FLEMENGHO

Inhibition of vascular calcification

Role of matrix Gla protein

Yan-Ping Liu, Fang-Fei Wei, Cees Vermeer, and Jan A. Staessen,
Research Unit Hypertension and Cardiovascular Epidemiology,
Department of Cardiovascular Sciences,
jan.staessen@med.kuleuven.be / ja.staessen@maastrichtuniversity.nl

MGP

Outline of presentation

- What is MGP?
- Macrovascular complications in relation to MGP:
  - total, CV, and non-CV mortality;
  - fatal plus non-fatal CV events, CHD, stroke;
- Microvascular complications in relation to MGP:
  - eGFR;
  - micro-albuminuria;
- Implications for public health and prevention.

2015

What is MGP?

Biomarker of vitamin K status and arterial calcification

MGP

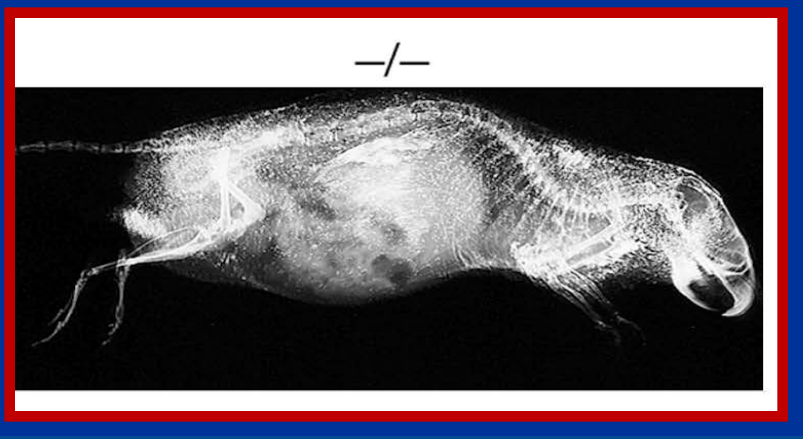
The major calcification inhibitors

- **Fetuin A:**
- **Small Gla proteins:**
  - Matrix Gla protein (MGP);
  - Osteocalcin;
  - Gla-rich protein (GRP).

MGP

Characteristics of fetuin-A

- Large protein (59 kD);
- Synthesized in the liver;
- ***Systemic*** calcification inhibitor;
- Too large to penetrate into vascular elastin and collagen fibrils;

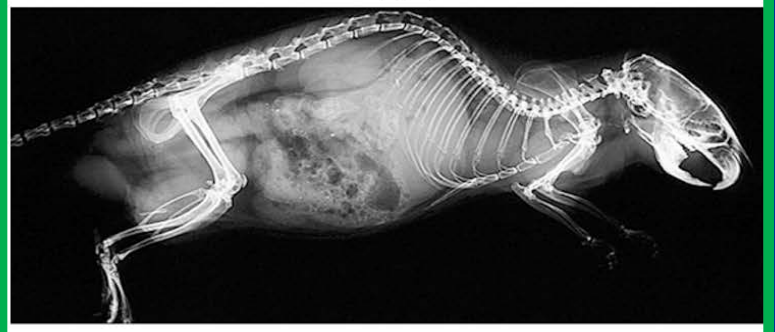


MGP

Characteristics of MGP

- Small protein (10 kD);
- Synthesized by VSMCs;
- ***Local*** calcification inhibitor;
- Penetrates into vascular elastin and collagen fibrils.

+/+



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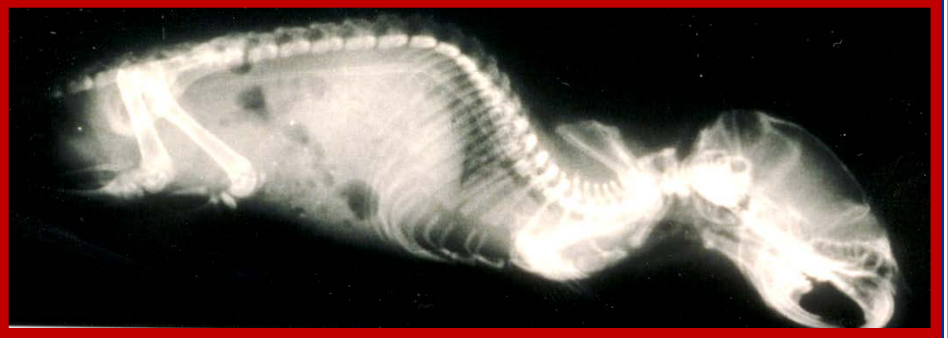
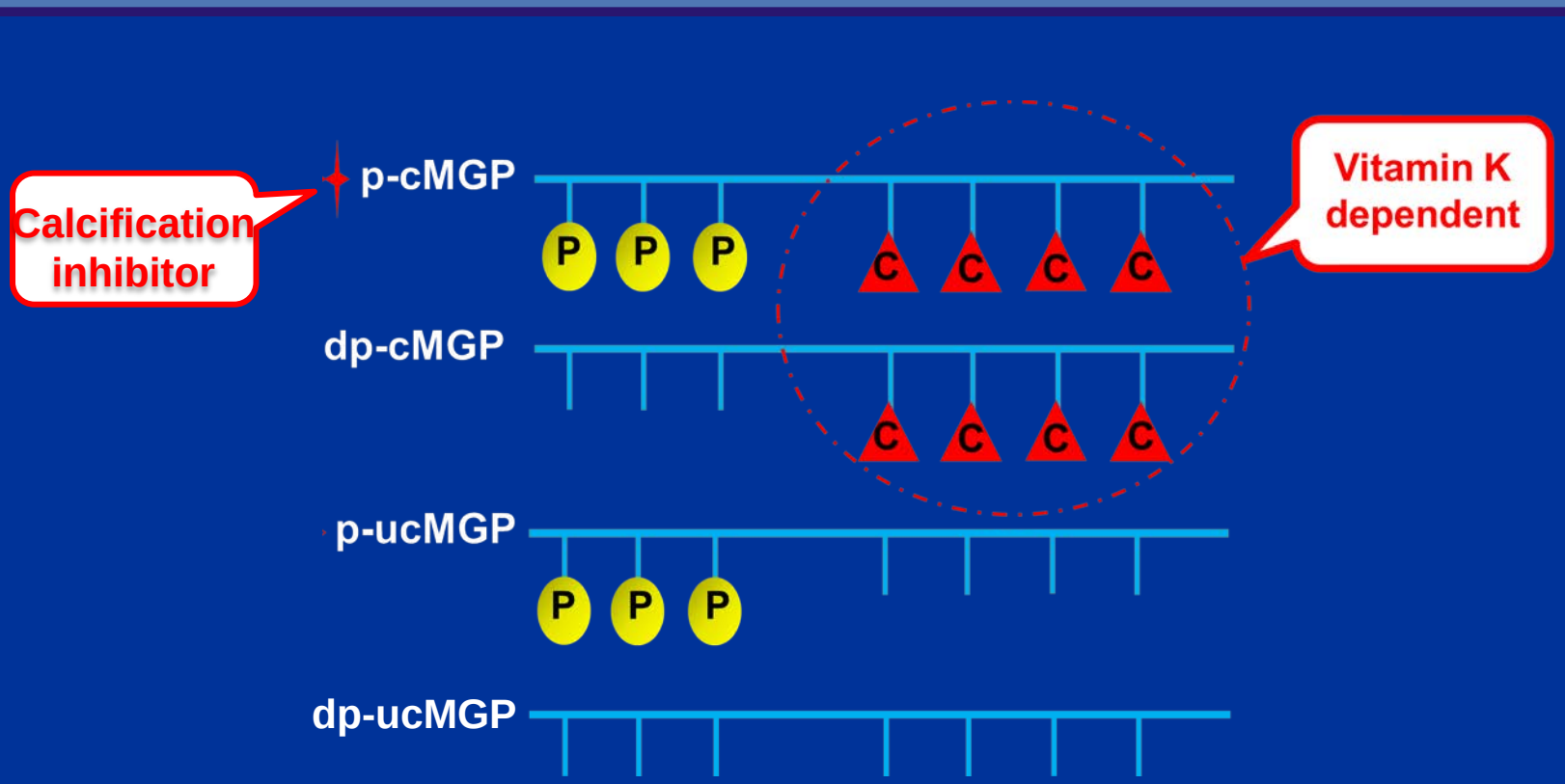


MGP

Post-translational modifications of MGP



2015

Adverse health outcomes

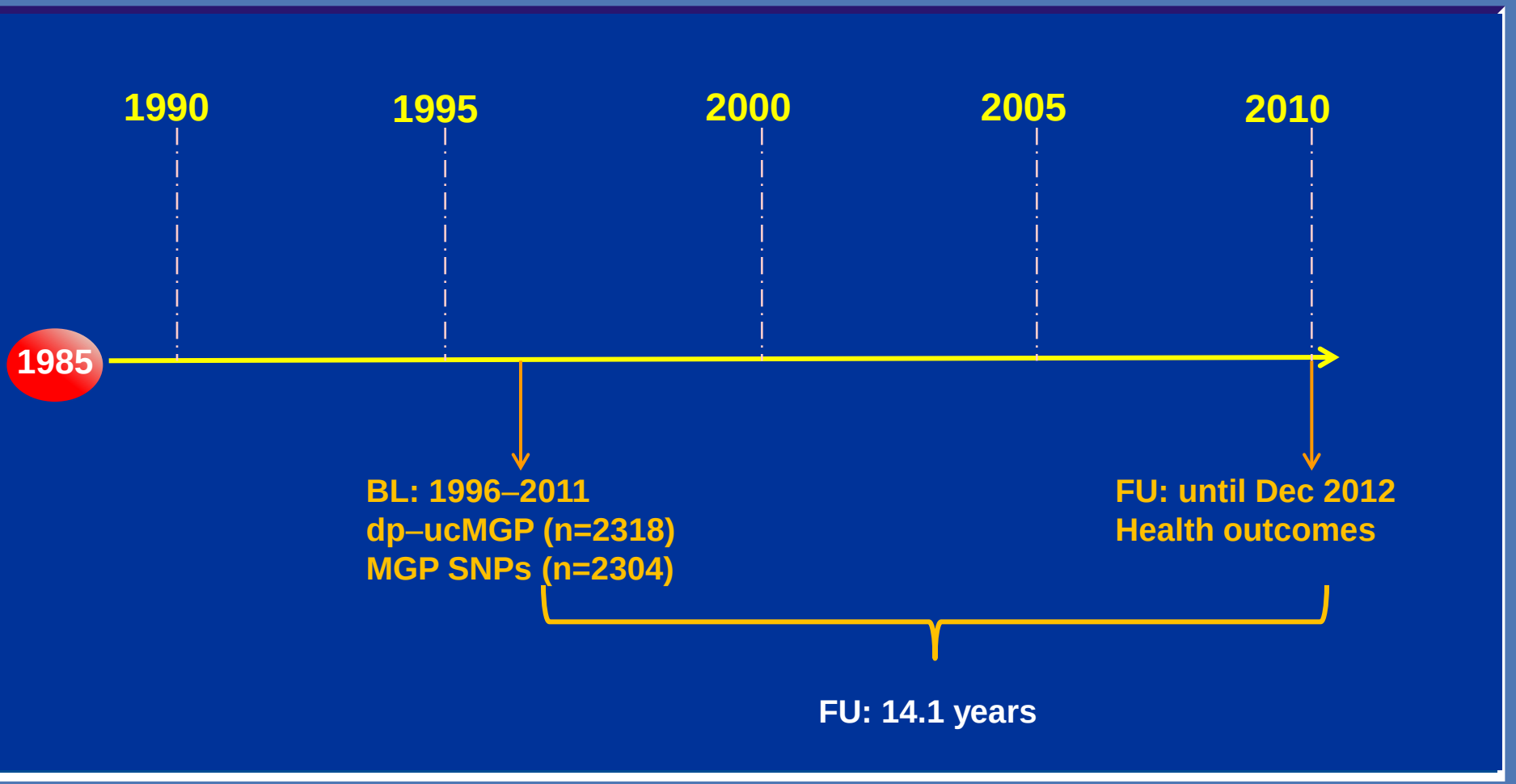
Focus on the macrocirculation

MGP Background

- Calcification of the conduit arteries is a hallmark of CV disease;
- Matrix Gla-protein (MGP) is produced by VSMC and is the most powerful inhibitor of vascular calcification presently known;
- In case-control studies of patients with CKD or DM, or in terminally ill patients, MGP is associated with CV complications.

Hypertension 2015; 65:463-470.

MGP Timeline



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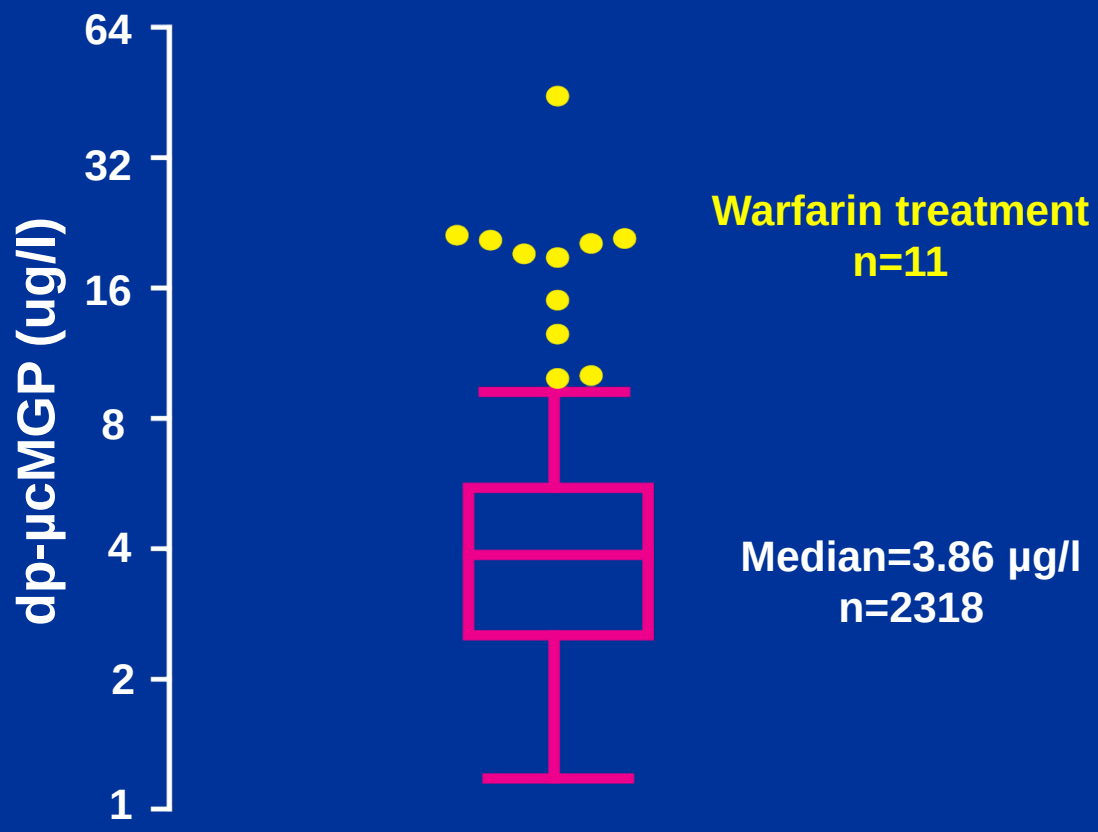
MGP

Distribution of dp-ucMGP



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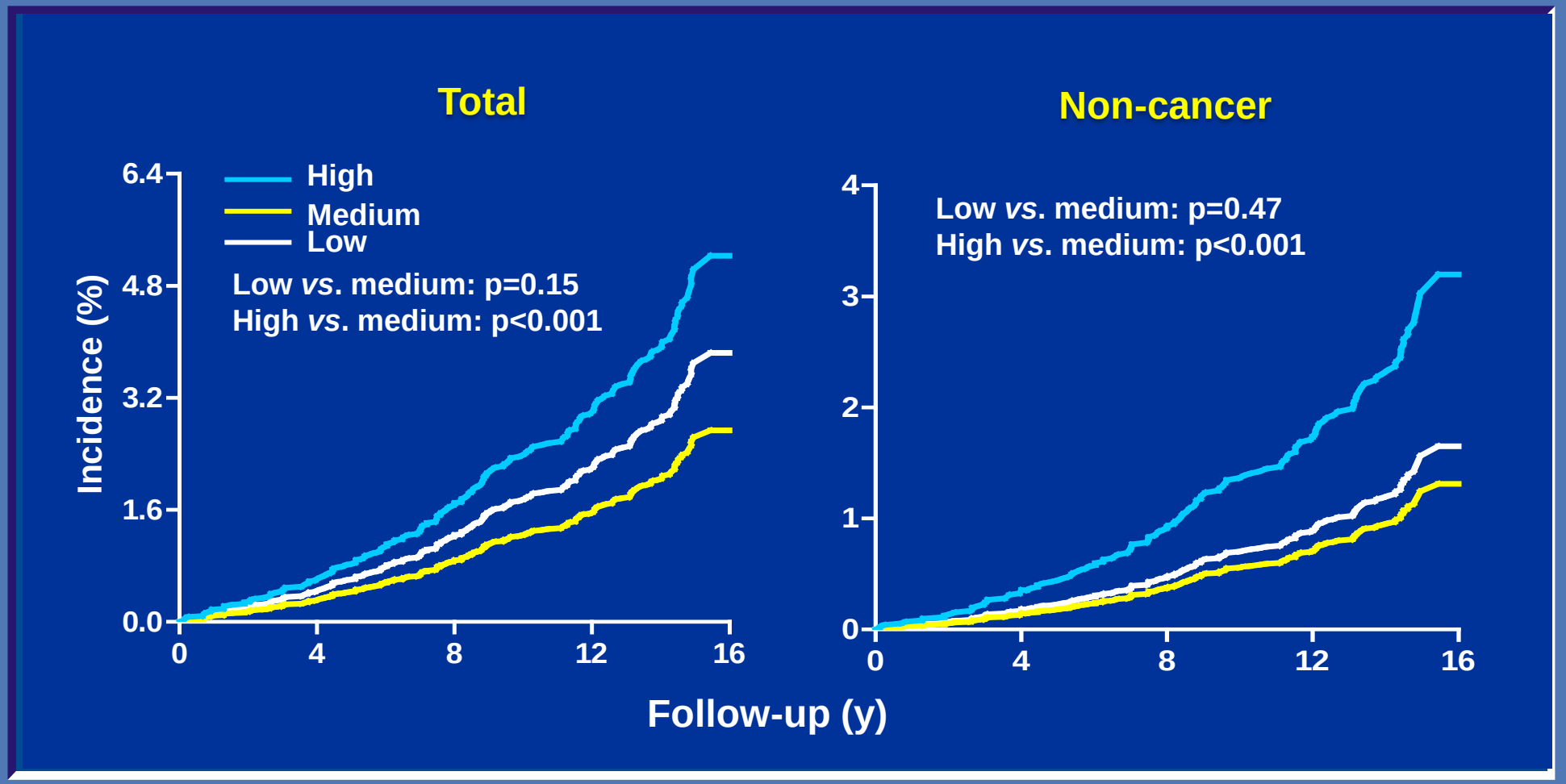
MGP

Sex- and age-standardised mortality rates by thirds of dp-ucMGP



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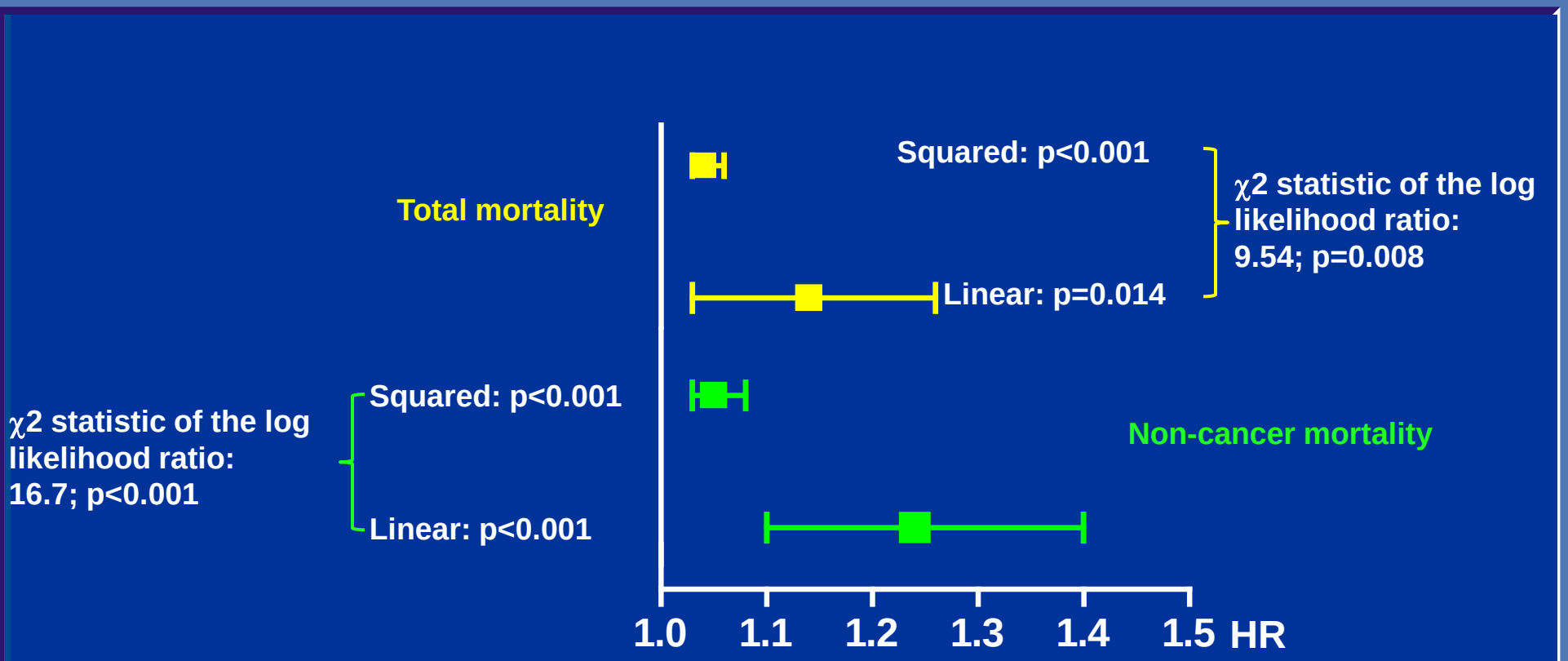
MGP

HRs of total and non-cancer mortality



HRs express the risk associated with a doubling of dp–ucMGP, account for family clusters, and were adjusted for sex, age, BMI, SBP, HR, CSMK, drinking, TCHOL, AHT, DM, and CVD.

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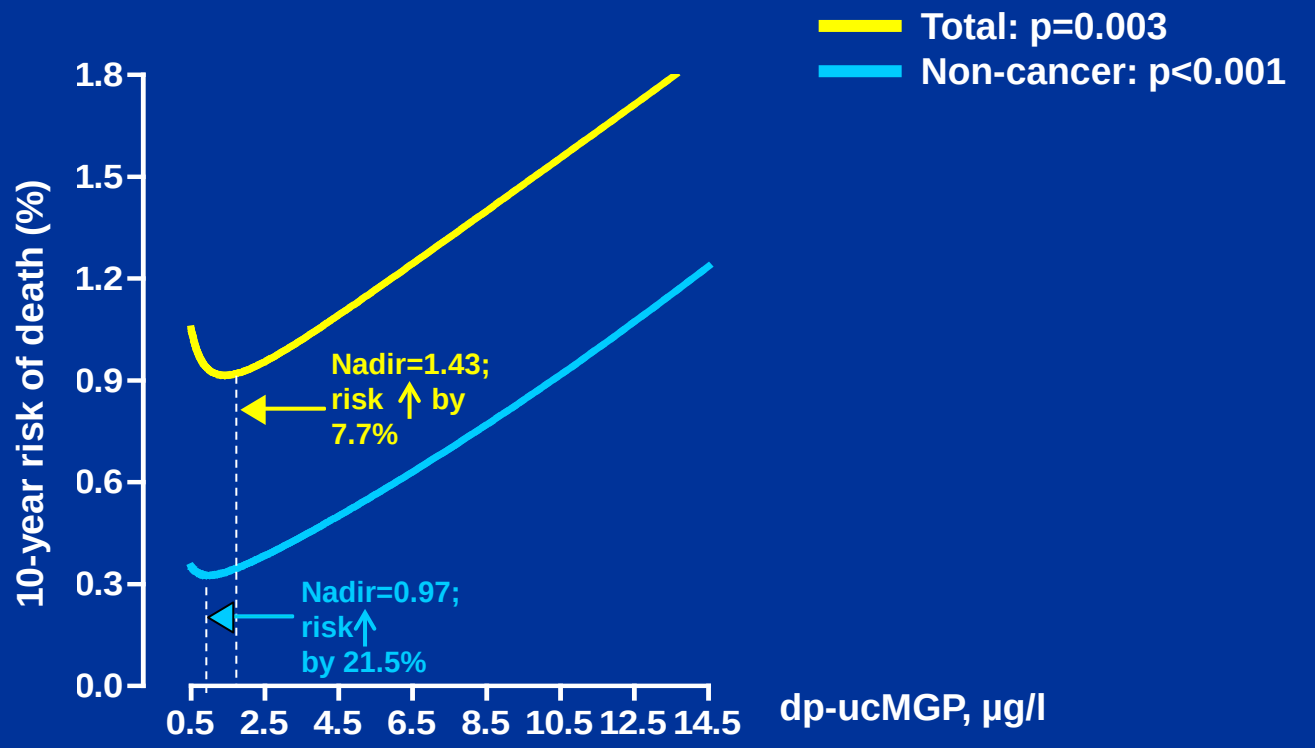
MGP

10-year absolute risk of total and non-cancer mortality



Risk functions were standardised for sex, age, BMI, SBP, HR, CSMK, drinking, TCHOL, AHT, DM, and CVD.

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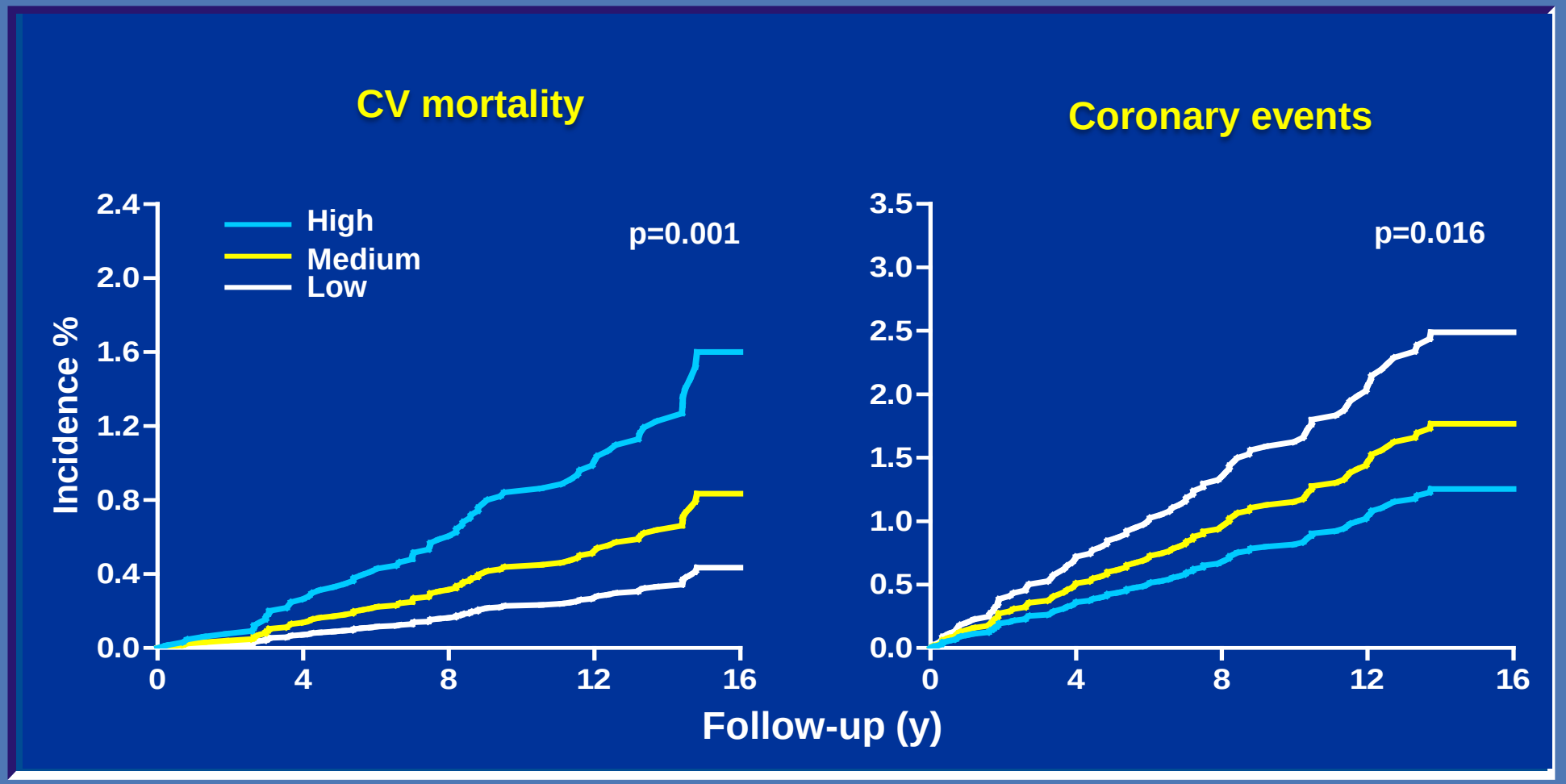
MGP

Sex and age standardised rates by thirds of the dp-ucMGP distribution



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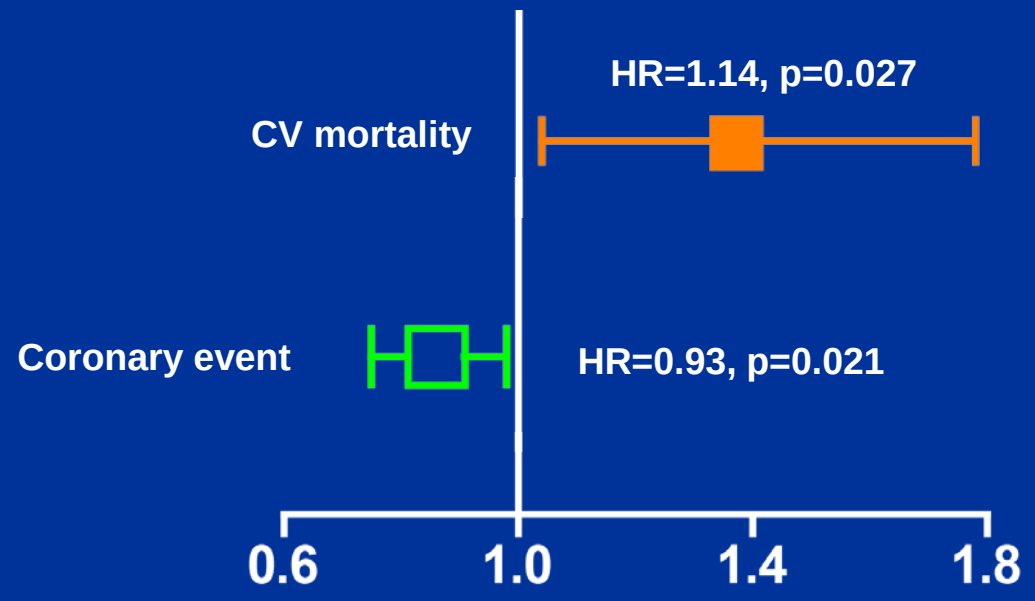
MGP

HRs of CV mortality and CHD



HRs express the risk associated with doubling of dp–ucMGP and account for family clusters, sex, age, BMI, SBP, HR, CSMK, drinking, TCHOL, AHT, DM, and CVD.

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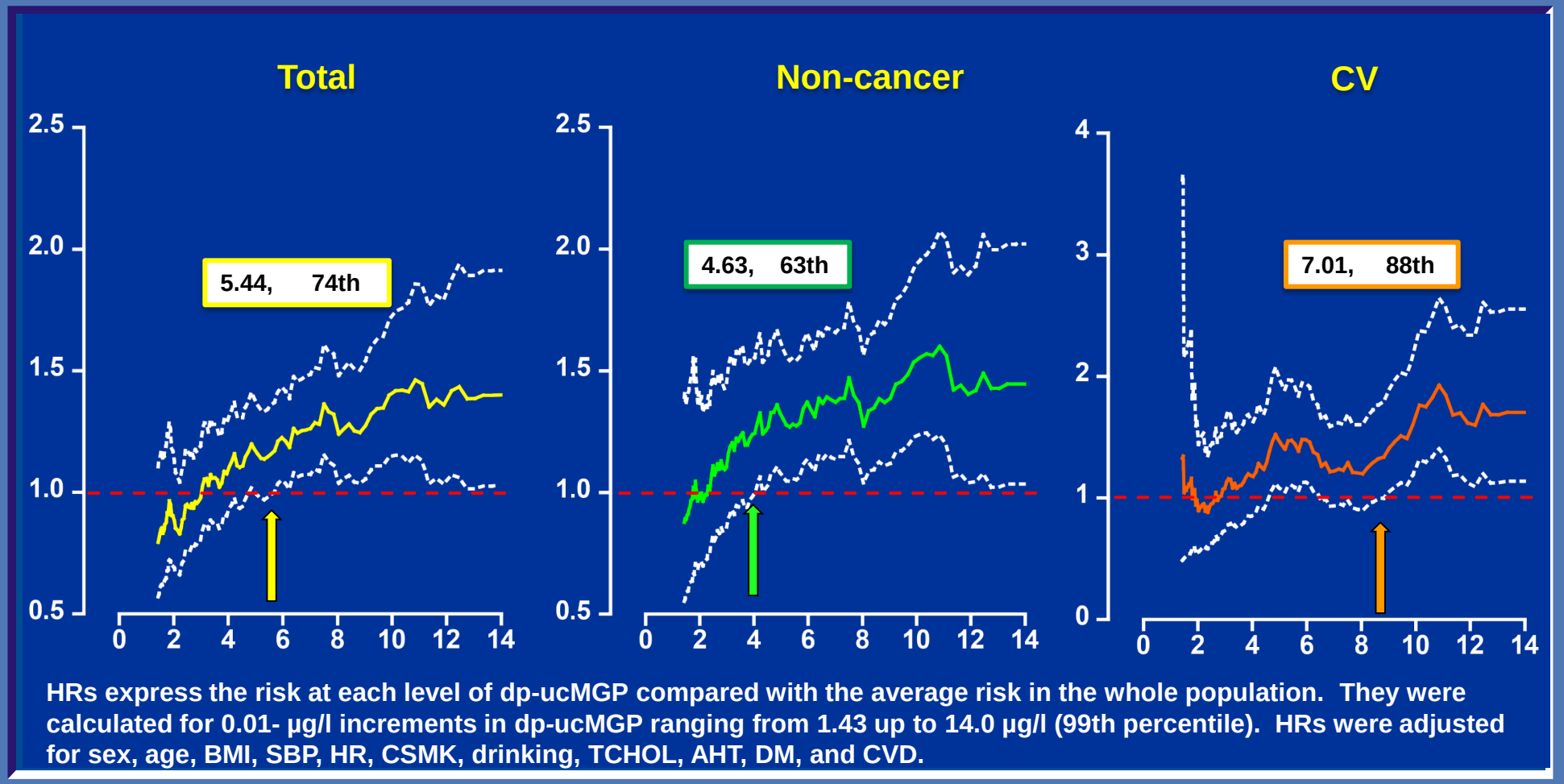
MGP

HRs of mortality associated with increasing level of dp-ucMGP



HRs express the risk at each level of dp-ucMGP compared with the average risk in the whole population. They were calculated for 0.01- µg/l increments in dp-ucMGP ranging from 1.43 up to 14.0 µg/l (99th percentile). HRs were adjusted for sex, age, BMI, SBP, HR, CSMK, drinking, TCHOL, AHT, DM, and CVD.

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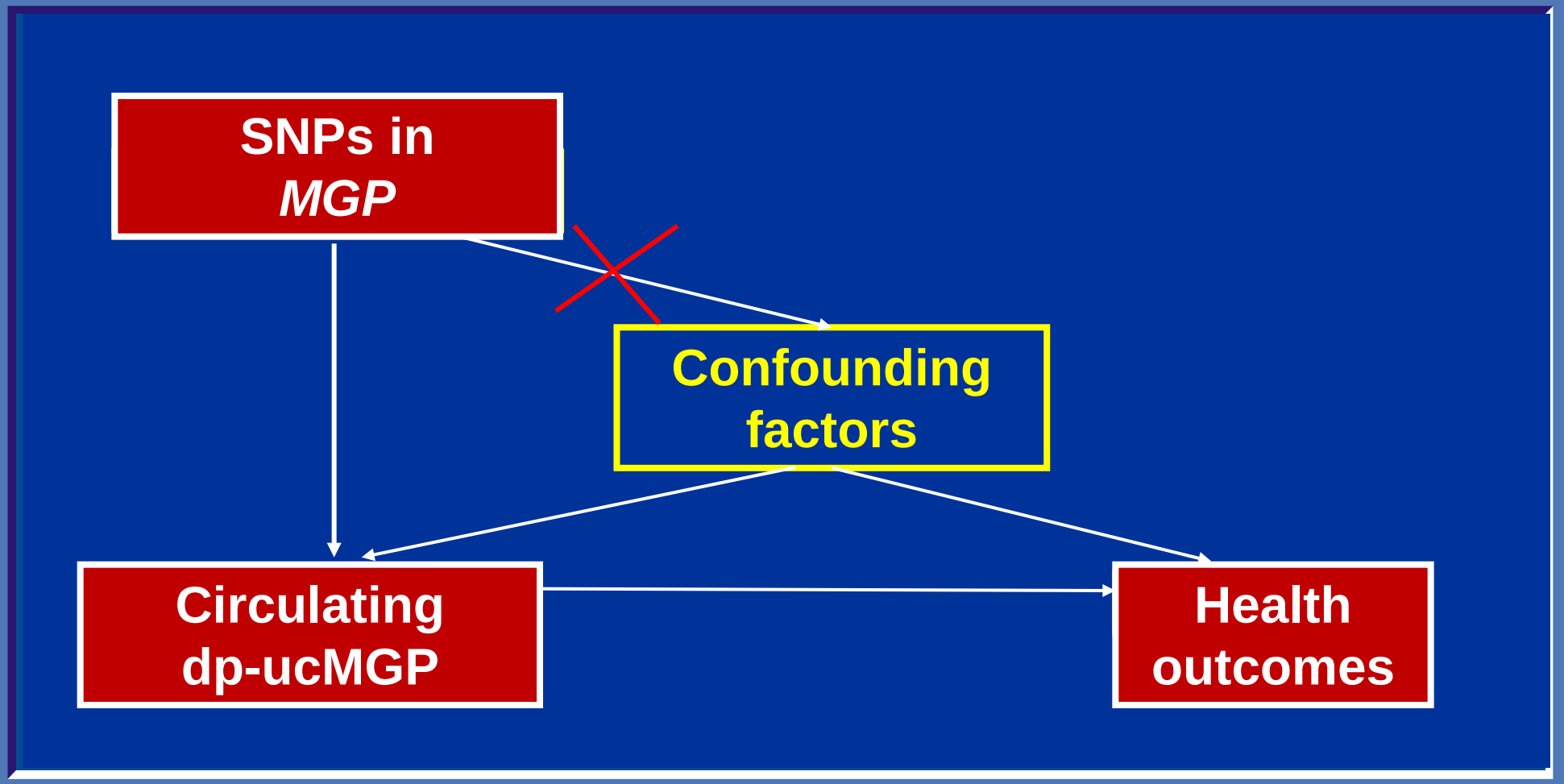
MGP

Instrumental variable



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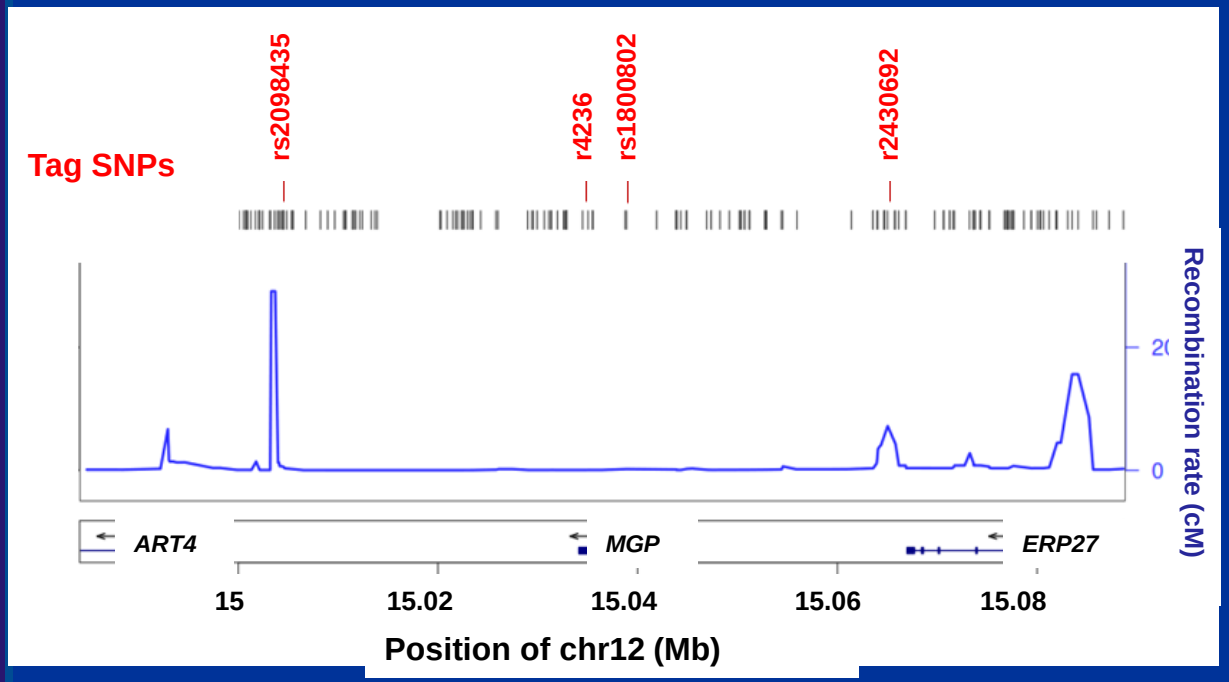
MGP

Coverage of *MGP*



- Four SNPs in high LD (r^2>0.80) with 223 tagged SNPs;
- Covering the entire gene with extension to the 3' and 5' flanking regions.

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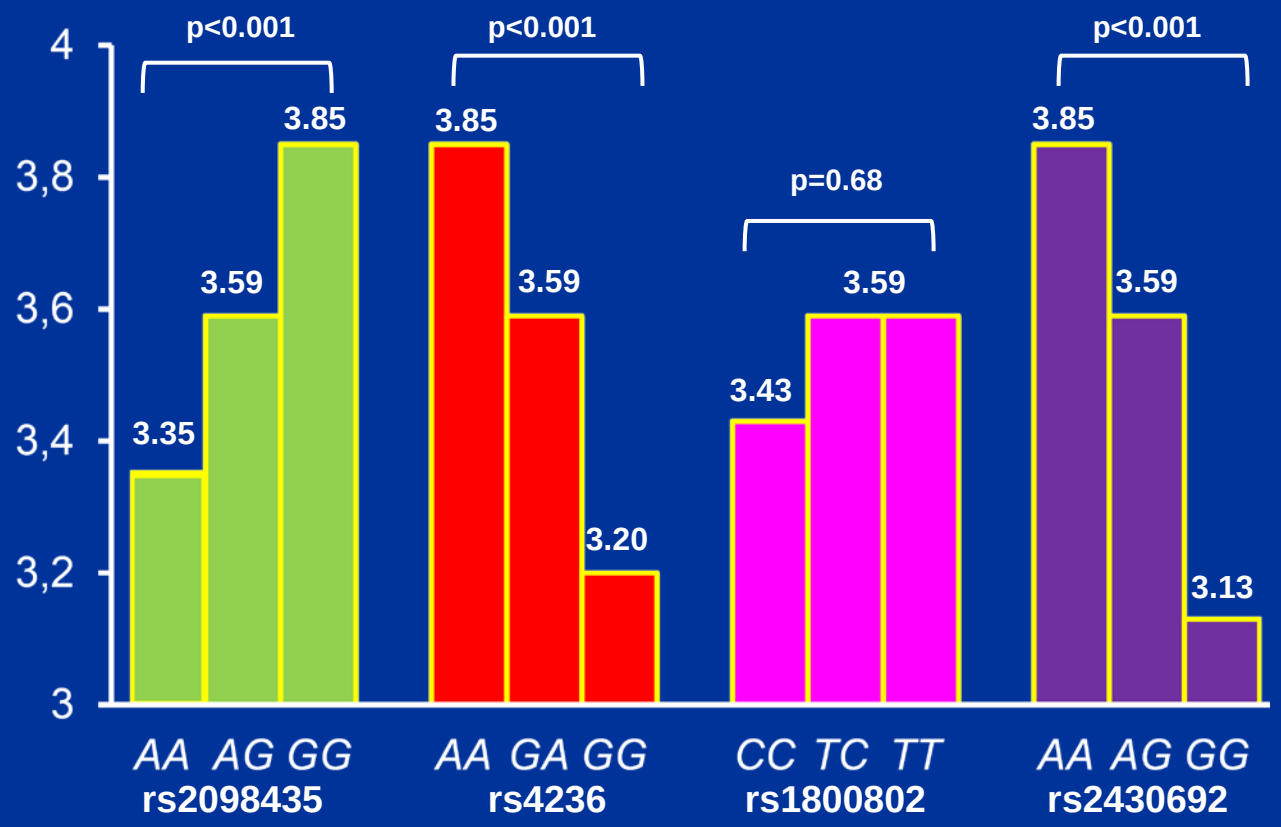
MGP

dp-ucMGP by *MGP* genotype



Geometric means of dp-ucMGP adjusted for age, BMI, CSMK and drinking.

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MGP

Predicted dp–ucMGP

Log dp–ucMGP was regressed on age (r^2=7.0), BMI (0.8), smoking (2.7) and drinking (0.24) and the genetic variants of *MGP* (≥0.7).

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MGP

HRs associated with the predicted dp-ucMGP

Mortality	Predicted dp-ucMGP	*rs2098435*	*rs4236*	*rs2430692*
Total (194)	linear	0.89	0.87	0.89
	squared	1.05*	1.04	1.03
	p	0.13	0.13	0.23
Non-cancer (136)	linear	0.82	0.79*	0.81*
	squared	1.09**	1.09**	1.07*
	p	0.007	0.004	0.010

P-values for model fit (log likelihood test). Significance of HRs: *p<0.05; and **p<0.01.

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MGP

HRs associated with the predicted dp-ucMGP

Event	Predicted dp-ucMGP	*rs2098435*	*rs4236*	*rs2430692*
CV death (67)	linear	0.95	0.91	0.89
Coronary events (85)	linear	0.75*	0.87	0.85

Significance of HRs: *p<0.05; and **p<0.01.

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MGP

Conclusions

- In a general population, dp-ucMGP predicts total, non-cancer and CV mortality, but lower coronary risk;
- The associations of dp-ucMGP with non-cancer mortality is probably causal. The same conclusion might also be applicable to coronary events;
- dp-ucMGP reflects vitamin K status. Our findings suggests that from 12% to 37% of people are vitamin K deficient.

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2015

Adverse health outcomes

Related to the microcirculation

MGP

t-ucMGP as marker of arterial calcification

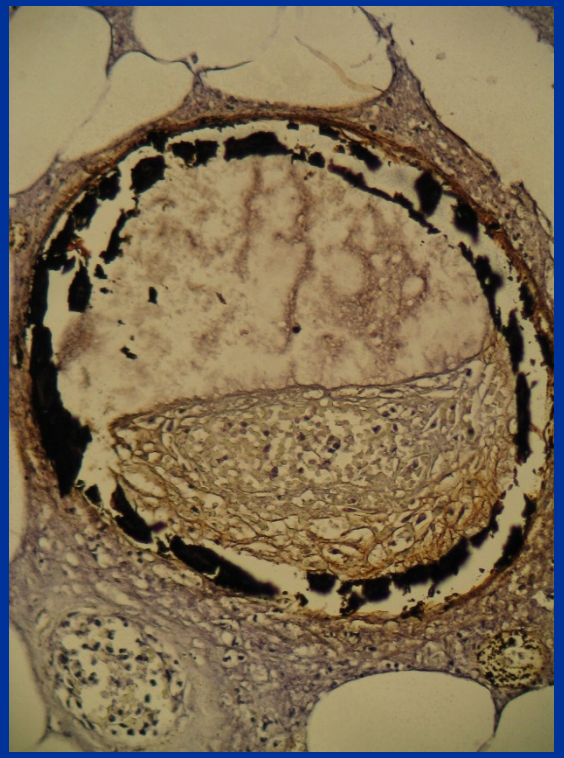
- t-ucMGP (ucMGP) predominantly consists of phosphorylated MGP and is not a biomarker of vitamin K status, but reflects the extent of arterial calcification.
- Up-regulation of MGP transcription in response to vascular stress influences circulating t-ucMGP levels.
- In CKD patients, t-ucMGP levels are lower than in healthy age-matched controls (193 *vs.* 441 nM) and correlated inversely with CAC scores determined by multi-slice computed tomography (r= 0.41; p=0.009).

Cranenburg EC, Thromb Haemost 2009; 10: 359-366

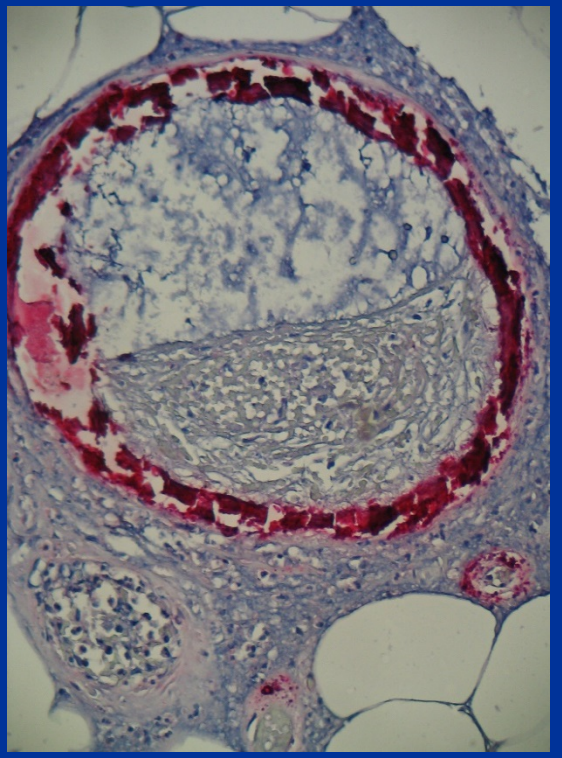
MGP

MGP in skin capillary

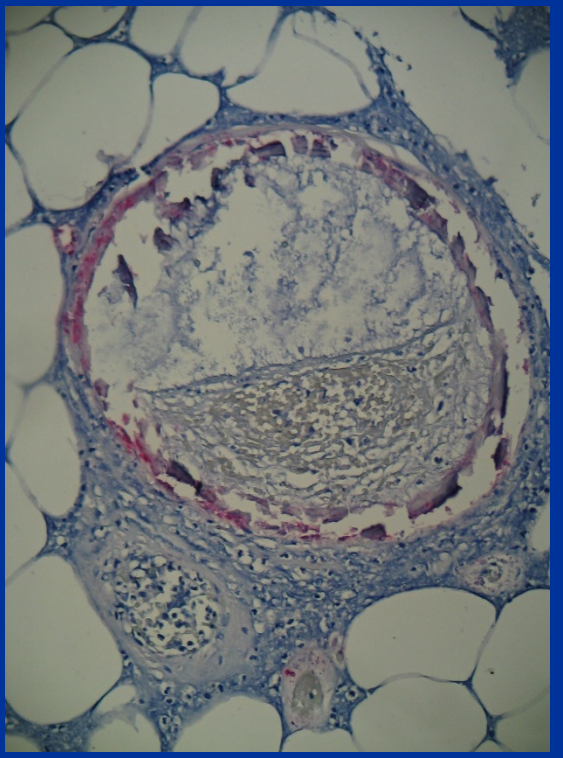
Calcium (von Kossa)



ucMGP (inactive)



cMGP (active)



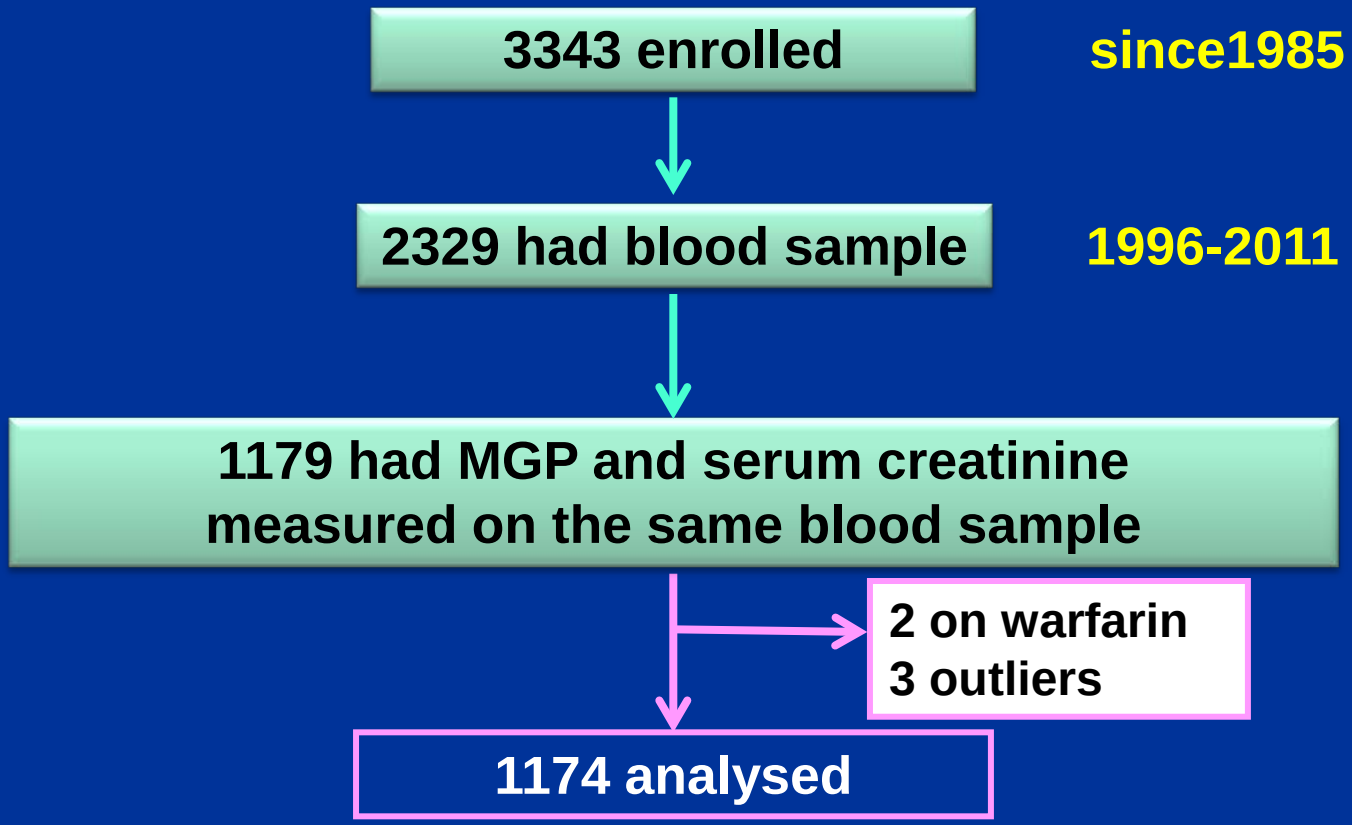
MGP

Research objective

- Previous research on the role of MGP in CV disease focused on macrovascular complications.
- In skin biopsies pericapillary microcalcifications co-localised with MGP. We hypothesised that MGP might be involved in adverse health effects related to the microcirculation.
- We tested the hypothesis that renal microcirculatory phenotypes, as exemplified by eGFR and microalbuminuria might be related to circulating MGP.

MGP

Study population



MGP

Continuous traits by thirds of the dp-ucMGP distribution

Characteristic	Low (n=390)	Medium (n=392)	High (n=392)	p
MGP, µg/L	<3.02	3.02 to 4.75	≥4.75	<0.001
Age, y	34.0	36.8	43.6	<0.001
BMI, kg/m^2	24.4	25.1	26.8	<0.001
SBP/DBP, mmHg	122.5/77.3	126.1/78.5	129.1/79.5	≤0.008
Heart rate, bpm	65.8	65.8	67.0	0.12
Cholesterol, mmol/L	5.00	5.05	5.36	<0.001
Glucose, mmol/L	4.89	5.05	5.11	0.03

p for trend.

MGP

Categorical traits by thirds of the dp-ucMGP distribution

Characteristic	Low (n=390)	Medium (n=392)	High (n=392)	p
Women, %	49.2	49.7	55.1	0.19
Smoker, %	27.2	24.7	13.8	<0.001
Drinker, %	67.7	60.0	57.1	0.007
CV history, %	1.5	2.8	4.6	0.04
Diabetes, %	2.8	6.1	4.6	0.08
Microalbuminuria, %	5.6	3.3	5.6	0.15
HT (treated), %	18.5 (37.5)	28.3 (49.5)	39.5 (55.5)	<0.001

p for trend.

MGP

Renal function by thirds of the dp-ucMGP distribution

Characteristic	Low (n=390)	Medium (n=392)	High (n=392)	p
eGFR, mL/min/1.73 m^2	92.9	90.9	85.0	<0.001
24-h microalbuminuria, mg	12.0	12.1	14.6	0.45
Stage of CKD, %				
1	52.1	50.5	37.8	<0.001
2	46.9	45.2	52.3	<0.001
3	1.0	4.3	10.0	<0.001

p for trend.

MGP

Multivariable-adjusted associations

	eGFR		Log ACR	
	Estimate	p	Estimate	p
Log dp-ucMGP				
Adjusted	–1.57	0.02	0.021	0.12
Fully adjusted	–1.54	0.02	0.021	0.12
Log t-ucMGP				
Adjusted	1.89	0.04	0.004	0.85
Fully adjusted	1.83	0.048	0.004	0.84

All models account for MAP, PR, BSUG, total-to-HDL cholesterol ratio, γ-GT, SMK, and AHT (DIU, βb, RAS inhibitors, vasodilators); ACR additionally adjusted for sex, age, and BMI. Fully adjusted models included both dp-ucMGP and t-ucMGP.

MGP

Multivariable-adjusted odds ratios

	CKD		Microalbuminuria	
	Estimate	p	Estimate	p
Log dp-ucMGP				
Adjusted	1.19	0.02	1.43	0.07
Fully adjusted	1.18	0.02	1.43	0.07
Log t-ucMGP				
Adjusted	0.90	0.32	0.73	0.18
Fully adjusted	0.91	0.35	0.74	0.20

CKD is an eGFR <60 mL/min/1.73 m^2. Microalbuminuria was ACR ≥3.5 mg/mmol in women or ≥2.5 mg/mmol in men. Odds ratio express the risk associated with a doubling of dp-ucMGP or t-ucMGP. All models accounted for covariables and confounders as in the previous slide.

MGP

Conclusions

In the general population, eGFR is inversely correlated with dp-ucMGP, a marker of a vitamin K deficiency, whereas the opposite is the case for t-ucMGP, a marker of prevalent arterial calcification.

MGP

Perspectives

- MGP, a marker of vitamin K status, is associated with adverse health outcomes, including endpoints driven by macro- and micro-circulatory events.
- From 20% to 40% of Flemish have suboptimal vitamin K status. Nothing is known about other populations!
- Current optimal daily allowances for vitamin K address clothing, but not vascular health.
- Time for revision?