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Cardiovascular-kidney-metabolic syndrome modifies smoking-related risk for cardiovascular diseases: findings from an observational cohort study in UK Biobank

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Abstract

Background The present study aims to investigate the association of smoking behaviors and cardiovascular-kidney-metabolic (CKM) syndrome with incident cardiovascular disease (CVD), and to evaluate whether the cardiovascular benefits of smoking cessation vary across different CKM conditions.

Methods This study included 242,636 white European participants from the UK Biobank who were classified as CKM syndrome Stages 0 to 3 and free of CVD at baseline. Covariates adjusted Cox proportional hazards models were employed to evaluate the associations of CKM syndrome with the risks of total CVD, stroke, coronary heart disease (CHD), major adverse cardiovascular events (MACE), and 13 CVD subtypes. The impact of smoking behavior across different CKM stages and the joint effect of smoking and CKM syndrome on CVD risk were also evaluated. To investigate the potential effect modification by CKM syndrome, we examined the multiplicative scale by interaction terms in Cox models, and quantified the additive scale using statistics such as the relative excess risk due to interaction (RERI).

Results The risk of total CVD, stroke, and CHD increased progressively with advancing CKM stages, with Stage 3 associated with hazard ratios (HRs) of 3.38 (95% *CI*: 3.05–3.74), 3.01 (2.49–3.64), and 3.65 (3.25–4.10), respectively (*P* for trend < 0.001). The time required to reduce CVD risk to a level not significantly different from that of never smokers tends to be longer for individuals with advancing CKM stage: smokers at Stages 0–1 achieved this after approximately 10 years of cessation, whereas those at Stages 2–3 required more than 25 years. Compared with never smokers at CKM Stage 0, current smokers at CKM Stage 3 had substantially higher risk of total CVD (*HR* = 4.14, 95% *CI*: 3.54–4.83) and several subtypes, particularly abdominal aortic aneurysm (*HR* = 17.68, 95% *CI*: 6.33–49.43) and peripheral vascular disease (*HR* = 10.53, 95% *CI*: 6.79–16.34). CKM syndrome appeared to act as a positive additive effect modifier in smoking-related risk of total CVD (RERI = 0.20, 95% *CI*: 0.05–0.32), as well as several CVD subtypes, suggesting that the combined effect of smoking and CKM progression exceeds the sum of their individual effects.

Conclusions Our finding emphasizes the importance of smoking cessation among individuals with advanced CKM syndrome, as they face heightened CVD risk. However, compared to those at earlier CKM stages, the short-term

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benefits of smoking cessation may be less pronounced in this population. Interventions that combine smoking cessation promotion with CKM syndrome management may yield greater reductions in the risk of several CVD outcomes.

Keywords Cardiovascular-kidney-metabolic syndrome, Smoking cessation, Cardiovascular disease, Effect modification

Background

Tobacco smoking remains one of the well-recognized and preventable contributors that substantially increases the risk of cardiovascular disease (CVD), contributing to a substantial global disease burden and high mortality rates [1–5]. Notably, smoking-attributed CVD risk is further elevated among individuals experiencing additional health conditions, including diabetes [6, 7], chronic kidney disease (CKD) [8], and metabolic syndrome (MetS) [9], compared with never smokers without such conditions. Evidence from large-scale observational studies [3, 10] has shown that smoking cessation can substantially reduce the deleterious cardiovascular effects associated with smoking, and it is strongly recommended in clinical guidelines for CVD prevention [11]. However, the relatively low success rates of smoking cessation highlight that investigating the harmful effects of smoking on CVD remains a critical task requiring ongoing attention. Moreover, the benefits of smoking cessation have also been shown to vary across different health conditions [12, 13]. Although the interplay between smoking behaviors and individual health conditions has been explored in previous studies, evidence remains limited on the association between smoking status and CVD risk across varying levels of overall health status.

Cardiovascular-kidney-metabolic (CKM) syndrome is a multifactorial condition encompassing metabolic risk factors, CKD, and CVD [1]. Recently, the American Heart Association (AHA) presidential advisory [14] classified the CKM syndrome into five progressive stages (0 to 4), emphasizing that the CVD risk increases with advancing stage [15]. This classification framework provides a clearer understanding of individuals' overall health status. Individuals in stages prior to CKM Stage 4 (before the onset of clinical CVD) comprise the predominant proportion of the population [16]. Among this group, the potential benefits of smoking cessation may differ between early and later stages of CKM syndrome.

Elucidating the independent and joint contributions of smoking and CKM syndrome to CVD risk, as well as exploring whether CKM syndrome modifies the effect of smoking behaviors, are of great significance for the precise development and implementation of smoking prevention and cessation strategies in different populations. Notably, integrating smoking prevention and cessation with effective management of CKM syndrome may lead to greater gains in CVD prevention. Furthermore, smoking-related CVD risk and the potential benefit from reversal of CKM progression may vary across specific CVD subtypes [1, 17], yet this remains poorly characterized.

To address these gaps, we constructed a population-based retrospective cohort using data from the UK Biobank to investigate the independent and joint effects of smoking behavior and CKM syndrome on a comprehensive range of cardiovascular outcomes, including total CVD, stroke, coronary heart disease (CHD), major adverse cardiovascular events (MACE), and 13 specific CVD subtypes. We further examined whether CKM syndrome modifies the association between smoking and incident CVD. This cohort study aims to inform targeted strategies for smoking prevention and cessation among populations with different CKM health conditions.

Methods

Study population

The UK biobank recruited more than 500,000 individuals aged 40 to 69 years between 2006 and 2010, most of whom were of white European ancestry [18]. This research has been approved by the North West Multicenter Research Ethical Committee, and each enrolled participant signed the informed consent form prior to participation. Baseline assessments were conducted across 22 assessment centers including data collection through touchscreen questionnaires, physical measures, sample assays, a wide range of health-related outcomes, etc. Further details have been described elsewhere [18].

We analyzed data from the UK biobank study, accessed through application 98273. Data from 502,370 participants were available at the time of this study. To minimize heterogeneity introduced by different ethnic groups in the cohort study, we included only 472,675 individuals of white European ancestry. After further excluding 122,678 participants with missing data on any key variables (including smoking status) required for the definition of CKM syndrome, 448 individuals failed to define the baseline CKM syndrome stage, 35,626 individuals diagnosed with CVD, any of its 13 subtypes, or CKM syndrome Stage 4 at baseline, and 71,287 missing key covariates, a total of 242,636 participants were finally included in the subsequent analyses (Fig. 1). The definitions of

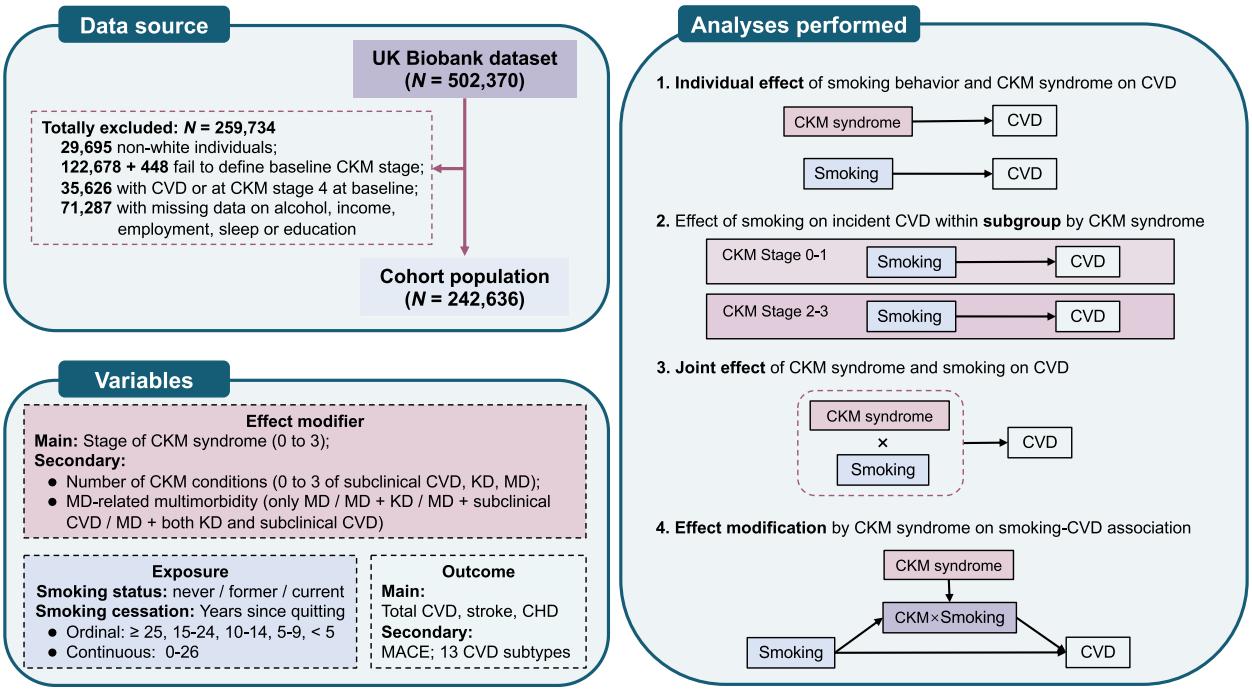

Fig. 1 Overview of study population, variables, and analytical framework. Abbreviations: *N*, sample size; CKM, cardiovascular-kidney-metabolic; CVD, cardiovascular disease; KD, kidney diseases; MD, metabolic disorders, CHD, coronary heart disease; MACE, major adverse cardiovascular events

baseline CVD and the covariates used to define baseline CKM syndrome stage are detailed below.

Definition of CKM syndrome stage

The AHA presidential advisory [14] established a framework for defining the progression of CKM syndrome along a continuum of increasing cardiometabolic and renal burden: *Stage 0* is defined as the absence of CKM related risk factors, including excess and/or dysfunctional adiposity, metabolic risk factors (hypertriglyceridemia, hypertension, MetS, and diabetes), and CKD. Individuals presenting only with excess and/or dysfunctional adiposity are classified as *Stage 1*. When metabolic risk factors and/or moderate- to high-risk CKD are present, individuals are considered to be in *Stage 2*. Building upon the preceding stages, those with a predicted 10-year CVD risk > 20% or the presence of very high-risk CKD without established clinical CVD (including coronary heart disease (CAD), heart failure (HF), stroke, peripheral artery disease (PAD) and atrial fibrillation (AF)) are categorized as *Stage 3*. Finally, *Stage 4* reflects individuals with clinical CVD in combination with ongoing CKM risk factors. The baseline covariates used for classifying participants into CKM syndrome stages are described in Supplemental Method 1 and Table S1. These include age, smoking status (current vs. non-current), waist circumference, body mass index (BMI), blood pressure, lipid profile, glycated hemoglobin, estimated glomerular filtration rate (eGFR) [19–21], urinary albumin-to-creatinine ratio (UACR) [22], history of clinical CVD, and use of relevant medications. The full definitions of CKM conditions and stages [23–27] are provided in Supplemental Table S2-S4.

Smoking traits

We focused on smoking traits including smoking status (never, former and current) as well as years since quitting for former smokers. Both smoking traits were assessed with questions from the touchscreen questionnaire on smoking lifestyle during the initial assessment visit (2006–2010). Specifically, all participants were classified as current, former, and never smokers based on two questions: "*Do you smoke tobacco now?*" and "*In the past, how often have you smoked tobacco?*". For those individuals who had stopped smoking, years since quitting were derived by subtracting the age at smoking cessation from baseline age. Additional details are available in Supplemental Table S5.

Diagnosis of CVDs

We assessed first record diagnosis of total CVD, or one of its two major subtypes: CHD and stroke, as the primary outcome. Diagnostic information was obtained from hospital inpatient records (Field ID 41270), and outcomes were defined using International Classification of

Diseases, 10 th Revision (ICD-10) codes as follows: (1) total CVD: I20-I25, I60-I64, and I69; (2) CHD: I20-I25; (3) stroke: I60-I64, I69 [28]. In addition, we considered MACE and 13 CVD subtypes, including cerebrovascular diseases (e.g., ischemic stroke (IS)), aortic aneurysms, thrombotic diseases, and other CVDs such as AF, HF, and peripheral vascular disease (PVD). MACE was based on the earliest of the listed events: non-fatal myocardial infarction (ICD-10: I21-I23, I24.1, I25.2), non-fatal stroke (ICD-10: I60, I61, I63, I64), or cardiovascular death (ICD-10: I20-I25, I60-I64, Field ID 40001). Definition of CVD subtypes was based on ICD-9, ICD-10, and self-report health conditions (Field ID 41270, 41271, and 20002) [29]. The date of each CVD subtype was extracted from Field ID 41280, 41281, and 20008. More details regarding the definition of each CVD subtype are provided in Supplemental Table S6. Furthermore, we verified the vital and dropout status of each participant. For each CVD subtype, the latest date among the date of first diagnosis, death (Field ID 40000), loss to follow-up (Field ID 191), and censoring (defined as October 31, 2022, the latest diagnosis date for ICD 10 in Field ID 41280) was used to calculate the follow-up time.

Assessment of covariates

Consistent with previous smoking-related studies [3], we predefined a set of baseline covariates for adjustment prior to the statistical analysis process in order to fully consider the potential confounders between the exposure and outcome. These covariates included age, sex, employment status (working, unemployed, retired, and other) [30], income levels (level 1 to 4), education (< 10 and ≥10 years) [31], physical activity (PA) (low, moderate, and high) [30, 32], diet (total fruit and vegetable intake < 5 and ≥5 portions/day) [30], healthy sleep score (0 to 5) [33], alcohol consumption (never and consumer), BMI, systolic blood pressure (SBP), total cholesterol (TC), diabetes mellitus, the use of antihypertensive and statin/other cholesterol-lowering medication. Additional information on the definition of covariates was provided in Supplemental Method 2 and Table S7. Missing covariate data were treated as missing without imputation.

Statistical analysis

Statistics of baseline covariates in the whole population were presented according to the four CKM stages and smoking status, respectively. For continuous variables, Shapiro–Wilk test was applied to examine whether they followed a normal distribution, then these variables were summarized using mean with standard deviation (SD) or median with interquartile range (IQR), and compared across groups using analysis of variances (ANOVA) or the Kruskal–Wallis H test, respectively. Categorical variables were reported as frequencies (percentages) and compared using the χ^2 test.

We used multivariable Cox proportional hazard regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between different stages of CKM syndrome and CVD risk. The proportional hazard assumption was assessed and verified based on Schoenfeld residuals. Each covariate-adjusted Cox regression accounted for age, sex, lifestyle (smoking, alcohol use, PA, diet, and sleep) and socioeconomic (employment, income, and education) factors. We evaluated linear trends by modeling CKM stage as ordinal. Then the association between smoking behavior (never smokers, former smokers with ≥25, 15 to 24, 10 to 14, 5 to 9, <5 years since quitting, and current smokers) and CVD risk was estimated via Cox regression, stratified by CKM stages and adjusted for baseline covariates. Fully adjusted HRs were calculated for each category compared with never smokers, to determine the duration required for CVD risk in former smokers to reach a level that is not significantly different from that of never smokers. Additionally, CVD risk was compared with that of current smokers to assess the years needed for smoking cessation to lead to a significant risk reduction.

To assess the joint effect of CKM syndrome and smoking status on incident CVD, we performed Cox regression, controlling for demographic, lifestyle, and socioeconomic covariates. HRs were estimated for each stratum of CKM syndrome stage and smoking status, with never smokers at CKM Stage 0 serving as the reference category. We assessed the effect modification on the multiplicative scale by adding a multiplicative interaction term between continuous CKM syndrome and smoking traits in the Cox models, or performing a likelihood ratio test comparing models with and without a cross-product term when both variables were treated as categorized. Additionally, we calculated the relative excess risk due to interaction (RERI) to quantify effect modification on the additive scale. The additional additive interaction statistics, including the attributable proportion (AP) and synergy index (S), were also calculated to further assess the interaction detected by the RERI [34]. The presence of additive interaction is suggested when RERI >0, AP >0, or S> 1. To be noted, previous studies [34, 35] have indicated that the multiplicative interaction is less relevant as a basis for mechanistic inference.

A series of additional analyses were undertaken to confirm the consistency of the findings. Firstly, we examined the associations between the number of CKM conditions (subclinical CVD, kidney diseases (KD), and metabolic disorders (MD)) and CVD risk. Secondly, we assessed the relationship between different MD-related multimorbidity (MD + KD, MD + subclinical CVD,

and MD + both KD and subclinical CVD) and CVD risks, using individuals with MD only as the reference group [23]. Thirdly, we explored the temporal pattern and extent of cardiovascular risk decline after quitting smoking, following the approach used in previous studies [3, 10]. Years since quitting were treated as a continuous variable, with durations exceeding 25 years set to 26 (range: 0–26). A Cox model with restricted cubic splines (five knots) was employed to capture potential nonlinear association with the log hazard of CVD. Two analyses were performed: (1) comparing former and current smokers (assigning a value of 0 for years since quitting) to never smokers (for whom years since quitting was set to 50, significantly larger than all former smokers [3, 10]); and (2) comparing former smokers to current smokers. Fourthly, the main analyses were repeated in the multiple imputation dataset. Fifthly, we assessed the joint and interaction effects of smoking and CKM syndrome within subgroups based on age or sex.

We conducted all analyses in R software (version 4.4.1), considering two-sided *P* values less than 0.05 as statistically significant. Bonferroni correction was applied to control for the inflation of false positives due to multiple pairwise testing, using a corrected threshold $\alpha = 0.05$/number of pairwise comparisons. We noted that Bonferroni correction might be over-conservative as the tests are not completely independent of one another. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines throughout the analysis and reporting process (Supplemental Table S8).

Results

Baseline characteristics

Table 1 and Supplemental Table S9 show the baseline characteristics of the study population. Of 242,636 participants, the median age was 57 years (IQR: 49–62), with 45.3% being male. At baseline, 9.7%, 6.0%, 82.8%, and 1.5% of participants were categorized as CKM Stage 0, 1, 2, and 3, respectively. Participants with higher stage of CKM syndrome were more likely to be older, male, and smokers, they tend to have lower income, education years, physical activity level, fruit/vegetable intake, and healthy sleep scores.

Former smokers accounted for 34.9% of the study population, while current smokers comprised 10.3%. Smoking rate progressively increased from 38.3% in CKM Stage 0 to 69.8% in Stage 3. The median (IQR) quitting years for former smokers with CKM Stage 0 to 3 were 18 (8–27), 15 (6–25), 20 (8–29), and 22 (10–32), respectively.

Incidence of CVDs in each smoking status and according to CKM stages

In total, 20,984 individuals experienced CVD events over a follow-up period of 13.6 years, with 5,080 cases of stroke and 16,840 cases of CHD. Notably, there were substantially higher CVD incidents in CKM Stages 2–3 than that in Stages 0–1 ($P < 0.001$ for the comparison between two groups). CAD and AF were two of the most common CVD subtypes, particularly among ever smokers and individuals in CKM Stages 2 to 3 (Supplemental Figure S1).

Impact of CKM syndrome on incident CVD and its subtypes

A progressively increasing risk of total CVD, stroke, CHD, MACE, as well as all 13 CVD subtypes was exhibited by CKM stages (*P* for trend < 0.05) (Fig. 2). Compared with Stage 0, the adjusted HRs for total CVD were 1.14 (95% *CI* 1.01–1.28) for Stage 1, 2.08 (95% *CI* 1.93–2.25) for Stage 2, and 3.38 (95% *CI* 3.05–3.74) for Stage 3. In addition, individuals with Stage 3 had significantly increased risks of CHD (*HR* = 3.65, 95% *CI* 3.25–4.10), stroke (*HR* = 3.01, 95% *CI* 2.49–3.64), and MACE (*HR* = 4.41, 95% *CI* 3.66–5.31) in the following years, compared with those at Stage 0. After Bonferroni correction, the risk for 11 of 13 CVD subtypes remained significantly elevated for individuals at CKM syndrome Stage 3, including aortic valve stenosis (*HR* = 6.09, 95% *CI* 4.31–8.60), HF (*HR* = 4.59, 95% *CI* 3.80–5.55), IS (*HR* = 3.91, 95% *CI* 3.11–4.93), CAD (*HR* = 3.84, 95% *CI* 3.39–4.34), and PVD (*HR* = 3.34, 95% *CI* 2.47–4.52). These findings were further supported by the results based on the imputed dataset (Supplemental Figure S2).

The relationships in relation to the number of CKM conditions and CVD risk (Supplemental Figure S3) were mostly similar to the analysis for CKM stages. Compared with individuals without any CKM condition, those with an increased number of CKM conditions faced an elevated risk for all 13 CVD subtypes (*P* for trend < 0.05). Moreover, the comorbidity status of MD in combination with KD, subclinical CVD, or both exhibited higher risks of total CVD, stroke, CHD, MACE, IS, transient ischemic attack, CAD, aortic valve stenosis, AF, HF, and PVD, compared with those with MD only (Supplemental Figure S4). Elevated risks of abdominal aortic aneurysm, deep vein thrombosis, and pulmonary embolism were observed only among individuals with MD combined with KD or subclinical CVD, whereas subarachnoid hemorrhage and thoracic aortic aneurysm were significantly associated only with the combination of MD and KD.

Table 1 Baseline characteristics of study participants enrolled in UK Biobank according to CKM syndrome stages

Characteristics	CKM syndrome				*P* value
	CKM Stage 0 (*N* = 23,430)	CKM Stage 1 (*N* = 14,588)	CKM Stage 2 (*N* = 200,995)	CKM Stage 3 (*N* = 3,623)	
Age, years, median (IQR)	51.00 (45.00, 58.00)	51.00 (45.00, 58.00)	58.00 (50.00, 63.00)	66.00 (63.00, 68.00)	< 0.001
Sex, No. (%)					
Male	5541 (23.6)	4203 (28.8)	97,460 (48.5)	2818 (77.8)	< 0.001
Female	17,889 (76.4)	10,385 (71.2)	103,535 (51.5)	805 (22.2)	
Alcohol, No. (%)					
Never	1256 (5.4)	757 (5.2)	11,599 (5.8)	374 (10.3)	< 0.001
Drinker	22,174 (94.6)	13,831 (94.8)	189,396 (94.2)	3249 (89.7)	
Physical activity level, No. (%)					
Low	4300 (18.4)	3274 (22.4)	47,731 (23.7)	1099 (30.3)	< 0.001
Moderate	12,222 (52.2)	7295 (50.0)	97,132 (48.3)	1591 (43.9)	
High	6908 (29.5)	4019 (27.6)	56,132 (27.9)	933 (25.8)	
Income, No. (%)					
Level 1	3136 (13.4)	2155 (14.8)	41,885 (20.8)	1505 (41.5)	< 0.001
Level 2	4739 (20.2)	3160 (21.7)	51,775 (25.8)	1149 (31.7)	
Level 3	6558 (28.0)	4301 (29.5)	54,373 (27.1)	614 (16.9)	
Level 4	8997 (38.4)	4972 (34.1)	52,962 (26.3)	355 (9.8)	
Employment, No. (%)					
Working	17,956 (76.6)	11,179 (76.6)	123,589 (61.5)	968 (26.7)	< 0.001
Unemployed	268 (1.1)	196 (1.3)	2822 (1.4)	40 (1.1)	
Retired	3551 (15.2)	2383 (16.3)	64,304 (32.0)	2467 (68.1)	
Other	1655 (7.1)	830 (5.7)	10,280 (5.1)	148 (4.1)	
Education, No. (%)					
< 10 years	4995 (21.3)	3858 (26.4)	63,678 (31.7)	1723 (47.6)	< 0.001
≥ 10 years	18,435 (78.7)	10,730 (73.6)	137,317 (68.3)	1900 (52.4)	
Diet, No. (%)					
< 5 portions/day	18,306 (78.1)	11,470 (78.6)	158,213 (78.7)	2847 (78.6)	0.232
≥ 5 portions/day	5124 (21.9)	3118 (21.4)	42,782 (21.3)	776 (21.4)	
Healthy sleep score, No. (%)					
0	20 (0.1)	25 (0.2)	441 (0.2)	14 (0.4)	< 0.001
1	540 (2.3)	543 (3.7)	9426 (4.7)	256 (7.1)	
2	3297 (14.1)	2801 (19.2)	42,856 (21.3)	923 (25.5)	
3	8468 (36.1)	5561 (38.1)	77,525 (38.6)	1378 (38.0)	
4	8632 (36.8)	4464 (30.6)	57,731 (28.7)	872 (24.1)	
5	2473 (10.6)	1194 (8.2)	13,016 (6.5)	180 (5.0)	
Smoking status, No. (%)					
Never smoker	14,459 (61.7)	8262 (56.6)	109,182 (54.3)	1093 (30.2)	< 0.001
Former smoker	6693 (28.6)	4843 (33.2)	71,716 (35.7)	1390 (38.4)	
Current smoker	2278 (9.7)	1483 (10.2)	20,097 (10.0)	1140 (31.5)	
Years since quitting (among former smokers), No. (%)					
≥ 25	1208 (33.3)	877 (28.9)	18,102 (37.8)	503 (46.3)	< 0.001
15 to 24	1010 (27.9)	768 (25.3)	11,994 (25.0)	267 (24.6)	
10 to 14	439 (12.1)	378 (12.5)	5320 (11.1)	100 (9.2)	
5 to 9	455 (12.6)	449 (14.8)	6172 (12.9)	111 (10.2)	
< 5	512 (14.1)	559 (18.4)	6348 (13.2)	106 (9.8)	

Continuous variables were presented as mean (SD) or median (IQR), based on the result of normality assessment using the Shapiro–Wilk test. Categorical variables were presented as No. (%). Years since quitting was reported only among former smokers

Abbreviations: *N* sample size, *P P* value, No. number of subjects, % percentage, *SD* standard deviation, *IQR* interquartile range, *CVD* cardiovascular disease, *CKM* cardiovascular-kidney-metabolic

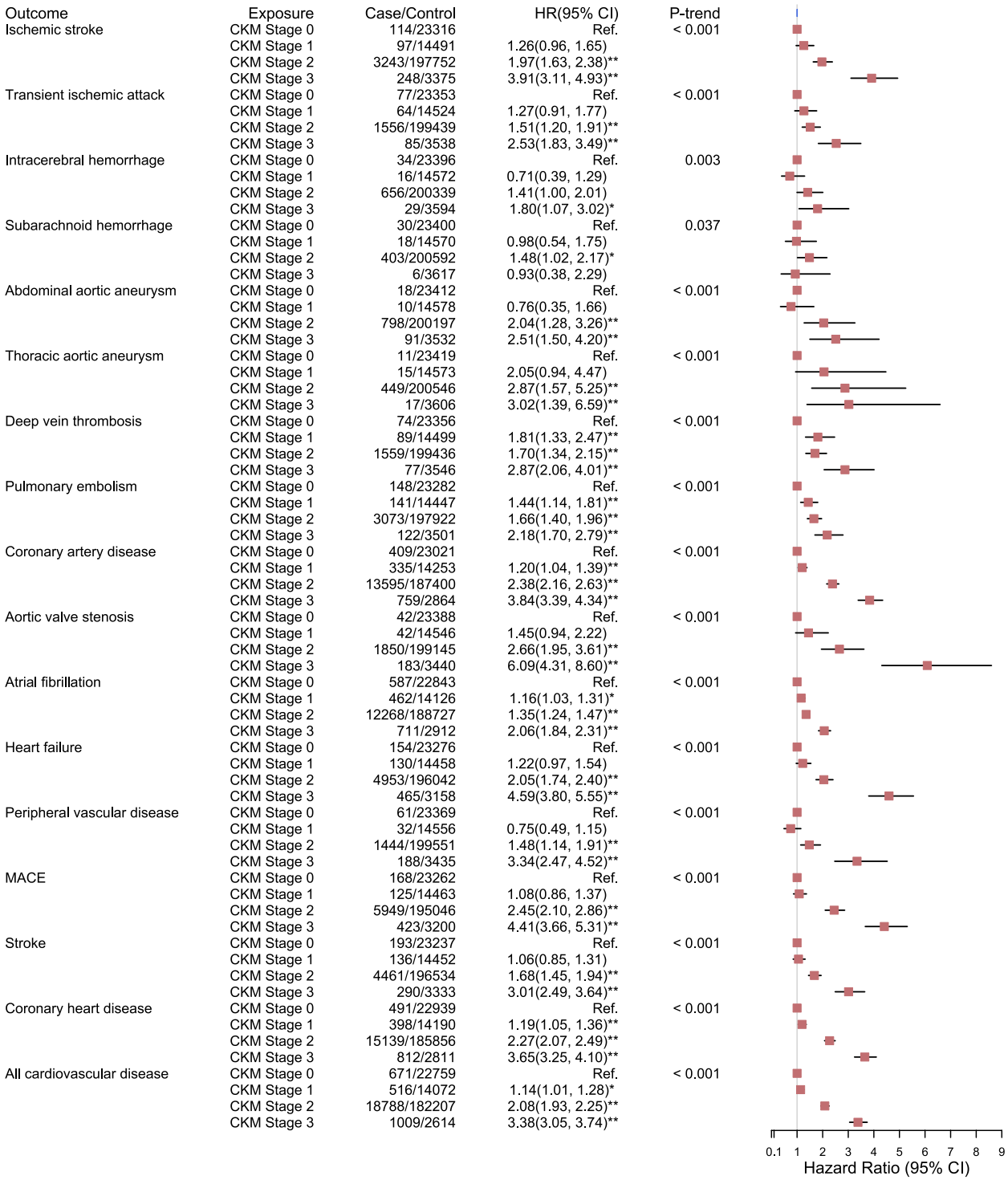

Fig. 2 Association between different stages of CKM syndrome and CVD risk. All models adjusted for age, sex, employment status, income levels, education, physical activity, diet, healthy sleep score, smoking status and alcohol consumption. Abbreviations: *HR*, hazard ratio; *CI*, confidence interval; *P*, *P* value; Ref., reference group for each outcome; MACE, major adverse cardiovascular events; CKM, cardiovascular-kidney-metabolic. Note: * indicates statistical significance at $\alpha = 0.05$; ** indicates statistical significance after Bonferroni correction ($\alpha = 0.05/3$)

Association of smoking behavior with incident CVD by CKM syndrome stages

Figure 3 presents the adjusted HRs for the effect of smoking behavior on CVD events, both in the overall population (CKM Stages 0 to 3) and within categories by CKM syndrome stage. In the overall population, compared with never smoking, higher-risk smoking behaviors were associated with greater risks of total CVD, stroke, CHD, MACE, and 13 CVD subtypes. However, the association for transient ischemic attack did not remain statistically significant after Bonferroni correction (Fig. 3(A)). For major CVD outcomes, current smokers (*HR* = 1.75, 95% *CI* 1.61–1.90) and individuals who had quit smoking for less than 5 years (*HR* = 1.38, 95% *CI* 1.19–1.61) exhibited a markedly elevated risk of stroke, whereas no significant risk increase was observed among those who had quit for more than 5 years after Bonferroni correction. However, former smokers still exhibited significantly elevated risks for CHD and total CVD compared with never smokers, even after more than 25 years of smoking cessation. Compared with current smokers, smoking cessation demonstrated an immediate protective role in reducing the risk of various cardiovascular events, including IS, CAD, HF, PVD, and MACE (Fig. 3(B)). Even among those who had quit smoking for less than 5 years, the risk was reduced by 21% for stroke and 17% for CHD, respectively. Similar results were obtained when years since quitting were treated as a continuous variable (Fig. 4(A)-(C)).

According to the statistical description results, CVD incidence was substantially higher among individuals at CKM Stages 2–3 compared with those at Stages 0–1 ($P < 0.001$ for the comparison between the two groups). To increase statistical power given the limited number of participants in each subgroup categorized by years since quitting, we merged CKM Stages 0 and 1, as well as Stages 2 and 3 into two respective groups. As shown in Fig. 3(C), in the CKM Stage 0–1 subgroup, it takes around 10 years of smoking cessation for the risk of total CVD and CHD to reach a level that is not significantly different from that of never smokers. In contrast, this

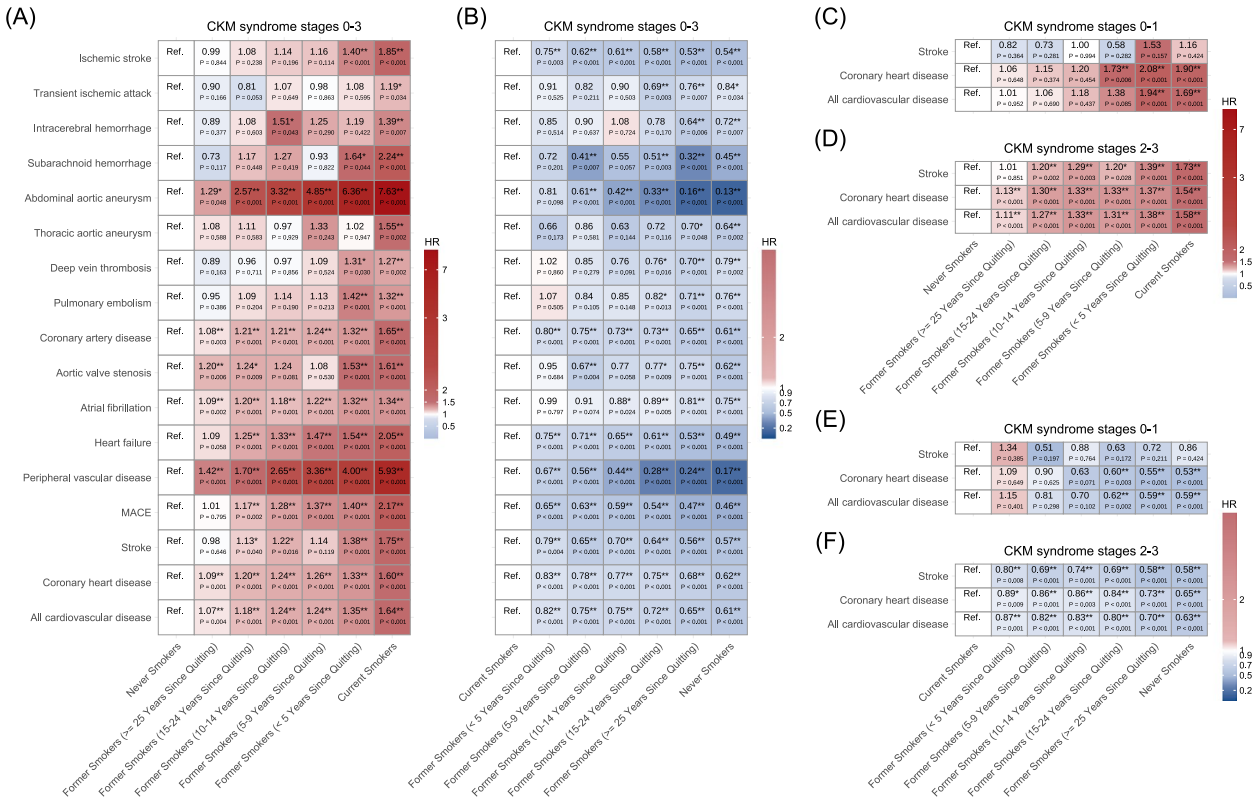

Fig. 3 Association between smoking behavior and incident CVD in the overall population and CKM syndrome subgroups. Multivariable Cox model in the overall population adjusted for age, sex, employment status, income levels, education, physical activity, diet, healthy sleep score, alcohol consumption, body mass index, systolic blood pressure, total cholesterol, diabetes mellitus, the use of antihypertensive and statin/cholesterol lowering medication, and model in subgroups adjusted for age, sex, employment status, income levels, education, physical activity, diet, healthy sleep score, and alcohol consumption. Abbreviations: Ref., reference group for each CVD type; *P*, *P* value; CVD, cardiovascular disease; CKM, Cardi ovascular-kidney-metabolic; MACE, major adverse cardiovascular events. Note: * indicates statistical significance at $\alpha = 0.05$; ** indicates statistical significance after Bonferroni correction ($\alpha = 0.05/6$)

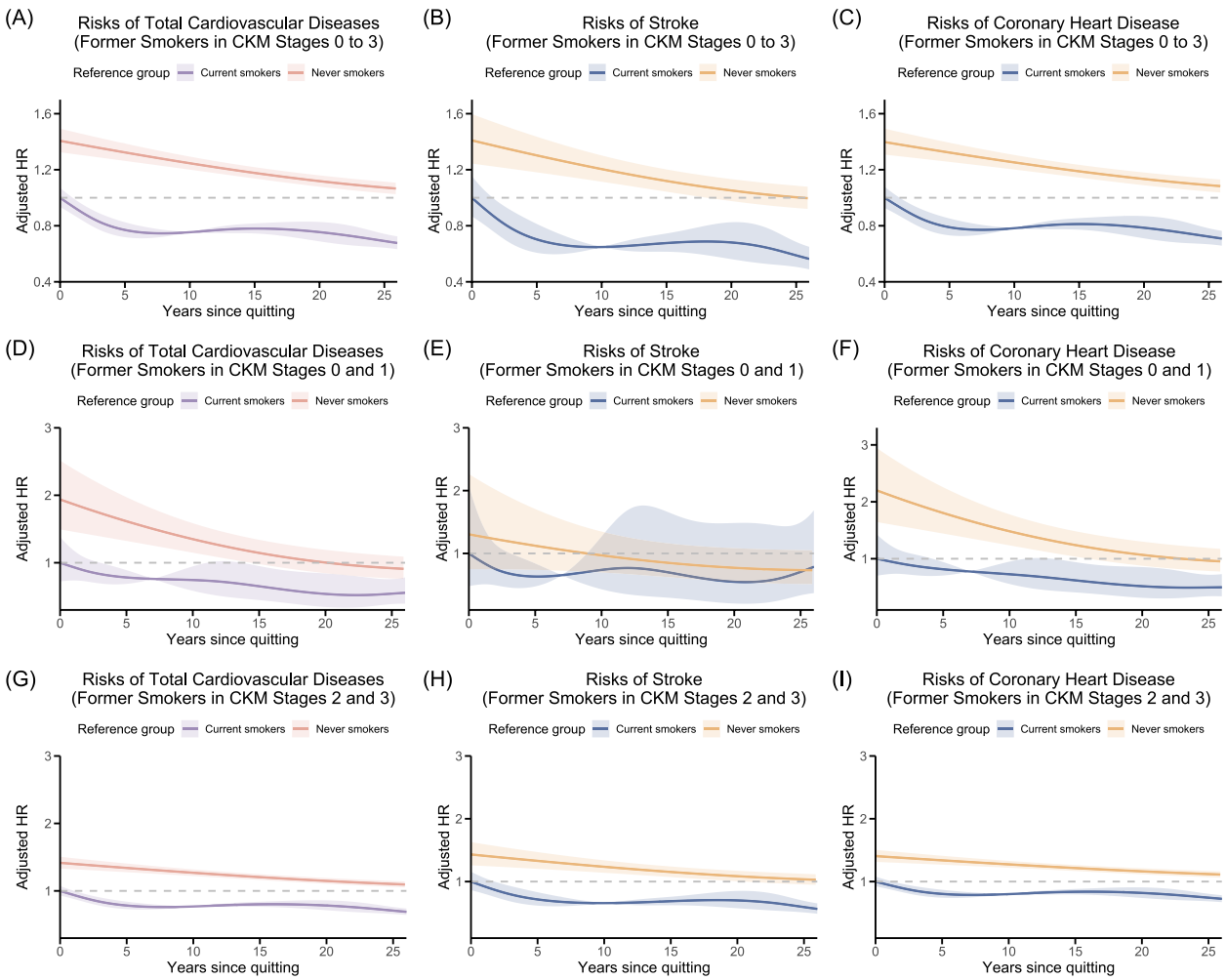

Fig. 4 Incident CVD risk by years of smoking before quitting stratified by CKM syndrome stages. Restricted cubic splines with five knots were employed to capture potential nonlinear associations with the log hazard of CVD. Models in the overall population were adjusted for age, sex, employment status, income levels, education, physical activity, diet, healthy sleep score, alcohol consumption, body mass index, systolic blood pressure, total cholesterol, diabetes mellitus, the use of antihypertensive and statin/cholesterol lowering medication. Models in subgroups were adjusted for the same covariates, excluding diabetes and medication use. Abbreviations: *HR*, hazard ratio; CVD, cardiovascular disease; CKM, cardiovascular-kidney-metabolic

period extended to more than 25 years in the CKM Stage 2–3 group (Fig. 3(D)), suggesting that the protective effect of smoking cessation on CVD may take longer to manifest in individuals with advanced CKM syndrome. However, when using current smokers as the reference group, individuals in the CKM Stages 2–3 showed a significant reduction in CVD risk even after < 5 years of smoking cessation, whereas those in the Stage 0–1 required a longer cessation period (around 15 years) to observe a significant benefit (Fig. 3(E), (F)). Analyses treating years since quitting as a continuous variable (Fig. 4) revealed similar patterns. The associations between smoking behavior and major CVD outcomes within each CKM stage (presented in Supplemental Table S10, S11 and Figure S5) were broadly consistent with the main results, although the statistical power may be insufficient to reach significance due to the limited sample size.

Joint effect of smoking and CKM syndrome on incident CVD and its subtypes

As shown in Table 2 and Supplemental Table S12, compared with never smokers at CKM Stage 0, current smokers at CKM Stage 3 face a 4.14 times higher risk of total CVD over the next decade (95% *CI* 3.54–4.83). Moreover, they experience significant increases in the risk of several CVD subtypes, including a 17.68-fold higher risk of abdominal aortic aneurysm, a 10.53-fold higher risk

Table 2 Joint effects of smoking status and CKM syndrome on CVD outcomes with significant interaction

	Never smokers		Former smokers		Current smokers		*P* for trend	Multiplicative interaction		Additive interaction
	Case/control	*HR* (95% *CI*)	Case/control	*HR* (95% *CI*)	Case/control	*HR* (95% *CI*)		*HR*	*P*	RERI[c] (95% *CI*)
Ischemic stroke										
CKM stage 0	60/14399	Ref	39/6654	1.24 (0.83, 1.85)	15/2263	1.47 (0.84, 2.59)	< 0.001	1.03	0.594[a]	0.32(0.02,0.58)
CKM stage 1	56/8206	1.53 (1.06, 2.2)	31/4812	1.23 (0.79, 1.89)	10/1473	1.53 (0.78, 2.98)			0.007[b]	
CKM stage 2	1480/107702	1.98 (1.53, 2.57)	1316/70400	2.23 (1.71, 2.89)	447/19650	3.47 (2.65, 4.56)				
CKM stage 3	84/1009	5.66 (4.04, 7.92)	78/1312	3.82 (2.71, 5.39)	86/1054	5.74 (4.1, 8.03)				
Abdominal aortic aneurysm										
CKM stage 0	4/14455	Ref	6/6687	2.67 (0.75, 9.45)	8/2270	10.39 (3.12, 34.56)	< 0.001	0.83	0.082[a]	2.79(1.12,5.55)
CKM stage 1	4/8258	1.58 (0.39, 6.31)	3/4840	1.46 (0.33, 6.52)	3/1480	6.26 (1.4, 27.98)			0.182[b]	
CKM stage 2	178/109004	2.46 (0.91, 6.62)	380/71336	5.54 (2.06, 14.87)	240/19857	19.05 (7.08, 51.27)				
CKM stage 3	10/1083	3.91 (1.22, 12.53)	36/1354	9.49 (3.36, 26.82)	45/1095	17.68 (6.33, 49.43)				
Coronary artery disease										
CKM stage 0	208/14251	Ref	118/6575	1.12 (0.89, 1.4)	83/2195	2.26 (1.75, 2.91)	< 0.001	0.88	< 0.001[a]	0.22(0.04,0.41)
CKM stage 1	160/8102	1.26 (1.02, 1.55)	124/4719	1.45 (1.16, 1.81)	51/1432	2.11 (1.55, 2.87)			< 0.001[b]	
CKM stage 2	6143/103039	2.5 (2.17, 2.87)	5645/66071	2.93 (2.55, 3.37)	1807/18290	3.99 (3.45, 4.61)				
CKM stage 3	236/857	5.41 (4.48, 6.54)	306/1084	5.05 (4.22, 6.04)	217/923	4.57 (3.77, 5.54)				
Aortic valve stenosis										
CKM stage 0	22/14437	Ref	13/6680	1.08 (0.55, 2.15)	7/2271	1.96 (0.84, 4.59)	< 0.001	0.86	0.038[a]	0.38(−0.18,0.82)
CKM stage 1	19/8243	1.41 (0.76, 2.6)	16/4827	1.63 (0.86, 3.11)	7/1476	3.01 (1.28, 7.05)			0.071[b]	
CKM stage 2	802/108380	2.61 (1.7, 3.99)	854/70862	3.37 (2.2, 5.15)	194/19903	3.85 (2.47, 5.99)				
CKM stage 3	60/1033	8.12 (4.95, 13.32)	77/1313	7.64 (4.72, 12.36)	46/1094	6.34 (3.79, 10.6)				
Heart failure										
CKM stage 0	77/14382	Ref	54/6639	1.32 (0.94, 1.88)	23/2255	1.65 (1.04, 2.64)	< 0.001	0.94	0.157[a]	0.31(0.004,0.58)
CKM stage 1	58/8204	1.21 (0.86, 1.71)	46/4797	1.36 (0.95, 1.96)	26/1457	2.94 (1.88, 4.58)			< 0.001[b]	
CKM stage 2	2104/107078	2.04 (1.62, 2.56)	2158/69558	2.59 (2.06, 3.25)	691/19406	3.78 (2.98, 4.79)				
CKM stage 3	140/953	6.27 (4.73, 8.31)	184/1206	6.01 (4.59, 7.89)	141/999	6.18 (4.66, 8.2)				
Peripheral vascular disease										
CKM stage 0	27/14432	Ref	15/6678	1.05 (0.56, 1.98)	19/2259	3.59 (1.99, 6.46)	< 0.001	1.07	0.368[a]	1.42(0.87,2)
CKM stage 1	13/8249	0.76 (0.39, 1.48)	9/4834	0.75 (0.35, 1.59)	10/1473	3 (1.45, 6.2)			0.003[b]	
CKM stage 2	388/108794	1.04 (0.71, 1.54)	636/71080	2.1 (1.43, 3.1)	420/19677	6.04 (4.08, 8.94)				
CKM stage 3	34/1059	3.99 (2.39, 6.67)	63/1327	5.42 (3.42, 8.59)	91/1049	10.53 (6.79, 16.34)				
MACE										
CKM stage 0	84/14375	Ref	37/6656	0.88 (0.59, 1.29)	47/2231	2.99 (2.09, 4.28)	< 0.001	0.85	< 0.001[a]	0.41(0.13,0.68)
CKM stage 1	57/8205	1.1 (0.78, 1.54)	40/4803	1.14 (0.78, 1.66)	28/1455	2.75 (1.79, 4.22)			< 0.001[b]	

Table 2 (continued)

	Never smokers		Former smokers		Current smokers		*P* for trend	Multiplicative interaction		Additive interaction
	Case/control	*HR* (95% *CI*)	Case/control	*HR* (95% *CI*)	Case/control	*HR* (95% *CI*)		*HR*	*P*	RERI[c] (95% *CI*)
CKM stage 2	2567/106615	2.49 (2, 3.09)	2341/69375	2.85 (2.29, 3.55)	1041/19056	5.25 (4.2, 6.57)				
CKM stage 3	126/967	6.44 (4.86, 8.51)	168/1222	6.07 (4.65, 7.93)	129/1011	6.1 (4.62, 8.06)				
Stroke										
CKM stage 0	109/14350	Ref	61/6632	1.08 (0.79, 1.47)	23/2255	1.27 (0.81, 1.99)	< 0.001	1.05	0.279[a]	0.31(0.08,0.52)
CKM stage 1	76/8186	1.16 (0.86, 1.55)	46/4797	1.03 (0.73, 1.45)	14/1469	1.2 (0.69, 2.09)			0.002[b]	
CKM stage 2	2061/107121	1.59 (1.31, 1.92)	1803/69913	1.79 (1.47, 2.18)	597/19500	2.69 (2.19, 3.31)				
CKM stage 3	100/993	4.08 (3.09, 5.38)	93/1297	2.81 (2.12, 3.73)	97/1043	3.96 (3, 5.24)				
Coronary heart disease										
CKM stage 0	253/14206	Ref	147/6546	1.15 (0.94, 1.41)	91/2187	2.03 (1.6, 2.58)	< 0.001	0.90	< 0.001[a]	0.16(0.001,0.33)
CKM stage 1	186/8076	1.2 (1, 1.46)	156/4687	1.51 (1.24, 1.84)	56/1427	1.91 (1.43, 2.55)			< 0.001[b]	
CKM stage 2	6919/102263	2.37 (2.09, 2.68)	6251/65465	2.76 (2.43, 3.13)	1969/18128	3.66 (3.21, 4.18)				
CKM stage 3	249/844	4.94 (4.14, 5.9)	328/1062	4.74 (4.01, 5.6)	235/905	4.3 (3.59, 5.14)				
All cardiovascular disease										
CKM stage 0	352/14107	Ref	206/6487	1.15 (0.97, 1.37)	113/2165	1.84 (1.49, 2.28)	< 0.001	0.93	< 0.001[a]	0.2(0.05,0.32)
CKM stage 1	252/8010	1.18 (1, 1.38)	198/4645	1.38 (1.16, 1.64)	66/1417	1.65 (1.27, 2.14)			< 0.001[b]	
CKM stage 2	8619/100563	2.13 (1.91, 2.37)	7716/64000	2.47 (2.22, 2.75)	2453/17644	3.37 (3.01, 3.78)				
CKM stage 3	319/774	4.64 (3.98, 5.41)	385/1005	4.07 (3.51, 4.72)	305/835	4.14 (3.54, 4.83)				

All models adjusted for age, sex, employment status, income levels, education, physical activity, diet, healthy sleep score, and alcohol consumption

Abbreviations: *N* total sample size, *Case* number of cases, *HR* hazard ratio, *CI* confidence interval, *P P* value, *RERI* relative excess risk due to interaction, *CVD* cardiovascular disease, *CKM* cardiovascular-kidney-metabolic, *Ref.* reference group for each CVD type, *MACE* major adverse cardiovascular events

[a] *P* value for effect modification on the multiplicative scale, evaluated by including a multiplicative interaction term between CKM syndrome stage and smoking traits (both treated as ordinal variables) in the Cox regression models

[b] *P* value for effect modification on the multiplicative scale, evaluated using a likelihood ratio test comparing models with and without the cross-product term, with CKM syndrome (Stage 0 to 3) and smoking traits (never, former, current smoker) treated as categorical variables

[c] RERI calculated by transformed smoking status (smoker vs. non-smoker) and CKM syndrome (Stage 0–1 vs. Stage 2–3) into binary variables

of PVD, a 6.34-fold higher risk of aortic valve stenosis, a 6.18-fold higher risk of HF, and a 6.1-fold higher risk of MACE. The combined effect of smoking and CKM progression was associated with significant increased risk of total CVD, CHD, stroke, MACE, and 8 CVD subtypes (P for trend <0.05). In addition, the protective effect of smoking cessation on CVD appeared at lower CKM stages, where former smokers showed risk levels approaching those of never smokers at CKM Stage 0. Results based on the imputed dataset were similar (Supplemental Table S13). Subgroup analyses revealed significant linear trends of increasing total CVD risk with more severe smoking status and higher CKM stages among females and individuals aged over 60 years (Supplemental Table S14).

The modifying effect of CKM syndrome on the relationship of smoking with incident CVD

The analysis of the modifying effect of CKM syndrome in relation to smoking and incident CVD is displayed in the right panel in Table 2 and Supplemental Table S12. We found a significant positive effect modification of CKM syndrome on the additive scale for total CVD, CHD, stroke, MACE, as well as 5 CVD subtypes, including IS, abdominal aortic aneurysm, CAD, HF, and PVD, across categories of smoking status. These effect modifications remained stable in the additional analyses using the imputed dataset and in subgroup analyses (Supplemental Table S13 and S14), except for IS and HF, where the effect estimates were directionally consistent but did not reach statistical significance. The positive effect modification on additive scale for aortic valve stenosis and AF was significant only in the imputed dataset, perhaps due to increased statistical power. These findings indicate that, for several CVD outcomes, the risk among smokers at CKM Stages 2–3 exceeds the sum of the individual effects of CKM syndrome and smoking. The additional additive interaction statistics (AP and S) further support these findings (Supplemental Table S15). In contrast, we found consistent negative modifying effect on the multiplicative scale by CKM syndrome in the relationship between smoking status and total CVD, CHD, MACE, and CAD across all analysis and modeling approaches (Table 2, Supplemental Table S12 to S14), indicating that the HRs for these CVD outcomes among smokers at CKM Stages 2–3 were lower than expected compared to those at CKM syndrome Stages 0–1. Significant multiplicative interaction was observed for aortic valve stenosis only in the main dataset, and for HF only in the imputed dataset. We found no consistent evidence that CKM syndrome modifies the effect of smoking behavior on other CVD subtypes.

Discussion

Using data from UK Biobank, this cohort study systematically explored the relationships between smoking behavior, CKM syndrome, and a broad range of cardiovascular outcomes. Our main findings included four key points. First, individuals with more advanced CKM stages faced progressively greater CVD risk, with those at Stage 3 exhibiting consistently higher risk for 11 of 13 CVD subtypes in the following years compared to those at Stage 0. Second, the protective effect of smoking cessation took a longer period to manifest in individuals with higher CKM stages. It elapsed around 10 years for former smokers at CKM Stage 0–1 and more than 25 years for those at CKM Stage 2–3 to reach a CVD risk level that was not significantly different from never smokers. Third, CKM syndrome seemed to be a (positive and addictive) effect modifier on the association between smoking status and total CVD, stroke, as well as 3 CVD subtypes. This suggests that smokers with advanced CKM syndrome stages face a higher CVD risk compared to the risk observed when smoking and CKM syndrome are considered separately. Therefore, maintaining smoking cessation is particularly important for individuals in later CKM stages to lower the probability of developing CVD over the coming years. Finally, the simultaneous implementation of smoking cessation and CKM stage reversal may yield greater benefits for CVDs, especially for abdominal aortic aneurysm and PVD.

Although the damaging impact of cigarette smoking on CVDs has been a frequently discussed topic, recent studies continue to focus on further elucidating the impact of smoking as well as the benefits of smoking cessation in populations with different health conditions, aiming to guide the development of precise smoking prevention and cessation strategies for more effective prevention of CVD events. For instance, smokers with diabetes faced a substantially higher CVD risk than smokers without diabetes, with a significant multiplicative interaction observed [6]. A positive additive interaction between tobacco use and abdominal obesity on CVD risk was identified in a prospective cohort study based on the Chinese population [36]. Smoking was also found to have a positive additive interaction with metabolic syndrome in previous studies [9, 37]. High BMI combined with smoking has been shown to significantly increase the CVD risk, although no statistically significant interaction was detected [38]. However, conditions such as diabetes and metabolic syndrome often co-exist, exploring the association between smoking behavior and CVD risk in single health conditions may not provide sufficiently valuable evidence for personalized guidance.

The concept of CKM syndrome formally proposed by the AHA presidential advisory offered the possibility of

a comprehensive assessment of metabolic conditions, chronic kidney disease, and the state of the cardiovascular system [39] through different CKM stages (Stages 0 to 4). Among this predominantly middle-aged and elderly cohort comprising individuals across CKM stages 0 to 3, we found that only 15.7% of the participants were at CKM stage 0 or 1, individuals with more advanced stages comprised the majority of the population. In addition, the proportion of men increased progressively with advancing CKM stage, reaching 77.8% at Stage 3. These patterns were consistent with findings from previous studies [16, 40, 41]. For populations with different CKM conditions, targeted smoking cessation strategies are particularly essential, as those with severe CKM conditions may gain greater benefits from quitting. The CVD subtypes requiring attention may also differ across these groups. Additionally, the time period needed to mitigate smoking's effect on incident CVD may differ depending on the overall health status of individual. Therefore, this study examined how smoking behavior relates to incident CVD across subgroups at different stages of CKM syndrome, the potential effect modification role of CKM syndrome was also explored. According to our current knowledge, this study offers the first comprehensive prospective evaluation of the underlying relationship between smoking behavior, CKM conditions, and CVD risks.

In this study, we consider individuals with different CKM conditions and systematically assessed the independent and combined effects of smoking and CKM syndrome on CVD risk. Both additive and multiplicative interactions between smoking and CKM conditions were evaluated. We found that although the joint effect was smaller than expected on the multiplicative scale (negative interaction), the additive impact of smoking on CVD risk was greater in population at advanced CKM stages (Stage 2–3) compared to those with better CKM conditions. It is worth noting that it is not rare that the estimates of additive and multiplicative interactions are in opposite directions, as observed in the study of Timpka et al. [35]. And additive interaction is more suitable for assessing the public health significance and the cumulative impact of risk factors on disease risk. Several biological underpinnings for this finding may include chronic inflammation, endothelial dysfunction, and oxidative stress which are common to both smoking and CKM syndrome [42].

To reduce the harmful effects of smoking on CVD, smoking cessation has been widely recommended by guidelines. In recent years, numerous studies evaluated the effectiveness of smoking cessation on CVD outcomes in different populations [3, 10, 43, 44]. For instance, in a population from Framingham Heart Study with an average age of 42.2 (SD, 11.8) years, former smokers have a significantly higher CVD risk (including myocardial infarction, stroke, HF and CVD death) until 15 years after cessation [3]. Then using cohort from Korean National Health Insurance Service database with a mean age of 45.8 (SD, 14.7) years, the CVD risk of former light smokers (less than 8 pack-years) aligns with that of never smokers within 10 years, while it takes more than 25 years for the risk of former heavy smokers to reach a comparable level [10]. Our findings from the entire population revealed different patterns for these two major CVDs: the time period elapsed after smoking cessation to eliminate the statistical difference in risk between former and never smokers was longer for cardiovascular diseases (more than 25 years) than for cerebrovascular diseases (around 15 years). When stratified by CKM stages, the protective effect of smoking cessation on total CVDs was diminished in populations with advanced CKM stages (over 25 years) compared to those in the early stages (around 10 years). Possible reasons may include the higher baseline CVD risk for individuals with advanced CKM stages, or the synergistic interaction between smoking and CKM on CVD risk. Although this is the case, encouraging smoking cessation in individuals with advanced CKM stages remains a crucial measure to reduce CVD incidence.

In addition to encouraging smoking cessation, our results also suggested that it may yield more pronounced benefits in reducing the risk of several CVD subtypes by simultaneously controlling CKM-related risk factors to reverse CKM stages. For individuals with a stable CKM stage, the change of smoking behaviors shows the greatest influence on the risks of abdominal aortic aneurysm and peripheral vascular disease, consistent with the results in a previous Mendelian randomization study from UK Biobank [17]. The mechanisms of smoking on abdominal aortic aneurysm may include that smoking destruct the lamellar elastin matrix of the arterial media by promoting the production and upregulation of matrix metalloproteinases and exacerbating chronic inflammatory infiltration [45–48]. In addition, smoking affects lipid metabolism and distribution, inducing phenotypic changes and dysfunction of macrophages, endothelial cells and smooth muscle cells, all of which are crucial to the pathogenesis of atherosclerosis and contribute to the primary pathological basis of peripheral vascular disease [49–52]. Results of smoking on other CVD subtypes were also broadly aligned with prior studies on coronary artery disease [53], aortic valve stenosis [54], heart failure [55], etc. Moreover, the reversal of CKM stages was associated with a substantial reduction in the risk of several CVDs, particularly aortic valve stenosis. This was also in line with previous research exploring the effect of CKM-related risk factors, including lipid, SBP, and BMI,

on the risk of aortic valve stenosis [56]. The combined improvement of both smoking and CKM conditions yields the greatest benefit in reducing the risk of several CVD subtypes such as abdominal aortic aneurysm and PVD, which can also be supported by existing research [57]. Therefore, prevention strategies to reduce CVD risk through smoking cessation and CKM control should be further refined and tailored based on individual overall health conditions, with particular attention to CVD subtypes most significantly affected by both factors.

Our study has several limitations. Firstly, baseline blood glucose measurements in the UK Biobank were not strictly measured in a fasting state, and the fasting time variable was not available in our application. As a result, the definition of prediabetes and metabolic syndrome relied solely on glycosylated hemoglobin, following previous literatures [24–27]. Secondly, when the population was further classified into subgroups based on both smoking behavior and CKM stage, the case number in several subgroups decreased substantially, especially for analyses focusing on CVD subtypes. This reduction may have led to insufficient statistical power to detect some significant associations. Thirdly, all smoking traits were derived from baseline self-reported questionnaires, we cannot rule out the possibility of measurement error or misclassification. Fourthly, although this study employed multivariate adjustment based on a preselected set of covariates to account for potential confounders between smoking and CVDs, residual confounding may still exist. So, the association in this study should be interpreted with caution when inferring causality. Fifthly, the inclusion of only white participants from the UK Biobank in this study constrains the extent to which our results can be extrapolated to other ethnic populations. Future studies involving diverse ethnic groups are warranted. Sixthly, considering that individuals from the UK Biobank tend to be healthier and exhibit greater health consciousness compared to the broader population, our findings may be subjected to volunteer selection bias, potentially affecting their generalizability. Finally, this study focused on the association between baseline smoking and CKM status with future CVD risk. Further investigations are needed to examine how changes in smoking behavior or CKM status affect CVD outcomes.

Conclusions

Our findings suggested that individuals with advanced CKM syndrome may require a longer duration of smoking cessation for their CVD risk to become not significantly different from that of never smokers. However, promoting smoking cessation is more important in this group, as smokers in the advanced stages of CKM syndrome face a higher CVD risk due to the additive effect modification of the smoking-CVD association by CKM syndrome. Simultaneously improvement of CKM conditions and smoking cessation may gain more benefits in reducing the CVD risk.

Abbreviations

CVD	Cardiovascular Disease
CKD	Chronic Kidney Disease
MetS	Metabolic Syndrome
CKM	Cardiovascular-Kidney-Metabolic
AHA	The American Heart Association
CHD	Coronary Heart Disease
MACE	Major Adverse Cardiovascular Events
CAD	Coronary Heart Disease
HF	Heart Failure
PAD	Peripheral Artery Disease
AF	Atrial Fibrillation
BMI	Body Mass Index
eGFR	Estimated Glomerular Filtration Rate
UACR	Urinary Albumin-to-Creatinine Ratio
ICD-10	International Classification of Diseases, 10th Revision
IS	Ischemic Stroke
PVD	Peripheral Vascular Disease
PA	Physical Activity
SBP	Systolic Blood Pressure
TC	Total Cholesterol
SD	Standard Deviation
IQR	Interquartile Range
ANOVA	Analysis of Variances
HRs	Hazard Ratios
CIs	Confidence Intervals
RERI	Relative Excess Risk Due to Interaction
AP	Attributable Proportion
S	Synergy Index
KD	Kidney Diseases
MD	Metabolic Disorders
STROBE	The Strengthening the Reporting of Observational Studies in Epidemiology

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-025-22865-3.

Supplementary Material 1

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Authors' contributions

X.L.: conceptualization, data curation, methodology, statistical analysis, visualization, writing—original draft. H.Z.: conceptualization, variable definition, supervision, results interpretation, literature search, writing—review, and editing. F.X. and H.L.: conceptualization, supervision, validation, investigation, methodology, writing—review, and editing. H.Z., F.X., and H.L.: funding acquisition. All authors contributed to the planning, execution, and analysis of the study and reviewed and approved the final submitted version.

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Data availability
All data used in this study can be download from public UK Biobank Resource (www.ukbiobank.ac.uk/) via application. This study performed using the application number 98273.

Declarations

Ethics approval and consent to participate
All data used in this study can be download from public UK Biobank, which has been approved by the North West Multicenter Research Ethical Committee, and informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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