

Supplemental Material

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Table S1. Definitions of CKM syndrome stages.

CKM syndrome stages	Definition
Stage 0: No CKM risk factors	<p>Individuals without overweight/obesity, abdominal obesity, metabolic risk factors (hypertension, hypertriglyceridemia, prediabetes, diabetes, MetS), CKD, or subclinical/clinical CVD.</p> <p>All criteria are met:</p> <ul style="list-style-type: none">● BMI < 23 kg/m²● Waist circumference <80/90 cm in female/male● SBP < 130 mmHg, DBP < 80 mmHg and without self-reported diagnosis of hypertension or use of anti-hypertensive medications● TG < 135 mg/dL● Fasting blood glucose < 100 mg/dL, HbA1c < 5.7% and without self-reported diagnosis of diabetes, use of insulin, or oral hypoglycemic agents● No MetS● eGFR ≥ 60 ml/min/1.73m²● Predicted 10-year CVD risk based on the Framingham risk score (female <21.5%, male <21.6%)● No clinical CVD
Stage 1: Excess or dysfunctional adiposity	<p>Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD.</p> <p>Any of the three criteria is met:</p> <ul style="list-style-type: none">● Overweight/obesity● Abdominal obesity● Prediabetes <p>All criteria are met:</p> <ul style="list-style-type: none">● SBP <130 mmHg and DBP <80 mmHg without self-reported diagnosis of hypertension or use of anti-hypertensive medications● TG < 135 mg/dL● Fasting plasma glucose < 126 mg/dL and HbA1c < 6.5% and without self-reported diagnosis of diabetes, use of insulin, or oral hypoglycemic agents● No MetS● eGFR ≥ 60 ml/min/1.73m²● Predicted 10-year CVD risk based on the Framingham risk score (female <21.5%, male <21.6%)● No clinical CVD

Stage 2: Metabolic risk factors and CKD

Individuals with metabolic risk factors (hypertriglyceridemia, hypertension, diabetes, MetS), or CKD (moderate- or high-risk).

Any of the five criteria is met:

- Hypertriglyceridemia
- Hypertension
- Diabetes
- MetS
- Moderate-to-high-risk CKD

All criteria are met:

- No very high-risk CKD
- Predicted 10-year CVD risk based on the Framingham risk score (female < 21.5%, male < 21.6%)
- No clinical CVD

Stage 3: Subclinical CVD in CKM

Subclinical CVD among individuals with metabolic risk factors, or CKD.

Any of the two criteria is met:

- Very high-risk CKD
- Predicted 10-year CVD risk based on the Framingham risk score (female \geq 21.5%, male \geq 21.6%)

Any of the eight criteria is met:

- Overweight/obesity
- Abdominal obesity
- Prediabetes
- Hypertriglyceridemia
- Hypertension
- Diabetes
- MetS
- Moderate-to-high-risk CKD

The criterion is met:

- No clinical CVD
-

Overweight/obesity was defined as BMI \geq 23 kg/m².

Abdominal obesity was defined as waist circumference (WC) \geq 80 cm for women and \geq 90 cm for men.

Hypertension was defined as systolic blood pressure (SBP) \geq 130 mmHg or diastolic blood pressure (DBP) \geq 80 mmHg or self-reported diagnosis of hypertension or use of antihypertensive medications.

Diabetes was defined as fasting plasma glucose (FPG) \geq 126 mg/dL (7.0 mmol/L) or HbA1c \geq 6.5% or self-reported diagnosis of diabetes or use of antidiabetic medications.

Prediabetes was defined as FPG \geq 100–125 mg/dL or HbA1c between 5.7% and 6.4%.

Metabolic syndrome (MetS) is defined by the presence of 3 or more of the following:(1) abdominal obesity; (2) HDL-C $<$ 50 mg/dL for women and $<$ 40 mg/dL for men; (3) TG \geq 150 mg/dL; (4) elevated blood pressure (SBP \geq 130 mm Hg or DBP \geq 80 mm Hg and/or use of antihypertensive medications); and (5) FPG \geq 100 mg/dL.

Moderate-to-high-risk CKD is defined as eGFR \geq 30 and $<$ 60 ml/min/1.73m².

Very high-risk CKD is defined as eGFR $<$ 30 ml/min/1.73m².

Table S2. Detailed missing data for covariates.

Variables	Missing data
Dyslipidemia	49 (1.3%)
WBC	34 (0.9%)
Hemoglobin	34 (0.9%)
Platelets	33 (0.87%)
SBP	12 (0.32%)
DBP	12 (0.32%)
LDL-C	6 (0.16%)
Hypertension	3 (0.08%)
Drinking Status	4 (0.11%)
Diabetes	3 (0.08%)

Abbreviations: WBC, white blood cell count; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

Table S3. Baseline characteristics of participants with CKM stages 0–3 according to CVD status.

Variables	Total	Non-CVD	CVD	<i>P</i> value
No. of participants	3783	2879	904	
CKM syndrome stages, n (%)				
Stage 0	139 (3.7)	121 (4.2)	18 (2.0)	<0.001
Stage 1	413 (10.9)	345 (12.0)	68 (7.5)	
Stage 2	1087 (28.7)	810 (28.1)	277 (30.6)	
Stage 3	2144 (56.7)	1603 (55.7)	541 (59.8)	
Age, years	57.00 (51.00, 64.00)	57.00 (51.00, 63.00)	59.00 (54.00, 66.00)	<0.001
Gender, n (%)				
Male	1737 (45.9)	1367 (47.5)	370 (40.9)	0.001
Female	2046 (54.1)	1512 (52.5)	534 (59.1)	
Marital status, n (%)				
Married	3421 (90.4)	2630 (91.4)	791 (87.5)	
Other	362 (9.6)	249 (8.6)	113 (12.5)	0.001
Education level, n (%)				
Elementary school and below	2545 (67.3)	1928 (67.0)	617 (68.3)	0.498
Secondary school and above	1238 (32.7)	951 (33.0)	287 (31.7)	
Residence, n (%)				
Rural	2483 (65.6)	1935 (67.2)	548 (60.6)	<0.001
Urban	1300 (34.4)	944 (32.8)	356 (39.4)	
Smoking status, n (%)				
No	2317 (61.2)	1756 (61.0)	561 (62.1)	0.593
Yes	1466 (38.8)	1123 (39.0)	343 (37.9)	
Drinking status, n (%)				
No	2320 (61.3)	1752 (60.9)	568 (62.8)	0.305
Yes	1463 (38.7)	1127 (39.1)	336 (37.2)	
BMI, kg/m²	23.32 (21.09, 25.92)	23.13 (20.97, 25.59)	24.16 (21.62, 26.86)	<0.001
Waist circumference, cm	85.00 (78.00, 92.20)	84.20 (77.70, 91.00)	88.00 (80.00, 96.00)	<0.001
SBP, mmHg	126.00 (113.50, 140.75)	124.50 (112.50, 139.00)	131.75 (117.88, 146.50)	<0.001
DBP, mmHg	74.00 (66.50, 82.50)	73.50 (66.50, 81.50)	76.00 (68.50, 85.00)	<0.001
FPG, mg/dL	102.96 (95.22, 112.68)	102.60 (95.04, 112.14)	103.95 (95.58, 114.88)	0.002
HbA1c, %	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.20 (4.90, 5.50)	<0.001
TC, mg/dL	191.75 (168.56, 216.50)	190.59 (167.40, 216.11)	195.23 (172.42, 219.59)	0.002
TG, mg/dL	106.20 (75.22, 155.76)	103.54 (72.57, 152.22)	113.28 (82.97, 164.61)	<0.001
HDL-C, mg/dL	49.48 (40.59, 59.92)	49.87 (40.98, 60.70)	47.94 (39.43, 57.22)	<0.001
LDL-C, mg/dL	116.37 (95.10, 139.76)	115.59 (95.10, 138.98)	118.88 (97.42, 141.59)	0.013
Scr,mg/dL	0.75 (0.64, 0.87)	0.75 (0.64, 0.87)	0.73 (0.64, 0.87)	0.806
WBC, ×10⁹/L	5.90 (4.92, 7.20)	5.90 (4.90, 7.10)	6.04 (5.10, 7.40)	0.003
PLT, ×10⁹/L	209.00 (164.00, 257.00)	207.00 (162.00, 254.00)	216.00 (170.00, 266.00)	0.001
BUN, mg/dl	15.07 (12.60, 17.98)	15.15 (12.65, 18.16)	14.80 (12.46, 17.67)	0.014
UA, mg/dl	4.21 (3.51, 5.04)	4.21 (3.51, 5.04)	4.21 (3.51, 5.06)	0.815
CRP, mg/dl	1.00 (0.53, 2.02)	0.94 (0.51, 1.88)	1.17 (0.61, 2.37)	<0.001
Hemoglobin, g/dL	14.40 (13.10, 15.60)	14.30 (13.10, 15.60)	14.40 (13.30, 15.80)	0.089

eGFR, ml/min/1.73m²	95.57 (85.50, 103.14)	96.31 (86.17, 103.70)	93.58 (83.37, 100.96)	<0.001
Hypertension, n (%)				
No	2358 (62.3)	1914 (66.5)	444 (49.1)	<0.001
Yes	1425 (37.7)	965 (33.5)	460 (50.9)	
Dyslipidaemia, n (%)				
No	3468 (91.7)	2700 (93.8)	768 (85.0)	<0.001
Yes	315 (8.3)	179 (6.2)	136 (15.0)	
Diabetes, n (%)				
No	3566 (94.3)	2737 (95.1)	829 (91.7)	<0.001
Yes	217 (5.7)	142 (4.9)	75 (8.3)	
HGI₂₀₁₁, %	-0.06 (-0.33, 0.23)	-0.06 (-0.33, 0.22)	-0.04 (-0.29, 0.24)	0.043
Follow-up time, months	79.57 (13.80)	83.88 (0.99)	65.86 (23.38)	<0.001

Abbreviations: CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; WBC, white blood cell count; BUN, blood urea nitrogen; UA, uric acid; CRP, C-reactive protein; HGI, hemoglobin glycation index; SD, standard deviation.

Table S4. Association between HGI median and incident CVD in participants with CKM syndrome stages 0–3 (sensitivity analysis).

	Event/total, n (%)	Model 1		Model 2		Model 3	
		HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
HGI median group							
Low (< -0.057)	437/1891 (23.1%)	Ref		Ref		Ref	
High (\geq -0.057)	467/1892 (24.7%)	1.17 (1.02-1.33)	0.021	1.16 (1.02-1.32)	0.029	1.15 (1.01-1.31)	0.04

Model 1: non-adjusted. Model 2: adjusted for age, gender, marital status, education level, and residence. Model 3: adjusted for age, gender, marital status, education level, residence, hypertension, dyslipidaemia, diabetes, and BMI. Abbreviations: HR, hazard ratio; CI, confidence interval; HGI, hemoglobin glycation index; CVD, cardiovascular disease; BMI, body mass index.

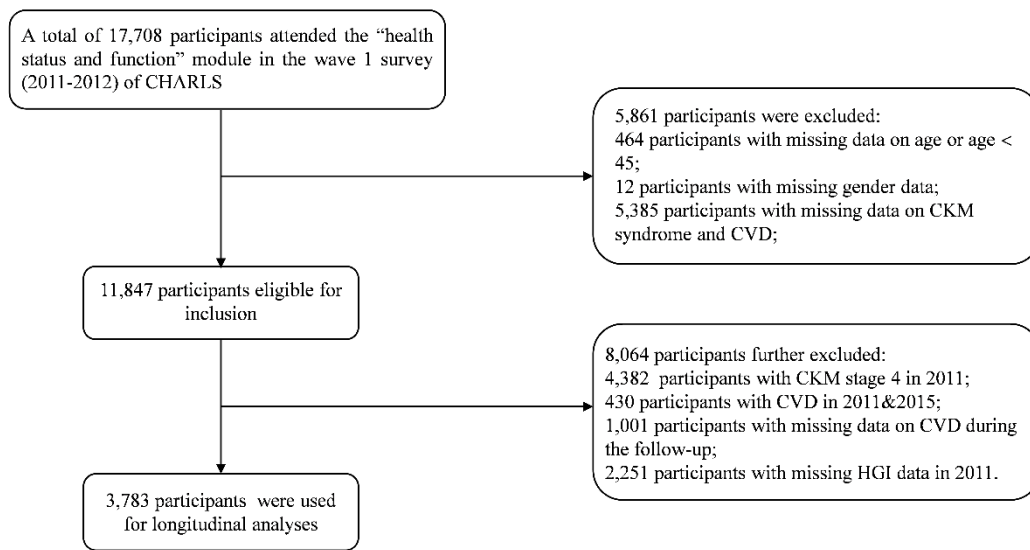


Figure S1. Flowchart of study participant selection.

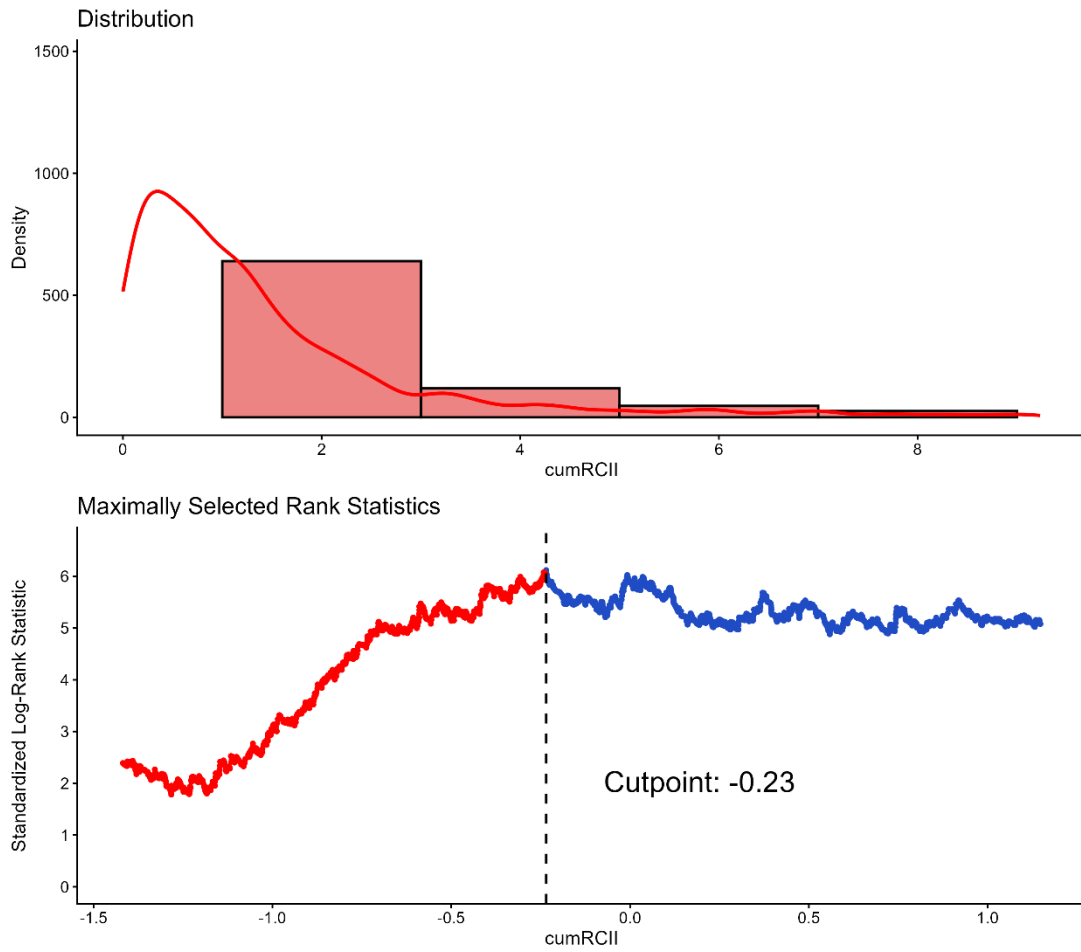


Figure S2. The optimal cut-off value of CumHGI. Abbreviations: CumHGI, cumulative hemoglobin glycation index.

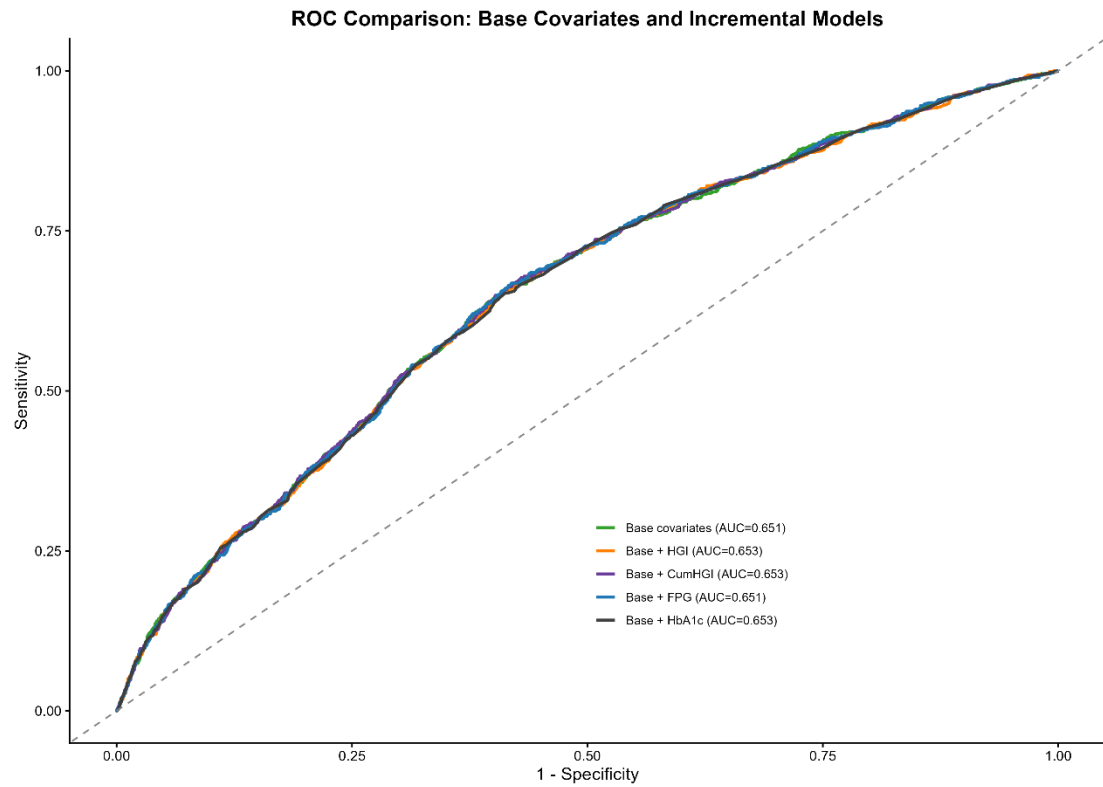


Figure S3. ROC curves comparing the predictive performance of HbA1c, FPG, HGI, and CumHGI for incident CVD in participants with CKM stages 0–3. Abbreviations: ROC, receiver operating characteristic; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; HGI, hemoglobin glycation index; CumHGI, cumulative hemoglobin glycation index; CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic.

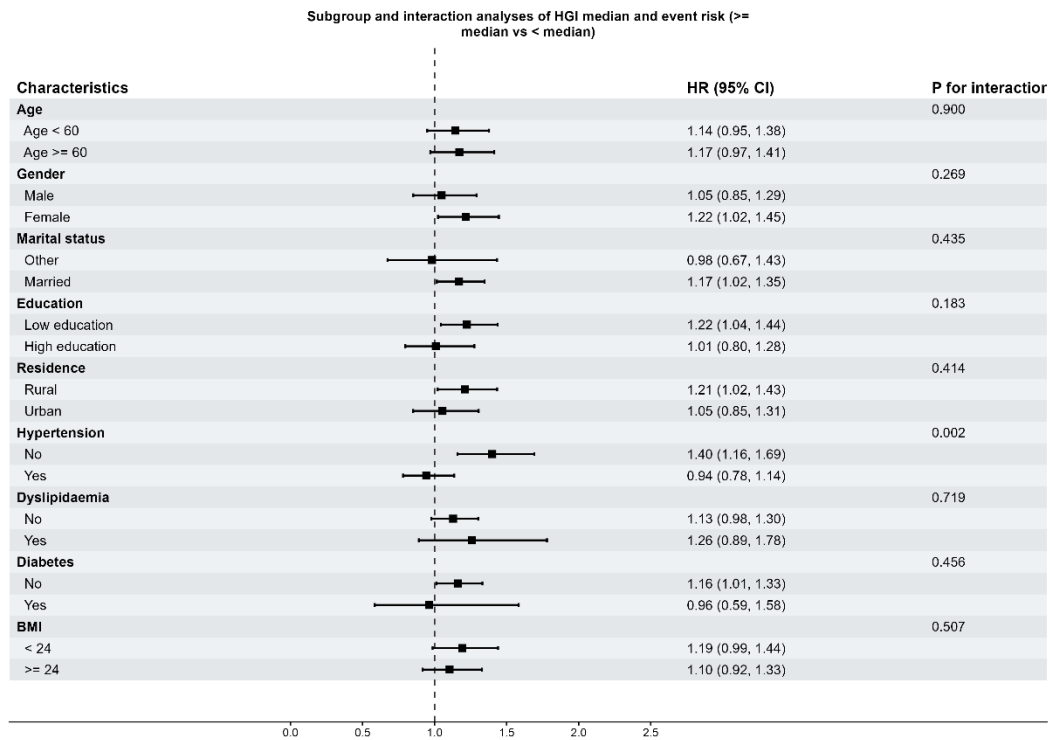


Figure S4. Subgroup analysis of HGI median and CVD risk in participants with CKM stage 0–3 (sensitivity analysis). All models were adjusted for age, gender, marital status, education level, residence, hypertension, dyslipidemia, diabetes, and BMI. Abbreviations: HR, hazard ratio; CI, confidence interval; HGI, hemoglobin glycation index; BMI, body mass index; CKM, cardiovascular-kidney-metabolic.