

Supplementary Table S1. Stages of CKM syndrome according to AHA definitions

CKM syndrome stage	AHA definition	Definition in the present study
Stage 0	Normal BMI and waist circumference, normoglycemia, normotension, normal lipid profile, and no evidence of CKD or subclinical or clinical CVD	All the following six conditions are met: (1) $18.5 \text{ kg/m}^2 \leq \text{BMI} < 25 \text{ kg/m}^2$ (2) Waist circumference $< 80 \text{ cm}$ (3) No hypertension and no drug-treated elevated blood pressure ^a (4) No diabetes or drug-treated hyperglycemia, and HbA1c of 4.0%–5.6% (5) HDL cholesterol $> 50 \text{ mg/dL}$, triglycerides $< 135 \text{ mg/dL}$, and no hypertriglyceridemia (6) No CKD or CVD
Stage 1	Overweight/obesity, abdominal obesity, or dysfunctional adipose tissue without the presence of other metabolic risk factors or CKD	Conditions 1 and/or 2 are met, without the presence of other metabolic risk factors (3–6): (1) $\text{BMI} \geq 25 \text{ kg/m}^2$ or diagnosis of obesity (2) Waist circumference $\geq 88 \text{ cm}$ or diagnosis of localized adiposity (3) HbA1c of 5.7%–6.4% (4) HDL cholesterol $\leq 50 \text{ mg/dL}$ (5) Triglycerides $\geq 150 \text{ mg/dL}$ (6) Elevated blood pressure
Stage 2	Hyperlipidemia, hypertension, metabolic syndrome, diabetes, or CKD	At least one of the following three conditions are met: (1) Metabolic syndrome ^b (2) Diagnosis of hyperlipidemia, hypertension, or diabetes, or no diagnosis of the above but controlled with medication (3) Stage G1–G3 CKD, hypertensive nephropathy without renal failure, or diabetes nephropathy without renal failure
Stage 3	Subclinical ASCVD or subclinical HF among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD	Both of the following two conditions are met: (1) Very high-risk CKD (stage G4 or G5 CKD) or renal failure
Stage 4	Clinical CVD among individuals with excess/dysfunctional adiposity, other CKM risk factors, or CKD	(2) CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, or atrial fibrillation)

Note. ^aElevated blood pressure: systolic blood pressure $\geq 130 \text{ mmHg}$ or diastolic blood pressure $\geq 80 \text{ mmHg}$ and/or use of antihypertensive medications. ^bMetabolic syndrome is defined by the presence of three or more of the following: (1) waist circumference $\geq 88 \text{ cm}$, (2) HDL cholesterol $\leq 50 \text{ mg/dL}$, (3) triglycerides $\geq 150 \text{ mg/dL}$, (4) elevated blood pressure, or (5) HbA1c of 5.7%–6.4% Abbreviations: CKM, cardiovascular-kidney-metabolic; AHA, American Heart Association; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

Supplementary Table S2. Disease codes and field IDs of components used in CKM syndrome diagnosis

Components	ICD10	ICD9	Self-report	Field ID
Low-risk chronic kidney disease	N18			
High-risk chronic kidney disease	I12, I13, N17–N19, Z49, Z94	585	1192, 1193, 1194	
Coronary heart disease	I20–I25	410-414	1074, 1075	53,
Heart failure	I50	428	1076	191,
Stroke	I160–I164	430-438	1081, 1086, 1491, 1583	2443, 6150,
Peripheral artery disease	I70, I73	443	1067	20002,
Atrial fibrillation	I48	427	1471	40000, 40001,
Localized adiposity/obesity	E65, E66	278		41270,
Type 2 diabetes	E11–E14	250	1220, 1223	41280
Hypertension	I10–I15	401, 405	1065, 1072	
Hyperlipidemia	E78	272		
Body mass index				21001
Waist circumference				48
Systolic blood pressure				93, 4080
Diastolic blood pressure				94, 4079
Medication for cholesterol, blood pressure, or diabetes				6177
Medication for cholesterol, blood pressure, or diabetes or treatment with exogenous hormones				6153
Glycated hemoglobin				30750
High-density lipoprotein cholesterol				30760
Triglycerides				30870

Note. Abbreviations: ICD10, International Classification of Diseases, 10th Edition; ICD9, International Classification of Diseases, 9th Edition.

Supplementary Table S3. Biological traits and corresponding UK Biobank data fields used to calculate biological ages

Biological ages	Full name in UK Biobank data dictionary	Field ID
KDM-BA	FEV1	3063
	Systolic blood pressure, automated reading	4080
	Cholesterol	30690
	HbA1c	30750
	Urea	30670
PhenoAge	Lymphocyte percentage	30180
	Mean sphered cell volume	30270
	Glucose	30740
	Red blood cell (erythrocyte) distribution width	30070
	White blood cell (leukocyte) count	30000
Overlapped	Albumin	30600
	Creatinine	30700
	C-reactive protein	30710
	Alkaline phosphatase	30610

Note. Abbreviation: KDM-BA, Klemera–Doubal biological age; FEV1, forced expiratory volume in 1 second; HbA1c, glycated hemoglobin.

Supplementary Table S4. Definitions and distributions of social risk factors

Social risk factors	Definition	Observation <i>n</i> (%)
Socioeconomic status		
Low education attainment	Education level lower than college	59,831 (68.85)
Poor education quality	Education quality score ^a below the median	57,339 (65.98)
Low household income	Less than £31,000	71,386 (82.14)
Unemployment	Not engaged in paid employment or self-employed	45,739 (52.63)
Psychosocial factors		
Living alone	Living alone	20,489 (23.58)
Lack of social support	Unable to confide in people nearby at least once a week	20,216 (23.26)
Social inactivity	Attends group activities less than once a week	25,198 (29.00)
Social isolation	Visits friends or family once a week or less	44,281 (50.95)
Emotional distress	Experience of illness, injury, bereavement, or stress	38,877 (44.74)
Neighborhood and living environment		
Area-level material deprivation	Townsend deprivation index above the median	58,070 (66.82)
High local crime rate	Crime score ^b for the neighborhood above the median	57,954 (66.69)
Unstable accommodation	Does not own current accommodation outright	30,732 (35.36)
Greenspace remoteness	Percentage of greenspace within home location buffer below the median	57,672 (66.36)
Bluespace remoteness	Percentage of bluespace within home location buffer below the median	58,026 (66.77)
Natural environment remoteness	Percentage of natural land within home location buffer below the median	45,623 (52.50)
Not living in urban area	Resides outside an urban area	12,948 (14.90)

Note. ^aEducation score indicates the local level of deprivation related to education, training, and skills.

^bCrime score reflects the incidence of major crime types within a given area. Both scores were obtained from a UK government qualitative study of deprived areas across British local councils.

Supplementary Table S5. Associations between social risk factors and incident CKM risk

Social risk factors	HR (95% CI) ^a	P value
Socioeconomic status		
Low education attainment	1.52 (1.33-1.72)	< 0.001
Poor education quality	1.63 (1.45-1.84)	< 0.001
Low household income	1.83 (1.48-2.25)	< 0.001
Not engaged in paid employment	1.42 (1.25-1.61)	< 0.001
Psychosocial factors		
Living alone	1.28 (1.15-1.42)	< 0.001
Lack of social support	1.20 (1.08-1.34)	0.001
Social inactivity	1.18 (1.06-1.31)	0.003
Social isolation	1.00 (0.91-1.11)	0.986
Emotional distress	1.39 (1.26-1.54)	< 0.001
Neighborhood and living environment		
Area-level material deprivation	1.45 (1.29-1.63)	< 0.001
High local crime rate	1.25 (1.12-1.40)	< 0.001
Unstable accommodation	1.38 (1.24-1.54)	< 0.001
Greenspace remoteness	1.26 (1.13-1.40)	< 0.001
Bluespace remoteness	0.95 (0.85-1.05)	0.284
Natural environment remoteness	1.29 (1.16-1.42)	< 0.001
Not living in urban area	0.70 (0.59-0.82)	< 0.001

Note. ^aEstimates were obtained using Cox regression models adjusted for age at recruitment, body mass index, ethnicity, alcohol intake, smoking status, healthy diet status, physical activity, and family history of diabetes and heart disease. Abbreviations: CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; CI, confidence interval.

Supplementary Table S6. Additive interactions between age at menopause and PsRS on risk of CKM syndrome

Additive interaction	Crude		Adjusted [†]	
	Coef (95% CI)	P value	Coef (95% CI)	P value
Synergy index	0.366 (-0.368, 1.100)	0.328	0.238 (-0.484, 0.961)	0.518
Relative excess risk due to interaction	0.439 (-0.191, 1.069)	0.172	0.315 (0.127, 0.503)	0.001
Attributable proportion for premature menopause	-0.141 (-1.775, 1.493)	0.866	-0.047 (-2.663, 2.569)	0.972
Attributable proportion for PsRS	0.654 (-0.335, 1.643)	0.195	0.449 (-0.202, 1.101)	0.176
Attributable proportion for additive interaction	0.487 (-0.178, 1.152)	0.152	0.598 (-1.405, 2.601)	0.559

Note. [†]Adjusted for age at recruitment, body mass index, ethnicity, alcohol intake, smoking status, healthy diet status, physical activity, and family history of diabetes and heart disease. Abbreviations: PsRS, polysocial risk score; CKM, cardiovascular-kidney-metabolic; Coef, coefficient; CI, confidence interval.

Supplementary Table S7. Competing risk analyses with death and loss to follow-up as competing events

Category	HR (95% CI)		
	Crude	Model 1 [†]	Model 2 [‡]
Premature menopause			
No	Ref	Ref	Ref
Yes	2.22 (1.86-2.66)	1.88 (1.56-2.28)	1.73 (1.43-2.10)
Menopause status			
Not premature	Ref	Ref	Ref
Natural premature	1.89 (1.44-2.48)	1.97 (1.49-2.62)	1.84 (1.38-2.44)
Surgical premature	2.54 (2.01-3.19)	1.82 (1.42-2.34)	1.66 (1.29-2.14)
Per SD age at menopause increase	0.81 (0.78-0.86)	0.81 (0.78-0.85)	0.83 (0.80-0.87)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
KDM-BA acceleration			
Per SD increase	1.59 (1.52-1.66)	1.47 (1.40-1.54)	1.44 (1.37-1.51)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
PhenoAge acceleration			
Per SD increase	1.52 (1.44-1.60)	1.47 (1.42-1.52)	1.45 (1.40-1.50)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
Polysocial risk score			
Low (≤ 3)	Ref.	Ref.	
Intermediate (4–6)	2.04 (1.49-2.78)	1.46 (1.06-2.01)	
High (≥ 7)	4.54 (3.36-6.14)	2.32 (1.70-3.16)	
Each 1-point increase	1.31 (1.28-1.34)	1.18 (1.15-1.21)	
<i>P</i> for trend	< 0.001	< 0.001	

Note. [†]Model 1: adjusted for age at recruitment, body mass index, ethnicity, alcohol intake, smoking status, healthy diet status, physical activity, and family history of diabetes and heart disease. [‡]Model 2: Model 1 + education and employment. Abbreviations: CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; *CI*, confidence interval; SD, standard deviation; KDM-BA, Kleméra–Doubal biological age.

Supplementary Table S8. Associations of menopause status, accelerated biological aging, and polysocial risk score with CKM syndrome stages

Category	HR (95% CI)		
	Crude	Model 1 [†]	Model 2 [‡]
Premature menopause			
No	Ref	Ref	Ref
Yes	1.67 (1.55–1.79)	1.68 (1.56–1.82)	1.57 (1.45–1.69)
Menopause status			
Not premature	Ref	Ref	Ref
Natural premature	1.20 (1.09–1.33)	1.53 (1.37–1.71)	1.44 (1.29–1.61)
Surgical premature	2.24 (2.03–2.47)	1.84 (1.65–2.04)	1.69 (1.52–1.88)
Per SD age at menopause increase	0.96 (0.95–0.97)	0.89 (0.87–0.90)	0.90 (0.89–0.92)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
KDM-BA acceleration			
Per SD increase	1.70 (1.67–1.72)	1.61 (1.58–1.63)	1.58 (1.56–1.61)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
PhenoAge acceleration			
Per SD increase	1.72 (1.70–1.75)	1.29 (1.27–1.31)	1.27 (1.25–1.29)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001
Polysocial risk score			
Low (≤ 3)	Ref.	Ref.	
Intermediate (4–6)	1.44 (1.37–1.51)	1.16 (1.09–1.22)	
High (≥ 7)	2.29 (2.18–2.40)	1.47 (1.40–1.55)	
Each point increase	1.164 (1.157–1.171)	1.082 (1.075–1.089)	
<i>P</i> for trend	< 0.001	< 0.001	

Note. [†]Model 1: adjusted for age at recruitment, body mass index, ethnicity, alcohol intake, smoking status, healthy diet status, physical activity, and family history of diabetes and heart disease. [‡]Model 2: Model 1 + education and employment. Abbreviations: CKM, cardiovascular-kidney-metabolic; HR, hazard ratio; CI, confidence interval; SD, standard deviation; KDM-BA, Klemera–Doubal biological age.

Supplementary Table S9. Differences in baseline characteristics between included and excluded postmenopausal women

Characteristics	Included (n = 86,904)	Excluded (n = 67,594)	P value
Age at recruitment, years	59.88 ± 5.46	60.36 ± 5.49	< 0.001
Body mass index, kg/m ²	27.50 ± 5.14	26.59 ± 4.86	< 0.001
Ethnicity, White British	78,104 (90.0)	60,050 (89.1)	< 0.001
Education			< 0.001
Work-related practical qualifications	4,103 (4.7)	3,024 (4.7)	
Lower secondary education	24,347 (28.0)	17,117 (26.3)	
Upper secondary education	9,797 (11.3)	6,609 (10.2)	
Higher education	32,940 (37.9)	21,898 (33.7)	
None of the above	15,717 (18.1)	16,335 (25.1)	
Employment			< 0.001
Engaged in paid employment or self-employed	41,165 (47.6)	27,114 (40.7)	
Not engaged in paid employment	5,901 (6.8)	5,726 (8.6)	
Retired	39,419 (45.6)	33,762 (50.7)	
Smoking status			< 0.001
Current	6,905 (8.0)	5,812 (8.6)	
Previous	30,433 (35.1)	21,674 (32.2)	
Never	49,357 (56.9)	39,751 (59.1)	
Healthy alcohol intake [†]	40,329 (46.4)	30,111 (44.6)	< 0.001
Healthy diet [†]	15,478 (17.9)	11,816 (17.7)	0.333
Healthy physical activity [†]	59,341 (69.3)	45,300 (69.5)	0.359
Family history of diabetes	19,568 (22.5)	10,290 (22.7)	0.353
Family history of heart disease	68,618 (79.0)	35,284 (78.0)	< 0.001

Note. [†]Healthy alcohol intake: alcohol consumption ≤ 14 g/day; Healthy diet: fruit ≥ 3 servings/day, vegetables ≥ 3 servings/day, fish ≥ 2 servings/week, processed meat ≤ 1 serving/week, and unprocessed meat ≤ 1.5 servings/week; Healthy physical activity: moderate activity ≥ 150 minutes/week, vigorous activity ≥ 75 minutes/week, or an equivalent combination. Abbreviations: CKM, cardiovascular-kidney-metabolic; SD, standard deviation; KDM-BA, Kleméra–Doubal biological age.