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Vitamin K status and physical decline in older adults—The Longitudinal Aging Study Amsterdam

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ABSTRACT

Objective: We examined the association between vitamin K status and physical functioning over 13 years in the Longitudinal Aging Study Amsterdam.
Study design: Longitudinal cohort study of 633 community-dwelling adults from the Longitudinal Aging Study Amsterdam (LASA) aged 55–65 years (54% women).
Main outcome measures: At baseline (2002–2003), plasma desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) was measured with a sandwich ELISA as a marker of vitamin K status. The outcome measures handgrip strength, calf circumference, self-reported functional limitations and functional performance were obtained at baseline and four follow-up examinations. We used generalized estimating equations to determine the relationship between dp-ucMGP tertiles and the various outcome measurements after adjusting for potential confounders. The lowest dp-ucMGP tertile reflects a high vitamin K status and was the reference.
Results: Mean dp-ucMGP was 376 ± 233 pmol/L and mean follow-up was 11.1 years. Participants showed a decline in the outcome measures over time. Compared with the lowest tertile, the highest dp-ucMGP tertile had: lower handgrip strength, 1.1 kg (95% confidence interval (−2.1, −0.1; P-trend < 0.001); smaller calf circumference, −0.5 cm (−0.9 −0.1; P-trend = 0.018); and, only among women, a 0.7-point poorer functional performance score (−1.1, −0.3; P-interaction = 0.002). Dp-ucMGP was not related to self-reported functional limitations. No interaction effects between time and dp-ucMGP were observed.
Conclusions: Low vitamin K status was associated with lower handgrip strength, smaller calf circumference, and, in women only, with poorer functional performance score. A low vitamin K status was however not related to the 13-year decline in these measures.

1. Introduction

Recently, there has been wide interest in the function of the fat-soluble vitamin K. Vitamin K_1 is the primary source of vitamin K in our diet. It is present in green leafy vegetables, algae and plant oils. Vitamin K_2 comes in lower quantities, but has a longer half-life and data suggest a higher absorption and bioavailability than vitamin K_1 [1]. It is present in meat, eggs, fermented dairy products and in limited amounts it can be formed by bacteria in the gut from vitamin K_1 [2].

Besides its well-known role in blood coagulation, vitamin K also plays an important role as cofactor in the carboxylation of vitamin-K dependent proteins present in vascular and skeletal tissue [3]. Matrix Gla (γ-carboxyglutamate) protein (MGP) is a vitamin K-dependent protein in the vascular wall, which requires vitamin K for posttranslational carboxylation and both carboxylation and phosphorylation for full activation [4]. MGP inhibits vascular calcification by binding to calcium [5,6]. This suggests that sufficient vitamin K is required for optimal vascular health. Vitamin K deficiency leads to higher amounts of uncarboxylated (inactive) fragments of MGP, and can be measured by plasma desphospho-uncarboxylated matrix Gla protein (dp-ucMGP) concentrations [7].

Several cross-sectional studies observed that high dp-ucMGP concentrations, indicative for a low vitamin K status, were associated with higher concentrations of inflammatory markers [8] renal function decline [9] and coronary heart disease [10] and below-knee arterial calcification [11]. A prospective study observed that low plasma vitamin K_1 was associated with a 1.6 (1.1–2.3) higher risk of incident knee osteoarthritis after 2.5 years follow-up [12]. Another prospective study

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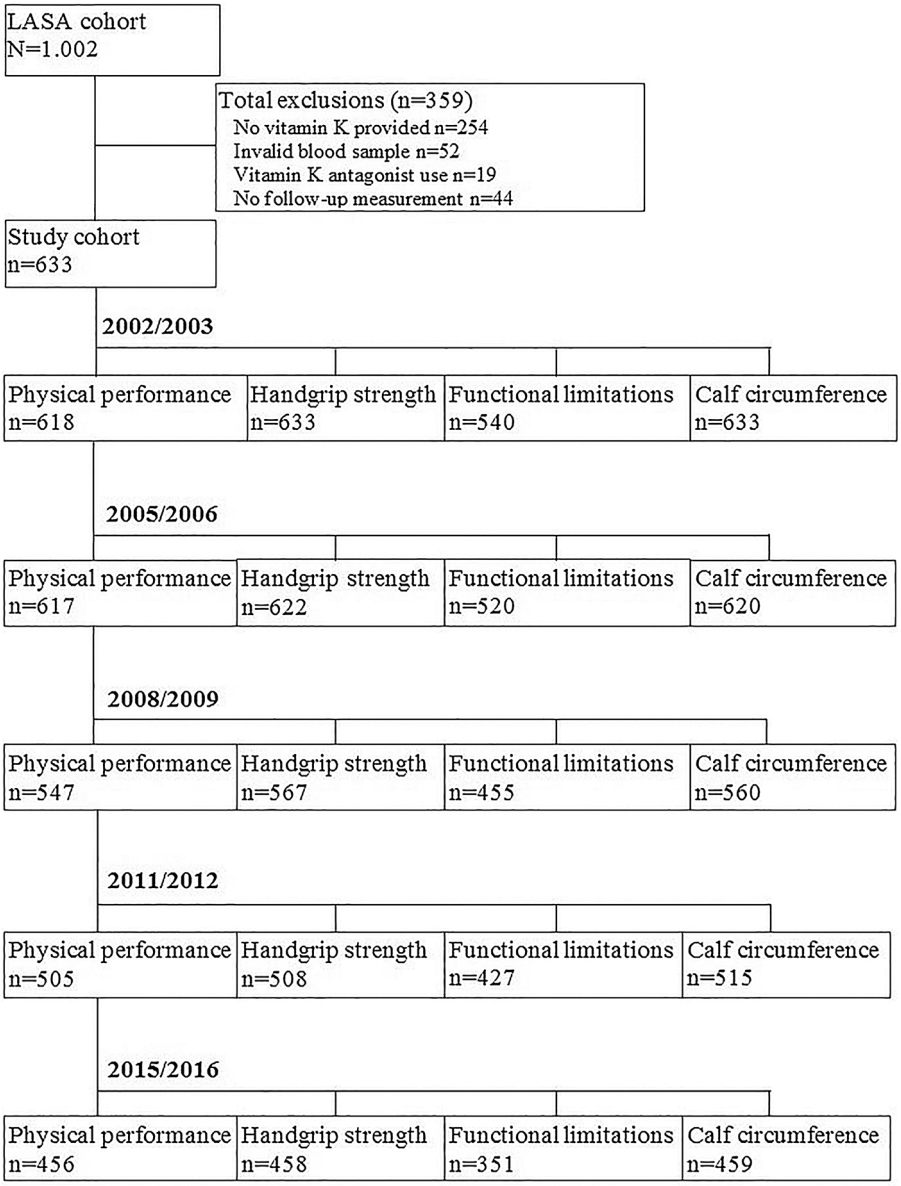

Fig. 1. Flow diagram of LASA participants per physical functioning outcome for each follow-up measurement between 2002 and 2016.

observed that both phylloquinone and dp-ucMGP were associated with better functional performance scores and faster gait speed at baseline, however, after 4–5 years, neither vitamin K measure was associated with the change in these outcomes [13].

Vitamin K-dependent mechanisms are involved in calcium metabolism, and as a consequence of vitamin K deficiency, high dp-ucMGP concentrations attenuate vascular calcium deposition [14–17]. This leads to multiple comorbidities associated with functional decline such as cartilage degeneration and vascular calcification. Hence, these findings suggest that vitamin K deficiency may impair neuromuscular as well as vascular function, which may negatively influence physical functioning. Further, vitamin K promotes vascular smooth muscle differentiation and has beneficial effects on both the large and small arteries, which may lead to a better perfusion of muscle tissue [18].

Most previous studies were cross-sectional and the relationship with physical functioning is largely unknown [8–13]. Therefore, we examined the longitudinal association between plasma dp-ucMGP and physical functioning over 13 years in the Longitudinal Aging Study Amsterdam.

2. Subjects and methods

2.1. Design and participants

We used data from the Longitudinal Aging Study Amsterdam (LASA). LASA is an ongoing population-based study in Dutch adults that started in 1992 to determine predictors and consequences of aging. A detailed description of the cohort sampling and data collection procedures has been described elsewhere [19]. Briefly, men and women aged 55–85 years were recruited by LASA personnel using registers of 11 municipalities in 3 geographical areas (Amsterdam/Zwolle/Oss) in the Netherlands. The sample was randomly selected from municipal registries in 1992, with an oversampling of the oldest old and older men. The initial response rate was 60% (n = 3805). At each examination, 2 interviews were conducted: a main interview and a medical interview with clinical measurements about 4–6 weeks apart.

For this present study, we included participants from the second cohort, which started in 2002–2003. This cohort consisted of 1002 men and women (aged 55–65 years). Four follow-up measurements took place in 2005/2006, 2008/2009, 2011/2012 and 2015/2016. We

Table 1
Baseline characteristics of 643 LASA participants stratified by plasma dp-ucMGP tertiles.

	Dephosphorylated uncarboxylated matrix gla protein		
	Low < 272 pmol/L	Medium 274–415 pmol/L	High ≥ 416 pmol/L
	N = 220	N = 216	N = 197
Demographic			
Age (years)	59.6 ± 2.9	59.7 ± 2.9	60.2 ± 3.0
Women	116(47%)	112(52%)	114(58%)
Education			
Low	87 (40%)	99 (46%)	83 (42%)
Intermediate	81 (37%)	74 (34%)	76 (39%)
High	52 (24%)	43 (20%)	38 (19%)
Lifestyle			
Physical activity (min/day)	135 (84–222)	161 (93–231)	152 (100–226)
BMI (kg/m^2)	26.3 ± 3.6	26.9 ± 3.8	28.7 ± 4.6
Smoking status			
Never	125 (57%)	116 (54%)	116 (59%)
Former	35 (16%)	38 (17%)	39 (20%)
Current	60 (27%)	62 (29%	42 (21%)
Alcohol consumption			
Non-drinker	3 (1%)	8 (4%)	4 (2%)
Light drinker	117 (53%)	98 (45%)	104 (53%)
Moderate drinker	78 (36%)	87 (40%)	70 (35%)
(Very) excessive drinker	22 (10%)	23 (11%)	19 (10%)
Disease state			
Hypertension	40 (18%)	45 (21%)	57 (29%)
Osteoarthritis	64 (29%)	66 (31%)	63 (32%)
Type 2 diabetes	11 (5%)	9 (4%)	17 (9%)
Number of chronic diseases (0–7)	0.6 ± 0.8	0.6 ± 0.7	0.8 ± 0.9
Metabolic			
SBP (mmHg)	137 ± 21.3	141 ± 21.2	142 ± 28.5
DBP (mmHg)	82.2 ± 11.0	83.7 ± 11.9	84.4 ± 15.6
25(OH)D (nmol/L)	57.5 ± 21.2	55.5 ± 19.2	59.1 ± 20.8
eGFR (ml/min/ 1.73m^2)	72.2 ± 10.9	71.3 ± 12.6	67.5 ± 11.8
Dp-ucMGP (pmol/L)	186 ± 60	344 ± 40	622 ± 257
Physical functioning			
Handgrip strength (kg)	35.8 ± 11.1	34.9 ± 11.6	34.3 ± 11.7
≥1 functional limitation	30 (15%)	28 (15%)	35 (21%)
Physical performance (0–12)	9.3 ± 2.0	9.1 ± 2.3	8.8 ± 2.3
Calf circumference (cm)	37.1 ± 2.8	37.2 ± 2.9	37.9 ± 3.2

Note: Values are mean ± SD or median and interquartile range. Abbreviations: dp-ucMGP: dephosphorylated uncarboxylated Matrix Gla protein, SBP: systolic blood pressure, DBP: Diastolic blood pressure, eGFR: estimated glomerular filtration rate.

excluded 369 participants from our analysis: n = 254 no blood sample, n = 52 no vitamin K measurement, and n = 19 used vitamin K antagonists. Further, we excluded participants with no follow-up measurements for physical functioning n = 44.

The analytical sample for the current analysis contained 633 LASA participants with at least 1 follow-up measurements. Excluded participants (n = 369) had more often type 2 diabetes (10% vs. 6%), number of chronic diseases (range 0.9 vs. 0.7), were more current smokers (40% vs. 26%) and more excessive alcohol drinkers (15% vs. 10%) $P < 0.008$. The study was approved by the Ethics Review Board of the VU University Medical Center, and informed consent was obtained from all respondents.

Table 2
Longitudinal associations between baseline plasma dp-ucMGP tertiles with handgrip strength, calf circumference, and self-reported functional limitations over 13 years follow-up.

	Model 1	Model 2
Dp-ucMGP tertiles (pmol/L)	**Handgrip strength (kg)** N = 633	
Low	0.0	0.0
Medium	−0.8 (−1.8, 0.2)	−1.0 (−1.9, 0.0)
High	−0.7 (−1.7, 0.3)	−1.1 (−2.1, −0.1)
P-trend	0.141	0.022
P-time	< 0.001	< 0.001
	Calf circumference (cm) N = 633	
Low	0.0	0.0
Medium	0.1 (−0.4, 0.6)	−0.3 (−0.6, 0.1)
High	0.9 (0.3, 1.5)	−0.5 (−0.9, −0.1)
P-trend	0.003	0.018
P-time	0.071	0.111
	≥1 functional limitation N = 540	
Low	1.0	1.0
Medium	1.2 (0.8, 1.8)	1.0 (0.6, 1.6)
High	1.8 (1.2, 2.8)	1.3 (0.8, 2.2)
P-trend	0.005	0.230
P-time	< 0.001	< 0.001

Note: Values for handgrip strength and calf circumference are regression coefficients with 95% confidence intervals analyzed with generalized estimating equations. For ≥1 functional limitation values represent odds ratios with 95% confidence intervals.
dp-ucMGP: dephosphorylated uncarboxylated matrix gla protein.
Model 1: adjusted for time (years) and age (years) and sex.
Model 2: additionally adjusted for number of chronic diseases, BMI (kg/m^2), education (low/intermediate/high), alcohol consumption (non/light/moderate/excessive), smoking status (never/former/current), physical activity (min/day), diabetes (yes/no), hypertension (yes/no), vitamin D (nmol/l) and eGFR (ml/min/1.73 m^2).

2.2. Vitamin K status

At baseline (2002–2003) LASA study personnel collected morning blood samples during a medical interview in a non-fasted state and samples were shipped to the VU University Medical Center before.

Blood samples were centrifuged and stored at −80° until analysis in 2010–2011 and shipped to the laboratory of VitaK, Maastricht to estimate dp-ucMGP concentrations. Plasma dp-ucMGP was measured with a sandwich (dual antibody) ELISA, with the capture antibody directed against the non-phosphorylated MGP sequence 3–15 and the detecting antibody directed against the uncarboxylated MGP sequence 35–49 (mAbucMGP; VitaK, Maastricht, the Netherlands). High dp-ucMGP concentrations reflect a low vitamin K status. The reported intra- and inter-assay variation for plasma dp-ucMGP were 5.6 and 9.9%, respectively [7].

2.3. Physical functioning

Handgrip strength is measured with a hand-held dynamometer adjusted for hand size to the nearest 1 kg (Takei TKK 5401, Takei Scientific Instruments, Tokyo, Japan). The measurements were performed in duplicate for both hands and calculated as the mean of both hands in kilogram. Handgrip strength is commonly used as an indicator of muscle strength, and is positively related to lower-extremity strength [20].

Calf circumference is used as an indicator of skeletal muscle mass, and is associated with higher strength [21]. Trained interviewers measured calf circumference to the nearest 1 mm on the left leg with the participant standing straight, feet 20 cm apart, body weight equally distributed on both feet, at the widest circumference of the calf.

Self-reported functional limitations was measured with a questionnaire adapted from the Organization for Economic Cooperation and

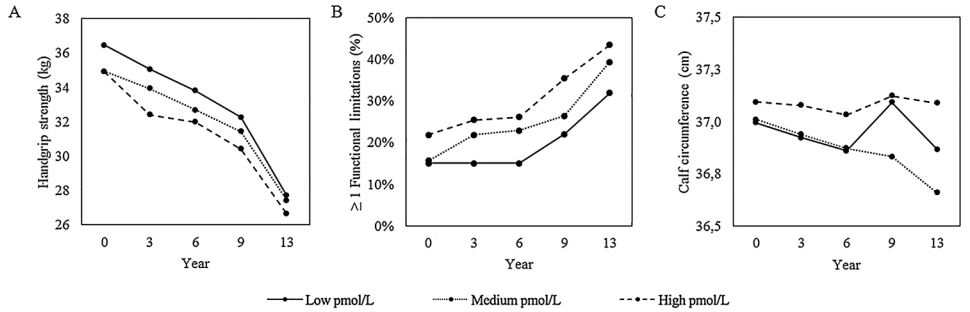

Fig. 2. Mean values of (A) handgrip strength (B) ≥1 functional limitation (C) calf circumference by dp-ucMGP tertiles.
Low dp-ucMGP solid line, medium dp-ucMGP dotted line, high dp-ucMGP dashed line.
Data are presented as means (handgrip strength/calf circumference N = 633) or cross-sectional percentages (≥1 functional limitation, N = 540) adjusted for time (years), age (years), sex, number of chronic diseases, BMI (kg/m^2), education (low/intermediate/high), alcohol consumption (non/light/moderate/excessive), smoking status (never/former/current), physical activity (min/day), diabetes (yes/no), hypertension (yes/no), vitamin D (nmol/L) and eGFR (ml/min/1.73 m^2)

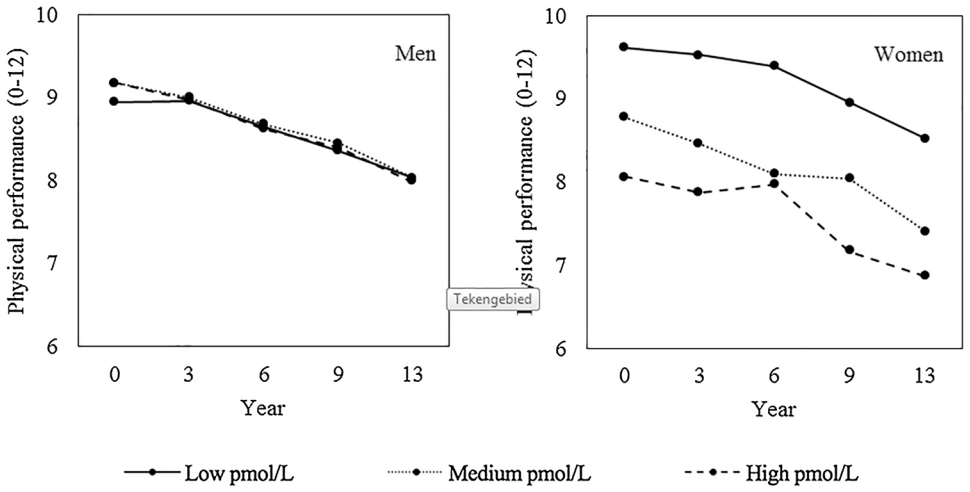

Fig. 3. Sex-stratified mean values of physical performance score by dp-ucMGP tertiles.
Low dp-ucMGP solid line, medium dp-ucMGP dotted line, high dp-ucMGP dashed line (N = 286 men, N = 332 women).
Data are presented as means adjusted for time (years), age (years), number of chronic diseases, BMI (kg/m^2), education (low/intermediate/high), alcohol consumption (non/light/moderate/excessive), smoking status (never/former/current), physical activity (min/day), diabetes (yes/no), hypertension (yes/no), vitamin D (nmol/L) and eGFR (ml/min/1.73 m^2)

Table 3
Longitudinal associations between baseline plasma dp-ucMGP tertiles and functional performance over 13 years follow-up.

	Physical performance (0–12)			
	Men N = 286		Women N = 332	
	Model 1	Model 2	Model 1	Model 2
dp-ucMGP tertiles (pmol/L)				
Low	0.0	0.0	0.0	0.0
Medium	0.1 (−0.4, 0.5)	0.0 (−0.3, 0.4)	−0.8 (−1.3, −0.3)	−0.6 (−1.0, −0.2)
High	0.1 (−0.3, 0.6)	0.1 (−0.3, 0.5)	−1.1 (−1.6, −0.6)	−0.7 (−1.1, −0.3)
P-trend	0.601	0.701	< 0.001	0.002
P-time	< 0.001	< 0.001	< 0.001	< 0.001

Note: Values are regression coefficients and 95% confidence intervals analyzed with generalized estimating equations.
dp-ucMGP: dephosphorylated uncarboxylated matrix gla protein.
Model 1: adjusted for time (years) and age (years).
Model 2: additionally adjusted for number of chronic diseases, BMI (kg/m^2), education (low/intermediate/high), alcohol consumption (non/light/moderate/excessive), smoking status (never/former/current), physical activity (min/day), diabetes (yes/no), hypertension (yes/no), vitamin D (nmol/l) and eGFR (ml/min/1.73 m^2).

Development (OECD) questionnaire and validated by Statistics Netherlands. Participants were asked whether they have difficulty performing 7 common daily activities: 1) walk up and down a 15-step staircase without resting, 2) dress and undress oneself, 3) sit down and get up from a chair, 4) cut their own toenails, 5) walk 5 min outside without resting, 6) drive or use public transport 7) take a bath/shower. The total score ranged from no limitation to limitations for all functions (stairs/transport/toenails/dress/chair/walk/shower) score 0–7.

Functional performance was assessed with 3 objective functioning tests. For the walk test, the participants were asked to walk 3 m, turn 180°, and walk back 3 m. For the chair-stand test participants were asked to fold their arms across their chest and stand up from a sitting position and sit down 5 times. The cardigan test measures upper extremity function. The participants were asked to put on and take off a cardigan. The scores of the tests for all follow-up measurements were based on quartiles of the time required at baseline. Participants unable to perform the test scored 0. By summing up the scores of the individual performance tests, the total physical performance score ranges from low to high physical performance (0–12).

2.4. Baseline covariates

LASA interviewers obtained comprehensive data on participants' demographics, anthropometrics and co-morbid conditions. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured without clothes and shoes to the nearest 0.1 kg using a calibrated bathroom scale. Corrections have been made to adjust measured weight for clothing (−2 kg) or a corset (−1 kg). Body mass index (BMI) was calculated by dividing body weight by height squared (kg/m^2).

A self-administered questionnaire was used to assess participants' education level, smoking status, alcohol use and physical activity level. Education was reported on a 9-category scale. We distinguished education into 3 categories: low (elementary school or less), medium (lower vocational or general intermediate education) and high (intermediate vocational education, general secondary school, higher vocational education, college or university). Smoking status was categorized as never, former and current smoker. Alcohol use was based on the number of days and amount of alcohol used characterized into 3 categories: none/light (0–3 glasses/week), moderate (4–7 glasses/week), excessive or very excessive (≥8 glasses/week) according to the Garretsen index.

The number of chronic diseases was based on self-report of the most frequent somatic chronic diseases in the Netherlands. Physical activity was assessed using the validated LASA physical activity questionnaire in minutes per day by multiplying the frequency and duration of each activity in the previous 2 weeks, and summing these values across activities [19].

Furthermore, we estimated glomerular filtrate rate from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration 2009 equation, as indicator of kidney function. For vitamin D status, serum 25(OH)D concentrations were determined using a radioimmunoassay (DiaSorin, Stillwater, Minnesota, USA). The inter-assay coefficient of variation was 10.0%. All biochemical analyses were carried out by the Endocrine Laboratory of the VU University Medical Center Amsterdam [19].

2.5. Statistical analysis

We divided dp-ucMGP concentrations into tertiles with the first tertile as reference for all analyses indicating high vitamin K status as no validated cut-off values for dp-ucMGP are established yet. Baseline characteristics stratified by plasma dp-ucMGP concentrations were reported as mean and standard deviation for normally distributed variables and skewed variables were reported as median and interquartile range. Categorical variables are presented as number and percentage.

Functional limitations were dichotomized into ≥1 functional limitation vs. no limitation as the reference group. Physical performance was used as a continuous variable.

To determine the longitudinal relationship between the dp-ucMGP tertiles and physical functioning, we used a generalized estimating equation analysis to estimate regression coefficients or in case of functional limitations odds ratios (OR) with 95% confidence intervals from the WALD-test adjusting for potential confounders. We used an exchangeable correlation structure because of the close correlation between follow-up examination within participants [22].

A minimally adjusted model included dp-ucMGP, adjusted for follow-up time (years) and baseline age and sex (model 1). Model 2 additionally included baseline number of chronic diseases, BMI (kg/m^2), education (low/intermediate/high), alcohol consumption (non/light/moderate/excessive), smoking status (never/former/current), physical activity (min/day), depression (CES-D 0–6), type 2 diabetes (yes/no), hypertension (yes/no), vitamin D (nmol/L) and estimate glomerular filtration rate (ml/min/1.73 m^2).

Sex was tested as potential effect modifier because of previously observed sex differences for vitamin K supplementation and insulin by including an interaction term (dp-ucMGP*sex) in both unadjusted and adjusted models [23]. In case of significant effect modification ($P < 0.10$), stratified analyses were performed.

To measure the rate of decline in physical functioning by dp-ucMGP tertiles, an interaction term dp-ucMGP*time was added to the model. *P*-for-trend was calculated over the dp-ucMGP tertiles using dp-ucMGP tertiles as continuous exposure. We performed data analysis using SPSS Statistics 23.0 with 2-sided *P*-values of 0.05.

3. Results

3.1. Study population

Of the 633 participants, the mean age was 59.9 ± 2.9 years and 54% (n = 342) were women. Mean BMI was 27.3 ± 4.2 kg/m^2, 26% were current smokers and 43% had a lower education level.

During a mean follow-up of 11.1 years (range 3–13), 432 participants completed all four subsequent examinations, 81 participants completed three, 64 participants completed two, and 56 participants completed one follow-up examination (Fig. 1).

3.2. Dp-ucMGP concentrations

Plasma dp-ucMGP was slightly skewed to the right with mean concentrations of 376 ± 233 pmol/L. Plasma dp-ucMGP was divided into tertiles: low: < 272 pmol/L, medium: 274–415 pmol/L and high ≥416 pmol/L dp-ucMGP (Table 1). Participants in the highest dp-ucMGP tertile were slightly older, more often women, more likely to have a higher BMI, and had more chronic diseases.

3.3. Longitudinal associations physical functioning

All groups declined in handgrip strength over time (*P*-time < 0.001), but participants in the lowest dp-ucMGP tertile had the greatest handgrip strength (Table 2/Fig. 2). After adjusting for confounders, the medium and highest tertile were associated with lower handgrip strength: regression coefficient −1.0 kg (95% confidence interval −1.9, 0.0) and −1.1 kg (−2.1, −0.1) respectively, *P*-trend = 0.022.

The relationship between dp-ucMGP tertiles was positively associated with greater calf circumference in model 1, but showed a reversed trend in the fully adjusted model: −0.3 (−0.6, 0.1) and −0.5 (−0.9, −0.1), *P*-trend = 0.018 for the medium and highest dp-ucMGP tertiles, respectively.

For the relationship between dp-ucMGP tertiles and functional limitation, we observed a gradual increase in the unadjusted percentage of ≥1 functional limitations (*P*-time < 0.001). In the fully adjusted model, the relationship between dp-ucMGP tertiles attenuated and was no longer significant: OR 1.0 (0.6–1.6) and 1.3 (0.8–2.2) for the medium and high dp-ucMGP tertiles, respectively. No significant interaction was observed by sex in the relationship between dp-ucMGP tertiles with handgrip strength, calf circumference and ≥1 functional limitation (*P*-interaction > 0.165). In none of the models, the interaction dp-ucMGP*time with handgrip strength, calf circumference and ≥1 functional limitation was significant (P-decline > 0.208), indicating no difference in decline of physical functioning by dp-ucMGP tertiles.

Sex was a significant effect modifier in the relationship between dp-ucMGP and physical performance (*P*-interaction < 0.001). Both men and women, decreased in physical performance over time (*P*-time < 0.001) (Fig. 3). For women, higher dp-ucMGP concentrations were associated with lower physical performance scores in the fully adjusted model: medium tertile −0.6 (−1.0, −0.2), high tertile −0.7 (−1.1, −0.3), *P*-trend = 0.002 (Table 3), but the interaction term for decline was not significant (*P*-decline = 0.812). No statistically significant associations were observed between dp-ucMGP and physical performance in men.

4. Discussion

We examined whether vitamin K status, measured by plasma dp-ucMGP, was associated with physical functioning over a period of 13 years. Our findings show that higher dp-ucMGP concentrations, indicating a lower vitamin K status, were associated with lower handgrip strength and calf circumference. In the relationship between dp-ucMGP with physical performance, effect modification was present. In women, not in men, higher dp-ucMGP was related to lower physical performance scores. The rate of decline was not significantly different by dp-ucMGP tertiles for any physical functioning measure.

Our findings suggest that higher dp-ucMGP is associated with lower handgrip strength, calf circumference, and with better physical performance in women. Particularly, handgrip strength is an essential component of physical functioning [20]. We observed meaningful differences in physical performance scores in women (low vs. high dp-ucMGP tertile −0.7 (−1.1, −0.3) since a clinical meaningful change in physical performance score is between 0.4-1.5 points on a 12-point scale [24]. Overall, our results suggest that optimal vitamin K concentrations are an important determinant for physical functioning in

old age.

Our study is the first that investigated vitamin K status in relation with physical functioning over long-term follow-up in older adults. In the Health-ABC study, both phylloquinone and dp-ucMGP were associated with better functional performance (using short physical performance battery) scores) and greater 20 m gait speed, however, the results attenuated after 4–5 years follow-up and none of the vitamin K status measures were associated with decline in walking speed or functional performance [13]. Up to now, only one randomized controlled trial has been conducted of vitamin K supplementation using physical functioning as an outcome. A daily dose of 100 μg of vitamin K_2 versus placebo for 6 months did not improve handgrip strength and the short physical performance battery in participants ≤70 years with established vascular disease [25]. It should be noted that these physical function measures were secondary outcomes of the trial.

Our findings indicate that dp-ucMGP was not associated with physical functioning when measured with performance tests in men. To our knowledge, no other study observed effect modification for sex between vitamin K status and physical performance. Previous studies indicate that the function and absorption of vitamin K is not sex specific [26], however, vitamin K supplementation only reduced progression of insulin resistance in men [23]. Hormonal differences may act differently for physical functioning measures and might be an explanation for our observed interaction effect. Another explanation might be sex-differences in body composition. Lower vitamin K status is associated with increased body fat in older adults, which is more evident in women [27]. Also, lifestyle factors might play a role in the relationship between vitamin K status and physical functioning. In our study, more men were excessive alcohol drinkers; 19% vs. 3%), smokers (31% vs. 21%) and were less physically active (228 min/day vs. 336 min/day; $P < 0.001$), compared to women. It is plausible that a high vitamin K status reflects a healthy diet and lifestyle, as the primary source of vitamin K are characteristics of a healthy diet.

4.1. Strength and limitations

The strengths of this study include the comprehensive phenotyping and long-term follow-up with 68% of the sample attending all follow-up examinations. We used a comprehensive set of physical functioning measures assessed in a standardized way minimalizing potential bias and misclassification. This contributes to an extensive understanding of the role of vitamin K in physical function, which is related to daily functioning. Moreover, we used plasma dp-ucMGP as a marker of vitamin K status. Previous research has shown that plasma dp-ucMGP is a reliable marker to determine overall vitamin K status [7]. In addition, plasma dp-ucMGP has advantages over plasma phylloquinone (vitamin K_1), which only reflects recent intake, and plasma menaquinone (vitamin K_2), which is often below detection limit in the general population [3].

This study also has some limitations. The excluded participants were older, had more often chronic diseases, were more current smokers, excessive alcohol drinkers, and therefore, the observed associations in a relatively healthier group might have been underestimated. In addition, dp-ucMGP is only measured at baseline, and it is unknown if vitamin K intake would be stable over 13 years follow-up. Since multiple mechanisms are involved in physical functioning, future studies would benefit from measuring multiple vitamin K status markers to discriminate between different mechanisms including the total amount of MGP. Also, no nutritional information was available. It is possible that participants with a low vitamin K status also have other nutritional deficiencies that potentially influence physical functioning [28].

4.2. Public health implications

Our findings implicate that dp-ucMGP may be associated with physical functioning, which may have important public health implications. A sufficient vitamin K status can be obtained with a balanced diet, which includes vitamin K rich foods such as green leafy vegetables, animal and fermented dairy products such as meat, eggs, yoghurt and cheese. The adequate intake by the European Food Safety Authority panel is set on 1 μg vitamin K_1 per kg body weight per day [29], however adequate controlled feeding trials are needed to accurately determine the amount of vitamin K that is required to achieve any level of vitamin K status. Future studies are needed to determine whether vitamin K rich foods or vitamin K supplementation could improve physical functioning in those with vitamin K insufficiency and clarify underlying mechanisms.

5. Conclusion

A low vitamin K status was associated with lower handgrip strength, smaller calf circumference and in women a low vitamin K status was related to poorer physical performance. A low vitamin K status was however not related to the 13 year decline in these measures.

Contributors

Adriana J. van Ballegooijen conceived and designed the experiments, contributed to data collection, analysed the data and wrote the paper.

Sinony R. van Putten contributed to data collection, analysed and interpreted the data, and wrote the paper.

Marjolein Visser designed and performed the experiments, contributed to data collection, interpreted the data, and revised the manuscript for intellectual content.

Joline W. Beulens contributed to data collection, analysed and interpreted the data, and revised the manuscript for intellectual content.

Emiel O. Hoogendijk designed and performed the experiments, contributed to data collection, interpreted the data, and revised the manuscript for intellectual content.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

The study was approved by the Ethics Review Board of the VU University Medical Center. The work described was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and informed consent was obtained from all participants.

Provenance and peer review

This article has undergone peer review.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available on request.

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