Vitamin K Status and Cognitive Function in Adults with Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort

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ABSTRACT

Vitamin K is linked to cognitive function, but studies in individuals with chronic kidney disease (CKD), who are at risk for vitamin K insufficiency and cognitive impairment, are lacking. The cross-sectional association of vitamin K status biomarkers with cognitive performance was evaluated in $\geq$55-y-old adults with CKD ($N = 714$, 49% female, 44% black). A composite score of a cognitive performance test battery, calculated by averaging the z scores of the individual tests, was the primary outcome. Vitamin K status was measured using plasma phylloquinone and dephospho-uncarboxylated matrix Gla protein [(dp)ucMGP]. Participants with low plasma (dp)ucMGP, reflecting higher vitamin K status, had better cognitive performance than those in the two higher (dp)ucMGP categories based on the composite outcome ($P = 0.03$), whereas it did not significantly differ according to plasma phylloquinone categories ($P = 0.08$). Neither biomarker was significantly associated with performance on individual tests (all $P > 0.05$). The importance of vitamin K to cognitive performance in adults with CKD remains to be clarified. *Curr Dev Nutr* 2022;6:nzac111.

Introduction

Individuals with chronic kidney disease (CKD) are 35%–40% more likely to experience cognitive decline and develop dementia (1). Even mildly to moderately impaired kidney function has been associated with faster declines in cognitive performance (2). Health-related quality of life in adults with CKD is determined in part by their cognitive function (3). Identifying strategies to preserve cognitive performance in CKD is important to improve patient quality of life and reduce disease burden (4, 5).

There is accumulating support for nutritional strategies to delay the onset of cognitive impairment. One potential prevention strategy involves vitamin K, an essential fat-soluble nutrient that primarily functions as an enzymatic cofactor for γ-carboxylation in certain

calcium-binding proteins, known as vitamin K–dependent (VKD) proteins. Several VKD proteins are involved in brain aging, including Gas6 and protein S, which are expressed in the central nervous system, implicated in neuroinflammation and neurodegeneration, and linked to cognitive decline (6). In community-based studies of older adults, higher vitamin K status has been associated with better cognitive performance and less cognitive decline (7). However, studies focused on individuals with CKD, a group at heightened risk for low vitamin K status (8) and cognitive impairment, are lacking. Therefore, we evaluated the association of vitamin K status biomarkers with cognitive performance in the Chronic Renal Insufficiency Cohort (CRIC), which is composed of adults with moderate CKD.

Methods

Full details of the CRIC study design, recruitment, and human subjects' protection have been described previously (9). The institutional review boards of all participating centers approved the protocols, and all participants provided informed consent. Vitamin K status biomarkers were measured in 3402 CRIC participants. Of these, 794 participated in the CRIC Cognitive study beginning in 2006 (10). CRIC Cognitive participants were all ≥55 y old at baseline. After exclusion of 58 participants who were taking the vitamin K antagonist anticoagulant warfarin and 23 who were missing pertinent covariate data, 714 participants were available for inclusion.

Vitamin K Status
Vitamin K status was assessed by measuring two biomarkers from fasting samples obtained at the 12-mo visit as described (11). Plasma phylloquinone (vitamin K1) is an indicator of overall vitamin K status, and plasma dephospho-uncarboxylated matrix Gla protein [(dp)ucMGP] is considered a functional measure of vitamin K status in tissues that use matrix Gla protein (MGP). Higher plasma (dp)ucMGP reflects lower vitamin K status.

Cognitive Performance
The following test battery was administered annually over 4 y (10): Trails Making Tests A and B (12), Buschke Immediate and Delayed Recall (13), and Verbal Fluency and Boston Naming (14). Forty-four percent of participants had their first test battery administered at the 12-mo visit, when vitamin K status was measured, and 42% participants completed their first test battery within 2 y of the 12-mo visit. The remaining 14% completed their first test battery 1 y before vitamin K status was measured. Additionally, the Modified Mini-Mental State Examination (3MS), a test of global cognitive function with scores ranging 0–100 (15), was administered ≤10 times over 11 y. The first 3MS test was completed 1 y prior to the vitamin K status measurement, with subsequent 3MS tests administered annually or biannually.

Covariates
The following covariates were measured and/or defined as previously described (11): age, sex, education, race and ethnicity, BMI, diabetes (present/absent), hypertension (present/absent), cardiovascular disease history (present/absent), use of any alcohol (yes/no), smoking history (dichotomized based on having smoked ≥100 cigarettes over the lifetime), estimated glomerular filtration rate (eGFR), urine albumin, systolic and diastolic blood pressure, and triglycerides. For participants missing covariate data from the 12-mo visit, measurements from the baseline or nearest clinic visit were used ($n = 66$ for triglycerides, 46 for eGFR, 16 for BMI, 5 for blood pressure, 5 for alcohol use, and all urine albumin measured at baseline).

Statistical Approach
Plasma phylloquinone was categorized as <0.50, 0.50–0.99, or ≥1.00 nmol/L based on the results of metabolic feeding studies, which indicated that plasma phylloquinone concentrations are approximately 1.0 nmol/L when the vitamin K adequate intake is met (16, 17). Plasma (dp)ucMGP was categorized as <300 (the assay's lower detectable limit), 300–449, or ≥450 pmol/L [the median concentration among those with detectable (dp)ucMGP] (11). Data-driven categories were used since a threshold defining high (dp)ucMGP has not been established. These categories are directly relevant only to the sample from which they were derived.

Baseline characteristics were compared across plasma phylloquinone and (dp)ucMGP categories using analysis of variance or a chi-square test. Cognitive test scores were transformed to z-scores using the mean and standard deviation from the participants' first assessment. The z-scores for the timed Trails A and B tests were multiplied by –1, so higher z-scores reflect better performance on all tests. A composite cognition score was calculated by averaging the z-scores of the Trails A and B, Buschke Immediate and Delayed Recall, and Verbal Fluency and Boston Naming tests, and it served as the primary outcome of the analysis (18). Individual test z-scores and 3MS scores were analyzed as secondary outcomes. 3MS scores were transformed to improve normality by taking the negative of the natural log of 101 minus the 3MS score: $-1*\ln(101 - 3MS)$. Least squares means and 95% CIs were reported in the original units of 3MS (100-point scale). Linear mixed models were used to evaluate the association of vitamin K status with cognitive performance. No interactions of test visit with the primary exposures were detected (all test visit*vitamin K status, $P > 0.34$), so these interactions were not included in the final models and test visit was considered a fixed effect. Additional covariates included age, sex, education, race and ethnicity, BMI, diabetes, hypertension, cardiovascular disease history, alcohol use, smoking, eGFR, urine albumin, systolic and diastolic blood pressure, and triglycerides. Analyses were conducted using SAS version 9.4 (SAS Institute), and $P < 0.05$ was considered statistically significant.

Results

Participants were 64 ± 6 y old (mean ± SD). Forty-nine percent were female, and 44% self-identified as non-Hispanic black. Plasma phylloquinone was positively associated with triglycerides, and 54% of participants with plasma phylloquinone <0.50 nmol/L were non-Hispanic black. Plasma (dp)ucMGP was positively associated with age, female sex, and systolic blood pressure and was inversely associated with eGFR and alcohol use (**Table 1**).

The change in cognitive performance over repeated follow-up tests did not differ across plasma phylloquinone or (dp)ucMGP categories, so the presented results are based on between-group comparisons

TABLE 1 Participant baseline characteristics[1]

	Overall (N = 714)	Plasma phylloquinone, nmol/L[2]				Plasma (dp)ucMGP, pmol/L[2]			
		<0.50 (n = 136)	0.50–0.99 (n = 230)	≥1.00 (n = 347)	P value	< 300 (n = 326)	300–449 (n = 222)	≥450 (n = 166)	P value
Age, y	64 ± 6	64 ± 6	64 ± 5	64 ± 6	0.75	63 ± 5	64 ± 5	65 ± 6	0.01
Female	350 (49)	65 (48)	122 (53)	162 (47)	0.31	139 (43)	116 (52)	95 (57)	0.005
Race and ethnicity					0.0007				0.27
Non-Hispanic white	341 (48)	53 (39)	101 (44)	187 (54)		152 (47)	118 (53)	71 (43)	
Non-Hispanic black	311 (44)	74 (54)	113 (49)	123 (35)		145 (44)	89 (40)	77 (46)	
Other	62 (9)	9 (7)	16 (7)	37 (11)		29 (9)	15 (7)	18 (11)	
Education					0.001				0.008
Less than high school	110 (15)	28 (21)	34 (15)	47 (14)		52 (16)	24 (11)	34 (20)	
High school graduate	139 (19)	28 (21)	51 (22)	60 (17)		58 (18)	46 (21)	35 (21)	
Some college	201 (28)	43 (32)	75 (33)	83 (24)		80 (25)	67 (30)	54 (33)	
College graduate or more	264 (37)	37 (27)	70 (30)	157 (45)		136 (42)	85 (38)	43 (26)	
BMI, kg/m^2					0.72				0.30
≤25	110 (15)	23 (17)	34 (15)	52 (15)		50 (15)	37 (17)	23 (14)	
25–29.9	223 (31)	47 (35)	74 (32)	102 (29)		100 (31)	67 (30)	56 (34)	
30–39.9	292 (41)	49 (36)	90 (39)	153 (44)		141 (43)	93 (42)	58 (35)	
≥40	89 (12)	17 (13)	32 (14)	40 (12)		35 (11)	25 (11)	29 (17)	
Hypertension	648 (91)	124 (91)	216 (94)	307 (88)	0.09	290 (89)	200 (90)	158 (95)	0.07
Diabetes	360 (50)	75 (55)	111 (48)	173 (50)	0.43	164 (50)	101 (45)	95 (57)	0.07
Smoking history: smoked ≥100 cigarettes in lifetime	425 (60)	79 (58)	139 (60)	206 (59)	0.91	198 (61)	124 (56)	103 (62)	0.39
History of CVD	273 (38)	57 (42)	85 (37)	131 (38)	0.62	117 (36)	82 (37)	74 (45)	0.15
Use of any alcohol	431 (60)	78 (57)	139 (60)	214 (62)	0.68	216 (66)	136 (61)	79 (48)	0.0003
Blood pressure, mm Hg									
Systolic	129 ± 22	130 ± 22	131 ± 21	127 ± 23	0.21	127 ± 21	129 ± 21	133 ± 24	0.02
Diastolic	68 ± 12	68 ± 13	69 ± 12	68 ± 12	0.82	69 ± 12	69 ± 13	67 ± 12	0.41
eGFR, mL/min/1.73 m^2	43 ± 16	44 ± 15	40 ± 15	44 ± 16	0.01	47 ± 16	43 ± 15	35 ± 13	<0.0001
Urine albumin, mg/L					0.25				0.01
<30	392 (55)	77 (57)	129 (56)	186 (54)		190 (58)	127 (57)	75 (45)	
30–299	198 (28)	38 (28)	53 (23)	106 (31)		84 (26)	65 (29)	49 (30)	
≥300	124 (17)	21 (15)	48 (21)	55 (16)		52 (16)	30 (14)	42 (25)	
Triglycerides, mg/dL[3]	121 (88)	101 (60)	117 (68)	134 (112)	<0.0001	118 (84)	121 (86)	125 (109)	0.14

[1] Data are reported as mean ± SD or n (%) unless noted otherwise. P values are based on chi-square test for categorical outcomes or ANOVA for continuous outcomes, unless indicated otherwise, and reflect differences in participant baseline characteristics across categories of plasma phylloquinone and plasma (dp)ucMGP. CVD, cardiovascular disease; (dp)ucMGP, dephospho-uncarboxylated matrix Gla protein; eGFR, estimated glomerular filtration rate.

[2] One participant did not have plasma phylloquinone measurement, and a different participant did not have plasma (dp)ucMGP measurement. Therefore, although the total sample size is 714, 713 were included in the analyses of plasma phylloquinone and 713 in the analyses of plasma (dp)ucMGP.

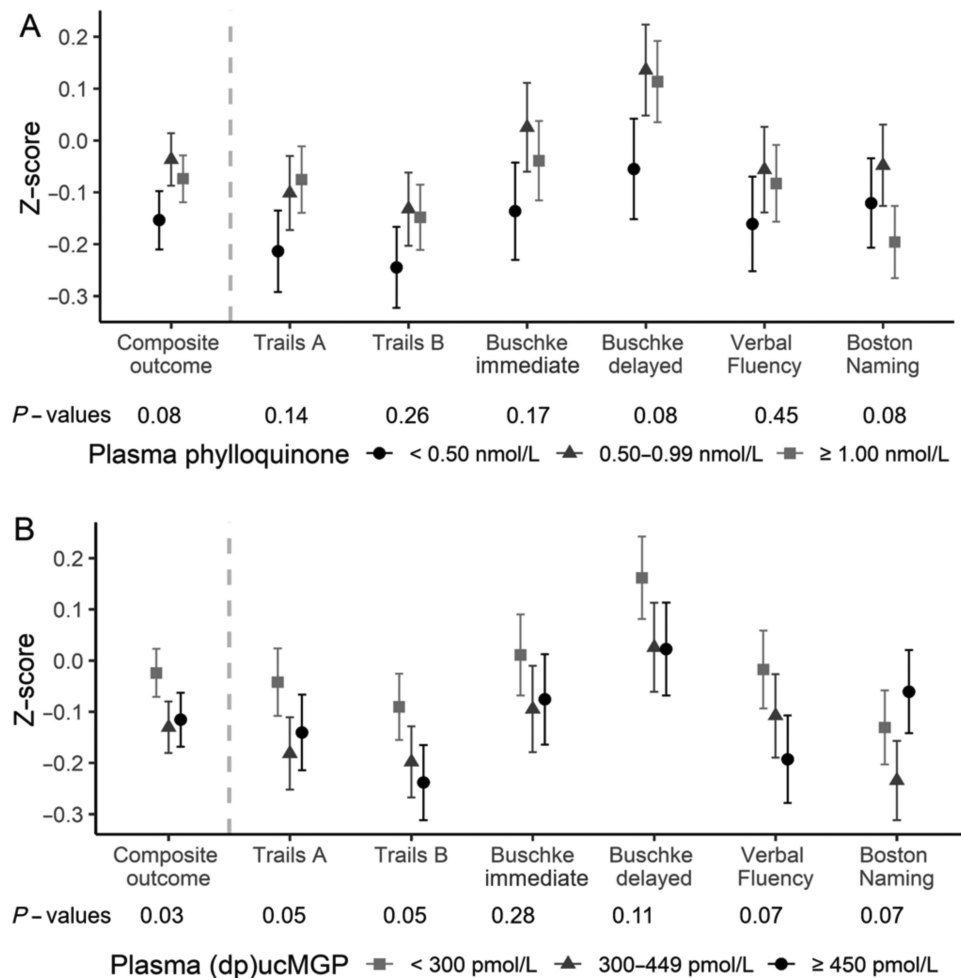[3] Median (IQR). P value based on Kruskal–Wallis test.

FIGURE 1 Composite cognitive z-score and 6 individual test z-scores according to (A) plasma phylloquinone and (B) plasma (dp)ucMGP. Data are least squares means, and error bars are SEM, adjusted for age, sex, education, race and ethnicity, BMI, diabetes, hypertension, cardiovascular disease history, use of any alcohol (yes/no), smoking history (dichotomized by having smoked ≥100 cigarettes over the lifetime), estimated glomerular filtration rate, urine albumin, systolic and diastolic blood pressure, and triglycerides. (dp)ucMGP, dephospho-uncarboxylated matrix Gla protein.

over all administered tests. In unadjusted cross-sectional analyses, participants with plasma phylloquinone <0.50 nmol/L had a significantly lower composite cognitive z-score compared with those with 0.50–0.99 and ≥1.00 nmol/L. However, the association was not statistically significant in fully adjusted models (**Figure 1**). Plasma phylloquinone was not significantly associated with any of the individual cognitive test scores after adjustment for confounders (Figure 1).

Participants with plasma (dp)ucMGP < 300 pmol/L had a significantly higher composite cognitive z score compared with those with 300–449 and ≥ 450 pmol/L in unadjusted and adjusted models (Figure 1). A similar qualitative pattern was observed for the Trails A, Trails B, Buschke Delayed Recall, and Verbal Fluency tests, although none of the associations of the individual test scores achieved statistical significance when adjusted for confounders (Figure 1).

After adjustment for pertinent covariates, the 3MS scores did not differ according to plasma phylloquinone [least squares mean (95% CI): <0.50 nmol/L, 94.6 (93.7, 95.4); 0.50–0.99 nmol/L, 95.0 (94.2,

95.6); ≥1.00 nmol/L, 95.0 (94.4, 95.6); $P = 0.54$] or plasma (dp)ucMGP [<300 pmol/L, 95.2 (94.5, 95.8); 300–449 pmol/L, 94.9 (94.1, 95.5); ≥450 pmol/L, 94.6 (93.7, 95.3); $P = 0.20$].

Discussion

Among adults with CKD, higher plasma phylloquinone and lower plasma (dp)ucMGP concentrations (both reflective of higher vitamin K status) were associated with better global cognitive performance based on the composite cognitive z-score. However, the association with plasma phylloquinone did not reach statistical significance after adjustment for confounders. Neither biomarker was significantly associated with performance on the 3MS or on the individual tests after adjustment for confounders (although some associations bordered significance). The collective results provide initial but incomplete evidence regarding the association of vitamin K status with overall cognitive performance

in adults with CKD. The association with specific cognitive domains needs to be clarified.

We found that participants with lower plasma (dp)ucMGP had significantly better cognitive performance based on the composite z-score, but we are cautious about the interpretation because the 3MS scores did not differ across plasma (dp)ucMGP categories. It is possible that ceiling effects limited our ability to detect associations with 3MS scores. However, plasma phylloquinone (another vitamin K status biomarker) was not significantly associated with any cognitive outcome evaluated, after adjusted for confounders. The only other available study of (dp)ucMGP and cognitive function was conducted in 599 community-dwelling 55- to 65-y-old Dutch adults. Over 6 y of follow-up it found no association between plasma (dp)ucMGP and general cognitive performance (based on a composite z-score that combined information processing speed, episodic memory, and fluid intelligence). Generally healthy 55- to 65-y-olds do not usually experience substantial changes in cognitive status, which may have limited the ability to detect an association in this population (19). The amount of (dp)ucMGP in circulation depends on MGP synthesis, in addition to the availability of vitamin K to carboxylate the protein. It is possible that the association of (dp)ucMGP with cognitive performance is related to factors involved in MGP synthesis, which is independent of vitamin K. Although there is limited evidence from microarray experiments that indicate that MGP is expressed in human brain tissue (20), the extent to which this is reflected by circulating MGP is unknown. It will be important to replicate our findings and elucidate the biological mechanisms through which MGP carboxylation is related to cognitive performance in future studies.

Significant inverse associations between circulating phylloquinone and cognitive performance have been reported. In Irish adults ≥64 y old (mean ± SD age: 78 ± 9 y), higher circulating phylloquinone was associated with higher Mini-Mental State Examination scores (21). In 67- to 84-y-old individuals without apparent cognitive impairment, higher plasma phylloquinone was associated with better verbal episodic memory scores but not with nonverbal episodic memory, executive function, or processing speed (22). In 80- to 90-y-olds without cognitive impairment at baseline, higher plasma phylloquinone was associated with a slower rate of cognitive decline (based on the person-specific change in scores on 19 cognitive tests) (7). It is not clear why our results diverge from previously published studies. It is plausible that there was overall less cognitive impairment due to the younger age of study participants (although all had CKD and nearly all were hypertensive, which can perpetuate cognitive dysfunction) (23). Alternatively, it is possible that the relevance of vitamin K to brain health is not entirely reflected by the amount of phylloquinone in circulation (7). There are multiple forms of vitamin K. Phylloquinone, found in green leafy vegetables and vegetable oils, is the primary circulating form. Menaquinones (vitamin K2) are found in some meat and dairy products and fermented foods because they are bacterially synthesized. There are multiple menaquinone forms, which, with phylloquinone, are converted to menaquinone-4 in brain tissue (24). Menaquinone-4 is the primary form of vitamin K in the human brain (25) but is not typically detected in circulation.

To the best of our knowledge, this is the first study to evaluate the association of vitamin K status with cognitive performance in adults with CKD, a group at risk for cognitive decline. It is strengthened by the well-characterized diverse cohort of individuals with CKD, the administration of tests evaluating multiple cognitive domains, and the use of two biomarkers of vitamin K status. However, there are limitations. The observational design precludes inferring causation. CRIC participants' cognitive test performance generally improved during the follow-up (data not shown), which may be attributable to practice effects (26) and thereby limited our ability to evaluate the association of vitamin K status with cognitive decline. Because vitamin K status was inversely associated with all-cause mortality risk in CRIC (11) and mortality is a competing event for cognitive impairment (27), our findings may be influenced by survivor bias. Gas-6 and protein S are VKD proteins involved in neuronal function (6). Assays that measure the carboxylated and/or uncarboxylated fractions of these proteins are not available, so we utilized (dp)ucMGP as representative of VKD protein carboxylation. Plasma (dp)ucMGP was lower in CRIC compared with other studies of individuals with CKD that used the same assay that we used (28), suggestive of a better vitamin K status, which may have influenced our findings. We excluded vitamin K antagonist users from our analyses, so our results are not generalizable to individuals taking vitamin K antagonist medications.

Although this study's results provide preliminary evidence for general associations of vitamin K status with cognitive function in CKD, additional research is needed to obtain a better understanding of the domains of cognitive function affected by vitamin K.

Acknowledgments

Data Availability

Data described in the article, code book, and analytic code will be made available upon request pending approval of the CRIC Study Steering Committee.

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