The Journal of Prevention of Alzheimer's Disease 13 (2026) 100325

Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Cardiovascular-kidney-metabolic health, genetic susceptibility, and the risk of dementia: A prospective cohort study

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ARTICLE INFO

Keywords:
UK Biobank
Cardiovascular-kidney-metabolic syndrome
Dementia
Polygenic risk score
Apoe genotypes

ABSTRACT

Background: The joint effect of cardiovascular-kidney-metabolic (CKM) health and genetic susceptibility on dementia remains unclear.

Methods: This prospective cohort study utilized data from the UK Biobank. CKM syndrome was characterized by the presence of metabolic risk factors, cardiovascular disease, and chronic kidney disease. We employed Cox proportional hazards models to examine the association between CKM syndrome and dementia incidence, while also investigating the influence of genetic risk via polygenic risk score (PRS) and apolipoprotein E (APOE) ε4 status. We also examined the association between CKM syndrome and cognitive function via linear regression model.

Results: Among 331,731 participants (mean ± SD age, 56.53 ± 8.1 years; 156,762 [47.26 %] male), 4413 (1.33 %) developed dementia during a mean follow-up of 12.8 years. Advanced CKM syndrome correlated with higher risk of dementia; compared to stage 0, HRs for dementia were 1.19 (95 % CI 1.01–1.39, $P = 0.036$), 1.26 (95 % CI 1.09–1.45, $P = 0.002$), and 2.06 (95 % CI 1.77–2.39, $P < 0.001$) for stages 1, 2, and 3–4, respectively. Genetic susceptibility further strengthened this association, and the synergistic effect of CKM syndrome, dementia PRS, and *APOE* ε4 status surpasses the individual contributions of any single factor. These findings remained robust in a series of subgroups and sensitivity analyses. Individuals in the later stages of CKM syndrome demonstrated poorer performance on cognitive function tests.

Conclusions: Poor CKM health was independently associated with cognitive impairment and an increased risk of dementia. The association between CKM syndrome and risk of dementia could be further strengthened by genetic susceptibility.

1. Introduction

Dementia is a highly prevalent condition among older adults. By 2050, the number of individuals affected by dementia is expected to reach 150 million, contributing to an estimated 115.8 million disability-adjusted life years [1]. Dementia is a widespread condition that is linked to an increased hazard of mortality, as well as an elevated risk of disability, diminished quality of life, and greater financial burden. Given the absence of effective treatments for dementia, identifying and comprehensively understanding its risk factors is crucial for alleviating the disease's burden.

Risk factors associated with dementia, as identified by the Lancet Commission, encompass hearing impairment, depression, traumatic brain injury, air pollution, and limited social engagement. Furthermore, metabolic disorders and cardiovascular health determinants, including obesity, diabetes, smoking, and physical inactivity are also considered to be related to dementia occurrence [1]. Epidemiological studies have demonstrated that metabolic, cardiovascular, and renal diseases frequently coexist, with emerging evidence supporting the pathophysiological interactions between these diseases [2–4]. Recently, the

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https://doi.org/10.1016/j.tjpad.2025.100325
Received 1 July 2025; Received in revised form 31 July 2025; Accepted 3 August 2025
Available online 10 August 2025

American Heart Association (AHA) introduced the concept of cardiovascular-kidney-metabolic (CKM) syndrome, underscoring the necessity of an integrated management strategy to alleviate the potential adverse outcomes [5]. Prior research indicated that several individual components of CKM syndrome, such as metabolic syndrome [6], diabetes [7], hypertension [8,9] and other cardiovascular disease (CVD) [10,11] were associated with an elevated risk of dementia. A longitudinal study in the United States revealed that each additional chronic condition (including hypertension, diabetes, heart disease, and stroke) is associated with a 15 % heightened risk of developing dementia [12].

A recent study involving approximately 3000 elderly individuals aged 70–79 indicates that advanced CKM syndrome is associated with an increased risk of dementia [13]. Another study, featuring a larger cohort encompassing individuals aged 40 to 69, also yielded similar results. While the former study did not find evidence that the effect of CKM syndrome on dementia risk was modified by apolipoprotein E (*APOE*) ε4 status, the later research demonstrated that the presence of the *APOE* ε4 allele, in conjunction with poor CKM health, synergistically elevates the risk of dementia, suggesting that the impact of CKM syndrome on dementia may be modified by genetic risk [14]. However, the combined effect of CKM syndrome and polygenic risk score (PRS) on dementia has yet to be thoroughly investigated. Thus, utilizing data from a large-scale cohort study of more than 330,000 participants, our primary objectives were to examine: the association between CKM syndrome and dementia risk; the influence of genetic risk on the relationship between CKM syndrome and dementia, taking into account both PRS and *APOE* ε4 status; and the combined impact of CKM syndrome and genetic predisposition on dementia risk. The secondary objective was to explore the cross-sectional association between CKM syndrome stages and cognitive impairment.

2. Materials and methods

2.1. Study population

The UK Biobank is a large prospective cohort study that includes approximately 500,000 individuals aged 40–69 years at baseline, recruited from the general UK population. Participants have undergone a range of physical measurements, detailed assessments of health-related factors, and sampling of blood. The UK Biobank's ethical approval was granted by the North West Multicenter Research Ethics Committee. All participants gave written informed consent. This research was done under UK Biobank application number 91090.

Data from a total of 502,394 participants were available for our study. We excluded participants with missing information on CKM syndrome assessment ($n = 111{,}123$), a history of baseline dementia ($n = 14{,}837$) and incomplete data on other covariates ($n = 44{,}703$), leaving 331,731 participants for the final analysis. The flowchart outlining the participant selection process is presented in Fig. S1.

2.2. Definition of CKM syndrome stages

According to the AHA's definition, CKM syndrome was defined as a medical condition caused by connections between obesity, diabetes, chronic kidney disease, and CVD, and was categorized into five stages. Details of the definition of each CKM syndrome stages and related comorbidities are available in the supplemental methods and Table S1. It is noteworthy that due to the lack of data on subclinical CVD in the UK Biobank, we determined stage 3 as a high 10-year CVD risk, specifically a risk of 20 % or greater, as predicted by the AHA Predict Risk of Cardiovascular Disease EVENTs (PREVENT) base model [15]. The algorithm used to calculate the 10-year CVD risk is provided in Table S2.

2.3. Identification of dementia

The outcome event in this study was incident all-cause dementia, including dementia subtypes of Alzheimer's dementia (AD), vascular dementia (VaD), and other or unspecific type of dementia. Incident dementia cases were ascertained using data linkage to hospital inpatient records and death registries. Participants with a primary or secondary diagnosis of dementia were identified from hospital records or underlying or contributory cause of death from death registries using *International Classification of Diseases* (*ICD*), *Tenth Revision* (Table S1). The censoring events were defined as death during the follow-up period or the absence of dementia at the end of the follow-up. The follow-up time was coded from recruitment until the first diagnosis of dementia, the date of death, or the last date of follow-up (31 December 2021), whichever occurred first.

2.4. Genetic risk assessment

The process of genotyping, imputation, and quality control of the genetic data used in the UK Biobank study has been described elsewhere [16]. A PRS for dementia was calculated as described previously [17], using 25 single nucleotide polymorphisms (SNPs) (excluding *APOE* SNPs) with a minor allele frequency > 1 % and reaching significance level ($P < 5 \times 10^{-8}$) in genome-wide association studies (GWAS) of AD [18,19]. Detailed information of the selected 25 SNPs is provided in Table S3. The dementia PRS was computed by summing the product of the weight based on regression coefficients and the number of risk alleles (0, 1, or 2) for each of the selected SNPs for each participant. This score was then divided into quintiles and further categorized into "low" (quintile 1), "intermediate" (quintiles 2–4), and "high" (quintile 5) groups, with higher PRS indicating a higher risk of dementia. *APOE* allele status was determined based on two single nucleotide polymorphisms: rs7412 and rs429358. The *APOE* ε4 status was categorized into two groups: carriers and non-carriers.

2.5. Identification of cognitive function

Between 2014 and 2015, participants in the UK Biobank who completed the baseline assessment (between 2006 and 2010) were invited via e-mail to participate in a web-based questionnaire. The questionnaire included web-based versions of two widely recognized cognitive tasks: the Trail-Making Test A/B (TMTA and TMTB), which measured processing speed and speed/executive function, respectively, and the Digit Symbol Substitution Test (DSST), which measured executive function. Besides, we also included reaction time and fluid intelligence as cognitive function endpoints. These measures were derived from the UK Biobank cognitive battery, which has been validated in previous studies [20,21] (Table S4).

2.6. Covariates

We considered several characteristics as potential covariates in the analysis, including age, gender, ethnicity, Townsend Deprivation Index, smoking status, physical activity, low-density lipoprotein cholesterol (LDL-c), social isolation, sense of loneliness, depressive symptoms, hearing difficulty, *APOE* ε4 status, and family history of dementia. Ethnicity was categorized into "White" and "Other". Townsend deprivation index is a composite measure derived from four dimensions: unemployment, non-car ownership, non-home ownership, and household overcrowding. It is calculated using census information linked to residents' postcodes, with a higher score indicating a higher level of deprivation. Smoking status was categorized as current or non-current smokers. Physical activity was assessed through self-report and quantified as the sum of walking, moderate, and vigorous activities, measured in metabolic equivalents (MET-min/week). Social isolation was quantified using a composite score previously derived in the UK Biobank. This score considered three questions: the number of people living together in the household (score of 1 for living alone), frequency of visits to or by friends or family (score of 1 for visiting friends or family less

than once a month), and engagement in leisure or social activities such as a religious groups or sports clubs (1 score for no participation at least weekly). Participants with a sum score of 2 or 3 were classified as socially isolated, while those with a sum score of 0 or 1 were classified as not socially isolated. Sense of loneliness was assessed with the question, "Do you often feel lonely?" with optional responses of "yes" or "no". Depressive symptoms were measured with the question, "Over the past 2 weeks, how often have you felt down, depressed, or hopeless?". Responses were categorized as "several days or not at all", "more than half the days" and "nearly every day". Hearing difficulty was assessed with the question, "Do you have any difficulty with your hearing?" with responses of "yes", "I am completely deaf" and "no". Participants who selected "yes" or "I am completely deaf" were considered to have hearing difficulty.

2.7. Negative controls and falsification end points

Negative control exposure and falsification end points (or negative control outcomes) have been used to detect residual confounding and bias due to unobserved confounders. For negative control exposure, we used phlebitis or thrombophlebitis, vascular conditions which are unlikely to be associated with the risk of dementia. We hypothesized that an association between phlebitis or thrombophlebitis and dementia may imply possible unmeasured confounding.

We used interstitial cystitis and sicca syndrome, which are not associated with CKM syndrome according to any known pathophysiologic mechanisms, as the falsification end points. Details of the definition of interstitial cystitis and sicca syndrome are provided in Table S2.

2.8. Statistical analysis

The baseline characteristics of participants were presented as mean ± standard deviations (SD) for continuous variables or as number (percentage) for categorical variables. Differences in participants' characteristics between stages of CKM syndrome were analyzed by analysis of variance (ANOVA) test or $\chi 2$ test. Cumulative incidences of outcomes were calculated by the Kaplan–Meier method (R packages "survminer", "survival", and "ggplot"). Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with participants in stage 0 serving as the reference group. The proportional hazards assumption was examined by Schoenfeld residuals, and we found no significant deviation from the assumption. Because of the small number of participants in CKM syndrome stage 3 ($n = 5326$, 4.52 %), we combined the stage 3 and stage 4 into stages 3–4. Two incremental models were constructed for each outcome: model 1 was adjusted for age, gender and ethnicity; model 2 was adjusted for age, gender, ethnicity, current smoking, physical activity, Townsend deprivation index, LDL-c, social isolation, loneliness, depressive symptoms, hearing difficulty, family history of dementia, presence of *APOE* ε4. For the cognitive function outcome, we examined the association between CKM syndrome and the cognitive function endpoints via linear regression model, adjusting for the aforementioned covariates in the model. Moreover, we used phlebitis or thrombophlebitis as the negative control exposures. In analyses of the falsification outcomes, the dependent variables used in the Cox model were interstitial cystitis and sicca syndrome instead of dementia.

The interaction between CKM syndrome and genetic risk was investigated by entering CKM syndrome stage × dementia PRS and CKM syndrome stage × *APOE* ε4 status (absence of *APOE* ε4, presence of *APOE* ε4) interaction terms separately into the fully adjusted model. To investigate possible joint effects by genetic risk and CKM syndrome, a 12-level categorical variable was derived containing each combination of dementia PRS categories (low, intermediate, high), *APOE* ε4 status (absence of *APOE* ε4, presence of *APOE* ε4), and CKM syndrome (stages 0–2, stages 3–4). The main analysis was repeated with this variable entered with "low dementia PRS, absence of *APOE* ε4, and CKM syndrome stages 0–2" as the reference group.

Subgroup analyses were performed by rerunning the Cox proportional hazards models, stratified by age, gender, ethnicity, and other relevant covariates. And the interactions between CKM syndrome and the covariates were investigated by entering CKM syndrome stage × covariates separately into the main model. To test the robustness of our results, we conducted several sensitivity analyses: first, outcome events occurring within the first 3 years of follow-up were excluded to minimize the potential influence of reverse causality. Second, participants with prevalent Parkinson's disease were excluded from the analysis, as patients with Parkinson's disease are more likely to develop dementia [22]. Third, the analysis was repeated using the Fine-Gray model to account for the influence of competitive mortality risk on the results. Fourth, we included participants with incomplete covariate information and reiterated the analysis to assess the impact of missing data on our analysis. Multiple imputations with chained equations were applied to estimate missing continuous covariates; while for missing categorical covariates, a value of "missing" was assigned to denote the missing status. Detailed information on missing covariates can be seen in Table S5. Finally, we used the E-value methodology (calculated via R package "EValue") to assess the robustness of the results to unmeasured confounding [23].This estimates the extent to which the relative risk of any unmeasured confounder would need to be in order to overcome the observed association of CKM syndrome and dementia incidence in this study.

All statistical analyses were performed using SAS (version 3.6.3) and R (version 4.4.3). A two-sided $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics according to CKM syndrome stages

In total, 331,731 participants were involved in this study. The mean age of participants was 56.53 ± 8.1 years, with women constituting 52.74 % of the population. At baseline, 42,079 participants (12.68 %) were classified into stage 0, 65,432 (19.72 %) into stage 1, 191,322 (57.67 %) into stage 2, and 32,898 (9.92 %) into stages 3–4 of CKM syndrome. Table 1 illustrates the distribution of participants' characteristics according to stages of CKM syndrome. As the stages of CKM syndrome advanced, participants were older, exhibited a higher proportion of men, and an increased prevalence of various health risk factors, including smoking and insufficient physical activity. They were found to be more likely to experience social isolation, loneliness, and hearing difficulties. Additionally, they were also more likely to be *APOE* ε4 carriers and have a family history of dementia (Table 1).

3.2. Associations of CKM health with incident dementia

During a median follow-up of 12.8 years (interquartile range: 12.1–13.5 years), we identified 4413 (1.33 %) incident cases of all-cause dementia. The cumulative incidence of the outcome was highest in stages 3–4 (log-rank test $P < 0.0001$) compared with earlier stages (Table 2 and Fig. S2). After adjustment for all covariates, when compared to participants in stage 0, participants in later stages exhibited an elevated risk of dementia. The HRs for participants in stages 1, 2 and 3–4 were 1.19 (95 % CI 1.01–1.39, $P = 0.036$), 1.26 (95 % CI 1.09–1.45, $P = 0.002$), and 2.06 (95 % CI 1.77–2.39, $P < 0.001$), respectively. The association of CKM syndrome stages with dementia displayed dose-dependent relationships (P for trend < 0.001) (Table 2). Further analyses of different types of dementia also showed similar results, especially for VaD (Table S6 and Fig. S2). When categorized into five stages, the risk of incident dementia also demonstrated a progressive increase corresponding to the advancement of CKM syndrome (Table S7).

Table 1
. Baseline characteristics of participants according to stages of CKM syndrome.

Characteristics	Total	Stage 0	Stage 1	Stage 2	Stages 3–4	*P* value
N (%)	331,731	42,079 (12.68 %)	65,432 (19.72 %)	191,322 (57.67 %)	32,898 (9.92 %)	
Age, years	56.53 ± 8.1	52.24 ± 7.79	54.96 ± 8.12	57.07 ± 7.80	61.39 ± 6.19	<0.001
Gender, n (%)						<0.001
Male	156,762 (47.26 %)	11,217 (26.66 %)	25,529 (39.02 %)	97,287 (50.85 %)	22,729 (69.09 %)	
Female	174,969 (52.74 %)	30,862 (73.34 %)	39,903 (60.98 %)	94,035 (49.15 %)	10,169 (30.91 %)	
Ethnicity, n (%)						
White	314,546 (94.82 %)	40,240 (95.63 %)	61,789 (94.34 %)	186,297 (94.77 %)	26,220 (95.10 %)	<0.001
LDL-c, mmol/L	3.56 ± 0.87	3.31 ± 0.72	3.54 ± 0.76	3.73 ± 0.88	2.94 ± 0.86	<0.001
Townsend Deprivation Index	−1.39 ± 3.02	−1.55 ± 2.93	−1.52 ± 2.93	−1.40 ± 3.02	−0.93 ± 3.24	<0.001
Physical activity, MET-min/week	2566 ± 2569	2706 ± 2514	2697 ± 2630	2509 ± 2557	2461 ± 2566	<0.001
Current smoker, n (%)	34,239 (10.32 %)	3784 (8.99 %)	5691 (8.70 %)	19,969 (10.44 %)	4795 (14.58 %)	<0.001
Social isolation, n (%)	29,671 (8.94 %)	3216 (7.64 %)	4993 (7.62 %)	18,285 (9.30 %)	3177 (11.52 %)	<0.001
Lack of social interaction, n (%)	27,407 (8.26 %)	3334 (7.92 %)	4997 (7.64 %)	16,056 (8.39 %)	3020 (9.18 %)	<0.001
Social activity participation, n (%)	231,400 (69.76 %)	30,219 (71.81 %)	46,968 (71.78 %)	132,068 (69.03 %)	22,145 (67.31 %)	<0.001
Living alone, n (%)	60,159 (18.13 %)	6967 (16.56 %)	10,829 (16.55 %)	35,159 (18.38 %)	7204 (21.90 %)	<0.001
Loneliness, n (%)	58,505 (17.64 %)	7148 (16.99 %)	10,776 (16.45 %)	34,755 (17.68 %)	5826 (21.13 %)	<0.001
Hearing difficulty, n (%)	85,669 (25.82 %)	8159 (19.39 %)	15,059 (23.01 %)	50,668 (26.48 %)	11,783 (35.82 %)	<0.001
Depressive symptoms, n (%)						<0.001
Several days or not at all	315,608 (95.14 %)	40,319 (95.82 %)	62,768 (95.93 %)	181,756 (95.00 %)	30,765 (93.52 %)	
More than half the days	9884 (2.98 %)	1104 (2.62 %)	1687 (2.58 %)	5849 (3.06 %)	1244 (3.78 %)	
Nearly everyday	6239 (1.88 %)	656 (1.56 %)	977 (1.49 %)	3717 (1.94 %)	889 (2.70 %)	
Family history of dementia, n (%)	38,723 (11.67 %)	4464 (10.61 %)	7493 (11.45 %)	22,764 (11.90 %)	4002 (12.16 %)	<0.001
Presence of *APOE* ε4, n (%)						<0.001
No	237,358 (71.55 %)	30,201 (71.77 %)	47,798 (73.05 %)	136,044 (71.11 %)	23,315 (70.87 %)	
Yes	94,373 (28.45 %)	11,878 (28.23 %)	17,634 (26.95 %)	55,278 (28.89 %)	9583 (29.13 %)	

Note: Categorical variables were expressed as number (percentages) of the participants. Continuous variables were expressed as mean ± standard deviations (SD). *APOE*: apolipoprotein E, CKM: cardiovascular-kidney-metabolic, LDL-c: low-density lipoprotein cholesterol, MET: metabolic equivalents.

Table 2
. Association of CKM syndrome stages with risk of all-cause dementia.

CKM syndrome stages	Cases/population (%)	Model 1 HR (95 %CI)	*P* value	Model 2 HR (95 %CI)	*P* value	E-value (CI)
Stage 0	211/42,079 (0.50 %)	1 (reference)		1 (reference)		
Stage 1	571/65,432 (0.87 %)	1.14 (0.97–1.33)	0.108	1.19 (1.01–1.39)	0.036	1.51 (1.09)
Stage 2	2379/191,322 (1.24 %)	1.28 (1.11–1.47)	0.001	1.26 (1.09–1.45)	0.002	1.63 (1.32)
Stages 3–4	1252/32,898 (3.81 %)	2.40 (2.07–2.79)	<0.001	2.06 (1.77–2.39)	<0.001	2.68 (2.33)
P for trend		1.37 (1.32–1.42)	<0.001	1.27 (1.22–1.31)	<0.001	1.64 (1.56)

Note: These models utilized the Cox proportional hazards model. Model 1 was adjusted for age, gender, ethnicity. Model 2 was adjusted for age, gender, ethnicity, current smoking, physical activity, Townsend deprivation index, low-density lipoprotein cholesterol, social isolation, loneliness, depressive symptoms, hearing difficulty, family history of dementia, presence of *APOE* ε4. *APOE*: apolipoprotein E, CI: confidence interval, CKM: cardiovascular-kidney-metabolic, HR, hazard ratios.

3.3. Genetic risk analysis

Compared to individuals at low dementia PRS, the fully adjusted HRs for the risk of incident dementia were 1.24 (95 % CI 1.12–1.36) and 1.64 (95 % CI 1.48–1.83) for intermediate and high dementia PRS, respectively. These associations remained highly similar when additionally

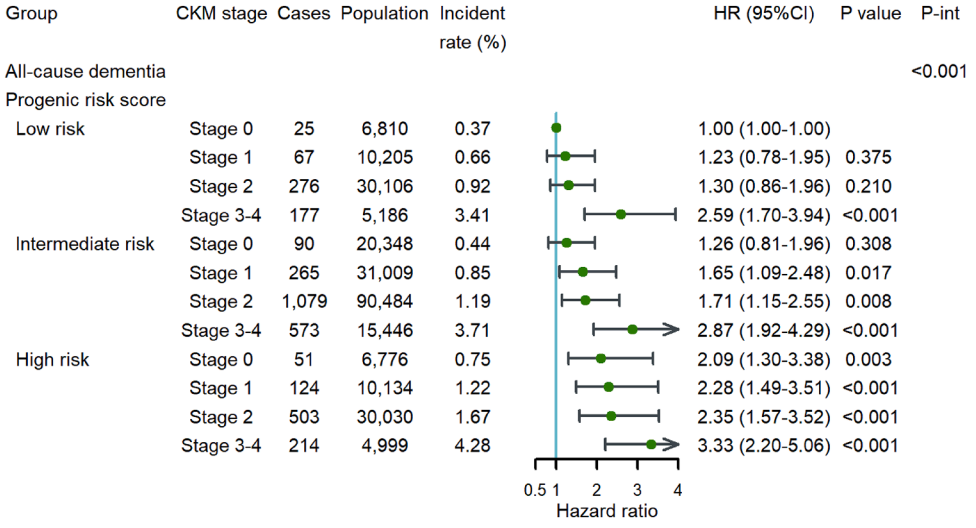

Fig. 1. The joint association of stages of CKM syndrome and polygenic risk scores with risk of all-cause dementia.

adjusting for *APOE* ε4 status: the HR for intermediate dementia PRS was 1.24 (95 % CI: 1.13–1.36), while for high dementia PRS it was 1.64 (95 % CI: 1.48–1.83). Carriers of *APOE* ε4 had an increased risk of dementia compared to noncarriers (fully adjusted HR = 2.87, 95 % CI 2.68–3.07, additional adjustment for dementia PRS HR = 2.87, 95 % CI 2.68–3.07). Multiplicative interactions were identified between CKM syndrome stages and dementia PRS (P for interaction < 0.01), as well as between CKM syndrome stages and *APOE* ε4 status (P for interaction < 0.01) in relation to the risk of incident dementia. In models investigating the joint effect of genetic risk of dementia and CKM health, the highest risk of dementia was observed in those at high dementia PRS and in CKM syndrome stages 3–4 (HR = 3.33, 95 % CI 2.20–5.06) compared to those at low dementia PRS and in CKM syndrome stage 0 (Fig. 1), in *APOE* ε4 carriers in CKM syndrome stages 3–4 (HR = 6.08, 95 % CI 4.70–7.86) compared to non-*APOE* ε4 carriers in stage 0 (Fig. 2), and in those in stages 3–4 with a high dementia PRS and presence of *APOE* ε4 (HR = 6.63, 95 % CI 5.16–8.52) compared to those in stages 0–2 with a low dementia PRS and absence of *APOE* ε4 (Fig. 3).

The association between CKM syndrome and incident dementia was stronger in participants at low dementia PRS and non-*APOE* ε4 carriers. And in participants at high dementia PRS and those who were *APOE* ε4 carriers, only those in stages 3–4 exhibited a higher risk of incident dementia compared with those in stage 0 (Table S8 and Table S9).

3.4. Subgroup and sensitivity analyses

The associations remained robust across subgroup analyses based on gender, ethnicity, smoking status, social isolation, and the three questions assessing social isolation, sense of loneliness, hearing difficulty, depressive symptoms, and family history of dementia (Table S10). Moreover, significant interactions were observed between CKM syndrome and family history of dementia. The association between CKM syndrome and dementia risk was more pronounced in participants without a family history of dementia (Table S10).

To assess the robustness of our analysis, we performed several sensitivity analyses (Table 2 and Table S11). First, we excluded events that occurred within the initial 3 years of follow-up to minimize the potential effects of reverse causation. The association between CKM health and dementia remained consistent. Second, we excluded participants with Parkinson's disease, and the analysis continued to yield consistent results. Third, when accounting for the competing risk of death, the findings remained largely unchanged. Fourth, we included participants with incomplete covariate data and re-ran the Cox proportional hazards model. To address missing values, we employed multiple imputation for continuous covariate values and assigned a "missing" category for categorical covariates, with no substantial alteration in the observed association. Finally, we used the E-value methodology to assess the robustness of the results to unmeasured confounding. For individuals in CKM syndrome stages 3–4, the hazard ratio of 2.06 for incident dementia could plausibly be accounted for only by an unmeasured confounder that has a risk ratio exceeding 2.68 in relation to both CKM syndrome and dementia risk. Given that this risk ratio exceeds that of most known dementia risk factors identified in our analysis, such as advancing age, smoking, social isolation, depression, and hearing difficulty, it is unlikely that an unmeasured confounder exists that can overcome the effect of CKM syndrome observed in the present study (Table S12).

3.5. Negative control exposure and falsification end points

Analyses of the negative control of exposure indicated no significant association between phlebitis or thrombophlebitis with risk of dementia. In the fully adjusted model, the HR of dementia was 1.03 (95 % CI, 0.71–1.49) for individuals with phlebitis or thrombophlebitis compared to those without (Table S13). Analyses of the falsification end points revealed no correlation between CKM syndrome and risk of interstitial cystitis or sicca syndrome (Table S14).

3.6. Associations of CKM health with cognitive function

Estimates of the association between CKM health and cognitive assessments are presented in Table S15. Compared to participants in the earliest stage, the difference in the TMTA score were 0.44 (95 % CI: 0.097~0.79, $P = 0.012$), 0.51 (95 % CI: 0.19~0.81, $P = 0.001$), and 1.53 (95 % CI: 1.03~2.03, $P < 0.001$) for participants in stages 1, 2, and 3–4, respectively. Similarly, significant differences were observed in the TMTB outcomes, which assess executive function and processing speed. Participants in the later stages of CKM syndrome also exhibited notably prolonged reaction times and reduced fluid intelligence, both of which are indicative of cognitive decline. However, no cross-sectional association was found between CKM syndrome and the DSST score. This result was consistent in the gender-stratified analysis. Notably, interactions were observed in both TMTB and reaction time: as CKM syndrome stages progressed, males exhibited poorer performance on the TMTB, whereas females demonstrated a more rapid increase in reaction time (Table S16).

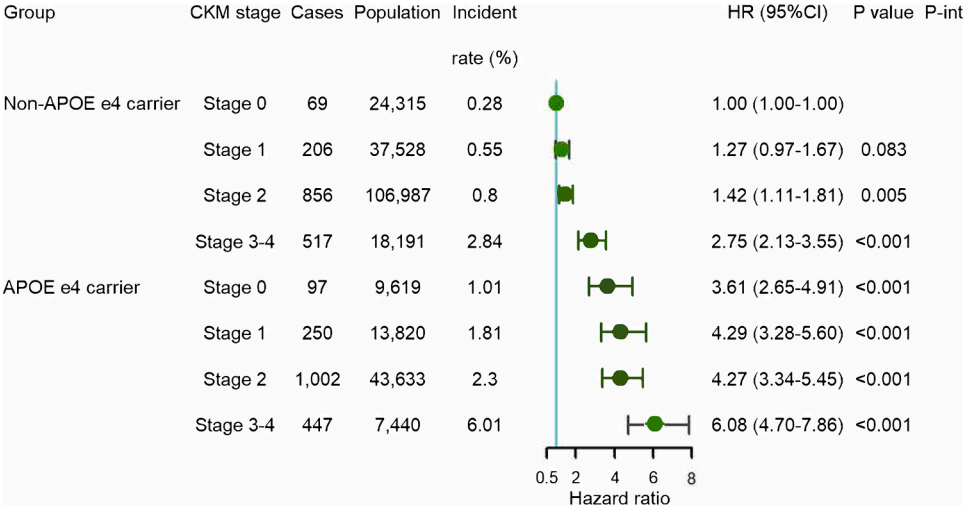

Fig. 2. The joint association of stages of CKM syndrome and presence of *APOE* ε4 with risk of all-cause dementia.

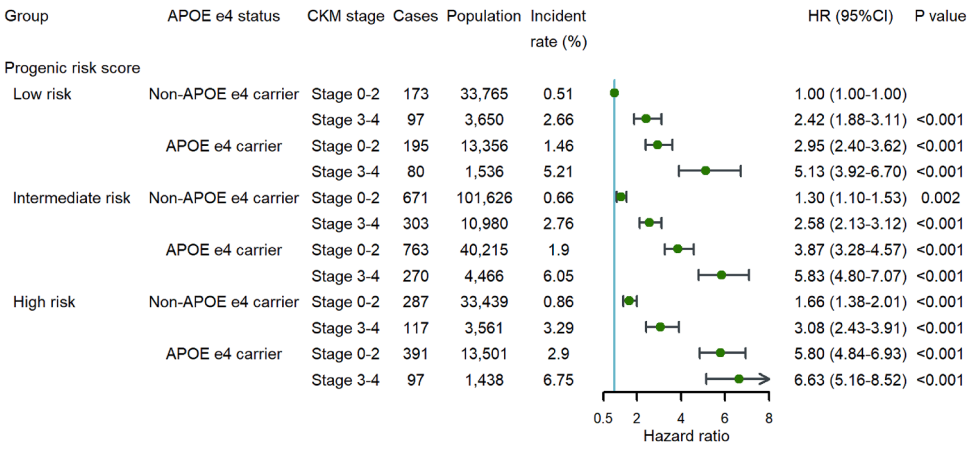

Fig. 3. The joint association of stages of CKM syndrome, polygenic risk scores and *APOE* ε4 status with risk of all-cause dementia.

4. Discussion

In this prospective cohort study involving 331,731 participants from the UK Biobank, we identified a dose–response association between the stages of CKM syndrome and the risk of developing dementia. Participants in the later stages of CKM syndrome exhibited an increased risk of incident dementia, encompassing AD and VaD. Significant interactions were observed between CKM syndrome stages and dementia PRS, as well as between CKM syndrome stages and *APOE* ε4 status. Notably, genetic susceptibility strengthened this association, and the synergistic effect of CKM health, dementia PRS, and *APOE* ε4 status surpasses the contributions of each individual factor. Individuals in the later stages of CKM syndrome demonstrated poorer performance on cognitive function tests.

Our findings are consistent with two previous longitudinal studies that also reported a significant association between poor CKM health and an elevated risk of dementia. A prospective study conducted in the United States found that individuals in CKM syndrome stages 3–4 had a 50 % higher risk of all-cause dementia compared to those in stages 0–2. However, this study, which included approximately 3000 participants aged over 70 (36 % of whom identified as Black), did not find evidence that the effect of CKM syndrome on dementia risk was modified by *APOE* ε4 status [13]. In contrast, within the UK Biobank cohort, research from Xinghe H, et al. indicated that the relationship between CKM syndrome and dementia was stronger in non-*APOE* ε4 carriers [14]. This suggests that the impact of CKM syndrome on dementia risk may be influenced by genetic predispositions. The differences in sample size, age, and racial composition between the studies could help explain the discrepancies in findings. Our study also observed significant interactions between CKM health and *APOE* ε4 status, as well as CKM health and dementia PRS. The association between CKM syndrome and incident dementia was found to be stronger in individuals with a low dementia PRS and those who were non-*APOE* ε4 carriers. This may be because *APOE* ε4 carriers and individuals with a high dementia PRS already face a greater absolute background risk of developing dementia. Consequently, the additional risk associated with other acquired risk factors, such as CKM unhealth, might have been relatively attenuated. The finding derived from the subgroup analysis, which reveals a more pronounced relationship among individuals without a family history of dementia, also supports this viewpoint to a certain extent.

Our study observed that, compared to those in stage 0, individuals in stage 1 and stage 2 had a 19 % and 26 % increased risk of dementia, respectively. Moreover, once individuals progressed to CKM syndrome stages 3–4, which involves a combination of subclinical CVD or CVD, the risk of dementia doubled. These findings highlight the importance of early intervention. Even for patients with excess or dysfunctional adiposity or who are metabolically unhealthy (in stage 1 or 2), taking proactive measures to prevent or delay progression to subclinical CVD or CVD could significantly reduce the risk of developing dementia.

In addition, the association was reinforced by the influence of genetic susceptibility to dementia. The combined effect of CKM syndrome and genetic risk exceeded the sum of their individual influences. But poorer CKM health was consistently associated with an increased risk of dementia regardless of dementia PRS category or *APOE* ε4 status. Therefore, it may be feasible to implement strategies to halt or delay the progression of CKM syndrome, particularly by focusing on preventing CVD to decrease the likelihood of developing dementia, regardless of genetic risk.

The precise mechanism linking CKM syndrome to dementia remains unclear, shared risk factors may assume a crucial role. One key pathological feature of AD, the leading cause of clinically diagnosed dementia in western countries, is the accumulation of amyloid-β (Aβ). Atherosclerosis, which is linked to hypoxia, inflammation, and oxidative stress [24], may enhance the deposition of Aβ or impede its clearance in the brain. Studies have shown that the severity of atherosclerosis correlates with increased Aβ load [25,26]. Various components or risk factors of CKM syndrome, including hypertension [27], hyperlipidemia [28], metabolic syndrome [29], and cigarette smoking [30] may predispose individuals to AD by promotion of Aβ accumulation. Additionally, for VaD, it is reasonable to hypothesize that individuals with advanced CKM syndrome, which is marked by impaired vascular integrity, are at greater risk for developing dementia related to vascular issues. Recent research has demonstrated that individuals genetically predisposed to coronary artery disease also experience an elevated risk of developing dementia, illustrating the complex interplay between the two conditions [31]. Further research is warranted to better understand the pathways connecting CKM health and dementia.

Research has demonstrated that the risk of cognitive decline is markedly elevated among individuals with cardiovascular disease [32], chronic kidney disease [33], and metabolic disorders such as diabetes [7]. Our study is the first to elucidate the substantial association between overall deterioration in CKM health and cognitive decline. Although the underlying mechanisms driving this relationship remain unclear, shared risk factors—including age, hypertension, and smoking—may partially account for this association. Additionally, cerebral hypoperfusion, chronic inflammation, malnutrition and the accumulation of uremic neurotoxins may also contribute to this phenomenon [33,34]. While cognitive impairment may be reversible in its early stages, its progressive nature can ultimately lead to dementia. Consequently, promoting CKM health and the early identification of clues that suggest cognitive impairment in populations with poor CKM health are vital for alleviating the burden of dementia.

The main strengths of the analysis included large sample size, long follow-up period and prospective design. However, it is important to

interpret our findings with caution due to some limitations. First, the nature of observational study poses challenges in establishing the causal relationship, even if the results in sensitivity analysis were consistent when excluding incident cases during the initial 3 years of follow-up. Second, although confounding factors had been carefully controlled in the analysis, the possibility of unmeasured or unknown residual confounding factors cannot be entirely ruled out. However, a series of sensitivity analyses including E-value methodology indicated that the results were robust. Third, the participants in the UK Biobank were recruited from a community setting, which may introduce participation bias. This population is likely to be more affluent and healthier than the general UK population, potentially affecting the generalizability of the findings. Fourth, the study was primarily based on data from the UK Biobank, which predominantly consists of individuals of European descent. Caution should be exercised when generalizing the findings to other populations with different genetic backgrounds. Finally, because of the insufficient data, we are unable to identify participants with subclinical CVD (defined as stage 3 of CKM syndrome by the AHA). To address this limitation, we used the PREVENT model to evaluate 10-year CVD risk and those in high risk ($\geq$20 %) were defined as in CKM syndrome stage 3. Although we combined CKM syndrome stage 3 and stage 4 in the main analyses due to the small number of participants in stage 3, the analysis separating stages 3 and 4 yielded consistent results. Future studies with more detailed data on subclinical CVD would be valuable to explore the impact of the exact stage of CKM syndrome on dementia risk more thoroughly.

5. Conclusion

Our study suggested that poor CKM health was independently associated with cognitive impairment, an increased risk of dementia and its subtypes. The association between poor CKM health and the risk of dementia could be further strengthened by genetic susceptibility to dementia. These findings support the importance of comprehensive interventions to promote CKM health as a strategy to reduce the disease burden of dementia.

Funding

This study was supported by grants from the National Natural Science Foundation of China (NO. 82270254, 82200306, 82271609, U23A20397); Guangzhou Science and Technology Plan Project (NO. 2023B01J1011, 2025A04J5385); Guangdong Basic and Applied Basic Research Foundation (NO. 2025A1515010683).

Data sharing

All data used in this study were obtained from the UK Biobank. Further information including the procedures to obtain and access data from the UK Biobank can be found at https://www.ukbiobank.ac.uk/. Code book, and analytic code used in this study can be made available upon reasonable request to the corresponding authors.

CRediT authorship contribution statement

Yi-Peng Zhang: Writing – review & editing, Writing – original draft. **Jing-Wei Gao:** Writing – review & editing, Methodology, Visualization. **Guang-Hong Liao:** Formal analysis, Validation. **Qing-Yuan Gao:** Investigation. **Ze-Gui Huang:** Investigation. **Chuan-Rui Zeng:** Investigation. **Yang-Wei Cai:** Investigation. **Yong-Xiang Ruan:** Investigation. **Zhi-Teng Chen:** Writing – review & editing, Methodology. **Yang-Xin Chen:** Conceptualization. **Jing-Feng Wang:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Acknowledgement

The authors would like to appreciate the participants from the UK Biobank studies for their contributions. This research has been conducted using the UK Biobank resource (https://www.ukbiobank.ac.uk) under application number 91090.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100325.

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