SUPPLEMENTAL MATERIAL

Table S1. Central Hemodynamic Characteristics by Tertiles of the dp-ucMGP Distribution.

Characteristics	Category of dp–ucMGP			*P* Value
Limits (μg/L)	<3.35	3.35–5.31	≥5.31	
Augmentation ratio (%)	107.5±6.7	109.3±7.2†	111.8±7.2†	<0.001
Augmentation index (%)	21.4±11.8	23.9±12.0*	26.7±10.9†	<0.001
Pulse wave velocity (m/s)	6.84±1.26	7.21±1.63*	8.09±1.78†	<0.001
Forward wave amplitude (mm Hg)	32.3±9.4	32.7±10.3	34.7±10.8*	0.013
Backward wave amplitude (mm Hg)	19.8±6.4	21.2±7.9*	24.6±10.4†	<0.001

Values are means (SD). dp-ucMGP, desphospho-uncarboxylated matrix Gla protein. To convert dp-ucMGP from μg/L into pmol/L, multiply by 94.299. Pulse wave velocity was available in 657 participants. The augmentation ratio and index, pulse wave velocity, and forward and backward wave amplitudes were not standardized to a heart rate of 65 beats per minute (population mean). *P*-values denote the significance of the difference in means (ANOVA) across tertiles of the dp-ucMGP distribution. Significance of the difference with the adjacent lower tertile: * $P \leq 0.05$; † $P \leq 0.01$.

Table S2. Hemodynamic Traits in the Top Quintile versus the Other Quintiles of the dp-ucMGP Distribution.

Hemodynamics	Unadjusted Models		Adjusted Models		Fully Adjusted Models	
	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*
Central pulse pressure (mm Hg)	9.19 (6.68 to 11.7)	<0.001	3.27 (0.86 to 5.68)	0.008	3.33 (0.96 to 5.70)	0.006
Forward wave amplitude (mm Hg)	3.16 (1.43 to 4.88)	0.0004	1.81 (0.01 to 3.60)	0.048	1.84 (0.06 to 3.61)	0.043
Backward wave amplitude (mm Hg)	5.48 (4.07 to 6.90)	<0.001	1.25 (0.09 to 2.42)	0.035	1.28 (0.12 to 2.43)	0.030
Reflection magnitude (%)	7.97 (4.92 to 11.0)	<0.001	–1.92 (–4.48 to 0.63)	0.14	–1.93 (–4.48 to 0.63)	0.14

Association sizes (95% confidence interval) express the difference in the hemodynamic indexes between highest quintile and the remaining quintiles. Adjusted models accounted for sex, age, body mass index, mean arterial pressure (not for central pulse pressure), heart rate, waist-to-hip circumference ratio, serum total cholesterol and high-density lipoprotein cholesterol, plasma glucose, smoking and drinking, and use of antihypertensive drugs by class. Fully adjusted models additionally accounted for the ankle-to-arm systolic blood pressure ratio as index of subclinical atherosclerosis.

Table S3. Correlates of Central Blood Pressure and the Augmentation Ratio and Augmentation Index.

Variables	Central Blood Pressure (n=835)			Systolic Augmentation (n=835)	
	SBP (mm Hg)	DBP (mm Hg)	PP (mm Hg)	Ratio (%)	Index (%)
R^2	0.35	0.20	0.31	0.67	0.57
Association size					
Female sex (0,1)	–4.33±1.0†	–3.78±0.78†	…	5.32±0.31†	8.81±0.59†
Age (+15.2 years)	8.66±0.56†	1.65±0.36†	6.80±0.54†	4.65±0.17†	6.87±0.31†
Mean arterial pressure (+10.8 mm Hg)	…	…	…	1.28±0.17†	2.16±0.32†
Waist-to-hip circumference ratio (+0.08)	…	0.87±0.45*	–0.93±0.54	…	…
Body mass index (+4.1 kg/m^2)	…	0.92±0.36*	…	–0.60±0.16†	–0.73±0.29*
Heart rate (+9.2 beats per minute)	…	1.44±0.31†	–1.85±0.45†	–1.79±0.15†	–2.72±0.29†
Serum total cholesterol (+0.92 mmol/L)	0.87±0.50	1.62±0.30†	–1.03±0.48*	…	0.52±0.28
HDL cholesterol (+0.35 mmol/L)	…	…	0.82±0.52	…	…
Plasma glucose (+0.76 mmol/L)	…	…	0.99±0.47*	…	–0.44±0.28
Smoking (0,1)	–3.03±1.36*	…	…	1.56±0.40†	3.85±0.75†
Drinking (0,1)	…	1.04±0.64	…	…	…
Use of antihypertensive drugs (0,1)	5.55±1.35†	–1.20±0.82	6.32±1.22†	0.81±0.40*	…

SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure. Correlates of the central hemodynamic indexes were identified by stepwise regression with *P*-values for covariables to enter and stay in the models set at 0.15. For continuously distributed variables, the association size (β) expresses the difference in central hemodynamic indexes associated with a 1-SD increment in the explanatory variable. R^2 is the coefficient of multiple determination and indicates the total variance explained by the models. Significance of the association sizes: * $P \leq 0.05$; † $P \leq 0.01$.

Table S4. Correlates of Pulse Wave Velocity, the Forward and Backward Wave and the Reflection Magnitude.

Variables	PWV (m/s) (n=657)	Forward Wave (n=835)		Backward Wave (n=835)		RM (%) (n=835)
		Peak Time (ms)	Amplitude (mm Hg)	Peak Time (ms)	Amplitude (mm Hg)	
R^2	0.46	0.07	0.14	0.35	0.49	0.53
Association size					.	
Female sex (0,1)	–0.32±0.10†	–6.25±0.90†	–3.20±0.79†	11.0±1.4†	2.74±0.56†	12.4±0.95†
Age (+15.2 years)	0.79±0.06†	…	…	7.48±0.72†	3.75±0.28†	9.86±0.49†
Mean arterial pressure (+10.8 mm Hg)	0.34±0.06†	–2.19±0.47†	2.68±0.38†	2.01±0.74†	2.95±0.26†	2.95±0.52†
Waist-to-hip circumference ratio (+0.08)		…	–1.49±0.42†	…	–0.61±0.33	…
Body mass index (+4.1 kg/m^2)		0.71±0.46	…	–1.39±0.67*	–0.63±0.26*	–0.98±0.46*
Heart rate (+9.2 beats per minute)	0.09±0.05	…	…	–9.94±0.66†	–2.00±0.23†	–5.40±0.46†
Serum total cholesterol (+0.92 mmol/L)		…	–1.54±0.35†	1.34±0.66*	–0.56±0.23*	1.35±0.46†
HDL cholesterol (+0.35 mmol/L)		…	…	…	…	…
Plasma glucose (+0.76 mmol/L)	0.13±0.05†	…	0.85±0.34*	–1.05±0.66	0.42±0.23	…
Smoking (0,1)		…	–1.96±0.92*	…	…	4.89±1.21†
Drinking (0,1)		…	…	…	…	…
Use of antihypertensive drugs (0,1)	0.29±0.14*	1.77±1.13	3.37±0.87†	…	2.25±0.60†	…

PWV, aortic pulse wave velocity; RM, reflection magnitude. Correlates of the central hemodynamic indexes were identified by stepwise regression with *P*-values for covariables to enter and stay in the models set at 0.15. For continuously distributed variables, the association size (β) expresses the difference in central hemodynamic indexes associated with a 1-SD increment in the explanatory variable. R^2 is the coefficient of multiple determination and indicates the total variance explained by the models. Significance of the association sizes: * $P \leq 0.05$; † $P \leq 0.01$.

Table S5. Association of Central Hemodynamic Traits and dp-ucMGP in Untreated Participants.

Hemodynamics	Unadjusted Models		Adjusted Models	
	Estimate (95%CI)	*P*	Estimate (95%CI)	*P*
Central systolic pressure (mm Hg)	5.64 (4.14 to 7.14)	<0.001	1.52 (0.02 to 3.03)	0.047
Central diastolic pressure (mm Hg)	2.17 (1.25 to 3.10)	<0.001	–0.21 (–1.16 to 0.74)	0.66
Central pulse pressure (mm Hg)	3.45 (2.20 to 4.71)	<0.001	1.75 (0.42 to 3.09)	0.010
Augmentation pressure (mm Hg)	2.72 (1.97 to 3.48)	<0.001	0.56 (–0.02 to 1.13)	0.056
Augmentation ratio (%)	2.06 (1.42 to 2.69)	<0.001	0.31 (–0.14 to 0.76)	0.18
Augmentation index (%)	3.03 (1.90 to 4.17)	<0.001	0.11 (–0.77 to 1.00)	0.80
Pulse wave velocity (m/s, n=657)	0.58 (0.42 to 0.74)	<0.001	0.16 (0.02 to 0.30)	0.032
Forward wave amplitude (mm Hg)	0.84 (–0.13 to 1.80)	0.088	1.11 (0.07 to 2.15)	0.037
Backward wave amplitude (mm Hg)	2.10 (1.40 to 2.80)	<0.001	0.74 (0.10 to 1.38)	0.023
Reflection magnitude (%)	3.87 (2.12 to 5.61)	<0.001	–0.27 (–1.67 to 1.14)	0.71

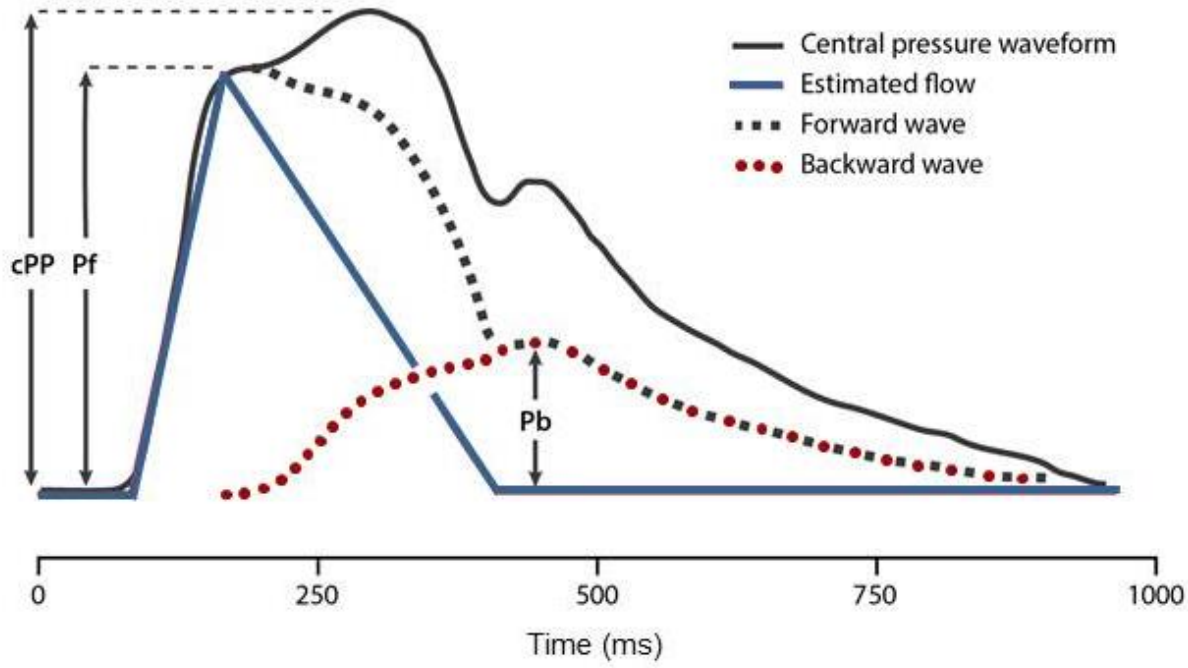
Association sizes (95% confidence interval) express the difference in the hemodynamic indexes associated with a doubling higher matrix Gla protein. Adjusted models accounted for sex, age, body mass index, waist-to-hip circumference ratio, heart rate, serum total cholesterol and high-density lipoprotein cholesterol, plasma glucose, and smoking and drinking. The augmentation ratio and index, pulse wave velocity, forward and backward wave amplitudes and reflection magnitude were also adjusted for mean arterial pressure.

Table S6. Characteristics of Participants Analyzed and Not Analyzed.

Characteristics	Analyzed	Not Analyzed	*P*
Number of participants (%)	835	560	
All patients in category			
Women	381 (45.6)	331 (59.1)	<0.001
Smokers	132 (15.8)	109 (19.5)	0.077
Drinking alcohol	353 (42.3)	208 (37.1)	0.06
Hypertension	341 (40.8)	259 (46.2)	0.045
Antihypertensive treatment	174 (20.8)	164 (29.3)	<0.001
History of cardiovascular disease	39 (4.7)	34 (6.1)	0.25
Mean (SD) of characteristic			
Age (years)	49.7±15.2	53.0±16.6	0.001
Body mass index (kg/m^2)	26.2±4.1	26.8±4.8	0.005
Systolic pressure (mm Hg)	128.6±16.2	130.5±19.3	0.044
Diastolic pressure (mm Hg)	78.6±9.3	78.6±10.3	0.87
Serum total cholesterol (mmol/L)	5.04±0.92	5.26±1.01	<0.001
Plasma glucose (mmol/L)	4.87±0.76	4.89±0.65	0.61

HDL, high-density lipoprotein. Hypertension was a blood pressure of ≥140 mm Hg systolic or ≥90 mm Hg diastolic or use of antihypertensive drugs. The *P*-value denotes the significance of the difference between participants analyzed and not analyzed.

Figure S1. Pressure-based wave separation analysis algorithm.



A central pressure waveform is separated in its forward and backward wave component using s triangular-shaped flow estimate. Start, peak and end of the estimated flow curve are derived from the ejection period and the first shoulder of the central pressure curve. cPP indicates central pulse pressure; Pb, backward wave amplitude; Pf, forward wave amplitude.

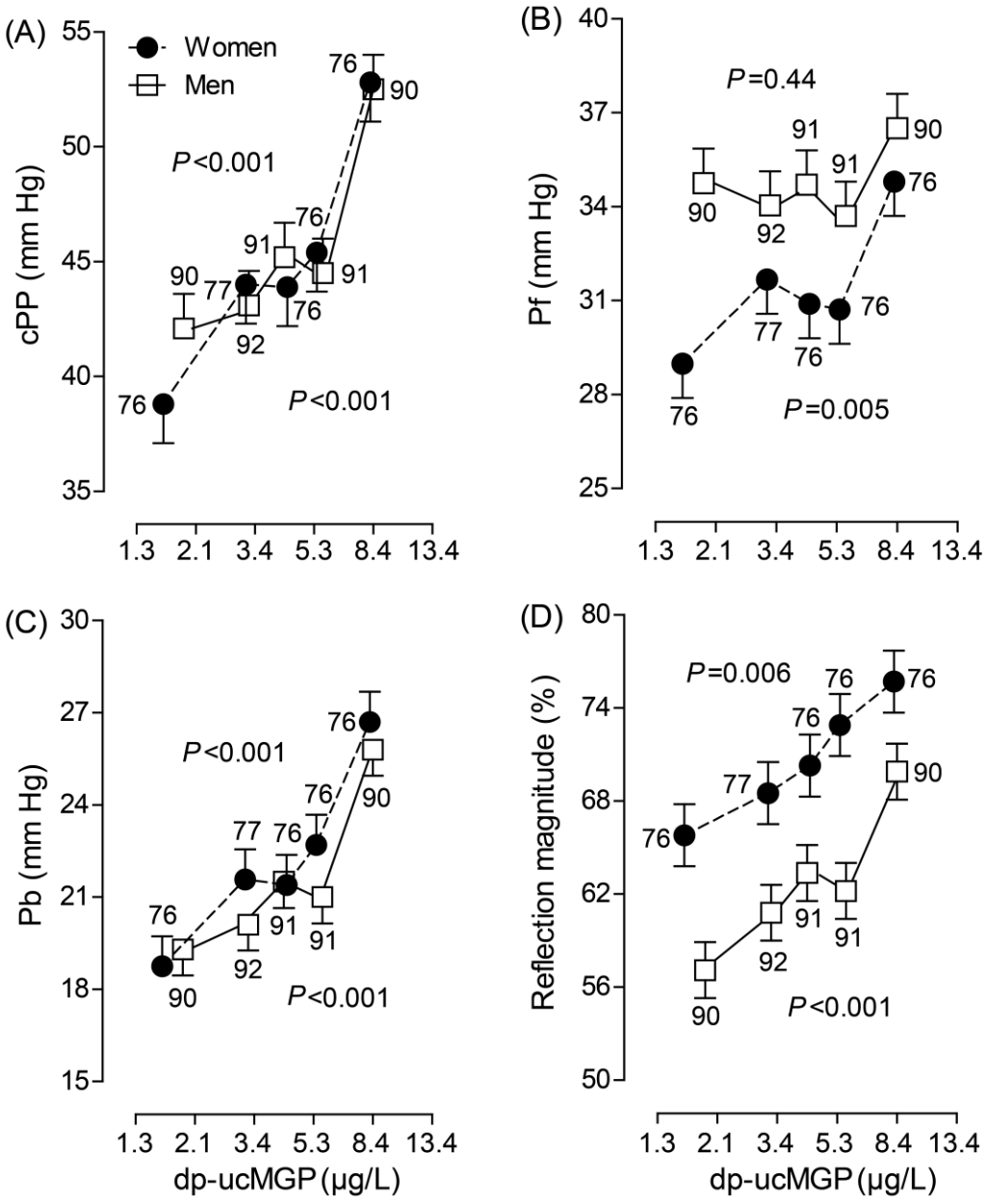


Figure S2. Central pulse pressure (A [cPP]), forward wave amplitude (B [Pf]), backward wave amplitude (C [Pb]) and reflection magnitude (D) by quintiles of the sex-specific distribution of inactive desphospho-uncarboxylated matrix Gla protein (dp-ucMGP). Vertical bars indicate standard errors. *P*-values are for linear trend across the quintiles of the dp-ucMGP distribution.

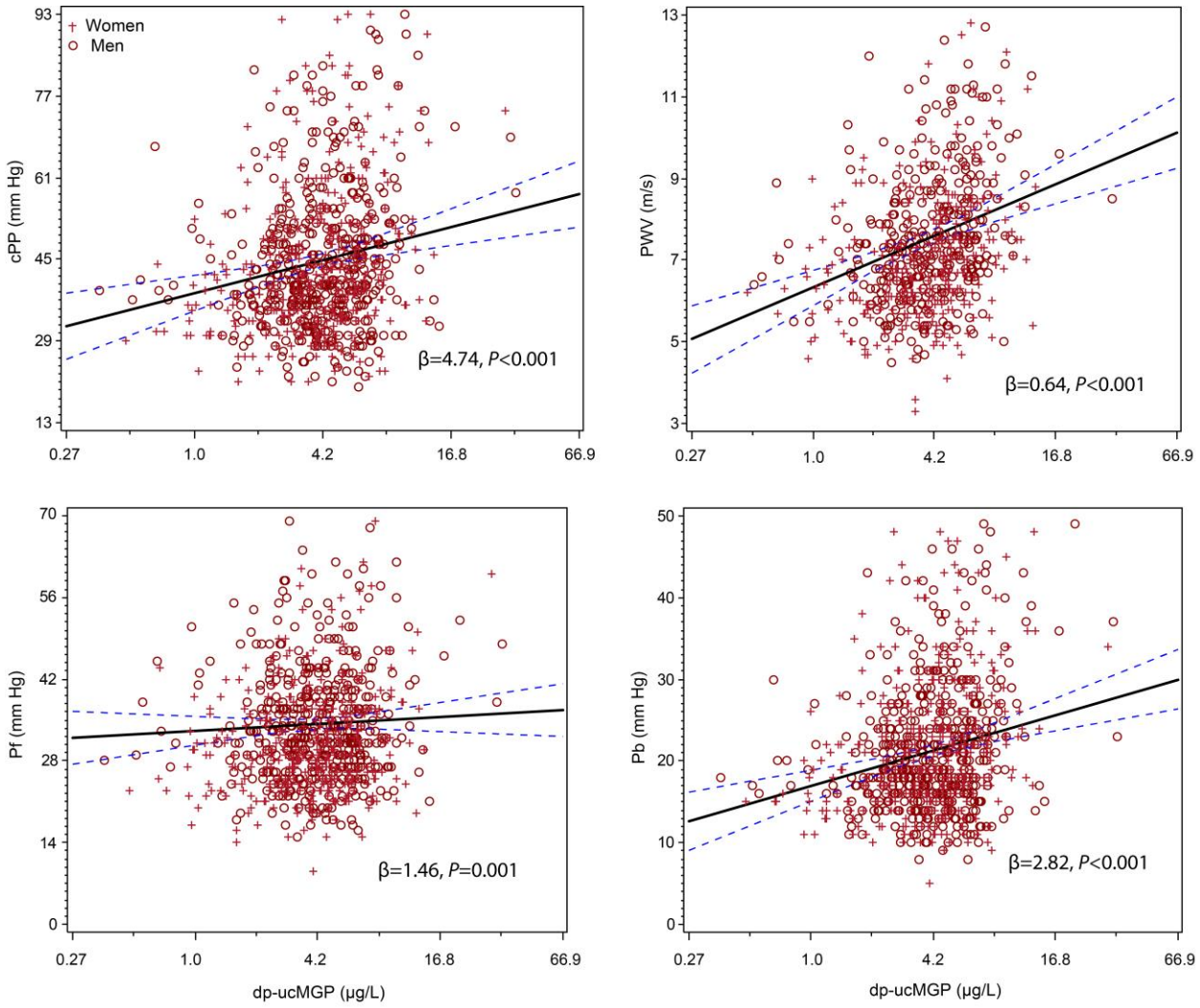
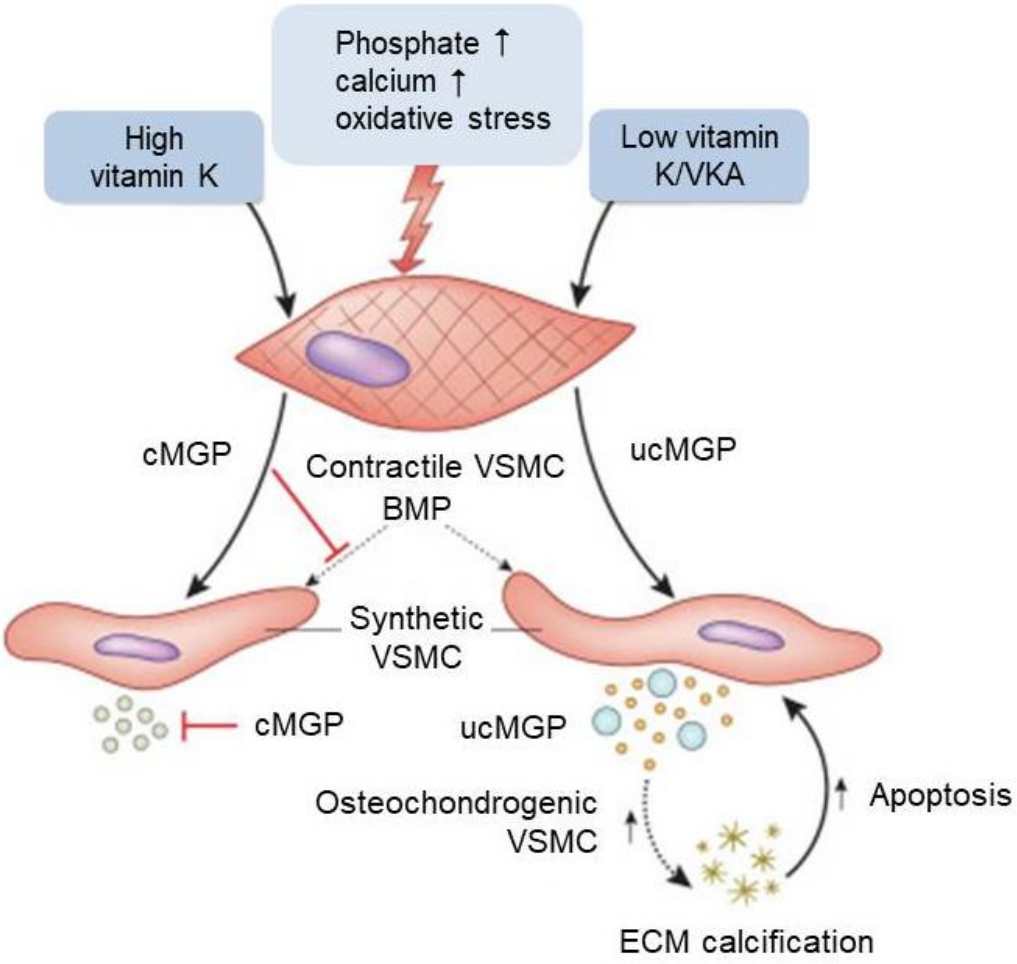


Figure S3. Unadjusted associations of central pulse pressure (A [cPP]), aortic pulse wave velocity (B [PWV]), the forward wave amplitude (C [Pf]) and the backward wave amplitude (D [Pb]) with inactive desphospho-uncarboxylated matrix Gla protein (dp-ucMGP). The forward and backward pulse pressure amplitudes were derived from the central pulse wave by a triangular-flow pressure-based wave separation algorithm. Regression lines are given with the 95% confidence interval for prediction of the mean.

Figure S4. Contractile vascular smooth muscle cells (VSMCs) synthesize matrix Gla protein (MGP).



In the presence of sufficient vitamin K, MGP is carboxylated (cMGP) and thereby prevents mineralization of VSMCs and the extracellular matrix (ECM) and inhibits transdifferentiation of VSMCs. Under pathologic conditions (e.g., high calcium, high phosphate or increased oxidative stress), VSMCs differentiate from a contractile to an osteochondrogenic phenotype. In the case of vitamin K deficiency, MGP remains uncarboxylated (ucMGP). Transdifferentiated VSMCs produce less MGP, are susceptible to apoptosis, and secrete more matrix vesicles and apoptotic bodies, resulting in extracellular mineralization. Reprinted with adaptations from Schurgers et al[1] with permission.

Supplemental Reference:

1. Schurgers LJ. Vitamin K: key vitamin in controlling vascular calcification in chronic kidney disease. *Kidney Intern.* 2013;83:782–784.