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RESEARCH ARTICLE

Association of cardiometabolic multimorbidity with motoric cognitive risk syndrome in older adults

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Abstract

INTRODUCTION: Motoric cognitive risk syndrome (MCR) is a predementia syndrome that is characterized by cognitive complaints and slow gait. Cardiometabolic multimorbidity (CMM) is associated with an increased risk of dementia. However, the relationship between CMM and MCR is still unclear.

METHODS: We included 4744 participants (aged 65+ years) without MCR at baseline from the National Health and Aging Trends Study (NHATS), who were followed-up from 2011 to 2018. CMM was defined as the presence of two or more cardiometabolic diseases (including diabetes mellitus, heart disease, and stroke).

RESULTS: CMM was significantly associated with an increased risk of MCR (hazard ratio [HR] 1.41, 95% confidence interval [CI] 1.13–1.75) in fully adjusted models. Consistent results were observed from stratified analyses of different subgroups. Increasing numbers of cardiometabolic diseases were dose-dependently associated with increased MCR risk (HR 1.33, 95% CI 1.20–1.48).

DISCUSSION: CMM is associated with an increased risk of MCR in older adults.

KEYWORDS
cardiometabolic multimorbidity, cohort study, motoric cognitive risk syndrome, older adults

HIGHLIGHTS

- Motoric cognitive risk syndrome (MCR) is a predementia syndrome characterized by slow gait speed and cognitive complaints.

Hui Zhang and Shuai Jiang authors contributed equally to this work.

- Cardiometabolic multimorbidity was associated with an increased MCR risk.
- An increased number of cardiometabolic diseases were dose-dependently associated with increased MCR risk.

1 | BACKGROUND

Motoric cognitive risk syndrome (MCR), a prodromal phase of dementia,[1–3] is characterized by the combination of slow gait speed and cognitive complaints among individuals without dementia or a mobility disability.[2] The prevalence of MCR ranges from 2% to 27% in older adults worldwide.[4–6] There is growing evidence that MCR is a strong and early risk factor for dementia,[5–7] and approximately one in three older adults with MCR may progress to dementia during a median follow-up of 4.0 years.[8,9] Previous studies have also demonstrated that MCR is associated with increased risks of mortality, falls, and disability.[6,7] In addition, smaller volumes of total gray matter, total cortical gray matter, premotor cortex, prefrontal cortex, and dorsolateral segment of the prefrontal cortex were found in individuals with MCR compared to those without MCR.[10] Hence, considering the higher prevalence and adverse effect of MCR, identifying risk factors would be beneficial to prevent or delay the incidence of MCR and then implement efficient prevention strategies. At present, many factors have been observed to be associated with MCR, such as lifestyle factors, chronic diseases, demographic factors, and psychosocial factors.[10–13] Among them, cardiometabolic multimorbidity (CMM), defined as the presence of two or more cardiometabolic diseases (CMDs, including heart disease, diabetes mellitus, and stroke), affects approximately one in three older adults with increased population aging[14] and is associated with an increased risk of mortality.[15–17]

There has been significant progress in establishing the epidemiology of CMM on dementia,[18–23] which recommended that more attention be given to individuals with CMM to prevent and/or delay the development of dementia. The development of dementia may need a long preclinical phase (e.g., MCR, cognitive impairment) that lasts years to decades,[10] and an adverse relationship between CMM and cognitive function may be apparent in the prodromal phases of dementia. Therefore, the potential relationship between CMM and prodromal phases of dementia also needs to be examined. For instance, one study recently observed that CMM was associated with accelerated cognitive decline[18] and an increased risk of cognitive impairment[24] in older adults. In addition, a systematic review and meta-analysis also illustrated a significant relationship between single CMDs and the risk of MCR.[11] However, the association of their combined effects with MCR has not been investigated at present. In summary, evidence regarding whether CMM is associated with MCR is still limited. Investigation of the potential relationship between CMM and MCR risk may be effective in identifying intervention strategies for dementia.

To address this knowledge gap, we first hypothesized that CMM was associated with an increased risk of MCR and then performed a population-based, longitudinal, and prospective cohort study to examine the association of CMDs and CMM with the risk of MCR in older adults using data from the National Health and Aging Trends Study (NHATS).

2 | METHODS

2.1 | Study population

In this study, data were obtained from NHATS, which was a longitudinal survey of Medicare beneficiaries ≥65 years of age residing in the United States.[25] Starting in 2011, data were collected annually. We used data from Round 1 (2011) to Round 8 (2018). At baseline (Round 1), a total of 8245 participants were recruited. Of them, 1146 participants were excluded due to a lack of information on MCR and/or CMDs. In addition, 399 and 629 participants were also excluded due to being diagnosed with MCR and dementia at baseline, respectively. Therefore, 6071 participants without MCR or dementia were followed-up. Over a median follow-up of 6 years, 1297 participants were excluded because of attrition ($n = 958$), developing dementia before being diagnosed with MCR ($n = 339$), or death before being diagnosed with MCR ($n = 268$). Finally, a total of 4474 participants were included and analyzed in this study (Figure 1).

2.2 | Clinical information

In this study, participants or proxies were asked to report any clinical diagnosis received, including arthritis, hypertension, diabetes mellitus, lung disease, cancer, osteoporosis, stroke, and heart disease (including heart attack, myocardial infarction, angina, and congestive heart failure). In addition, anxiety and depression were assessed by the Patient Health Questionnaire for Depression and Anxiety, which combines a two-item measure of depression and a two-item measure of generalized anxiety disorder. Significant depressive symptoms and anxiety symptoms were both assessed using a cutoff score of 3.[26,27] In this study, participants or proxies were asked to report CMDs, including heart disease, diabetes mellitus, and stroke. CMM was defined as the presence of two or more CMDs.[15]

2.3 | Motoric cognitive risk syndrome

In NHATS, MCR was defined based on previous studies.[3,12,28] Similarly, cognitive complaints were assessed by three questions: (1) "How would you rate your memory at the present time?"; (2) "Compared to 1 year

ago, would you say your memory is better now, about the same, or worse now than it was then?"; and (3) "In the last month, how often did memory problems interfere with your daily activities?" An anomaly in one of these questions was indicative of having cognitive complaints. Information about cognition was obtained each year from Round 1 to Round 8. Gait speed was measured using a 3-meter test in NHATS. Slow gait speed was defined as walking speed one standard deviation (SD) or below or SD below age-specific and sex-specific.[3] The detailed definitions of cognitive complaints and slow gait speed are presented in Table 1. The NHATS classified participants as having dementia if they met either of the following criteria: (1) a report from the participant or a proxy respondent that a doctor had diagnosed the participant with dementia or Alzheimer's disease; (2) a score of 2 or higher on the AD8 Dementia Screening Interview, which indicated likely dementia, as reported by a proxy respondent.[29] MCR was defined as the presence of both cognitive complaints and slow gait speed in older adults without dementia or mobility disability.[2]

2.4 | Covariates

In NHATS, participants or proxies were asked to report their date of birth, race/ethnicity (White non-Hispanic, Black non-Hispanic, Hispanic, and Others), marital status (married, living with a partner, separated, divorced, widowed, and never married), sex (male/female), body mass index (BMI), vigorous exercise (yes/no), and smoking status (ever/never). Specifically, we categorized marital status into married/partnered (including married and living with a partner) and single/widowed (including separated, divorced, widowed, and never married) in our analyses. Vigorous exercise was assessed by asking participants to report whether they had ever spent time on vigorous activities in the last month (yes/no). Sleep disorders included difficulty initiating sleep, difficulty falling back asleep, and sleep medication use. Participants who had one or more adverse sleep events were recognized as having sleep disorders.[30,31] In detail, difficulty initiating sleep was assessed by the question "In the last month, how often has it taken more than 30 min to fall asleep at night?" Difficulty falling back asleep was assessed by the question "In the last month, on the nights you woke up before you wanted, how often did you have trouble falling back asleep?" Sleep medication use was assessed by the question "In the last month, how often did you take medication to help you sleep?" The responses were "every night," "most nights," "some nights," "rarely," and "never." Participants who responded "most nights or every night" were recognized as having difficulty initiating sleep, difficulty falling back asleep, or having sleep medication use.

2.5 | Statistical analysis

First, we described the data by the means with SD or frequency (%) based on continuous and categorical variables, respectively. Group differences were analyzed by chi-square analysis or analysis of variance (ANOVA).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched the literature using the PubMed database and references from relevant articles. Motoric cognitive risk syndrome (MCR) is a predementia syndrome. There is evidence that cardiometabolic multimorbidity (CMM) is significantly associated with cognitive decline and dementia. However, no study has investigated the relationship between CMM and MCR.
2. **Interpretation**: In this prospective, population-based, longitudinal study, we analyzed 4774 older adults without MCR at baseline. We found that CMM was associated with an increased risk of MCR. In addition, an increasing number of cardiometabolic diseases were dose-dependently associated with increased MCR risk. Our study takes further steps to provide evidence of the important relationship between CMM and dementia and we recommended that more attention should be given to individuals with CMM to prevent and/or delay the development of MCR.
3. **Future directions**: Future studies with diverse cohorts are needed to validate these findings.

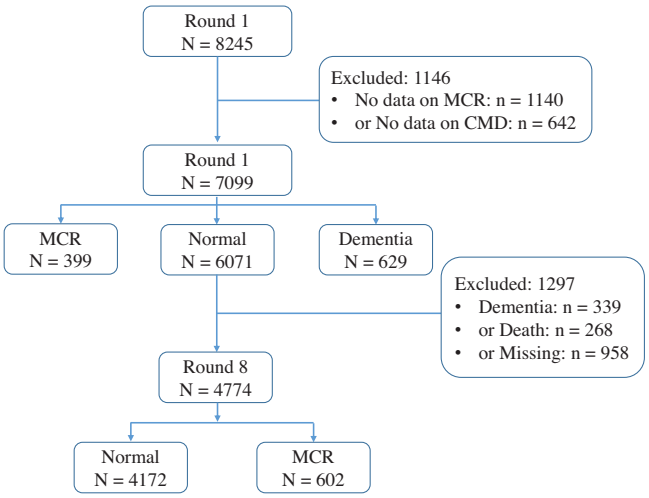

FIGURE 1 Flowchart of the study population.

Second, we utilized the Cox proportional hazard model to estimate the hazard ratio (HR) of MCR associated with CMM using three models: Model 1 was unadjusted; Model 2 was adjusted for demographic information (age, sex, marital status, race) and lifestyles (smoking, BMI, vigorous activity, and sleep disorders); and Model 3 was adjusted for Model 2 and for additional chronic diseases (arthritis, hypertension, lung disease, cancer, osteoporosis, depression, and anxiety). When an individual in the sample was confirmed as deceased, typically by a

TABLE 1 Definition of cognitive complaints and slow gait speed.

Cognitive complaints	NHATS questions	Responses	Definition of cognitive complaints
	(1) "How would you rate your memory at the present time?"	Excellent, very good, good, fair, poor	Fair or poor
	(2) "Compared to 1 year ago, would you say your memory is better now, about the same, or worse now than it was then?"	Much better, better, same, worse, much worse	Worse or much worse
	(3) "In the last month, how often did memory problems interfere with your daily activities?"	Every day, most days, some days, rarely	Every day, or most days, or some days
Slow gait speed	**Gender**	**Age groups**	**Definition of slow gait speed**
	Men	Age <75 years	<0.69 m/s
		Age ≥75 years	<0.52 m/s
	Women	Age <75 years	<0.59 m/s
		Age ≥75 years	<0.40 m/s

family member, the Last Month of Life portion of the sample person interview was administered. Person-time was calculated from the study baseline (Round 1) to the year of death, loss to follow-up, or study endpoint. For further analyses, we categorized different subgroups by the numbers, categories, and status of CMDs. Then, we investigated the association of CMDs with MCR. In addition, we described the cumulative incidence of MCR by Kaplan–Meier survival analysis.

Third, sensitivity analyses were also conducted in stratified groups of sex (male vs female), married status (married/partnered vs single/widowed), race/ethnicity (White non-Hispanic vs Black non-Hispanic vs Hispanic vs Others), smoking status (never vs ever), vigorous exercise (yes vs no), sleep disorder (yes vs no), depression (yes vs no), anxiety (yes vs no), arthritis (yes vs no), hypertension (yes vs no), lung disease (yes vs no), osteoporosis (yes vs no), and cancer (yes vs no). The heterogeneity between subgroups was assessed based on meta-regression analysis. All results were considered significant at a p value < 0.05 (two-tailed). All analyses were conducted using R statistical software (version 4.2.1; www.r-project.org).

3 | RESULTS

3.1 | Characteristics of study participants

In this study, data from 4774 older adults without MCR or dementia at baseline (42.46% male, 57.54% female) were analyzed. The baseline sociodemographic, lifestyle, and clinical characteristics of the study population are presented in Table 2. At baseline, the mean age was 76.55 (7.43) years, and 2076 (56.68%) participants had 0 CMDs (CMD-free), 1534 (32.13%) had a single CMD, and 534 (11.19%) had CMM. During a median follow-up of 6 years (from 2011 to 2018), 602 older adults were defined as having MCR.

3.2 | Association between CMM and risk of MCR

The results of Cox proportional hazard analyses between CMM and the risk of MCR are shown in Table 3. We found that participants with CMM had a higher risk of MCR in the unadjusted model (hazard ratio [HR] 1.79, 95% confidence interval [CI] 1.45–2.21) than participants without CMM. A significant association persisted after adjusting for age, sex, marital status, race, smoking, body mass index (BMI), vigorous activity, sleep disorders, arthritis, hypertension, lung disease, cancer, osteoporosis, depression, and anxiety (HR 1.41, 95% CI 1.13–1.75).

In further analyses, we categorized participants into CMD-free, single, two, and three CMD groups (Table 4). Compared with the CMD-free group, the single-CMD (HR 1.46, 95% CI 1.22–1.75), two-CMD (HR 1.54, 95% CI 1.19–2.00), and three-CMD groups (HR 3.04, 95% CI 1.91–4.84) were associated with an increased risk of MCR after controlling for confounding factors. In the fully adjusted model, the risk for MCR was significantly increased for participants with diabetes alone (HR 1.37, 95% CI 1.15–1.64), stroke alone (HR 1.70, 95% CI 1.17–2.46), or heart disease alone (HR 1.44, 95% CI 1.13–1.83). Risk was also increased in participants with both diabetes and heart disease (HR 1.53; 95% CI 1.12–2.08). Increasing numbers of CMDs were dose-dependently associated with an increased risk of MCR (HR 1.33, 95% CI 1.20–1.48). In addition, participants with any CMDs were also associated with a higher risk of MCR (HR 1.54, 95% CI 1.30–1.82). Figure 2A,B presents Kaplan–Meier curves indicating the change in the proportion of participants stratified by CMD status at baseline and followed over the study period.

We also conducted stratified analyses across various strata defined by sex, marital status, race/ethnicity, smoking status, vigorous exercise, sleep disorder, depression, anxiety, arthritis, hypertension, lung disease, osteoporosis, and cancer using Model 3 (Table 4). We found significant associations of CMM with MCR in each stratum, and the interaction tests comparing the HRs across the strata were not significant (p value > 0.05), suggesting that older adults with CMM had significantly higher risks of MCR, regardless of confounding factors.

TABLE 2 Characteristics of study population at baseline.

	Total sample	Non-CMM	CMD-free	Single CMD	CMM	*p*-value#
Sample, *N* (%)	4774	4240 (88.81)	2706 (56.68)	1534 (32.13)	534 (11.19)	
Age, year, mean (SD)	76.55 (7.43)	76.46 (7.44)	76.12 (7.46)	77.04 (7.38)	77.27 (7.27)	<0.001
BMI, kg/m^2, mean (SD)	27.66 (5.40)	27.44 (5.30)	26.99 (5.10)	28.27 (5.53)	29.37 (5.90)	<0.001
Gender, *N* (%)						<0.001
Male	2027 (42.46)	1762 (42.56)	1070 (39.54)	692 (45.11)	265 (49.63)	
Female	2747 (57.54)	2478 (58.44)	1636 (60.46)	842 (54.89)	269 (50.37)	
Marital status, *N* (%)						0.039
Married/partnered	2549 (53.39)	2269 (53.51)	1487 (54.95)	782 (50.98)	280 (52.43)	
Single/widowed	2220 (46.50)	1967 (46.39)	1216 (44.94)	751 (48.96)	253 (47.38)	
Race/ethnicity, *N* (%)						<0.001
White non-Hispanic	3507 (73.46)	3136 (73.96)	2042 (75.46)	1094 (71.32)	371 (69.49)	
Black non-Hispanic	903 (18.91)	785 (18.51)	448 (16.56)	337 (21.97)	118 (22.10)	
Hispanic	220 (4.61)	197 (4.65)	130 (4.80)	67 (4.37)	23 (4.31)	
Others	144 (3.02)	122 (2.88)	86 (3.18)	36 (2.34)	22 (4.12)	
Smoking status, *N* (%)						<0.001
Ever	2459 (51.51)	2092 (49.34)	1391 (51.40)	701 (45.70)	222 (41.57)	
Never	2314 (48.47)	2147 (50.64)	1315 (48.60)	832 (54.24)	312 (58.43)	
Vigorous exercise, *N* (%)						<0.001
Yes	1939 (40.62)	1771 (41.77)	1207 (44.60)	564 (36.77)	168 (31.46)	
No	2834 (59.36)	2469 (58.23)	1499 (55.40)	970 (63.23)	365 (68.35)	
Sleep disorder, *N* (%)						<0.001
Yes	1518 (31.80)	1292 (30.47)	762 (28.16)	530 (34.55)	226 (42.32)	
No	3247 (68.01)	2941 (69.36)	1941 (71.73)	1000 (65.19)	306 (57.30)	
Chronic disease, *N* (%)						
Arthritis	2552 (53.46)	2214 (52.22)	1333 (49.26)	881 (57.43)	338 (63.30)	<0.001
Hypertension	3155 (66.09)	2711 (63.94)	1562 (57.72)	1149 (74.90)	444 (83.15)	<0.001
Lung disease	680 (14.24)	569 (13.42)	328 (12.12)	241 (15.71)	111 (20.79)	<0.001
Cancer	1263 (26.46)	1101 (25.97)	685 (25.31)	416 (27.12)	162 (30.34)	0.041
Osteoporosis	928 (19.44)	814 (19.20)	510 (18.85)	304 (19.82)	114 (21.35)	0.366
Stroke	405 (8.48)	172 (4.06)	–	172 (11.21)	233 (43.63)	<0.001
Diabetes mellitus	1104 (23.13)	678 (15.99)	–	678 (44.20)	426 (79.78)	<0.001
Heart disease	1158 (24.26)	684 (16.13)	–	684 (44.59)	474 (88.76)	<0.001
Anxiety	420 (8.80)	336 (7.92)	183 (6.76)	153 (9.97)	84 (15.73)	<0.001
Depression	514 (10.77)	422 (9.95)	235 (8.68)	187 (12.19)	92 (17.23)	< 0.001

Abbreviations: CMD, cardiometabolic disease; CMM, cardiometabolic multimorbidity; SD, standard deviation.

4 | DISCUSSION

4.1 | Principal findings

In this nationally representative cohort of 4774 older adults, we examined the association of CMM with MCR over a median follow-up period of 6 years for the first time. We found that CMM was significantly associated with the risk of MCR, and that the risk of MCR was significantly increased with an increasing number of CMDs (diabetes, stroke, and heart disease).

4.2 | Comparison with other studies

To our knowledge, this is the first study to examine the association of CMM with MCR in older adults. MCR has been proven to be a

TABLE 3 Association of single and CMD status with incident MCR.

			Model 2		Model 3		
	Events/*N* (%)	Model 1 HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
CMM category							
Non-CMM	497/4240 (11.72)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
CMM	105/534 (19.66)	1.79 (1.45, 2.21)	<0.001	1.44 (1.17, 1.79)	<0.001	1.41 (1.13, 1.75)	0.002
CMD category							
CMD-free	257/2706 (9.50)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Single CMD	240/1534 (15.65)	1.76 (1.48, 2.10)	<0.001	1.48 (1.24, 1.77)	<0.001	1.46 (1.22, 1.75)	<0.001
Diabetes mellitus alone	105/678 (15.49)	1.69 (1.35, 2.12)	<0.001	1.37 (1.15, 1.64)	<0.001	1.37 (1.15, 1.64)	<0.001
Heart disease alone	102/684 (14.91)	1.70 (1.35, 2.14)	<0.001	1.48 (1.17, 1.88)	0.001	1.44 (1.13, 1.83)	0.003
Stroke alone	33/172 (19.19)	2.25 (1.56, 3.23)	<0.001	1.71 (1.19, 2.47)	0.004	1.70 (1.17, 2.46)	0.005
Two CMDs	85/469 (18.12)	2.05 (1.61, 2.63)	<0.001	1.55 (1.20, 2.01)	<0.001	1.54 (1.19, 2.00)	0.001
Diabetes mellitus + heart disease	55/301 (18.27)	2.04 (1.52, 2.73)	<0.001	1.56 (1.15, 2.11)	0.004	1.53 (1.12, 2.08)	0.007
Diabetes mellitus + stroke	11/60 (18.33)	2.07 (1.13, 3.78)	0.018	1.66 (0.90, 3.04)	0.104	1.69 (0.91, 3.12)	0.095
Heart disease + stroke	19/108 (17.59)	2.09 (1.31, 3.34)	<0.001	1.42 (0.88, 2.29)	0.149	1.37 (0.84, 2.24)	0.194
Three CMDs	20/65 (30.77)	3.90 (2.47, 6.14)	<0.001	3.21 (2.03, 5.09)	<0.001	3.04 (1.91, 4.84)	<0.001
Per additional CMD	602/4774 (12.61)	1.52 (1.38, 1.67)	<0.001	1.35 (1.22, 1.49)	<0.001	1.33 (1.20, 1.48)	<0.001
Any CMDs	345/2068 (16.68)	1.89 (1.61, 2.22)	<0.001	1.56 (1.32, 1.84)	<0.001	1.54 (1.30, 1.82)	<0.001

Note: Model 1: unadjusted; Model 2: adjusted for age, gender, marital status, race, smoking, Body mass index, vigorous activity, and sleep disorders; Model 3: adjusted for Model 2 and additional for arthritis, hypertension, lung disease, cancer, osteoporosis, depression, and anxiety.
Abbreviations: CMD, cardiometabolic disease; CMM, cardiometabolic multimorbidity; MCR, motoric cognitive risk syndrome.

prodromal phase of dementia.[1–3] Although no studies have investigated the association of CMM with MCR in older adults, researchers have paid attention to the association of CMM with dementia. Dove et al. included 2577 dementia-free participants (60 years of age or older) and followed-up for 12 years from the ongoing longitudinal Swedish National Study on Aging and Care-Kungsholmen.[18] They found that CMM was associated with cognitive impairment (HR 1.73, 95% CI 1.23–2.44) and its progression to dementia (HR 1.86, 95% CI 1.17–2.97). CMM also accelerated the onset of cognitive impairment by 2.3 years and dementia by 1.8 years.[18] In a further study, they validated their findings in 17,913 dementia-free individuals (60 years of age or older) from the Swedish Twin Registry. Similarly, a significant association of CMM with increased dementia risk was observed in a classic cohort study design (HR 2.10, 95% CI 1.73–2.57). In a twin analysis, the association was preserved among dizygotic but not monozygotic twin pairs, suggesting that the association may have a genetic underpinning.[19] In addition, Tai et al. conducted a study using data from 200,000 UK Biobank participants (60 years of age or older) of European ancestry and without dementia and found that CMM was independently associated with an increased risk of incident dementia, regardless of low (HR 3.53, 95% CI 2.42–5.17), moderate (HR 4.65, 95% CI 3.80–5.69), or high (HR 5.74, 95% CI 4.26–7.74) genetic risks.[20] In summary, previous studies conducted in different populations demonstrated a robust and independent association of CMM with dementia or cognitive impairment in older adults.[19–23] Our study further included 4744 individuals 65 years of age or older from the NHATS and found a strong association between CMM and increased MCR risk. In summary, we took further steps to examine the association of CMM with MCR, which could fill gaps in the continuum of cognitive phenotypes leading up to dementia and provide evidence of the considerable association of CMM with dementia once more.

In our study, we examined the relationship between a single CMD and the risk of MCR and observed that diabetes mellitus, stroke, and heart disease were all associated with increased risks of MCR in older adults. Similarly, previous studies demonstrated that CMDs were established risk factors for MCR.[11] Kinza Iqbal et al. included both cross-sectional and longitudinal studies and conducted a meta-analysis. They found that diabetes mellitus (21 included studies, odds ratio [OR] 1.50, 95% CI 1.37–1.64), stroke (16 included studies, OR 2.03, 95% CI 1.70–2.42), heart disease (7 included studies, OR 1.45, 95% CI 1.13–1.86), and coronary artery disease (5 included studies, OR 1.49, 95% CI 1.16–1.19) were all associated with increased risks of MCR.[11] Meanwhile, cardiovascular-related factors were also associated with higher MCR risk, such as smoking (13 included studies, OR 2.03, 95% CI 1.70–2.42), obesity (12 included studies, OR 1.34, 95% CI 1.13–1.59), and a sedentary lifestyle (11 included studies, OR 2.00, 95% CI 1.59–2.52).[11] In brief, the findings in our study are consistent with those of previous studies.

TABLE 4 Association of CMM with incident MCR in subgroups.

	Events/*N* (%)	HR (95% CI)	*p*-value	P-int
Age				0.217
75 years	187/2109 (8.87)	1.51 (1.02, 2.11)	0.035	
≥75 years	415/2665 (15.57)	1.23 (0.94, 1.60)	0.137	
Gender				0.507
Male	282/2027 (13.91)	1.32 (0.97, 1.80)	0.079	
Female	320/2747 (11.65)	1.53 (1.13, 2.09)	0.006	
Marital status				0.497
Married/partnered	283/2549 (11.10)	1.49 (1.10, 2.03)	0.011	
Single/widowed	318/2220 (14.32)	1.28 (0.94, 1.76)	0.121	
Race/ethnicity				0.277
White non-Hispanic	368/3507 (10.49)	1.56 (1.18, 2.06)	0.002	
Black non-Hispanic	165/903 (18.27)	1.44 (0.97, 2.15)	0.069	
Hispanic	52/220 (23.64)	0.74 (0.29, 1.92)	0.546	
Others	17/144 (9.72)	0.43 (0.07, 2.83)	0.385	
Smoking status				0.086
Yes	322/2459 (13.09)	1.18 (0.87, 1.59)	0.278	
No	280/2314 (12.101)	1.73 (1.26, 2.37)	<0.001	
Vigorous exercise				0.170
Yes	185/1939 (9.54)	1.77 (1.19, 2.63)	0.005	
No	417/2834 (14.71)	1.27 (0.98, 1.65)	0.069	
Sleep disorder				0.949
Yes	232/1518 (15.28)	1.39 (1.01, 1.94)	0.049	
No	369/3247 (11.36)	1.41 (1.06, 1.88)	0.019	
Depression				0.250
Yes	89/514 (17.32)	1.00 (0.56, 1.77)	0.988	
No	511/4241 (12.05)	1.44 (1.14, 1.82)	0.002	
Anxiety				0.080
Yes	86/420 (20.48)	0.85 (0.48, 1.51)	0.588	
No	515/4342 (11.86)	1.48 (1.16, 1.87)	0.001	
Arthritis				0.448
Yes	394/2552 (15.43)	1.33 (1.02, 1.73)	0.033	
No	208/2215 (9.39)	1.59 (1.09, 2.32)	0.0156	
Hypertension				0.082
Yes	441/3155 (13.98)	1.50 (1.19, 1.89)	<0.001	
No	161/1612 (9.99)	0.82 (0.43, 1.55)	0.536	
Lung disease				0.321
Yes	95/680 (13.97)	1.09 (0.64, 1.83)	0.759	
No	507/4091 (12.39)	1.46 (1.15, 1.86)	0.002	
Osteoporosis				0.552
Yes	127/928 (13.69)	1.23 (0.76, 2.00)	0.401	
No	474/3837 (12.35)	1.45 (1.14, 1.86)	0.003	
Cancer				0.661
Yes	146/1263 (11.56)	1.30 (0.86, 1.98)	0.213	
No	456/3509 (13.00)	1.45 (1.13, 1.88)	0.004	

Note: All models were compared with non-CMM groups and adjusted for age, gender, marital status, race, smoking status, Body mass index, vigorous activity and sleep disorder, arthritis, hypertension, lung disease, cancer, osteoporosis. P-int represents the heterogeneity between subgroups based on the meta-regression analysis.

Abbreviations: CMM, cardiometabolic multimorbidity; MCR, motoric cognitive risk syndrome.

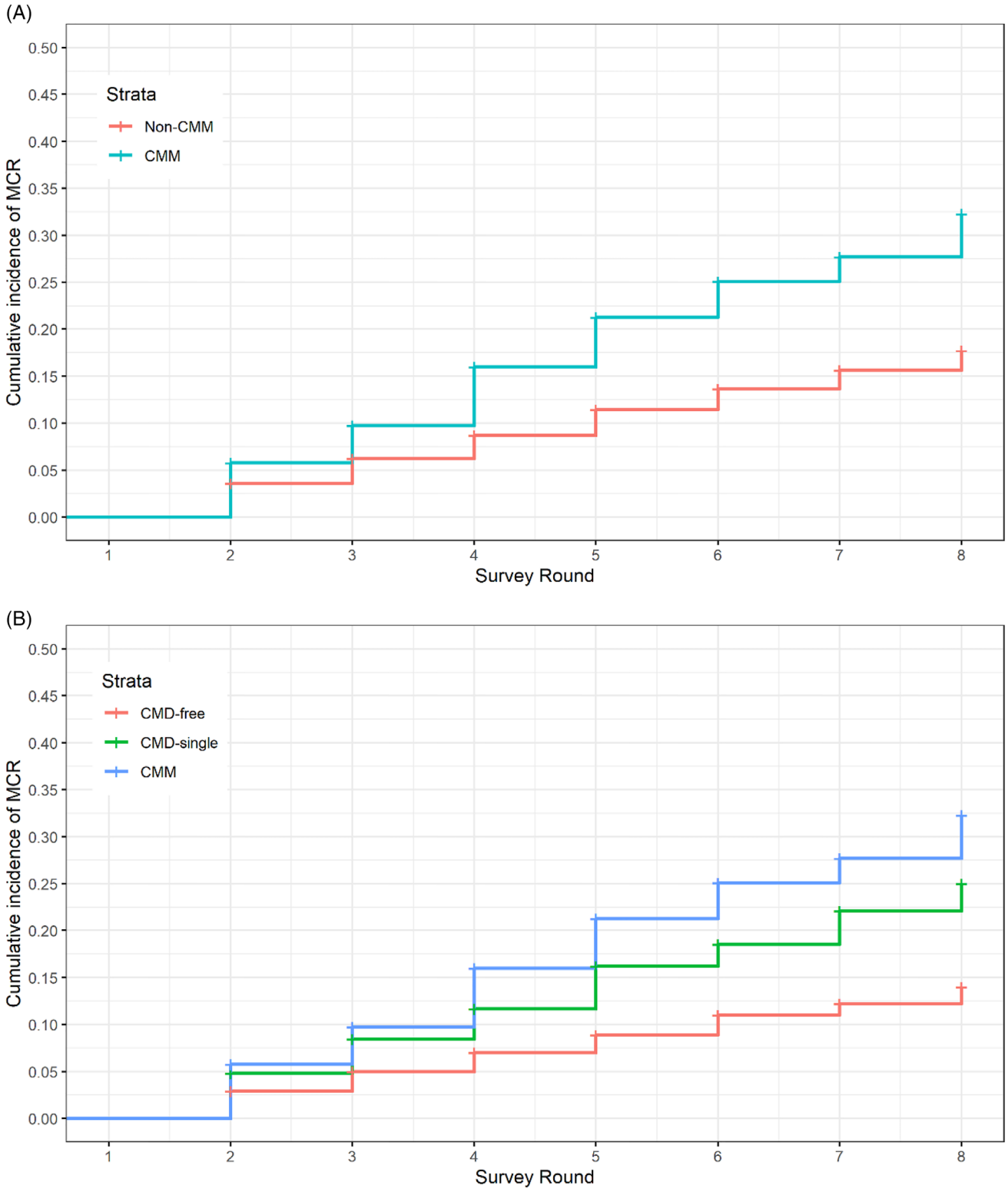

FIGURE 2 Kaplan–Meier curves reflecting the risk of MCR across the different CMM groups.

4.3 | The potential mechanism

Epidemiologic studies have demonstrated strong and significant associations of heart disease, diabetes mellitus, and stroke with adverse cognitive outcomes.[32–34] The mechanism by which CMDs are related to MCR is not understood. One plausible explanations of the association may be subject to inflammation. CMDs are associated with increased inflammatory levels.[35–37] A significant association of higher inflammation (such as C-reactive protein, interleukin-6, interleukin-10) with an increased risk of MCR was widely revealed in previous

studies.[38–40] In addition, inflammatory markers were demonstrated to be associated with the two components of MCR, including slow walking speed[41,42] and cognitive complaints[43] in older adults. In summary, we speculate that the potential mechanism by which CMDs are related to MCR may be attributed partly to inflammation. In addition, other plausible explanations may also be involved. The association of heart-related diseases (heart failure, coronary heart disease, and atrial fibrillation) with cognitive dysfunction were also commonly reported.[44–46] Many pathophysiological systems participated, regulating heart–brain interactions, including the vascular, neurohumoral, and immune systems.[47,48] The damaging impact of heart-related disease on cognition may be driven by regional cerebral hypoperfusion that affects cognitive regulatory cerebral sites.[47]

4.4 | Strengths and limitations

Our study has several strengths. This study is a population-based, longitudinal, and prospective cohort study. It includes a longer follow-up period and larger sample size. We also controlled for several representative confounding factors (such as sleep and depression[49–52]) and examined the association of CMM with MCR risk. Nevertheless, limitations should also be noted in the interpretation of our findings. In this study, due to the observational setting, the significant association between CMM and CMR risk merely reflects a correlational rather than a causal relationship. In addition, the clinical information was obtained based on self- or proxy-reported diagnosis, which might be subject to recall bias and misclassification. Another limitation is the lack of genetic data. We cannot determine the effect of genes on the association between CMM and MCR risk. Therefore, it would be beneficial for future research to obtain more data on genes (such as apolipoprotein E [*APOE*]) and other cognition-related factors to validate our findings. Finally, it is worth noting that the mean age of the included population in our study was 76.55 (7.43) years, and many older adults may have been showing early dementia at baseline. Further studies should include younger populations to validate our findings.

5 | CONCLUSION

In this study, for the first time, we examined the association of CMM with MCR risk in 4744 individuals 65 years of age or older. We found that having CMM as well as a single CMD were associated with an increased risk of MCR. An increasing number of CMDs are dose-dependently associated with increased MCR risk in older adults. Our study takes further steps to provide evidence of a momentous relationship between CMM and dementia, which fills gaps in the continuum of cognitive phenotypes leading up to dementia. In addition, considering the tremendous number of individuals with diabetes mellitus, heart disease, and/or stroke worldwide, more attention should be given to individuals with both single and combined CMDs to prevent and/or delay the development of MCR.

AUTHOR CONTRIBUTIONS

Hui Zhang, Shuai Jiang, and Xiaofeng Wang designed and conducted the research. Shuai Jiang, Yi Li, Meng Hao, Xiao-Yan Jiang, and Zixin Hu analyzed the data and performed the statistical analyses. Hui Zhang drafted the manuscript. Xiaofeng Wang and Li Jin supervised the whole study. Hui Zhang and Xiaofeng Wang had primary responsibility for the final content, and all authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

This study uses publicly available, non-identifiable data and was approved by the John Hopkins University Institutional Review Board. Informed consent was obtained by National Health and Aging Trends Study (NHATS) investigators from all participants or their proxy respondents. Our analysis of publicly available, de-identified data was considered exempt from institutional review board review.

DATA AVAILABILITY STATEMENT

The data sets analyzed in the study are publicly available after registration and application at https://www.nhats.org/researcher. The data sets generated and analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Gomez GT, Gottesman RF, Gabriel KP, et al. The association of motoric cognitive risk with incident dementia and neuroimaging characteristics: the atherosclerosis risk in communities study. *Alzheimers Dement*. 2022;18(3):434-444. doi:10.1002/alz.12412
2. Verghese J, Wang C, Lipton RB, Holtzer R. Motoric cognitive risk syndrome and the risk of dementia. *J Gerontol A Biol Sci Med Sci*. 2013;68(4):412-418. doi:10.1093/gerona/gls191
3. Ayers E, Verghese J. Motoric cognitive risk syndrome and risk of mortality in older adults. *Alzheimers Dement*. 2016;12(5):556-564. doi:10.1016/j.jalz.2015.08.167
4. Wen ZF, Peng SH, Wang JL, et al. Prevalence of motoric cognitive risk syndrome among older adults: a systematic review and meta-analysis. *Aging Ment Health*. 2023;27(8):1443-1455. doi:10.1080/13607863.2022.2158305
5. Verghese J, Annweiler C, Ayers E, et al. Motoric cognitive risk syndrome: multicountry prevalence and dementia risk. *Neurology*. 2014;83(8):718-726. doi:10.1212/wnl.0000000000000717

6. Maggio M, Lauretani F. Prevalence, incidence, and clinical impact of cognitive-motoric risk syndrome in Europe, USA, and Japan: facts and numbers update 2019. *J Cachexia Sarcopenia Muscle*. 2019;10(5):953-955. doi:10.1002/jcsm.12476
7. Mullin DS, Cockburn A, Welstead M, Luciano M, Russ TC, Muniz-Terrera G. Mechanisms of motoric cognitive risk-Hypotheses based on a systematic review and meta-analysis of longitudinal cohort studies of older adults. *Alzheimers Dement*. 2022;18(12):2413-2427. doi:10.1002/alz.12547
8. Verghese J, Wang C, Bennett DA, Lipton RB, Katz MJ, Ayers E. Motoric cognitive risk syndrome and predictors of transition to dementia: a multicenter study. *Alzheimers Dement*. 2019;15(7):870-877. doi:10.1016/j.jalz.2019.03.011
9. Meiner Z, Ayers E, Bennett DA, Wang C, Verghese J. Risk factors for the progression of motoric cognitive risk syndrome to dementia: retrospective cohort analysis of two populations. *Eur J Neurol*. 2021;28(6):1859-1867. doi:10.1111/ene.14841
10. Semba RD, Tian Q, Carlson MC, Xue QL, Ferrucci L. Motoric cognitive risk syndrome: integration of two early harbingers of dementia in older adults. *Ageing Res Rev*. 2020;58:101022. doi:10.1016/j.arr.2020.101022
11. Iqbal K, Hasanain M, Ahmed J, et al. Association of motoric cognitive risk syndrome with cardiovascular and noncardiovascular factors: a systematic review and meta-analysis. *J Am Med Dir Assoc*. 2022;23(5):810-822. doi:10.1016/j.jamda.2021.11.035
12. Sutin AR, Luchetti M, Stephan Y, Terracciano A. Purpose in life and motoric cognitive risk syndrome: replicable evidence from two national samples. *J Am Geriatr Soc*. 2021;69(2):381-388. doi:10.1111/jgs.16852
13. Stephan Y, Sutin AR, Canada B, Terracciano A. The association between subjective age and motoric cognitive risk syndrome: results from a population-based cohort study. *J Gerontol B Psychol Sci Soc Sci*. 2021;76(10):2023-2028. doi:10.1093/geronb/gbab047
14. Gerdts E, Regitz-Zagrosek V. Sex differences in cardiometabolic disorders. *Nat Med*. 2019;25(11):1657-1666. doi:10.1038/s41591-019-0643-8
15. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA*. 2015;314(1):52-60. doi:10.1001/jama.2015.7008
16. Canoy D, Tran J, Zottoli M, et al. Association between cardiometabolic disease multimorbidity and all-cause mortality in 2 million women and men registered in UK general practices. *BMC Med*. 2021;19(1):258. doi:10.1186/s12916-021-02126-x
17. Joseph JJ, Rajwani A, Roper D, et al. Associations of cardiometabolic multimorbidity with all-cause and coronary heart disease mortality among Black adults in the Jackson Heart Study. *JAMA Netw Open*. 2022;5(10):e2238361. doi:10.1001/jamanetworkopen.2022.38361
18. Dove A, Marseglia A, Shang Y, et al. Cardiometabolic multimorbidity accelerates cognitive decline and dementia progression. *Alzheimers Dement*. 2023;19:821-830. doi:10.1002/alz.12708
19. Dove A, Guo J, Marseglia A, et al. Cardiometabolic multimorbidity and incident dementia: the Swedish twin registry. *Eur Heart J*. 2023;44(7):573-582. doi:10.1093/eurheartj/ehac744
20. Tai XY, Veldsman M, Lyall DM, et al. Cardiometabolic multimorbidity, genetic risk, and dementia: a prospective cohort study. *Lancet Healthy Longev*. 2022;3(6):e428-e436. doi:10.1016/s2666-7568(22)00117-9
21. Wang Z, Marseglia A, Shang Y, Dintica C, Patrone C, Xu W. Leisure activity and social integration mitigate the risk of dementia related to cardiometabolic diseases: a population-based longitudinal study. *Alzheimers Dement*. 2020;16(2):316-325. doi:10.1016/j.jalz.2019.09.003
22. Khondoker M, Macgregor A, Bachmann MO, Hornberger M, Fox C, Shepstone L. Multimorbidity pattern and risk of dementia in later life: an 11-year follow-up study using a large community cohort and linked electronic health records. *J Epidemiol Community Health*. 2023;77(5):285-292. doi:10.1136/jech-2022-220034
23. Chen Y, Zhang Y, Li S, et al. Cardiometabolic diseases, polygenic risk score, APOE genotype, and risk of incident dementia: a population-based prospective cohort study. *Arch Gerontol Geriatr*. 2023;105:104853. doi:10.1016/j.archger.2022.104853
24. 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-e273. doi:10.1016/s2666-7568(23)00054-5
25. Freedman VA, Kasper JD. Cohort profile: the national health and aging trends study (NHATS). *Int J Epidemiol*. 2019;48(4):1044-1045g. doi:10.1093/ije/dyz109
26. Löwe B, Kroenke K, Gräfe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). *J Psychosom Res*. 2005;58(2):163-171. doi:10.1016/j.jpsychores.2004.09.006
27. Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry*. 2016;39:24-31. doi:10.1016/j.genhosppsych.2015.11.005
28. Stephan Y, Sutin AR, Canada B, Terracciano A. Personality and motoric cognitive risk syndrome. *J Am Geriatr Soc*. 2020;68(4):803-808. doi:10.1111/jgs.16282
29. Galvin JE, Roe CM, Powlishta KK, et al. The AD8: a brief informant interview to detect dementia. *Neurology*. 2005;65(4):559-564. doi:10.1212/01.wnl.0000172958.95282.2a
30. Robbins R, Weaver MD, Barger LK, Wang W, Quan SF, Czeisler CA. Sleep difficulties, incident dementia and all-cause mortality among older adults across 8 years: findings from the National Health and Aging Trends Study. *J Sleep Res*. 2021;30(6):e13395. doi:10.1111/jsr.13395
31. Robbins R, DiClemente RJ, Troxel AB, et al. Sleep medication use and incident dementia in a nationally representative sample of older adults in the US. *Sleep Med*. 2021;79:183-189. doi:10.1016/j.sleep.2020.11.004
32. Ben Hassen C, Fayosse A, Landré B, et al. Association between age at onset of multimorbidity and incidence of dementia: 30 year follow-up in Whitehall II prospective cohort study. *BMJ*. 2022;376:e068005. doi:10.1136/bmj-2021-068005
33. Xue M, Xu W, Ou YN, et al. Diabetes mellitus and risks of cognitive impairment and dementia: a systematic review and meta-analysis of 144 prospective studies. *Ageing Res Rev*. 2019;55:100944. doi:10.1016/j.arr.2019.100944
34. Craig L, Hoo ZL, Yan TZ, Wardlaw J, Quinn TJ. Prevalence of dementia in ischaemic or mixed stroke populations: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2022;93(2):180-187. doi:10.1136/jnnp-2020-325796
35. Liberale L, Montecucco F, Schwarz L, Lüscher TF, Camici GG. Inflammation and cardiovascular diseases: lessons from seminal clinical trials. *Cardiovasc Res*. 2021;117(2):411-422. doi:10.1093/cvr/cvaa211
36. Lutgens E, Atzler D, Döring Y, Duchene J, Steffens S, Weber C. Immunotherapy for cardiovascular disease. *Eur Heart J*. 2019;40(48):3937-3946. doi:10.1093/eurheartj/ehz283
37. Diedisheim M, Carcarino E, Vandiedonck C, Roussel R, Gautier JF, Venteclef N. Regulation of inflammation in diabetes: from genetics to epigenomics evidence. *Mol Metab*. 2020;41:101041. doi:10.1016/j.molmet.2020.101041
38. Groeger JL, Ayers E, Barzilai N, et al. Inflammatory biomarkers and motoric cognitive risk syndrome: multicohort survey. *Cereb Circ Cogn Behav*. 2022;3:100151. doi:10.1016/j.cccb.2022.100151
39. Bai A, Shi H, Huang X, Xu W, Deng Y. Association of C-reactive protein and motoric cognitive risk syndrome in community-dwelling older adults: the China Health and Retirement Longitudinal Study. *J Nutr Health Aging*. 2021;25(9):1090-1095. doi:10.1007/s12603-021-1678-3

40. Sathyan S, Barzilai N, Atzmon G, Milman S, Ayers E, Verghese J. Association of anti-inflammatory cytokine IL10 polymorphisms with motoric cognitive risk syndrome in an Ashkenazi Jewish population. *Neurobiol Aging*. 2017;58(238):e1-238.e8. doi:10.1016/j.neurobiolaging.2017.06.006
41. Guo J, Zhang H, Li Y, et al. Neutrophil-lymphocyte ratio as a predictor of slow gait speed in older adults: the Rugao Longitudinal Aging Study. *Exp Gerontol*. 2021;152:111439. doi:10.1016/j.exger.2021.111439
42. Nidadavolu LS, Feger D, Chen D, et al. Associations between circulating cell-free mitochondrial DNA, inflammatory markers, and cognitive and physical outcomes in community dwelling older adults. *Immun Ageing*. 2023;20(1):24. doi:10.1186/s12979-023-00342-y
43. Merchant RA, Chan YH, Anbarasan D, Aprahamian I. Association of motoric cognitive risk syndrome with sarcopenia and systemic inflammation in pre-frail older adults. *Brain Sci*. 2023;13(6):936. doi:10.3390/brainsci13060936
44. Wolters FJ, Segufa RA, Darweesh SKL, et al. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14(11):1493-1504. doi:10.1016/j.jalz.2018.01.007
45. Bagge CN, Henderson VW, Laursen HB, Adelborg K, Olsen M, Madsen NL. Risk of dementia in adults with congenital heart disease: population-based cohort study. *Circulation*. 2018;137(18):1912-1920. doi:10.1161/circulationaha.117.029686
46. Rivard L, Friberg L, Conen D, et al. Atrial fibrillation and dementia: a report from the AF-SCREEN International Collaboration. *Circulation*. 2022;145(5):392-409. doi:10.1161/circulationaha.121.055018
47. Rossi A, Mikail N, Bengs S, et al. Heart-brain interactions in cardiac and brain diseases: why sex matters. *Eur Heart J*. 2022;43(39):3971-3980. doi:10.1093/eurheartj/ehac061
48. Jensen M, Zeller T, Twerenbold R, Thomalla G. Circulating cardiac biomarkers, structural brain changes, and dementia: emerging insights and perspectives. *Alzheimers Dement*. 2023;19(4):1529-1548. doi:10.1002/alz.12926
49. Reynolds G, Buckley R, Papp K, et al. Relation of modifiable lifestyle and mood factors to cognitive concerns among participants and their study partners in the A4 screen data. *Alzheimers Dement (Amst)*. 2023;15(2):e12435. doi:10.1002/dad2.12435
50. Xu W, Bai A, Liang Y, Lin Z. Association between depression and motoric cognitive risk syndrome among community-dwelling older adults in China: a 4-year prospective cohort study. *Eur J Neurol*. 2022;29(5):1377-1384. doi:10.1111/ene.15262
51. Zeng W, Zhang L, Feng B, et al. Association between sleep disturbance with motoric cognitive risk syndrome in Chinese older adults. *Eur J Neurol*. 2021;28(5):1470-1478. doi:10.1111/ene.14681
52. Borelli WV, Zimmer ER, Bieger A, et al. Subjective cognitive decline in Brazil: prevalence and association with dementia modifiable risk factors in a population-based study. *Alzheimers Dement (Amst)*. 2022;14(1):e12368. doi:10.1002/dad2.12368

SUPPORTING INFORMATION

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