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Longitudinal Effects of Cardiometabolic Phenotypes and Socioeconomic Status on Psychological-cognitive comorbidity: Cohort Evidence from China, the United States, and the United Kingdom

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Abstract

Background

Cardiometabolic disease (CMD), such as hypertension, diabetes, heart disease, and stroke, are closely associated with psychological disorders and cognitive decline. Psychological-cognitive comorbidity (PCC), defined as the co-occurrence of psychological disorders and cognitive impairment, reflects the interaction between the two conditions and is associated with reduced daily functioning and an increased risk of all-cause mortality. However, the longitudinal impact of different disease combinations and socioeconomic status (SES) on PCC remains unclear.

Methods

This study integrated three nationally representative longitudinal aging cohort datasets: the HRS (2004–2021), ELSA (2002–2019), and CHARLS (2011–2018), including 14,093 eligible middle-aged and older participants. Baseline CMD status was defined by self-reported physician diagnosis, and CMD burden was constructed as 0, 1, 2, or ≥ 3 diseases, along with mutually exclusive CMD types (no CMD, single cardiometabolic risk factor (CM RF), dual cardiometabolic risk factors (CM RFs), and cardiovascular disease (CVD). SES was divided into four groups based on combined education and household wealth. PCC was determined using depression scales and cognitive function assessments. Multivariable Cox models were used to analyse the independent and joint effects of CMD and SES on PCC, and a multi-state transition model was constructed to characterize the dynamic progression of psychological disorders, cognitive impairment, and comorbidity.

Results

During the follow-up period, 2,617 participants developed PCC. The Cox model indicated a dose–response relationship with CMD burden: HR = 1.17 for one disease, HR = 1.45 for two diseases, and HR = 1.55 for ≥ three diseases. Among the CMD types, dual CM RFs and CVD were significantly associated with an increased risk of PCC (HR = 1.55 and 1.43, respectively). Low SES was significantly associated with PCC risk (low SES HR = 3.33). However, no significant interaction was observed between CMD and SES. The multi-state transition model showed that CMD not only promoted the transition from a healthy state to a single psychological or cognitive disorder but also that CVD was a key factor for direct progression to PCC. Multiple sensitivity analyses yielded results that were consistent with those of the main analysis.

Conclusions

CMD burden and type, as well as low SES, independently increased the risk of PCC in middle-aged and older adults, suggesting that CMD management should be integrated with socioeconomic interventions in PCC prevention and control, with particular attention to individuals facing dual risk and those with CVD.

Introduction

With the accelerating global population aging, the comorbidity of cardiometabolic disease (CMD), central nervous system degenerative disorders, and psychological disorders has become a significant public health challenge [1]. Chronic metabolic and vascular diseases, such as hypertension, diabetes, heart disease, and stroke, have been shown to be closely associated with depressive symptoms and cognitive decline [2]. Approximately 30%–50% of patients with CMD worldwide exhibit varying degrees of depressive symptoms, and older adults with a history of diabetes or stroke have a 1.5–2-fold increased risk of cognitive impairment compared to healthy individuals[3–5]. In this context, increasing attention has been paid to the “Psychological-cognitive comorbidity” (PCC) state, in which individuals simultaneously present with both psychological disorders and cognitive impairment[6–8]. Compared to a single psychological disorder or isolated cognitive impairment, PCC presents as a concurrent impairment of both psychological and cognitive functions, which may reflect an interaction between the two or suggest the existence of shared neurobiological underpinnings and pathological processes[9, 10]. Epidemiological studies indicate that, compared to impairment in a single domain, the rate of decline in activities of daily living among patients with PCC accelerates by approximately 40%–60%, and the risk of all-cause mortality increases significantly [11–13]. Therefore, accurately identifying modifiable upstream factors of PCC and elucidating their patterns of progression is of great significance for delaying functional decline in middle-aged and older adults.

Although previous studies have extensively explored the association between CMD and impaired brain health, most existing studies have certain limitations[14, 15]. Previous studies have mostly focused on the independent effects of individual diseases or simple disease counting, overlooking differences in "pathological patterns" during CMD progression[15, 16]. From the perspective of the natural course of disease, CMD exhibits a clear phasic progression: hypertension and diabetes are mostly early metabolic and vascular risk factors, whereas heart disease and stroke indicate more severe end-stage target organ damage[15]. The impact of lesions at different stages on the central nervous system and the risk of triggering PCC may be fundamentally different[15]. Therefore, categorizing CMD into mutually exclusive composite patterns based on pathophysiological characteristics to explore its longitudinal association with PCC can provide more targeted early warning cues than traditional disease count models [17, 18]. However, the current longitudinal evidence on this topic is limited.

The specific mechanisms by which socioeconomic status (SES) influences brain health in CMD require further clarification[18]. Studies have shown that higher educational attainment and socioeconomic resources can enhance the compensatory capacity of neural networks, thereby buffering the effects of

vascular and metabolic damage on cognitive function[19]. Due to the lack of standardized multinational large-sample integration, it remains inconclusive whether SES serves as an interactive buffering factor or acts as an independent risk factor accelerating brain health deterioration in broad populations, encompassing different macro-level systems and resource allocations[20, 21]. Individuals who are healthy at baseline may experience different disease course trajectories, such as the onset of psychiatric symptoms preceding cognitive decline, cognitive impairment occurring first and subsequently accompanied by psychiatric disorders, or both appearing simultaneously within a similar time window[22–24]. Different progression pathways may reflect distinct pathological processes and intervention windows; however, existing studies rarely systematically characterize this micro-level disease course evolution from a multi-state transition perspective[25, 26]. The absence of such microscopic disease progression trajectories greatly restricts the identification of key pathological nodes and the development of precise and targeted intervention strategies [27].

To address this research gap, this study integrated three nationally representative prospective aging cohort datasets: the Health and Retirement Study (HRS), the English Longitudinal Study of Aging (ELSA), and the China Health and Retirement Longitudinal Study (CHARLS). This study aimed to evaluate the longitudinal impact of baseline CMD burden and distinct disease-combination patterns on the incidence of PCC. Additionally, it sought to examine the independent and combined effects of socioeconomic status (SES) in this context. To achieve a comprehensive understanding, a multi-state transition model was constructed to characterize the dynamic transition patterns of individuals initially free from psychological and cognitive disorders. By integrating cross-country aging cohorts and introducing a dynamic outcome perspective, this study helps identify high-risk disease patterns and key transition points for PCC onset and provides more comprehensive evidence for understanding how socioeconomic factors and cardiometabolic risks jointly shape the psychological and cognitive health of middle-aged and older adults.

Methods

Study design and data sources

This study integrated individual-level data from three sister cohort studies in the Global Aging, Health, and Policy Project: the HRS (2004–2021), ELSA (2002–2019), and CHARLS (2011–2018)[28–30]. All cohort studies employed similar research designs, conducting questionnaire surveys every two to three years, with samples consisting of nationally representative middle-aged and older adults in each country[28–30]. Further details of each study have been described in the literature[28–30].

All enrolled subjects were required to complete the baseline survey and participate in at least one follow-up, and must also have key variable information, such as chronic disease status, psychological health assessment, and cognitive function measurement. The exclusion criteria were as follows: (1) age < 45 years at baseline; (2) PCC at baseline; (3) missing baseline SES; (4) missing baseline CMD information;

(5) missing psychological or cognitive status at the final follow-up; (6) missing survey year or month at any wave; and (7) death during follow-up.

All projects involved in this study were approved by the respective Institutional Review Boards, and all respondents provided written informed consent.

Exposure assessment

This study focused on four CMD categories: hypertension, diabetes, heart disease, and stroke. The baseline status of each disease was defined based on the participants' self-reported, clearly physician-diagnosed condition. This study aimed to investigate the longitudinal effect of baseline CMD status on the subsequent risk of developing new-onset PCC. In the primary analysis, the participants' baseline disease status was uniformly used as the main exposure variable. First, by summing the number of the above four diseases each participant had at baseline, this study constructed the "CMD burden" variable and divided it into four levels (0, 1, 2, and ≥ 3). This indicator was intended to assess whether there was a cumulative effect between the simple addition of disease numbers and the risk of PCC.

To further elucidate the heterogeneous effects arising from the pathophysiological characteristics and disease course progression of different conditions, this study constructed four mutually exclusive "CMD type" variables. This classification strategy is based on rigorous clinical considerations: hypertension and diabetes are typically regarded as early metabolic and vascular risk factors, whereas heart disease and stroke indicate more severe terminal target organ damage or major vascular events. Based on the baseline disease status, respondents were explicitly categorized into the following four mutually exclusive groups: No CMD: No hypertension, diabetes, heart disease, or stroke at baseline. Single cardiometabolic risk factor (CM RF): At baseline, diagnosed with either hypertension or diabetes only, with no history of cardiovascular diseases (CVD). Dual cardiometabolic risk factors (CM RFs): At baseline, diagnosed with both hypertension and diabetes but with no history of CVD. CVD: At baseline, participants were diagnosed with heart disease or stroke (regardless of coexisting hypertension or diabetes) (Table 1).

Table 1
Mutually exclusive classification and defining criteria of CMD type

CMD Type	Hypertension	Diabetes	Heart disease	Stroke
No CMD	No	No	No	No
Single CM RF	Yes or No	No or Yes	No	No
Dual CM RFs	Yes	Yes	No	No
CVD	Any	Any	Yes or No	No or Yes

Note: CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease. "Yes" indicates the presence of a self-reported physician diagnosis at baseline; "No" indicates the absence of the corresponding diagnosis; and "Any" indicates that the condition may or may not be present (regardless of its co-occurrence).

Socioeconomic status

The majority of participants in this study were middle-aged and older adults, most of whom were retired and lacked a stable wage income. Therefore, we used both educational attainment and total household wealth as composite indicators to assess SES, consistent with our previous studies. The total SES score was calculated as the sum of the scores for educational attainment and total household wealth (total possible score: 0–5)[8, 31, 32]. Scores for educational attainment were based on each cohort's classification standards, with the highest level of education reported by each participant standardized into three categories: primary school or below (0 points), secondary school (1 point), and university or above (2 points). Total household wealth was defined as the sum of all physical and financial assets owned by the participant's household (including real estate, business assets, vehicles, and savings account balances) without deducting any debts or loans. To standardize data across cohorts, each study categorized total household wealth within its cohort using quartiles and assigned scores from 0 to 3 accordingly (0 for the lowest quartile and 3 for the highest quartile).Finally, based on the total score, participants' overall SES levels were divided into four mutually exclusive tiers: low (0 points), lower-middle (1–2 points), upper-middle (3–4 points), and high (5 points). In addition, in the sensitivity analysis, we substituted total household wealth with total household income, grouped by quartiles in the same way, and reconstructed an income-based SES indicator to further verify the robustness of the main results. For more details, see Supplementary Table 1.

Psychological-cognitive comorbidity

The primary outcome variable of this study was the incidence of PCC. The presence of psychological and cognitive conditions was determined using study-specific symptom assessments and self-reported diagnoses by the participants. Psychological status assessment tools included the 8-item version of the Center for Epidemiologic Studies Depression Scale (CESD-8) used in the HRS and the ELSA, and the 10-item version (CESD-10) used in the CHARLS[8, 33–35]. In all three studies, participants were asked whether they had ever been diagnosed with affective, emotional, neurotic, or psychiatric disorders[8, 33–35]. Detailed descriptions of the methods used to determine the psychological status in each study are provided in Supplementary Table 1. In each study, cognitive performance was assessed across the following domains: episodic memory (immediate and delayed word recall), executive function (Serial Sevens Test), orientation (time, place, and person recall test), and semantic fluency (animal naming test). Within the baseline cohorts, the mean scores for each cognitive domain were calculated separately for eight age groups (Group 1:45–49 years; Group 2:50–54 years; Group 3:55–59 years; Group 4:60–64 years; Group 5:65–69 years; Group 6:70–74 years; Group 7:75–79 years; Group 8: ≥80 years)[15]. Cognitive impairment was defined as a score 1.5 standard deviations below the age-specific mean in at least one cognitive domain. The HRS, ELSA, and CHARLS databases included self-reported diagnoses of cognitive impairment by participants (e.g., memory-related problems, dementia, and Alzheimer's disease)[36]. Detailed descriptions of the methods used to determine cognitive impairment in each study are provided in Supplementary Table 1.

Covariates

Based on the prior literature and potential biopsychosocial mechanisms, this study included a range of potential confounders that may simultaneously affect both CMD status and the risk of incident PCC. The selection of covariates strictly followed the directed acyclic graph (DAG) theoretical framework, prioritizing the identification and inclusion of common causes (upstream variables) of both exposure and outcome, while rigorously avoiding over-adjustment for mediators that may lie on the causal pathway[37–39]. The covariates ultimately adjusted for in the main model included age, gender, marital status, smoking status, drinking status, and body mass index (BMI)[39] (Fig. 2). The study also incorporated country (cohort source) as a key covariate in the model to effectively control for heterogeneity in the macro-level sociocultural, healthcare system, and institutional backgrounds inherent to the CHARLS, ELSA, and HRS cohorts[7, 39] (Fig. 2).

Statistical analysis

Baseline characteristics were grouped and described according to the presence or absence of PCC during the follow-up period. Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range [IQR], depending on their distribution. Categorical variables are expressed as frequencies and percentages (%). Group differences in continuous variables were compared using analysis of variance (ANOVA) or the Kruskal–Wallis test, and comparisons of categorical variables were performed using the chi-square test.

This study employed the Cox proportional hazards model to assess longitudinal associations between baseline CMD status, SES, and incident PCC. Follow-up time was defined as the period from the baseline survey to the first occurrence of PCC, loss to follow-up, or last follow-up. If psychological disorders and cognitive impairments manifested during distinct follow-up waves, the onset of PCC was determined by the time of the initial diagnosis of the second disorder. If both conditions were first identified within the same wave, the time point of that wave was utilized. All Cox models reported hazard ratios (HR) and 95% confidence intervals (CI).

For the burden of CMD (number of diseases) and CMD type (combinations of diseases), this study identified potential confounders based on a DAG and constructed a multivariable Cox proportional hazards model accordingly (using the “no CMD” group as reference). The model was directly adjusted for covariates identified by the DAG, including SES, age, gender, cohort source, marital status, smoking status, drinking status, and BMI. After model fitting, the Schoenfeld residual test and residual plots were used to assess the proportional hazards (PH) assumption. If the core exposure variables met the PH assumption but some non-core covariates violated it, the corresponding covariates were included as stratification variables to construct stratified Cox models, allowing different strata to have independent baseline hazard functions (Supplementary Tables 2 and 3). Before the data were pooled, multiple

imputations for missing variables were performed in each database dataset using the mice package. The proportions of missing variables for each variable are presented in Supplementary Table 4.

SES was routinely included in the main effects model. In this study, SES was constructed based on participants' educational attainment and total household assets and categorized into four groups: low, lower-middle, upper-middle, and high (the high SES group served as the reference). To further investigate whether SES demonstrates an effect modification on the association between CMD and the risk of PCC, this study incorporated multiplicative interaction terms between the main exposure variable (CMD burden or type) and SES into the multivariable stratified Cox model constructed based on the DAG. The interaction model strictly maintained the same covariate adjustment strategy and baseline risk structure as the main effects model to ensure the reliability of the interaction effect estimates.

To verify the robustness of the study results, the following three sensitivity analyses were conducted: (1) the main analysis was repeated separately in the three independent cohorts (CHARLS, ELSA, and HRS) to assess the reproducibility of the results across regions; (2) participants who experienced outcome events within the first two years of follow-up were excluded, and the analysis was repeated to minimize potential reverse causation bias; and (3) SES indicators were reconstructed using education level and total household income to examine the impact of changes in exposure definition on the results.

To further delineate the dynamic trajectory by which CMD combinations evolve into PCC, we constructed multi-state transition models. Based on the assessment results of each survey wave, participants were classified into four mutually exclusive states: State 0 (neither psychological nor cognitive disorders), State 1 (psychological disorder only), State 2 (cognitive disorder only), and State 3 (PCC). The model allows respondents to transition from state 0 to state 1, state 2, or state 3, and also permits transitions from state 1 and state 2 to state 3, thus effectively distinguishing among the "psychological disorder first pathway," the "cognitive disorder first pathway," and the "direct comorbidity pathway." Transition-specific Cox models were used to assess the impact of CMD type on the risk of different state transitions, with each transition pathway assigned an independent baseline hazard. The time scale was defined as the duration from the baseline to the first observation of the respective state transitions.

All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant. All data analyses were performed using R software (version 5.4).

Results

Basic Characteristics of Participants

This study included 14, 093 eligible participants (Fig. 1). Of these, 2,617 developed PCC during follow-up, whereas 11,476 did not develop new-onset PCC (Table 2). Compared with the non-PCC group, the PCC group had a higher proportion of women (64.9% vs. 54.1%), a higher proportion with an education level of primary school or below (59.8% vs. 29.5%), and a higher proportion with low SES (17.7% vs. 7.9%) (all $P < 0.001$). In addition, the PCC group had a lower baseline median age, median BMI, and lower

proportions of smoking and drinking than the non-PCC group (all P < 0.001). There was no statistically significant difference in the marital status between the two groups (P = 0.495) (Table 2).

There were no statistically significant differences between the two groups in terms of overall baseline hypertension (P = 0.202) or diabetes prevalence (P = 0.396). However, the baseline prevalence of heart disease (12.2% vs. 9.8%, P < 0.001) and stroke (2.9% vs. 2.0%, P = 0.004) was higher in the PCC group than in the non-PCC group. Among the CMD-related variables, the proportion of the PCC group classified as having CVD (14.2% vs. 11.4%) and the proportion with ≥ 2 comorbid CMD were higher than those in the non-PCC group (both P < 0.01). In addition, the prevalence of pulmonary disease was higher in the PCC group than in the non-PCC group, while the prevalence of cancer was lower, and the proportion of participants from the CHARLS cohort was the highest (65.5%) (all P < 0.001). The PCC group was mainly derived from the CHARLS cohort (65.5%), whereas the non-PCC group had a higher proportion from the HRS cohort (46.5%), with significant differences in the distribution between cohorts (P < 0.001) (Table 2).

Table 2
Basic characteristics.

Variables	Overall (n = 14,093)	Non- PCC (11476)	PCC (2617)	P
Age, median [IQR]	59.00 [54.00, 66.00]	59.00 [54.00, 66.00]	58.00 [53.00, 64.00]	< 0.001
BMI, median [IQR]	25.78 [22.83, 29.10]	25.90 [23.10, 29.30]	24.51 [21.76, 28.08]	< 0.001
Gender, n (%)				< 0.001
man	6188 (43.9)	5270 (45.9)	918 (35.1)	
woman	7905 (56.1)	6206 (54.1)	1699 (64.9)	
Marital, n (%)				0.495
Married	11986 (85.0)	9772 (85.2)	2214 (84.6)	
Others	2107 (15.0)	1704 (14.8)	403 (15.4)	
Drinking status, n (%)				< 0.001
Drinker	8259 (58.6)	7090 (61.8)	1169 (44.7)	
Non-drinker	5834 (41.4)	4386 (38.2)	1448 (55.3)	
Smoking status, n (%)				< 0.001
Non-smoker	7093 (50.3)	5635 (49.1)	1458 (55.7)	
Smoker	7000 (49.7)	5841 (50.9)	1159 (44.3)	
Education, n (%)				
Primary education	4950 (35.1)	3386 (29.5)	1564 (59.8)	< 0.001
Upper secondary education	6740 (47.8)	5824 (50.7)	916 (35.0)	
Tertiary education	2403 (17.1)	2266 (19.7)	137 (5.2)	
Heart disease, n (%)				< 0.001
No	12648 (89.7)	10351 (90.2)	2297 (87.8)	
Yes	1445 (10.3)	1125 (9.8)	320 (12.2)	
Stroke, n (%)				0.004

Note. PCC, psychological-cognitive comorbidity; IQR, interquartile range; BMI, body mass index; CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease; SES, socioeconomic status; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study.

Variables	Overall (n = 14,093)	Non- PCC (11476)	PCC (2617)	P
No	13794 (97.9)	11252 (98.0)	2542 (97.1)	
Yes	299 (2.1)	224 (2.0)	75 (2.9)	
Hypertension, n (%)				0.202
No	9439 (67.0)	7658 (66.7)	1781 (68.1)	
Yes	4654 (33.0)	3818 (33.3)	836 (31.9)	
Diabetes, n (%)				0.396
No	13026 (92.4)	10618 (92.5)	2408 (92.0)	
Yes	1067 (7.6)	858 (7.5)	209 (8.0)	
CMD type, n (%)				< 0.001
No CMD	8309 (59.0)	6763 (58.9)	1546 (59.1)	
Single CM RF	3575 (25.4)	2971 (25.9)	604 (23.1)	
Dual CM RFs	533 (3.8)	437 (3.8)	96 (3.7)	
CVD	1676 (11.9)	1305 (11.4)	371 (14.2)	
Cancer, n (%)				< 0.001
No	13442 (95.4)	10902 (95.0)	2540 (97.1)	
Yes	651 (4.6)	574 (5.0)	77 (2.9)	
Lung disease, n (%)				< 0.001
No	13375 (94.9)	10979 (95.7)	2396 (91.6)	
Yes	718 (5.1)	497 (4.3)	221 (8.4)	
SES, n (%)				< 0.001
High	1279 (9.1)	1205 (10.5)	74 (2.8)	
Upper-middle	5959 (42.3)	5212 (45.4)	747 (28.5)	
Lower-middle	5484 (38.9)	4151 (36.2)	1333 (50.9)	
Low	1371 (9.7)	908 (7.9)	463 (17.7)	
CMD burden, n (%)				0.003

Note. PCC, psychological-cognitive comorbidity; IQR, interquartile range; BMI, body mass index; CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease; SES, socioeconomic status; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study.

Variables	Overall (n = 14,093)	Non- PCC (11476)	PCC (2617)	P
0	8309 (59.0)	6763 (58.9)	1546 (59.1)	
1	4308 (30.6)	3551 (30.9)	757 (28.9)	
2	1283 (9.1)	1020 (8.9)	263 (10.0)	
≥ 3	193 (1.4)	142 (1.2)	51 (1.9)	
Source, n (%)				< 0.001
CHARLS	5431 (38.5)	3718 (32.4)	1713 (65.5)	
ELSA	2786 (19.8)	2425 (21.1)	361 (13.8)	
HRS	5876 (41.7)	5333 (46.5)	543 (20.7)	

Note. PCC, psychological-cognitive comorbidity; IQR, interquartile range; BMI, body mass index; CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease; SES, socioeconomic status; CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; HRS, Health and Retirement Study.

Association and Interaction of CMD Burden, SES, and the Risk of PCC

Multivariable Cox regression model analysis indicated that both CMD burden and SES were significant independent predictors of outcome risk. In the main effects model without the inclusion of interaction terms, compared with participants with no CMD burden (score of 0), individuals with CMD burden scores of 1, 2, and ≥ 3 had a significantly increased risk of outcome events, with HRs and 95% CIs of 1.17 (1.07–1.28, P < 0.001), 1.45 (1.27–1.66, P < 0.001), and 1.55 (1.17–2.06, P = 0.002), respectively. SES showed a pronounced gradient effect on outcome risk: using the high SES group as the reference, the risk of incidence increased progressively among the upper-middle, lower-middle, and low SES groups, with HRs of 1.45 (1.14–1.85, P = 0.003), 2.56 (2.01–3.25, P < 0.001), and 3.33 (2.58–4.30, P < 0.001), respectively (Table 3).

To further evaluate the joint effect of the two factors, this study introduced multiplicative interaction terms into the model. The analysis showed that no significant multiplicative interaction was observed between CMD burden and SES (all specific interaction terms, P > 0.05; overall interaction, P = 0.986) (Table 3).

In the model that included interaction terms, the association between lower SES and increased risk of the outcome remained robust, showing a clear dose–response pattern across SES categories. No statistically significant associations were observed between CMD burden categories. In addition, there was no evidence of an interaction between SES and CMD burden. Overall, the association between SES and outcome risk was consistent across different CMD burden levels (Table 4).

Table 3
Association analysis of CMD burden and SES with the risk of developing PCC and assessment of overall interaction effect.

Variable	Category	HR (95% CI)	P value
CMD burden	0	Reference	-
	1	1.17 (1.07–1.28)	< 0.001
	2	1.45 (1.27–1.66)	< 0.001
	≥ 3	1.55 (1.17–2.06)	0.002
SES	High	Reference	-
	Upper-middle	1.45 (1.14–1.85)	0.003
	Lower-middle	2.56 (2.01–3.25)	< 0.001
	Low	3.33 (2.58–4.30)	< 0.001
Overall interaction	CMD × SES	-	0.986

Note. To satisfy the proportional hazards assumption and stringently control for confounding bias, the model was stratified by cohort source, gender, marital status, drinking status, and age group, allowing each combined stratum to have its own baseline hazard function. The overall interaction between CMD burden and SES was evaluated using a likelihood ratio test (P = 0.986). CMD, cardiometabolic disease; SES, socioeconomic status; HR, hazard ratio; CI, confidence interval.

Table 4
Multivariable Cox regression model including the interaction term between CMD burden and SES on the risk of PCC.

Variable	Category	HR (95% CI)	P value
CMD burden	0	1.00 (Ref.)	—
	1	1.06 (0.63–1.77)	0.830
	2	1.61 (0.75–3.46)	0.220
	≥ 3	1.54 (0.37–6.41)	0.555
SES	High	1.00 (Ref.)	—
	Upper-middle	1.41 (1.02–1.94)	0.039
	Lower-middle	2.48 (1.80–3.41)	< 0.001
	Low	3.40 (2.43–4.75)	< 0.001
Interaction terms	CMD burden 1 × Upper-middle SES	1.14 (0.67–1.95)	0.633
	CMD burden 2 × Upper-middle SES	0.91 (0.41–2.03)	0.813
	CMD burden ≥ 3 × Upper-middle SES	0.99 (0.21–4.68)	0.985
	CMD burden 1 × Lower-middle SES	1.14 (0.67–1.93)	0.626
	CMD burden 2 × Lower-middle SES	0.90 (0.41–1.98)	0.801
	CMD burden ≥ 3 × Lower-middle SES	1.01 (0.23–4.41)	0.993
	CMD burden 1 × Low SES	0.97 (0.56–1.68)	0.905
	CMD burden 2 × Low SES	0.86 (0.37–1.96)	0.711
	CMD burden ≥ 3 × Low SES	1.04 (0.22–4.85)	0.965

Note: To satisfy the proportional hazards assumption and stringently control for confounding bias, the model was stratified by cohort source, gender, marital status, drinking status, and age group, allowing each combined stratum to have its own baseline hazard function. The reference group was participants with cardiometabolic burden = 0 and high socioeconomic status. CMD, cardiometabolic disease; HR, hazard ratio; CI, confidence interval; SES, socioeconomic status.

Association and Interaction Between CMD type, SES, and the Risk of PCC

Multivariate Cox regression analysis indicated that both CMD type and SES were significant independent predictors of PCC risk. In the model without interaction terms, compared to participants without CMD, individuals with a single CM RF, dual CM RFs, or CVD had significantly elevated risks of PCC, with HRs and 95% Cis of 1.17 (1.06–1.29, P = 0.002), 1.55 (1.25–1.92, P < 0.001), and 1.43 (1.27–1.61, P < 0.001), respectively. Additionally, lower SES was significantly associated with an increased risk of PCC and

exhibited a clear worsening gradient; using the high SES group as the reference, the risk increased sequentially in the upper-middle, lower-middle, and low SES groups, with HRs of 1.46 (1.14–1.86, P = 0.002), 2.56 (2.01–3.26, P < 0.001), and 3.29 (2.55–4.26, P < 0.001), respectively (Table 5).

To further assess the joint effect of the two factors, this study introduced a multiplicative interaction term between CMD type and SES into the model. The analysis showed no significant multiplicative interaction between CMD type and SES (all specific interaction terms P > 0.05; overall interaction P = 0.790) (Table 5).

In models including interaction terms, the association between lower SES and increased risk of PCC remained stable, showing a graded pattern across SES categories among individuals without CMD (HRs for medium-high, medium-low, and low SES: 1.39, 2.44, and 3.31, respectively). In the high SES stratum, dual CM RFs were associated with a higher risk of PCC (HR, 2.93; 95% CI, 1.04–8.26; P = 0.042), whereas single CM RFs were not statistically significant. No statistically significant interactions were observed between SES and CMD type. Lower SES was associated with a higher PCC risk across all CMD types, with effect estimates remaining directionally consistent (Table 6).

Table 5
Association analysis of CMD type and SES with the risk of developing PCC and assessment of the overall interaction effect.

Variable	Category	HR (95% CI)	P value
CMD type	No CMD	Reference	-
	Single CM RF	1.17 (1.06–1.29)	0.002
	Dual CM RFs	1.55 (1.25–1.92)	< 0.001
	CVD	1.43(1.27–1.61)	< 0.001
SES	High	1.23 (1.11–1.35)	< 0.001
	Upper-middle	1.46 (1.14–1.86)	0.002
	Lower-middle	2.56 (2.01–3.26)	< 0.001
	Low	3.29 (2.55–4.26)	< 0.001
Overall interaction	CMD type × SES	-	0.790

Note. To satisfy the proportional hazards assumption and stringently control for confounding bias, the model was stratified by cohort source, gender, marital status, drinking status, and BMI group, allowing each combined stratum to have its own baseline hazard function. The overall interaction (P = 0.790) was evaluated using a likelihood ratio test, which indicated no statistically significant overall multiplicative interaction between CMD type and SES. CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease; SES, socioeconomic status; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Table 6
Multivariable Cox regression model including the interaction term between CMD type and SES on the risk of PCC.

Variable	Category	HR (95% CI)	P value
CMD type	No CMD	Reference	-
	Single CM RF	1.17 (0.69–1.99)	0.559
	Dual CM RFs	2.93 (1.04–8.26)	0.042
	CVD	0.91 (0.42–1.97)	0.807
SES	High	Reference	-
	Upper-middle	1.39 (1.01–1.93)	0.045
	Lower-middle	2.44 (1.77–3.37)	< 0.001
	Low	3.31 (2.36–4.65)	< 0.001
Interaction terms	Single CM RF × Upper-middle SES	1.05 (0.60–1.83)	0.870
	Dual CM RFs × Upper-middle SES	0.55 (0.18–1.69)	0.299
	CVD × Upper-middle SES	1.56 (0.70–3.48)	0.278
	Single CM RF × Lower-middle SES	1.03 (0.60–1.77)	0.922
	Dual CM RFs × Lower-middle SES	0.51 (0.17–1.49)	0.220
	CVD × Lower-middle SES	1.63 (0.74–3.59)	0.222
	Single CM RF × Low SES	0.86 (0.48–1.53)	0.603
	Dual CM RFs × Low SES	0.50 (0.15–1.61)	0.244
	CVD × Low SES	1.51 (0.67–3.41)	0.321

Note. To satisfy the proportional hazards assumption and stringently control for confounding bias, the model was stratified by cohort source, gender, marital status, drinking status, and BMI group, allowing each combined stratum to have its own baseline hazard function. The reference group comprised participants with no CMD and high SES. CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease; SES, socioeconomic status; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

Sensitivity analysis

In repeated analyses across the CHARLS, ELSA, and HRS cohorts, the direction and magnitude of the associations were largely consistent with the main analysis (Supplementary Tables 5–16). After excluding participants who experienced outcome events within two years of follow-up, the results remained robust (Supplementary Tables 17–20). When SES was reconstructed using education level and

total household income, the main findings were not substantially altered (Supplementary Tables 21–24). These results suggest that the conclusions of this study are robust across different cohorts, follow-up time windows, and SES construction methods.

Multi-state trajectories of CMD type and PCC progression

A total of 11,876 participants without psychological disorders or cognitive impairment at baseline were included in the multi-state transition model of this study. During follow-up, 1,923 transitions from “no psychological disorder and no cognitive impairment” to “psychological disorder” (16.2%) and 6,171 transitions to “cognitive impairment” (52.0%) were observed in the adjacent follow-up intervals. Additionally, 755 direct transitions from “no psychological disorder and no cognitive impairment” to “PCC” were recorded (6.4%). Furthermore, among participants already at risk for either a single psychological disorder or a single cognitive impairment, 1,272 transitions from “psychological disorder” to “PCC” (56.9%) and 982 transitions from “cognitive impairment” to “PCC” (29.2%) were observed (Fig. 3A).

The multi-state Cox proportional hazards model showed that different baseline CMD type had a significant impact on the risk of transition at each stage (Fig. 3A). Compared with the no CMD group, at the initial onset stage, having dual CM RFs at baseline significantly increased the risk of progression from a healthy state to psychological disorders (HR = 1.28, 95% CI: 1.00–1.64) and cognitive impairment (HR = 1.22, 95% CI: 1.06–1.40). CVD significantly increased the risk of incident psychological disorders (HR = 1.32, 95% CI: 1.15–1.52) and was the only factor significantly associated with an increased risk of developing PCC directly (HR = 1.31, 95% CI: 1.04–1.65) (Fig. 3B).

During the disease progression stage, in patients with pre-existing psychological disorders, all abnormal CMD type significantly increased the risk of progression to PCC; the HRs (95% CI) for single CM RF, dual CM RFs, and CVD were 1.18 (1.02–1.36), 1.31 (1.01–1.71), and 1.22 (1.05–1.43), respectively. In contrast, among patients with pre-existing cognitive impairment, only the presence of CVD significantly increased the risk of further progression to PCC (HR = 1.25, 95% CI: 1.03–1.53) (Fig. 3B).

Discussion

This study systematically evaluated the relationship between CMD status, SES, and incident PCC in middle-aged and older adults based on three nationally representative multi-state aging cohorts: the HRS, ELSA, and CHARLS. The results showed that a heavier CMD burden was associated with a higher risk of PCC, exhibiting a dose-response trend. When categorized by CMD type, dual risk factors and CVD type presented more pronounced individual risks. A clear social gradient was observed between SES and PCC, and no significant multiplicative interaction was observed between CMD and SES, suggesting that the two may influence psychological and cognitive health through relatively independent pathways. The multi-state transition model further indicated that CMD not only affects the ultimate occurrence of comorbidity but also participates in the dynamic progression from a healthy state to a single

psychological disorder, a single cognitive disorder, and PCC. This provides new longitudinal evidence for understanding the dynamic evolution of PCC.

A large body of research has shown that hypertension, diabetes, heart disease, and stroke are associated with depressive symptoms, cognitive decline, and an increased risk of dementia[40–44]. This study found that comorbidity with one CMD already elevates the risk of PCC, and when the number of CMD increases to two or more, the risk rises further, suggesting that cardiometabolic abnormalities may have a cumulative effect on brain health. The potential underlying mechanisms include chronic low-grade inflammation, insulin resistance, endothelial dysfunction, atherosclerosis, cerebral small vessel disease, white matter lesions, reduced cerebral perfusion, and dysregulation of the hypothalamic–pituitary–adrenal axis[45–50]. Hypertension can affect executive functioning and information processing speed through chronic vascular wall injury and cerebral arteriolosclerosis[40, 51]. Diabetes may affect hippocampal and frontal lobe function via hyperglycaemic toxicity, abnormal insulin signalling, oxidative stress, and microvascular damage[41, 48]. Heart disease and stroke not only indicate that systemic vascular injury has reached a more advanced stage, but are also often accompanied by cerebral hypoperfusion, silent cerebral infarction, and neuroinflammatory responses[43]. These biological processes may also induce or exacerbate depressive symptoms through fatigue, functional limitations, sleep disturbances, reduced social participation, and increased disease burden, ultimately resulting in the overlay of psychological and cognitive disorders within an individual[43, 52, 53].

Compared with traditional disease-count models, this study further classified CMD type according to pathological stages and disease combination patterns. The results showed that both dual CM RFs and CVD were associated with a higher PCC risk, suggesting that pathological stages reflected in disease combination patterns may provide additional early clinical warning information. Although hypertension and diabetes are often regarded as early, modifiable risk factors, their coexistence may indicate that a mutually reinforcing pathological network of metabolic dysfunction and vascular injury has already formed, substantially enhancing the long-term impact on cerebral small vessels, neuroinflammation, and energy metabolism. Consequently, the dual CM RFs group exhibited a higher risk of PCC[52, 54, 55]. Individuals with CVD have already developed end-organ damage, such as heart disease or stroke, and their increased risk may reflect brain structural damage, reduced mobility, and restricted social functioning following serious vascular events[1, 43]. In other words, the dual CM RFs may represent the stage where "no major vascular events have occurred but risk has highly accumulated," whereas the cardio-cerebrovascular disease type represents the stage where "vascular injury has already become clinically overt."[1, 18]. Both populations require focused identification for the prevention and control of PCC. However, their intervention priorities are not entirely the same: the former emphasizes early comprehensive management of metabolism and blood pressure/blood glucose, whereas the latter requires simultaneous psychological screening, cognitive monitoring, and functional rehabilitation built upon secondary prevention[1, 56].

The findings of this study regarding SES are also of significant importance. The results indicate a strong and consistent gradient association between lower SES and the risk of PCC, with individuals of low SES demonstrating a markedly higher risk than those with high SES. This relationship was consistent across different CMD burdens and types. Previous research suggests that individuals with higher educational attainment may possess a better cognitive reserve, enabling them to withstand the clinical manifestations of neuropathological damage. Those with greater wealth or income typically enjoy better access to healthcare, more comprehensive health information, more stable living environments, higher-quality diets, and more opportunities for social engagement[57, 58]. In contrast, individuals with low SES may be exposed to poor nutrition, education, and living environments early in life, and as they enter middle and older age, they are more susceptible to insufficient management of chronic diseases, limited use of medical resources, persistent psychological stress, and inadequate social support[59, 60]. These factors not only increase the risk of CMD incidence and poor disease control but also directly affect psychological and cognitive functions through mechanisms such as chronic stress, loneliness, sleep problems, elevated inflammation levels, and restricted health behaviour[59, 61]. Therefore, the independent gradient effect of SES observed in this study suggests that PCC is not merely a biomedical outcome determined solely by disease burden but rather the result of the long-term interplay of biological risk and social structure.

A noteworthy finding of this study that warrants further exploration is that no significant multiplicative interaction was observed between CMD and SES. On the surface, this result does not fully align with the conventional theoretical expectation that "high SES buffers the adverse effects of CMD through abundant resources," yet from the perspective of disease progression and brain health impairment, it carries profound biological and public health implications[62]. We propose the following explanations for this "independent effect rather than interactive effect" result. First, organic brain damage caused by CMD is biologically irreversible[62, 63]. When CMD progresses to multimorbidity or reaches the stage of target organ damage (such as heart disease or stroke), its impact on the central nervous system surpasses mild functional changes, instead exerting profound organic damage to brain structure through pathways such as cerebral small vessel disease, chronic hypoperfusion, blood-brain barrier disruption, and neuroinflammation[62–64]. At this stage, cognitive reserve and high-quality medical care associated with high SES remain beneficial, but their protective effects are insufficient to fully offset the strong biological impact of CMD, resulting in damaging effects crossing social strata[62].Second, although individuals with high SES have better access to medical care and early intervention opportunities, their nervous systems can still sustain cumulative damage when chronically exposed to metabolic disorders, such as hypertension and diabetes. This is particularly true for those with dual CM RFs and CVD profiles, in whom the high level of systemic pathological burden represented by CMD may already exceed the threshold that socioeconomic resources can buffer[4, 65]. Third, conventional SES measurement scales have limitations[66]. The education level and household assets used in this study reflect long-term material resources but fail to capture dynamic social and behaviour factors more directly related to brain health protection (such as cognitive stimulation after retirement, quality of social engagement, ability to

self-manage chronic diseases, and dietary and exercise patterns)[5, 66, 67]. If these micro-level protective factors are not included, the potential buffering effect of SES may be underestimated[5, 66, 67].Finally, a non-significant multiplicative interaction does not statistically imply that the joint effect of the two is unimportant; CMD and SES may influence PCC through parallel and independent pathways (the former tending toward biomedical impairment and the latter toward structural resource deprivation)[68, 69]. Even without deviation from the multiplicative scale, individuals face the highest absolute disease burden when low SES coexists with CMD[70]. This finding has important implications for public health and clinical practice, emphasizing that CMD management and social support should be considered two complementary preventive approaches rather than simply viewing SES as an effect modifier of CMD[71]. Low SES also has a significant independent detrimental effect on populations without CMD; thus, public health screening should not be limited to patients with CMD but should be extended to socially and economically disadvantaged groups[72, 73]. For clinical practice, this means that when assessing the risk of PCC in middle-aged and older adults, physicians should pay attention not only to traditional medical indicators such as blood pressure, blood glucose, and history of CVD, but also incorporate social factors such as educational attainment, household wealth, healthcare accessibility, and social support into a comprehensive risk assessment[74].

The multi-state transition model further elucidates the stage-specific impact of CMD on PCC. The traditional Cox model can only determine whether comorbidity ultimately occurs, whereas this study shows that participants without psychological or cognitive disorders at baseline may experience multiple transition pathways between single psychological disorders, single cognitive disorders, and PCC. The influence of different CMD types on these pathways is not uniform. Dual CM RFs are more likely to facilitate the early onset of individual psychological or cognitive impairments. CVD is not only linked to the occurrence of psychological disorders but also serves as a significant risk factor for direct entry into the PCC and for the progression to comorbidity following cognitive disorders. This suggests that early metabolic and vascular risk factors may mainly contribute to the initiation of single disorders, whereas severe cardiovascular events may accelerate the development of combined psychological and cognitive impairments.

This trajectory finding further suggests that psychological disorders and cognitive impairment do not occur in isolation but may mutually reinforce each other under the influence of CMD as a shared upstream factor[1]. Depressive symptoms can increase the risk of cognitive decline through inflammatory responses, elevated cortisol levels, hippocampal atrophy, sleep disturbances, and social withdrawal[5]. Cognitive impairment may also trigger psychological problems due to a decline in daily functioning, loss of independence, and disease-related worries[75]. The focus of CMD management should be stratified according to the individual's current condition[13, 76]. For individuals with pre-existing psychological disorders, early assessment and control of metabolic and vascular risks should be prioritized [76]. For those with existing cognitive impairment, particular attention should be given to heart disease, stroke, and the resulting functional limitations and emotional consequences[13].

This study has several strengths. It initially incorporated three extensive, nationally representative cohorts from China, the United States, and the United Kingdom. These cohorts encompassed diverse social systems, health care systems, and cultural backgrounds, thereby ensuring robust external validity and facilitating cross-national comparability. The study's second focus was on both the burden and type of CMDs. It not only confirmed the cumulative impact of the number of diseases but also highlighted the varied effects of different pathological stages and disease combinations. This approach addresses the limitations of prior research, which overly depended on disease counts. Third, SES was included as one of the core exposures, and its main effect and interaction with CMD were systematically tested, providing a joint explanation of PCC from both biomedical risk and social determinant perspectives. Fourth, the multi-state transition model facilitates the decomposition of the dynamic progression from a healthy state to a single disorder and subsequently to PCC. This approach advances research from merely predicting static outcomes to identifying disease trajectories, thereby providing more precise time windows and target populations for early clinical intervention. Fifth, the study conducted multiple sensitivity analyses, including repeating analyses in different cohorts, excluding participants who experienced the outcome within the first two years of follow-up, and reconstructing the SES indicator using income instead of wealth; overall, the results remained consistent, indicating the good robustness of the main findings.

This study had several limitations. First, CMD status was primarily based on respondents' self-reported physician diagnoses, which may be subject to recall bias and underreporting, particularly among populations with limited healthcare accessibility or low health awareness. Undiagnosed conditions may lead to an underestimation of CMD exposure. Second, despite attempts to standardize the measurement of psychological and cognitive disorders across the three cohorts, variations persist in the versions of depression scales, cognitive assessment items, and diagnostic information employed by each cohort. These differences may lead to measurement heterogeneity. Third, SES was constructed based on education and household wealth, which may be suitable for middle-aged and older adults who are retired or are nearing retirement. However, it still cannot fully capture more complex social factors, such as occupational complexity, community resources, medical insurance, childhood socioeconomic circumstances, and long-term social mobility. Fourth, the study employed baseline CMD type as the primary exposure, which limited the ability to effectively capture new-onset CMD, treatment and control status, disease duration, and changes in severity during follow-up. Consequently, this restriction impeded further analysis of the impact of dynamic cardiometabolic management on the risk of PCC. Fifth, although this study employed a DAG framework to guide covariate selection and adjusted for factors such as age, gender, marital status, smoking status, drinking status, BMI, and country/cohort origin in the main model, as an observational study, it still cannot entirely rule out residual confounding and unmeasured confounding. Physical activity may be associated with both CMD status and the risk of PCC, but it can also be influenced by pre-existing CMD status and therefore may have potential mediating properties. Furthermore, the proportion of missing data for this variable was relatively high across the three cohorts, and including it in the main model may have led to a reduced sample size and selection bias. Therefore, physical activity was not further adjusted for in the main model; although

including BMI can partially control for risks related to weight status, residual confounding associated with physical activity cannot be entirely eliminated. Sixth, the exclusion of individuals who died during follow-up could introduce selection bias, particularly as those with a greater burden of CMD are more likely to die. Consequently, the estimated association between CMD and the risk of PCC in this study may be conservative.

The findings of this study have clear implications for public health and clinical practices. Prevention of PCC should be advanced to chronic disease management and primary healthcare settings, prioritizing CMD patients—especially those with dual CM RFs and CVD —as key targets for integrated psychological and cognitive screening. Simultaneously, individuals with low SES, even if they have not yet developed CMD, should be included within the scope of early prevention and resource support. Future interventions should implement a dual strategy that integrates chronic disease management with social support. This approach should aim to control blood pressure, blood glucose, and the risk of cardiovascular and cerebrovascular events, while also mitigating the long-term effects of socioeconomic disadvantage on psychological and cognitive health in middle-aged and older adults. Measures to achieve these goals include health education, enhanced access to screening, the promotion of social participation, and the provision of psychological support.

Future studies can explore several directions based on this study. First, more refined biomarkers and objective measurement indices should be introduced to validate the dynamic transfer pathways observed in the future. For example, neurofilament light chain, inflammatory factors, glycated haemoglobin, lipid profile, long-term blood pressure variability, and renal function indicators can help explain how CMD influences PCC through axonal injury, chronic inflammation, microvascular damage, and metabolic abnormalities[77, 78]. Second, future research should incorporate neuroimaging data, including white matter hyperintensities, lacunar infarcts, cerebral microbleeds, hippocampal volume, cortical thickness, and cerebral perfusion indices, to further determine whether dual risk factors and CVD correspond to different types of brain structural damage[71, 79]. Third, subsequent studies should include dynamic SES and lifestyle trajectories[71]. For example, changes in social participation after retirement, cognitive activity, feelings of loneliness, diet quality, physical activity patterns, and utilisation of healthcare services, so as to more accurately identify which social resources can truly buffer the adverse effects of CMD on brain health[71]. Fourth, future studies should conduct interventional research to examine whether integrated chronic disease management, psychological interventions, cognitive training, and social support services can delay the progression of a single psychological disorder or cognitive disorder to a comorbid state[80].

Conclusion

This study, based on large longitudinal cohorts from China, the United States, and the United Kingdom, found that increased CMD burden, specific CMD type, and lower SES were independently associated with a heightened risk of developing PCC in middle-aged and older adults. No significant multiplicative

interactions were observed between CMD and SES. The multi-state transition model further revealed that Dual CM RFs and the CVD play differentiated roles at various stages of the development of psychological disorders, cognitive impairment, and PCC. These findings underscore that the prevention and control of PCC require simultaneous attention to cardiovascular–metabolic health, brain health, and psychological health, and that socioeconomic vulnerability should be integrated into risk assessment frameworks. Future longitudinal studies incorporating biomarkers and neuroimaging data will help further elucidate the causal pathways and modifiable points between CMD, SES, and PCC.

Abbreviations

CMD
Cardiometabolic Disease
PCC
Psychological-cognitive comorbidity
SES
Socioeconomic Status
HRS
Health and Retirement Study
ELSA
English Longitudinal Study of Ageing
CHARLS
China Health and Retirement Longitudinal Study
CM RF
Cardiometabolic Risk Factor
CM RFs
Cardiometabolic Risk Factors
CVD
Cardiovascular Disease
BMI
Body Mass Index
DAG
Directed Acyclic Graph
CESD
Center for Epidemiologic Studies Depression Scale
HR
Hazard Ratio
CI
Confidence Interval
IQR
Interquartile Range

SD
Standard Deviation
ANOVA
Analysis of Variance

Declarations

Ethics approval and consent to participate

The English Longitudinal Study of Ageing was approved by the Ethics Review Committee of the London Multi-Centre Research. The Health and Retirement Study was approved by the Ethics Review Committee of the University of Michigan. The China Health and Retirement Longitudinal Study was approved by the Ethics Review Committee of Peking University.

All participants provided written informed consent at the time of original data collection. The original studies were conducted in accordance with the principles of the Declaration of Helsinki.

This study used publicly available de-identified secondary data; therefore, no additional ethical approval or informed consent was required.

Clinical trial registration number: Not applicable.

Human ethics and consent to participate: Not applicable.

Consent for publication

The authors consent to the publication of this paper.

Data availability

The original data for this study are available on their respective websites: The Health and Retirement Study (https://hrs.isr.umich.edu/), the English Longitudinal Study of Ageing (https://www.elsa-project.ac.uk/) and the China Health and Retirement Longitudinal Study (https://charls.pku.edu.cn/en/).

Competing interests

The authors declare no conflicts of interest.

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Author contributions

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Figures

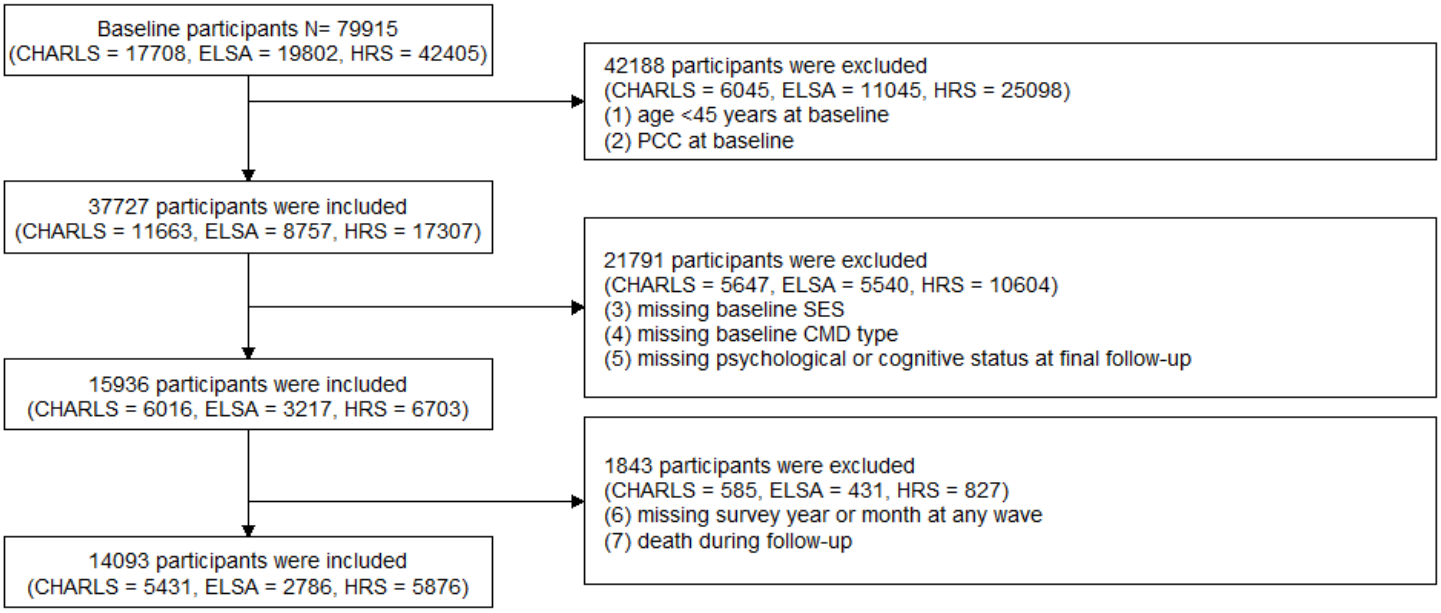


Figure 1

Screening flow chart.

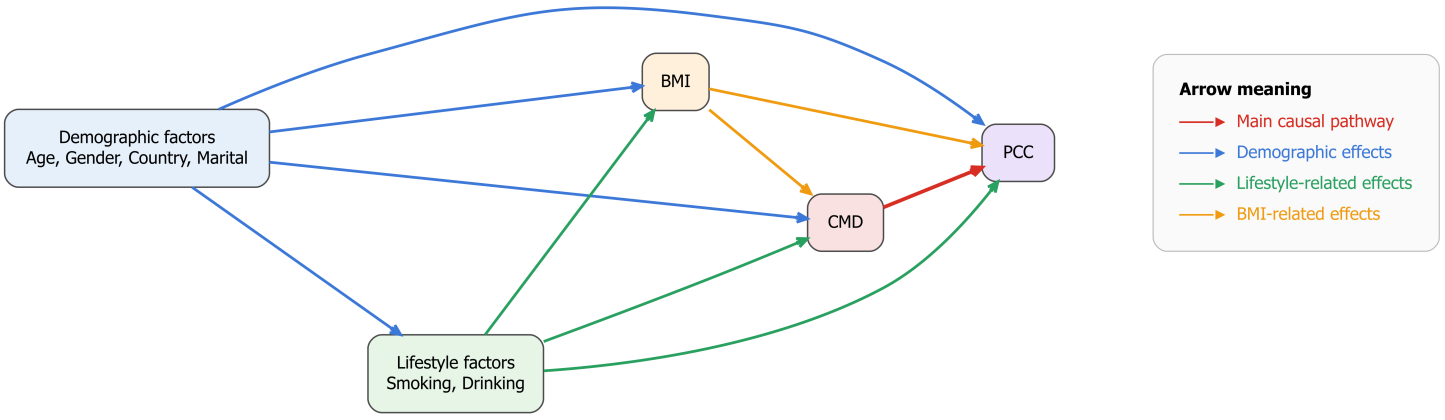


Figure 2

Directed acyclic graph illustrating the causal relationship between CMD and PCC. This figure presents the hypothesized causal structure among the key exposure variables, outcome variables, and potential confounders in the study. This DAG framework was used to guide the selection of covariates in the multivariable analyses to minimize confounding bias. The arrows in the figure represent the directional paths of influence between variables: red arrows (main causal pathway) represent the primary causal path of interest in this study, namely, the effect of CMD on the risk of developing PCC. Blue arrows (demographic effects) indicate the potential influence of demographic factors (age, gender, country, marital status) on lifestyle, BMI, CMD, and the outcome PCC. Green arrows (lifestyle-related effects) indicate the potential impact of lifestyle factors (smoking and alcohol consumption) on BMI, CMD, and the outcome PCC. Orange arrows (BMI-related effects) indicate the potential impact of BMI on CMD and outcome PCC. CMD, Cardiometabolic disease；PCC, Psychological-cognitive comorbidity；BMI, Body mass index; DAG, directed acyclic graph.

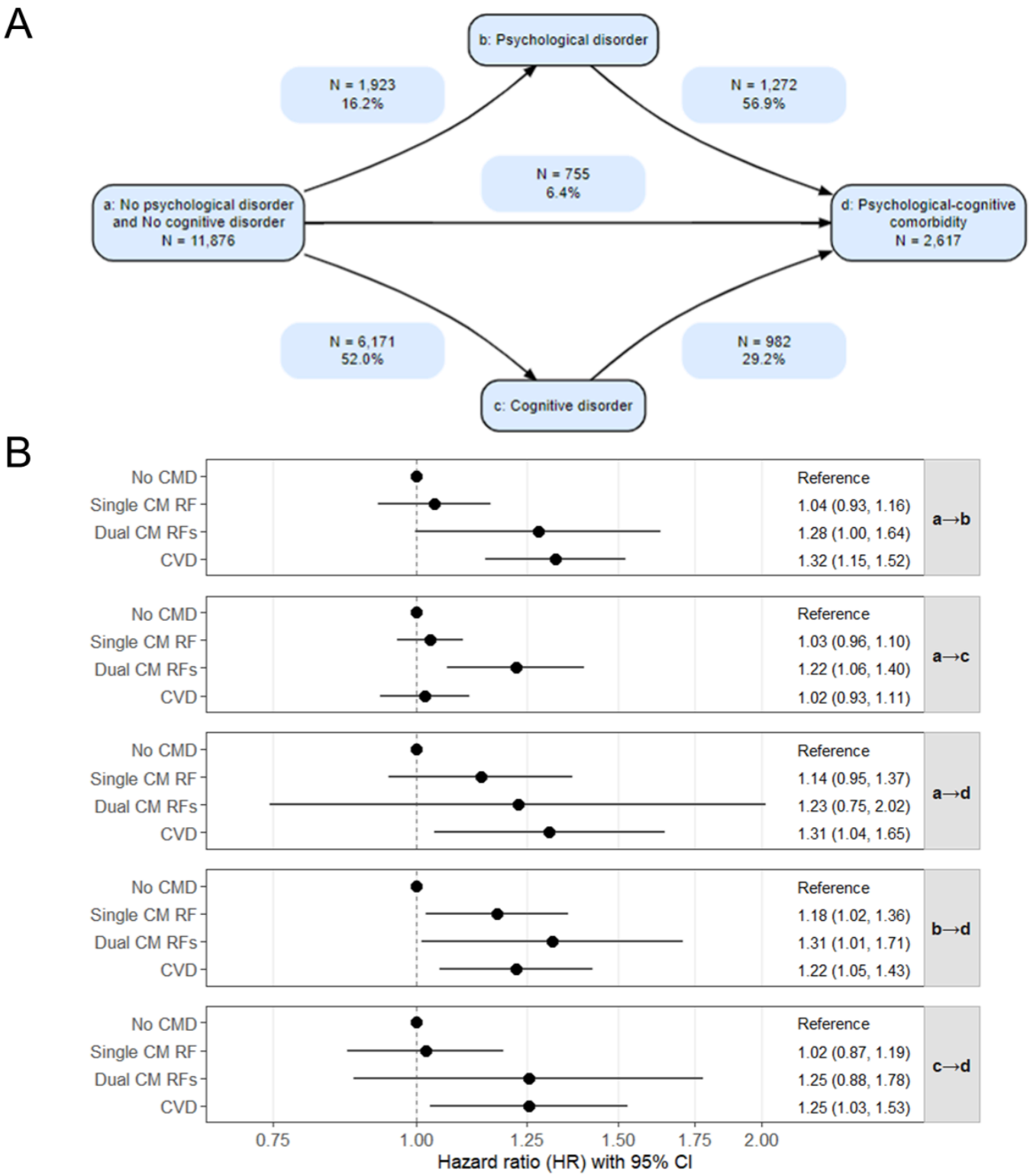


Figure 3

Multi-state transition model and risk associations between CMD type and PCC progression.
A.Schematic diagram of the multi-state transition model structure and event distribution. Boxes represent different health states: a, no psychological disorder and no cognitive impairment; b, psychological disorder; c, cognitive impairment; and d, psychological–cognitive comorbidity. Arrows indicate the direction of disease progression; the numbers next to the arrows represent the number of

state transition events (N) observed during the adjacent follow-up intervals and their incidence (%) within the corresponding risk set. Because these values represent the number of transition events rather than the deduplicated number of unique participants, they cannot be directly summed or compared with the number of new PCC cases during the overall follow-up. **B.** Effects of different CMD type on the risk of each transition pathway. The forest plot shows HR and 95%CI estimated using a multi-state Cox proportional hazards model. The horizontal axis represents the HR, and the vertical dashed line indicates the null value (HR=1.00). The no CMD group served as the reference group. No CMD group, no hypertension, diabetes, heart disease, or stroke at baseline; Single CM RF, hypertension only or diabetes only at baseline, without CVD; Dual CM RFs, both hypertension and diabetes at baseline, without CVD; CVD, heart disease or stroke at baseline (may be accompanied by hypertension and/or diabetes). PCC, psychological–cognitive comorbidity; CMD, cardiometabolic disease; CM RF, cardiometabolic risk factor; CM RFs, cardiometabolic risk factors; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval.

Supplementary Files

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