Association between cardiovascular-kidney-metabolic syndrome, lifestyle, and all-cause and cause-specific mortality: a prospective cohort study

Supplementary methods

Supplementary tables

Table S16. Joint associations of CKM syndrome stages (re-defined by incorporating hospital-diagnosed CKD) and lifestyle categories on the risks of all-cause and cause-specific mortality

Table S17. Associations of lifestyle categories (based on weighted lifestyle score) with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome

Table S18. Associations of lifestyle categories (including no heavy alcohol as an additional component) with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome

Table S19. Associations of lifestyle categories with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome (re-defined by incorporating hospital-diagnosed CKD)

Method S1. Assessment of lifestyle factors

Physical activity: We used the data-field of the UK Biobank as shown below.

Data-Field	Description
884	Number of days/week of moderate physical activity 10+ minutes
894	Duration of moderate activity
904	Number of days/week of vigorous physical activity 10+ minutes
914	Duration of vigorous activity

We calculated the weekly total amount of moderate or vigorous physical activity by multiplying the number of days by the duration per day. Adequate physical activity was defined as the presence of any of five conditions: ≥ 150 min/week of moderate activity, ≥ 75 min/week of vigorous activity, ≥150 min/week of combined moderate and vigorous activity, moderate activity ≥ 5 times/week, or vigorous activity ≥1 time/week.[1]

Current smoking: We used the data-field 1239 - current tobacco smoking. Participants were asked via the following question: "Do you smoke tobacco now? with the response options: 1) Yes, on most or all days; 2) Only occasionally; 3) No; 4) Prefer not to answer. Participants who answered "No" were classified as non-current smokers, and those who answered "Yes, on most or all days" or "Only occasionally" were classified as current smokers.

Sleep duration: We used the data-field 1160 - sleep duration. Participants were asked "About how many hours sleep do you get in every 24 hours? (please include naps)". Healthy sleep was defined as sleep duration ≥ 7 and < 9 hours per day.[2]

Diet intakes: We selected 10 food groups recommended as dietary priorities for cardiometabolic health to assess diet intakes, based on a previous publication using the UK Biobank.[3] Healthy diet was defined as meeting ideal intake for at least 5 of the 10 recommended components: 1) Fruit: ≥ 3 servings/day; 2) Vegetable: ≥ 3 servings/day; 3) Whole grains: ≥ 3 servings/day; 4) (Shell)fish: ≥ 2 servings/week; 5) Dairy: ≥ 2 servings/day; 6) Vegetable oils: ≥ 2 servings/day; 7) Refined grains: ≤ 2 servings/day; 8) Processed meats: ≤ 1 serving/week; 9) Unprocessed meats: ≤ 2 servings/week;10) Sugar-sweetened beverages: don't drink.

Alcohol consumption: We used the data-field of the UK Biobank which was showed below.

Data-Field	Description
20117	Alcohol drinker status
1558	Alcohol intake frequency.
1568	Average weekly red wine intake
1578	Average weekly champagne plus white wine intake
1588	Average weekly beer plus cider intake
1598	Average weekly spirits intake
1608	Average weekly fortified wine intake
5364	Average weekly intake of other alcoholic drinks
4407	Average monthly red wine intake
4418	Average monthly champagne plus white wine intake
4429	Average monthly beer plus cider intake
4440	Average monthly spirits intake
4451	Average monthly fortified wine intake
4462	Average monthly intake of other alcoholic drinks

According to the previous publication,[4] we assumed a pint of beer contained 20 g of alcohol and other drinks 10 g, then calculated total weekly and monthly alcohol consumption. The more details about calculation and imputation were same as those described in the publication by Bradbury KE, et al.[4] To estimate daily alcohol consumption, we divided weekly consumption by 7 (preferably), and monthly consumption by 30.4375, if weekly consumption was unavailable. No heavy alcohol consumption was defined as women ≤ 8 g/day and men ≤ 16 g /day.[5]

Method S2. Re-defining CKM by incorporating hospital-diagnosed CKD to supplement the original CKD definition

CKM syndrome was defined following the Presidential Advisory from the American Heart Association (AHA),[6] with hospital-diagnosed CKD incorporated to supplement the original CKD definition. The original CKD definition was based on estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR), according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification.[7]

We identified participants with CKD by searching ICD-10 codes from UK Biobank data Field-ID 41270 and 41280. Specifically, ICD-10 codes N18.1, N18.2, and N18.3 were used to supplement the moderate- to high-risk CKD group, while codes N18.0, N18.4, N18.5, N18.8, and N18.9 were used to supplement the very high-risk CKD group. Using this updated definition, 76 participants originally classified as CKM stages 0-2 were reclassified to stage 3 in this sensitivity analysis.

Method S3. Construction of the weighted lifestyle score and categories

To construct a weighted adulthood lifestyle score, we identified four key healthy lifestyle factors: adequate physical activity, no current smoking, healthy sleep, and healthy diet. Each factor was categorized as healthy (coded as 1) or unhealthy (coded as 0). The Cox proportional hazards regression model was used to estimate the associations between each of four lifestyle factors and all-cause mortality, adjusting for potential confounders (sex, age, ethnicity, education degree, Townsend Deprivation Index, and alcohol consumption). The corresponding regression coefficients (β) for each of four lifestyle factors were extracted, all of which were inverse, indicating the protective effects of healthy lifestyle behaviours.

To determine the relative contribution of each factor, the absolute values of the β coefficients were normalized to sum to 1, creating a set of weights. The weighted lifestyle score for each individual was then calculated as a weighted sum of their lifestyle factor values (0 or 1) multiplied by the corresponding normalized weights. Higher scores indicate a healthier lifestyle. The weighted score was subsequently classified into three categories based on tertiles: unfavourable, intermediate, and favourable.

Table S1. Summary of missing information on CKM syndrome definition in the UK biobank

Variable	Data-Field	Number of missing	Percentage of Missing	Note
HDL cholesterol	30760	72610	14.45	
Systolic BP	4080	45536	9.06	
Diastolic BP	4079	45524	9.06	
HbA1c	30750	35990	7.16	
Triglycerides	30870	33279	6.62	
Serum creatinine	30700	33136	6.6	
Serum cystatin C	30720	32935	6.56	
Total cholesterol	30690	32904	6.55	
Heart failure	See Table S3	23055	4.59	
Atrial fibrillation	See Table S3	23034	4.59	
Peripheral artery disease	See Table S3	22979	4.57	
Microalbumin in urine (imputed)	30500, 30505	18211	3.63	Urinary microalbumin results below the detection limit (6.7 mg/L) were assigned as 6.7 mg/L to estimate urinary albumin-to-creatinine ratio for all participants following the quality control information for the urinary biomarker data in the UK Biobank.
Microalbumin in urine (raw)	30500	349507	69.57	This variable was not included in the analysis
Urine creatinine	30510	18191	3.62	
Statin use (imputed)	20003, 6153, 6177	8605	1.71	If any values were available in UK Biobank Data-Field 6153 or 6177, corresponding missing entries in statin use (raw) were not coded as NA.
Statin use (raw)	20003	138479	27.57	This variable was not included in the analysis
Medication for blood pressure	6153, 6177	8605	1.71	
Medication for diabetes	6153, 6177	8605	1.71	
Body mass index	21001	3107	0.62	
Ethnicity	21000	2778	0.55	
Waist circumference	48	2163	0.43	
Current smoking status	1239	1321	0.26	

Coronary heart disease	See Table S3	132	0.03
Stroke	See Table S3	132	0.03
Age	21022	0	0
Sex	31	0	0

Abbreviations: CKM, cardiovascular-kidney-metabolic; HDL, high-density lipoprotein; BP, blood pressure; HbA1c, glycated haemoglobin. The imputed variables were highlighted in bold.

Table S2. Baseline characteristics of included and excluded participants

Characteristic	Included	Excluded
No. of participants, (%)	319,291 (63.6)	183,075 (36.4)
Age, years, mean (SD)	56.75 (8.04)	56.15 (8.18)
Sex, n (%)		
Male	147,963 (46.3)	81,105 (44.3)
Female	171,328 (53.7)	101,970 (55.7)
Ethnicity, n (%)		
White	305,301 (95.6)	167,269 (92.8)
Others	13,990 (4.4)	13,028 (7.2)
Townsend Deprivation Index, median [IQR]	-2.24 [-3.68, 0.29]	-1.93 [-3.56, 1.02]
Education degree, n (%)		
College/university	104,595 (32.8)	56,507 (32.7)
Less than college/university	214,696 (67.2)	116,436 (67.3)
Alcohol consumption, g/day, median [IQR]	8.57 [1.97, 20.00]	8.57 [1.97, 20.00]
No current smoking, n (%)	286,998 (89.9)	161087 (88.6)
Adequate physical activity, n (%)	234,825 (73.5)	123,711 (72.4)
Healthy sleep duration (≥ 7 and <9 hours/day), n (%)	217,025 (68.0)	119,572 (66.9)
Healthy diet, n (%)	47,027 (14.7)	24,475 (14.8)
BMI, kg/m^2, mean (SD)	27.40 (4.71)	27.49 (4.97)
Waist circumference, cm, mean (SD)	90.39 (13.37)	90.17 (13.68)
HbA1c, mmol/mol, median [IQR]	35.20 [32.80, 37.90]	35.30 [32.80, 38.00]
SBP, mm Hg, mean (SD)	137.99 (18.57)	137.29 (18.75)
DBP, mm Hg, mean (SD)	82.28 (10.09)	82.01 (10.19)
Total cholesterol, mmol/L, mean (SD)	5.70 (1.14)	5.69 (1.15)
Triglycerides, mmol/L, median [IQR]	1.49 [1.05, 2.15]	1.47 [1.03, 2.14]
HDL-C, mmol/L, mean (SD)	1.45 (0.38)	1.44 (0.39)
LDL-C, mmol/L, mean (SD)	3.56 (0.87)	3.55 (0.88)
CRP, mg/L, median [IQR]	1.33 [0.66, 2.74]	1.34 [0.65, 2.81]

Serum creatinine, umol/L, median [IQR]	70.60 [61.50, 81.00]	70.00 [61.10, 80.50]
Serum cystatin C, mg/L, median [IQR]	0.89 [0.80, 0.98]	0.89 [0.80, 0.98]
Urine creatinine, micromole/L, median [IQR]	7,503.00 [4,360.00, 11,953.00]	7,637.00 [4,409.00, 12,262.00]
Urine microalbumin, mg/L, median [IQR] *	11.40 [8.40, 19.30]	11.60 [8.50, 19.80]
Urine microalbumin, mg/L, median [IQR] (imputed)	6.70 [6.70, 8.00]	6.70 [6.70, 8.30]
Coronary heart disease, n (%)	17,598 (5.5)	10,469 (5.7)
Heart failure, n (%)	1,640 (0.5)	1,117 (0.7)
Stroke, n (%)	5,455 (1.7)	3,543 (1.9)
Peripheral artery disease, n (%)	3,871 (1.2)	2,333 (1.5)
Atrial fibrillation, n (%)	5,456 (1.7)	2,956 (1.8)

*: Urinary microalbumin values are presented as measured, without imputation. This variable was not included in the analysis.
Abbreviations: BMI, body mass index; CKM, cardiovascular-kidney-metabolic; CRP, C-reactive protein; DBP, diastolic blood pressure; HbA1c, haemoglobin a1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SD, standard deviation.

Table S3. Codes used to identify prevalent diseases

Diseases	Self-reported	ICD-9	ICD-10	First occurrences	Medications	Diagnosed by doctor
Diabetes	20002 (1220, 1222, 1223)	250	E10, E11, E13, E14	130706, 130708, 130710, 130712, 130714	6153 (3), 6177 (3)	2443
Hypertension	20002 (1065, 1072)	401-405	I10-I13, I15	131286	6153 (2), 6177 (2)	6150 (4)
Coronary heart disease	20002 (1074, 1075)	410-414	I20-I25	131296, 131298, 131300, 131302, 131304, 131306		6150 (1, 2)
Heart failure	20002 (1076)	428	I50	131354		
Stroke	20002 (1081, 1086, 1491, 1583)	430, 431, 434, 436	I60-I64	131368		6150 (3)
Peripheral artery disease	20002 (1067, 1087, 1088, 1492, 1591, 1592)	4400, 4402, 4408,4409, 4438, 4439	I70, I70.0, I70.2, I70.8, I70.9, I73.8, I73.9	131380, 131386		
Atrial fibrillation	20002 (1471)	4273	I48, I48.0, I48.1, I48.2, I48.9	131350		
Kidney failure			N17, N18.8, N18.9, N19			

ICD9 codes are drawn from fields 41271 and 41281; ICD10 codes are drawn from fields 41270 and 41280. Where a 3-digit code is given, it includes both the 3-digit code itself and all of its 4-digit sub-codes. For example, I50 includes I50, I50.0, I50.1, and I50.9.
Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.

Table S4. Definitions of components of CKM syndrome

CKM components	Definition	Criterion
Excess or dysfunctional adiposity	Overweight/obesity	BMI ≥ 25 kg/m^2 (or ≥ 23 kg/m^2 if Asian ancestry)
	Abdominal obesity	Waist circumference ≥ 88/102 cm in women/men (or if Asian ancestry ≥ 80/90 cm in women/men)
	Prediabetes	HbA1c ≥ 5.7%-6.4% (39-47 mmol/mol) and without diagnosis of diabetes (see definition below)
Metabolic risk factors	Diabetes	HbA1c ≥ 6.5% (48 mmol/mol), or diagnosis of diabetes, including 6 methods: medications, self-reported, ICD-9, ICD-10, diagnosed by doctor, and first occurrences.
	Hypertension	SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg, or diagnosis of hypertension, including 6 methods: medications, self-reported, ICD-9, ICD-10, diagnosed by doctor, and first occurrences.
	Hypertriglyceridemia	Triglycerides ≥ 135 mg/dL (1.5 mmol/L)
	MetS	The presence of 3 or more of the following:
		(1) Abdominal obesity； (2) HDL cholesterol < 40 mg/dL (1.0 mmol/L) for men and < 50 mg/dL (1.3 mmol/L) for women; (3) Triglycerides ≥ 150 mg/dL (1.7 mmol/L); (4) Hypertension; (5) HbA1c ≥ 5.7% (39 mmol/mol)
Chronic kidney diseases (CKD)	Moderate- to high-risk CKD in KDIGO classification [7]	eGFR ≥ 60 ml/min/1.73m^2 and UACR ≥ 30 mg/g (3 mg/mmol);
		OR eGFR ≤ 45-60 ml/min/1.73m^2 and UACR < 300 mg/g (30 mg/mmol);
		OR eGFR ≤ 30-45ml/min/1.73m^2 and UACR < 30 mg/g (3 mg/mmol)
	Very high-risk CKD in KDIGO classification [7]	eGFR <30 ml/min/1.73m^2;
		OR eGFR ≤ 45-60 ml/min/1.73m^2 and UACR ≥ 300 mg/g (30 mg/mmol);
		OR eGFR ≤ 30-45 ml/min/1.73m^2 and UACR ≥ 30 mg/g (3 mg/mmol);
Cardiovascular diseases (CVD)	Clinical CVD	The presence of 1 or more of the following: coronary heart disease, heart failure, stroke, peripheral artery disease, and atrial fibrillation.

	Risk equivalents of subclinical CVD	Any of the following criterion is met: (1) Very high-risk CKD in KDIGO classification; (2) Predicted 10-year CVD risk (PREVENT) ≥ 10%.

eGFR was estimated using both serum creatinine and cystatin C based on the CKD-EPI 2021 equation.[8] UACR was calculated as the ratio of urinary microalbuminuria to creatinine. The predicted 10-year CVD risk (PREVENT) was calculated using base models incorporating age, sex, SBP, HDL cholesterol, total cholesterol, eGFR, current smoking status, anti-hypertensive medications, statin use, and diabetes, using R package "preventr".[9,10] Note, to approximate PREVENT risk strata, values exceeding or falling below the allowable bounds were adjusted to the respective upper or lower limits.

Abbreviations: BMI, body mass index; CKM, cardiovascular-kidney-metabolic syndrome; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; KDIGO, Kidney Disease: Improving Global Outcomes; MetS, metabolic syndrome; PREVENT, American Heart Association Predicting Risk of CVD EVENTs; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.

Table S5. Definition of stages of CKM syndrome in the present study

CKM health stages	Definition	Criterion	CKM components
Stage 0: No CKM health risk factors	Individuals without overweight/obesity, abdominal obesity, metabolic risk factors (prediabetes/diabetes, hypertension, hypertriglyceridemia, MetS), CKD, subclinical or clinical CVD.	**Absence** of all these conditions (11)	Overweight/obesity
			Abdominal obesity
			Prediabetes
			Diabetes
			Hypertension
			Hypertriglyceridemia
			MetS
			Moderate- to high-risk CKD in KDIGO classification
			Very high-risk CKD in KDIGO classification
			Predicted 10-year CVD risk ⩾ 10%
			Clinical CVD
Stage 1: Excess or dysfunctional adiposity	Individuals with overweight/obesity, abdominal obesity, or dysfunctional adipose tissue, without the presence of other metabolic risk factors or CKD. • BMI ≥25 kg/m2 (or ≥23 kg/m2 if Asian ancestry) OR • Waist circumference ≥88/102 cm in women/men (or if Asian ancestry, ≥80/90 cm in women/men) and/or • HbA1c between 5.7% and 6.4%	**Presence** of any of three conditions (3)	Overweight/obesity
			Abdominal obesity
			Prediabetes
		Absence of all these conditions (8)	Diabetes
			Hypertension
			Hypertriglyceridemia
			MetS
			Moderate- to high-risk CKD in KDIGO classification
			Very high-risk CKD in KDIGO classification
			Predicted 10-year CVD risk ⩾ 10%
			Clinical CVD

Stage 2: Metabolic risk factors or CKD	Individuals with metabolic risk factors (hypertriglyceridemia (⩾135 mg/dL), hypertension, MetS, diabetes), or CKD (moderate- to high-risk).	**Presence** of any of five conditions (5)	Diabetes
			Hypertension
			Hypertriglyceridemia
			MetS
			Moderate- to high-risk CKD in KDIGO classification
		Absence of all these conditions (3)	Very high-risk CKD in KDIGO classification
			Predicted 10-year CVD risk ⩾ 10%
			Clinical CVD
Stage 3: Subclinical CVD in CKM	Risk equivalents of subclinical CVD among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD. • Very high-risk CKD (G4 or G5 CKD or very high risk per KDIGO classification) • High predicted 10-year CVD risk	**Presence** of any of two conditions (2)	Very high-risk CKD in KDIGO classification
			Predicted 10-year CVD risk ⩾ 10%
		Presence of any of eight conditions (8)	Overweight/obesity
			Abdominal obesity
			Prediabetes
			Diabetes
			Hypertension
			Hypertriglyceridemia
			MetS
			Moderate- to high-risk CKD in KDIGO classification
		Absence of the condition (1)	Clinical CVD
Stage 4: Clinical CVD in CKM	Clinical CVD (coronary heart disease, heart failure, stroke, peripheral artery disease, atrial fibrillation) among individuals with excess/dysfunctional adiposity, other metabolic risk factors, or CKD. • Stage 4a: no kidney failure • Stage 4b: kidney failure present	**Presence** of the condition (1)	Clinical CVD
		Presence of any of nine conditions (9)	Overweight/obesity
			Abdominal obesity
			Prediabetes
			Diabetes

	Hypertension
	Hypertriglyceridemia
	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; HbA1c, haemoglobin A1c; KDIGO, Kidney Disease Improving Global Outcomes; MetS, metabolic syndrome.
MetS is defined by the presence of ≥3 of the following conditions: (1) waist circumference ≥88 cm for women and ≥102 cm for men (if Asian ancestry, ≥80 cm for women and ≥90 cm for men), (2) high-density lipoprotein cholesterol <40 mg/dL for men and <50 mg/dL for women; (3) triglycerides ≥150 mg/dL (1.7 mmol/L); (4) elevated blood pressure (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥80 mm Hg and/or use of antihypertensive medications); and (5) HbA1c ≥ 5.7% (39 mmol/mol).

Table S6. Distribution of other-cause mortality by ICD-10 major chapters and CKM syndrome stages

Other-cause mortality (ICD10 major chapter) *	Total	CKM syndrome				
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Infectious and parasitic diseases (A-B)	224	5	4	87	83	45
Non-malignant neoplasms (D00-D48)	187	2	2	66	76	41
Blood/immune diseases (D50-D89)	67	1	2	25	31	8
Endocrine, nutritional and metabolic diseases (E)	299	6	4	79	112	98
Mental and behavioural disorders (F)	668	13	9	166	316	164
Nervous system diseases (G)	1,579	73	45	604	610	247
Eye/ear diseases (H)	2	0	0	2	0	0
Respiratory diseases (J)	1,885	38	37	503	768	539
Digestive diseases (K)	990	22	17	329	384	238
Skin diseases (L)	45	1	2	11	13	18
Musculoskeletal diseases (M)	154	3	3	49	50	49
Genitourinary diseases (N)	175	1	2	22	87	63
Congenital diseases (Q)	39	0	4	15	7	13
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R)	98	3	2	51	29	13
External causes (V-Y)	657	38	20	293	197	109
COVID-19 (U07)	848	12	20	259	357	200
Other/Unknown	226	11	7	85	82	41
Kidney disease (N00-N08, N10-N19, N20.0, N20.2, N25-N29)	87	0	1	10	47	29
Incidence per 1000 person-years	0.0204	0	0.0043	0.0040	0.0570	0.0800

*Other-cause mortality refers to death from other causes other than cardiovascular disease and cancer.
Note, Deaths classified under genitourinary diseases (ICD-10 chapter N) include deaths due to kidney diseases.
Results are presented as the number of deaths. Abbreviations: CKM, cardiovascular-kidney-metabolic syndrome; COVID-19, coronavirus disease 2019; ICD-10, International Classification of Diseases, Tenth Revision.

Table S7. Subgroup and interaction analyses on associations of CKM syndrome with the risks of all-cause and cause-specific mortality

Mortality/ CKM stage	Sex			Age group		
	Male (n=147,963)	Female (n=171,328)	*P*-interaction value *	< 60 years (n=177,296)	≥ 60 years (n=141,995)	*P*-interaction value *
All-cause			0.0003			<0.0001
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	1.01 (0.85, 1.21)	1.06 (0.93, 1.20)		0.98 (0.85, 1.14)	1.13 (0.98, 1.31)	
Stage 2	1.12 (0.99, 1.28)	1.26 (1.15, 1.38)		1.45 (1.31, 1.60)	1.14 (1.02, 1.27)	
Stage 3	1.48 (1.30, 1.68)	1.60 (1.45, 1.77)		3.02 (2.68, 3.40)	1.83 (1.64, 2.04)	
Stage 4	2.25 (1.98, 2.56)	2.21 (1.99, 2.45)		3.61 (3.22, 4.06)	2.62 (2.35, 2.92)	
CVD-specific			0.0003			<0.0001
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	1.60 (0.89, 2.85)	1.37 (0.75, 2.48)		1.48 (0.89, 2.46)	1.46 (0.99, 2.14)	
Stage 2	2.11 (1.37, 3.25)	2.40 (1.61, 3.58)		3.25 (2.32, 4.54)	1.70 (1.24, 2.33)	
Stage 3	4.07 (2.63, 6.28)	4.63 (3.10, 6.92)		9.60 (7.07, 13.04)	3.95 (2.90, 5.37)	
Stage 4	10.01 (6.51, 15.38)	8.99 (5.93, 13.63)		17.40 (12.19, 24.82)	8.93 (6.51, 12.25)	
Cancer-specific			0.0001			<0.0001
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	1.09 (0.86, 1.38)	1.07 (0.90, 1.27)		0.99 (0.84, 1.17)	1.20 (0.95, 1.52)	
Stage 2	1.18 (1.00, 1.39)	1.18 (1.04, 1.34)		1.35 (1.20, 1.51)	1.16 (0.97, 1.39)	
Stage 3	1.30 (1.10, 1.55)	1.23 (1.09, 1.40)		2.53 (2.17, 2.96)	1.54 (1.28, 1.86)	
Stage 4	1.37 (1.15, 1.63)	1.26 (1.09, 1.45)		1.95 (1.67, 2.27)	1.58 (1.30, 1.93)	
Other-cause			<0.0001			<0.0001
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	0.79 (0.60, 1.03)	0.98 (0.74, 1.29)		0.90 (0.67, 1.20)	0.93 (0.67, 1.29)	
Stage 2	0.83 (0.71, 0.98)	1.20 (0.96, 1.50)		1.36 (1.14, 1.61)	0.94 (0.73, 1.20)	
Stage 3	1.12 (0.94, 1.34)	1.72 (1.38, 2.15)		2.52 (2.12, 2.98)	1.69 (1.31, 2.17)	
Stage 4	1.51 (1.24, 1.85)	2.54 (2.03, 3.16)		3.38 (2.71, 4.22)	2.24 (1.76, 2.84)	
	Education			TDI category		

	College/university (n=104,595)	Less than college/university (n=214,696)	*P*-interaction value *	≤ median (n=159,683)	> median (n=159,608)	*P*-interaction value *
All-cause			0.68			0.0024
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	1.08 (0.91, 1.28)	1.02 (0.90, 1.16)		1.02 (0.88, 1.19)	1.06 (0.92, 1.22)	
Stage 2	1.24 (1.10, 1.40)	1.19 (1.08, 1.30)		1.17 (1.06, 1.31)	1.23 (1.11, 1.37)	
Stage 3	1.67 (1.46, 1.90)	1.49 (1.35, 1.64)		1.49 (1.33, 1.67)	1.59 (1.43, 1.77)	
Stage 4	2.39 (2.09, 2.73)	2.23 (2.02, 2.47)		2.13 (1.90, 2.39)	2.46 (2.21, 2.74)	
CVD-specific			0.21			0.071
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	1.86 (1.01, 3.41)	1.31 (0.85, 2.04)		0.90 (0.49, 1.63)	2.05 (1.39, 3.02)	
Stage 2	2.56 (1.48, 4.43)	2.21 (1.56, 3.12)		2.12 (1.47, 3.05)	2.60 (1.83, 3.68)	
Stage 3	5.45 (3.09, 9.60)	3.95 (2.73, 5.73)		4.07 (2.74, 6.04)	4.77 (3.39, 6.72)	
Stage 4	12.06 (7.26, 20.02)	9.36 (6.58, 13.32)		9.53 (6.25, 14.54)	11.27 (7.78, 16.33)	
Cancer-specific			0.058			0.11
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	1.09 (0.84, 1.41)	1.05 (0.88, 1.25)		1.15 (0.91, 1.45)	0.98 (0.81, 1.19)	
Stage 2	1.18 (1.04, 1.34)	1.13 (0.99, 1.29)		1.17 (1.02, 1.34)	1.12 (0.99, 1.28)	
Stage 3	1.31 (1.14, 1.50)	1.23 (1.07, 1.42)		1.30 (1.12, 1.52)	1.21 (1.05, 1.40)	
Stage 4	1.29 (1.10, 1.53)	1.30 (1.11, 1.52)		1.28 (1.10, 1.49)	1.34 (1.15, 1.56)	
Other-cause			0.20			0.70
Stage 0	1.00	1.00		1.00	1.00	
Stage 1	0.87 (0.59, 1.27)	0.92 (0.74, 1.15)		0.79 (0.56, 1.12)	1.01 (0.84, 1.22)	
Stage 2	1.08 (0.87, 1.34)	1.07 (0.91, 1.26)		0.97 (0.77, 1.22)	1.18 (0.99, 1.41)	
Stage 3	1.56 (1.20, 2.03)	1.44 (1.21, 1.71)		1.24 (0.99, 1.55)	1.70 (1.40, 2.06)	
Stage 4	2.21 (1.65, 2.96)	2.00 (1.71, 2.34)		1.78 (1.39, 2.27)	2.36 (1.96, 2.83)	

Data are presented as hazard ratios (95% confidence intervals).

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age (not for age group), sex (not for sex group), ethnicity, region of assessment, education degree (not for education group), TDI (not for TDI group), alcohol consumption, physical activity, smoking status, sleep duration, diet intake, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; TDI, Townsend Deprivation Index. Other-cause mortality: causes other than CVD, and cancer.
P-interaction value *: Statistical significance of interactions was tested by comparing models with and without cross-product terms between CKM syndrome and the stratifying variables (sex, age group, education, and TDI), using likelihood ratio tests for all-cause mortality and pseudo-likelihood ratio tests for cause-specific mortality.

Table S8. Associations of CKM syndrome with the risks of all-cause and cause-specific mortality, stratified by combined sex–age groups

Mortality/	Male		Female		*P*-interaction value *
CKM stage	< 60 years (n= 79,398)	≥ 60 years (n= 68,565)	< 60 years (n= 97,898)	≥ 60 years (n= 73,430)	
All-cause					<0.0001
Stage 0	1	1	1	1	
Stage 1	0.97 (0.76, 1.25)	1.07 (0.83, 1.37)	0.96 (0.80, 1.15)	1.17 (0.97, 1.40)	
Stage 2	1.30 (1.09, 1.55)	0.97 (0.81, 1.17)	1.49 (1.32, 1.69)	1.23 (1.07, 1.40)	
Stage 3	2.78 (2.30, 3.35)	1.65 (1.38, 1.98)	3.21 (2.66, 3.89)	1.96 (1.71, 2.25)	
Stage 4	3.58 (2.97, 4.32)	2.44 (2.03, 2.92)	2.84 (2.40, 3.36)	2.53 (2.19, 2.92)	
CVD-specific					<0.0001
Stage 0	1	1	1	1	
Stage 1	1.66 (0.69, 4.02)	1.53 (0.71, 3.29)	1.15 (0.43, 3.11)	1.41 (0.86, 2.31)	
Stage 2	2.70 (1.25, 5.84)	1.51 (0.85, 2.69)	3.53 (1.87, 6.67)	1.83 (1.10, 3.04)	
Stage 3	7.81 (3.50, 17.44)	3.78 (2.16, 6.61)	13.01 (6.33, 26.73)	4.35 (2.65, 7.14)	
Stage 4	14.60 (6.73, 31.67)	9.29 (5.35, 16.16)	17.37 (8.57, 35.21)	7.53 (4.40, 12.89)	
Cancer-specific					<0.0001
Stage 0	1	1	1	1	
Stage 1	0.95 (0.62, 1.45)	1.28 (0.90, 1.82)	0.98 (0.76, 1.27)	1.17 (0.95, 1.45)	
Stage 2	1.18 (0.91, 1.53)	1.20 (0.91, 1.57)	1.39 (1.15, 1.68)	1.15 (0.97, 1.37)	
Stage 3	2.35 (1.74, 3.16)	1.70 (1.33, 2.19)	2.39 (1.78, 3.21)	1.46 (1.20, 1.78)	
Stage 4	1.98 (1.52, 2.57)	1.75 (1.33, 2.29)	1.46 (1.19, 1.80)	1.45 (1.19, 1.76)	
Other-cause					<0.0001
Stage 0	1	1	1	1	
Stage 1	0.85 (0.52, 1.39)	0.75 (0.49, 1.13)	0.90 (0.66, 1.22)	1.06 (0.66, 1.70)	

Stage 2	1.12 (0.86, 1.46)	0.63 (0.46, 0.87)	1.43 (1.09, 1.88)	1.19 (0.87, 1.62)
Stage 3	2.01 (1.50, 2.69)	1.10 (0.80, 1.53)	3.40 (2.20, 5.26)	2.24 (1.60, 3.13)
Stage 4	2.72 (2.00, 3.69)	1.44 (1.03, 2.03)	3.63 (2.70, 4.88)	3.00 (2.13, 4.23)

Data are presented as hazard ratios (95% confidence intervals).

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, physical activity, smoking status, sleep duration, diet intake, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease. Other-cause mortality: causes other than CVD, and cancer.

P-interaction value *: Statistical significance of three-way interactions among sex, age group, and CKM stages. These were assessed by comparing models with and without the corresponding cross-product terms between CKM syndrome and sex and age group, using likelihood ratio tests for all-cause mortality and pseudo-likelihood ratio tests for cause-specific mortality.

Table S9. Sensitivity analyses on associations of CKM syndrome stages with the risks of all-cause and cause-specific mortality

Mortality	CKM syndrome, hazard ratios (95% CIs)					*P*-trend value
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Re-defining CKM based on high predicted 10-y CVD risk, defined as PREVENT risk ≥ 20%						
No. of participants (%)	23,694 (7.4)	17,647 (5.5)	244,847 (76.7)	4,570 (1.4)	28,533 (8.9)	
All-cause						
Events/person-years	828/322,261	747/238,821	18,557/3,282,212	1,346/56,483	5,789/362,487	
Incidence per 1000 person-years	2.57	3.13	5.65	23.83	15.97	
Model 1	1.00	1.09 (0.99, 1.21)	1.34 (1.25, 1.43)	2.96 (2.71, 3.24)	2.65 (2.46, 2.86)	<0.0001
Model 2	1.00	1.03 (0.93, 1.14)	1.25 (1.16, 1.34)	2.01 (1.84, 2.20)	2.12 (1.97, 2.29)	<0.0001
CVD-specific						
Events/person-years	62/322,261	75/238,821	3,138/3,282,212	360/56,483	1,923/362,487	
Incidence per 1000 person-years	0.19	0.31	0.96	6.37	5.31	
Model 1	1.00	1.44 (0.96, 2.15)	2.84 (2.12, 3.80)	8.74 (6.49, 11.75)	10.21 (7.70, 13.55)	<0.0001
Model 2	1.00	1.36 (0.91, 2.02)	2.65 (1.98, 3.53)	6.05 (4.50, 8.14)	8.33 (6.29, 11.04)	<0.0001
Cancer-specific						
Events/person-years	514/322,261	469/238,821	10,065/3,282,212	538/56,483	1,980/362,487	
Incidence per 1000 person-years	1.59	1.96	3.07	9.52	5.46	
Model 1	1.00	1.12 (0.99, 1.26)	1.22 (1.11, 1.35)	2.01 (1.75, 2.30)	1.50 (1.34, 1.68)	<0.0001
Model 2	1.00	1.07 (0.95, 1.21)	1.16 (1.05, 1.29)	1.47 (1.27, 1.70)	1.28 (1.15, 1.44)	<0.0001
Other-cause						
Events/person-years	252/322,261	203/238,821	5,354/3,282,212	448/56,483	1,886/362,487	
Incidence per 1000 person-years	0.78	0.85	1.63	7.93	5.20	
Model 1	1.00	0.96 (0.80, 1.15)	1.20 (1.04, 1.39)	2.74 (2.30, 3.26)	2.49 (2.18, 2.85)	<0.0001
Model 2	1.00	0.89 (0.74, 1.08)	1.12 (0.97, 1.29)	1.79 (1.52, 2.12)	1.82 (1.59, 2.08)	<0.0001
Excluding participants with microalbumin in urine below 6.7 mg/L						
No. of participants (%)	4,595 (4.6)	3,538 (3.6)	53,012 (53.3)	27,034 (27.2)	11,330 (11.4)	
All-cause						
Events/person-years	179/62,334	185/47,605	3,351/713,388	5,052/347,061	3,028/139,414	
Incidence per 1000 person-years	2.87	3.89	4.70	14.56	21.72	
Model 1	1.00	1.24 (1.01, 1.53)	1.33 (1.14, 1.55)	2.11 (1.81, 2.46)	3.60 (3.08, 4.20)	<0.0001

Model 2	1.00	1.18 (0.96, 1.45)	1.29 (1.11, 1.50)	1.71 (1.47, 2.00)	2.72 (2.33, 3.18)	<0.0001
CVD-specific						
Events/person-years	14/62,334	18/47,605	558/713,388	1,163/347,061	1,059/139,414	
Incidence per 1000 person-years	0.22	0.38	0.78	3.35	7.60	
Model 1	1.00	1.53 (0.82, 2.85)	2.78 (1.57, 4.94)	6.29 (3.58, 11.06)	15.44 (8.88, 26.84)	<0.0001
Model 2	1.00	1.46 (0.79, 2.72)	2.75 (1.55, 4.87)	5.20 (2.97, 9.11)	11.90 (6.82, 20.78)	<0.0001
Cancer-specific						
Events/person-years	104/62,334	118/47,605	1,869/713,388	2,271/347,061	963/139,414	
Incidence per 1000 person-years	1.67	2.48	2.62	6.54	6.91	
Model 1	1.00	1.37 (1.11, 1.69)	1.29 (1.10, 1.50)	1.64 (1.38, 1.95)	1.84 (1.56, 2.18)	<0.0001
Model 2	1.00	1.32 (1.07, 1.63)	1.26 (1.08, 1.47)	1.38 (1.16, 1.66)	1.52 (1.27, 1.81)	<0.0001
Other-cause						
Events/person-years	61/62,334	49/47,605	924/713,388	1,618/347,061	1,006/139,414	
Incidence per 1000 person-years	0.98	1.03	1.30	4.66	7.22	
Model 1	1.00	0.96 (0.59, 1.55)	1.07 (0.81, 1.41)	1.91 (1.44, 2.54)	3.21 (2.39, 4.30)	<0.0001
Model 2	1.00	0.90 (0.56, 1.45)	1.04 (0.79, 1.36)	1.54 (1.16, 2.03)	2.24 (1.69, 2.96)	<0.0001
Excluding participants with less than two years of follow-up						
No. of participants (%)	23,430 (7.4)	17,311 (5.4)	185,916 (58.5)	63,052 (19.8)	28,151 (8.9)	
All-cause						
Events/person-years	731/319,479	645/235,052	9,313/2,519,987	9,740/824,014	5,407/362,048	
Incidence per 1000 person-years	2.29	2.74	3.70	11.82	14.93	
Model 1	1.00	1.11 (0.99, 1.23)	1.27 (1.18, 1.37)	1.96 (1.81, 2.13)	3.03 (2.80, 3.29)	<0.0001
Model 2	1.00	1.05 (0.94, 1.17)	1.22 (1.13, 1.32)	1.56 (1.44, 1.69)	2.30 (2.12, 2.49)	<0.0001
CVD-specific						
Events/person-years	51/319,479	68/235,052	1,314/2,519,987	2,021/824,014	1,778/362,048	
Incidence per 1000 person-years	0.16	0.29	0.52	2.45	4.91	
Model 1	1.00	1.66 (1.11, 2.48)	2.54 (1.88, 3.43)	5.67 (4.19, 7.67)	13.51 (9.84, 18.55)	<0.0001
Model 2	1.00	1.58 (1.06, 2.36)	2.44 (1.81, 3.28)	4.55 (3.38, 6.14)	10.42 (7.56, 14.36)	<0.0001
Cancer-specific						
Events/person-years	461/319,479	400/235,052	5,456/2,519,987	4,600/824,014	1,825/362,048	
Incidence per 1000 person-years	1.44	1.70	2.17	5.58	5.04	
Model 1	1.00	1.09 (0.95, 1.25)	1.20 (1.10, 1.30)	1.55 (1.39, 1.72)	1.62 (1.45, 1.81)	<0.0001

Model 2	1.00	1.05 (0.92, 1.21)	1.16 (1.06, 1.27)	1.28 (1.15, 1.42)	1.33 (1.19, 1.49)	<0.0001
Other-cause						
Events/person-years	219/319,479	177/235,052	2,543/2,519,987	3,119/824,014	1,804/362,048	
Incidence per 1000 person-years	0.69	0.75	1.01	3.79	4.98	
Model 1	1.00	1.00 (0.84, 1.19)	1.13 (1.00, 1.29)	1.89 (1.68, 2.13)	2.99 (2.65, 3.37)	<0.0001
Model 2	1.00	0.94 (0.79, 1.12)	1.09 (0.96, 1.24)	1.47 (1.30, 1.66)	2.05 (1.81, 2.33)	<0.0001
Re-defining CKM by incorporating hospital-diagnosed CKD						
No. of participants (%)	23,474 (7.4)	17,348 (5.4)	186,333 (58.4)	63,603 (19.9)	28,533(8.9)	
All-cause						
Events/person-years	776/319,526	683/235,085	9,793/2,519,618	10,226/825,547	5,789/362,487	
Incidence per 1000 person-years	2.43	2.91	3.89	12.39	15.97	
Model 1	1.00	1.10 (1.00, 1.22)	1.26 (1.17, 1.36)	1.96 (1.81, 2.12)	3.07 (2.84, 3.32)	<0.0001
Model 2	1.00	1.05 (0.94, 1.16)	1.21 (1.12, 1.30)	1.54 (1.43, 1.67)	2.30 (2.13, 2.49)	<0.0001
CVD-specific						
Events/person-years	55/319,526	70/235,085	1,377/2,519,618	2,133/825,547	1,923/362,487	
Incidence per 1000 person-years	0.17	0.30	0.55	2.58	5.31	
Model 1	1.00	1.58 (1.01, 2.49)	2.47 (1.81, 3.39)	5.59 (4.02, 7.77)	13.54 (9.86, 18.61)	<0.0001
Model 2	1.00	1.51 (0.97, 2.35)	2.37 (1.74, 3.23)	4.47 (3.25, 6.15)	10.42 (7.63, 14.23)	<0.0001
Cancer-specific						
Events/person-years	492/319,526	433/235,085	5,771/2,519,618	4,890/825,547	1,980/362,487	
Incidence per 1000 person-years	1.54	1.84	2.29	5.92	5.46	
Model 1	1.00	1.11 (0.97, 1.26)	1.19 (1.07, 1.32)	1.54 (1.37, 1.72)	1.63 (1.45, 1.84)	<0.0001
Model 2	1.00	1.06 (0.93, 1.21)	1.15 (1.03, 1.28)	1.26 (1.12, 1.41)	1.32 (1.17, 1.48)	<0.0001
Other-cause						
Events/person-years	229/319,526	180/235,085	2,645/2,519,618	3,203/825,547	1,886/362,487	
Incidence per 1000 person-years	0.72	0.77	1.05	3.88	5.20	
Model 1	1.00	0.97 (0.80, 1.18)	1.13 (0.98, 1.31)	1.91 (1.64, 2.23)	3.04 (2.65, 3.49)	<0.0001
Model 2	1.00	0.92 (0.75, 1.11)	1.09 (0.94, 1.26)	1.49 (1.29, 1.72)	2.08 (1.81, 2.38)	<0.0001
Adjusted for centre of assessment, instead of region of assessment						
All-cause						
Events/person-years	776/319,539	683/235,097	9,804/2,520,564	10,215/824,576	5,789/362,487	

Incidence per 1000 person-years	2.43	2.91	3.89	12.39	15.97	
Model 3	1.00	1.04 (0.94, 1.15)	1.20 (1.11, 1.29)	1.52 (1.41, 1.64)	2.26 (2.09, 2.45)	<0.0001
CVD-specific						
Events/person-years	55/319,539	70/235,097	1,381/2,520,564	2,129/824,576	1,923/362,487	
Incidence per 1000 person-years	0.17	0.30	0.55	2.58	5.31	
Model 3	1.00	1.50 (0.96, 2.34)	2.35 (1.73, 3.21)	4.39 (3.18, 6.06)	10.19 (7.44, 13.95)	<0.0001
Cancer-specific						
Events/person-years	492/319,539	433/235,097	5,777/2,520,564	4,884/824,576	1,980/362,487	
Incidence per 1000 person-years	1.54	1.84	2.29	5.92	5.46	
Model 3	1.00	1.06 (0.93, 1.21)	1.14 (1.03, 1.27)	1.25 (1.11, 1.40)	1.30 (1.16, 1.46)	<0.0001
Other-cause						
Events/person-years	229/319,539	180/235,097	2,646/2,520,564	3,202/824,576	1,886/362,487	
Incidence per 1000 person-years	0.72	0.77	1.05	3.88	5.20	
Model 3	1.00	0.91 (0.75, 1.10)	1.08 (0.93, 1.25)	1.47 (1.27, 1.70)	2.04 (1.77, 2.34)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Model 1: Adjusted for age, sex, and ethnicity; Model 2: Model 1 + additionally adjusted for region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, physical activity, smoking status, sleep duration, diet intake, low-density lipoprotein cholesterol, and C-reactive protein; Model 3: Model 1 + additionally adjusted for centre of assessment, education degree, Townsend Deprivation Index, alcohol consumption, physical activity, smoking status, sleep duration, diet intake, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; PREVENT, American Heart Association Predicting Risk of CVD EVENTs.

Other-cause mortality: causes other than CVD, and cancer.

To test for linear trends, we modelled the CKM syndrome as a continuous variable.

Table S10. Joint associations of CKM syndrome stages and smoking status on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	No current smoking	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Yes	21,379	657/291,235	2.26	1.00	
	No	2,096	119/28,303	4.20	2.00 (1.65, 2.43)	<0.0001
Stage 1	Yes	15,656	582/212,262	2.74	1.06 (0.95, 1.18)	0.33
	No	1,693	101/22,835	4.42	1.96 (1.59, 2.41)	<0.0001
Stage 2	Yes	171,302	8,530/2,318,109	3.68	1.19 (1.10, 1.29)	<0.0001
	No	15,105	1,274/202,455	6.29	2.64 (2.40, 2.91)	<0.0001
Stage 3	Yes	53,468	7,951/696,999	11.41	1.57 (1.45, 1.71)	<0.0001
	No	10,059	2,264/127,577	17.75	2.80 (2.56, 3.07)	<0.0001
Stage 4	Yes	25,193	4,705/322,364	14.60	2.31 (2.12, 2.51)	<0.0001
	No	3,340	1,084/40,123	27.02	4.49 (4.06, 4.96)	<0.0001
CVD-specific mortality						
Stage 0	Yes	21,379	43/291,235	0.15	1.00	
	No	2,096	12/28,303	0.42	2.87 (1.30, 6.32)	0.0090
Stage 1	Yes	15,656	56/212,262	0.26	1.55 (0.91, 2.63)	0.10
	No	1,693	14/22,835	0.61	3.84 (1.98, 7.47)	<0.0001
Stage 2	Yes	171,302	1,165/2,318,109	0.50	2.47 (1.67, 3.67)	<0.0001
	No	15,105	216/202,455	1.07	6.11 (4.02, 9.28)	<0.0001
Stage 3	Yes	53,468	1,643/696,999	2.36	4.86 (3.26, 7.26)	<0.0001
	No	10,059	486/127,577	3.81	8.37 (5.53, 12.66)	<0.0001
Stage 4	Yes	25,193	1,580/322,364	4.90	11.49 (7.74, 17.06)	<0.0001
	No	3,340	343/40,123	8.55	18.56 (12.35, 27.89)	<0.0001
Cancer-specific mortality						
Stage 0	Yes	21,379	430/291,235	1.48	1.00	

	No	2,096	62/28,303	2.19	1.65 (1.32, 2.07)	<0.0001
Stage 1	Yes	15,656	379/212,262	1.79	1.07 (0.94, 1.23)	0.31
	No	1,693	54/22,835	2.36	1.67 (1.32, 2.10)	<0.0001
Stage 2	Yes	171,302	5,111/2,318,109	2.20	1.12 (1.00, 1.25)	0.042
	No	15,105	666/202,455	3.29	2.22 (1.99, 2.48)	<0.0001
Stage 3	Yes	53,468	3,744/696,999	5.37	1.24 (1.09, 1.40)	0.0008
	No	10,059	1,140/127,577	8.94	2.34 (2.08, 2.62)	<0.0001
Stage 4	Yes	25,193	1,580/322,364	4.90	1.27 (1.13, 1.43)	<0.0001
	No	3,340	400/40,123	9.97	2.64 (2.22, 3.13)	<0.0001
Other-cause mortality						
Stage 0	Yes	21,379	184/291,235	0.63	1.00	
	No	2,096	45/28,303	1.59	2.52 (1.68, 3.78)	<0.0001
Stage 1	Yes	15,656	147/212,262	0.69	0.93 (0.74, 1.17)	0.54
	No	1,693	33/22,835	1.45	2.15 (1.45, 3.18)	0.0001
Stage 2	Yes	171,302	2,254/2,318,109	0.97	1.11 (0.95, 1.30)	0.20
	No	15,105	392/202,455	1.94	2.71 (2.28, 3.21)	<0.0001
Stage 3	Yes	53,468	2,564/696,999	3.68	1.63 (1.40, 1.90)	<0.0001
	No	10,059	638/127,577	5.00	2.36 (1.99, 2.80)	<0.0001
Stage 4	Yes	25,193	1,545/322,364	4.79	2.23 (1.93, 2.57)	<0.0001
	No	3,340	341/40,123	8.50	3.59 (3.05, 4.23)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, C-reactive protein, physical activity, sleep duration, and diet intake.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease. Other-cause mortality: causes other than CVD, and cancer.

Table S11. Joint associations of CKM syndrome stages and physical activity on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	Adequate physical activity	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Yes	18,661	579/254,128	2.28	1.00	
	No	4,814	197/65,410	3.01	1.30 (1.11, 1.53)	0.0013
Stage 1	Yes	13,064	480/177,078	2.71	1.04 (0.92, 1.17)	0.53
	No	4,285	203/58,019	3.50	1.37 (1.17, 1.61)	0.0001
Stage 2	Yes	137,661	6,883/1,861,639	3.70	1.24 (1.14, 1.35)	<0.0001
	No	48,746	2,921/658,925	4.43	1.46 (1.34, 1.60)	<0.0001
Stage 3	Yes	45,945	6,925/598,583	11.57	1.56 (1.43, 1.70)	<0.0001
	No	17,582	3,290/225,993	14.56	1.94 (1.77, 2.12)	<0.0001
Stage 4	Yes	19,494	3,559/249,948	14.24	2.27 (2.07, 2.48)	<0.0001
	No	9,039	2,230/112,539	19.82	3.03 (2.76, 3.33)	<0.0001
CVD-specific mortality						
Stage 0	Yes	18,661	42/254,128	0.17	1.00	
	No	4,814	13/65,410	0.20	1.20 (0.42, 3.45)	0.73
Stage 1	Yes	13,064	52/177,078	0.29	1.55 (0.96, 2.48)	0.071
	No	4,285	18/58,019	0.31	1.69 (0.89, 3.23)	0.11
Stage 2	Yes	137,661	983/1,861,639	0.53	2.42 (1.74, 3.35)	<0.0001
	No	48,746	398/658,925	0.60	2.74 (1.93, 3.90)	<0.0001
Stage 3	Yes	45,945	1,422/598,583	2.38	4.36 (3.13, 6.07)	<0.0001
	No	17,582	707/225,993	3.13	5.61 (3.95, 7.97)	<0.0001
Stage 4	Yes	19,494	1,197/249,948	4.79	10.29 (7.47, 14.18)	<0.0001
	No	9,039	726/112,539	6.45	12.83 (9.11, 18.08)	<0.0001
Cancer-specific mortality						
Stage 0	Yes	18,661	372/254,128	1.46	1.00	
	No	4,814	120/65,410	1.83	1.22 (0.99, 1.51)	0.058
Stage 1	Yes	13,064	302/177,078	1.71	1.04 (0.89, 1.20)	0.64

	No	4,285	131/58,019	2.26	1.37 (1.12, 1.69)	0.0027
Stage 2	Yes	137,661	4,114/1,861,639	2.21	1.17 (1.06, 1.30)	0.0029
	No	48,746	1,663/658,925	2.52	1.31 (1.17, 1.47)	<0.0001
Stage 3	Yes	45,945	3,383/598,583	5.65	1.28 (1.14, 1.43)	<0.0001
	No	17,582	1,501/225,993	6.64	1.46 (1.30, 1.64)	<0.0001
Stage 4	Yes	19,494	1,283/249,948	5.13	1.35 (1.20, 1.52)	<0.0001
	No	9,039	697/112,539	6.19	1.51 (1.32, 1.72)	<0.0001
Other-cause mortality						
Stage 0	Yes	18,661	165/254,128	0.65	1.00	
	No	4,814	64/65,410	0.98	1.48 (1.10, 1.99)	0.0099
Stage 1	Yes	13,064	126/177,078	0.71	0.95 (0.77, 1.17)	0.61
	No	4,285	54/58,019	0.93	1.25 (0.92, 1.70)	0.16
Stage 2	Yes	137,661	1,786/1,861,639	0.96	1.12 (0.96, 1.32)	0.15
	No	48,746	860/658,925	1.31	1.49 (1.25, 1.78)	<0.0001
Stage 3	Yes	45,945	2,120/598,583	3.54	1.55 (1.32, 1.82)	<0.0001
	No	17,582	1,082/225,993	4.79	2.01 (1.67, 2.42)	<0.0001
Stage 4	Yes	19,494	1,079/249,948	4.32	2.04 (1.74, 2.39)	<0.0001
	No	9,039	807/112,539	7.17	3.07 (2.64, 3.56)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, C-reactive protein, smoking status, sleep duration, and diet intake.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease. Other-cause mortality: causes other than CVD, and cancer.

Table S12. Joint associations of CKM syndrome stages and sleep duration on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	Healthy sleep duration	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Yes	17,369	511/236,889	2.16	1.00	
	No	6,106	265/82,650	3.21	1.29 (1.11, 1.49)	0.0008
Stage 1	Yes	12,056	405/163,871	2.47	0.99 (0.87, 1.13)	0.86
	No	5,293	278/71,227	3.90	1.46 (1.26, 1.68)	<0.0001
Stage 2	Yes	127,684	6,303/1,729,361	3.64	1.26 (1.15, 1.38)	<0.0001
	No	58,723	3,501/791,204	4.42	1.44 (1.31, 1.58)	<0.0001
Stage 3	Yes	42,582	6,498/554,693	11.71	1.60 (1.46, 1.76)	<0.0001
	No	20,945	3,717/269,883	13.77	1.84 (1.67, 2.03)	<0.0001
Stage 4	Yes	17,334	3,268/221,339	14.76	2.38 (2.16, 2.62)	<0.0001
	No	11,199	2,521/141,148	17.86	2.77 (2.51, 3.06)	<0.0001
CVD-specific mortality						
Stage 0	Yes	17,369	35/236,889	0.15	1.00	
	No	6,106	20/82,650	0.24	1.42 (0.75, 2.68)	0.29
Stage 1	Yes	12,056	41/163,871	0.25	1.47 (0.82, 2.60)	0.19
	No	5,293	29/71,227	0.41	2.18 (1.27, 3.74)	0.0048
Stage 2	Yes	127,684	897/1,729,361	0.52	2.59 (1.74, 3.84)	<0.0001
	No	58,723	484/791,204	0.61	2.86 (1.94, 4.20)	<0.0001
Stage 3	Yes	42,582	1,346/554,693	2.43	4.77 (3.14, 7.23)	<0.0001
	No	20,945	783/269,883	2.90	5.52 (3.69, 8.27)	<0.0001
Stage 4	Yes	17,334	1,089/221,339	4.92	11.22 (7.54, 16.70)	<0.0001
	No	11,199	834/141,148	5.91	12.73 (8.52, 19.01)	<0.0001
Cancer-specific mortality						
Stage 0	Yes	17,369	332/236,889	1.40	1.00	
	No	6,106	160/82,650	1.94	1.21 (1.00, 1.47)	0.053
Stage 1	Yes	12,056	261/163,871	1.59	1.00 (0.83, 1.20)	0.98

	No	5,293	172/71,227	2.41	1.42 (1.17, 1.72)	0.0003
Stage 2	Yes	127,684	3,771/1,729,361	2.18	1.18 (1.03, 1.35)	0.015
	No	58,723	2,006/791,204	2.54	1.31 (1.13, 1.52)	0.0003
Stage 3	Yes	42,582	3,169/554,693	5.71	1.30 (1.13, 1.50)	0.0003
	No	20,945	1,715/269,883	6.35	1.42 (1.22, 1.65)	<0.0001
Stage 4	Yes	17,334	1,172/221,339	5.30	1.39 (1.20, 1.62)	<0.0001
	No	11,199	808/141,148	5.72	1.44 (1.23, 1.70)	<0.0001
Other-cause mortality						
Stage 0	Yes	17,369	144/236,889	0.61	1.00	
	No	6,106	85/82,650	1.03	1.43 (0.99, 2.07)	0.054
Stage 1	Yes	12,056	103/163,871	0.63	0.88 (0.68, 1.15)	0.35
	No	5,293	77/71,227	1.08	1.37 (0.98, 1.92)	0.065
Stage 2	Yes	127,684	1,635/1,729,361	0.95	1.15 (0.95, 1.38)	0.16
	No	58,723	1,011/791,204	1.28	1.43 (1.15, 1.76)	0.0010
Stage 3	Yes	42,582	1,983/554,693	3.57	1.59 (1.34, 1.89)	<0.0001
	No	20,945	1,219/269,883	4.52	1.91 (1.56, 2.32)	<0.0001
Stage 4	Yes	17,334	1,007/221,339	4.55	2.16 (1.82, 2.57)	<0.0001
	No	11,199	879/141,148	6.23	2.76 (2.27, 3.35)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, C-reactive protein, smoking status, physical activity, and diet intake.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease. Other-cause mortality: causes other than CVD, and cancer.

Table S13. Joint associations of CKM syndrome stages and diet intake on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	Healthy diet intake	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Yes	3,780	149/51,441	2.90	1.00	
	No	19,695	627/268,098	2.34	0.95 (0.79, 1.14)	0.57
Stage 1	Yes	2,430	100/32,934	3.04	0.93 (0.72, 1.20)	0.56
	No	14,919	583/202,163	2.88	1.02 (0.85, 1.22)	0.86
Stage 2	Yes	26,452	1,486/357,746	4.15	1.16 (0.98, 1.37)	0.089
	No	159,955	8,318/2,162,818	3.85	1.16 (0.99, 1.36)	0.072
Stage 3	Yes	9,684	1,470/126,566	11.61	1.46 (1.23, 1.73)	<0.0001
	No	53,843	8,745/698,011	12.53	1.48 (1.26, 1.75)	<0.0001
Stage 4	Yes	4,681	905/60,052	15.07	2.16 (1.82, 2.58)	<0.0001
	No	23,852	4,884/302,435	16.15	2.22 (1.88, 2.61)	<0.0001
CVD-specific mortality						
Stage 0	Yes	3,780	12/51,441	0.23	1.00	
	No	19,695	43/268,098	0.16	0.79 (0.36, 1.74)	0.55
Stage 1	Yes	2,430	8/32,934	0.24	0.93 (0.31, 2.75)	0.89
	No	14,919	62/202,163	0.31	1.29 (0.55, 3.05)	0.56
Stage 2	Yes	26,452	189/357,746	0.53	1.82 (0.85, 3.89)	0.12
	No	159,955	1,192/2,162,818	0.55	1.97 (0.92, 4.22)	0.080
Stage 3	Yes	9,684	337/126,566	2.66	4.06 (1.91, 8.61)	0.0003
	No	53,843	1,792/698,011	2.57	3.58 (1.70, 7.56)	0.0008
Stage 4	Yes	4,681	325/60,052	5.41	9.35 (4.40, 19.89)	<0.0001
	No	23,852	1,598/302,435	5.28	8.38 (3.98, 17.67)	<0.0001
Cancer-specific mortality						
Stage 0	Yes	3,780	94/51,441	1.83	1.00	
	No	19,695	398/268,098	1.48	0.95 (0.80, 1.14)	0.60
Stage 1	Yes	2,430	69/32,934	2.10	1.03 (0.82, 1.30)	0.79

	No	14,919	364/202,163	1.80	1.02 (0.85, 1.24)	0.80
Stage 2	Yes	26,452	901/357,746	2.52	1.13 (0.97, 1.31)	0.13
	No	159,955	4,876/2,162,818	2.25	1.10 (0.94, 1.29)	0.21
Stage 3	Yes	9,684	644/126,566	5.09	1.09 (0.94, 1.27)	0.26
	No	53,843	4,240/698,011	6.07	1.24 (1.05, 1.45)	0.010
Stage 4	Yes	4,681	285/60,052	4.75	1.15 (0.96, 1.37)	0.13
	No	23,852	1,695/302,435	5.60	1.29 (1.10, 1.53)	0.0022
Other-cause mortality						
Stage 0	Yes	3,780	43/51,441	0.84	1.00	
	No	19,695	186/268,098	0.69	0.98 (0.68, 1.41)	0.91
Stage 1	Yes	2,430	23/32,934	0.70	0.73 (0.42, 1.25)	0.25
	No	14,919	157/202,163	0.78	0.93 (0.63, 1.38)	0.73
Stage 2	Yes	26,452	396/357,746	1.11	1.06 (0.74, 1.50)	0.76
	No	159,955	2,250/2,162,818	1.04	1.07 (0.75, 1.54)	0.70
Stage 3	Yes	9,684	489/126,566	3.86	1.54 (1.05, 2.25)	0.028
	No	53,843	2,713/698,011	3.89	1.45 (1.00, 2.10)	0.052
Stage 4	Yes	4,681	295/60,052	4.91	2.03 (1.40, 2.96)	0.0002
	No	23,852	1,591/302,435	5.26	2.04 (1.43, 2.91)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, C-reactive protein, smoking status, physical activity, and sleep duration.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease. Other-cause mortality: causes other than CVD, and cancer.

Table S14. Joint associations of CKM syndrome stages and lifestyle categories (based on weighted lifestyle score) on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	Lifestyle category	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Favourable	2,194	83/29,886	2.78	1.00	
	Intermediate	14,874	415/202,707	2.05	0.86 (0.68, 1.09)	0.22
	Unfavourable	6,407	278/86,946	3.20	1.35 (1.06, 1.73)	0.016
Stage 1	Favourable	1,237	44/16,814	2.62	0.83 (0.58, 1.20)	0.33
	Intermediate	10,596	372/143,621	2.59	0.95 (0.75, 1.21)	0.68
	Unfavourable	5,516	267/74,663	3.58	1.38 (1.07, 1.76)	0.011
Stage 2	Favourable	14,036	743/189,970	3.91	1.12 (0.89, 1.40)	0.35
	Intermediate	113,138	5,342/1,530,875	3.49	1.09 (0.88, 1.36)	0.43
	Unfavourable	59,233	3,719/799,719	4.65	1.51 (1.21, 1.88)	0.0002
Stage 3	Favourable	4,667	643/61,433	10.47	1.44 (1.15, 1.81)	0.0018
	Intermediate	34,503	4,865/450,750	10.79	1.46 (1.18, 1.82)	0.0006
	Unfavourable	24,357	4,707/312,393	15.07	2.16 (1.74, 2.69)	<0.0001
Stage 4	Favourable	2,176	358/28,279	12.66	2.00 (1.58, 2.54)	<0.0001
	Intermediate	15,277	2,601/196,752	13.22	2.09 (1.68, 2.60)	<0.0001
	Unfavourable	11,080	2,830/137,457	20.59	3.27 (2.63, 4.07)	<0.0001
CVD-specific mortality						
Stage 0	Favourable	2,194	7/29,886	0.23	1.00	
	Intermediate	14,874	24/202,707	0.12	0.59 (0.21, 1.68)	0.32
	Unfavourable	6,407	24/86,946	0.28	1.36 (0.43, 4.34)	0.60
Stage 1	Favourable	1,237	6/16,814	0.36	1.39 (0.35, 5.52)	0.64
	Intermediate	10,596	34/143,621	0.24	1.01 (0.33, 3.12)	0.98
	Unfavourable	5,516	30/74,663	0.40	1.78 (0.59, 5.41)	0.31
Stage 2	Favourable	14,036	104/189,970	0.55	1.87 (0.67, 5.21)	0.23
	Intermediate	113,138	740/1,530,875	0.48	1.75 (0.63, 4.89)	0.28
	Unfavourable	59,233	537/799,719	0.67	2.49 (0.87, 7.13)	0.089

Stage 3	Favourable	4,667	172/61,433	2.80	4.53 (1.59, 12.90)	0.0047
	Intermediate	34,503	949/450,750	2.11	3.30 (1.18, 9.21)	0.023
	Unfavourable	24,357	1,008/312,393	3.23	5.16 (1.82, 14.60)	0.0020
Stage 4	Favourable	2,176	133/28,279	4.70	8.73 (3.10, 24.58)	<0.0001
	Intermediate	15,277	885/196,752	4.50	8.20 (2.96, 22.76)	<0.0001
	Unfavourable	11,080	905/137,457	6.58	11.30 (3.99, 31.97)	<0.0001
Cancer-specific mortality						
Stage 0	Favourable	2,194	56/29,886	1.87	1.00	
	Intermediate	14,874	274/202,707	1.35	0.84 (0.66, 1.06)	0.15
	Unfavourable	6,407	162/86,946	1.86	1.16 (0.88, 1.54)	0.29
Stage 1	Favourable	1,237	30/16,814	1.78	0.85 (0.53, 1.38)	0.52
	Intermediate	10,596	238/143,621	1.66	0.91 (0.71, 1.18)	0.48
	Unfavourable	5,516	165/74,663	2.21	1.26 (0.97, 1.64)	0.079
Stage 2	Favourable	14,036	458/189,970	2.41	1.02 (0.80, 1.31)	0.84
	Intermediate	113,138	3,236/1,530,875	2.11	0.99 (0.79, 1.25)	0.94
	Unfavourable	59,233	2,083/799,719	2.60	1.27 (1.02, 1.58)	0.032
Stage 3	Favourable	4,667	273/61,433	4.44	0.97 (0.78, 1.21)	0.80
	Intermediate	34,503	2,365/450,750	5.25	1.13 (0.91, 1.41)	0.26
	Unfavourable	24,357	2,246/312,393	7.19	1.63 (1.30, 2.04)	<0.0001
Stage 4	Favourable	2,176	123/28,279	4.35	1.08 (0.77, 1.52)	0.65
	Intermediate	15,277	920/196,752	4.68	1.16 (0.92, 1.47)	0.21
	Unfavourable	11,080	937/137,457	6.82	1.64 (1.30, 2.08)	<0.0001
Other-cause mortality						
Stage 0	Favourable	2,194	20/29,886	0.67	1.00	
	Intermediate	14,874	117/202,707	0.58	1.02 (0.62, 1.67)	0.95
	Unfavourable	6,407	92/86,946	1.06	1.83 (1.05, 3.19)	0.034
Stage 1	Favourable	1,237	8/16,814	0.48	0.62 (0.23, 1.71)	0.36
	Intermediate	10,596	100/143,621	0.70	1.05 (0.62, 1.78)	0.85
	Unfavourable	5,516	72/74,663	0.96	1.50 (0.92, 2.44)	0.11
Stage 2	Favourable	14,036	181/189,970	0.95	1.12 (0.70, 1.80)	0.63
	Intermediate	113,138	1,366/1,530,875	0.89	1.16 (0.71, 1.88)	0.55

	Unfavourable	59,233	1,099/799,719	1.37	1.82 (1.12, 2.97)	0.016
Stage 3	Favourable	4,667	198/61,433	3.22	1.70 (1.00, 2.87)	0.048
	Intermediate	34,503	1,551/450,750	3.44	1.78 (1.10, 2.88)	0.018
	Unfavourable	24,357	1,453/312,393	4.65	2.44 (1.47, 4.03)	0.0005
Stage 4	Favourable	2,176	102/28,279	3.61	2.03 (1.23, 3.35)	0.0056
	Intermediate	15,277	796/196,752	4.05	2.27 (1.39, 3.70)	0.0011
	Unfavourable	11,080	988/137,457	7.19	3.75 (2.37, 5.93)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Other-cause mortality: causes other than CVD, and cancer.

Note. The weighted lifestyle score for each individual was calculated as a weighted sum of their lifestyle factor values (0 or 1) multiplied by the corresponding normalized weights, then classified into three categories based on tertiles: unfavourable, intermediate, and favourable.

Table S15. Joint associations of CKM syndrome stages and lifestyle categories (including no heavy alcohol as an additional component) on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	Lifestyle category	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Favourable	8,446	247/115,065	2.15	1.00	
	Intermediate	14,068	468/191,500	2.44	1.18 (1.01, 1.38)	0.036
	Unfavourable	961	61/12,974	4.70	2.25 (1.70, 2.98)	<0.0001
Stage 1	Favourable	5,567	192/75,470	2.54	1.04 (0.86, 1.26)	0.69
	Intermediate	10,926	426/148,140	2.88	1.24 (1.06, 1.45)	0.0082
	Unfavourable	856	65/11,487	5.66	2.54 (1.93, 3.34)	<0.0001
Stage 2	Favourable	57,648	2,770/779,624	3.55	1.26 (1.11, 1.44)	0.0004
	Intermediate	117,870	6,174/1,594,625	3.87	1.42 (1.25, 1.61)	<0.0001
	Unfavourable	10,889	860/146,315	5.88	2.31 (2.00, 2.66)	<0.0001
Stage 3	Favourable	18,899	2,574/247,462	10.40	1.66 (1.46, 1.90)	<0.0001
	Intermediate	39,539	6,450/512,841	12.58	2.05 (1.80, 2.33)	<0.0001
	Unfavourable	5,089	1,191/64,273	18.53	3.21 (2.79, 3.69)	<0.0001
Stage 4	Favourable	8,206	1,369/105,878	12.93	2.37 (2.06, 2.71)	<0.0001
	Intermediate	17,938	3,690/227,599	16.21	2.99 (2.62, 3.40)	<0.0001
	Unfavourable	2,389	730/29,010	25.16	4.69 (4.05, 5.43)	<0.0001
CVD-specific mortality *						
Stage 0	Favourable	8,446	17/115,065	0.15	1.00	
	Intermediate	14,068	35/191,500	0.18	1.30 (0.73, 2.32)	0.38
	Unfavourable	961	3/12,974	0.23	1.59 (0.47, 5.42)	0.46
Stage 1	Favourable	5,567	19/75,470	0.25	1.50 (0.78, 2.88)	0.23
	Intermediate	10,926	46/148,140	0.31	1.93 (1.11, 3.36)	0.021
	Unfavourable	856	5/11,487	0.44	2.79 (1.03, 7.57)	0.044
Stage 2	Favourable	57,648	380/779,624	0.49	2.52 (1.55, 4.09)	0.0002
	Intermediate	117,870	863/1,594,625	0.54	2.83 (1.75, 4.57)	<0.0001
	Unfavourable	10,889	138/146,315	0.94	5.11 (3.09, 8.47)	<0.0001

Stage 3	Favourable	18,899	556/247,462	2.25	5.15 (3.17, 8.37)	<0.0001
	Intermediate	39,539	1,304/512,841	2.54	5.82 (3.60, 9.43)	<0.0001
	Unfavourable	5,089	269/64,273	4.19	9.93 (6.06, 16.26)	<0.0001
Stage 4	Favourable	8,206	474/105,878	4.48	11.84 (7.28, 19.26)	<0.0001
	Intermediate	17,938	1,217/227,599	5.35	14.04 (8.68, 22.72)	<0.0001
	Unfavourable	2,389	232/29,010	8.00	20.52 (12.51, 33.67)	<0.0001
Cancer-specific mortality						
Stage 0	Favourable	8,446	155/115,065	1.35	1.00	
	Intermediate	14,068	302/191,500	1.58	1.20 (1.02, 1.43)	0.030
	Unfavourable	961	35/12,974	2.70	2.08 (1.51, 2.87)	<0.0001
Stage 1	Favourable	5,567	123/75,470	1.63	1.08 (0.83, 1.39)	0.57
	Intermediate	10,926	268/148,140	1.81	1.25 (1.01, 1.55)	0.042
	Unfavourable	856	42/11,487	3.66	2.65 (1.91, 3.67)	<0.0001
Stage 2	Favourable	57,648	1,694/779,624	2.17	1.24 (1.04, 1.48)	0.017
	Intermediate	117,870	3,625/1,594,625	2.27	1.35 (1.13, 1.61)	0.0010
	Unfavourable	10,889	458/146,315	3.13	2.01 (1.67, 2.41)	<0.0001
Stage 3	Favourable	18,899	1,187/247,462	4.80	1.30 (1.12, 1.52)	0.0007
	Intermediate	39,539	3,144/512,841	6.13	1.70 (1.42, 2.04)	<0.0001
	Unfavourable	5,089	553/64,273	8.60	2.51 (2.06, 3.06)	<0.0001
Stage 4	Favourable	8,206	461/105,878	4.35	1.34 (1.10, 1.63)	0.0031
	Intermediate	17,938	1,277/227,599	5.61	1.72 (1.42, 2.07)	<0.0001
	Unfavourable	2,389	242/29,010	8.34	2.51 (2.02, 3.11)	<0.0001
Other-cause mortality						
Stage 0	Favourable	8,446	75/115,065	0.65	1.00	
	Intermediate	14,068	131/191,500	0.68	1.08 (0.77, 1.50)	0.66
	Unfavourable	961	23/12,974	1.77	2.64 (1.68, 4.17)	<0.0001
Stage 1	Favourable	5,567	50/75,470	0.66	0.87 (0.66, 1.15)	0.34
	Intermediate	10,926	112/148,140	0.76	1.05 (0.75, 1.46)	0.79
	Unfavourable	856	18/11,487	1.57	2.15 (1.20, 3.84)	0.010
Stage 2	Favourable	57,648	696/779,624	0.89	1.03 (0.83, 1.29)	0.76
	Intermediate	117,870	1,686/1,594,625	1.06	1.26 (0.99, 1.60)	0.056

	Unfavourable	10,889	264/146,315	1.80	2.23 (1.67, 2.97)	<0.0001
Stage 3	Favourable	18,899	831/247,462	3.36	1.62 (1.25, 2.09)	0.0003
	Intermediate	39,539	2,002/512,841	3.90	1.87 (1.47, 2.38)	<0.0001
	Unfavourable	5,089	369/64,273	5.74	2.77 (2.12, 3.63)	<0.0001
Stage 4	Favourable	8,206	434/105,878	4.10	2.10 (1.62, 2.71)	<0.0001
	Intermediate	17,938	1,196/227,599	5.25	2.61 (2.06, 3.30)	<0.0001
	Unfavourable	2,389	256/29,010	8.82	4.08 (3.20, 5.19)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Other-cause mortality: causes other than CVD, and cancer.

Note. A healthy lifestyle score (adequate physical activity, no current smoking, healthy sleep, healthy diet, and no heavy alcohol) was categorized into unfavourable (0-1 healthy factors), intermediate (2-3), and favourable (4-5) groups.

*****: For CVD-specific mortality, the number of events in some subgroups (<10) was too small to allow stable estimation in Fine–Gray competing risks models. Therefore, Cox proportional hazards models were used for CVD-specific mortality, treating deaths from other causes as censored.

Table S16. Joint associations of CKM syndrome stages (re-defined by incorporating hospital-diagnosed CKD) and lifestyle categories on the risks of all-cause and cause-specific mortality

Mortality/CKM stage	Lifestyle category	No of participants	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality						
Stage 0	Favourable	2,194	83/29,886	2.78	1.00	
	Intermediate	19,350	571/263,662	2.17	0.92 (0.73, 1.16)	0.47
	Unfavourable	1,930	122/25,977	4.70	1.92 (1.45, 2.54)	<0.0001
Stage 1	Favourable	1,237	44/16,814	2.62	0.84 (0.58, 1.21)	0.34
	Intermediate	14,256	509/193,392	2.63	0.98 (0.78, 1.24)	0.87
	Unfavourable	1,855	130/24,879	5.23	2.03 (1.54, 2.67)	<0.0001
Stage 2	Favourable	14,030	742/189,889	3.91	1.12 (0.89, 1.40)	0.34
	Intermediate	151,358	7,460/2,048,471	3.64	1.15 (0.93, 1.43)	0.19
	Unfavourable	20,945	1,591/281,257	5.66	1.87 (1.50, 2.33)	<0.0001
Stage 3	Favourable	4,673	644/61,514	10.47	1.45 (1.15, 1.83)	0.0015
	Intermediate	49,405	7,477/643,281	11.62	1.61 (1.30, 2.00)	<0.0001
	Unfavourable	9,525	2,105/120,752	17.43	2.57 (2.06, 3.20)	<0.0001
Stage 4	Favourable	2,176	358/28,279	12.66	2.01 (1.58, 2.55)	<0.0001
	Intermediate	21,426	3,993/274,055	14.57	2.31 (1.86, 2.88)	<0.0001
	Unfavourable	4,931	1,438/60,154	23.91	3.87 (3.10, 4.84)	<0.0001
CVD-specific mortality						
Stage 0	Favourable	2,194	7/29,886	0.23	1.00	
	Intermediate	19,350	38/263,662	0.14	0.72 (0.27, 1.88)	0.50
	Unfavourable	1,930	10/25,977	0.38	1.77 (0.33, 9.51)	0.50
Stage 1	Favourable	1,237	6/16,814	0.36	1.39 (0.35, 5.49)	0.64
	Intermediate	14,256	51/193,392	0.26	1.15 (0.39, 3.40)	0.81
	Unfavourable	1,855	13/24,879	0.52	2.25 (0.69, 7.40)	0.18
Stage 2	Favourable	14,030	104/189,889	0.55	1.88 (0.68, 5.18)	0.22
	Intermediate	151,358	1,027/2,048,471	0.50	1.84 (0.66, 5.13)	0.24
	Unfavourable	20,945	246/281,257	0.87	3.24 (1.15, 9.12)	0.026

Stage 3	Favourable	4,673	172/61,514	2.80	4.55 (1.61, 12.86)	0.0042
	Intermediate	49,405	1,490/643,281	2.32	3.68 (1.32, 10.25)	0.013
	Unfavourable	9,525	471/120,752	3.90	6.25 (2.23, 17.53)	0.0005
Stage 4	Favourable	2,176	133/28,279	4.70	8.76 (3.14, 24.46)	<0.0001
	Intermediate	21,426	1,323/274,055	4.83	8.74 (3.15, 24.24)	<0.0001
	Unfavourable	4,931	467/60,154	7.76	13.12 (4.67, 36.91)	<0.0001
Cancer-specific mortality						
Stage 0	Favourable	2,194	56/29,886	1.87	1.00	
	Intermediate	19,350	368/263,662	1.40	0.87 (0.69, 1.10)	0.25
	Unfavourable	1,930	68/25,977	2.62	1.60 (1.20, 2.14)	0.0014
Stage 1	Favourable	1,237	30/16,814	1.78	0.86 (0.53, 1.38)	0.52
	Intermediate	14,256	326/193,392	1.69	0.94 (0.74, 1.19)	0.61
	Unfavourable	1,855	77/24,879	3.09	1.79 (1.33, 2.41)	0.0001
Stage 2	Favourable	14,030	457/189,889	2.41	1.03 (0.80, 1.31)	0.84
	Intermediate	151,358	4,463/2,048,471	2.18	1.03 (0.82, 1.30)	0.77
	Unfavourable	20,945	851/281,257	3.03	1.51 (1.21, 1.88)	0.0002
Stage 3	Favourable	4,673	274/61,514	4.45	0.98 (0.79, 1.22)	0.86
	Intermediate	49,405	3,636/643,281	5.65	1.25 (1.00, 1.55)	0.046
	Unfavourable	9,525	980/120,752	8.12	1.87 (1.47, 2.38)	<0.0001
Stage 4	Favourable	2,176	123/28,279	4.35	1.09 (0.77, 1.53)	0.64
	Intermediate	21,426	1,397/274,055	5.10	1.26 (1.00, 1.59)	0.049
	Unfavourable	4,931	460/60,154	7.65	1.85 (1.47, 2.34)	<0.0001
Other-cause mortality						
Stage 0	Favourable	2,194	20/29,886	0.67	1.00	
	Intermediate	19,350	165/263,662	0.63	1.11 (0.68, 1.81)	0.69
	Unfavourable	1,930	44/25,977	1.69	2.76 (1.51, 5.05)	0.0010
Stage 1	Favourable	1,237	8/16,814	0.48	0.62 (0.23, 1.71)	0.36
	Intermediate	14,256	132/193,392	0.68	1.05 (0.63, 1.72)	0.86
	Unfavourable	1,855	40/24,879	1.61	2.44 (1.43, 4.17)	0.0011
Stage 2	Favourable	14,030	181/189,889	0.95	1.13 (0.70, 1.80)	0.62
	Intermediate	151,358	1,970/2,048,471	0.96	1.26 (0.78, 2.05)	0.34

	Unfavourable	20,945	494/281,257	1.76	2.33 (1.43, 3.81)	0.0007
Stage 3	Favourable	4,673	198/61,514	3.22	1.71 (1.01, 2.89)	0.046
	Intermediate	49,405	2,351/643,281	3.65	1.92 (1.18, 3.11)	0.0085
	Unfavourable	9,525	654/120,752	5.42	2.84 (1.70, 4.75)	<0.0001
Stage 4	Favourable	2,176	102/28,279	3.61	2.04 (1.24, 3.36)	0.0052
	Intermediate	21,426	1,273/274,055	4.65	2.57 (1.59, 4.16)	0.0001
	Unfavourable	4,931	511/60,154	8.49	4.39 (2.79, 6.90)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Other-cause mortality: causes other than CVD, and cancer.

Note. CKM syndrome was defined according to the Presidential Advisory from the American Heart Association, incorporating hospital-diagnosed CKD to supplement the CKD definition.

Table S17. Associations of lifestyle categories (based on weighted lifestyle score) with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome

Mortality/CKM stage/Lifestyle category	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality				
Stage 0				
Unfavourable	278/86,946	3.20	1.00	
Intermediate	415/202,707	2.05	0.63 (0.54, 0.74)	<0.0001
Favourable	83/29,886	2.78	0.72 (0.56, 0.93)	0.010
Stage 1				
Unfavourable	267/74,663	3.58	1.00	
Intermediate	372/143,621	2.59	0.68 (0.58, 0.79)	<0.0001
Favourable	44/16,814	2.62	0.58 (0.42, 0.80)	0.0010
Stage 2				
Unfavourable	3,719/799,719	4.65	1.00	
Intermediate	5,342/1,530,875	3.49	0.72 (0.69, 0.76)	<0.0001
Favourable	743/189,970	3.91	0.74 (0.68, 0.80)	<0.0001
Stage 3				
Unfavourable	4,707/312,393	15.07	1.00	
Intermediate	4,865/450,750	10.79	0.68 (0.66, 0.71)	<0.0001
Favourable	643/61,433	10.47	0.67 (0.62, 0.73)	<0.0001
Stage 4				
Unfavourable	2,830/137,457	20.59	1.00	
Intermediate	2,601/196,752	13.22	0.64 (0.61, 0.68)	<0.0001
Favourable	358/28,279	12.66	0.62 (0.55, 0.69)	<0.0001
CVD-specific mortality				
Stage 0				
Unfavourable	24/86,946	0.28	1.00	
Intermediate	24/202,707	0.12	0.43 (0.25, 0.74)	0.0021
Favourable	7/29,886	0.23	0.70 (0.21, 2.29)	0.56
Stage 1				

Unfavourable	30/74,663	0.40	1.00	
Intermediate	34/143,621	0.24	0.55 (0.32, 0.96)	0.035
Favourable	6/16,814	0.36	0.74 (0.29, 1.85)	0.52
Stage 2				
Unfavourable	537/799,719	0.67	1.00	
Intermediate	740/1,530,875	0.48	0.71 (0.63, 0.81)	<0.0001
Favourable	104/189,970	0.55	0.77 (0.62, 0.95)	0.015
Stage 3				
Unfavourable	1,008/312,393	3.23	1.00	
Intermediate	949/450,750	2.11	0.65 (0.60, 0.71)	<0.0001
Favourable	172/61,433	2.80	0.89 (0.79, 1.00)	0.050
Stage 4				
Unfavourable	905/137,457	6.58	1.00	
Intermediate	885/196,752	4.50	0.72 (0.65, 0.80)	<0.0001
Favourable	133/28,279	4.70	0.76 (0.63, 0.92)	0.0040
Cancer-specific mortality				
Stage 0				
Unfavourable	162/86,946	1.86	1.00	
Intermediate	274/202,707	1.35	0.72 (0.62, 0.83)	<0.0001
Favourable	56/29,886	1.87	0.85 (0.63, 1.15)	0.30
Stage 1				
Unfavourable	165/74,663	2.21	1.00	
Intermediate	238/143,621	1.66	0.71 (0.59, 0.84)	<0.0001
Favourable	30/16,814	1.78	0.65 (0.40, 1.06)	0.086
Stage 2				
Unfavourable	2,083/799,719	2.60	1.00	
Intermediate	3,236/1,530,875	2.11	0.78 (0.73, 0.83)	<0.0001
Favourable	458/189,970	2.41	0.80 (0.72, 0.88)	<0.0001
Stage 3				
Unfavourable	2,246/312,393	7.19	1.00	
Intermediate	2,365/450,750	5.25	0.71 (0.66, 0.75)	<0.0001
Favourable	273/61,433	4.44	0.61 (0.54, 0.69)	<0.0001

Stage 4				
Unfavourable	937/137,457	6.82	1.00	
Intermediate	920/196,752	4.68	0.72 (0.65, 0.79)	<0.0001
Favourable	123/28,279	4.35	0.68 (0.53, 0.85)	0.0011
Other-cause mortality				
Stage 0				
Unfavourable	92/86,946	1.06	1.00	
Intermediate	117/202,707	0.58	0.54 (0.21, 1.36)	0.19
Favourable	20/29,886	0.67	0.51 (0.25, 1.04)	0.064
Stage 1				
Unfavourable	72/74,663	0.96	1.00	
Intermediate	100/143,621	0.70	0.68 (0.49, 0.95)	0.025
Favourable	8/16,814	0.48	0.40 (0.13, 1.26)	0.12
Stage 2				
Unfavourable	1,099/799,719	1.37	1.00	
Intermediate	1,366/1,530,875	0.89	0.64 (0.59, 0.70)	<0.0001
Favourable	181/189,970	0.95	0.63 (0.53, 0.76)	<0.0001
Stage 3				
Unfavourable	1,453/312,393	4.65	1.00	
Intermediate	1,551/450,750	3.44	0.73 (0.68, 0.79)	<0.0001
Favourable	198/61,433	3.22	0.68 (0.59, 0.78)	<0.0001
Stage 4				
Unfavourable	988/137,457	7.19	1.00	
Intermediate	796/196,752	4.05	0.60 (0.54, 0.67)	<0.0001
Favourable	102/28,279	3.61	0.53 (0.43, 0.67)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, alcohol consumption, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Other-cause mortality: causes other than CVD, and cancer.

Note. The weighted lifestyle score for each individual was calculated as a weighted sum of their lifestyle factor values (0 or 1) multiplied by the corresponding normalized weights, then classified into three categories based on tertiles: unfavourable, intermediate, and favourable.

Table S18. Associations of lifestyle categories (including no heavy alcohol as an additional component) with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome

Mortality/CKM stage/Lifestyle category	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality				
Stage 0				
Unfavourable	61/12,974	4.70	1.00	
Intermediate	468/191,500	2.44	0.52 (0.40, 0.68)	<0.0001
Favourable	247/115,065	2.15	0.44 (0.33, 0.58)	<0.0001
Stage 1				
Unfavourable	65/11,487	5.66	1.00	
Intermediate	426/148,140	2.88	0.47 (0.36, 0.61)	<0.0001
Favourable	192/75,470	2.54	0.40 (0.30, 0.52)	<0.0001
Stage 2				
Unfavourable	860/146,315	5.88	1.00	
Intermediate	6,174/1,594,625	3.87	0.61 (0.57, 0.66)	<0.0001
Favourable	2,770/779,624	3.55	0.54 (0.50, 0.59)	<0.0001
Stage 3				
Unfavourable	1,191/64,273	18.53	1.00	
Intermediate	6,450/512,841	12.58	0.65 (0.61, 0.69)	<0.0001
Favourable	2,574/247,462	10.40	0.53 (0.49, 0.57)	<0.0001
Stage 4				
Unfavourable	730/29,010	25.16	1.00	
Intermediate	3,690/227,599	16.21	0.65 (0.60, 0.70)	<0.0001
Favourable	1,369/105,878	12.93	0.52 (0.47, 0.57)	<0.0001
CVD-specific mortality				
Stage 0				
Unfavourable	3/12,974	0.23	1.00	
Intermediate	35/191,500	0.18	0.89 (0.08, 10.24)	0.92
Favourable	17/115,065	0.15	0.68 (0.06, 7.37)	0.75
Stage 1				

Unfavourable	5/11,487	0.44	1.00	
Intermediate	46/148,140	0.31	0.72 (0.27, 1.91)	0.50
Favourable	19/75,470	0.25	0.54 (0.22, 1.37)	0.20
Stage 2				
Unfavourable	138/146,315	0.94	1.00	
Intermediate	863/1,594,625	0.54	0.57 (0.47, 0.68)	<0.0001
Favourable	380/779,624	0.49	0.51 (0.41, 0.64)	<0.0001
Stage 3				
Unfavourable	269/64,273	4.19	1.00	
Intermediate	1,304/512,841	2.54	0.62 (0.55, 0.71)	<0.0001
Favourable	556/247,462	2.25	0.56 (0.47, 0.67)	<0.0001
Stage 4				
Unfavourable	232/29,010	8.00	1.00	
Intermediate	1,217/227,599	5.35	0.73 (0.62, 0.86)	0.0001
Favourable	474/105,878	4.48	0.63 (0.54, 0.74)	<0.0001
Cancer-specific mortality				
Stage 0				
Unfavourable	35/12,974	2.70	1.00	
Intermediate	302/191,500	1.58	0.57 (0.39, 0.83)	0.0029
Favourable	155/115,065	1.35	0.47 (0.33, 0.68)	<0.0001
Stage 1				
Unfavourable	42/11,487	3.66	1.00	
Intermediate	268/148,140	1.81	0.45 (0.34, 0.62)	<0.0001
Favourable	123/75,470	1.63	0.39 (0.29, 0.53)	<0.0001
Stage 2				
Unfavourable	458/146,315	3.13	1.00	
Intermediate	3,625/1,594,625	2.27	0.66 (0.59, 0.74)	<0.0001
Favourable	1,694/779,624	2.17	0.61 (0.54, 0.68)	<0.0001
Stage 3				
Unfavourable	553/64,273	8.60	1.00	
Intermediate	3,144/512,841	6.13	0.70 (0.62, 0.77)	<0.0001
Favourable	1,187/247,462	4.80	0.54 (0.49, 0.59)	<0.0001

Stage 4				
Unfavourable	242/29,010	8.34	1.00	
Intermediate	1,277/227,599	5.61	0.71 (0.61, 0.82)	<0.0001
Favourable	461/105,878	4.35	0.56 (0.48, 0.66)	<0.0001
Other-cause mortality				
Stage 0				
Unfavourable	23/12,974	1.77	1.00	
Intermediate	131/191,500	0.68	0.41 (0.26, 0.65)	0.0001
Favourable	75/115,065	0.65	0.37 (0.24, 0.56)	<0.0001
Stage 1				
Unfavourable	18/11,487	1.57	1.00	
Intermediate	112/148,140	0.76	0.49 (0.32, 0.74)	0.0008
Favourable	50/75,470	0.66	0.40 (0.23, 0.70)	0.0014
Stage 2				
Unfavourable	264/146,315	1.80	1.00	
Intermediate	1,686/1,594,625	1.06	0.57 (0.50, 0.66)	<0.0001
Favourable	696/779,624	0.89	0.47 (0.41, 0.55)	<0.0001
Stage 3				
Unfavourable	369/64,273	5.74	1.00	
Intermediate	2,002/512,841	3.90	0.67 (0.60, 0.75)	<0.0001
Favourable	831/247,462	3.36	0.57 (0.50, 0.66)	<0.0001
Stage 4				
Unfavourable	256/29,010	8.82	1.00	
Intermediate	1,196/227,599	5.25	0.63 (0.55, 0.73)	<0.0001
Favourable	434/105,878	4.10	0.51 (0.44, 0.59)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Other-cause mortality: causes other than CVD, and cancer.

Note. A healthy lifestyle score (adequate physical activity, no current smoking, healthy sleep, healthy diet, and no heavy alcohol) was categorized into unfavourable (0-1 healthy factors), intermediate (2-3), and favourable (4-5) groups.

Table S19. Associations of lifestyle categories with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome (re-defined by incorporating hospital-diagnosed CKD)

Mortality/CKM stage/Lifestyle category	Events/person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
All-cause mortality				
Stage 0				
Unfavourable	122/25,977	4.70	1.00	
Intermediate	571/263,662	2.17	0.48 (0.39, 0.58)	<0.0001
Favourable	83/29,886	2.78	0.51 (0.38, 0.68)	<0.0001
Stage 1				
Unfavourable	130/24,879	5.23	1.00	
Intermediate	509/193,392	2.63	0.47 (0.38, 0.57)	<0.0001
Favourable	44/16,814	2.62	0.39 (0.28, 0.55)	<0.0001
Stage 2				
Unfavourable	1,591/281,257	5.66	1.00	
Intermediate	7,460/2,048,471	3.64	0.62 (0.59, 0.65)	<0.0001
Favourable	742/189,889	3.91	0.60 (0.55, 0.66)	<0.0001
Stage 3				
Unfavourable	2,105/120,752	17.43	1.00	
Intermediate	7,477/643,281	11.62	0.64 (0.61, 0.67)	<0.0001
Favourable	644/61,514	10.47	0.57 (0.52, 0.62)	<0.0001
Stage 4				
Unfavourable	1,438/60,154	23.91	1.00	
Intermediate	3,993/274,055	14.57	0.60 (0.57, 0.64)	<0.0001
Favourable	358/28,279	12.66	0.53 (0.47, 0.59)	<0.0001
CVD-specific mortality				
Stage 0				
Unfavourable	10/25,977	0.38	1.00	
Intermediate	38/263,662	0.14	0.43 (0.15, 1.23)	0.12
Favourable	7/29,886	0.23	0.56 (0.02, 13.06)	0.72
Stage 1				

Unfavourable	13/24,879	0.52	1.00	
Intermediate	51/193,392	0.26	0.51 (0.25, 1.02)	0.057
Favourable	6/16,814	0.36	0.59 (0.24, 1.44)	0.25
Stage 2				
Unfavourable	246/281,257	0.87	1.00	
Intermediate	1,027/2,048,471	0.50	0.58 (0.50, 0.67)	<0.0001
Favourable	104/189,889	0.55	0.60 (0.48, 0.75)	<0.0001
Stage 3				
Unfavourable	471/120,752	3.90	1.00	
Intermediate	1,490/643,281	2.32	0.61 (0.55, 0.66)	<0.0001
Favourable	172/61,514	2.80	0.74 (0.62, 0.89)	0.0009
Stage 4				
Unfavourable	467/60,154	7.76	1.00	
Intermediate	1,323/274,055	4.83	0.66 (0.58, 0.74)	<0.0001
Favourable	133/28,279	4.70	0.65 (0.53, 0.81)	<0.0001
Cancer-specific mortality				
Stage 0				
Unfavourable	68/25,977	2.62	1.00	
Intermediate	368/263,662	1.40	0.54 (0.42, 0.69)	<0.0001
Favourable	56/29,886	1.87	0.61 (0.42, 0.90)	0.011
Stage 1				
Unfavourable	77/24,879	3.09	1.00	
Intermediate	326/193,392	1.69	0.50 (0.40, 0.63)	<0.0001
Favourable	30/16,814	1.78	0.45 (0.31, 0.66)	<0.0001
Stage 2				
Unfavourable	851/281,257	3.03	1.00	
Intermediate	4,463/2,048,471	2.18	0.68 (0.63, 0.73)	<0.0001
Favourable	457/189,889	2.41	0.67 (0.60, 0.75)	<0.0001
Stage 3				
Unfavourable	980/120,752	8.12	1.00	
Intermediate	3,636/643,281	5.65	0.68 (0.64, 0.72)	<0.0001
Favourable	274/61,514	4.45	0.54 (0.48, 0.61)	<0.0001

Stage 4				
Unfavourable	460/60,154	7.65	1.00	
Intermediate	1,397/274,055	5.10	0.70 (0.63, 0.78)	<0.0001
Favourable	123/28,279	4.35	0.61 (0.49, 0.77)	<0.0001
Other-cause mortality				
Stage 0				
Unfavourable	44/25,977	1.69	1.00	
Intermediate	165/263,662	0.63	0.40 (0.26, 0.63)	<0.0001
Favourable	20/29,886	0.67	0.35 (0.11, 1.07)	0.066
Stage 1				
Unfavourable	40/24,879	1.61	1.00	
Intermediate	132/193,392	0.68	0.42 (0.30, 0.58)	<0.0001
Favourable	8/16,814	0.48	0.24 (0.07, 0.87)	0.030
Stage 2				
Unfavourable	494/281,257	1.76	1.00	
Intermediate	1,970/2,048,471	0.96	0.56 (0.51, 0.61)	<0.0001
Favourable	181/189,889	0.95	0.51 (0.43, 0.59)	<0.0001
Stage 3				
Unfavourable	654/120,752	5.42	1.00	
Intermediate	2,351/643,281	3.65	0.67 (0.61, 0.73)	<0.0001
Favourable	198/61,514	3.22	0.58 (0.50, 0.68)	<0.0001
Stage 4				
Unfavourable	511/60,154	8.49	1.00	
Intermediate	1,273/274,055	4.65	0.58 (0.52, 0.65)	<0.0001
Favourable	102/28,279	3.61	0.46 (0.36, 0.58)	<0.0001

Multivariable Cox proportional hazards models and Fine-Gray proportional subdistribution hazards models were used to assess all-cause and cause-specific mortality, respectively. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, Townsend Deprivation Index, low-density lipoprotein cholesterol, and C-reactive protein.

Abbreviations: CIs, confidence intervals; CKD, chronic kidney disease; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease. Other-cause mortality: causes other than CVD, and cancer.

Note. CKM syndrome was defined according to the Presidential Advisory from the American Heart Association, incorporating hospital-diagnosed CKD to supplement the CKD definition.

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