into account, because only 12 women reported the use of these medications. Instead, we have corrected for self reported hypercholesterolemia. This is due to the fact that only hypercholesterolemia is not an indication for treatment in The Netherlands, but treatment is indicated for women with a high enough 10-year risk, such is a manifest myocardial infarction or stroke. However, we excluded women with prevalent disease.

In our analyses for vitamin K_2 we additionally corrected for calcium intake. Obviously, it is a point of discussion whether or not it is necessary to adjust for calcium intake, as calcium and vitamin K_2 intake were strongly correlated with each other. However, it seems that adding calcium to the model has led to an imprecise estimate, as the estimate remained similar, but the CI's became wider. This was also observed for the subtypes of vitamin K_2. More research into this is necessary.

In our study, we did not have access to patient charts and were therefore not able to validate the diagnosis of CHD. However, validation studies for non-fatal coronary outcomes have already been conducted in other centres of the EPIC study using similar registries to identify potential cases. Overall, 89% of suspected non-fatal coronary outcomes were confirmed against internationally agreed criteria [27]. These findings suggest that outcome misclassification is probably not a major issue in our study.

Our findings that usual intakes of vitamin K_2 were not strongly, but statistically significantly associated with lower incidence of CHD, support the data from the Rotterdam study [10]. Moreover, recent results from our group show similar inverse associations for vitamin K_2 with coronary calcification [28]. Mechanistically, there are indications that vitamin K_2 is involved in vascular calcification. Arteries with atherosclerotic plaques were found to have a 20–50 fold lower vitamin K_2 concentration than arteries without plaque in the same human body [2], suggesting that vitamin K_2 protects against calcification. In addition, high doses of vitamin K_2 (subtype MK-4) were shown to prevent medial calcification in rats [9].

Until now, only the Nurses' Health Study did find a borderline significant protective effect of vitamin K_1 and CHD. However, as this weak association was attenuated by dietary factors associated with risk of CVD, the authors concluded that dietary and lifestyle patterns associated with vitamin K_1 intake, rather than the nutrient itself might account for this association [11]. Indeed, the Rotterdam study [10] and the Health Professionals' Follow-up Study [12] could not confirm a protective effect for vitamin K_1. Similarly, recent findings from our group [28] in addition to our results did not show an association between vitamin K_1 and coronary calcification and CHD respectively. Residual confounding by healthier dietary patterns and lifestyles associated with vitamin K_1 intake might explain the lack of association [11,12]. The low relative validity of vitamin K_1 as estimated by our FFQ may be involved also.

The concept of proposing beneficial effect to vitamin K_2 seems to have different basis as for vitamin K_1. Vitamin K_1 has been associated with a heart-healthy dietary pattern in the earlier work in the USA and this attenuated their associations with CHD [11,12]. Vitamin K_2 has different sources and relate to different dietary patterns than vitamin K_1. This suggests that the risk reduction with vitamin K_2 is not driven by dietary patterns, but through biological effects. Indeed, the different effects of vitamin K_2 and vitamin K_1 seem to reflect differences in metabolism

as a result of different distributions over plasma lipoproteins. Vitamin K_1 is primarily transported with the triacylglycerol-rich lipoprotein fraction, which is mainly cleared by the liver [29]. Therefore, vitamin K_1 is very effectively cleared from circulation by the liver to function as a cofactor for proteins in blood coagulation [30]. Hence, accumulation and utilization of vitamin K_1 in extrahepatic tissues such as the vessel wall is lower.

In contrast to vitamin K_1, however, vitamin K_2 is found in both triacylglycerol-rich lipoprotein and low-density protein, the latter forming a major transport system to extrahepatic tissues [29]. This has been confirmed by animal experiments showing that extrahepatic tissues, such as the vessel wall, preferentially accumulate vitamin K_2 [9]. Menaquinone could therefore more successfully influence MGP and coronary calcification. Moreover, an animal study showed that MK-4 but not phylloquinone inhibited warfarin-induced coronary calcification [9].

Thus, although our findings may have important practical implications on CVD prevention, it is important to mention that in order to increase the intake of vitamin K_2, increasing the portion vitamin K_2 rich foods in daily life might not be a good idea. Vitamin K_2 might be, for instance more relevant in the form of a supplement or in low-fat dairy. More research into this is necessary.

In our population, the total supply of vitamins K_1 and K_2 was sufficient for optimal carboxylation of the coagulation enzymes in the liver. However, prospective studies, including randomized trials, evaluating the relationship of vitamin K supplementation with vascular calcification are needed to define optimal intake levels of vitamin K intake for the inhibition of vascular calcification.

Of the subtypes of vitamin K_2, it appeared that particularly MK-7, MK-8 and MK-9 affected the risk of CHD. A stronger effect of the longer subtypes could be due to a slower hepatic clearance of these subtypes, making them longer available for carboxylation reactions [2].

In conclusion, the findings in this prospective study among elderly women suggest that a high intake of vitamin K_2 might protect against CHD. This may particularly reflect an effect of the higher subtypes of vitamin K_2, mainly MK-7, MK-8 and MK-9.

Conflict of interest

The authors have no conflict of interest.

Funding

None.

Disclosure statement

None.

Acknowledgements

The help of J.H. den Breeijen, Msc, data manager, and J.J.M. Drijvers, dietician, with the calculation of vitamin K intake is gratefully acknowledged.

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