Manuscript Title: Associations of estimated pulse wave velocity with cardiovascular-kidney-metabolic syndrome in US adults: NHANES 1999-2018: the role of sex and ethnicity

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Supplementary Table 1 Definitions of CKM conditions

CKM conditions	Definition	CKM indicators	Threshold for CKM indicators
CVD	Individuals with clinical CVD or subclinical CVD	Clinical CVD	History of chronic heart failure, coronary heart disease, heart attack, or stroke
		Subclinical CVD	Any of the following criterion is met: 1) Very high-risk CKD in KDIGO classification: UACR ≥ 300 mg/g and eGFR ≤ 45-59 ml/min/1.73m^2, UACR ≥ 30 mg/g and eGFR ≤ 30-44 ml/min/1.73m^2, or eGFR ≤ 29 ml/min/1.73m^2. 2) Predicted 10-year CVD risk ≥ 20%
Kidney diseases	Individuals with CKD	CKD	Moderate-to-high-risk CKD in KDIGO classification: UACR ≥ 30 mg/g and eGFR ≥ 60 ml/min/1.73m^2, UACR < 300 mg/g and eGFR ≤ 45-59 ml/min/1.73m^2, or UACR < 30 mg/g and eGFR ≤ 30-44 ml/min/1.73m^2.
Metabolic disorders	Individuals with overweight/obesity, abdominal obesity, prediabetes, diabetes, hypertension, hypertriglyceridemia or MetS	Overweight/obesity	BMI ≥25 kg/m^2 (or ≥23 kg/m^2 if Asian ancestry) [a]
		Abdominal obesity	Waist circumference ≥88/102 cm in female/male (or if Asian ancestry ≥80/90 cm in female/male)
		Prediabetes	Fasting blood glucose ≥ 100-124 mg/dL or HbA1c ≥ 5.7%-6.4% and without self-reported diagnosis of diabetes, use of insulin, or oral hypoglycemic agents

		Diabetes	Fasting blood glucose ≥ 125 mg/dL or HbA1c ≥ 6.5% or self-reported diagnosis of diabetes, use of insulin, or oral hypoglycemic agents
		Hypertension	SBP ≥130 mm Hg or DBP ≥80 mm Hg or self-reported diagnosis of hypertension or use of antihypertensive medications
		Hypertriglyceridemia	Triglycerides ≥ 135 mg/dL
		MetS	MetS is defined by the presence of 3 or more of the following: 1) Waist circumference ≥88/102 cm in female/male (or if Asian ancestry ≥80/90 cm in female/male). 2) HDL cholesterol ≥50/40 mg/dL in female/male. 3) Triglycerides ≥150 mg/dL. 4) Elevated blood pressure (SBP ≥130 mm Hg or DBP ≥80 mm Hg and/or use of antihypertensive medications) 5) Prediabetes

Abbreviations: BMI: body mass index; CKD: chronic kidney disease; CKM: cardiovascular-kidney-metabolic; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; KDIGO: The Kidney Disease: Improving Global Outcomes; MetS: metabolic syndrome; SBP: systolic blood pressure; UACR: urinary albumin to creatinine ratio.

[a] Asian was not listed as a separate ethnicity until NAHNES 2011-2012, therefore the uniform threshold for BMI and waist circumference was used in all participants in NHANES 1999-2010.

Supplementary Table 2 Detailed algorithm of the simplified 10-year CVD risk models

Women	**log-Odds** = -3.307728 + 0.7939329 × (age – 55) /10 + 0.0305239 × (TC – HDL-C – 3.5) – 0.1606857 × (HDL-C – 1.3) /0.3 – 0.2394003 × (min(SBP, 110) – 110) /20 + 0.360078 × (max(SBP, 110) – 130) /20 + 0.8667604 × (if diabetes) + 0.5360739 × (if current smoker) + 0.6045917 × (min(eGFR, 60) – 60) / -15 + 0.0433769 × (max(eGFR, 60) – 90) / -15 + 0.3151672 × (if using anti-hypertensive medication) – 0.1477655 × (if using statin) – 0.0663612 × (if using anti-hypertensive medication) × (max(SBP, 110) – 130) /20 + 0.1197879 × (if using statin) × (TC – HDL-C – 3.5) – 0.0819715 × (age – 55) /10 × (TC – HDL-C – 3.5) + 0.0306769 × (age – 55) /10 × (HDL-C – 1.3) /0.3 – 0.0946348 × (age – 55) /10 × (max(SBP, 110) – 130) /20 – 0.27057 × (age – 55) /10 × (if diabetes) – 0.078715 × (age – 55) /10 × (if current smoker) – 0.1637806 × (age – 55) /10 × (min(eGFR, 60) – 60) / -15 **Risk** = exp(log-Odds) / (1 + exp(log-Odds))
Men	**log-Odds** = -3.031168 + 0.7688528 × (age – 55) /10 + 0.0736174 × (TC – HDL-C – 3.5) – 0.0954431 × (HDL-C – 1.3) /0.3 – 0.4347345 × (min(SBP, 110) – 110) /20 + 0.3362658 × (max(SBP, 110) – 130) /20 + 0.7692857 × (if diabetes) + 0.4386871 × (if current smoker) + 0.5378979 × (min(eGFR, 60) – 60) / -15 + 0.0164827 ×

	(max(eGFR, 60) – 90) / -15 + 0.288879 × (if using anti-hypertensive medication) – 0.1337349 × (if using statin) – 0.0475924 × (if using anti-hypertensive medication) × (max(SBP, 110) – 130) /20 + 0.150273 × (if using statin) × (TC – HDL-C – 3.5) – 0.0517874 × (age – 55) /10 × (TC – HDL-C – 3.5) + 0.0191169 × (age – 55) /10 × (HDL-C – 1.3) /0.3 – 0.1049477 × (age – 55) /10 × (max(SBP, 110) – 130) /20 – 0.2251948 × (age – 55) /10 × (if diabetes) – 0.0895067 × (age – 55) /10 × (if current smoker) – 0.1543702 × (age – 55) /10 × (min(eGFR, 60) – 60) / -15 **Risk** = exp(log-Odds) / (1 + exp(log-Odds))

The PREVENT equations were developed and validated for adults 30-79 years of age. As such, risk was not estimated for adults <30 years. However, to minimize underestimation of CKD Stage 3, adults ≥80 years were not excluded from 10-year CVD risk. Instead, adults ≥80 years were assigned an age of 79 years when determining 10-year CVD risk to allow for conservative estimates. Further, PREVENT was developed for variables with the following ranges: total cholesterol 130-320 mg/dL, HDL-C 20-100 mg/dL, systolic blood pressure 90-200 mmHg, and eGFR 14-140 mL/min/1.73m^2. To approximate PREVENT risk strata, values for these variables above or below these bounds were set to the upper or lower bounds of allowable values respectively (for example, total cholesterol of 330 mg/dL was set as 320 mg/dL).

Abbreviations: eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein cholesterol; SBP: systolic blood pressure; TC: total cholesterol.

Supplementary Table 3 Methods for evaluating each CKM stage

CKM stages	Definition	Criterion	Threshold for CKM conditions
Stage 0: No CKM risk factors	Individuals with normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD	All criteria are met	BMI <25 kg/m^2 (or <23 kg/m^2 if Asian ancestry) [a]
			Waist circumference <88/102 cm in female/male (or if Asian ancestry <80/90 cm in female/male)
			Fasting blood glucose < 100 mg/dL and HbA1c < 5.7% and without self-reported diagnosis of diabetes, use of insulin, or oral hypoglycemic agents
			SBP <130 mm Hg and DBP <80 mm Hg without self-reported diagnosis of hypertension or use of antihypertensive medications
			HDL cholesterol <50/40 mg/dL in female/male and triglycerides < 150 mg/dL
			Low-risk CKD in KDIGO classification according to eGFR and UACR: UACR < 30 mg/g and eGFR ≥ 60 ml/min/1.73m^2.
			Predicted 10-year CVD risk < 20%
			No clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other	Any of the three criteria is met	Overweight/obesity
			Abdominal obesity
			Prediabetes
		All criteria are met	SBP <130 mm Hg and DBP <80 mm Hg without self-

	metabolic risk factors or CKD		reported diagnosis of hypertension or use of antihypertensive medications
			HDL cholesterol <50/40 mg/dL in female/male and triglycerides < 150 mg/dL
			Low-risk CKD in KDIGO classification according to eGFR and UACR: UACR < 30 mg/g and eGFR ≥ 60 ml/min/1.73m^2.
			Predicted 10-year CVD risk < 20%
			No clinical CVD
Stage 2: Metabolic risk factors and CKD	Individuals with metabolic risk factors (hypertriglyceridemia, hypertension, MetS, diabetes), or CKD	Any of the five criteria is met	Hypertriglyceridemia
			Hypertension
			diabetes
			MetS
			Moderate-to-high-risk CKD in KDIGO classification
		All criteria are met	No very high-risk CKD in KDIGO classification
			Predicted 10-year CVD risk < 20%
			No clinical CVD
Stage 3: Subclinical CVD in CKM	Subclinical CVD among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD	Any of the two criteria is met	Very high-risk CKD in KDIGO classification
			Predicted 10-year CVD risk ≥ 20%
		Any of the eight criteria is met	Overweight/obesity
			Abdominal obesity
			Prediabetes
			Hypertriglyceridemia
			Hypertension
			diabetes

			MetS
			Moderate-to-high-risk CKD in KDIGO classification
		The criterion is met	No clinical CVD
Stage 4: Clinical CVD in CKM	Clinical CVD among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD	The criterion is met	Clinical CVD
		Any of the nine criteria is met	Overweight/obesity
			Abdominal obesity
			Prediabetes
			Hypertriglyceridemia
			Hypertension
			diabetes
			MetS
			Moderate-to-high-risk CKD in KDIGO classification
			Very high-risk CKD in KDIGO classification

Abbreviations: BMI: body mass index; CKD: chronic kidney disease; CKM: cardiovascular-kidney-metabolic; CVD: cardiovascular disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; KDIGO: The Kidney Disease: Improving Global Outcomes; SBP: systolic blood pressure; UACR: urinary albumin to creatinine ratio.

[a] Asian was not listed as a separate ethnicity until NAHNES 2011-2012, therefore the uniform threshold for BMI and waist circumference was used in all participants in NHANES 1999-2010.

eTable 4. The percentages of participants with missing covariates in study sample (N=21,397)

Variables	N	%
Poverty to income ratio	1833	8.6
Education	23	0.1
Employment	12	0.1
Alcohol drinking	1176	5.5
Physical activity	8	0.0
HEI-2010 score	781	3.7

Abbreviations: HEI: healthy eating index

Supplementary Table 5. Baseline characteristics of eligible participants who had complete information about ePWV or CKM stages and who did not

Characteristic [a]	**Overall** N = 23,839	**Non-completed** N = 2,442	**Completed** N = 21,397	**P value**
Age (year)	50.16 (18.10)	53.98 (19.75)	49.73 (17.85)	<0.001
Female %	12,255 (51.4)	1,367 (56.0)	10,888 (50.9)	<0.001
Ethnicity %				<0.001
Non-Hispanic White	10,614 (44.5)	983 (40.3)	9,631 (45.0)	
Non-Hispanic Black	4,808 (20.2)	607 (24.9)	4,201 (19.6)	
Mexican	4,191 (17.6)	387 (15.9)	3,804 (17.8)	
Other Hispanic	2,023 (8.5)	200 (8.2)	1,823 (8.5)	
Other [b]	2,203 (9.2)	265 (10.9)	1,938 (9.1)	

Income level %				<0.001
Low	6,608 (27.7)	873 (35.7)	5,735 (26.8)	
Medium	11,624 (48.8)	1,171 (48.0)	10,453 (48.9)	
High	5,607 (23.5)	398 (16.3)	5,209 (24.3)	
Education level %				<0.001
Low	6,528 (27.4)	812 (33.4)	5,716 (26.7)	
Medium	5,463 (22.9)	556 (22.9)	4,907 (23.0)	
High	11,813 (49.6)	1,062 (43.7)	10,751 (50.3)	
Missing	35	12	23	
Employment %				<0.001
Unemployment	5,366 (22.5)	698 (28.6)	4,668 (21.8)	
Employment	18,460 (77.5)	1,743 (71.4)	16,717 (78.2)	
Missing	13	1	12	
Smoking %				0.351
Never	12,834 (53.8)	1,347 (55.2)	11,487 (53.7)	
Former	6,042 (25.3)	608 (24.9)	5,434 (25.4)	
Current	4,962 (20.8)	487 (19.9)	4,475 (20.9)	
Alcohol drinking %				<0.001
Never	3,098 (14.1)	355 (20.6)	2,743 (13.6)	
Former	3,454 (15.7)	317 (18.4)	3,137 (15.5)	
Current	15,392 (70.1)	1,051 (61.0)	14,341 (70.9)	
Missing	1,895	719	1,176	
Physical activity %				<0.001
Inactive	11,916 (50.0)	1,528 (62.6)	10,388 (48.6)	

Active	11,915 (50.0)	914 (37.4)	11,001 (51.4)	
Missing	8	0	8	
HEI-2010 score	51.78 (14.47)	51.87 (14.25)	51.77 (14.49)	<0.001
Missing	1,325	544	781	
BMI (kg/m^2)	28.90 (6.79)	29.85 (8.87)	28.81 (6.55)	0.031
Missing	383	383	0	
HbA1c (%)	5.73 (1.09)	5.85 (1.19)	5.72 (1.08)	<0.001
Missing	42	42	0	
TC (mg/dl)	195.06 (42.52)	192.68 (43.09)	195.30 (42.45)	0.002
Missing	269	269	0	
HDL-C (mg/dl)	53.64 (16.18)	54.03 (17.65)	53.60 (16.03)	0.981
Missing	269	269	0	
eGFR (mL/min/1.73 m^2)	94.63 (22.76	90.55 (26.86)	95.03 (22.28)	<0.001
Missing	325	325	0	
Cancer %	2,202 (9.2)	272 (11.1)	1,930 (9.0)	<0.001
Liver diseases %	949 (4.0)	101 (4.1)	848 (4.0)	0.679
Lung diseases %	499 (2.1)	83 (3.4)	416 (1.9)	<0.001

Abbreviations: BMI: body mass index; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol; HEI: healthy eating index; TC: total cholesterol.

[a] We did not weight the estimates. Data were expressed as mean (standard deviation) or frequency (percentage) when appropriate.

[b] Including Asian and multiracial.

Supplementary Table 6 Weighted prevalence of combinations of CKM conditions in overall participants and according to ePWV subgroups

Combinations of CKM conditions [b]	No. (%) [a]		
	Overall	ePWV < 10 m/s	ePWV ≥ 10 m/s
None	1,970 (11.7)	1,937 (14.1)	33 (0.9)
Only CVD	31 (0.1)	18 (0.1)	13 (0.2)
Only CKD	114 (0.6)	110 (0.8)	4 (0.1)
Only MD	13,692 (68.2)	11,804 (74.4)	1,888 (39.9)
CVD + CKD	9 (0.0)	0 (0.0)	9 (0.1)
CVD + MD	2,544 (8.8)	842 (4.3)	1,702 (29.4)
CKD + MD	1,521 (6.0)	1,048 (5.4)	473 (9.2)
CVD + CKD + MD	1,516 (4.4)	232 (1.0)	1,284 (20.1)

Abbreviations: CKD: chronic kidney disease; CKM: cardiovascular-kidney-metabolic; CVD: cardiovascular diseases; MD: metabolic disorders.

[a] Data were weighted estimates and expressed as frequency (weighted percentage).

[b] CKM conditions include CVD (i.e., clinical or subclinical CVD), kidney diseases (i.e., CKD) and metabolic disorders (i.e., overweight/obesity, abdominal obesity, prediabetes, diabetes, hypertension, hypertriglyceridemia or MetS).

Supplementary Table 7 The associations of ePWV (in continuous, 1 m/s increase) with CKM stages in participants with complete covariates data (N=18149)

Unadjusted		Adjusted [a]		Adjusted [b]		Adjusted [c]
OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
Reference		Reference		Reference		Reference
1.74 (1.56, 1.94)	<0.001	1.77 (1.58, 1.97)	<0.001	1.72 (1.54, 1.91)	<0.001	1.52 (1.35, 1.7
3.26 (2.94, 3.63)	<0.001	3.42 (3.09, 3.80)	<0.001	3.44 (3.10, 3.82)	<0.001	3.10 (2.75, 3.4

9.22 (8.21, 10.36)	<0.001	10.00 (8.89, 11.24)	<0.001	10.14 (8.99, 11.44)	<0.001	8.32 (7.23, 9.5
5.51 (4.91, 6.17)	<0.001	5.91 (5.29, 6.61)	<0.001	5.95 (5.31, 6.66)	<0.001	4.62 (4.06, 5.2

Abbreviations: CI: confidence interval; CKM: cardiovascular-kidney-metabolic; OR: odds ratio.

[a] Models were adjusted for socio-demographic covariates, including sex (male, female), ethnicity (non-Hispanic white, non-Hispanic black, Mexican, other Hispanic, other), and SES levels (poor, medium, good).

[b] Models were adjusted for socio-demographic covariates and lifestyle covariates: self-reported smoking (current smoker, former smoker, never smoker), self-reported alcohol drinking (current drinker, former drinker, never drinker), self-reported physical activity (inactive, active), and diet quality (HEI-2010 score, continuous).

[c] Models were adjusted for socio-demographic covariates, lifestyle covariates and CKM risk factors: BMI, HbA1c, TC, HDL-C, eGFR, self-reported cancer (yes, no), self-reported liver diseases (yes, no), and self-reported lung diseases (yes, no).

Supplementary Table 8 The associations of ePWV (in continuous, 1 m/s increase) with numbers of CKM conditions

M	Unadjusted		Adjusted [a]		Adjusted [b]		Adjusted [c]
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
	Reference		Reference		Reference		Reference
	2.55 (2.34, 2.79)	<0.001	2.63 (2.41, 2.87)	<0.001	2.61 (2.39, 2.84)	<0.001	2.17 (1.98, 2.3
	4.33 (3.95, 4.75)	<0.001	4.57 (4.17, 5.01)	<0.001	4.55 (4.15, 4.99)	<0.001	3.34 (3.02, 3.7
	6.51 (5.92, 7.16)	<0.001	6.87 (6.25, 7.55)	<0.001	6.83 (6.22, 7.49)	<0.001	4.81 (4.34, 5.3

Abbreviations: CI: confidence interval; CKM: cardiovascular-kidney-metabolic; OR: odds ratio.

[a] Models were adjusted for socio-demographic covariates, including sex (male,

female), ethnicity (non-Hispanic white, non-Hispanic black, Mexican, other Hispanic, other), and SES levels (poor, medium, good).

[b] Models were adjusted for socio-demographic covariates and lifestyle covariates: self-reported smoking (current smoker, former smoker, never smoker), self-reported alcohol drinking (current drinker, former drinker, never drinker), self-reported physical activity (inactive, active), and diet quality (HEI-2010 score, continuous).

[c] Models were adjusted for socio-demographic covariates, lifestyle covariates and CKM risk factors: BMI, HbA1c, TC, HDL-C, eGFR, self-reported cancer (yes, no), self-reported liver diseases (yes, no), and self-reported lung diseases (yes, no).

[d] CKM conditions include CVD (i.e., clinical or subclinical CVD), kidney diseases (i.e., CKD) and metabolic disorders (i.e., overweight/obesity, abdominal obesity, prediabetes, diabetes, hypertension, hypertriglyceridemia or MetS).

Supplementary Table 9 The associations of ePWV (in continuous, 1 m/s increase) with combinations of CKM conditions

of [d]	Unadjusted		Adjusted [a]		Adjusted [b]		Adjusted [c]
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)
	Reference		Reference		Reference		Reference
	3.86 (3.05, 4.89)	<0.001	4.06 (3.20, 5.15)	<0.001	4.04 (3.03, 5.37)	<0.001	2.64 (1.97, 3.5
	0.97 (0.74, 1.26)	0.802	1.07 (0.83, 1.38)	0.594	1.10 (0.86, 1.42)	0.439	1.04 (0.82, 1.3
	2.59 (2.37, 2.84)	<0.001	2.67 (2.45, 2.92)	<0.001	2.65 (2.43, 2.89)	<0.001	2.25 (2.05, 2.4
	8.33 (7.32, 9.48)	<0.001	9.07 (8.12, 10.13)	<0.001	8.69 (7.73, 9.78)	<0.001	6.65 (4.82, 9.1
	5.20 (4.73, 5.72)	<0.001	5.53 (5.03, 6.08)	<0.001	5.54 (5.04, 6.10)	<0.001	4.13 (3.72, 4.5
	3.51 (3.18, 3.86)	<0.001	3.70 (3.37, 4.08)	<0.001	3.70 (3.36, 4.07)	<0.001	2.83 (2.53, 3.1
+	6.85 (6.22, 7.56)	<0.001	7.27 (6.60, 8.01)	<0.001	7.25 (6.59, 7.97)	<0.001	5.30 (4.78, 5.8

Abbreviations: CKD: chronic kidney disease; CI: confidence interval; CKM: cardiovascular-kidney-metabolic; CVD: cardiovascular diseases; MD: metabolic disorders; OR: odds ratio.

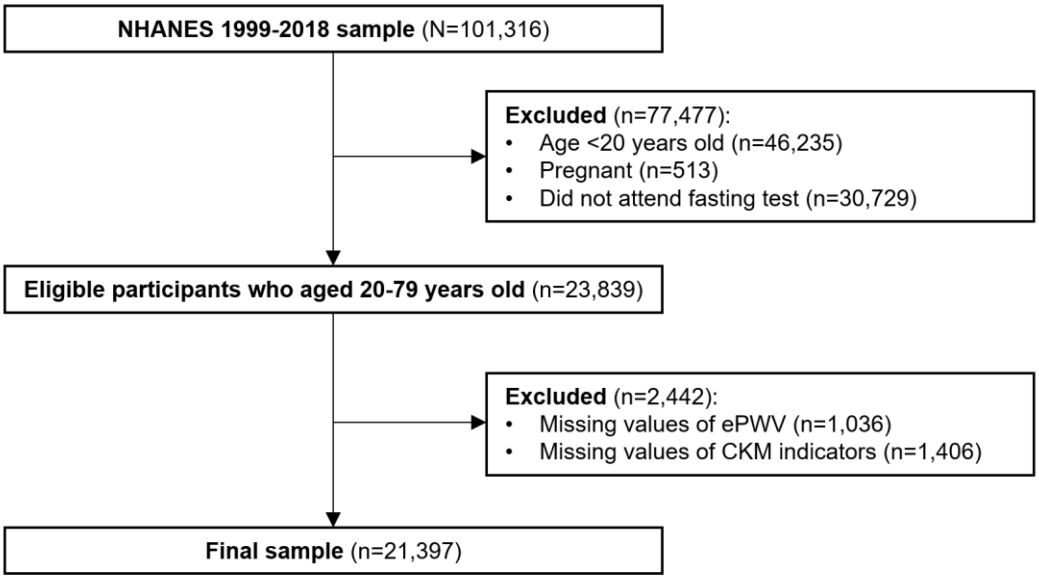
[a] Models were adjusted for socio-demographic covariates, including sex (male, female), ethnicity (non-Hispanic white, non-Hispanic black, Mexican, other Hispanic, other), and SES levels (poor, medium, good).

[b] Models were adjusted for socio-demographic covariates and lifestyle covariates: self-reported smoking (current smoker, former smoker, never smoker), self-reported alcohol drinking (current drinker, former drinker, never drinker), self-reported physical activity (inactive, active), and diet quality (HEI-2010 score, continuous).

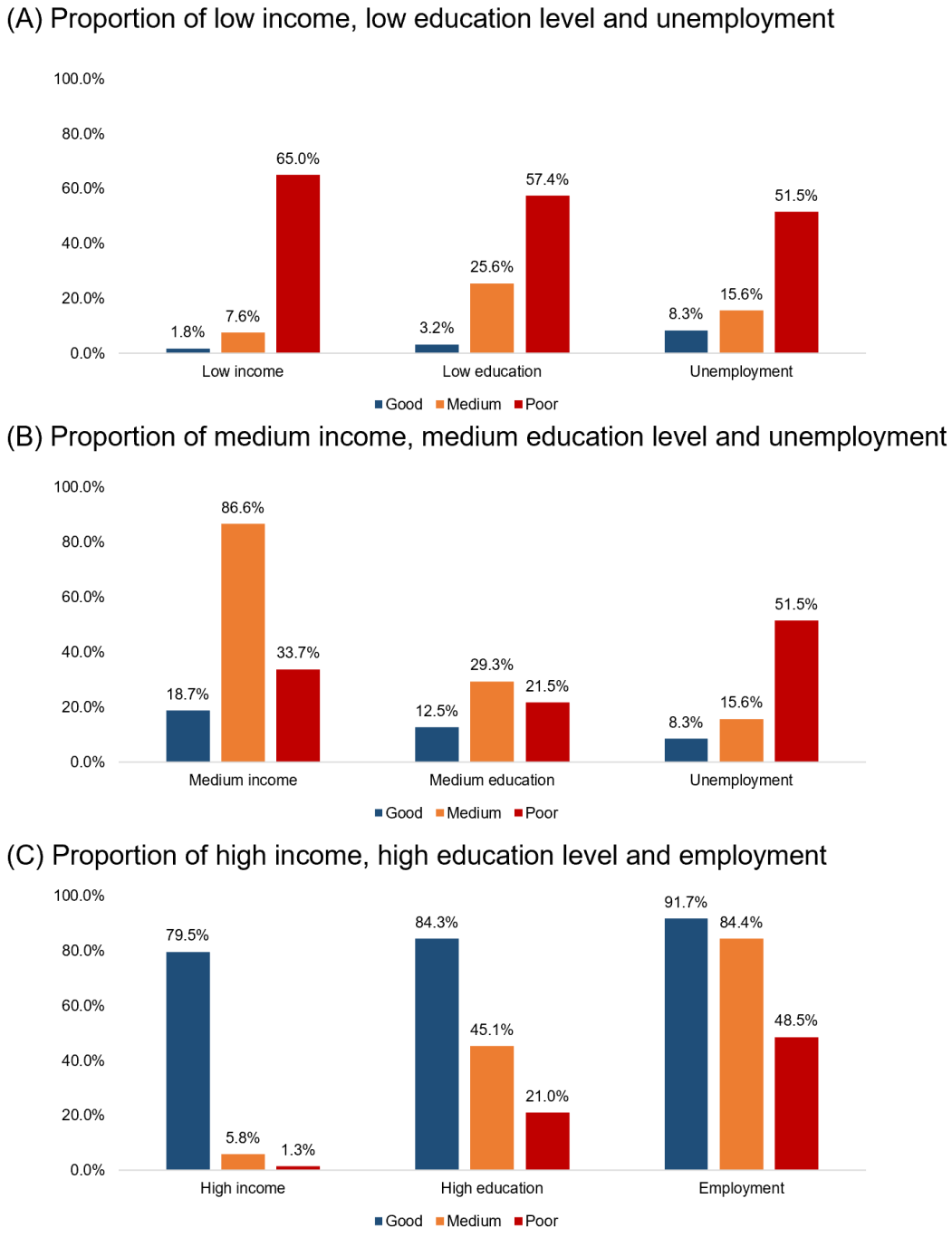
[c] Models were adjusted for socio-demographic covariates, lifestyle covariates and CKM risk factors: BMI, HbA1c, TC, HDL-C, eGFR, self-reported cancer (yes, no), self-reported liver diseases (yes, no), and self-reported lung diseases (yes, no).

[d] CKM conditions include CVD (i.e., clinical or subclinical CVD), kidney diseases (i.e., CKD) and metabolic disorders (i.e., overweight/obesity, abdominal obesity, prediabetes, diabetes, hypertension, hypertriglyceridemia or MetS).

Supplementary Figure:



Supplementary Figure 1. Flowchart of study design. CKM: cardiovascular-kidney-metabolic; NHANES: National Health and Nutrition Examination Survey; ePWV: estimated pulse wave velocity.

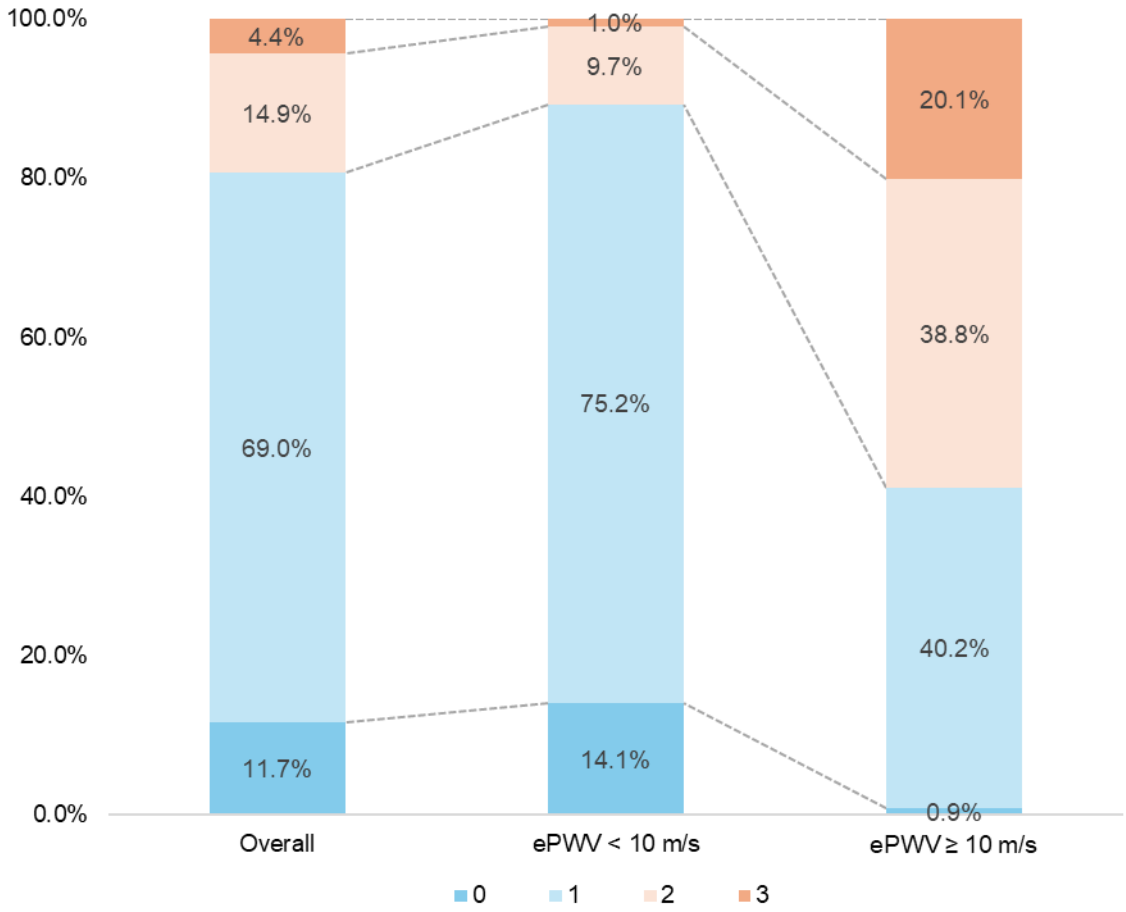


eFigure 2. Item-related proportion of each socioeconomic latent class

(A) Proportion of low income, low education level and unemployment in three socioeconomic latent class: good (color in blue), medium (color in orange), poor (color in red); (B) Proportion of medium income, medium education level and unemployment in three socioeconomic latent class: good (color in blue), medium (color in orange), poor (color in red); (C) Proportion of high income, high education

level and employment in three socioeconomic latent class: good (color in blue), medium (color in orange), poor (color in red).

Income levels were categorized into three levels according to the poverty to income ratio: low (≤1), medium (1-4), and high (≥4); education levels were categorized into less than high school diploma (low), high school graduate or equivalent (medium), and college or above (high); Employment was categorized into two groups: unemployment and employment (including retirees and students).



eFigure 3. Weighted prevalence of numbers of CKM conditions in overall participants and according to ePWV subgroups

Abbreviations: CKM: cardiovascular-kidney-metabolic; ePWV: estimated pulse wave velocity. CKM conditions include CVD (i.e., clinical or subclinical CVD), kidney diseases (i.e., CKD) and metabolic disorders (i.e., overweight/obesity, abdominal obesity, prediabetes, diabetes, hypertension, hypertriglyceridemia or MetS).