High Vitamin K Status is Prospectively Associated with Decreased Left Ventricular Mass in Women: The Hoorn Study

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Abstract

Background: Vitamin K is associated with reduced cardiovascular disease risk such as heart failure, possibly by carboxylation of matrix-gla protein (MGP), a potent inhibitor of vascular calcification. The relationship of vitamin K intake or status with cardiac structure and function is largely unknown. Therefore this study aims to investigate the prospective association of vitamin K status and intake with echocardiographic measures.

Methods: This study included 427 participants from the Hoorn Study, a population-based cohort. Vitamin K status was assessed at baseline by plasma desphospho-uncarboxylated MGP (dp-ucMGP) with higher concentrations reflecting lower vitamin K status. Vitamin K intake was assessed at baseline with a validated food-frequency questionnaire. Echocardiography was performed at baseline and after 7.6 years follow-up. We used linear regression for the association of vitamin K status and intake with left ventricular ejection fraction (LVEF), left atrial volume index (LAVI) and left ventricular mass index (LVMI), adjusted for potential confounders.

Results: The mean age was 66.8±6.1 years (51% were male). A high vitamin K status was prospectively associated with decreased LVMI -5.0 (-10.5;0.4) $g/m^{2.7}$ for the highest quartile compared to the lowest in women (*P*-interaction sex=0.07). No association was found in men. Vitamin K status was not associated with LVEF or LAVI. Intakes of vitamin K were not associated with any of the echocardiographic measures.

Conclusions: This study indicates that a high vitamin K status is associated with decreased LVMI only in women. These results extend previous findings for a role of vitamin K status to decrease heart failure risk.

Introduction

Vitamin K is a fat-soluble vitamin occurring in two biologically active forms; phylloquinone (vitamin K_1) and menaquinones (vitamin K_2) (1). Vitamin K_1 is mainly derived from green leafy vegetables, while vitamin K_2 mainly occur in fermented animal products like cheese and meat. Vitamin K functions a co-factor for carboxylation (activation) of gla-proteins.

Matrix-gla protein (MGP) is a vitamin-K dependent protein and a potent inhibitor of vascular calcification (2). Luo et al. showed that MGP knock-out mice died within 6–8 weeks due to massive calcification (2). In humans, the Keutel syndrome, resulting from a loss-of-function mutation, is associated with vascular calcification (3). Use of vitamin K antagonists is also associated with increased vascular calcification in animal models (4, 5). Similarly, a high vitamin K intake has been associated with a reduced risk of vascular calcification and cardiovascular diseases (CVD) in prospective population-based cohorts (6). Finally, animal and human intervention studies showed that vitamin K supplementation may reduce vascular calcification by carboxylating MGP (7–9).

Uncarboxylated MGP, as measured by desphospho-uncarboxylated MGP (dp-ucMGP) has been suggested as a marker for vitamin K status, with high concentrations indicating a low vitamin K status (7). High

concentrations of dp-ucMGP have been associated with increased vascular calcification (10) and risk of cardiovascular outcomes (11, 12), although the results are inconsistent (13, 14). Dalmeijer et al. showed that high concentrations of dp-ucMGP were associated with increased risk of CVD and especially with heart failure (HF) (10).

Studies on the relationship of vitamin K intake or status with cardiac structure and function are, however, scarce. In patients with HF, high dp-ucMGP concentrations were associated with the degree of left ventricular (LV) systolic dysfunction (15) and with mortality (16). Conversely, a high vitamin K intake has been associated with a reduced HF mortality (17). Finally, three cross-sectional studies investigated the relation of vitamin K status with cardiac function. Among patients with aortic stenosis, high concentrations of dp-ucMGP were associated with reduced left ventricular ejection fraction (LVEF) (18). Hashmath et al. showed that patients with HF had a lower vitamin K status than controls (19). Finally, Wei et al. showed that high dp-ucMGP concentrations were associated with LV diastolic dysfunction at echocardiography(20). However, prospective studies investigating the relationship between vitamin K status and intake with cardiac structure and function are currently lacking.

Therefore, the aim of this study is to investigate the association of vitamin K status and vitamin K intake with cardiac structure and function in a prospective, population-based cohort, the Hoorn Study.

Materials/ Subjects And Methods

Study population

The Hoorn Study is a prospective observational cohort study in Dutch older adults (N = 2,484) initiated in 1989. Detailed information on the research design, procedures and methods, has been published previously (21). We included 831 participants of the Hoorn Study, who participated in extensive cardiovascular examinations between 2000–2001, considered as baseline. This group was oversampled for individuals with impaired glucose tolerance (IGT) and type 2 diabetes mellitus to enable investigation of effect modification by glucose tolerance status (21). After 8 years of follow-up (2007–2009), a repeated echocardiogram was obtained in 438 participants (details about loss to follow up are displayed in Additional File 1).

Participants with unsatisfactory echocardiograms at follow-up, and with missing data on vitamin K status or intake for the respective analyses were excluded, resulting in 405 participants for analyses on vitamin K status and 427 participants for analyses on intake (Additional File 1). We did not have complete data on all three echocardiographic outcomes, which resulted in different analytic samples for each outcome measure with N = 301 for LVEF, N = 309 for LV mass index (LVMI) and of N = 324 for left atrial volume index (LAVI) for vitamin K status and of N = 312 for LVEF, N = 324 for LVMI and N = 335 for LAVI for vitamin K intake. All participants provided written informed consent and the local ethics committee of the VU University Medical Center approved the study.

Vitamin K status

Study personnel collected morning blood samples in a 8–12 h fasted state. Samples were stored at -80°C until assessment of biochemical measures. Vitamin K status was measured at baseline by plasma dp-ucMGP concentrations using a sandwich ELISA with the capture of antibody directed against the nonphosphorylated MGP sequence 3 to 15 (mAb-dpMGP; VitaK BV, Maastricht, the Netherlands). High levels of dp-ucMGP reflect a low vitamin K status (7). The interassay coefficient of variation was 9.9%.

Vitamin K intake

At baseline, dietary intake was assessed using a self-administered validated food frequency questionnaire (FFQ) (22), allowing the estimation of the average daily intake of 178 foods over 77 main food categories in the year preceding enrolment.. The 1993 Dutch food consumption table (NEVO) was used to calculate energy and nutrient intakes (23). This table does not include information on vitamin K content of all food products. Therefore, the vitamin K_1, short chain vitamin K_2 and long chain vitamin K_2 concentrations in a series of Dutch foods were assessed at the R&D Group VitaK, Maastricht University. These values were supplemented with earlier analyses by Schurgers and Vermeer and the U.S. food composition database (24). Finally the vitamin K database was completed by estimating vitamin K1 and vitamin K_2 content through recipes and ingredient information. The relative validity of the FFQ for vitamin K, with this database, has been assessed against 12 monthly 24-hour recalls among 121 men and women (24). The relative validity for energy adjusted vitamin K_1, vitamin K_2, short- and long- chain vitamin K_2 intake were 0.34, 0.56, 0.32 and 0.66, respectively.

Echocardiography

Experienced ultrasound analysts performed the echocardiographic imaging at baseline (2000/2001) and at follow-up (2007/2009), using the HP SONOS 5500 echocardiography system (2–4 MHz transducer, Andover, MA, USA) according to a standardized protocol consisting of two-dimensional, M-mode and pulsed wave Doppler assessments (25). All echocardiograms were evaluated afterwards by a senior cardiologist.

Cardiac structure was measured by LVMI, which was calculated from linear dimensions by using the American Society of Echocardiography recommended formula and indexed to height$^{2.7}$. (25). LV systolic function was determined by LVEF (%), which was calculated using the modified Simpson's rule (25). As a marker of LV diastolic function the left atrial volume was measured at end-systole and indexed by body surface area resulting in LAVI (mL/m^2) (26).

Covariates

At baseline, participants were asked to fill out questionnaires about lifestyle factors (physical activity), medical history, medication use and smoking status (never/former/current smokers) (21). Dietary intake of other nutrients than vitamin K was based on self-report using by the same validated FFQ (22). Educational level was self-reported based on the highest ascertainment, and stratified according to three categories: 1) low (no/primary education); 2) middle (secondary education); 3 high (tertiary education). Information on prior and incident CVD was based on self-report in combination with medical records.

Weight was divided by height squared to calculate body mass index (BMI, kg/m2). Blood pressure (mmHg) was measured twice at the left upper arm in a sitting position using an oscillometric device and averaged (Collin Press-Mate, BP-8800).Glucose tolerance status (NGT, IGT or diabetes) was determined using the results of an oral glucose tolerance test combined with the fasting glucose levels, according to the WHO 1999 criteria (27). The estimated glomerular filtration rate (eGFR, mL/min) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI 2009) Eq. (28). Plasma BNP was determined in spare frozen EDTA samples, which had been stored at − 80ºC for 4 years. B-type natriuretic peptide was determined in pmol/L (equivalent to 3.5 pg/mL) using an immunoradiometric assay kit (Shionoria, Osaka, Japan) with inter- and intra-assay variability coefficients in the relevant range < 10% (29).

Statistical analyses

All analyses were performed using SPSS Statistics, version 22.0 and R software version 3.1.1 (R-Foundation Statistical Computing). Two-sided P-values of < 0.05 were considered statistically significant. Vitamin K status and energy-adjusted intakes of all forms of vitamin K were categorized into quartiles. For vitamin K status the quartile with the highest dp-ucMGP concentrations and thus the lowest vitamin K status was used as the reference category. For quartiles of vitamin K intake, the lowest quartile was used as the reference category. Baseline characteristics were summarized by quartiles of vitamin K status and intake.

Missing values for any covariates were present in 279 and 301 participants respectively for analyses on vitamin K status and intake, ranging from 0.2% for HbA1c to 2.9% for presence of CVD, and only BNP had 20.1% missing data. Multiple imputations were used combining ten iterations into one imputation model. The longitudinal association of vitamin K status and intake with LVEF, LVMI and LAVI at follow-up were estimated using linear regression models adjusted for follow-up duration, glucose tolerance status and baseline value of the echocardiographic outcome. We additionally adjusted for confounders in a stepwise manner. Model 1 additionally adjusted for age and sex. Model 2 adjusted for BMI, smoking, physical activity, systolic blood pressure, presence of CVD, cholesterol, HbA1c and education. For vitamin K intake, we additionally adjusted for dietary factors associated with vitamin K intake: total energy intake and energy-adjusted intakes of protein, saturated fat, fiber, calcium and vitamin C. The median level of vitamin K status or intake in each quartile was included as a continuous factor in the analysis to assess the P-trend over the categories.

We also included the quadratic term of continuous vitamin K status or intake along with the continuous term to assess evidence for deviation of a linear relationship. In case this quadratic term was significant, we used spline regression to explore the functional forms of the prospective associations between continuous vitamin K status or intake and echocardiographic measures.

Sex, glucose tolerance status and prior CVD were assessed as effect modifiers by including interaction terms in the fully adjusted models. Wald tests were used to assess whether the models with the

interaction terms differed significantly from the initial models. In case interaction was present ($P < 0.10$), we stratified the results (30).

Sensitivity analyses were conducted by excluding cases with incident CVD during follow-up and by adjusting the final model for changes over time in smoking, physical activity and BMI. Finally, to investigate selection bias due to loss to follow-up, baseline characteristics of participants and dropouts were compared and a sensitivity analysis was performed using inverse-probability weighting for the longitudinal models.

Results

Baseline characteristics

Our study population for vitamin K status of 405 participants had a mean age of 66.8±6.1 years and 50.9% was male. At baseline, participants with a higher vitamin K status were younger, more often male, more often current smokers, had a lower systolic blood pressure and lower BMI than those with a low vitamin K status (Table 1). Among the 427 participants for vitamin K intake analyses, those with a high vitamin K intake were younger, less often male, lower educated, more physically active and had higher intakes of protein, fiber, vitamin C and calcium than those with a low vitamin K intake (Additional File 2). Those excluded in this study were older, had lower vitamin K status, more comorbidities and a slightly worse cardiac structure and function (Additional File 3).

Table 1

Baseline characteristics of 405 participants stratified by quartiles of vitamin K status

	Quartiles of dp-ucMGP (pmol/L)				
Dp-ucMGP (pmol/l) (min-max)	Total population 578±410 97-4608	Quartile 1 1047±581 680-4608	Quartile 2 597±56 508-697	Quartile 3 432±41 366-507	Quartile 4 258±70 97-366
N	405	98	102	103	102
Age (years)	66.8±6.1	67.7±4.9	69.0±5.7	66.2±6.1	64.5±6.7
Male sex (%)	50.9	39.8	47.1	59.2	56.9
High education (%)	22.0	19.8	19.2	27.2	22.5
Current smoking (%)	12.3	8.2	9.9	13.6	17.6
Physical activity (h/week)	22.5±17.0	22.1±14.8	21.5±17.3	24.0±19.8	22.2±15.7
Type 2 diabetes (%)	30.1	32.0	27.7	27.5	34.3
Previous CVD (%)	42.5	44.2	53.1	35.3	42.9
Systolic blood pressure (mmHg)	139±394	143±20	142±19	139±17	134±20
Total cholesterol (mmol/l)	5.7±1.0	5.8±1.1	5.8±0.9	5.7±1.0	5.6±1.1
HDL cholesterol (mmol/l)	1.4±0.4	1.4±0.4	1.4±0.4	1.4±0.4	1.4±0.4
HbA1c (%)	6.0 ±0.8	6.1 ±0.8	6.0 ±0.7	6.0 ±0.8	5.9 ±0.7
BMI (kg/m^2)	27.3±3.5	28.3±3.3	27.4±3.2	27.4±3.9	26.3±3.2
eGFR ($ml/min/1.73m^2$)	63.7±10.2	60.6±8.7	61.8±10.5	64.1±9.5	68.1±10.3
Echocardiographic measures					
LVMI ($g/m^{2.7}$)	40.3±11.3	42.9±12.7	41.0±11.4	39.2±9.1	38.5±11.4
Ejection fraction (%)	62.0±8.0	63.3±8.0	60.8±8.8	62.6±7.6	61.4±7.3
LAVI (mL/m^2)	24.7±7.9	26.4±11.1	25.0±7.2	22.9±5.7	24.5±6.3
BNP (pg/ml)	0.5 [0.2, 0.9]	0.6 [0.3, 0.9]	0.7 [0.4, 1.1]	0.3 [0.2, 0.7]	0.4 [0.2, 0.7]
Dietary intake					
Energy (kcal/day)	1980±508	1875±489	2016±490	2056±512	1970±528
Saturated fat (g/day)[1]	31.0±6.4	31.2±6.0	30.4±7.2	32.3±7.0	30.4±5.0

Protein (g/day)[1]	73.3±11.1	71.3±10.4	72.2±10.8	75.0±10.0	74.8±12.6
Fiber (g/day)[1]	24.3±4.7	23.2±4.9	24.6±4.4	24.0±4.5	25.3±4.7
Vitamin C (mg/day)[1]	107±42.1	107±46.9	109±41.4	105±36.4	109±43.8
Calcium (mg/day)[1]	1058±297	1028±281	1073±281	1065±293	1065±333
Alcohol (g/day)	7.2 [1.1-18.0]	5.9 [0.7-22.7]	7.5 [1.1-18.2]	8.2 [1.7-18.1]	6.9 [1.0-12.1]
Vitamin K_1 (mg/day)[1]	185±75.8	172±72.2	184±83.1	192±69.8	189±76.9
Vitamin K_2 (mg/day)[1]	35.4±13.6	35.0±12.1	33.2±13.1	35.6 ±12.2	37.7±16.4
Total vitamin K (mg/day)[1]	220±77.9	207±74.3	218±85.0	227±71.2	227±79.7
Short-chain vit K_2 (mg/day)[1]	22.6±7.5	22.6±6.8	21.1±7.6	23.9±7.1	23.0±8.4
Long-chain vit K_2 (mg/day)[1]	12.2±10.5	11.8±9.5	11.6 ±8.7	11.2 ±9.6	14.1±13.3

[1] Energy-adjusted intakes

Values represent mean values and standard deviation, percentages or median (interquartile range)

Table 2

Prospective association between vitamin K status and echocardiographic measurements in 405 participants

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
LVMI ($g/m^{2.7}$)[1]					
Men N=206	45.2±11.7	43.6±13.3	40.7±10.4	40.9±9.2	
Model 1	Ref (0.0)	2.1 (-2.9; 7.1)	-0.7 (-5.4; 4.0)	-1.8 (-6.6; 3.0)	0.353
Model 2	Ref (0.0)	1.8 (-3.1; 6.8)	-0.5 (-5.2; -4.1)	-1.3 (-6.4; 3.7)	0.611
Women N=199	46.7±15.6	45.1±12.5	38.9±7.7	35.6±9.3	
Model 1	Ref (0.0)	-0.3 (-4.8; 4.2)	-7.2 (-11.9; -2.6)	-6.5 (-11.2;-1.8)	<0.001
Model 2	Ref (0.0)	0.4 (-2.9; 3.7)	-6.8 (-11.8; -1.8)	-5.0 (-10.5; 0.4)	<0.001
LVEF (%)[1]	52.3±10.2	52.0±11.2	53.3±9.8	53.4±9.2	
Model 1	Ref (0.0)	1.3 (-1.9; 4.4)	1.0 (-2.1; 4.1)	1.3 (-1.9; 4.5)	0.48
Model 2	Ref (0.0)	1.1 (-2.1; 4.3)	0.8 (-2.4; 3.9)	1.1 (-2.4; 4.5)	0.61
LAVI (mL/m^2)[1]	28.0 ±18.0	26.0±10.6	25.2±10.1	24.0±9.4	
Model 1	Ref (0.0)	-0.8 (-4.0; 2.3)	0.50 (-2.6; 3.6)	-1.8 (-5.1; 1.4)	0.43
Model 2	Ref (0.0)	-0.4 (-3.5; 2.6)	0.9 (-2.2; 3.9)	-0.1 (-3.3; 3.3)	0.79

[1] Mean echocardiographic measures at follow-up

P-for interaction vitamin K status and LVMI by sex=0.07

Abbreviations: LVMI: left ventricle mass index; LVEF left ventricular ejection fraction; LAVI: left atrium volume index

Quartile 1: reflects a low vitamin K status (high dp-ucMGP)

Model 1: Adjusted for baseline echo value (i.e. LVMI at follow-up adjusted for baseline LVMI), follow-up duration, age, sex and glycemic status

Model 2: Adjusted for model 1 and physical activity, smoking, BMI, systolic blood pressure, total cholesterol, HbA1c, education, prior CVD, BNP and eGFR

3.1 Vitamin K status

Mean vitamin K status was 578±410 pmol/L and showed a distribution somewhat skewed to the right. The mean follow-up time was 7.6 years.

In the linear regression models, including interaction terms for sex, glycemic status or previous CVD showed only evidence of interaction between vitamin K status and sex for LVMI (P=0.07) and results are

therefore stratified by sex. Including a quadratic term in the model was statistically significant (P=0.018), suggesting evidence for a non-linear association. We observed a significant inverse relationship between vitamin K status and decreased LVMI in women for quartile 3 and 4 compared to quartile 1: -7.2(-11.9;-2.6) and -6.5(-11.2;-1.8), respectively, adjusted for model 1 (P-for trend<0.001). Further adjustment for model 2 slightly attenuated the association, and only quartile 3 was still significant, however the P-for trend remained strongly significant <0.001. In men, no significant association was observed. Evaluation of the continuous associations of vitamin K status with LVMI using splines revealed a similar pattern for men and women with some non-linearity in the tails (Figure 1).

Vitamin K status was not associated with either LVEF or LAVI after follow-up with estimates of -0.1 (-3.3;3.3) and 1.1 (-2.4;4.5 (mL/m^2) for quartile 4 compared to quartile 1, respectively, adjusted for model 2.

Vitamin K intake

Mean total vitamin K intake was 220±78 mg/day (184 mg/day vitamin K_1 and 35.5 mg/day vitamin K_2). We did not observe significant associations between any of the forms of energy-adjusted vitamin K intake at baseline and LVMI at follow-up adjusted for CVD risk factors and dietary factors (Table 3). Similarly, for LVEF we observed no significant associations for any of the forms of vitamin K intake. Although we found some evidence of a non-linear association for total vitamin K (P=0.041) and vitamin K_1 (P=0.059) with LVEF, the spline regression did not provide evidence for a clear association (Additional File 4).

In addition, we observed effect modification by presence of CVD for energy-adjusted vitamin K_2 and long-chain vitamin K_2 intake with LVEF (P-interaction<0.01), but no significant associations were observed when stratified for presence of CVD (Additional File 5). None of the forms of vitamin K intake at baseline were associated with changes in LAVI during follow-up.

Table 3

Prospective association between vitamin K intake and echocardiographic measurements in 427 participants

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P-trend
N	106	107	107	107	
LVMI ($g/m^{2.7}$)[1]	42.9±12.4	42.1 ±10.9	40.2±10.9	44.4±13.0	
Total vitamin K (mg/day)	Ref (0.0)	-2.3 (-5.4; 0.8)	-3.5 (-6.7; -0.3)	-0.7 (-4.1; 2.6)	0.54
Vitamin K_1	Ref (0.0)	0.1 (-3.1; 3.1)	-3.8 (-7.0; -0.6)	0.3 (-2.9; 3.6)	0.57
Vitamin K_2	Ref (0.0)	-1.4 (-4.8; 2.1)	-0.6 (-4.2; 2.9)	-0.6 (-4.7; 3.5)	0.88
Long-chain	Ref (0.0)	-0.1 (-3.4; 3.3)	-2.2 (-5.5; 1.1)	-0.9 (-5.0; 3.1)	0.32
Short-chain	Ref (0.0)	-3.0 (-6.3; 0.3)	-1.7 (-5.4; 1.9)	-0.2 (-4.5; 4.1)	0.88
LVEF (%)[1]	52.2±9.8	53.4±9.5	54.3±11.1	51.2±10.4	
Total vitamin K (mg/day)	Ref (0.0)	-0.3 (-3.3; 2.6)	-0.7 (-3.8; 2.3)	-1.6 (-4.4; 2.0)	0.29
Vitamin K_1	Ref (0.0)	1.3 (-1.7; 4.3)	1.2 (-2.1; 4.4)	-1.2 (-4.3; 2.1)	0.43
Vitamin K_2	Ref (0.0)	-1.3 (-4.6; 2.0)	-1.8 (-5.2; 1.5)	2.1 (-1.9; 6.1)	0.52
Long-chain	Ref (0.0)	-1.1 (-4.3; 2.1)	-2.6 (-5.7; 0.5)	-1.2 (-4.9; 2.6)	0.31
Short-chain	Ref (0.0)	-0.3 (-3.5; 2.9)	2.4 (-1.1; 5.9)	1.2 (-3.0; 5.5)	0.29
LAVI (mL/m^2)[1]	25.3±11.7	26.0±11.7	26.6±14.0	26.6±12.1	
Total vitamin K (mg/day)	Ref (0.0)	-0.2 (-3.1; 2.7)	-0.6 (-3.7; 2.5)	-1.6 (-4.7; 1.5)	0.29
Vitamin K_1	Ref (0.0)	0.2 (-2.7; 3.2)	-1.3 (-4.3; 1.8)	-1.1 (-4.2; 2.0)	0.33
Vitamin K_2	Ref (0.0)	1.8 (-1.3; 5.0)	1.8 (-1.5; 5.0)	1.5 (-2.3; 5.3)	0.46
Long-chain	Ref (0.0)	2.7 (-0.2; 5.6)	0.8 (-2.2; 3.8)	2.1 (-1.4; 5.6)	0.48
Short-chain	Ref (0.0)	3.1 (0.0; 6.2)	1.8 (-1.6; 5.2)	0.6 (-3.3; 4.6)	0.97

[1] Mean echocardiographic measures at follow-up

Abbreviations: LVMI: left ventricle mass index; LVEF left ventricular ejection fraction; LAVI: left atrium volume index

Adjusted for baseline echocardiographic value (i.e. LVMI at follow-up is adjusted for baseline LVMI), follow-up duration, age, sex, glycemic status, physical activity, smoking, BMI, systolic blood pressure, total cholesterol, HbA1c, education, presence of CVD, BNP, eGFR, energy intake and energy-adjusted intakes of protein, saturated fat, fiber, calcium and vitamin C.

Sensitivity analyses

Excluding participants who developed CVD during follow-up (n=7) and adjusting for updated measurements of BMI, physical activity and smoking status at follow-up did not materially change our findings (Additional File 6). Adjusting for selection bias due to loss-to-follow-up using inverse probability weighting did not alter our findings as well (Additional File 6).

Discussion

This study showed that a higher vitamin K status at baseline was associated with decreased LVMI after 7.6 years of follow-up, only among women. Vitamin K status was not associated with other cardiac measures. Vitamin K intake was not associated with cardiac structure and function.

This study is the first prospective study investigating the association between vitamin K status and cardiac structure and function measures. Our results are in line with earlier cross-sectional studies showing that a low vitamin K status was associated with reduced systolic function (18) or a higher prevalence of diastolic dysfunction (20). However, in our study, a higher vitamin K status was associated with LVMI only among women and not among men, but such effect modification by sex was not investigated in earlier studies. We didn't observe any association between vitamin K status and LVEF or LAVI.

Nevertheless, the studies that found an associations between vitamin K status and systolic or diastolic function were performed in populations with different features than those of the present study, the participants being affected by valvular diseases, HF or cardiomyopathy.
Despite this association between vitamin K status and LVMI, we could not detect any clear associations between any of the forms of vitamin K intake and cardiac measures. This is inconsistent with the study by Eshak et al. showing that a higher vitamin K intake was associated with a 37% reduced risk of HF mortality after 19 years of follow-up among Japanese women (17). The inconsistent findings between both studies could be due to the relatively low sample size of our study combined with the relatively low validity of the FFQ to accurately assess vitamin K intake. For LAVI and LVEF, we observed significant non-linear associations with several forms of vitamin K intake. These associations showed slightly, but non-significantly higher LVEF and LAVI in the second and third quartile of vitamin K intake.

The underlying mechanism of vitamin K status and intake, cardiac structure and function and risk of HF may be explained by improved arterial stiffness with increased vitamin K intake and status. Vitamin K functions as a co-factor to carboxylate MGP, a potent inhibitor of vascular calcification. Animal experiments indeed showed that antagonism of vitamin K leads to vascular calcification, in particular of the medial layer of the arteries (31). Medial calcification leads to vascular stiffness (32, 33), which in turn is consistently associated with diastolic dysfunction (34). In fact, vascular stiffness may increase the systolic load on the ventricles and decrease aortic pressure during diastole, thereby increasing pulse

pressure (35). Increased pulse pressure increases myocardial oxygen demand during systole and is associated with LV hypertrophy. These changes can lead to impaired relaxation and eventually LV diastolic dysfunction and HFpEF (36). Indeed, earlier studies have shown vitamin K status to be associated with increased arterial stiffness (19, 37, 38). One possible explanation of why in our study vitamin K status affected LV structure only in women, is that women, especially after menopause, seem to be more prone to develop LV hypertrophy in response to pressure overload compared to men. Consequently, the effect of vitamin K status on arterial stiffness and cardiac overload might manifest itself only in women [32].

Strengths of this study include its prospective design and detailed phenotyping of the participants, allowing to adjust for multiple confounders. However, certain limitations need to be addressed. First, the prospective associations may be biased due to the high loss to follow-up rates in this study. Although we observed similar associations in our analyses after inverse probability weighting, we cannot exclude some selection bias. Second, for the assessment of vitamin K intake we relied on self-reported data.

Although the FFQ was validated for the assessment of vitamin K intake, the relative validity in particular for the assessment of vitamin K1 and short-chain vitamin K2 was low.
In combination with the relatively small sample size, this may have yielded the study insufficiently sensitive to detect associations with vitamin K intake. Third, the definition of vitamin K status was based on a single baseline measurement of dp-ucMGP, which may only reflect short-term vitamin K status. Therefore these associations should be interpreted with caution.

Conclusions

This study showed that a high vitamin K status is associated with decreased LVMI in women. Altogether these results further extend previous associations of vitamin K status with improved cardiac structure and function and a decreased risk of HF. Future studies should investigate whether vitamin K supplementation is an effective strategy to improve cardiac structure and function and prevent HF.

Declarations

Ethics approval and consent to participate

All participants provided written informed consent and the local ethics committee of the VU University Medical Center approved the study.

Consent for publication

All participants provided informed consent for publication.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Joline W.J. Beulens, Coen D.A. Stehouwer, Roger J.M.W. Rennenberg and Adriana Johanne van Ballegooijen contributed to the study conception and design; Joline W.J. Beulens, Coen D.A. Stehouwer and Adriana Johanne van Ballegooijen contributed to data collection, assembly, analysis and interpretation of the data; Joline W.J. Beulens, Elisa Dal Canto and Adriana Johanne van Ballegooijen contributed to the revising of the manuscript; Joline W.J. Beulens, Elisa Dal Canto, Coen D.A. Stehouwer, Roger J.M.W. Rennenberg, Petra Elders and Adriana Johanne van Ballegooijen contributed to the manuscript drafting and approval of the final version of the manuscript.

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Figures

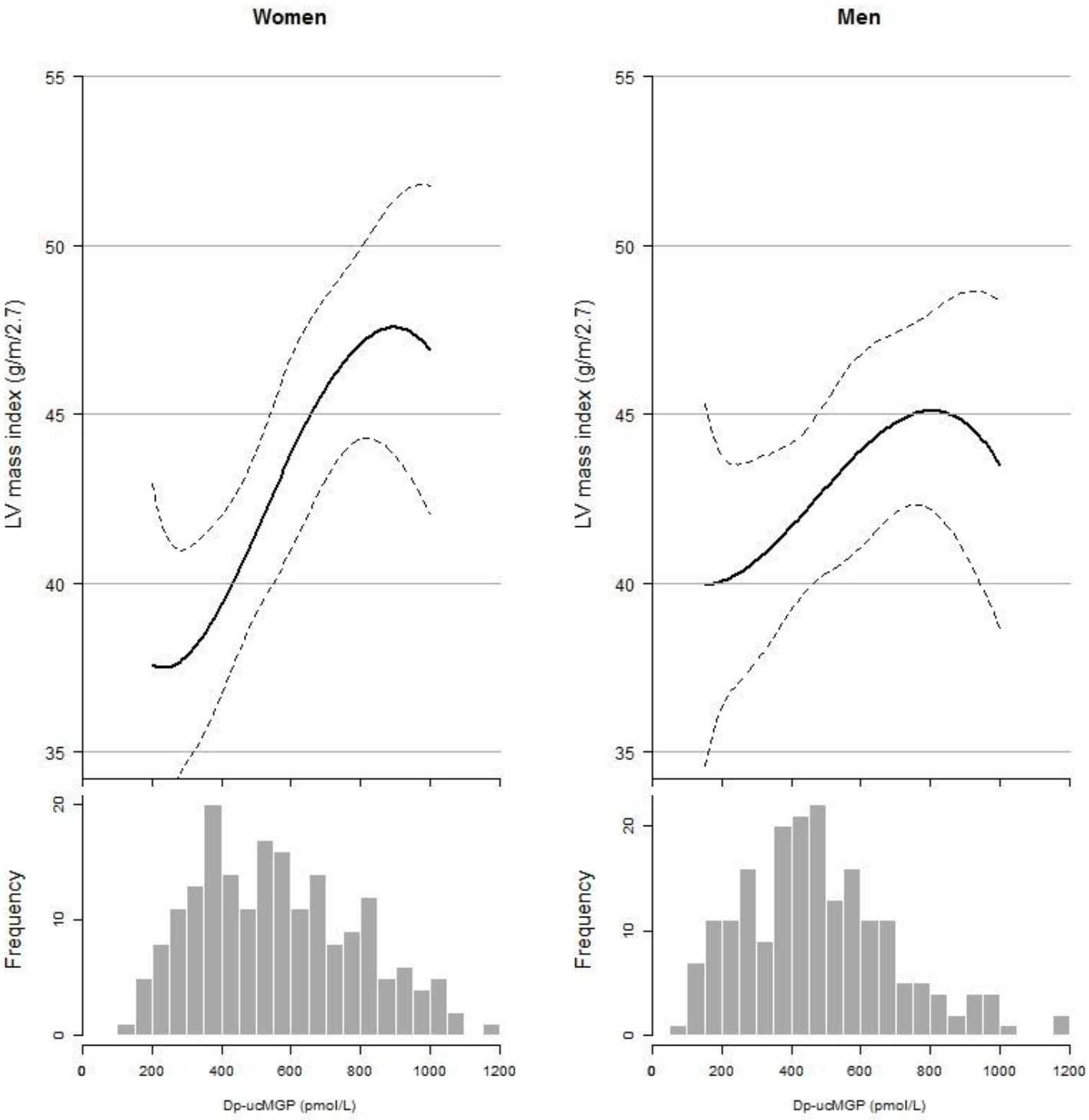

Figure 1

Continuous association of vitamin K status with left ventricular mass index stratified by sex among the inner 95% of concentrations. Women N=199; men N=206. Splines are adjusted for age, follow-up time, glucose status and baseline left ventricular mass index. Below each spline is the histogram depicted to illustrate the distribution of dp-ucMGP (pmol/L). High dp-ucMGP is indicative for low vitamin K status.

Supplementary Files

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