Cardiovascular Diabetology

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Life's Essential 8 cardiovascular health, cardiovascular-kidney-metabolic syndrome stages, and incident cardiovascular events: a nationwide 10-year prospective cohort study in China

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Abstract

Background Definition and staging rationale of cardiovascular-kidney-metabolic syndrome were developed. The utility of cardiovascular-kidney-metabolic construct in risk stratification and target strategies of health and behavior modifications needs to be addressed. The study aims to investigate the individual and combined associations of cardiovascular-kidney-metabolic stage and cardiovascular health (CVH) by Life's Essential 8 (LE 8) with incident cardiovascular events (CVD), and determine the distribution and contribution of domain-specific CVH across cardiovascular-kidney-metabolic stages.

Methods The study included 100,727 individuals in the China Cardiovascular Disease and Cancer Cohort with complete data on cardiovascular-kidney-metabolic factors and LE 8 metrics, with a median follow-up of 10.1 years. Cardiovascular-kidney-metabolic stages and CVH metrics (nicotine exposure, diet, physical activity, sleep, body mass index, blood lipids, blood pressure, blood glucose) were defined according to Presidential Advisory from the

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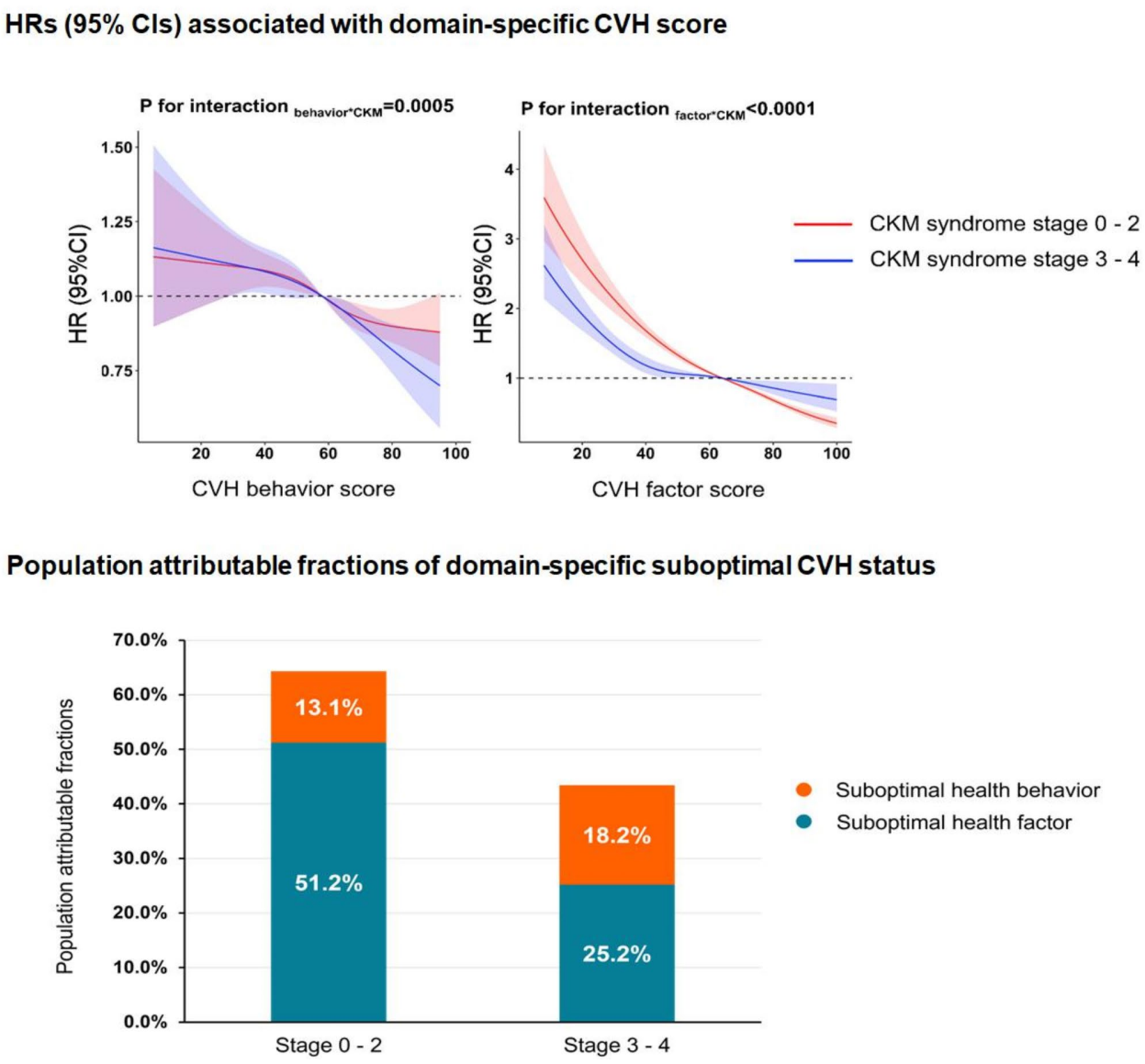
American Heart Association. Incident CVD events including cardiovascular death, myocardial infarction, and stroke were validated. The Fine-Gray hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of CKM stages or CVH status associated with CVD.

Results Compared with cardiovascular-kidney-metabolic stage 0, the adjusted competing HRs and 95% CIs of CVD events were 1.20 (0.95–1.51), 2.45 (1.97–3.04), 4.43 (3.53–5.58), and 5.95 (4.75–7.45) from stage 1 to stage 4, respectively. Optimal CVH status and each optimal CVH metric presented a significantly decreased risk of CVD events. Variation was observed in the association between cardiovascular-kidney-metabolic stage and CVD events with different CVH status or numbers of optimal CVH metrics. Compared with those in stage 0, Participants in stage 1 or 2 with optimal CVH no longer had elevated risks for incident CVD events. Suboptimal health factor contributed larger population attributable fractions to CVD events in cardiovascular-kidney-metabolic stage 0–2 (51.2%) than in stage 3–4 (25.2%), whereas suboptimal health behavior exhibited larger contribution in advanced stages (13.1% in stage 0–2 and 18.2% in stage 3–4).

Conclusions The study indicated that cardiovascular-kidney-metabolic stage was associated with cardiovascular events, and optimal cardiovascular health could attenuate this risk. Health factor contributed predominantly at the early-stage, whereas health behavior exhibited consistent and slightly increased contribution along the spectrum. These findings support the utility of cardiovascular-kidney-metabolic construct and highlight the importance of target health improvement based on LE 8 framework.

Graphic abstract



Keywords Cardiovascular health, Health behavior, Health factor, Cardiovascular-kidney-metabolic syndrome, Cardiovascular events

Introduction

Cardiac, renal, and metabolic conditions often coexist and intricately interconnect, which have a particularly critical impact on the incidence of cardiovascular disease (CVD) events and mortality [1–3]. Given the shared pathophysiology, risk factors, adverse outcomes, and potential therapeutic opportunities, cardiovascular-kidney-metabolic (CKM) health has been introduced to describe these conditions as comorbidity [4–6]. American Heart Association (AHA) proposed a conceptual framework for CKM syndrome [7–9]. Despite compelling evidence regarding CKM-related risk of CVD events, the distribution of different CKM stages in general population and its utility in CVD risk assessment needs to be addressed in large-scale population-based cohorts.

CKM stages provides a paradigm for the evaluation and prevention of CVD risk. Furthermore, as AHA mentioned, it is crucial to define strategies of health and behavior modifications across the CKM continuum to minimize the related CVD burden [7, 8]. AHA's presidential advisory has recommended that Life's Essential 8 (LE 8) construct can offer a practical framework for measuring, monitoring, and modifying cardiovascular health (CVH) [10]. Previous studies have shown that optimal CVH status was associated with lower cardiovascular morbidity and mortality [11–15]. However, no study has investigated whether and to what extent optimal CVH status defined by the LE 8 could affect the risk of CVD events associated with advanced CKM stages. Moreover, LE 8 incorporates two distinct domains: health behaviors (nicotine exposure, diet, physical activity, and sleep) and health factors (body mass index (BMI), blood lipids, blood glucose, and blood pressure). Considering the staging rationale of CKM syndrome, the proportion and complexity of suboptimal health factors inevitably increase with syndromic progression. Identifying CVH domain-specific distribution and contribution across different CKM stages can aid in formulating targeted strategies for improving CVH along the CKM spectrum.

Thus, in a large sample with a detailed assessment of 8-item cardiometabolic health and comprehensively-evaluated CKM status, we aimed to investigate (1) the individual and combined association of CKM stage and LE 8 CVH status with incident CVD events; (2) the domain-specific distribution and contribution of CVH in CVD risk among participants with different CKM stages.

Methods

Study design and population

The prospective China Cardiometabolic Disease and Cancer Cohort (4C) Study is a multicenter, population-based, prospective cohort study designed to investigate the risk factors of cardiovascular, cancer, and all-cause mortality in the Chinese population. The objectives and design have been described in detail in previous publications [16]. Briefly, the baseline survey was conducted in 2011–2012, and 193,846 participants aged 40 years or older were recruited from 20 communities covering 16 provinces in mainland China. During a median follow-up time of 10.1 years, 4430 (2.3%) participants were lost to follow-up due to incomplete death surveillance coverage in certain regions and 26,057 participants were further excluded due to incomplete information on CVD events during the follow-up period. Finally, 100,727 participants with complete baseline data to define CKM stage and LE 8 CVH score were included in the current analysis (eFigure 1 in the Supplement). Baseline key characteristics between the participants recruited and those excluded due to missing data were generally similar (eTable 1 in the Supplement). The protocol of 4C Study was approved by the Ethical Review Committee of Ruijin Hospital. Written informed consent was obtained from all participants.

Measurements

Data collection was conducted face-to-face at community clinics at baseline and follow-up visits. Baseline characteristics, including sociodemographic information, lifestyle habits, and medical history, were assessed by a standard questionnaire. Skilled nurses measured height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) according to standard protocols. Blood samples were collected after overnight fasting. Then, a standard oral glucose tolerance test (OGTT) was conducted, and 2-hour post-load blood specimens were collected. Fasting and 2-hour post-load plasma glucose were measured at local hospitals. Blood specimens and first-morning spot urine samples were collected and aliquoted into 0.5-mL Eppendorf tubes within 2 h of collection and shipped in dry ice to the central laboratory of the study located at Shanghai Institute of Endocrine and Metabolic Diseases, which is accredited by the College of American Pathologists. At the central laboratory, glycated hemoglobin (HbA1c) was determined using finger capillary whole blood by high-performance liquid chromatography (VARIANT™ II Systems, BIO-RAD, Hercules, CA, USA), serum lipids profiles and creatinine were measured by an autoanalyzer (Abbott Laboratories, IL, USA), and urinary albumin (immunonephelometry using Siemens BNII and BN ProSpec nephelometers [Siemens Healthcare Diagnostics, Marburg, Germany]) and urinary creatinine concentrations was also tested (by enzymatic method [ADVIA Chemistry XPT System; Siemens Healthcare, Erlangen, Germany]) for calculation of Urinary albumin-to-creatinine ratio (ACR). Estimated glomerular filtration rate (eGFR) was calculated based on age, sex, race, and centrally measured serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI 2009) for Asian individuals [17].

Definition of LE 8 CVH score and status

According to the definition proposed by AHA in 2022 [10], we scored the CVH score based on 8 components, including 2 domains of health behaviors (nicotine exposure, diet, physical activity, sleep) and health factors (BMI, blood lipids, blood glucose, and blood pressure). Health behavior information was collected by a standardized questionnaire. Health factors metrics were measured in the study center (BMI, blood pressure, and plasma glucose level) or central laboratory (blood lipids and HbA1c). Detailed methods and scoring criteria of CVH were presented in eTable 2 in the Supplement. The overall CVH score was calculated as the average of 8 component metric scores. Participants with high CVH scores of 80–100 were considered optimal CVH, while moderate CVH referred to 50–79 and low CVH of 0–49. For each CVH domain/metric, participants with a score of 80–100 were considered to have a corresponding optimal CVH domain/metric, while those with a score of 0–79 were regarded as suboptimal.

Definition of CKM stages

According to the definition proposed by AHA in 2023 [7, 8], we defined CKM syndrome as 5 stages: Stage 0: absence of any CKM risk factors; Stage 1: having excess body weight, abdominal obesity, or dysfunctional adipose tissue (clinically manifest as prediabetes), without the presence of other metabolic risk factors or CKD; Stage 2: presence of metabolic risk factors or moderate- to high-risk CKD; Stage 3: presence of subclinical CVD or its risk equivalents; Stage 4: clinical CVD including coronary heart disease, myocadiac infarction, stroke or peripheral artery disease. Detailed methods and staging rationales were presented in eTable 3 in the Supplement.

Follow-up and outcome assessment

Morbidity and mortality data until November 30, 2021 were obtained through linkage using the unique identification number of each participant to the local death registries of the National Disease Surveillance Point System, the registries of cardiovascular diseases, and the National Health Insurance System. Two members of the outcome adjudication committee, who were blinded to the baseline characteristics, independently verified each clinical event. Discrepancies were adjudicated through discussion involving other members of the committee. Incident CVD was defined as a composite of non-fatal myocardial infarction (I21–I22), non-fatal stroke (I60–I64, I69), and cardiovascular death (I00–I99).

Statistical analyses

Baseline characteristics of participants were summarized as mean ± standard deviation (SD), or number of participants and percentage, or median with interquartile range. The distributions of CKM stages were visualized by density ridgeline plot of overall CVH score, health behavior score, and health factor score range, respectively. The Fine-Gray hazard model was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of CKM stages or CVH status associated with incident CVD events, considering the competing risk of non-CVD death. A multivariable model was utilized to control potential confounding factors with adjustments for age, sex, and education duration based on biological plausibility. When analyzing the association between CVH domains/metrics and CVD events, we further adjusted for all other CVH metrics simultaneously. We also analyzed the combination association of CKM stages and different CVH strata (High [optimal] versus low and median) or different number of optimal CVH metrics (≥ 6, 5, 4, 3, < 2) with CVD events. We used cubic spline analysis to explore the association between continuous CVH score and incident CVD events among populations with different CKM stages. Average population attributable fractions (PAFs) of each suboptimal CVH metric, as well as clusters of CVH behavior and factor domains, were calculated using the approach described by Eide and Gefeller and implemented in the "averisk" R package [18, 19], to quantify the proportional reduction in disease prevalence that would be achieved if the risk factor is theoretically removed from the population. PAFs were calculated with adjustments for age, sex, education duration, and 8 individual-level CVH metrics simultaneously.

The main analysis was conducted in the unimputed dataset with complete information on key exposures and outcomes, and several sensitivity analyses were performed: (1) The main analysis separately in women and men (eTables 4 and 5 in the Supplement). (2) The main analysis among participants without diagnosed cancer at baseline (eTable 6 in the Supplement). (3) The main analysis after excluding participants who underwent CVD events or died within the first 2 years of observation time (eTable 7 in the Supplement). (4) The main analysis for non-fatal and fatal CVD events, respectively (eTables 8 and 9 in the Supplement). (5) The main analysis separately in participants aged < 60 years and ≥ 60 years, respectively (eTables 10–12 in the Supplement). (6) The analysis for CKM stages and the association with incident CVD events after excluding participants aged 80 years or older (eTable 13 in the Supplement). The primary analyses were conducted among participants without missing data, and the validity of the findings was tested in multiple imputation data sets imputed for missing baseline information and outcome, using *PROC MI* in SAS by fully conditional specification (FCS) method which assumed missing at random (MAR). (eTables 14–17 in the Supplement).

We used SAS software (version 9.4), and R software (version 4.1.1) for statistical analyses. All reported P values are nominal. Statistical significance was a two-tailed $P < 0.05$.

Results

Study population

The final study population comprised 100,727 adults (mean [SD] age, 56.7 [9.2] years; 34,340 [34.1%] men) and a median follow-up of 10.1 years (970991.1 person-years). From CKM stages 0–4, the proportions of participants were 4.1%, 21.4%, 61.5%, 6.5%, and 6.5%, respectively (eTable 18 in the Supplement). The mean (SD) CVH score of participants was 61.1(12.2), with 58.4(15.8) for health behaviors and 63.9 (17.9) for health factors. Generally, overall CVH status and health factors deteriorated along the spectrum of CKM syndrome, while health behavior presented a similar distribution across various stages (Fig. 1).

Individual associations of CKM stages and CVH with incident CVD events

During the duration of follow-up, a composite of fatal or non-fatal cardiovascular events occurred in 7891 participants, among whom 829 individuals experienced non-fatal myocardial infarction, 6002 endured non-fatal stroke, and 1882 died due to cardiovascular disease. Compared with participants in stage 0, the adjusted competing HRs and 95% CIs of incident CVD events were 1.20 (0.95–1.51) for stage 1, 2.45 (1.97–3.04) for stage 2, 4.43 (3.53–5.58) for stage 3, and 5.95 (4.75–7.45) for stage 4, respectively (Table 1). As for CVH status, compared with the low CVH group, moderate and high (optimal) CVH were associated with significantly lower incidence of CVD events (HR 0.56, 95% CI 0.53–0.59 for moderate CVH; HR 0.27, 95% CI 0.23–0.32 for high (optimal) CVH) (Table 1). The inverse association persisted in different CVH domains of behavior and factor. The associations remained similar in the sensitivity analyses (eTables 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 and 15 in the Supplement). Each CVH metric that met optimal criteria presented a significantly decreased risk of incident CVD events. According to the PAFs of CVD events, suboptimal blood pressure (26.6% of the PAF) was the first leading cause of CVD events, followed by suboptimal blood glucose (11.4%), BMI (9.0%), diet (8.2%), physical activity (5.2%), blood lipids (5.0%), nicotine exposure (2.0%), and sleep (1.3%). (Fig. 2)

Combined associations of CKM stages and CVH with incident CVD events

Variation was observed in the association between CKM stage and CVD events with different CVH status or numbers of optimal CVH metrics (Fig. 3). When subdividing all participants according to the combination of CKM stage and CVH status (Fig. 3A), participants in stage 1 or 2 with optimal CVH no longer had elevated risks for incident CVD events (HR [95% CI] 1.19 [0.70-2.00] for stage 1 with optimal CVH; 1.45 [0.86–2.44] for stage 2 with optimal CVH), in comparison with stage 0 combined optimal CVH. For the effect of the number of optimal CVH metrics (Fig. 3B), compared with stage 0, the risk of CVD events significantly increased in stage 1 with the least number of optimal CVH metrics (≤ 2) (HR [95% CI] 1.88 [1.44–2.45]), while those in stage 2 with the largest number (≥ 6) of optimal CVH metrics no longer conferred risks for incident CVD events (HR [95% CI] 1.22 [0.87–1.70]). However, CKM stage 3 or stage 4 represented a consistently higher risk of CVD events regardless of the number of optimal CVH metrics they met, and

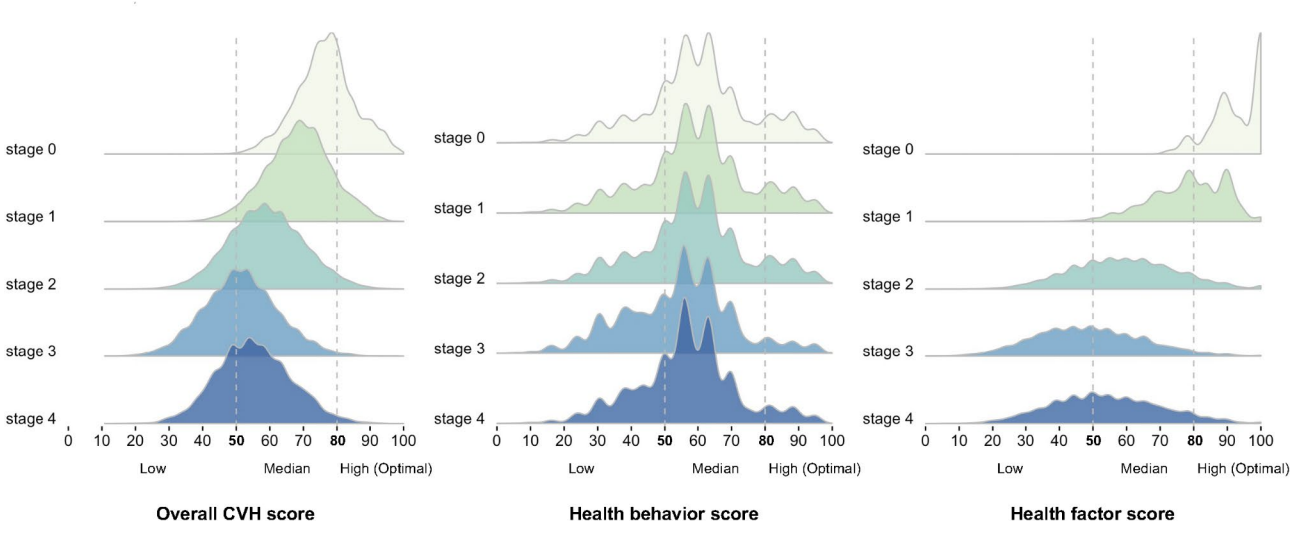


Fig. 1 Distribution of CVH status according to CKM stages

Table 1 Incidence rates and HRs of incident CVD events according to CKM stages or CVH status

	No. of events/no. of participants	Person-years	Incidence rate, per 1000 person-years	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [a]
CKM stage					
Stage 0	83/4168	41427.1	2.0	1.00	1.00
Stage 1	626/21,540	214302.1	2.9	1.45 (1.16–1.83)	1.20 (0.95–1.51)
Stage 2	4197/61,894	601133.9	7.0	3.47 (2.80–4.32)	2.45 (1.97–3.04)
Stage 3	1552/6598	56464.3	27.5	13.26 (10.63–16.53)	4.43 (3.53–5.58)
Stage 4	1433/6527	57663.7	24.9	12.38 (9.93–15.45)	5.95 (4.75–7.45)
CVH status					
Overall CVH					
Low	2580/18,129	167206.0	15.4	1.00	1.00
Moderate	5161/76,114	738720.6	7.0	0.45 (0.43–0.47)	0.56 (0.53–0.59)
High (Optimal)	150/6484	65064.5	2.3	0.15 (0.13–0.18)	0.27 (0.23–0.32)
Health behavior					
Low	2344/24,431	232014.5	10.1	1.00	1.00
Moderate	4860/64,349	621705.0	7.8	0.78 (0.74–0.82)	0.87 (0.83–0.92)
High (Optimal)	687/11,947	117271.6	5.9	0.59 (0.54–0.64)	0.75 (0.69–0.82)
Health factor					
Low	3173/22,831	211398.2	15.0	1.00	1.00
Moderate	4133/56,869	549899.5	7.5	0.50 (0.47–0.52)	0.59 (0.56–0.62)
High (Optimal)	585/21,027	209693.4	2.8	0.18 (0.17–0.20)	0.31 (0.28–0.34)

CVD cardiovascular disease; *CKM* cardiovascular-kidney-metabolic; *CVH* cardiovascular health; *HR* hazard ratio; *CI* confidence interval

[a] HRs according to CKM stage or overall CVH status were adjusted for age, sex, and educational attainment (< 9 years vs. ≥ 9 years). For the analysis health behavior or health factor, other metrics of CVH were mutually adjusted

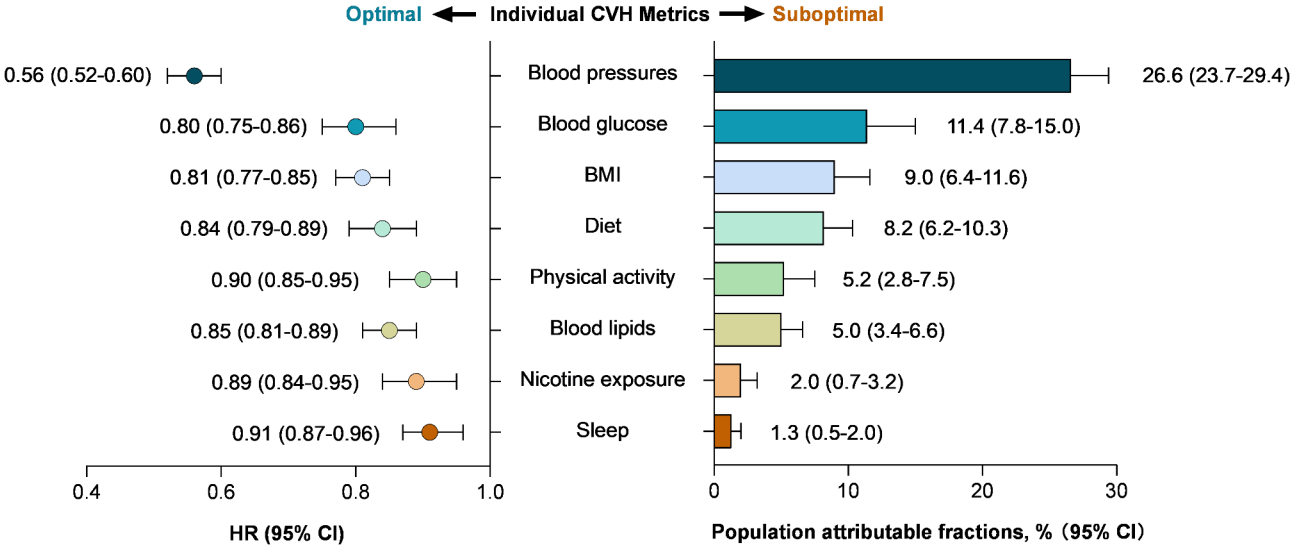


Fig. 2 HRs of incident CVD events according to individual optimal CVH metrics and population attributable fractions for incident CVD events associated with individual suboptimal CVH metrics. Multivariable models were adjusted for age, sex, educational attainment, each metric of Life's Essential 8 including nicotine exposure, diet, physical activity, sleep health, body mass index, blood lipids, blood glucose and blood pressures. *CVD* cardiovascular disease; *CVH* cardiovascular health; *HR* hazard ratio; *BMI* body mass index; *CI* confidence interval

the highest risk was observed in stage 4 combined with the fewest optimal CVH metrics. The results were similar in the multiple imputation data sets (eTable 16 in the Supplement).

Contributions of specific CVH domains on CVD events among different stages of CKM syndrome

Multivariable-adjusted restricted cubic spline analyses (Fig. 4A) were conducted to present the association between incident CVD events and domain-specific CVH scores among participants with and without advanced stages of CKM syndrome (stage 3–4), respectively. They

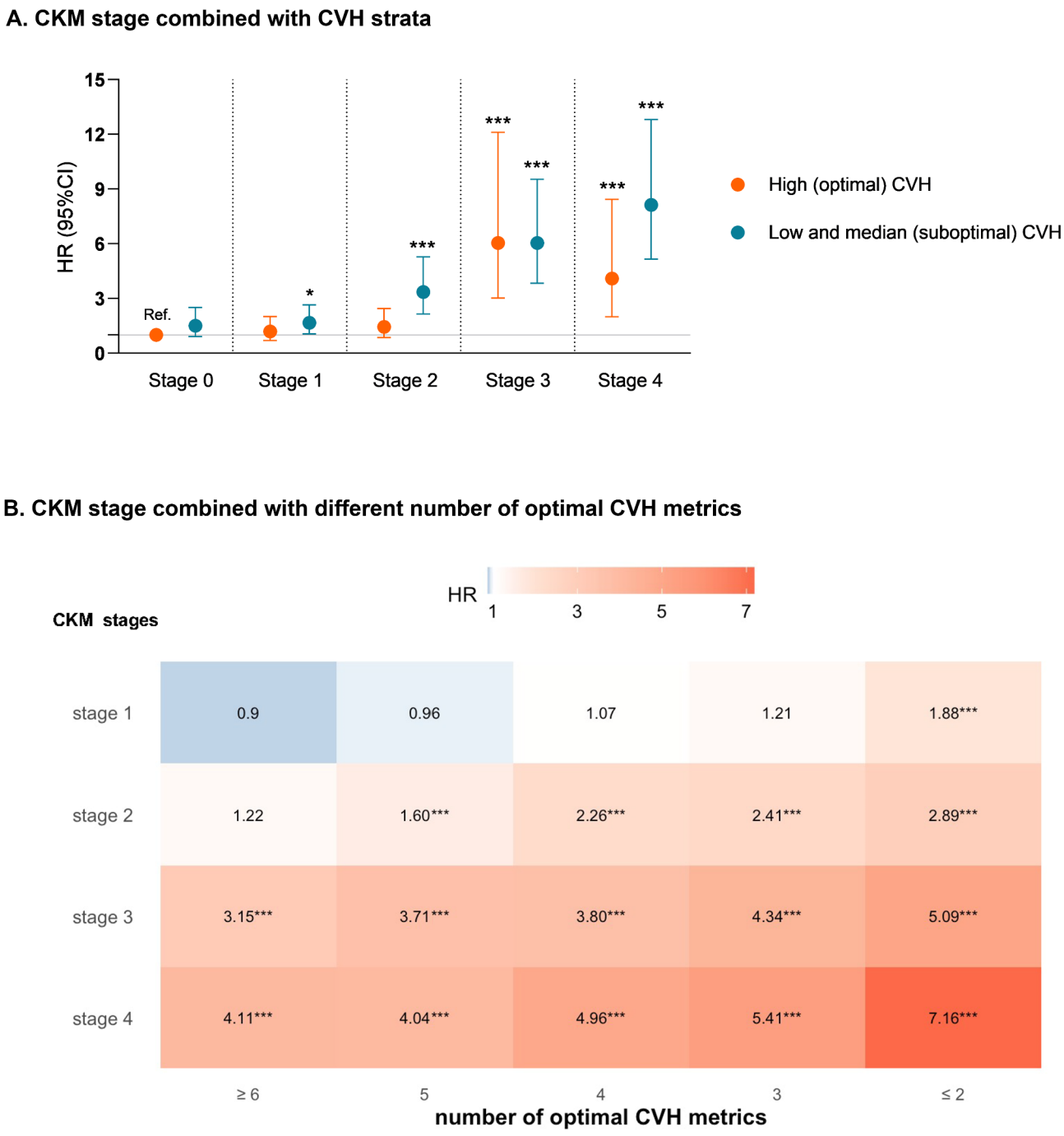


Fig. 3 Combined association of CKM stages and CVH status with the risk of incident CVD events. **A** HRs (95% CI) of incident CVD events for the combination of CKM stage and CVH strata, compared with participants in CKM stage 0 with optimal CVH. **B** HRs (95% CI) for incident CVD events for participants with CKM syndrome in relation to the number of optimal CVH metrics, compared with participants in CKM stage 0. HRs were adjusted for age, sex, and educational attainment (< 9 years vs. ≥ 9 years)

suggested an inverse linear relationship between health factor score and incident CVD events in the participants of CKM stage 0–2 (*P* for nonlinearity = 0.11), but not in advanced stages of CKM syndrome (stage 3–4) (P for nonlinearity = 0.0007). In contrast, results indicated a steeper linear association of health behavior score with CVD events for participants in stage 3–4 than individuals in stage 0–2, with a significant interaction between health behavior score and CKM stage (*P* for interaction: 0.0005). Similarly, achieving optimal health factor status was related to a higher reduction of CVD risk in CKM stage 0–2 (HR [95% CI] 0.45[0.41–0.50]) than in

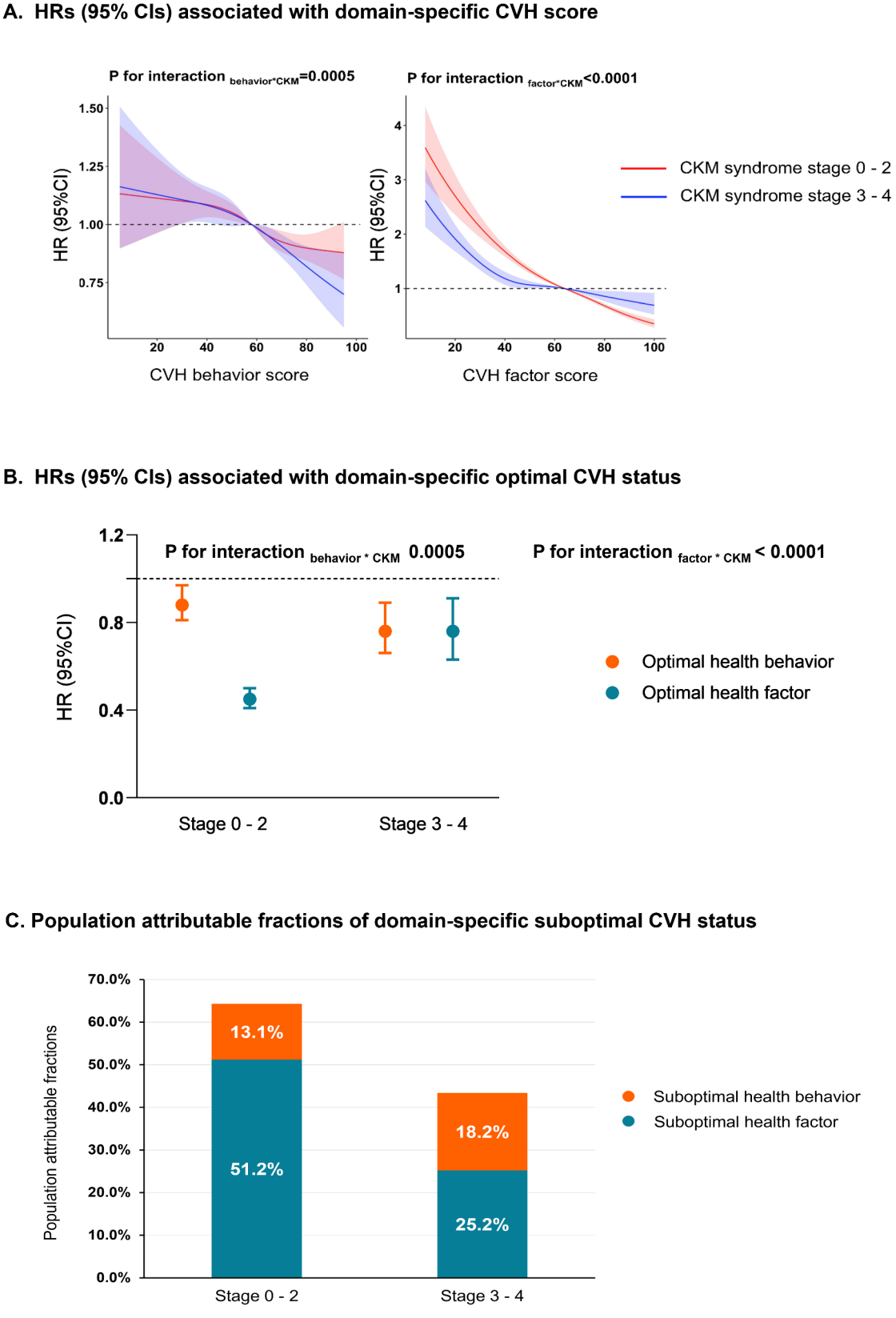


Fig. 4 (See legend on next page.)

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Fig. 4 Contributions of specific CVH domains on CVD events among different stages of CKM syndrome. **A** HRs (95% CI) of incident CVD events associated with CVH behavior score and factor score among different stages of CKM syndrome. **B** HRs (95% CI) for incident CVD events associated with optimal behavior status and optimal factor status among different stages of CKM syndrome. **C** Population attributable fractions for incident CVD events associated with suboptimal behavior status and optimal factor status among different stages of CKM syndrome. Models were adjusted for age, sex, educational attainment (< 9 years vs. ≥ 9 years), BMI, blood pressure, blood lipids, and blood glucose status for analysis of health behavior. Models were adjusted for age, sex, educational attainment (< 9 years vs. ≥ 9 years), nicotine exposure, diet, physical activity, and sleep status for analysis of health factor

stage 3–4 (HR [95% CI] 0.76 [0.63–0.91]), while achieving optimal health behavior status was associated with a higher reduction of CVD risk in CKM stage 3–4 (HR [95% CI] 0.76[0.66–0.89]) than in stage 0–2 (HR [95% CI] 0.88 [0.81–0.97]) (Fig. 4B). The results were similar in the multiple imputation data sets (eTable 17 in the Supplement). PAFs of CVD events associated with suboptimal CVH domains (Fig. 4C) showed that suboptimal health factor contributed larger PAF to CVD events in CKM stage 0–2 (51.2%) than in stage 3–4 (25.2%), whereas suboptimal health behavior contributed larger PAF in advanced stages of CKM syndrome (13.1% in stage 0–2 and 18.2% in stage 3–4).

Discussion

In this large-scale prospective cohort from China, we detected the higher risk of incident CVD events related to advanced CKM syndrome and described the distribution of CVH status defined by LE 8 in the general population and subgroups with different CKM stages, as well as its impact on improving CVD risk. Our findings suggested that achieving more optimal CVH metrics could attenuate the risk of incident CVD events related to CKM syndrome. Considering CVH domain differences, the contribution of health factor was predominant at the early-stage of CKM syndrome, whereas the CVD risk attributable to suboptimal behavior increased with the deterioration along the CKM spectrum, highlighting the importance of controlling optimal metabolic factors in early prevention and the necessity of maintaining optimal healthy behavior throughout the lifespan.

Previous studies have shown that adding ACR and eGFR to the traditional ASCVD scores can significantly optimize the prediction and stratification of major CVD events, thereby supporting their role as risk-enhancing factors for ASCVD [20, 21]. In addition, the complex interrelationships of the CKM conditions, as well as the emergence of medications with multiple beneficial effect on overall CKM health like SGLT2 inhibitors and GLP-1RA, have necessitated the development of the syndrome as an entity [22–25]. Our study provided valuable data on the distribution of CKM stages in Chinese population, based on a large-scale, nationwide cohort. The prevalence of CKM syndrome in our Chinese cohort (aged 40 years or older) was higher than that in US general populations [26, 27], yet comparable to that observed in American middle-aged (≥ 45 years) populations [28], highlighting the broad applicability of the concept of CKM stage. In addition, the stricter BMI and WC definitions of non-adiposity for Asians might also contribute to the scarcity of CKM stage 0 in our population. Given the variations in diagnostic criteria and population characteristics, caution was necessary when comparing proportion of CKM stages across different populations.

The present findings regarding the association between CVH status and incident CVD events are consistent with previous studies. Data in US adults from the National Health and Nutrition Examination Survey (NHANES) 2005–2008 reported 38% and 64% reduced risks of CVD mortality related to moderate and high CVH status, respectively [11]. Among Chinese population, the Kailuan Study reported a HR of 0.33 (95% CI, 0.20–0.54) for incident stroke comparing ideal versus poor health category of CVH [13]. Regarding individual LE 8 CVH metrics, the most evident PAF and HR of CVD was observed for blood pressure and in line with data from NHANES [29], while the following two factors were glucose and BMI in our study, but smoking and physical activity in US. The contribution of individual metrics might be impacted by cross-population heterogeneities regarding cardiovascular disease spectrum, with stroke-dominated profiles but a lower proportion of myocardial infarction in China [30]. Notably, while LE8 incorporated sleep as a new component, our analyses revealed that the relative attributable risk of sleep was not prominent among these modifiable factors, with the lowest PAF for CVD events (1.3%), aligning with studies demonstrating comparable predictive performance between LE 8 and Life's Simple 7 in CVD risk prediction [31]. However, the continuous scoring system of LE 8 offered granular tracking of health behavior changes, making it particularly advantageous for personalized lifestyle interventions requiring iterative feedback. Future implementation should prioritize integrating LE 8 with digital health platforms to maximize its monitoring capabilities.

Moreover, the current study extends the previous findings by providing the combination association of CVH status and CKM stage with CVD risk and found a substantial modifying effect of CVH status on the adverse CVD outcome related to CKM syndrome, particularly at the early-stages. We found that the deteriorative association between CKM stage 1 or 2 and CVD outcomes could be counteracted by the achievement of more optimal CVH metrics, while the effect was not detected for

advanced stages. These findings indicated the variability of CKM stage 1 and stage 2 as detailed in the AHA Scientific Statement, which defined stages 1 and 2 as low or borderline-to-moderate risk and a time window of opportunity to reduce the long-term burden of CVD by improving CVH based on LE 8.

However, it should be noticed that the overlap between the definitions of early CKM stages and LE 8 CVH status might create analytical complexity. The shared metabolic domains between CKM staging and LE 8 health factors made it necessary to analyze health factor and health behavior separately and consider CVH domain-specific contribution. As for health factors, we presented a skewed distribution of health factor score across different CKM stages, which might contribute to its predominant role at early stages. Intriguingly, we observed that health behavior exhibited consistent contribution to attenuating CVD risk, with an even slightly stronger effect at advanced stages. This finding aligns with previous studies regarding contribution of individual lifestyle factors in patients with different CVH status. A study conducted in Netherlands observed larger risk reduction of incident CVD events and all-cause mortality in individuals with risk factors, rather than healthy participants [32]. Studies also reported that CVD risk related to unhealthy sleep habit was more prominent in older adults than in younger adults with fewer metabolic disorders [33, 34] The potential explanation could be the cumulative and delayed effects of behaviors throughout the lifespan, in contrast to the effects of immediate control of health factors [35]. The interpretation of these findings warranted caution since they indicated more of a relative importance via hazard ratios. Taken together, prioritizing health factor improvement is crucial at early-stage of CKM syndrome, while promoting health behavior should be advocated along the entire CKM continuum, especially for advanced stages.

Strengths and limitations

The strengths of the present study include comprehensive evaluation for CKM stage and CVH status, the large sample size, and the prospective design. Several limitations of the study are worth noting. First, a large proportion of participants were excluded due to missing data. However, the overall CVD incidence was similar to what was reported in other Chinese studies, and we further validated our findings in a multiple imputation dataset where missing information was imputed. Second, the CVH metrics and CKM stages were evaluated only at baseline, and the diet metric failed to cover all items selected for original scoring which was designed for westerners, which introduced potential bias. The overlap in the definition of CKM stage 0–2 and CVH health factor metrics may also cause potential bias. Third, although comprising only 0.5% of the cohort, the presence of participant aged 80 years or older may introduce concerns about the extrapolation of PREVENT formula beyond validated ages. However, sensitivity analyses excluding these individuals confirmed minimal bias. Due to the design of 4C study, we also failed to include adults aged below 40 years, which might limit the generalizability of the findings to younger populations. Finally, heart failure information was unavailable in our study, so that incident CVD events might be underestimated.

Conclusion

Our study indicated that the advanced CKM stages were significantly associated with incident CVD events, and further demonstrated that optimal CVH assessed by LE 8 could attenuate this risk. Furthermore, the contribution of health factor to CVD risk was predominant at the early-stage of CKM syndrome, whereas health behavior exhibited consistent and even slightly increased contribution with the deterioration along the CKM spectrum. These findings suggest that the CKM stage construct is practical for evaluating adverse CVD risk and highlight the importance of target health improvement based on LE 8 to improve CKM health.

Abbreviations

CVD	Cardiovascular disease
CKM	Cardiovascular-kidney-metabolic
AHA	American Heart Association
LE 8	Life's Essential 8
CVH	Cardiovascular health
BMI	Body mass index
4C	China Cardiometabolic Disease and Cancer Cohort
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
OGTT	Oral glucose tolerance test
HbA1c	Glycated hemoglobin
ACR	Albumin-to-creatinine ratio
eGFR	Estimated glomerular filtration rate
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration equation
HR	Hazard ratio
CI	Confidence interval
PAF	Population attributable fraction
SD	Standard deviation
NHANES	National Health and Nutrition Examination Survey

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02735-3.

Supplementary Material 1

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Author contributions

Yufang Bi, Weiqing Wang and Jieli Lu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.Mian Li, Min Xu, Yi Ding, Hong Lin, Guijun Qi and Tiange Wang contributed equally to this work.Concept and design: Mian Li, Yufang

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Data availability
.The datasets that were used and evaluated in this study can be obtained from the corresponding author upon making a reasonable request.

Declarations

Ethics approval and consent to participate
The protocol of 4C Study was approved by the Ethical Review Committee of Ruijin Hospital. Written informed consent was obtained from all participants.

Competing interests
The authors declare no competing interests.

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