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Phylloquinone and Vitamin D Status: Associations with Incident Chronic Kidney Disease in the Framingham Offspring Cohort

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Abstract

Background—Cardiovascular risk factors are associated with the development of chronic kidney disease (CKD), and CKD and vascular disease are etiologically linked. Evidence suggests deficiencies of vitamins D and K may adversely affect the cardiovascular system, but data from longitudinal studies are lacking. We hypothesized that deficiencies of vitamins D and K may be associated with incident CKD and/or incident albuminuria amongst members of the general population.

Methods—We analyzed 1442 Framingham Heart Study participants (mean age 58 years; 50.5% women), free of CKD (eGFR<60 ml/min/1.73^2), with a mean follow-up of 7.8 years in 2005–2008. Incident albuminuria was defined using sex-specific cutoffs of urine albumin-to-creatinine ratio (≥17 mg/g men and ≥25 mg/g women). Baseline log plasma phylloquinone (vitamin K_1) and 25(OH)D levels, analyzed as continuous variables and by quartile, were related to risk of incident CKD (n=108) and incident albuminuria (n=106) using logistic regression models adjusted for standard risk factors.

Results—Participants in the highest phylloquinone quartile (≥1.78 nmol/L) had an increased risk of CKD (multivariable-adjusted OR Q_4 vs. Q_1 2.39; p=0.006) and albuminuria at follow-up (multivariable-adjusted OR Q_4 vs. Q_1 1.95; p=0.05), whereas no association was observed with continuous phylloquinone levels for either endpoint. Deficiency of 25(OH)D was not associated with incident CKD or albuminuria in either analysis.

Conclusions—Contrary to our hypothesis, higher plasma phylloquinone levels are associated with an increased risk of incident CKD. Whether plasma phylloquinone is a marker for another unmeasured risk factor requires further study. External validation is necessary given the unexpected nature of these results.

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Keywords

Chronic kidney disease; vitamin K; vitamin D

Introduction

Chronic kidney disease (CKD) is associated with cardiovascular disease, such that they commonly co-exist and the overlap in their etiologies is considerable.[1] However, vascular calcification is more commonly a feature of cardiovascular disease in CKD patients than is observed in the general population.[2] For example, at the time of initiating renal replacement therapy, the majority of end-stage renal disease patients exhibit extensive arterial calcification, typically involving the coronary arteries, aorta and cardiac valves,[3] and the presence and extent of such advanced vascular calcification predicts cardiovascular disease and mortality beyond conventional risk factors.[4, 5] Advances in imaging techniques have permitted the identification of vascular calcification at earlier stages of CKD in humans,[6] while data from animal studies indicates the processes that lead to vascular calcification begin with very mild degrees of renal injury, before the altered mineral metabolism of secondary hyperparathyroidism develops.[7]

Deficiencies of vitamins K and D are commonly observed across the spectrum of kidney disease stages.[8] Both are fat-soluble nutrients essential to bone health,[9, 10] and deficiencies have been linked to vascular calcification in animals,[11–13] members of the general population[14, 15] and people with kidney disease.[6, 12] Vitamin K administration causes regression of warfarin-induced medial elastocalcinosis in rats.[16] In the case of vitamin D, supplementation has been shown to prevent the development of albuminuria in an animal model of diabetic nephropathy.[17, 18] Furthermore, evidence from a recent randomized controlled trial indicates that treatment with the vitamin D agonist, paricalcitol, reduces proteinuria in established diabetic nephropathy.[19]

In light of these observations, we hypothesized that deficiencies of vitamins D and K may be associated with incident kidney disease. Using data from the Framingham Offspring Cohort, we tested this hypothesis by relating measures of vitamin K status (as measured by plasma phylloquinone level [vitamin K_1]) and vitamin D status (plasma 25(OH) D) to risk of incident CKD and incident albuminuria at 8 years follow-up in a community-based sample of men and women.

Methods

Study sample

Participants were drawn from the Framingham Offspring Study cohort.[20] Offspring participants underwent assessment in 4 to 8 year cycles, which included physical examination, blood biochemistries, assessment of cardiovascular risk factors and physician interview. Samples for vitamins K and D were collected between 1997 and 1999 (the end of examination cycle 6 [1995–1998] and the beginning of cycle 7 [1998–2001]). In total, 1,599 participants had baseline phylloquinone levels drawn and follow-up creatinine measures available. Of these, 147 were excluded due to baseline CKD, and 10 due to missing covariates, resulting in a final study sample of 1,442. For the 25(OH)D analysis, the total sample size was 1438. All participants provided written informed consent, and the institutional review boards of the Boston University Medical Center approved the study.

Exposure measurement: Vitamins K and D

Fasting morning blood samples were drawn and plasma was stored at −80 C until processing. Vitamin K status was assessed by plasma phylloquinone level, as measured by high-pressure liquid chromatography.[21] Low and high control specimens had average values of 0.56 and 3.15 nmol l^{-1}, with coefficients of variation (total CVs) of 15.2 and 10.9%, respectively. 25(OH)D status was estimated by measuring plasma 25(OH)D level using radioimmunassay (http://www.diasorin.com).

Primary outcome assessment: estimated glomerular filtration rate and incident CKD

The primary outcome was development of incident CKD, defined as eGFR < 60 ml/min/ 1.73^2 using the Modification of Diet in Renal Disease (MDRD) equation,[22] by the eighth examination cycle (2005–2008). Serum creatinine levels were measured using the modified Jaffé method. Calibration of serum creatinine values to the Cleveland Clinic Laboratory standard was performed using the correction factor of 0.23 mg/dL (20.33 μmol/L).[23] We utilized an alternate definition of incident CKD as a secondary outcome, CKDi25: eGFR <60 ml/min at follow-up *and* at least 25% decline in eGFR from baseline.

Secondary outcome assessment: incident albuminuria

Incident albuminuria was defined using the sex-specific cut-offs of urine albumin-to-creatinine ratio (UACR) ≥ 17 mg/g in men and ≥ 25 mg/g in women.[24] UACR was measured on spot morning urine samples collected between 1995 and 1998. After collection, urine samples were stored at −20°C and then transitioned to −80°C until quantification in October 1998 in Children's Hospital, Boston, MA. Urinary albumin concentration was measured using immunoturbidimetry (Tina-quant Albumin assay; Roche Diagnostics; http://www.roche-diagnostics.us/) and urinary creatinine levels were measured using the Jaffé method;[25] the intra-assay coefficient of variation varied from 1.7% to 3.8%.

Covariate assessment

Participants underwent blood testing and were assessed for CKD risk factors. High-density lipoprotein cholesterol and blood glucose were measured on fasting morning blood samples. Diabetes was defined as fasting blood glucose of 126 mg/dL (7 mmol/L) or greater or use of diabetic medication. Systolic and diastolic blood pressure measurements were taken as the mean of 2 physician readings using a mercury sphygmomanometer. Hypertension was defined as a systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg or self-reported use of antihypertensive medications. Body mass index was defined as an individual's weight in kilograms divided by height in meters squared. Current smoking status was defined by self-report. Season was also included as a covariate due to seasonal influences on vitamins D status.[26] Season was defined as: June-August; summer: September-November; fall: December-February; winter: March-May; spring, with fall, winter and spring being entered as dichotomous variables and summer as the reference.

Statistical analyses

Phylloquinone was log-transformed to approximate normality due to a skewed distribution (skewness 7.4). Following log transformation the distribution skewness improved to −0.3 and kurtosis was 1.06. Baseline characteristics of study participants were calculated by quartile of phylloquinone level and the statistical significance of differences was compared using χ^2 tests for categorical variables and 1-way ANOVA for continuous variables. Pearson's correlation coefficients were used to assess associations between plasma phylloquinone level with age, body mass index (BMI), systolic blood pressure, HDL-cholesterol, log triglycerides, eGFR, UACR and 25(OH) D.

Baseline phylloquinone level was considered both in quartiles and as a continuous variable (per 1 standard deviation increase). The association between phylloquinone quartile and risk of incident CKD was tested using logistic regression models. Three sets of regression models were constructed: (1) adjusting for age and sex, (2) a multivariable model adjusting for age, sex, diabetes, systolic blood pressure, hypertension treatment, high-density lipoprotein cholesterol, BMI, current smoking and estimated glomerular filtration rate and (3) additional adjustment to model 2 for the proportion of circulating undercarboxylated osteocalcin (%ucOC), a sensitive measure of vitamin K status. In these regression models, the reference category was quartile 1 (lowest phylloquinone level).

25(OH)D was also analyzed as both a continuous variable and by quartiles, and related to risk of incident CKD and albuminuria using logistic regression models. Participants in the lowest quartile plasma 25(OH)D levels were used as the reference group. Identical regression models were used as for the phylloquinone analysis. All analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

Secondary analyses

We examined incident albuminuria as a secondary outcome, defined using the sex-specific cut-points of UACR ≥17 mg/g (men) or ≥25 mg/g (women).[27] As for the CKD analysis, the association between vitamin quartile and risk of albuminuria was tested using two sets of logistic regression models: (1) age-and sex-adjusted (2) a multivariable model adjusted for age, sex, diabetes, high-density lipoprotein cholesterol, log triglycerides, current smoking, eGFR and baseline log urine albumin to creatinine ratio.

As an additional secondary analysis, we also adjusted for dietary phylloquinone intake, assessed by food frequency questionnaire, in the multivariable model for incident CKD.

Results

Baseline characteristics

Baseline characteristics of the cohort, by quartile of baseline plasma phylloquinone level, are presented in Table 1a. Participants with higher phylloquinone levels at baseline were more likely to be men and have hypertension but less likely to smoke tobacco. There were no significant differences in baseline eGFR or albuminuria across quartiles. Data by quartile of baseline plasma 25(OH)D are shown in Table 1b.

Age- and sex-adjusted cross-sectional correlations of log plasma phylloquinone and plasma 25(OH)D with established CKD risk factors are presented in Table 2. Log plasma phylloquinone was correlated with log plasma triglyceride level ($r=0.20$; $p<0.0001$), and inversely correlated with plasma HDL-cholesterol ($r=-0.11$; $p<0.0001$). Plasma 25(OH)D was inversely correlated with body mass index ($r=-0.22$; $p<0.0001$). Weaker correlations were observed between plasma 25(OH)D and log plasma triglyceride level ($r=-0.09$; $p=0.0002$), plasma HDL-cholesterol ($r=0.13$; $p<0.0001$) and systolic blood pressure ($r = -0.06$; $p=0.02$).

Incident CKD by Vitamin K Status

Of 1442 study participants, 108 (7.5%) developed incident CKD over a mean of 7.8 years follow-up. In an analysis by baseline phylloquinone quartile, participants in quartile 4 (≥1.78 nmol/L; highest plasma phylloquinone level) demonstrated an increased risk of incident CKD when compared with quartile 1 (≤0.55 nmol/L; lowest) in age- and sex-adjusted (OR 2.20; 95% confidence interval 1.20–4.00; p=0.01) and multivariable-adjusted models (OR 2.39 (1.28–4.46); p=0.006; Table 3). The inclusion of %ucOC in the multivariable incident

chronic kidney disease (CKD) logistic regression model did not materially alter the results, and %ucOC was not associated with incident CKD (p = 0.2).

When analyzed as a continuous variable, plasma phylloquinone was not associated with incident CKD (multivariable adjusted OR per standard deviation increase in plasma phylloquinone: 0.99 (0.83–1.19); p=1.0) (Table 3). There was no evidence of effect modification by sex (p-value range for sex-interaction terms: 0.5–1.0).

Incident CKD by 25(OH)D Status

Of 1438 study participants for the 25(OH)D analysis, 108 (7.5%) developed incident CKD over the study period. When analyzed by baseline quartile of 25(OH)D level, no association with risk of CKD was observed for any quartile compared to the referent in age- and sex-adjusted (for example, OR quartile(Q) 4 vs. Q1: 1.30 (0.74–2.27); p=0.4) and multivariable-adjusted models (OR 1.44 (0.79–2.61); p=0.2; Table 4). When analyzed as a continuous variable, plasma 25(OH)D was not associated with incident CKD in either age- and sex-adjusted or multivariable adjusted models (multivariable-adjusted OR per standard deviation increase in plasma 25(OH)D level: 0.85 (0.69–1.04); p=0.1, Table 4). There was no evidence of effect modification by sex (p-value for sex-interaction terms ranges from 0.4–0.9).

Secondary analyses

Alternate definition of CKD—Applying a more stringent alternate definition of CKD (follow-up eGFR<60 ml/min *and* at least 25% decline in eGFR from baseline) yielded fewer cases than the primary analysis (n=62; 4.3%). However, results were similar with participants in the highest phylloquinone quartile demonstrating increased risk of CKD at follow-up when compared with the lowest in both models (age- and sex-adjusted OR 2.83 (1.32–6.08); p=0.008; multivariable-adjusted OR 2.82 (1.28–6.22); p=0.01; data not shown), whereas no association with CKD risk seen in continuous analysis (multivariable-adjusted OR per standard deviation decrease in phylloquinone level 1.01 (0.83–1.23); p=0.9; data not shown).

For 25(OH)D, results were also similar to the primary analysis, with no evidence of association between plasma 25(OH)D level and CKD risk observed in quartile-based (multivariable-adjusted OR 1.43 (0.69–2.96); p=0.3; data not shown) or continuous analyses (multivariable-adjusted OR per standard deviation decrease in 25(OH)D level 1.10 (0.85–1.41); p=0.5; data not shown).

Incident albuminuria—Of 1151 participants with urinary data available, 106 developed new-onset albuminuria at follow-up (9.2%). In quartile-based analyses, risk of incident albuminuria was increased in all upper phylloquinone quartiles when compared to lowest (multivariable-adjusted OR for Q2 vs. Q1: 2.17 (1.11–4.22); p=0.02; Q3 vs. Q1: 2.21 (1.15–4.25); p = 0.02; Q4 vs. Q1: 1.95 (0.99–3.82); p=0.05; Table 3). There was no association observed between plasma phylloquinone level analyzed as a continuous variable and incident albuminuria (p=0.5; Table 3). Finally, no association with incident albuminuria was observed in any analysis of 25(OH)D (multivariable-adjusted OR 0.91 (0.50–1.66); p=0.8 for Q4 vs. reference; Table 4).

Dietary phylloquinone intake—Of 1442 participants in the primary analysis, 1293 had dietary information available. At baseline, there was a trend for greater dietary phylloquinone intake by plasma quartile (p for trend 0.02; Table 1). However, additional adjustment for dietary phylloquinone in the multivariable model of incident CKD did not materially affect the results (multivariable-adjusted OR for Q2 vs. Q1: OR 1.81 (95% CI

0.91–3.61, p=0.09); Q3 vs. Q1: OR 1.87 (95% CI 0.94–3.71, p = 0.07); Q4 vs. Q1: OR 2.65 (95% CI, 1.37–5.13, p=0.004).

Discussion

The findings of our study are twofold. First, contrary to our initial hypothesis, we observed no association between lower circulating phylloquinone levels and any of the 3 study endpoints, namely incident CKD, incident CKD with evidence of progression, and incident albuminuria. In fact, an unexpected excess risk for these endpoints was detected in the highest phylloquinone quartile. Second, 25(OH)D deficiency was not associated with incident CKD or incident albuminuria.

Vitamin K is a co-factor in the post-translational γ–carboxylation of glutamate residues of several vitamin K-dependent proteins, including matrix Gla protein, an inhibitory regulator of tissue mineralization in the arterial wall. Scientific interest in a potential role for vitamin K in vascular biology and cardiovascular health was stimulated by the demonstration of a lethal phenotype of vascular calcification in the matrix Gla protein knockout mouse.[28] Results from subsequent human studies supported this idea. For example, in a 3-year follow-up study of 388 healthy men and postmenopausal women, phylloquinone 500 mcg/day conferred a protective effect against progression of vascular calcification, assessed by coronary calcium score, when compared to placebo.[29] Furthermore, a placebo-controlled trial of phylloquinone supplementation in 108 postmenopausal women demonstrated improved vascular compliance, distensibility, and intima media thickness in the treatment arm.[30] Also, plasma phylloquinone levels were inversely associated with circulating inflammatory markers in the Framingham Offspring cohort.[31] In the setting of kidney disease, deficiencies of vitamin K and D are prevalent in patients with advanced CKD (stages 3 to 5).[8] However it should be noted that these deficiencies appear to be a function of an overall decline in nutritional status observed in CKD patients, as sufficiency of both vitamins was predicted by measures of improved nutritional status. In the present study, participants were free of kidney disease at the time of vitamin assay and were a far less sick cohort in general. As such, poor nutrition would not be expected to be a factor.

It is thus unexpected that we observed an increased risk of incident CKD in individuals with higher plasma phylloquinone levels in the present study. There is no tolerable upper intake limit set as there are no known cases of toxicity due to vitamin K.[32] Unlike other fat-soluble vitamins, vitamin K is not stored in any significant quantity in the liver; therefore toxic levels are rarely achieved. On the contrary, plasma phylloquinone levels are linearly associated with a 'healthy' dietary intake of green vegetables.[33] Consistent with these observations, adjusting for dietary phylloquinone intake or %ucOC in the multivariable model did not materially alter the results, and neither variable was associated with incident CKD. These observations suggest the excess risk of kidney disease seen in the highest plasma phylloquinone quartile is not directly mediated by dietary phylloquinone intake or phylloquinone gamma-carboxylase bioactivity.

With no data to support a direct toxic effect of phylloquinone, how might these results be explained? First, this may be an epiphenomenon, and plasma phylloquinone may be a marker of an unmeasured biochemical, genetic or environmental CKD risk factor in our dataset. For example, although variability in biomarkers of vitamin K status is mostly attributed to non-genetic factors,[34] polymorphisms in vitamin K epoxide reductase C1 (VKORC1), for which phylloquinone is a substrate, have been shown to be associated with cross-sectional measures of plasma phylloquinone.[35, 36] *VKORC1* haplotypes have also been shown to be associated with vascular calcification in rats,[37] accelerated renal allograft loss in humans[38] and aortic calcification in the Rotterdam study.[36] As such, it is possible

that similar polymorphisms in genes involved in phylloquinone metabolism may result in higher plasma phylloquinone levels due to reduced phylloquinone recycling or metabolism i.e. a functional phylloquinone deficiency state. A similar functional deficiency could result from a variety of factors, such as altered phylloquinone transport, disrupted cellular uptake of phylloquinone or altered conversion of phylloquinone to vitamin K2, and these potential mechanisms are interesting avenues for further study. A second possible explanation for these findings may be that individuals at risk for CKD have a different response to dietary phylloquinone, which may account for higher circulating levels. Clinical trials of phylloquinone to date have primarily focused on bone disease and have tended to screen out individuals with renal abnormalities. Finally, it is possible that this finding may be a false positive, and external replication of these results is required. However, we observed decreasing %ucOC with increasing phylloquinone quartiles (p for trend <.0001), indicatative of increasing phylloquinone bioactivity occurring in line with plasma levels, which argues against artefactual phylloquinone elevation in the highest quartile.

The fact that phylloquinone was only associated with CKD risk in the quartile analysis, and not when analyzed as continuous variable, may perhaps be explained by the presence of a "threshold effect". Similar threshold relationships have been noted for other biomarkers of incident CKD in the general population, such as plasma phosphorus level.[39]

Evidence that 25(OH)D deficiency plays a role in kidney disease initiation is lacking, although limited animal data suggests it may influence progression of kidney disease. For example, activated vitamin D negatively regulates both the renin-angiotensin system[40] and production of TGF-beta 1,[41] a key promoter of renal fibrosis in mice. Furthermore, 25(OH)D may be necessary for maintenance of podocyte structure and prevention of pathologic mesangial cell proliferation in response to renal injury.[42] Studies in humans of 25(OH)D and progression of kidney disease are scarce, although two small studies suggest a potential benefit of active vitamin D use in slowing the progression of kidney disease.[43, 44] Furthermore, a recent NHANES III analysis found that participants with 25(OH)D levels <15 ng/ml were more likely to progress to end-stage renal disease compared to those without deficiency.[45] Importantly, the excess risk for developing ESRD was primarily seen in non-Hispanic black individuals in that study. The fact that Framingham participants are white and generally of northern European descent is a critical difference, and may explain the lack of association in the present analysis.

Contrasting with these earlier studies, we did not observe any association with 25(OH)D deficiency and incident CKD or albuminuria. It should be emphasized that half of the cohort had 25(OH)D levels below current recommended guidelines, hence there was a sufficient distribution with which to identify an effect if it truly existed. Consistent with our null findings, 2 recent systemic reviews found that the available evidence that vitamin D influences cardiovascular outcomes is inconsistent and contradictory.[46, 47] Furthermore, a recent Institute of Medicine Committee report concluded that the evidence that vitamin D supplementation reduces the risk of non-skeletal chronic diseases is inconclusive, fails to establish a cause-and-effect relationship and is insufficient to inform nutritional recommendations.[48] While hypothesis-generating observational and pharmaco-epidemiological studies have stimulated much interest in the potential beneficial effects of vitamin D therapy in CKD amongst other diseases, large randomized controlled trials are now required to test the hypothesis that vitamin D therapy improves clinical outcomes. The planned NIH-sponsored VITAL study (ClinicalTrials.gov Identifier: NCT01169259) will attempt to clarify the role of vitamin D supplementation for these indications.

Our study has important implications. Existing observational studies that suggest a beneficial effect of phylloquinone on cardiovascular risk generally utilize dietary intake

estimates rather than plasma levels.[49–51] These studies may be confounded by phylloquinone intake being primarily a marker of a healthy lifestyle. As the present study indicates potential harm associated with higher plasma phylloquinone, it is essential to validate these findings in independent samples and determine the mechanism of excess CKD risk, which may be independent of dietary intake.

The richness of the dataset with well-defined cardiovascular disease risk factors and long duration of follow-up considerably strengthens our analysis. However, several limitations must also be acknowledged. First, higher cross-sectional rates of hypertension, use of antihypertensive medications and obesity were present in the highest phylloquinone group. While every effort was made to adjust for these CKD risk factors, the possibility of residual confounding cannot be completely ruled out. Second, CKD was defined using a single creatinine measure, which may have resulted in some misclassification. However, if misclassification occurred, it would be expected to bias our results towards the null and would not account for the positive association with CKD risk seen in the highest phylloquinone quartile. Third, there is no agreed global biomarker of vitamin K status, and each of the available markers address a different component of absorption, transport and function. For that reason, we chose plasma phylloquinone as a validated biomarker of exposure to vitamin K. Plasma phylloquinone reflects recent dietary intake and supplement use and responds to manipulation of phylloquinone, as validated in controlled human feeding studies.[33] The major limitation of this marker is its fluctuations in response to short-term changes in dietary phylloquinone intake. However, given our large sample size, this variability is likely modest and would be expected to attenuate our findings. Fourth, although the use of a single plasma phylloquinone measure as an indicator of long-term vitamin K status is imperfect, it is an acceptable measure for ranking participants over a range of levels.[33] Fifth, unlike incident cardiovascular events, the development of CKD is identified through the scheduled examination cycle. Consequently, no exact incident time for CKD can be ascertained and a survival-type analysis is not possible. Finally, the Framingham Offspring cohort participants are generally older, of northern European descent, and reside in the northeastern United States. As such, our findings should not be generalized to other ethnic/racial groups, younger individuals, or those residing in sunnier climates and have limited use of sunscreen.

Despite these limitations, we have identified that deficiency of vitamins K or D are not associated with the development of CKD. Further, an unexplained excess risk of CKD was observed in individuals with the highest plasma phylloquinone levels. Future research should be directed toward replicating these findings in independent samples.

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Table 1a

Baseline characteristics of study participants by quartile of plasma phylloquinone (vitamin K1) level, nmol/L.
Data presented mean with standard deviation in parenthesis for continuous variables or percent with number in parenthesis for categorical data

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P*[*]
Phylloquinone level (range), nmol/L	0.35 (0.05–0.55)	0.76 (0.56–0.98)	1.33 (0.99–1.77)	3.37 (1.78–35.02)	<.0001
Participants, n	361	357	361	363	-
Age, years	58 (9)	58 (9)	58 (8)	58 (8)	0.4
Female sex, % (n)	54 (194)	55 (195)	49 (175)	46 (165)	0.007
Body Mass Index, kg/m^2	27.8 (5.8)	27.6 (5.2)	28.2 (5.1)	28.7 (4.7)	0.02
Systolic blood pressure, mmHg	124 (17)	125 (17)	127 (18)	127 (16)	0.01
Hypertension, % (n)	33 (120)	33 (119)	37 (133)	46 (167)	0.0009
Hypertension treatment, % (n)	23 (84)	22 (80)	25 (90)	34 (123)	0.002
Smoking, % (n)	18 (64)	13 (46)	13 (46)	11 (40)	0.05
Diabetes mellitus, % (n)	8 (28)	8 (27)	6 (23)	9 (31)	0.95
Total cholesterol, mg/dL	190	200	203	208	<.0001
LDL cholesterol, mg/dL	117	123	125	125	0.002
HDL-cholesterol, mg/dL	53 (15)	53 (16)	52 (16)	48 (17)	0.004
Triglycerides (25th, 75th), mg/dL	85 (66,117)	92 (72,124)	105 (77,157)	121 (89,170)	<.0001
eGFR, ml/min/1.73 m^2	86 (17)	86 (20)	87 (17)	89 (21)	0.8
Chronic kidney disease	5.26% (19/361)	7.84% (28/329)	6.93% (25/361)	9.92% (36/363)	0.2
UACR (25th, 75th), mg/g	5.9 (2.8, 13.6)	6.4 (3.1, 14.1)	5.6 (2.3, 11.9)	5.0 (1.9, 11.7)	0.3
%ucOC	20.6	17.6	17.1	14.3	<.0001
Dietary phylloquinone intake, mcg/day	150 (137)	156 (86)	169 (101)	164 (94)	0.02

Abbreviation: HDL = High density lipoprotein, LDL = Low density lipoprotein, eGFR = estimated glomerular filtration rate, UACR = Urine albumin:creatinine ratio, %ucOC = proportion of circulating undercarboxylated osteocalcin

[*] P values are for significance of trend across quartiles, adjusted for age and sex (except age, which is sex adjusted and sex, which is age adjusted). Mean phylloquinone level: 1.46 nmol/L.

Table 1b

Baseline characteristics of study participants by quartile of plasma 25(OH) vitamin D level, ng/mL.
Data presented mean with standard deviation in parenthesis for continuous variables or percent with number in parenthesis for categorical data.

Characteristic	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P**
Plasma 25(OH) D, ng/ml	2.2–14.6	14.7–19.1	19.2–24.0	24.1–58.5	-
Participants, n	358	357	365	358	-
Age, years	58 (9)	58 (9)	58 (9)	58 (8)	0.4
Female sex, % (n)	49 (176)	47 (166)	51 (186)	56 (200)	0.03
Season of blood draw	-	-	-	-	-
Spring % (n)	39 (138)	28 (99)	27 (100)	20 (72)	<.0001
Summer % (n)	3 (10)	5 (17)	10 (38)	23 (83)	<.0001
Fall % (n)	16 (58)	32 (113)	37 (136)	37 (135)	<.0001
Winter % (n)	43 (152)	36 (127)	25 (91)	19 (68)	<.0001
Body Mass Index, kg/m^2	29.6 (6.1)	28.8 (5.5)	27.3 (4.4)	26.6 (4.1)	<.0001
Systolic blood pressure, mmHg	128 (17)	126 (16)	124 (17)	125 (18)	0.008
Hypertension, %	54 (193)	53 (187)	46 (169)	50 (178)	0.07
Hypertension treatment, %	28 (100)	26 (92)	27 (98)	24 (87)	0.4
Smoking, %	17 (60)	13 (48)	12 (45)	12 43)	0.06
Diabetes mellitus, %	10 (37)	7 (26)	7 (26)	6 (20)	0.04
HDL-cholesterol, mg/dL	49 (16)	49 (15)	53 (17)	55 (16)	<.0001
Triglycerides (25th, 75th), mg/dL	104 (79,148)	109 (79,164)	93 (68,134)	94 (69,131)	0.008
eGFR, ml/min/1.73 m^2	89 (18)	89 (20)	87 (19)	84 (17)	0.3
Urine albumin:creatinine ratio (25th, 75th), mg/g	4.6 (2.0, 9.3)	4.7 (1.9, 7.8)	4.8 (1.8, 8.6)	5.0 (2.6, 9.8)	0.9

Abbreviation: HDL = High density lipoprotein, LDL = Low density lipoprotein, eGFR = estimated glomerular filtration rate

* P values are for significance of trend across groups, adjusted for age and sex (except age, which is sex adjusted and sex, which is age adjusted). Mean 25(OH)D level: 19.7 ng/mL

Table 2

Age- and sex-adjusted cross-sectional partial Pearson correlation coefficients of log plasma phylloquinone (vitamin K_1) and 25(OH)D levels with kidney disease covariates

	Phylloquinone (vitamin K_1)		25(OH) D	
	r	P-value	r	P-value
Body Mass Index	0.05	0.4	−0.22	<.0001
Systolic blood pressure	0.04	0.17	−0.06	0.02
High density lipoprotein- cholesterol	−0.11	<0.0001	0.13	<.0001
Estimated Glomerular Filtration Rate	−0.002	0.93	−0.03	0.29
Urine albumin:creatinine ratio*	−0.022	0.46	0.006	0.83
Log Triglycerides	0.20	<.0001	−0.09	0.0002
25(OH)D	−0.03	0.24	-	-

Table 3

Results of logistic regression for quartile and continuous analyses of plasma phylloquinone level and incident kidney disease.
Quartile analysis presents odds of incident chronic kidney disease by baseline quartile of log plasma phylloquinone (vitamin K_1), with lowest quartile as reference. Continuous analysis presents odds of incident chronic kidney disease per standard deviation increase in log plasma phylloquinone. Data presented as odds ratio with 95% confidence interval in parentheses.

		Log plasma phylloquinone (vitamin K1) (nmol/L)							
		Quartile 2 vs. Quartile 1		Quartile 3 vs. Quartile 1		Quartile 4 vs. Quartile 1		Per 1 SD increase	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Incident CKD 108/1442 events (7.5%)	**Age and sex adjusted**	1.64 (0.88–3.07)	0.1	1.44 (0.76–2.72)	0.3	2.20 (1.20–4.00)	0.01	0.97 (0.81–1.18)	0.8
	Multivariable adjusted§	1.66 (0.87–3.17)	0.1	1.58 (0.82–3.05)	0.2	2.39 (1.28–4.46)	0.006	0.99 (0.83–1.19)	1.0
Incident albuminuria * 106/1151 events (9.2%)	**Age and sex adjusted**	2.21 (1.14–4.25)	0.02	2.21 (1.16–4.22)	0.02	1.89 (0.98–3.67)	0.06	0.92 (0.76–1.11)	0.4
	Multivariable adjusted§§	2.17 (1.11–4.22)	0.02	2.21 (1.15–4.25)	0.02	1.95 (0.99–3.82)	0.05	0.93 (0.78–1.12)	0.5

Abbreviation: CKD = chronic kidney disease; GFR = estimated glomerular filtration rate; SD standard deviation. CKD defined as eGFR of < 60 ml/min/1.73m^2

*Sex-specific cut-offs for quantitative albuminuria: urine albumin to creatinine ratio ≥ 17 mg/g in men; ≥ 25 mg/g in women.

§Multivariable model adjusted for age, sex, diabetes, systolic blood pressure, hypertension treatment, high-density lipoprotein cholesterol, log triglycerides, BMI, current smoking and estimated glomerular filtration rate.

§§Multivariable model adjusted for age, sex, diabetes, high-density lipoprotein cholesterol, current smoking, estimated glomerular filtration rate and baseline log urine albumin-to-creatinine ratio.

1 standard deviation of plasma phylloquinone: nmol/L

Table 4

Results of logistic regression for quartile and continuous analyses of plasma 25(OH)D level and incident kidney disease.
Quartile analysis presents odds of incident chronic kidney disease by baseline quartile of plasma 25(OH) D, with lowest quartile as reference. Continuous analysis presents odds of incident chronic kidney disease per standard deviation increase in plasma 25(OH) D. Data presented as odds ratio with 95% confidence interval in parentheses.

		Plasma 25(OH)D level (ng/mL)							
		Quartile 2 vs. Quartile 1		Quartile 3 vs. Quartile 1		Quartile 4 vs. Quartile 1		Per 1 SD increase	
		OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Incident CKD 108/1438 events (7.5%)	**Age and sex adjusted**	0.73 (0.39–1.37)	0.3	1.12 (0.63–1.99)	0.7	1.30 (0.74–2.27)	0.4	0.87 (0.71–1.06)	0.2
	Multivariate adjusted§	0.78 (0.41–1.50)	0.5	1.16 (0.63–2.12)	0.6	1.44 (0.79–2.61)	0.2	0.85 (0.69–1.04)	0.1
Incident albuminuria* 106/1345 events (7.8%)	**Age and sex adjusted**	0.83 (0.47–1.48)	0.5	0.84 (0.47–1.49)	0.5	0.80 (0.45–1.43)	0.5	1.06 (0.87–1.32)	0.5
	Multivariate adjusted§§	0.87 (0.48–1.57)	0.6	0.91 (0.51–1.65)	0.8	0.91 (0.50–1.66)	0.8	1.01 (0.82–1.25)	0.9

Abbreviation: CKD = chronic kidney disease; GFR = estimated glomerular filtration rate; SD standard deviation. CKD defined as eGFR of < 60 ml/min/1.73m^2

*Sex-specific cut-offs for quantitative albuminuria: urine albumin to creatinine ratio ≥ 17 mg/g in men; ≥ 25 mg/g in women.

§Multivariable model adjusted for age, sex, diabetes, systolic blood pressure, hypertension treatment, high-density lipoprotein cholesterol, log triglycerides, BMI, current smoking and estimated glomerular filtration rate.

§§Multivariable model adjusted for age, sex, diabetes, high-density lipoprotein cholesterol, current smoking, estimated glomerular filtration rate and baseline log urine albumin-to-creatinine ratio.

1 standard deviation of plasma 25(OH) D: ng/mL