

The role of geriatric syndromes in moderating the relationship between cardiometabolic multimorbidity and cognitive function in mid-to-late life: a multicohort study

Yating Liu

Peking University

Xiang Li

Peking University

Xin Yang

Peking University

Guangwen Liu

Peking University

Chenlu Hong

New York University

Yujie Huang

Peking University

Boyuan Guan

Peking University

Xueheng Wang

Peking University

Chong Chao

Peking University

Yanan Luo

luoyanan@bjmu.edu.cn

Peking University

Research Article

Keywords: Cardiometabolic diseases, Cardiometabolic multimorbidity, Cognitive function, geriatric syndromes

Posted Date: September 3rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10519030/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Geriatric syndromes (GSs) commonly coexist with cardiometabolic diseases (CMDs) and may contribute to differences in cognitive function among individuals with cardiometabolic multimorbidity (CMM). However, whether specific GSs, their cumulative number, and their multitrajectories modify the association between CMDs and cognitive function remains unclear. We aimed to examine the modifying role of GSs in the association between CMDs and cognitive function.

Methods

This multicohort study pooled harmonised longitudinal data from five prospective ageing cohorts in China, the UK, the USA, Mexico, and South Korea. CMDs included diabetes, heart disease, and stroke. Five GSs were assessed: frailty, depressive symptoms, falls, pain, and urinary incontinence. Fixed-effects linear regression models were used to examine interactions between the number of CMDs and individual GSs or the cumulative number of GSs in relation to global and domain-specific cognitive function. Group-based multi-trajectory modelling was used to identify joint eight-year trajectories of the five GSs and assess effect modification by trajectory group.

Results

Among 68,090 participants, 25.1% had one CMD and 5.7% had CMM at baseline. Frailty modified the associations between three CMDs and global cognitive function (interaction $\beta=-0.68$, 95% CI: -1.25 to -0.11), memory (interaction $\beta=-0.53$, 95% CI: -0.96 to -0.09), and orientation (interaction $\beta=-0.82$, 95% CI: -1.54 to -0.11). Depressive symptoms modified the association between two CMDs and orientation (interaction $\beta=-0.11$, -0.20 to -0.02), whereas falls, pain, and urinary incontinence showed no significant interactions. Three or more GSs modified the associations between three CMDs and global cognitive function (interaction $\beta=-0.34$, 95% CI: -0.62 to -0.07) and orientation (interaction $\beta=-0.50$, 95% CI: -0.88 to -0.12). Among 27,066 participants included in the trajectory analysis, five groups were identified: low-stable, pre-frailty progression, pain-dominant, multisymptom progression, and urinary incontinence progression. Compared with the low-stable group, the association between three CMDs and global cognitive function differed across all four progressive trajectory groups. Trajectory-specific associations were significant only in the multisymptom progression group, in which two CMDs ($\beta=-0.13$, 95% CI: -0.21 to -0.04) and three CMDs ($\beta=-0.38$, 95% CI: -0.59 to -0.17) were associated with lower global cognitive function.

Conclusions

Frailty, depressive symptoms, the accumulation of three or more GSs, and progressive GS trajectories modified the association between multiple CMDs and cognitive function. Assessment of the presence, accumulation, and longitudinal development of GSs may help identify middle-aged and older adults with CMM who have lower cognitive function.

Background

Cognitive decline is a major public health challenge in older adults, which can lead to reduced functional independence and quality of life and often precedes the development of dementia⁽¹⁾. Cardiometabolic multimorbidity (CMM), defined as the coexistence of two or more cardiometabolic diseases (CMDs) within an individual, are well-established risk factors for cognitive impairment⁽²⁾. Nevertheless, some individuals with multiple CMDs maintain relatively stable cognitive function over time, whereas others experience accelerated cognitive decline, which suggests that CMDs alone may not fully explain individual differences in cognitive ageing, and that identifying potentially modifiable factors that may alter the association between CMDs and cognitive function is important⁽³⁾.

Geriatric syndromes (GSs) are multifactorial conditions arising from interacting impairments across multiple physiological and functional systems that increase an individual's susceptibility to common stressors^(4, 5). Common GSs include frailty, depressive symptoms, falls, pain, and urinary incontinence. These syndromes frequently coexist, change over time, and collectively reflect impairments across physical, psychological, and functional domains^(6, 7). Increasing evidence suggests that individual GSs, as well as combined patterns and longitudinal trajectories of multiple co-occurring GSs, are associated with increased risks of cognitive impairment^(8–14). Importantly, GSs and CMDs also commonly coexist during mid-to-late life⁽¹⁵⁾. The coexistence of GSs among individuals with CMDs may indicate reduced health reserve and resilience, thereby may amplifying susceptibility to cognitive decline. However, whether GSs modify the association between CMDs and cognitive function remains unclear.

Previous studies have mainly examined the direct association between CMDs and cognitive function, with less attention given to factors that may modify this association⁽³⁾. Existing research on effect modification has mainly focused on lifestyle factors and genetic characteristics⁽³⁾, whereas GSs have rarely been considered. In addition, studies examining the relationships of GSs with cognitive impairment or CMDs have mostly focused on individual GSs, although GSs often occur together and their cumulative burden may better capture overall health status. The potential roles of the cumulative number of GSs in modifying the association between CMDs and cognitive function has not been well studied. Moreover, GSs can change over time, with some conditions developing, persisting or improving. However, whether the changes in longitudinal patterns of multiple GSs has not been systematically evaluated. Furthermore, most existing studies have also relied on a single cohort, which may limit the generalisability of their findings across different populations.

To address these gaps, we conducted a multicohort study using harmonised longitudinal data from nationally representative ageing cohorts in China, the United Kingdom, the United States, Mexico, and South Korea. We aimed to examine whether GSs modified the association between CMDs and cognitive function. Specifically, we assessed whether individual GSs and the cumulative number of coexisting GSs modified this association, and whether joint longitudinal trajectories of GSs further modified the association between CMDs and cognitive function.

Methods

Study design and population

The five prospective cohort studies included in this multicohort study were part of the Global Aging, Health, and Policy programme: the China Health and Retirement Longitudinal Study (CHARLS), the English Longitudinal Study on Ageing (ELSA), the US Health and Retirement Study (HRS), the Mexican Health and Aging Study (MHAS) and the Korean Longitudinal Study of Aging (KLoSA). These studies are sister studies following similar study protocols, enabling the cross-regional comparisons⁽¹⁶⁾.

Participants were interviewed every 2 or 3 years in each study where their information on sociodemographic characteristics, lifestyle behaviours, and health status were collected. Detailed study designs of the four cohorts are available elsewhere^(17–21).

The study design and population selection process are presented in Figure S1. To ensure consistent time periods across the five studies, we used data of five waves from each study: waves 1–4 of CHARLS (2011–2018), waves 10–14 of HRS (2010–2018), waves 7–9 of ELSA (2014–2018), waves 3–4 of MHAS (2012–2018) and wave 3–7 of KLoSA (2010–2018). We included participants aged 50 years.

Participants who were missing information on cardiometabolic diseases and cognitive function, or had been diagnosed with dementia or Parkinson's disease, were excluded. Participants with data from at least one wave of frailty status, depressive symptom, falls, pain and urinary incontinence were included ($n = 68,090$). A subpopulation of participants with more than three repeated measures across these domains was further included in the analysis of joint trajectories of frailty status, depressive symptom, falls, pain and urinary incontinence ($n = 27,066$). Baseline characteristics of participants included or not included in the analysis of joint trajectories are compared in Table S10.

Cardiometabolic diseases and multimorbidity

As in previous studies, the CMDs assessed in this study included diabetes, heart disease, and stroke^(22–24). The presence of these conditions was determined via self-reported history obtained through an in-person visit with study personnel via a questionnaire. Detailed definitions of CMDs in the five studies are presented in Table S1. We further defined CMM based on the number of individual CMDs, with the presence of two or more CMDs considered as CMM⁽²³⁾.

Cognitive function

Cognitive function was measured through study-specific cognitive tests, including episodic memory (immediate and delayed word recall), orientation (a recall test of the month, date, day of week, and year) and executive (a serial 7's subtraction test in CHARLS, HRS, ELSA, KLoSA; verbal fluency tests in MHAS)⁽²⁴⁾. The composite cognitive scores represented the level of participants' cognitive function, with a lower score representing a worse cognitive function. Detailed measures refer to Table S1. To compare cognitive domains across the five studies, and to ensure that the scores followed a normal distribution, all cognitive function measures were standardised by creating a Z-score for each domain, which was based on subtracting the mean and dividing by the SD of the corresponding categories.

Geriatric syndromes

Five geriatric syndromes were assessed: frailty, depressive symptoms, falls, pain, and urinary incontinence. Frailty was measured using a frailty index reflecting the accumulation of age-related health deficits^(25, 26). Based on data availability, the index comprised 24 items in CHARLS, HRS, and ELSA, 23 items in MHAS, and 17 items in KLoSA, covering chronic diseases, sensory impairment, self-rated health, limitations in basic and instrumental activities of daily living (BADL/IADL), and mobility (Table S2)⁽²⁷⁾. Each deficit was coded as 1 if present and 0 otherwise, and the frailty index was calculated as the number of deficits present divided by the total number of available items in the corresponding cohort. Frailty status was classified as robust ($FI \leq 0.10$), pre-frail ($0.10 < FI < 0.25$), or frail ($FI \geq 0.25$)^(28, 29). Depressive symptoms were assessed using cohort-specific versions of the Center for Epidemiologic Studies Depression Scale: the CES-D-10 in CHARLS and KLoSA, the CES-D-8 in HRS and ELSA, and the CES-D-9 in MHAS⁽³⁰⁾. Participants were classified as having depressive symptoms if their scores were ≥ 10 in CHARLS and KLoSA, ≥ 3 in HRS and ELSA, or ≥ 5 in MHAS^(31, 32). The diagnosis of depressive symptoms specific items saw Table S2. Falls were defined according to whether participants reported any fall during the previous 2 years^(33–35). Pain was defined as currently experiencing pain. Urinary incontinence was coded as a binary variable. In CHARLS, it was identified from reported difficulty controlling urination or defecation; in HRS, ELSA, and KLoSA, it referred to urinary incontinence in the past year, and in MHAS, in the past 2 years. The total number of geriatric syndromes was calculated by summing these five conditions and categorised as 0, 1, 2, or ≥ 3 . Detailed cohort-specific definitions and cut-off values are provided in Table S1.

Covariates

Covariates assessed in this study included sociodemographic characteristics (age, sex, educational level, total household wealth, marital status), lifestyle factors (current smoking status, alcohol consumption, physical activity and social activity) and countries (China, USA, HK, Mexico and Korea),

following previous study methodology^(24, 36). Missing covariates were assigned to the 'missing' groups. Further details of the harmonization strategies for covariates are presented in Table S4.

Statistical analysis

Baseline characteristics were summarised using each participant's first available observation. Continuous variables are presented as means with standard deviations, and categorical variables as frequencies and percentages. Characteristics were described overall and according to the cardiometabolic status.

In the primary analysis, fixed-effects linear regression models were used to examine the associations between the number of CMDs and global cognitive function and its specific domains, including memory, numeracy, and orientation. The number of CMDs was modelled as a categorical variable (0, 1, 2, or 3), with no CMDs as the reference group. Individual fixed effects were used to account for all measured and unmeasured time-invariant individual characteristics, and cohort-specific survey-wave fixed effects were included to control for temporal differences across cohorts. Robust standard errors were clustered at the participant level to account for repeated observations. The fully adjusted models included age, educational level, total household wealth, marital status, current smoking status, alcohol consumption, physical activity, and social activity; sex and other time-invariant characteristics were accounted for by the individual fixed effects.

We subsequently examined whether geriatric syndromes modified the association between CMDs and cognitive function. Interaction terms were first fitted separately for each specific geriatric syndrome, including frailty status, depressive symptoms, falls, pain, and urinary incontinence. We then examined the moderating role of the total number of geriatric syndromes, categorized as 0, 1, 2, or ≥ 3 . The overall significance of the interaction terms was evaluated using joint Wald tests. Post-estimation marginal predictions were calculated to illustrate adjusted cognitive function scores across number of CMDs according to each specific geriatric syndrome and the number of geriatric syndromes.

In the secondary analysis, group-based multi-trajectory modelling (GBMTM) was used to identify the multi-trajectory groups of frailty status, depressive symptoms, falls, pain, and urinary incontinence over follow-up. The optimal number and shapes of the trajectory groups were selected based on the Bayesian information criterion (BIC) close to zero, average posterior probabilities (AvePP) of group assignment greater than 0.70, adequate group sizes, and clinical interpretability⁽³⁷⁾. Participants were assigned to the trajectory group for which they had the highest posterior probability. Interaction terms between the number of CMDs and trajectory group were then added to the fixed-effects models, and trajectory-specific differences in cognitive function were estimated using participants without CMDs within each trajectory group as the reference.

Sensitivity analyses were conducted. First, missing data were addressed using a two-level multiple imputation by chained equation (MICE) method, with 30 imputed datasets generated and estimates

combined according to Rubin's rules. Second, cohort-specific analyses were conducted to examine whether the findings were consistent across five cohort studies. However, cohort-specific trajectory analyses were not conducted because the number of participants with at least three repeated measurements was insufficient within individual cohorts. Results are reported as regression coefficients with 95% confidence intervals. All tests were two-sided, and a p value < 0.05 was considered statistically significant. Analyses were conducted using Stata version MP 18.0.

Results

Baseline characteristics of participants

The final analysis included 68,090 participants, of whom 13,062 (19.18%) were from China, 18,485 (27.15%) from the USA, 9,693 (14.24%) from the UK, 18,877 (27.72%) from Mexico, and 7,973 (11.71%) from South Korea (Table 1). The mean (SD) age of participants at baseline was 63.84 (9.78%) years. Among the included participants, 25.09% had a single CMD and 5.71% had CMM at baseline. The characteristics of participants by baseline CMM status are shown in Table 1. Compared with participants without CMDs, those with a single CMD or CMM were more likely to be older, lower educated, lower household wealth, single, current smokers, physically inactive and socially inactive.

Table 1
Characteristics of the study population at baseline.

	Total (N = 68,090)	Cardiometabolic status			P value
		No CMD (N = 47,117)	Single CMD (N = 17,083)	CMM (N = 3890)	
Age, mean (SD)	63.84 (9.78)	62.67 (9.48)	65.98 (9.90)	68.67 (9.76)	< 0.001
Sex, n(%)					< 0.001
Male	30,909 (45.39)	21,562 (45.76)	7,484 (43.81)	1,863 (47.89)	
Female	37,181 (54.61)	25,555 (54.24)	9,599 (56.19)	2,027 (52.11)	
Educational level, n (%)					< 0.001
Primary	36,727 (53.94)	25,852 (54.87)	9,101 (53.28)	1,774 (45.60)	
Secondary	20,026 (29.41)	13,007 (27.61)	5,428 (31.77)	1,591 (40.90)	
Tertiary	10,204 (14.99)	7,415 (15.74)	2,306 (13.50)	483 (12.42)	
Missing	1,133 (1.66)	843 (1.79)	248 (1.45)	42 (1.08)	
Total household wealth, n (%)					< 0.001
Q1	20,406 (29.97)	13,266 (28.16)	5,652 (33.09)	1,488 (38.25)	
Q2	21,235 (31.19)	14,325 (30.40)	5,622 (32.91)	1,288 (33.11)	
Q3	21,768 (31.97)	15,805 (33.54)	4,993 (29.23)	970 (24.94)	
Missing	4,681 (6.87)	3,721 (7.90)	816 (4.78)	144 (3.70)	
Marital status, n (%)					< 0.001
Married	49,707 (73.00)	35,344 (75.01)	11,845 (69.34)	2,518 (64.73)	

	Total (N = 68,090)	Cardiometabolic status			P value
		No CMD (N = 47,117)	Single CMD (N = 17,083)	CMM (N = 3890)	
Single	18,366 (26.97)	11,763 (24.97)	5,233 (30.63)	1,370 (35.22)	
Missing	17 (0.03)	10 (0.02)	5 (0.03)	2 (0.05)	
Current smoking status, n (%)					< 0.001
No	36,509 (53.62)	25,829 (54.82)	8,930 (52.27)	1,750 (44.99)	
Yes	31,166 (45.77)	20,978 (44.52)	8,074 (47.26)	2,114 (54.34)	
Missing	415 (0.61)	310 (0.66)	79 (0.46)	26 (0.67)	
Alcohol consumption, n (%)					< 0.001
Less than weekly drinking	33,742 (49.56)	22,254 (47.23)	9,315 (54.53)	2,173 (55.86)	
Weekly drinking or more	33,147 (48.68)	24,037 (51.02)	7,477 (43.77)	1,633 (41.98)	
Missing	1,201 (1.76)	826 (1.75)	291 (1.70)	84 (2.16)	
Physical activity, n (%)					< 0.001
Physical inactive	34,775 (51.07)	22,107 (46.92)	9,995 (58.51)	2,673 (68.71)	
Physical active	26,306 (38.63)	19,466 (41.31)	5,806 (33.99)	1,034 (26.58)	
Missing	7,009 (10.29)	5,544 (11.77)	1,282 (7.50)	183 (4.70)	
Social activity, n (%)					0.040
Socially inactive	25,546 (37.52)	18,496 (39.26)	5,904 (34.56)	1,146 (29.46)	
Socially active	29,409 (43.19)	21,007 (44.58)	7,049 (41.26)	1,353 (34.78)	
Missing	13,135 (19.29)	7,614 (16.16)	4,130 (24.18)	1,391 (35.76)	

	Total (N = 68,090)	Cardiometabolic status			P value
		No CMD (N = 47,117)	Single CMD (N = 17,083)	CMM (N = 3890)	
Global cognitive function score, mean (SD)	0.02 (1.04)	0.08 (1.02)	-0.07 (1.07)	-0.27 (1.17)	< 0.001
Memory score	0.03 (1.00)	0.08 (0.99)	-0.08 (1.00)	-0.25 (1.02)	< 0.001
Orientation score	-0.02 (1.17)	0.01 (1.12)	-0.06 (1.21)	-0.23 (1.42)	< 0.001
Executive function score	0.02 (1.01)	0.06 (0.99)	-0.04 (1.03)	-0.17 (1.06)	< 0.001

Associations between cardiometabolic diseases and cognitive function

Compared with participants without CMDs, those with one CMD did not have a significantly different global cognitive function score. However, two CMDs were associated with lower global cognitive function ($\beta=-0.07$, 95% CI: -0.11 to -0.02), and the association was more pronounced for three CMDs ($\beta=-0.20$, 95% CI: -0.34 to -0.06). Across the individual cognitive domains, two and three CMDs were associated with lower memory scores ($\beta=-0.06$, 95% CI: -0.11 to -0.01; and $\beta=-0.16$, 95% CI: -0.29 to -0.03, respectively). Three CMDs were also associated with lower orientation scores ($\beta=-0.19$, 95% CI: -0.37 to -0.003), whereas no significant associations were observed between the number of CMDs and executive function. Among the individual CMDs, stroke showed the strongest association with global cognitive function ($\beta=-0.12$, 95% CI: -0.18 to -0.06) (Table S5).

Effect modification by specific geriatric syndromes and their number

There was a significant interaction between three CMDs and frailty status for global cognitive function, memory, and orientation (Table S6). Compared with robust participants, the association between three CMDs and cognitive function was more negative among frail participants for global cognitive function (interaction $\beta=-0.68$, 95% CI: -1.25 to -0.11), memory (interaction $\beta=-0.53$, 95% CI: -0.96 to -0.09), and orientation (interaction $\beta=-0.82$, 95% CI: -1.54 to -0.11). To further explore these interactions, marginal predictions showed that global cognitive function decreased with increasing CMD burden among frail participants, whereas no comparable decrease was observed among robust or pre-frail participants (Fig. 1). No significant interaction between CMD number and pre-frailty was observed for global cognitive function, memory, or orientation.

Similarly, there was a significant interaction between two CMDs and depressive symptoms for orientation (interaction $\beta=-0.11$, 95% CI: -0.20 to -0.02), indicating that the association between two CMDs and lower orientation was stronger among participants with depressive symptoms than among those without depressive symptoms. However, no significant interactions between CMD number and depressive symptoms were observed for global cognitive function, memory, or executive function. No significant interactions of falls, pain, or urinary incontinence with CMD number were observed across the cognitive outcomes, except for the association described above (Table S6).

There was also a significant interaction between three CMDs and three or more geriatric syndromes for global cognitive function and orientation (Table S7). Compared with participants without geriatric syndromes, the association between three CMDs and cognitive function was more negative among those with three or more geriatric syndromes for global cognitive function (interaction $\beta=-0.34$, 95% CI: -0.62 to -0.07) and orientation (interaction $\beta=-0.50$, 95% CI: -0.88 to -0.12). To further explore these interactions, marginal predictions showed that global cognitive function decreased markedly with increasing CMD burden among participants with three or more geriatric syndromes, whereas little change was observed among those without geriatric syndromes (Fig. 2). No significant interactions were observed between one or two CMD and geriatric syndrome number or between three CMDs and one or two geriatric syndromes (Table S7).

Geriatric syndrome multitrajectories and effect modification

Among 27,066 participants, group-based multi-trajectory modelling identified five patterns of concurrently changing trajectories of frailty status, depressive symptoms, falls, pain, and urinary incontinence: G1 (23.07%), low-stable; G2 (21.03%), pre-frailty progression; G3 (13.40%), pain-dominant; G4 (21.82%), multi-syndrome progression; and G5 (10.67%), urinary incontinence progression (Fig. 3).

There were significant interactions between three CMDs and trajectory group for global cognitive function (Table S9). Compared with G1, the association between three CMDs and global cognitive function was more negative in G2 (interaction $\beta=-0.57$, 95% CI: -1.00 to -0.15), G3 (interaction $\beta=-0.57$, 95% CI: -1.01 to -0.14), G4 (interaction $\beta=-0.85$, 95% CI: -1.22 to -0.48), and G5 (interaction $\beta=-0.75$, 95% CI: -1.34 to -0.17). No significant interactions between one or two CMDs and trajectory group were observed.

To further explore these interactions, trajectory-specific estimates were calculated (Fig. 4). In G4, participants with two CMDs had lower global cognitive function than those without CMDs ($\beta=-0.13$, 95% CI: -0.21 to -0.04), and the difference was larger among participants with three CMDs ($\beta=-0.38$, 95% CI: -0.59 to -0.17). No significant associations between CMD number and global cognitive function were observed in G2, G3, or G5. In G1, three CMDs were associated with higher global cognitive function ($\beta = 0.47$, 95% CI: 0.17 to 0.78); however, this estimate was based on only six participants and should be interpreted cautiously.

Sensitivity analyses

Multiple-imputation analyses using 30 imputed datasets were broadly consistent with the complete-case findings: two CMDs ($\beta = -0.04$, 95% CI: -0.08 to -0.001) and three CMDs ($\beta = -0.12$, 95% CI: -0.22 to -0.02) remained associated with lower global cognitive function. The interaction between two CMDs and three or more geriatric syndromes also remained significant ($\beta = -0.08$, 95% CI: -0.15 to -0.01), while significant interactions were additionally observed between two CMDs and frailty and between two CMDs and falls. Cohort-specific analyses showed that the magnitude and statistical significance of the associations varied across cohorts. However, although larger number of CMDs were generally associated with poorer global cognitive function, the modifying effect of geriatric syndrome number on the association between number of CMDs and global cognitive function varied across cohorts and was not consistently replicated. In contrast, the specific interaction terms were less consistently replicated across cohorts, suggesting some heterogeneity in the moderating effects of geriatric syndromes.

Discussion

To the best of our knowledge, this is the first study to examine whether GSs modify the association between CMDs and cognitive function among middle-aged and older adults, using data from five ageing cohorts across Asia, North America, and Europe. Among the five individual GSs, we found frailty and depressive symptom modified the associations between CMDs and cognitive function. Regarding the number of GSs, three or more GSs modified the associations between CMDs and cognitive function. We further identified five eight-year joint GS trajectory groups: low-stable, pre-frailty progression, pain-dominant, multisymptom progression, and urinary incontinence progression. Compared with the low-stable group, the association between CMDs and cognitive function differed across the other four trajectory groups. However, trajectory-specific analyses showed significant associations only in the multisymptom progression group, in which participants with two or three CMDs had lower global cognitive function than those without CMDs. Together, these findings underscore the importance of comprehensive assessment and management of GSs among individuals with CMDs to help prevent or delay further cognitive decline.

Firstly, we found that frailty modified the association between CMDs and cognitive function. Frailty is a dynamic biological process involving deterioration across multiple physiological systems, resulting in reduced capacity to respond to environmental stressors, such as injury or illness^(38, 39). Previous studies have associated frailty with poorer cognitive function, accelerated cognitive decline, and an increased risk of dementia^(40–42). CMDs may represent a chronic disease-related stressor, and frailty may intensify their adverse association with cognitive function by combining cardiometabolic abnormalities with multisystem functional impairment. In contrast, pre-frailty did not significantly modify this association, suggesting that such modification may occur mainly after frailty has progressed beyond its earlier stage rather than throughout the frailty continuum.

In addition to frailty, depressive symptoms worsened the association between two CMDs and orientation but not the associations with global cognitive function, memory, or executive function in this study. Previous studies have associated depressive symptoms with cognitive decline^[6], although whether they modify the association between CMDs and cognitive function remains insufficiently studied. The domain-specific finding for orientation may reflect its dependence on cognitive processes that can be affected by depressive symptoms⁽¹⁴⁾. Falls, pain, and urinary incontinence did not interact with CMDs, possibly because these conditions represent relatively specific functional or symptomatic impairments and may not capture the broader multisystem deterioration required to further intensify the association between CMDs and cognitive function.

Secondly, significant effect modification was observed mainly among participants with both three CMDs and three or more GSs, whereas no comparable interactions were found among those with only one or two GSs. Previous studies have shown that GSs rarely occur in isolation because they share common risk factors and often have overlapping clinical manifestations⁽⁷⁾. Accordingly, the accumulation of multiple GSs may better reflect overall health deterioration and multisystem impairment than any single syndrome. The coexistence of multiple CMDs and multiple GSs may represent a dual accumulation of cardiometabolic disease and age-related health deficits. When both accumulate, overlapping vascular, metabolic, psychological, and functional impairments may reinforce one another, reduce the capacity to cope with disease-related stress, and thereby amplify the association between CMDs and poorer cognitive function^(43, 44). This may explain why effect modification became apparent only when both the number of CMDs and the number of GSs were high.

Lastly, we further found that the joint trajectories of GSs modified the association between CMM and cognitive function. Compared with the low-stable group, the association of three CMDs with global cognitive function shifted towards lower scores in the pre-frailty progression, pain-dominant, multisymptom progression, and urinary incontinence progression groups, with similar differences observed for memory. However, trajectory-specific analyses identified significant associations only in the multisymptom progression group, where both two and three CMDs were associated with lower global cognitive function. This pattern suggests that sustained progression in a single predominant syndrome may alter the CMD-cognition association, whereas the concurrent progression of several GSs may be more strongly related to lower cognitive function among individuals with CMM. Previous studies have shown that worsening or persistent trajectories of frailty and depressive symptoms are associated with faster cognitive decline⁽¹⁴⁾. The multisymptom progression group captures persistent deterioration across physical, psychological, and functional domains, and may therefore indicate reduced capacity to compensate for the combined effects of multiple CMDs⁽⁴⁵⁾. Nevertheless, the interaction estimates should be interpreted cautiously because the reference estimate for three CMDs in the low-stable group was based on only six participants.

Strengths and limitations

This study has several strengths. First, it focused on the role of GSs in the association between CMDs and cognitive function and systematically examined effect modification by individual GSs, the cumulative number of GSs, and the eight-year joint trajectories of five GSs. Second, it combined harmonised longitudinal data from five population-based ageing cohorts across Asia, Europe, and North America, thereby enhancing the generalisability and robustness of the findings. Several limitations should be acknowledged. First, the observational design precludes causal inference. Second, GSs were assessed using self-reported information, which may have introduced recall and misclassification bias. Definitions and recall periods also differed across cohorts, particularly for falls and urinary incontinence. Third, the trajectory analysis was restricted to participants with at least three repeated assessments, which may have introduced healthy-survivor and selection bias. In addition, assigning participants to the trajectory group with the highest posterior probability did not fully account for classification uncertainty. Fourth, some combinations of CMD number and trajectory group included few participants, resulting in imprecise estimates.

Conclusions

In this multicohort study, frailty, depressive symptoms, the coexistence of three or more GSs, and the multisymptom progression trajectory modified the association between the number of CMDs and cognitive function. These findings support integrating comprehensive screening and repeated assessment of GSs into the clinical management of middle-aged and older adults with CMDs. Particular attention should be given to individuals with CMM and multiple or progressively worsening GSs, as they may be more likely to have lower cognitive function. Joint consideration of CMDs and GSs may improve risk stratification and guide targeted cognitive monitoring and early intervention to help prevent or delay further cognitive decline.

Declarations

Ethics Approval and Consent to Participate

This study is a secondary analysis based on publicly available datasets, which is exempted from Institutional Review Board. All studies were approved by Institutional Review Boards and the respondents provided written informed consent. The CHARLS was approved by the Ethical Review Committee at Peking University (IRB00001052-11015). The HRS was approved by the Institute for Social Research and Survey Research Center at the University of Michigan (NIA U01AG009740). The ELSA was approved by the South Central-Berkshire Research Ethics Committee (09/H0505/124; 11/SC/0374; 13/SC/0532; 15/SC/0526; 17/SC/0588). The MHAS was approved by the Institutional Review Board of the University of Texas Medical Branch (IRB Protocol #11-061), the National Institute of Statistics (INEGI) and the National Institute of Public Health (INSP). The KLoSA was approved by the National Statistical Office (approval number: 33602) and the Institutional Review Board (IRB) of the Korea National Institute for Ethics Policy.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Funding

Yanan Luo was supported by the Beijing Social Science Foundation (25BJ03219). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contribution

Y.L. contributed to the study conceptualization and supervised the whole project. Y.L. made the analysis plan, conducted the statistical analyses, and drafted the initial manuscript. X.L. verified the underlying data and statistical analyses. X.Y., G.W., and C.H. provided support on the statistical methods and manuscript revision. Y.J., B.G., XW., and C.C provided support on manuscript revision. All authors read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Acknowledgments

We thank all team members who contributed to the data collection and data cleaning of CHARLS, HRS, ELSA, MHAS and KLoSA. We thank all the volunteers who participated in the study. This analysis used data or information from the harmonized CHARLS, HRS, ELSA, MHAS and KLoSA data sets and codebooks developed by the Gateway to Global Aging Data and supported by the National Institute on Aging.

Data Availability

The original data for this study are available on their respective websites: The China Health and Retirement Longitudinal Study (CHARLS; <https://charls.pku.edu.cn/>), the Health and Retirement Study (HRS; <https://hrs.isr.umich.edu/>), the English Longitudinal Study on Ageing (ELSA; <https://www.elsa-project.ac.uk/>), Mexican Health and Aging Study (MHAS, <https://mhasweb.org/Home/index.aspx>) and Korean Longitudinal Study of Aging (KLoSA, <https://survey.keis.or.kr/eng/klosa/klosa01.jsp>)

References

1. Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. *lancet*. 2017;390(10113):2673–734. 10.1016/S0140-6736(17)31363-6.
2. Dove A, Guo J, Marseglia A, Fastbom J, Vetrano DL, Fratiglioni L, et al. Cardiometabolic multimorbidity and incident dementia: the Swedish twin registry. *Eur Heart J*. 2023;44(7):573–82. 10.1093/eurheartj/ehac744.
3. Liu H, Sun J, Wang T. The impact of cardiometabolic multimorbidity on cognitive function in older adults: a review. *Front Public Health*. 2026;14:1795161. 10.3389/fpubh.2026.1795161.
4. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc*. 2007;55(5):780–91. 10.1111/j.1532-5415.2007.01156.x.
5. Hazzard WR. Scientific progress in geriatric syndromes: earning an A on the 2007 Report Card on Academic Geriatrics. *Wiley Online Library*; 2007. pp. 794–6. 10.1111/j.1532-5415.2007.01157.x.
6. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *JAMA*. 1995;273(17):1348–53.
7. Tabue-Teguo M, Grasset L, Avila-Funes JA, Genuer R, Proust-Lima C, Péres K, et al. Prevalence and co-occurrence of geriatric syndromes in people aged 75 years and older in France: results from the Bordeaux three-city study. *Journals Gerontology: Ser A*. 2018;73(1):109–16. 10.1093/gerona/glx068.
8. Ward DD, Flint JP, Littlejohns TJ, Foote IF, Canevelli M, Wallace LMK, et al. Frailty Trajectories Preceding Dementia in the US and UK. *JAMA Neurol*. 2025;82(1):61–71. 10.1001/jamaneurol.2024.3774.
9. Forbes M, Lotfaliany M, Mohebbi M, Reynolds CF, Woods RL, Orchard S, et al. Depressive symptoms and cognitive decline in older adults. *Int Psychogeriatr*. 2024;36(11):1039–50. 10.1017/S1041610224000541.
10. Kou W, Shi S, Huang J, Xie Y, Qiu P. Falls and subsequent cognitive function in older adults in England and the USA, 2010–2020: a population-based, cross-nationally harmonized, longitudinal study. *Am J Epidemiol*. 2025;194(10):3007–17. 10.1093/aje/kwaf089.
11. He Z, Li G, Chen Z, Hu Z, Wang Q, Huang G, et al. Trajectories of pain and their associations with long-term cognitive decline in older adults: evidence from two longitudinal cohorts. *Age Ageing*. 2024;53(8). 10.1093/ageing/afae183.
12. Grant RL, Drennan VM, Rait G, Petersen I, Iliffe S. First diagnosis and management of incontinence in older people with and without dementia in primary care: a cohort study using The Health Improvement Network primary care database. *PLoS Med*. 2013;10(8):e1001505. 10.1371/journal.pmed.1001505.
13. Zou M, Gong H, Chen B, Chen S, Teng J, Zhou J, et al. Trajectories of cognitive decline before and after new-onset dual sensory impairment: findings from two longitudinal studies. *Alzheimer's Dement*. 2026;22(4):e71333. 10.1002/alz.71333.

14. Hu C, Sun X, Li Z, He Y, Han B, Wu Z, et al. Multitrajectories of Frailty and Depression With Cognitive Function: Findings From the Health and Retirement Longitudinal Study. *J Cachexia Sarcopenia Muscle*. 2025;16(2):e13795. 10.1002/jcsm.13795.
15. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: The Health and Retirement Study. *J Am Geriatr Soc*. 2009;57(3):511–6. 10.1111/j.1532-5415.2008.02150.x.
16. Lee J, Phillips D, Wilkens J. Gateway to Global Aging Data: Resources for Cross-National Comparisons of Family, Social Environment, and, Aging H. *J Gerontol B Psychol Sci Soc Sci*. 2021;76(Suppl 1). 10.1093/geronb/gbab050
17. Zhao Y, Hu Y, Smith JP, Strauss J, Yang G. Cohort profile: the China Health and Retirement Longitudinal Study (CHARLS). *Int J Epidemiol*. 2012;43(1):61–8. 10.1093/ije/dys203.
18. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JWR, Weir DR. Cohort Profile: the Health and Retirement Study (HRS). *Int J Epidemiol*. 2014;43(2):576–85. 10.1093/ije/dyu067.
19. Steptoe A, Breeze E, Banks J, Nazroo J. Cohort profile: the English longitudinal study of ageing. *Int J Epidemiol*. 2012;42(6):1640–8. 10.1093/ije/dys168.
20. Wong R, Michaels-Obregon A, Palloni A. Cohort Profile: The Mexican Health and Aging Study (MHAS). *Int J Epidemiol*. 2017;46(2):e2. 10.1093/ije/dyu263.
21. Jang S-N, Korean Longitudinal Study of Ageing (KLoSA). Overview of Research Design and Contents. In: Pachana NA, editor. *Encyclopedia of Geropsychology*. Singapore: Springer Singapore; 2015. pp. 1–9.
22. Xu X, Mishra GD, Dobson AJ, Jones M. Progression of diabetes, heart disease, and stroke multimorbidity in middle-aged women: A 20-year cohort study. *PLoS Med*. 2018;15(3):e1002516. 10.1371/journal.pmed.1002516.
23. Jin Y, Liang J, Hong C, Liang R, Luo Y. Cardiometabolic multimorbidity, lifestyle behaviours, and cognitive function: a multicohort study. *Lancet Healthy Longev*. 2023;4(6):e265–73. 10.1016/S2666-7568(23)00054-5.
24. Zhang Y, Zhou Y, Kivimäki M, Holt-Lunstad J, Carrillo-Larco RM, Xu X. Cardiometabolic multimorbidity, social activity, and joint trajectories of physical disability, depressive symptom, and cognitive function in mid-to-late life: a multicohort study. *BMC Med*. 2025;23(1):577. 10.1186/s12916-025-04400-8.
25. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr*. 2008;8:24. 10.1186/1471-2318-8-24.
26. He D, Wang Z, Li J, Yu K, He Y, He X, et al. Changes in frailty and incident cardiovascular disease in three prospective cohorts. *Eur Heart J*. 2024;45(12):1058–68. 10.1093/eurheartj/ehad885.
27. Zhang Z, Xu H, Zhang R, Yan Y, Ling X, Meng Y, et al. Frailty and depressive symptoms in relation to cardiovascular disease risk in middle-aged and older adults. *Nat Commun*. 2025;16(1):6008. 10.1038/s41467-025-61089-2.

28. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet*. 2019;394(10206):1365–75. 10.1016/S0140-6736(19)31786-6.
29. Fan J, Yu C, Guo Y, Bian Z, Sun Z, Yang L, et al. Frailty index and all-cause and cause-specific mortality in Chinese adults: a prospective cohort study. *Lancet Public Health*. 2020;5(12):e650–60. 10.1016/S2468-2667(20)30113-4.
30. Andresen EM, Malmgren JA, Carter WB, Patrick DL. Screening for depression in well older adults: evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *Am J Prev Med*. 1994;10(2):77–84.
31. Yan R, Liu X, Xue R, Duan X, Li L, He X, et al. Association between internet exclusion and depressive symptoms among older adults: panel data analysis of five longitudinal cohort studies. *EClinicalMedicine*. 2024;75:102767. 10.1016/j.eclinm.2024.102767.
32. Quashie NT, Arpino B, Antczak R, Mair CA. Childlessness and health among older adults: Variation across five outcomes and 20 countries. *Journals Gerontology: Ser B*. 2021;76(2):348–59. 10.1093/geronb/gbz153.
33. Liu Y, Soh SLH, Tan MP, Ji W, Chan WLS, Singh DKA, et al. Falls and frailty transitions in older adults: A multi-state analysis of a national longitudinal cohort. *J Nutr health aging*. 2026;30(8):100908. 10.1016/j.jnha.2026.100908.
34. Cotton K, Jin Y, Verghese J. Modifiable risk factors for falls in community-dwelling older adults. *Gerontologist*. 2026;66(6):gnag086. 10.1093/geront/gnag086.
35. Geng T, Zhao S, Xi W, Sheng C, Sun Z, Guo C. The relationship between a frailty index and fall risk in middle-aged and older adults: Findings from three prospective cohort studies—CHARLS, ELSA and HRS. *Maturitas*. 2026;108919. 10.1016/j.maturitas.2026.108919.
36. Wang D, Dai X, Mishra SR, Lim CCW, Carrillo-Larco RM, Gakidou E, et al. Association between socioeconomic status and health behaviour change before and after non-communicable disease diagnoses: a multicohort study. *Lancet Public Health*. 2022;7(8):e670–82. 10.1016/S2468-2667(22)00157-8.
37. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2016;27(7):2015–23. 10.1177/0962280216673085.
38. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Biol Sci Med Sci*. 2001;56(3):M146–56. 10.1093/gerona/56.3.m146.
39. Ahmed N, Mandel R, Fain MJ. Frailty: an emerging geriatric syndrome. *Am J Med*. 2007;120(9):748–53. 10.1016/j.amjmed.2006.10.018.
40. Buchner DM, Wagner EH. Preventing frail health. *Clin Geriatr Med*. 1992;8(1).
41. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. *Age Ageing*. 1997;26(4):315–8. 10.1093/ageing/26.4.315.
42. Morley JE, Malmstrom T, Miller D. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16(7):601–8. 10.1007/s12603-012-0084-2.

43. Chang C-M. Geriatric Syndrome, Conditions, or Syndemics: A Modifiable Intermediary and Vicious Cycle between Medical Treatment and Long-Term Care. *Int J Gerontol.* 2025;19(3):128–9.

44. Strandberg TE, Pitkälä KH, Tilvis RS, O’Neill D, Erkinjuntti TJ. Geriatric syndromes—vascular disorders? *Annals Med.* 2013;45(3):265–73. 10.3109/07853890.2012.727022.

45. Yuan Y, Peng C, Burr JA, Lapane KL. Frailty, cognitive impairment, and depressive symptoms in Chinese older adults: an eight-year multi-trajectory analysis. *BMC Geriatr.* 2023;23(1):843. 10.1186/s12877-023-04554-1.

Figures

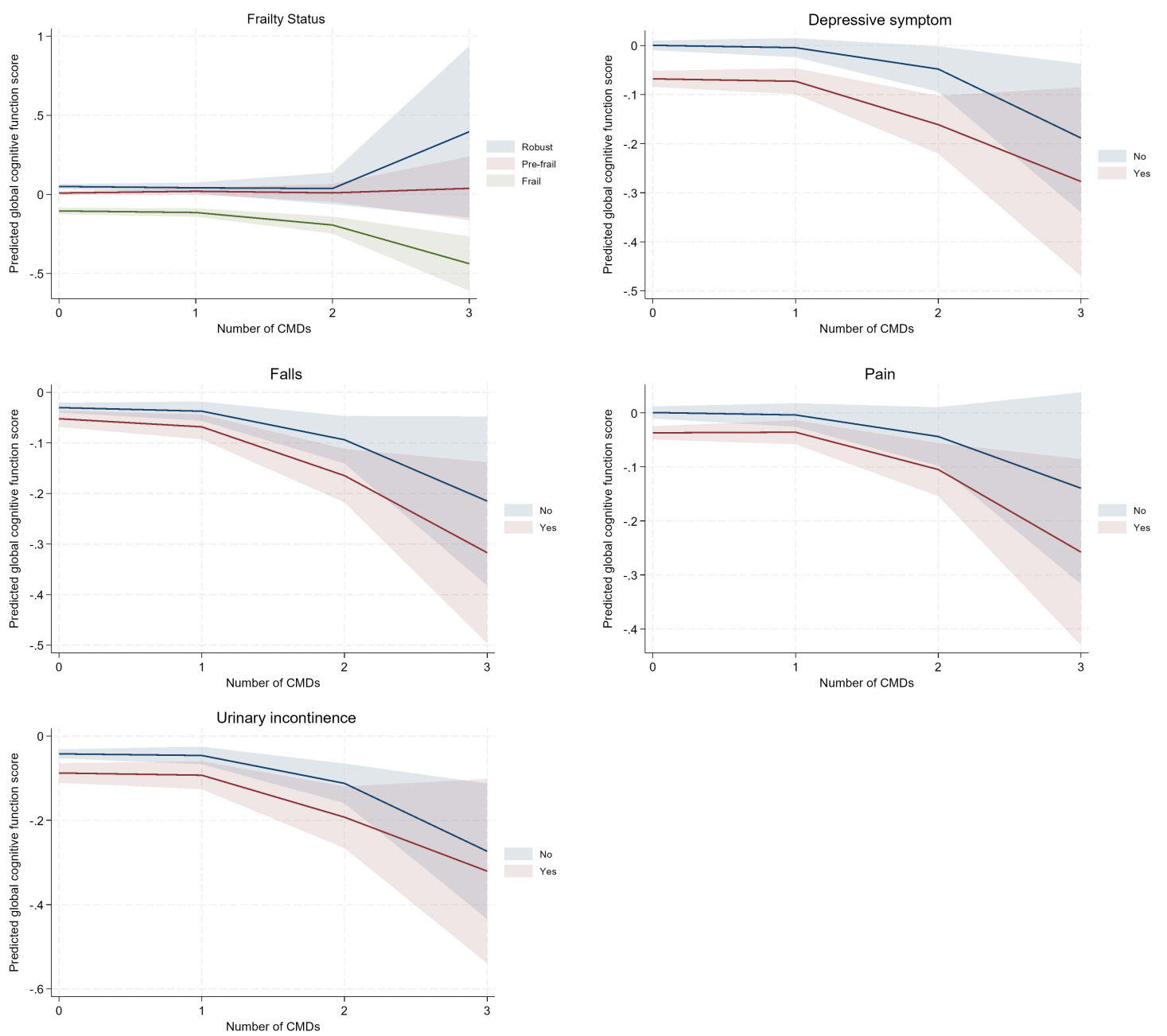


Figure 1

Margin effects of cardiometabolic disease on global cognitive function scores, stratified by specific geriatric syndromes.

Abbreviation: CMDs cardiometabolic diseases. All coefficients were estimated after adjusting for age, sex, educational level, total household wealth, marital status, current smoking status, alcohol consumption, physical activity and social activity.

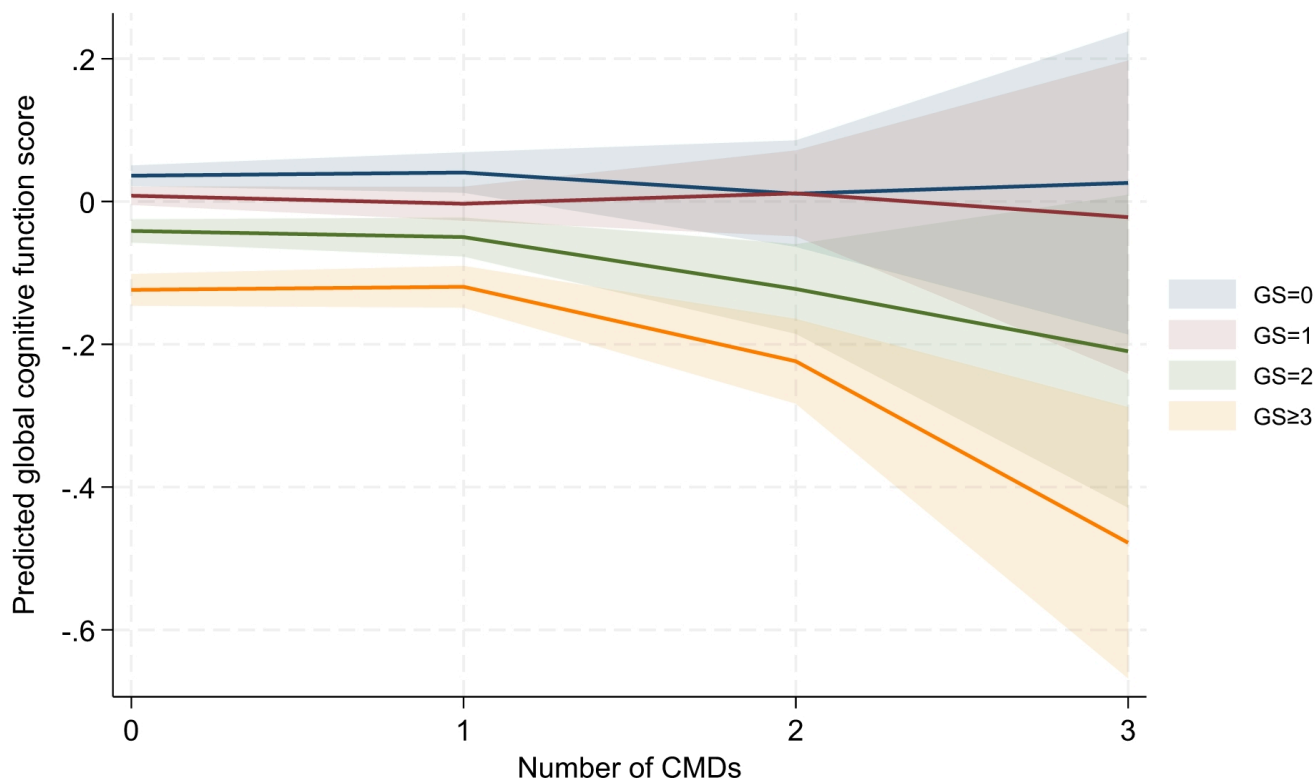


Figure 2

Margin effects of cardiometabolic disease on global cognitive function scores, stratified by number of geriatric syndromes (0, 1, 2 and 3 or more).

Abbreviation: CMDs cardiometabolic diseases, GS geriatric syndromes. All coefficients were estimated after adjusting for age, sex, educational level, total household wealth, marital status, current smoking status, alcohol consumption, physical activity and social activity

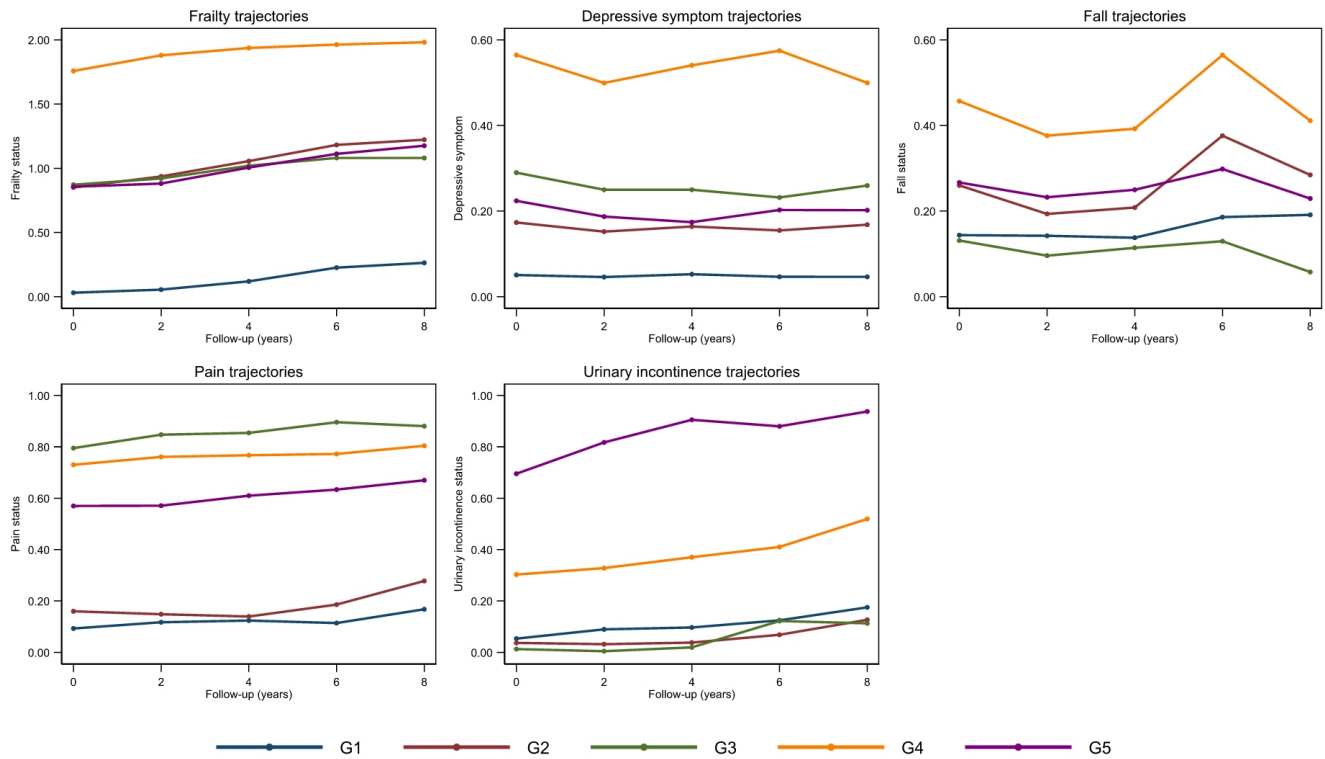


Figure 3

Multitrajectories of frailty, depressive symptom, falls, pain, urinary incontinence.

G1 (23.07%): Low-stable, G2 (21.03%): Pre-frailty progression, G3 (13.40%): Pain-dominant,

G4 (21.82%): Multisymptom progression, G5 (10.67%): Urinary incontinence progression

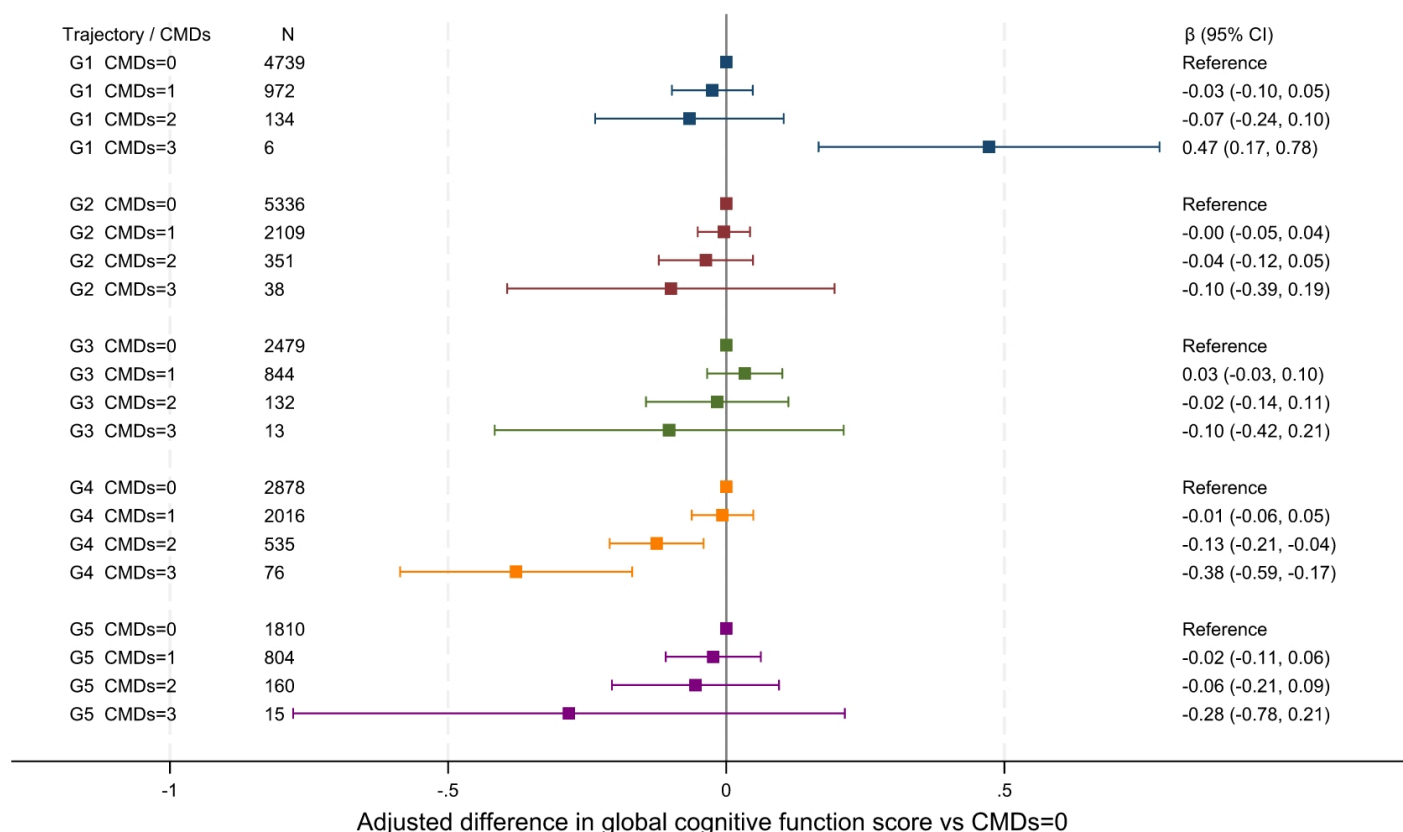


Figure 4

Trajectory-specific associations between cardiometabolic diseases and global cognitive function.

Abbreviation: CMDs cardiometabolic diseases, GS geriatric syndromes. All coefficients were estimated after adjusting for age, sex, educational level, total household wealth, marital status, current smoking status, alcohol consumption, physical activity and social activity

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMaterials20260726.docx](#)