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

Mingming Wang,[a] Yanan Qiao,[a] Ruilang Lin,[b] Yongfu Yu,[b] Min Zhao,[c] Marie Standl,[d,e] Costan G. Magnussen,[f,g,h,i] and Bo Xi[a,*]

[a]Department of Epidemiology/Department of Maternal, Child and Adolescent Health, School of Public Health, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China
[b]Department of Biostatistics, Key Laboratory of Public Health Safety of Ministry of Education, NHC Key Laboratory for Health Technology Assessment, School of Public Health, Fudan University, Shanghai, 200032, China
[c]Department of Nutrition and Food Hygiene, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China
[d]Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany
[e]German Center for Child and Adolescent Health (DZKJ), Partner Site Munich, Munich, Germany
[f]Baker Heart and Diabetes Institute, Melbourne, VIC, Australia
[g]Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
[h]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland
[i]Alliance for Research in Exercise, Nutrition and Activity (ARENA), Allied Health and Human Performance, University of South Australia, Adelaide, Australia

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Summary

Background Cardiovascular-kidney-metabolic (CKM) syndrome is reported to be associated with increased all-cause and CVD-specific mortality. However, the association between CKM and cancer-specific mortality, as well as the modifying or joint effects of healthy lifestyle on mortality remain unclear.

Methods In this prospective cohort study, we enrolled participants aged 37–73 years from the UK Biobank. Individuals with missing data on CKM status, lifestyle factors or potential confounders at baseline (between March 2006 and July 2010) were excluded. Followed-up was conducted until November 30, 2022. CKM stages (0-4) were defined per the American Heart Association criteria. A healthy lifestyle score (adequate physical activity, no current smoking, healthy sleep, and healthy diet) was categorized into unfavourable (0–1), intermediate (2–3), and favourable (4) groups. Outcomes included all-cause and cause-specific mortality (due to cardiovascular disease [CVD], cancer, and other causes). Cox proportional hazards models and Fine–Gray proportional subdistribution hazards models were used to assess associations with all-cause and cause-specific mortality, respectively.

Findings A total of 319,291 participants were included. Over a median follow-up of 13.7 years (interquartile ranges 13.0–14.3), 27,267 deaths occurred (5558 CVDs [20.4%], 13,566 cancers [49.8%], 8143 other-causes [29.8%]). Compared with CKM Stage 0, Stages 2–4 were associated with progressively higher risks of all-cause mortality (hazard ratios [HRs] (95% confidence intervals [CIs]): Stage 2: 1.21 [1.12–1.30]; Stage 3: 1.54 [1.43–1.66]; Stage 4: 2.30 [2.13–2.49]), CVD-specific mortality (Stage 2: 2.38 [1.74–3.24]; Stage 3: 4.46 [3.23–6.14]; Stage 4: 10.40 [7.61–14.21]), and cancer-specific mortality (Stage 2: 1.15 [1.03–1.28]; Stage 3: 1.26 [1.12–1.41]; Stage 4: 1.32 [1.17–1.48]). In addition, Stages 3 and 4 were positively associated with other-cause mortality (Stage 3: 1.49 [1.29–1.72]; Stage 4: 2.08 [1.81–2.38]) (all *P*-trend <0.0001). Additionally, these associations were more pronounced in adults aged <60 years compared to those ≥60 years (*P*-interaction <0.0001). Significant CKM-lifestyle interactions were found for associations with all-cause (*P*-interaction = 0.021), cancer-specific (*P*-interaction = 0.021), and other-cause mortality (*P*-interaction = 0.0031), but not for CVD-specific mortality (*P*-interaction = 0.33). A favourable or intermediate lifestyle was associated with reduced all-cause and cause-specific mortality across all CKM stages, with substantial benefits observed for non-smoking, adequate physical activity, and healthy sleep duration. For all-cause mortality, HRs (95% CIs) for a favourable vs. unfavourable lifestyle were: Stage 0: 0.51 (0.38–0.68); Stage 1: 0.39 (0.28–0.55); Stage 2: 0.60 (0.55–0.66); Stage 3: 0.57 (0.52–0.62); Stage 4: 0.53 (0.47–0.59). For CVD-specific mortality, corresponding HRs (95% CIs) across CKM Stages were 0.56 (0.14–2.30), 0.59 (0.18–1.90), 0.60 (0.46–0.79), 0.74 (0.63–0.87), and 0.65 (0.53–0.81),

*Corresponding author. Department of Epidemiology, School of Public Health, Cheeloo College of Medicine, Shandong University, 44 Wenhuaxi Road, Jinan 250012, China.
E-mail address: xibo2010@sdu.edu.cn (B. Xi).

respectively. For cancer-specific mortality, the values were 0.61 (0.44–0.85), 0.45 (0.28–0.73), 0.67 (0.59–0.76), 0.54 (0.47–0.61), and 0.61 (0.49–0.77), respectively. For other-cause mortality, the values were 0.35 (0.17–0.72), 0.24 (0.07–0.82), 0.50 (0.41–0.63), 0.59 (0.50–0.69), and 0.46 (0.36–0.58), respectively.

Interpretation Participants at CKM stages 2–4 demonstrated a graded increase in the risks of all-cause, CVD-specific, and cancer-specific mortality, particularly among younger adults. Having a healthy lifestyle can mitigate these risks, highlighting the importance of lifestyle intervention, especially through non-smoking, adequate physical activity, and healthy sleep duration. As both CKM stage and lifestyle were assessed solely at baseline and the study is observational in nature, the findings may be subject to unmeasured temporal variability and residual confounding, which should be considered when interpretating the results.

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Keywords: Cardiovascular-kidney-metabolic syndrome; healthy lifestyle; Mortality; Cardiovascular disease; Chronic kidney disease

Research in context

Evidence before this study

We searched PubMed and Embase up to July 1st, 2025 using the terms ("cardiovascular-kidney-metabolic") AND ("mortality" OR "death"), with no restrictions on language. Available evidence showed that advanced stages of cardiovascular-kidney-metabolic (CKM) syndrome were associated with increased risks of all-cause and cardiovascular disease (CVD) mortality. However, no studies have investigated the association with cancer-specific or other-cause mortality. Furthermore, to our knowledge, no previous studies have jointly examined CKM syndrome stages and healthy lifestyle in relation to both all-cause and cause-specific mortality.

Added value of this study

CKM syndrome Stages 2–4 were associated with progressively higher risks of all-cause, CVD-specific, and cancer-specific mortality, while Stages 3–4 were also linked to other-cause mortality, with stronger associations observed in adults younger than 60 years. Individuals at CKM Stage 4 with an unfavourable lifestyle had substantially higher risks of all-cause and cause-specific mortality, compared with those at Stage 0 with a favourable lifestyle. Importantly, having a healthier lifestyle significantly attenuated the risks of all-cause and cause-specific mortality across all CKM stages, especially through non-smoking, adequate physical activity, and healthy sleep duration.

Implications of all the available evidence

CKM syndrome represents a growing public health concern, with progressively increasing all-cause and cause-specific mortality risks even at early stages and among younger adults. Our findings suggest that promoting healthy lifestyle behaviours – including non-smoking, adequate physical activity, and healthy sleep duration - may effectively mitigate these risks across CKM stages. These results support the integration of lifestyle-focused interventions into CKM syndrome prevention strategies and public health policies. Given that CKM stages and lifestyle were assessed only at baseline and considering the observational nature of this study, future research is warranted to investigate how longitudinal changes in CKM stages and lifestyle behaviours influence mortality risk.

Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome, introduced by the American Heart Association (AHA) in 2023, represents a novel staging framework highlighting the interrelated nature among cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic disorders.[1] A nationally representative US study demonstrated the proportions of five CKM syndrome stages in the general population: 10.6% at stage 0 (no risk factor), 25.9% at stage 1 (excess/dysfunctional adiposity), 49.0% at stage 2 (metabolic risk factors or kidney dysfunction), 5.4% at stage 3 (subclinical CVD), and 9.2% at stage 4 (established CVD).[2] Several US cohort studies have shown that only advanced CKM stages (3 or 4) were positively associated with elevated risk of all-cause or CVD-specific mortality,[3–6] while a Chinese cohort revealed progressive all-cause mortality risk escalation from stage 1 to stage 4 compared to stage 0.[7] Recently, a cohort study from the UK Biobank reported advanced CKM stages were positively associated

with all-cause mortality and CVD-specific mortality.[8] However, that study did not investigate the associations of CKM stages with non-CVD mortality, such as cancer-specific mortality, thereby limiting the comprehensive assessment of the CKM syndrome's population health burden. Evidence suggests that non-cardiovascular deaths are common among individuals with CVD.[9] For instance, among participants with one CVD event, only 22.4% of deaths were due to CVD, while 50.5% were attributable to cancer.[9]

Modifiable lifestyle factors provide a critical opportunity for intervention and prevention of CKM syndrome and mortality.[10,11] The AHA Life's Essential 8 emphasizes the importance of four key lifestyle factors: adequate physical activity, no smoking, healthy sleep, and healthy diet.[12] For example, in individuals with type 2 diabetes or metabolic syndrome (MetS), having a healthy lifestyle has been associated with significant risk reductions in all-cause mortality, CVD-specific and cancer-specific mortality.[13,14] However, the combined effects of CKM syndrome and lifestyle factors on all-cause and cause-specific mortality remain unexplored. Importantly, to our knowledge, no studies have evaluated whether having a healthy lifestyle is associated with a mitigation in risks of all-cause and cause-specific mortality in individuals with CKM syndrome.

Therefore, we conducted a prospective analysis of UK Biobank data to investigate three objectives: (1) the associations of CKM syndrome stages with all-cause and cause-specific mortality; (2) the joint relationships of CKM stages and lifestyle factors with mortality risk; and (3) the potential modifying effects of having a healthy lifestyle on the associations between CKM stages and mortality.

Methods

Study population

The UK Biobank is a very large population-based prospective cohort study that enrolled more than 500,000 participants aged 37–73 years across England, Scotland, and Wales between March 2006 and July 2010 (exact dates were not provided by the UK Biobank). This ongoing study collects comprehensive information about participants' phenotypes and genotypes through questionnaires, physical examinations, sample assays, imaging, genotyping, accelerometry, and long-term health follow-up. The detailed study design and information have been reported previously.[15] The UK Biobank was approved by the North West Multi-Centre Research Ethics Committee (approval number: 11/NW/0382, 16/NW/0274 and 21/NW/0157), with all participants providing written informed consent. The present study was carried out under UK Biobank application number 98410. Among the 502,366 participants, we first excluded those with missing data on the defined CKM syndrome (n = 163,765), followed by exclusion of those with missing information on socioeconomic, lifestyle factors or related biomarkers (n = 19,310). The final analysis included 319,291 participants with complete information for all variables used in our analyses (Fig. 1). Details on missing information for the CKM syndrome definition are provided in Table S1, and baseline characteristics of included and excluded participants are shown in Table S2. This study was conducted in accordance with the RECORD reporting checklist.

Assessment of CKM syndrome stages

Data related to CKM syndrome at baseline were obtained through questionnaires, physical examinations, random blood and urine samples, and primary care and hospital inpatient records. The components of CKM syndrome included: (1) excess or dysfunctional adiposity: overweight/obesity, abdominal obesity, or prediabetes; (2) metabolic risk factors: diabetes, hypertension, hypertriglyceridemia, or MetS; (3) CKD: moderate- to high-risk, or very high-risk CKD based on the Kidney Disease: Improving Global Outcomes classification[16]; (4) CVD: clinical CVD, or risk equivalents of subclinical CVD. Notably, in the present study, 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.[17,18] The codes used to identify prevalent diseases in the UK Biobank are shown in Table S3, and definitions of CKM syndrome components are presented in Table S4.

The stages of CKM syndrome (0–4) were classified based on the Presidential Advisory from the AHA[1]: Stage 0, no CKM components; Stage 1, excess or dysfunctional adiposity; Stage 2, metabolic risk factors or moderate- to high-risk CKD; Stage 3, risk equivalents of subclinical CVD: very high-risk CKD or predicted 10-year CVD risk $\geq$10% using the Predicting Risk of CVD Events (PREVENT) base models[19–23]; Stage 4, clinical CVD: coronary heart disease, heart failure, stroke, peripheral artery disease, or atrial fibrillation, and is further classified into 4a (without kidney failure) or 4b (with kidney failure). Although PREVENT is not recommended by UK NICE guidelines, we used it due to its validated performance in the UK Biobank, which has shown comparable accuracy to QRISK3, the UK-recommended CVD risk algorithm.[23] The 10% threshold aligns with UK NICE guidelines.[21] The detailed definitions of stages of CKM syndrome are provided in Table S5.

Ascertainment of mortality

Mortality data were obtained from death certificates provided by the National Health Service (NHS) England for participants in England and Wales, and by the NHS Central Register (NHSCR), part of the National Records of Scotland for participants in Scotland.[24] Date and

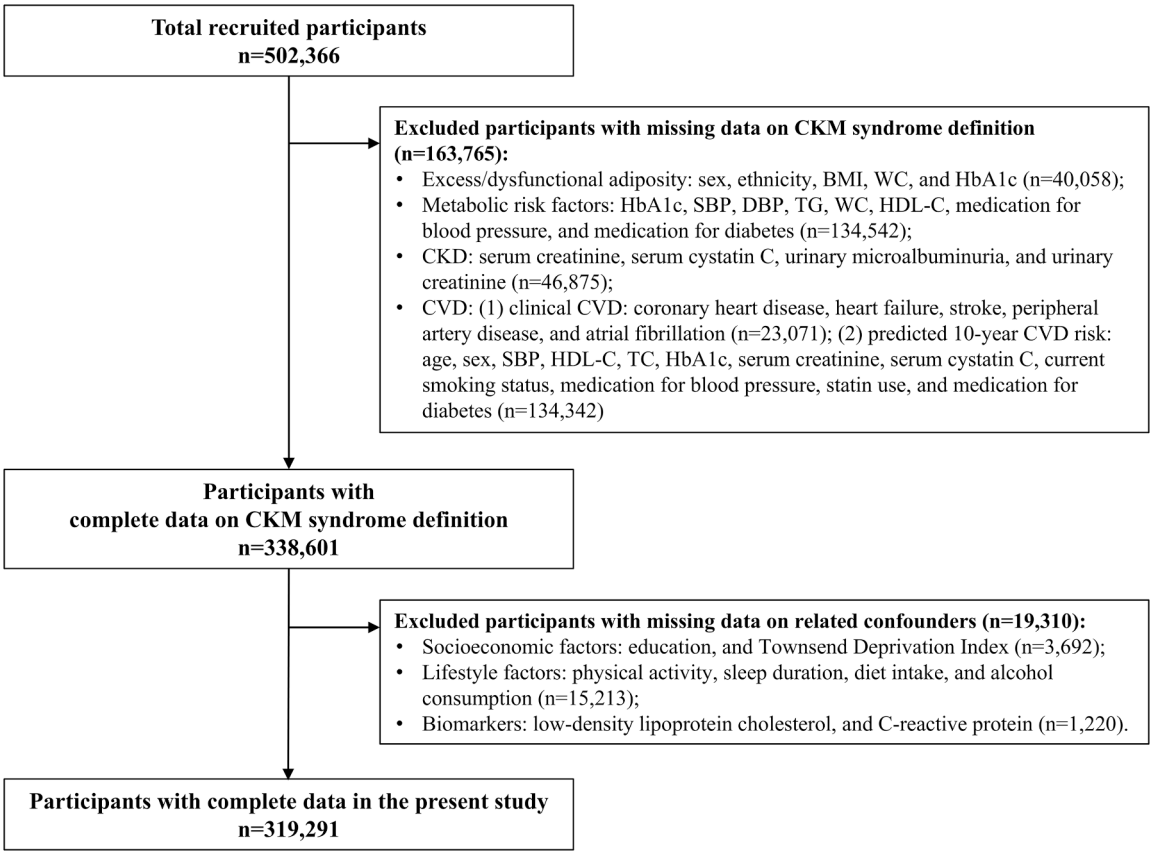

Fig. 1: Flow chart of study population inclusion and exclusion. *Note*: values below the detection limit (6.7 mg/L) for the urinary microalbumin were set to 6.7 mg/L to maximize the sample size. Additional details regarding missing data in the definition of CKM syndrome are provided in Table S1. CKD, chronic kidney diseases; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular diseases; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

primary cause of death were recorded to November 30, 2022. All-cause and cause-specific mortality were defined: CVD-specific mortality (ICD-10: I00–I99), cancer-specific mortality (C00–C97), and other-cause mortality (excluding deaths due to CVD and cancer). Table S6 shows the distribution of other-cause mortality by ICD-10 major chapters and CKM syndrome stages.

Assessment of lifestyle factors and potential confounders

All lifestyle factors and potential confounders were self-reported by touchscreen questionnaires at baseline, except for two biomarkers measured from blood samples. According to the recommended lifestyle factors in Life's Essential 8 by the AHA,[12] four modified lifestyle factors were included to generate a healthy lifestyle score: adequate physical activity, no current smoking, healthy sleep, and healthy diet. 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.[25] No current smoking was defined as no current tobacco smoking. Healthy sleep was defined as sleep duration ≥7 and <9 h per day.[12] Healthy diet was defined as meeting ideal intake for at least half of the 10 recommended components: fruit, vegetable, whole grains, (shell)fish, dairy, vegetable oils, refined grains, processed meats, unprocessed meats, and sugar-sweetened beverages.[26] Each lifestyle factor was scored as 1 for a healthy status and 0 for an unhealthy status. The healthy lifestyle score (0–4) was calculated by summing all four factors, with higher scores indicating greater adoption of a healthy lifestyle. The healthy lifestyle score was then classified into three categories: unfavourable (0–1), intermediate (2–3), and favourable (4).[27]

Potential confounders included age, sex (male or female), ethnicity (white or others), region of assessment, education degree (college/university degree or lower), Townsend Deprivation Index (TDI), alcohol consumption, low-density lipoprotein cholesterol (LDL-

C), and C-reactive protein (CRP). The region of assessment was categorized as England, Scotland, and Wales, based on the location of 22 assessment centres. The TDI was a comprehensive measure that quantified area-based deprivation, with higher values indicating greater deprivation.[28] Alcohol consumption (g/day) was calculated as detailed previously,[29] based on alcohol drinking status, alcohol intake frequency, average weekly and monthly intake of red wine, champagne plus white wine, beer plus cider, spirits, fortified wine, and other alcoholic drinks. Assessment details for lifestyle factors are presented in Method S1. LDL-C was measured by enzymatic protective selection analysis on a Beckman Coulter AU5800, and CRP was measured by immunoturbidimetric - high sensitivity analysis on a Beckman Coulter AU5800.

Statistical analyses

Baseline characteristics of participants across different stages of CKM syndrome (stages 0–4) were summarized using descriptive statistics, including means and standard deviations (SD), medians and interquartile ranges (IQR), or numbers and percentages, as appropriate. Cumulative incidence plots were constructed to visualize and compare rates of all-cause and cause-specific mortality across five CKM stages. For all-cause mortality, cumulative incidence was estimated as 1 minus the Kaplan–Meier survival probability. For cause-specific mortality, cumulative incidence functions (CIFs) accounting for competing risks from other causes of death were applied.

Cox proportional hazards models were applied to examine associations of CKM stages with all-cause mortality, and Fine–Gray proportional subdistribution hazards models[30] were used for associations with cause-specific mortality to account for competing risks from other causes of death. Results were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Schoenfeld's residuals method was employed to test the proportional hazards assumption, with no apparent violations observed based on residual plots. Person-year was calculated from baseline to the date of death or end of follow-up, whichever occurred first. Potential confounding effects were considered using two models: Model 1 was adjusted for age, sex, and ethnicity; Model 2 was additionally adjusted for region of assessment, education degree, TDI, alcohol consumption, physical activity, smoking status, sleep duration, diet intake, LDL-C, and CRP. Moreover, CKM syndrome (stages 0–4) was treated as a continuous variable to test for linear trends in associations with all-cause and cause-specific mortality.

Further, to explore joint effects of CKM stages with lifestyle on all-cause and cause-specific mortality, Cox proportional hazards models and Fine–Gray proportional subdistribution hazards models[30] were also used, respectively. In this analysis, participants were divided into 15 groups based on the combination of five CKM stages and three lifestyle categories, with the group of CKM stage 0 and a favourable lifestyle used as the reference. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, TDI, alcohol consumption, LDL-C, and CRP.

Moreover, associations of lifestyle categories with all-cause and cause-specific mortality stratifying by CKM stages, were examined using Cox proportional hazards models and Fine–Gray proportional subdistribution hazards models,[30] respectively. To test if having a healthy lifestyle modified the relationship with all-cause and cause-specific mortality across CKM stages, participants with an unfavourable lifestyle were used as the reference in each CKM stage. Statistical significance of interactions between lifestyle categories and CKM syndrome was assessed by comparing models with and without their cross-product terms, using likelihood ratio tests for all-cause mortality and pseudo-likelihood ratio tests for cause-specific mortality. Models were adjusted for age, sex, ethnicity, region of assessment, education degree, TDI, alcohol consumption, LDL-C, and CRP. We also evaluated the associations of each individual lifestyle factor with all-cause and cause-specific mortality across CKM stages, and tested for multiplicative interaction using the same modelling approach. These models were additionally adjusted for physical activity, smoking status, sleep duration, and dietary intake, except when the factor in question was the exposure of interest.

Additionally, subgroup analyses on associations of CKM stages with all-cause and cause-specific mortality were conducted by sex (male, female), age group (<60 years, ≥60 years), education (college/university degree or lower), TDI (≤median, > median), respectively. Statistical significance of interactions was tested by comparing models with and without cross-product terms between CKM syndrome and these subgroup variables, using likelihood ratio tests for all-cause mortality and pseudo-likelihood ratio tests for cause-specific mortality. Three-way interactions involving sex, age group, and CKM stages were further examined.

Five sensitivity analyses were conducted to test the robustness of the associations observed between CKM stages and all-cause and cause-specific mortality: (1) re-defining CKM using PREVENT risk ≥20% as the high predicted 10-year CVD risk according to the AHA[19,20]; (2) excluding participants with urinary microalbumin below the minimal detection level (6.7 mg/L, N = 99,509); (3) excluding those with less than two years of follow-up to minimize potential reverse causation; (4) re-defining CKM by incorporating hospital-diagnosed CKD to supplement the original CKD definition, which was based solely on estimated glomerular filtration rate and urine albumin-to-creatinine ratio (Method S2); (5) adjusting models for the center of assessment

instead of the region of assessment. Four additional sensitivity analyses were conducted to confirm the consistency of the associations between CKM stages, lifestyle, and all-cause and cause-specific mortality: (1) replacing lifestyle categories with each individual lifestyle factor in the models, mutually adjusted, to identify which factors were driving the associations; (2) constructing a weighted healthy lifestyle score (Method S3) to consider the varying impacts of each lifestyle factor on mortality risk; (3) constructing a healthy lifestyle score including no heavy alcohol consumption to account for the interrelations between alcohol and the four other lifestyle factors; (4) re-defining CKM by incorporating hospital-diagnosed CKD to supplement the original CKD definition. All statistical analyses were performed using R (version 4.3.1), with a two-sided *P* value < 0.05 considered statistically significant.

Role of the Funding source

The funders had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit for publication. All authors were not precluded from accessing data in the study and accept responsibility to submit for publication.

Results

Participants' characteristics

Table 1 presents the baseline characteristics of participants across different stages of CKM syndrome in the UK Biobank. Among 319,291 participants (mean age 56.8 years [SD 8.0], 53.7% [n = 171,328] women), the proportions of five CKM syndrome (Stages 0–4) were 7.4% (n = 23,475), 5.4% (n = 17,349), 58.4% (n = 186,407), 19.9% (n = 63,527), and 8.9% (n = 28,533), respectively. Within Stage 4, 28,110 (8.8%) participants were classified as CKM Stage 4a, and 423 (0.1%) as Stage 4b. Participant characteristics, including age, sex, ethnicity, TDI, education degree, alcohol consumption, current smoking status, physical activity, sleep duration, diet, and all CKM components, varied across the five stages of CKM syndrome (Table 1). Participants in advanced CKM stages (3 or 4) were more likely to be older, male, socioeconomically deprived, less educated, current smokers, less physically active, and have an unhealthy sleep duration.

During a median follow-up of 13.7 years (IQR 13.0-14.3), 27,267 deaths were recorded, with 5558 (20.4%) from CVD, 13,566 (49.8%) from cancer, and 8143 (29.8%) from other causes, which included 87 (0.3%) deaths due to kidney diseases (Table S6). The cumulative incidence of all-cause and cause-specific mortality increased progressively with increasing CKM stages (Fig. 2). Participants in Stages 3 and 4 showed a steeper rise in all-cause and cause-specific mortality over time compared to Stages 0–2, with Stage 4 exhibiting the most pronounced increase (except for cancer mortality, where Stage 3 showed similar risk with Stage 4).

Associations between CKM stages and all-cause and cause-specific mortality

In the multivariable-adjusted model, the stages of CKM syndrome displayed a stepwise increase in the risk of all-cause and cause-specific mortality (all *P*-trend <0.0001, Table 2). Compared to participants at CKM Stage 0, the adjusted HRs (95% CIs) for all-cause mortality were 1.05 (0.94, 1.16) for those at Stage 1, 1.21 (1.12, 1.30) for those at Stage 2, 1.54 (1.43, 1.66) for those at Stage 3, and 2.30 (2.13, 2.49) for those at Stage 4 (Table 2). Similarly, CKM stages 1–4 showed stronger associations with CVD-specific mortality, with HRs (95% CIs) of 1.51 (0.97, 2.35) for Stage 1, 2.38 (1.74, 3.24) for Stage 2, 4.46 (3.23, 6.14) for Stage 3, and 10.40 (7.61, 14.21) for Stage 4. The HRs (95% CIs) for cancer-specific mortality were 1.06 (0.93, 1.21) for Stage 1, 1.15 (1.03, 1.28) for Stage 2, 1.26 (1.12, 1.41) for Stage 3, and 1.32 (1.17, 1.48) for Stage 4. For other-cause mortality, the HRs (95% CIs) were 0.92 (0.75, 1.11) for Stage 1, 1.09 (0.94, 1.26) for Stage 2, 1.49 (1.29, 1.72) for Stage 3, and 2.08 (1.81, 2.38) for Stage 4 (Table 2).

Subgroup analyses by sex, age, education degree, and TDI category yielded consistent results, with significant interactions of sex and age groups with CKM syndrome on all-cause and cause-specific mortality (maximum *P*-interaction = 0.0003, Table S7). Notably, the associations between advanced CKM stages (2–4) and all-cause and cause-specific mortality risk were stronger among younger (<60 years) vs. older (≥60 years) participants (Fig. 3, Table S7). The three-way interaction involving sex, age group, and CKM stage was statistically significant for all outcomes (all *P*-interactions <0.0001, Table S8). In particular, younger females (<60 years) appeared to have higher risks of CVD-specific mortality at CKM stages 2–4 (Table S8).

Results remained largely consistent in all sensitivity analyses, including re-defining CKM based on high predicted 10-year CVD risk (PREVENT risk ≥20%), excluding participants with urinary microalbumin below 6.7 mg/L, excluding those with less than two years of follow-up, re-defining CKM by incorporating hospital-diagnosed CKD, and adjusting models for the center of assessment instead of the region of assessment (Table S9).

Lifestyle, CKM stages and mortality

Table 3 shows the joint associations of CKM stages and lifestyle categories with all-cause and cause-specific mortality. Compared to participants at CKM Stage 0 with a favourable lifestyle, those at CKM Stage 4 with an unfavourable lifestyle exhibited the highest HRs (95% CIs) for all-cause mortality (3.87 [3.10, 4.84]), CVD-specific mortality (13.08 [4.65, 36.84]), cancer-specific mortality (1.85 [1.47, 2.34]) and other-cause

Characteristic	Total	CKM syndrome				
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
No. of participants (%)	319,291	23,475 (7.4)	17,349 (5.4)	186,407 (58.4)	63,527 (19.9)	28,533 (8.9)
Age, years, mean (SD)	56.75 (8.04)	51.63 (7.64)	52.52 (7.85)	54.66 (7.39)	63.93 (4.41)	61.14 (6.53)
Age groups, n (%)						
<60 years	177,296 (55.5)	18,796 (80.1)	13,127 (75.7)	127,895 (68.6)	8521 (13.4)	8957 (31.4)
≥60 years	141,995 (44.5)	4679 (19.9)	4222 (24.3)	58,512 (31.4)	55,006 (86.6)	19,576 (68.6)
Sex, n (%)						
Male	147,963 (46.3)	5329 (22.7)	4828 (27.8)	74,144 (39.8)	45,407 (71.5)	18,255 (64.0)
Female	171,328 (53.7)	18,146 (77.3)	12,521 (72.2)	112,263 (60.2)	18,120 (28.5)	10,278 (36.0)
Ethnicity, n (%)						
White	305,301 (95.6)	22,662 (96.5)	16,220 (93.5)	177,817 (95.4)	61,272 (96.5)	27,330 (95.8)
Others	13,990 (4.4)	813 (3.5)	1129 (6.5)	8590 (4.6)	2255 (3.5)	1203 (4.2)
Region of assessment, n (%)						
England	293,832 (92.0)	21,836 (93.0)	16,070 (92.6)	171,337 (91.9)	58,549 (92.2)	26,040 (91.3)
Scotland	10,725 (3.4)	837 (3.6)	542 (3.1)	6156 (3.3)	2072 (3.3)	1118 (3.9)
Wales	14,734 (4.6)	802 (3.4)	737 (4.2)	8914 (4.8)	2906 (4.6)	1375 (4.8)
Townsend Deprivation Index, median [IQR]	−2.24 [−3.68, 0.29]	−2.25 [−3.70, 0.25]	−2.14 [−3.63, 0.45]	−2.26 [−3.70, 0.21]	−2.33 [−3.71, 0.14]	−1.87 [−3.48, 1.07]
Education degree, n (%)						
College/university	104,595 (32.8)	11,021 (46.9)	6397 (36.9)	64,150 (34.4)	16,185 (25.5)	6842 (24.0)
Less than college/university	214,696 (67.2)	12,454 (53.1)	10,952 (63.1)	122,257 (65.6)	47,342 (74.5)	21,691 (76.0)
Alcohol consumption, g/day, median [IQR]	8.57 [1.97, 20.00]	8.57 [1.97, 15.71]	8.57 [1.97, 17.14]	8.57 [1.97, 20.00]	11.43 [1.97, 25.71]	8.57 [1.43, 22.86]
No current smoking, n (%)	286,998 (89.9)	21,379 (91.1)	15,656 (90.2)	171,302 (91.9)	53,468 (84.2)	25,193 (88.3)
Adequate physical activity, n (%)	234,825 (73.5)	18,661 (79.5)	13,064 (75.3)	137,661 (73.8)	45,945 (72.3)	19,494 (68.3)
Sleep duration, hours/day, mean (SD)	7.16 (1.09)	7.17 (0.94)	7.10 (1.03)	7.12 (1.06)	7.26 (1.13)	7.19 (1.31)
Healthy sleep duration (≥7 and < 9 h/day), n (%)	217,025 (68.0)	17,369 (74.0)	12,056 (69.5)	127,684 (68.5)	42,582 (67.0)	17,334 (60.8)
Healthy diet, n (%)	47,027 (14.7)	3780 (16.1)	2430 (14.0)	26,452 (14.2)	9684 (15.2)	4681 (16.4)
Lifestyle factor categories, n (%)						
Unfavourable	39,186 (12.3)	1930 (8.2)	1855 (10.7)	20,957 (11.2)	9513 (15.0)	4931 (17.3)
Intermediate	255,795 (80.1)	19,351 (82.4)	14,257 (82.2)	151,414 (81.2)	49,347 (77.7)	21,426 (75.1)
Favourable	24,310 (7.6)	2194 (9.3)	1237 (7.1)	14,036 (7.5)	4667 (7.3)	2176 (7.6)
BMI, kg/m^2, mean (SD)	27.40 (4.71)	22.36 (1.71)	27.31 (3.12)	27.41 (4.64)	28.64 (4.64)	28.72 (5.03)
Overweight/obesity, n (%)	215,285 (67.4)	0 (0.0)	15,674 (90.3)	126,528 (67.9)	50,842 (80.0)	22,241 (77.9)
Waist circumference, cm, mean (SD)	90.39 (13.37)	75.41 (7.23)	86.93 (9.64)	89.49 (12.67)	96.96 (12.23)	96.08 (13.91)
Abdominal obesity, n (%)	109,437 (34.3)	0 (0.0)	4850 (28.0)	63,557 (34.1)	28,136 (44.3)	12,894 (45.2)
HbA1c, mmol/mol, median [IQR]	35.20 [32.80, 37.90]	33.50 [31.40, 35.50]	34.30 [32.00, 36.90]	34.90 [32.50, 37.30]	36.80 [34.10, 40.30]	37.10 [34.30, 40.50]
Prediabetes, n (%)	40,778 (12.8)	0 (0.0)	2370 (13.7)	22,006 (11.8)	10,603 (16.7)	5799 (20.3)
Diabetes, n (%)	19,307 (6.0)	0 (0.0)	0 (0.0)	3609 (1.9)	11,198 (17.6)	4500 (15.8)
SBP, mm Hg, mean (SD)	137.99 (18.57)	115.83 (8.26)	117.71 (7.48)	137.29 (15.26)	153.39 (17.80)	138.80 (18.83)
DBP, mm Hg, mean (SD)	82.28 (10.09)	70.75 (5.50)	72.48 (4.96)	83.40 (9.13)	86.74 (10.04)	80.44 (10.38)
Hypertension, n (%)	244,583 (76.6)	0 (0.0)	0 (0.0)	157,654 (84.6)	61,645 (97.0)	25,284 (88.6)
Total cholesterol, mmol/L, mean (SD)	5.70 (1.14)	5.43 (0.95)	5.51 (0.98)	5.91 (1.10)	5.57 (1.15)	4.90 (1.16)
Triglycerides, mmol/L, median [IQR]	1.49 [1.05, 2.15]	0.93 [0.74, 1.15]	1.05 [0.84, 1.26]	1.57 [1.10, 2.19]	1.82 [1.30, 2.55]	1.59 [1.12, 2.29]
Hypertriglyceridemia, n (%)	158,018 (49.5)	0 (0.0)	0 (0.0)	101,108 (54.2)	41,349 (65.1)	15,561 (54.5)
HDL-C, mmol/L, mean (SD)	1.45 (0.38)	1.69 (0.37)	1.55 (0.35)	1.49 (0.38)	1.30 (0.31)	1.30 (0.36)
LDL-C, mmol/L, mean (SD)	3.56 (0.87)	3.27 (0.71)	3.43 (0.74)	3.71 (0.84)	3.53 (0.88)	2.98 (0.86)
CRP, mg/L, median [IQR]	1.33 [0.66, 2.74]	0.60 [0.33, 1.15]	1.12 [0.59, 2.22]	1.31 [0.66, 2.69]	1.76 [0.92, 3.43]	1.53 [0.75, 3.18]
MetS, n (%)	95,713 (30.0)	0 (0.0)	0 (0.0)	52,109 (28.0)	30,502 (48.0)	13,102 (45.9)
eGFRcr-cys, ml/min/1.73m^2, mean (SD)	94.82 (14.39)	102.87 (11.39)	98.98 (12.29)	97.22 (12.85)	86.92 (14.57)	87.50 (16.52)
UACR, mg/mmol, median [IQR]	1.11 [0.70, 1.87]	1.15 [0.74, 1.76]	0.94 [0.62, 1.51]	1.12 [0.69, 1.92]	1.11 [0.71, 1.87]	1.12 [0.70, 1.97]
CKD risk in KDIGO classification, n (%)						
Low risk	283,376 (88.8)	23,475 (100.0)	17,349 (100.0)	164,820 (88.4)	54,175 (85.3)	23,557 (82.6)
Moderate- to high-risk	35,072 (11.0)	0 (0.0)	0 (0.0)	21,587 (11.6)	8832 (13.9)	4653 (16.3)
Very high-risk	843 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	520 (0.8)	323 (1.1)

(Table 1 continues on next page)

Characteristic	Total	CKM syndrome				
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
(Continued from previous page)						
Predicted 10-year CVD risk, %, median [IQR]	5.90 [3.10, 9.80]	1.80 [1.10, 3.30]	2.30 [1.30, 4.10]	4.90 [3.00, 7.10]	12.90 [11.20, 15.40]	9.70 [6.20, 13.80]
High predicted 10-y CVD risk, n (%)						
No (<10%)	242,076 (75.8)	23,475 (100.0)	17,349 (100.0)	186,407 (100.0)	69 (0.1)	14,776 (51.8)
Yes (≥10%)	77,215 (24.2)	0 (0.0)	0 (0.0)	0 (0.0)	63,458 (99.9)	13,757 (48.2)
Subclinical CVD, n (%)	77,296 (24.2)	0 (0.0)	0 (0.0)	0 (0.0)	63,527 (100.0)	13,769 (48.3)
Clinical CVD, n (%)	28,533 (8.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	28,533 (100.0)
Coronary heart disease, n (%)	17,598 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	17,598 (61.7)
Heart failure, n (%)	1640 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1640 (5.7)
Stroke, n (%)	5455 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5455 (19.1)
Peripheral artery disease, n (%)	3871 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3871 (13.6)
Atrial fibrillation, n (%)	5456 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5456 (19.1)

Note. A healthy lifestyle score (adequate physical activity, no current smoking, healthy sleep, and healthy diet) was categorized into unfavourable (0–1 healthy factors), intermediate (2–3), and favourable (4) groups. The included participants had complete information for all variables listed in this table. BMI, body mass index; CKM, cardiovascular-kidney-metabolic; CKD risk in KDIGO classification, chronic kidney disease risk in Kidney Disease: Improving Global Outcomes classification; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFRcr-cys, estimated glomerular filtration rate (creatinine-cystatin c); HbA1c, haemoglobin a1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; SD, standard deviation; UACR, urine albumin-to-creatinine ratio.

Table 1: **Baseline characteristics of participants across different stages of CKM syndrome.**

mortality (4.39 [2.79, 6.90]). Comparable trends were observed for each individual lifestyle factor (Tables S10–S13) and across all sensitivity analyses (Tables S14–S16).

Significant interactions between CKM syndrome and lifestyle categories were observed for all-cause, cancer-specific, and other-cause mortality (all *P*-interaction <0.05), but not for CVD-specific mortality (*P*-interaction = 0.33, Fig. 4). Within each CKM stage, having a favourable or intermediate lifestyle was associated with reduced risks of all mortality outcomes. For all-cause mortality, the HRs (95% CIs) for a favourable vs. unfavourable lifestyle were 0.51 (0.38, 0.68) at CKM Stage 0, 0.39 (0.28, 0.55) at Stage 1, 0.60 (0.55, 0.66) at Stage 2, 0.57 (0.52, 0.62) at Stage 3, and 0.53 (0.47, 0.59) at Stage 4. For CVD-specific mortality, corresponding HRs (95% CIs) were 0.56 (0.14, 2.30) at CKM Stage 0, 0.59 (0.18, 1.90) at Stage 1, 0.60 (0.46, 0.79) at Stage 2, 0.74 (0.63, 0.87) at Stage 3, and 0.65 (0.53, 0.81) at Stage 4 (Fig. 4).

When examining individual lifestyle factor, significant interactions with CKM syndrome on all-cause mortality were observed for smoking, physical activity, and sleep duration (all *P*-interaction <0.05), but not for dietary intake (Table 4). Not smoking, adequate physical activity, and healthy sleep duration were consistently associated with reduced risks of all-cause mortality across all CKM stages (0–4), with the most pronounced protective effect observed for non-smoking. These findings remained consistent in sensitivity analyses using the weighted healthy lifestyle (Table S17), including avoidance of heavy alcohol consumption as a component of healthy lifestyle (Table S18), and when redefining CKM stages to include hospital-diagnosed CKD (Table S19).

Discussion

In this prospective cohort study with 319,291 participants, those at CKM stages 2–4 demonstrated a stepwise increase in risks of all-cause, CVD-specific, and cancer-specific mortality, while stages 3–4 showed increased risks of other-cause mortality, with the highest risk observed in stage 4. These associations exhibited greater magnitude in younger participants (<60 years). Additionally, advanced CKM stages and having an unfavourable lifestyle jointly increased all-cause and cause-specific mortality risks, with exceptionally high risks observed in individuals at CKM stage 4 with an unfavourable lifestyle. Conversely, having a favourable or intermediate lifestyle was associated with significantly reduced risks of all-cause and cause-specific mortality across all CKM stages. Non-smoking, engaging in adequate physical activity, and having a healthy sleep duration were associated with reduced risks of all-cause mortality across all CKM stages (0–4).

Compared to the Rapid Communications article by Mayne et al.,[31] our study employed several key methodological enhancements, including Fine–Gray competing risk models, age-specific effect assessments, a refined stage 3 classification, and adjustment for additional confounders. These steps provided more precise and clinically interpretable estimates, thereby not only confirming the initial findings but also identifying a novel interaction with age, with significantly stronger associations observed in younger adults. Consistent with our findings, Huang et al., also observed significant associations of CKM stage 4 (vs. stage 0) with increased all-cause mortality risk, with similar estimates (HR: 2.68; 95% CI: 2.55, 2.83).[32] However, the authors did not differentiate between

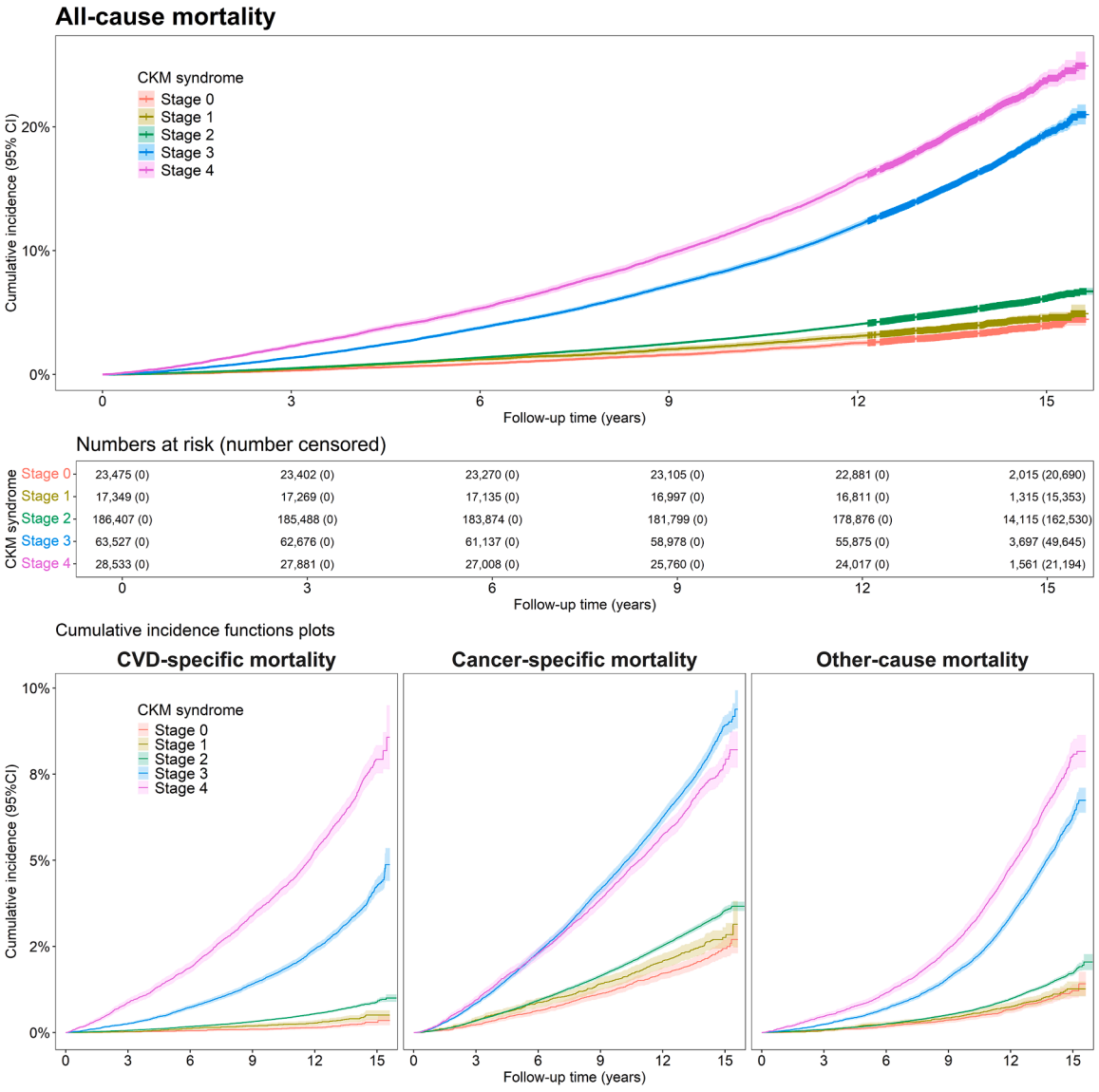

Fig. 2: Cumulative incidence of all-cause and cause-specific mortality across different stages of CKM syndrome. *Note*, for all-cause mortality, cumulative incidence was estimated as 1 minus the Kaplan–Meier survival probability. For cause-specific mortality, cumulative incidence functions (CIFs) accounting for competing risks from other causes of death were applied. Numbers at risk were the same for both all-cause and cause-specific mortality. CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

CKM stages 2 and 3, and they also did not investigate the associations of CKM stages with cause-specific mortality.[32] Similarly, Chen et al. found significant associations between CKM stages 2–4 and CVD-specific mortality among 110,933 participants from the UK Biobank.[8] However, this study did not account for competing risks even though death from one cause precludes death from another. Furthermore, a nationally representative US study with 27,909 participants reported a positive association between CKM stages 3–4 (vs. stage 0) and increased risk of CVD related premature mortality (deaths before age of 75 years), but no significant association for CKM stages 1–2.[4] The potential reason for inconsistent findings may be attributed to differences in study populations, statistical power, outcome definitions, socioeconomic and lifestyle risk factors.[10]

To our knowledge, no study has examined the relationships between CKM stages and deaths due to cancer or other diseases. In our study, CKM stages 2–4, defined by the presence of one or more of the following: hypertriglyceridemia, hypertension, MetS, diabetes,

Mortality	CKM syndrome, hazard ratios (95% CIs)					*P*-trend value
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
All-cause						
Events/person-years	776/319,539	683/235,097	9804/2,520,564	10,215/824,576	5789/362,487	
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, 2.11)	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, 1.66)	2.30 (2.13, 2.49)	<0.0001
CVD-specific						
Events/person-years	55/319,539	70/235,097	1381/2,520,564	2129/824,576	1923/362,487	
Incidence per 1000 person-years	0.17	0.30	0.55	2.58	5.31	
Model 1	1.00	1.58 (1.01, 2.48)	2.48 (1.81, 3.39)	5.57 (4.00, 7.75)	13.52 (9.84, 18.58)	<0.0001
Model 2	1.00	1.51 (0.97, 2.35)	2.38 (1.74, 3.24)	4.46 (3.23, 6.14)	10.40 (7.61, 14.21)	<0.0001
Cancer-specific						
Events/person-years	492/319,539	433/235,097	5777/2,520,564	4884/824,576	1980/362,487	
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)	1.53 (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	229/319,539	180/235,097	2646/2,520,564	3202/824,576	1886/362,487	
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, 1.32)	1.92 (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

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. Other-cause mortality: causes other than CVD and cancer. To test for linear trends, we modelled the CKM syndrome as a continuous variable. CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Table 2: **Associations of CKM syndrome stages with the risks of all-cause and cause-specific mortality.**

CKD, subclinical or clinical CVD, were associated with higher risks of cancer-specific mortality. Similarly, Drozd et al. reported that participants with one, two, or three or more CVDs had increased risks of cancer-specific mortality.[9] These associations may be explained by shared biological mechanisms such as oxidative stress, chronic inflammation, or metabolic dysregulation, which contribute to both CVD and cancer pathogenesis.[33] Additionally, CVD may promote tumour growth and spread through the release of signalling molecules.[34] Notably, cancer deaths were nearly 2.5 times higher than CVD deaths in our cohort, consistent with a previous study using the UK Biobank data,[9] which may reflect the higher national burden of cancer mortality in this age group. Furthermore, we observed that CKM stages 3–4 were associated with increased risks of other-cause mortality. Although Table S6 summarizes the distribution of other-cause deaths by ICD-10 major chapters and CKM stages, detailed analyses were limited by the small number of events. Therefore, further studies are warranted to explore these associations in greater depth.

Notably, our findings revealed that participants aged <60 years at CKM stages 2–4 had higher risks of all-cause and cause-specific mortality than those aged ≥60 years. For instance, in our study, participants aged <60 years at CKM stage 4 had a 3.61-fold higher risk of all-cause mortality compared to those at stage 0, whereas 2.62-fold was observed in those aged ≥60 years. Similarly, a study including 97,777 Chinese adults also reported a stronger association of CKM stage 4 with all-cause mortality in younger adults (aged <60 years) compared to older adults.[7] The early onset of CVD, CKD, and metabolic disorders, along with more aggressive progression and cumulative comorbidities over time, may contribute to the increased mortality risk in younger adults.[7,35,36] These findings highlight the importance of early risk identification and targeted prevention efforts, particularly in younger adults at advanced CKM stages.

Our analyses further demonstrated that advanced CKM stages combined with unhealthy lifestyle factors significantly increased all-cause and cause-specific mortality risks. Notably, in our study, the risks of all-cause and CVD-specific mortality were exceptionally high among individuals at CKM stage 4 and having an unfavourable lifestyle, with HRs (95% CIs) of 3.87 (3.10, 4.84) and 13.08 (4.65, 36.84), respectively. Several studies have assessed the combined effects of lifestyle factors with CKM components on mortality. A prospective cohort from the UK revealed that compared to individuals with no cardiometabolic disease (defined as having diabetes, coronary heart disease, or stroke) and a favourable lifestyle, the HR (95% CI) of all-cause

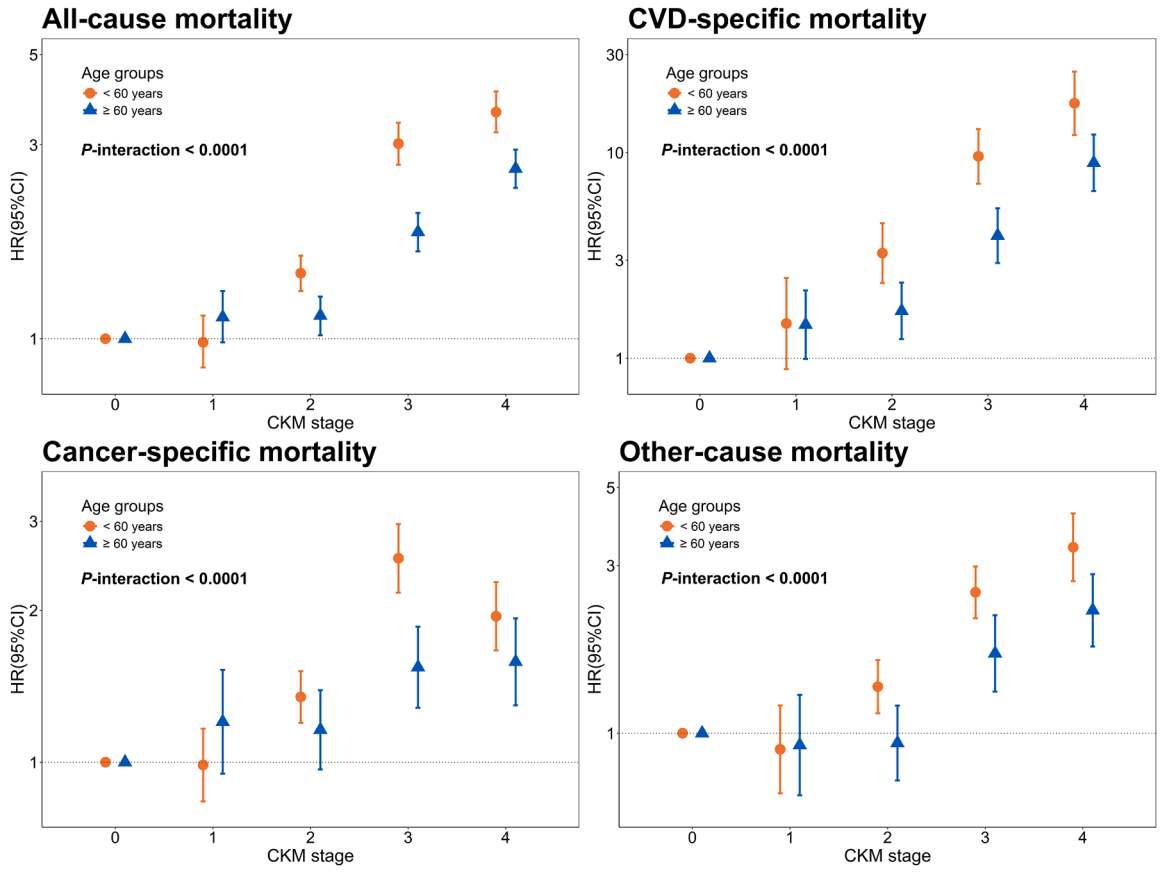

Fig. 3: Age-stratified associations of CKM syndrome stages with the risks of all-cause and cause-specific mortality. *P*-interaction: Interactions between CKM syndrome and age groups were tested using a likelihood ratio test by comparing models with and without cross-product terms. CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HR, hazard ratio.

mortality was 2.57 (2.38, 2.78) among those with cardiometabolic disease and an unfavourable lifestyle.[37] Another large cohort of 262,011 adults found that those with an unhealthy lifestyle and CKD had an increased risk of CVD-specific mortality.[38]

Accumulating evidence supports the beneficial impact of having a healthy lifestyle on reducing mortality risk in various populations.[13,14,39,40] A large cohort with 308,497 cancer-free adults observed that improving lifestyle behaviours was linked to lower risks of all-cause and cancer-specific mortality.[39] Similarly, two prospective studies from the UK reported that individuals with type 2 diabetes or MetS but maintaining a healthier lifestyle had significantly reduced risks of all-cause and cause-specific mortality.[13,14] However, the impact of having a healthy lifestyle across CKM stages has not been evaluated. In this study, we found that having a favourable or intermediate lifestyle was associated with lower risks of all-cause and cause-specific mortality across all CKM stages. Of note, we observed a potential benefit of a favourable or intermediate lifestyle on CVD-specific mortality within those with CKM stages 2–4, but not within CKM stages 0–1. This finding underscores the potential importance of lifestyle modification to achieve a healthier lifestyle (2 or more healthy factors), particularly for those at CKM stages 2–4 and having an unfavourable lifestyle.

Strengths included using the large-scale, prospective UK Biobank study with long-term follow-up and being the first study to systematically assess both the modifying and joint effects of lifestyle factors on the associations between CKM and all-cause and cause-specific mortality. However, several limitations should be acknowledged. First, urinary microalbumin results below the detection threshold (6.7 mg/L) were assigned a value of 6.7 mg/L to maximize statistical power in analyses, consistent with prior methodological approaches.[17,18] Sensitivity analysis excluding these participants reinforced our main findings. Second, the components of CKM syndrome were assessed only at baseline, without consideration of longitudinal changes over time. Future studies should investigate how changes in CKM syndrome status relate to mortality risk. Third, lifestyle factors were assessed only by self-

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	2194	83/29,886	2.78	1.00	
	Intermediate	19,351	571/263,675	2.17	0.92 (0.73, 1.16)	0.47
	Unfavourable	1930	122/25,977	4.70	1.92 (1.45, 2.54)	<0.0001
Stage 1	Favourable	1237	44/16,814	2.62	0.84 (0.58, 1.20)	0.34
	Intermediate	14,257	509/193,404	2.63	0.98 (0.78, 1.24)	0.87
	Unfavourable	1855	130/24,879	5.23	2.03 (1.54, 2.67)	<0.0001
Stage 2	Favourable	14,036	743/189,970	3.91	1.12 (0.89, 1.40)	0.33
	Intermediate	151,414	7469/2,049,188	3.64	1.16 (0.93, 1.43)	0.19
	Unfavourable	20,957	1592/281,407	5.66	1.87 (1.50, 2.33)	<0.0001
Stage 3	Favourable	4667	643/61,433	10.47	1.45 (1.15, 1.82)	0.0016
	Intermediate	49,347	7468/642,540	11.62	1.61 (1.29, 2.00)	<0.0001
	Unfavourable	9513	2104/120,603	17.45	2.57 (2.06, 3.20)	<0.0001
Stage 4	Favourable	2176	358/28,279	12.66	2.01 (1.58, 2.55)	<0.0001
	Intermediate	21,426	3993/274,055	14.57	2.31 (1.86, 2.88)	<0.0001
	Unfavourable	4931	1438/60,154	23.91	3.87 (3.10, 4.84)	<0.0001
CVD-specific mortality						
Stage 0	Favourable	2194	7/29,886	0.23	1.00	
	Intermediate	19,351	38/263,675	0.14	0.72 (0.27, 1.88)	0.50
	Unfavourable	1930	10/25,977	0.38	1.77 (0.33, 9.48)	0.50
Stage 1	Favourable	1237	6/16,814	0.36	1.39 (0.35, 5.51)	0.64
	Intermediate	14,257	51/193,404	0.26	1.14 (0.38, 3.40)	0.81
	Unfavourable	1855	13/24,879	0.52	2.25 (0.68, 7.40)	0.18
Stage 2	Favourable	14,036	104/189,970	0.55	1.87 (0.68, 5.18)	0.23
	Intermediate	151,414	1031/2,049,188	0.50	1.85 (0.66, 5.15)	0.24
	Unfavourable	20,957	246/281,407	0.87	3.23 (1.14, 9.11)	0.027
Stage 3	Favourable	4667	172/61,433	2.80	4.54 (1.60, 12.84)	0.0044
	Intermediate	49,347	1486/642,540	2.31	3.66 (1.31, 10.21)	0.013
	Unfavourable	9513	471/120,603	3.91	6.23 (2.22, 17.52)	0.0005
Stage 4	Favourable	2176	133/28,279	4.70	8.74 (3.13, 24.41)	<0.0001
	Intermediate	21,426	1323/274,055	4.83	8.72 (3.14, 24.20)	<0.0001
	Unfavourable	4931	467/60,154	7.76	13.08 (4.65, 36.84)	<0.0001
Cancer-specific mortality						
Stage 0	Favourable	2194	56/29,886	1.87	1.00	
	Intermediate	19,351	368/263,675	1.40	0.87 (0.69, 1.10)	0.25
	Unfavourable	1930	68/25,977	2.62	1.60 (1.20, 2.14)	0.0014
Stage 1	Favourable	1237	30/16,814	1.78	0.86 (0.53, 1.38)	0.52
	Intermediate	14,257	326/193,404	1.69	0.94 (0.74, 1.19)	0.61
	Unfavourable	1855	77/24,879	3.09	1.79 (1.33, 2.41)	0.0001
Stage 2	Favourable	14,036	458/189,970	2.41	1.03 (0.80, 1.31)	0.83
	Intermediate	151,414	4468/2,049,188	2.18	1.03 (0.82, 1.30)	0.77
	Unfavourable	20,957	851/281,407	3.02	1.51 (1.21, 1.88)	0.0002
Stage 3	Favourable	4667	273/61,433	4.44	0.98 (0.79, 1.21)	0.84
	Intermediate	49,347	3631/642,540	5.65	1.24 (1.00, 1.54)	0.048
	Unfavourable	9513	980/120,603	8.13	1.87 (1.47, 2.38)	<0.0001
Stage 4	Favourable	2176	123/28,279	4.35	1.09 (0.77, 1.53)	0.64
	Intermediate	21,426	1397/274,055	5.10	1.26 (1.00, 1.59)	0.050
	Unfavourable	4931	460/60,154	7.65	1.85 (1.47, 2.34)	<0.0001
Other-cause mortality						
Stage 0	Favourable	2194	20/29,886	0.67	1.00	
	Intermediate	19,351	165/263,675	0.63	1.11 (0.68, 1.81)	0.69
	Unfavourable	1930	44/25,977	1.69	2.76 (1.51, 5.05)	0.0010
Stage 1	Favourable	1237	8/16,814	0.48	0.62 (0.23, 1.71)	0.36
	Intermediate	14,257	132/193,404	0.68	1.05 (0.63, 1.72)	0.86
	Unfavourable	1855	40/24,879	1.61	2.44 (1.43, 4.17)	0.0011

(Table 3 continues on next page)

Mortality/CKM stage	Lifestyle category	No of participants	Events/ person-years	Incidence per 1000 person-years	Hazard ratios (95% CIs)	*P* value
(Continued from previous page)						
Stage 2	Favourable	14,036	181/189,970	0.95	1.13 (0.70, 1.80)	0.62
	Intermediate	151,414	1970/2,049,188	0.96	1.26 (0.78, 2.05)	0.34
	Unfavourable	20,957	495/281,407	1.76	2.34 (1.43, 3.82)	0.0007
Stage 3	Favourable	4667	198/61,433	3.22	1.71 (1.01, 2.89)	0.046
	Intermediate	49,347	2351/642,540	3.66	1.92 (1.18, 3.11)	0.0084
	Unfavourable	9513	653/120,603	5.41	2.84 (1.70, 4.75)	<0.0001
Stage 4	Favourable	2176	102/28,279	3.61	2.04 (1.24, 3.36)	0.0052
	Intermediate	21,426	1273/274,055	4.65	2.57 (1.59, 4.16)	0.0001
	Unfavourable	4931	511/60,154	8.49	4.39 (2.79, 6.90)	<0.0001

Note. A healthy lifestyle score (adequate physical activity, no current smoking, healthy sleep, and healthy diet) was categorized into unfavourable (0–1 healthy factors), intermediate (2–3), and favourable (4) groups. Other-cause mortality: causes other than CVD, and cancer. 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. CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease.

Table 3: **Joint associations of CKM syndrome stages and lifestyle categories on the risks of all-cause and cause-specific mortality.**

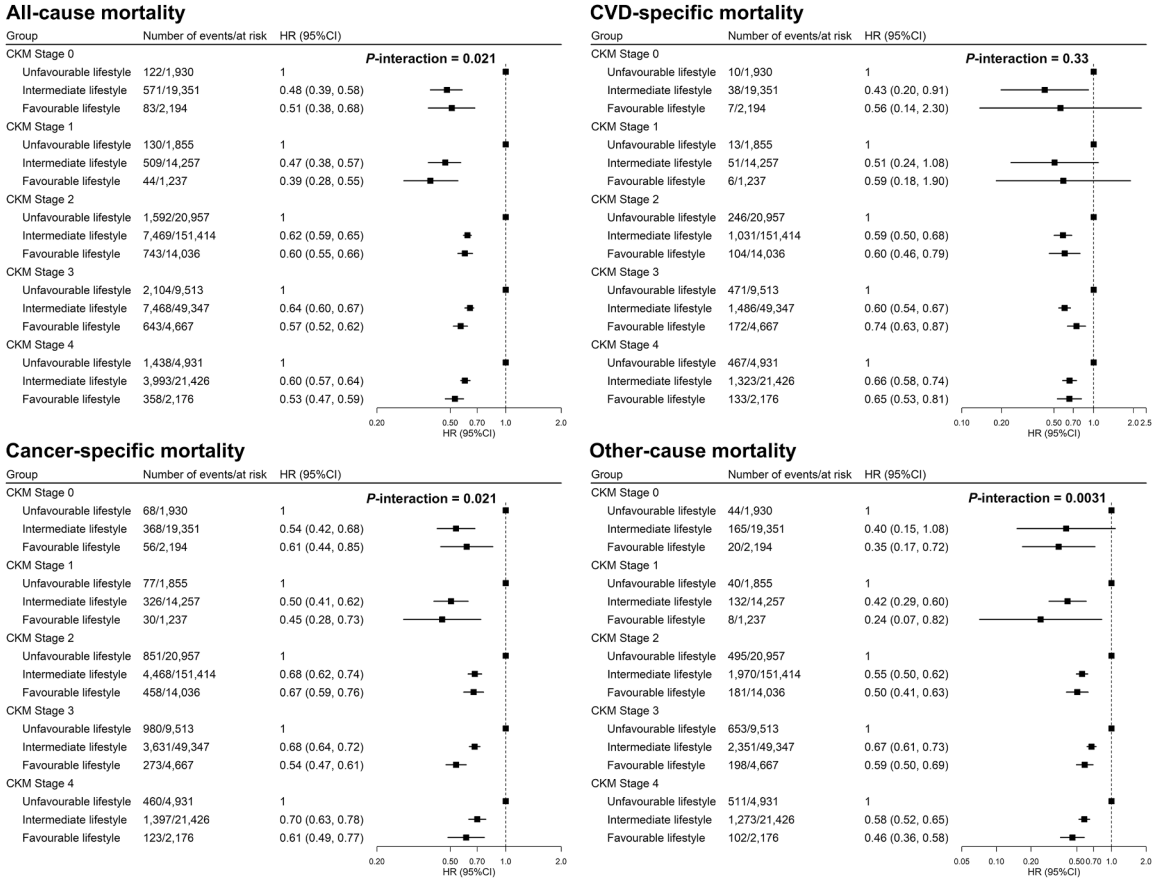

Fig. 4: Associations of healthy lifestyle categories with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome. A healthy lifestyle score (adequate physical activity, no current smoking, healthy sleep, and healthy diet) was categorized into unfavourable (0–1 healthy factors), intermediate (2–3), and favourable (4) groups. *P*-interaction: Interactions between CKM syndrome and lifestyle categories were assessed by comparing models with and without their cross-product terms, using likelihood ratio tests for all-cause mortality and pseudo-likelihood ratio tests for cause-specific mortality. CI, confidence interval; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HR, hazard ratio.

CKM stage/Lifestyle category	All-cause mortality	CVD-specific mortality	Cancer-specific mortality	Other-cause mortality
	HRs (95% CIs)	HRs (95% CIs)	HRs (95% CIs)	HRs (95% CIs)
Stage 0				
No current smoking (vs. current smoking)	0.49 (0.40, 0.61)	0.34 (0.15, 0.77)	0.60 (0.49, 0.74)	0.40 (0.003, 62.76)[a]
Adequate physical activity (vs. inadequate physical activity)	0.76 (0.65, 0.90)	0.85 (0.49, 1.46)	0.82 (0.69, 0.96)	0.65 (0.39, 1.09)
Healthy sleep duration (vs. unhealthy sleep duration)	0.78 (0.67, 0.91)	0.77 (0.45, 1.32)	0.82 (0.69, 0.98)	0.73 (0.33, 1.60)
Healthy diet (vs. unhealthy diet)	1.05 (0.87, 1.25)	1.22 (0.53, 2.81)	1.04 (0.89, 1.22)	1.03 (0.12, 9.14)
Stage 1				
No current smoking (vs. current smoking)	0.51 (0.41, 0.64)	0.41 (0.20, 0.85)	0.60 (0.43, 0.84)	0.43 (0.29, 0.64)
Adequate physical activity (vs. inadequate physical activity)	0.76 (0.65, 0.90)	0.91 (0.56, 1.47)	0.76 (0.62, 0.93)	0.76 (0.56, 1.04)
Healthy sleep duration (vs. unhealthy sleep duration)	0.68 (0.58, 0.79)	0.69 (0.42, 1.15)	0.70 (0.56, 0.87)	0.65 (0.47, 0.88)
Healthy diet (vs. unhealthy diet)	0.90 (0.72, 1.11)	0.67 (0.23, 1.97)	1.00 (0.80, 1.25)	0.77 (0.51, 1.15)
Stage 2				
No current smoking (vs. current smoking)	0.45 (0.42, 0.48)	0.41 (0.34, 0.50)	0.50 (0.45, 0.55)	0.42 (0.37, 0.47)
Adequate physical activity (vs. inadequate physical activity)	0.85 (0.82, 0.89)	0.89 (0.79, 1.01)	0.89 (0.83, 0.96)	0.76 (0.70, 0.83)
Healthy sleep duration (vs. unhealthy sleep duration)	0.88 (0.84, 0.91)	0.92 (0.81, 1.06)	0.90 (0.84, 0.96)	0.82 (0.76, 0.89)
Healthy diet (vs. unhealthy diet)	1.00 (0.95, 1.06)	0.94 (0.80, 1.10)	1.01 (0.94, 1.09)	1.01 (0.90, 1.14)
Stage 3				
No current smoking (vs. current smoking)	0.57 (0.54, 0.60)	0.60 (0.54, 0.66)	0.54 (0.51, 0.58)	0.68 (0.63, 0.75)
Adequate physical activity (vs. inadequate physical activity)	0.81 (0.77, 0.84)	0.79 (0.71, 0.86)	0.88 (0.83, 0.93)	0.76 (0.71, 0.82)
Healthy sleep duration (vs. unhealthy sleep duration)	0.87 (0.83, 0.90)	0.87 (0.79, 0.95)	0.92 (0.87, 0.97)	0.83 (0.77, 0.90)
Healthy diet (vs. unhealthy diet)	0.97 (0.92, 1.03)	1.11 (1.00, 1.24)	0.89 (0.81, 0.97)	1.02 (0.92, 1.13)
Stage 4				
No current smoking (vs. current smoking)	0.53 (0.49, 0.56)	0.61 (0.53, 0.71)	0.50 (0.46, 0.54)	0.62 (0.56, 0.69)
Adequate physical activity (vs. inadequate physical activity)	0.75 (0.71, 0.79)	0.79 (0.72, 0.87)	0.90 (0.82, 0.99)	0.66 (0.60, 0.73)
Healthy sleep duration (vs. unhealthy sleep duration)	0.87 (0.82, 0.91)	0.87 (0.77, 0.99)	0.98 (0.90, 1.06)	0.79 (0.73, 0.85)
Healthy diet (vs. unhealthy diet)	0.99 (0.92, 1.06)	1.10 (0.99, 1.23)	0.90 (0.79, 1.03)	0.99 (0.86, 1.15)
Interaction effects	***P*-interaction**	***P*-interaction**	***P*-interaction**	***P*-interaction**
CKM stage * No current smoking	<0.0001	<0.0001	0.19	<0.0001
CKM stage * Adequate physical activity	0.0065	0.54	0.54	0.13
CKM stage * Healthy sleep duration	0.020	0.70	0.050	0.33
CKM stage * Healthy diet	0.86	0.15	0.067	0.60

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, and, except when used as the exposure, physical activity, smoking status, sleep duration, and diet intake. Other-cause mortality: causes other than CVD, and cancer. CIs, confidence intervals; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; HRs, Hazard ratios. *P*-interaction: Interactions between CKM syndrome and each individual lifestyle were assessed by comparing models with and without their cross-product terms, using likelihood ratio tests for all-cause mortality and pseudo-likelihood ratio tests for cause-specific mortality. [a]For Other-cause mortality at CKM stage 0, some subgroups (*e.g.*, non-smokers) had relatively few events, resulting in unstable hazard ratio estimates with very wide CIs. These estimates should be interpreted with caution.

Table 4: **Associations of each individual lifestyle with the risks of all-cause and cause-specific mortality across different stages of CKM syndrome.**

report at baseline, which are subject to reporting bias and unmeasured temporal variability. Fourth, certain unhealthy behaviours, such as physical inactivity, may be consequences rather than causes of underlying health conditions. Fifth, some CVD-specific analyses involved subgroups with a limited number of events (*e.g.*, seven deaths in Stage 0 with favourable lifestyle group), which may reduce statistical power and precision. These results should therefore be interpreted with caution. Sixth, due to the small sample size in certain subgroups, we could not adjust for the assessment centre in all analyses. Sensitivity analyses including this adjustment for the associations between CKM and mortality yielded similar results. In the main analyses, we adjusted for the region of assessment (England, Scotland, and Wales), which have partially accounted for the potential effects of assessment centres. Seventh, heterogeneity in coding disease categories, regional data completeness, and the complexity of assigning primary vs. contributory causes may lead to differential misclassification, potentially affecting CVD-specific and cancer-specific mortality estimates. Eighth, this observational study limited our ability to make causal inferences, and residual and unmeasured confounding was inevitable despite adjusting for multiple variables. Ninth, caution is warranted when generalizing these findings, as the UK Biobank cohort predominantly includes individuals of European ancestry and may be affected by a "healthy volunteer" bias, with participants generally being healthier and more health-conscious than the general population.[41]

In this large prospective cohort study, CKM syndrome stages 2–4 (vs. stage 0) demonstrated a graded increase in the risks of all-cause, CVD-specific, and

cancer-specific mortality, with more pronounced risks observed in younger adults. Furthermore, the combination of progressive CKM stages and having an unhealthy lifestyle further amplified mortality risks, highlighting the potential role of lifestyle modification. Importantly, having a healthier lifestyle (non-smoking, adequate physical activity, and healthy sleep duration) was linked to lower risks of all-cause and cause-specific mortality across all CKM stages, emphasizing the need for targeted lifestyle interventions to mitigate mortality risk.

Contributors

BX contributed to the study design, interpretation of the data analysis, and critical revision of the manuscript as the principal investigator. MW contributed to the study design, conducted data analysis, drafted and revised the manuscript. YQ, LR, YY, MZ, MS, and CGM contributed to the data interpretation and critical revision of the manuscript. BX, MW, and YQ have access to and verify the underlying study data. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Data sharing statement

Data from UK Biobank are available on application at www.ukbiobank.ac.uk/register-apply.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103596.

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